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Survival Following Primary Androgen Deprivation Therapy Among Men With Localized Prostate Cancer

Grace L. Lu-Yao, MPH, PhD
Peter C. Albertsen, MD
Dirk F. Moore, PhD
Weichung Shih, PhD
Yong Lin, PhD
Robert S. DiPaola, MD
Siu-Long Yao, MD

PROSTATE CANCER IS THE MOST common nonskin cancer and the second most common cause of cancer death among men.1 For the majority of men with incident prostate cancer (approximately 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, an increasing number of clinicians 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 (ADT) as an adjunct to surgery or radiation for patients with high-risk cancer.5-10 In 1 trial,5,8 early ADT reduced mortality by approximately 50% when used with radiation in high-risk disease (poorly differentiated T1-T2 or T3-T4); whereas, in another trial,9

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 To evaluate the association between PADT and survival in elderly men with localized prostate cancer.

Design, Setting, and Patients A population-based cohort study of 19,271 men aged 66 years or older receiving Medicare who did not receive definitive local therapy for clinical stage T1-T2 prostate cancer. These patients were diagnosed in 1992-2002 within predefined US geographical areas, with follow-up through December 31, 2006, for all-cause mortality and through December 31, 2004, for prostate cancer–specific mortality. Instrumental variable analysis was used to address potential biases associated with unmeasured confounding variables.

Main Outcome Measures Prostate cancer–specific survival and overall survival.

Results Among patients with localized prostate cancer (median age, 77 years), 7867 (41%) received PADT, and 11,404 were treated with conservative management, not including PADT. During the follow-up period, there were 1560 prostate cancer deaths and 11,045 deaths from all causes. Primary androgen deprivation therapy was associated with lower 10-year prostate cancer–specific survival (80.1% vs 82.6%; hazard ratio [HR], 1.17; 95% confidence interval [CI], 1.03-1.33) and no increase in 10-year overall survival (30.2% vs 30.3%; HR, 1.00; 95% CI, 0.96-1.05) compared with conservative management. However, in a prespecified subset analysis, PADT use in men with poorly differentiated cancer was associated with improved prostate cancer–specific survival (59.8% vs 54.3%; HR, 0.84; 95% CI, 0.70-1.00; P = .049) but not overall survival (17.3% vs 15.3%; HR, 0.92; 95% CI, 0.84-1.01).

Conclusion 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.

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See also Patient Page.

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mortality was reduced by approximately 60% in patients with nodal disease identified at surgery. Consequently, many investigators have concluded that the early use of ADT is appropriate for patients with higher-risk 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 ADT has recently increased, because a growing body of literature now demonstrates that chronic ADT use has been associated with approximately 10% to 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. In the Prostate Cancer Outcomes Study (PCOS), the risk of gynecomastia and hot flashes increased 500% and a 267% increase in impotence was observed after 1 year of treatment. In addition, medical ADT is costly. The costs associated with ADT medication use in the United States reached $1.2 billion in 2003 and ADT drugs represented the second highest Medicare Part B drug expenditure.

A randomized clinical trial would provide the data needed to determine the usefulness of PADT vs conservatoive management in localized disease. However, because of the relatively indolent nature of most cases of localized prostate cancer, 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 used to provide insight under such circumstances, although they may be more subject to biases.

Instrumental variable analysis (IVA) techniques have been applied successfully to observational medical studies to help minimize many of these biases so that the results of randomized clinical trials may often be mimicked with observational data. 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 survival and overall survival in men with T1-T2 prostate cancer.

METHODS

Data Sources
Data 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 or older, and linkage to the SEER database was complete for approximately 93% of the patients. The study received institutional review board approval from the University of Medicine and Dentistry of New Jersey, as well as the SEER program, and the Center for Medicare & Medicaid Services. Informed consent was waived by the institutional review board because the data did not contain personal identifiers.

Study Participants
The study cohort consisted of 89,877 men aged 66 years or older who were SEER residents and diagnosed with T1-T2 cancer in 1992-2002. 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). Patients 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 care insurance coverage during the study period were excluded (n=33,987). Patients with missing data (n=2995), unknown cancer grade (n=255), or initiation of ADT before cancer diagnosis (n=123) were also excluded. Therefore, a total cohort of 19,271 men were included in our analysis.

Primary Androgen Deprivation Therapy
Patients undergoing PADT received ADT as primary cancer therapy (eg, no surgery or radiation) during the first 180 days following diagnosis. Patients in the conservative management group 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. Using a previously described algorithm, Medicare physician, inpatient and outpatient claims were used to identify orchiectomy (Healthcare Common Procedure Coding System codes 54520, 54521, 54522, 54530, or 54535, or the International Classification of Diseases, Ninth Revision code 624) and the use of luteinizing hormone-releasing hormone agonists (Healthcare Common Procedure Coding System codes J1950, J9202, J9217, J9218, or J9219). Luteinizing hormone-releasing hormone agonists and orchietomy were combined because previous studies have shown these treatments to be essentially equivalent.

Study End Points 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.

Cox proportional hazards regression model covariates included age at diagnosis, race (self-determined by the patients and included as a variable because race can be associated with outcomes in prostate cancer), zip code income, SEER region, urban area, marital status, can-
HORMONAL THERAPY USE FOR LOCALIZED PROSTATE CANCER

30,31 For cancer of prostate cancer diagnosis by using Medicare claims during the year before prostate cancer diagnosis by using a validated algorithm.30,31 For cancer grade, Gleason score 2 to 4, 5 to 7, and 8 to 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 1 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 less than 50 cases was combined with the nearest (in terms of distance between geographic centers) HSA with 50 or more cases. The threshold of 50 or more cases was chosen because lower thresholds were associated with more imbalances in patient characteristics in high-PADT and low-PADT use areas. The algorithm produced 66 utilization areas. High-use 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 nonmedical 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 be associated with 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 these factors comparable between low-PADT and high-PADT areas.

Statistical Analyses

Instrumental variable analysis methods based on the Rubin Causal Model21 were used to account for both measured and unmeasured (eg, prostate-specific antigen, family history, diet, weight) 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 listed above to ensure the validity of our IVA. Traditional Cox proportional hazards regression model results were also reported for comparison with the IVA results. Analyses were conducted by using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) 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 score 2-4) are not shown separately because results were unstable due to the limited sample size.

Patients who differ in the likelihood of receiving PADT are compared and the treatment effect on the marginal population is estimated. The marginal effect (local average treatment effect)20 of PADT was calculated as:

$$\text{Instrumental Variable Estimate} = \Delta = \frac{\text{Adjusted Outcomes}_{\text{Hi}} - \text{Adjusted Outcomes}_{\text{Lo}}}{P\text{r}(\text{PADT} | \text{Hi}) - P\text{r}(\text{PADT} | \text{Lo})}$$

where Hi = a geographic area in the upper tertile of PADT use, Lo = a geographic area in the lower tertile of PADT use, Pr(PADT | Hi/Lo) = 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, and Adjusted Outcomes$_{\text{Hi}}$/Adjusted Outcomes$_{\text{Lo}}$ = estimated survival probability at a particular time (eg, 5- or 10-year survival) among men who had localized prostate cancer and did not have surgery or radiation as their primary cancer therapy in high/low use region.

To compute the population-adjusted survival curves, we substituted the population means (for continuous covariates) into the Cox proportional hazards regression 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 patients in each class. In addition, the population-adjusted survival curve was computed from the weighted hazard function.32 Estimates of 5- and 10-year overall and cancer-specific survival for men at average risk were derived from these adjusted curves. Confidence intervals (CIs) were obtained by computing these adjusted survival curves for each of 10 000 bootstrap samples of the original data. P values and 95% CIs were derived from the bootstrap estimates. Testing was 2-sided, with $\alpha = .05$. 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 HSAs were performed by 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 or older 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 receiving conservative management 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).

Table 1. Characteristics of the Study Cohorta

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PADT (n = 7867)</th>
<th>Conservative Management (n = 11 404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>79 (74-83)</td>
<td>77 (72-81)</td>
</tr>
<tr>
<td>Black race</td>
<td>758 (9.6)</td>
<td>1307 (11.5)</td>
</tr>
<tr>
<td>Married at diagnosis</td>
<td>4911 (62.4)</td>
<td>7302 (64.0)</td>
</tr>
<tr>
<td>Urban residence</td>
<td>6299 (80.1)</td>
<td>9411 (82.5)</td>
</tr>
<tr>
<td>Income, median (IQR), US $</td>
<td>42 890 (33 861-57468)</td>
<td>44 022 (34 214-57983)</td>
</tr>
<tr>
<td>SEER regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>840 (10.7)</td>
<td>964 (8.5)</td>
</tr>
<tr>
<td>North central</td>
<td>1984 (25.2)</td>
<td>3134 (27.7)</td>
</tr>
<tr>
<td>West</td>
<td>4816 (61.2)</td>
<td>6903 (60.5)</td>
</tr>
<tr>
<td>South</td>
<td>227 (2.9)</td>
<td>403 (3.5)</td>
</tr>
<tr>
<td>Cancer grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>64 (0.8)</td>
<td>244 (2.1)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>5115 (65.0)</td>
<td>9545 (83.7)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>2688 (34.2)</td>
<td>1615 (14.2)</td>
</tr>
<tr>
<td>Clinical stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>3915 (49.8)</td>
<td>7325 (64.2)</td>
</tr>
<tr>
<td>T2</td>
<td>3952 (50.2)</td>
<td>4079 (35.8)</td>
</tr>
<tr>
<td>Comorbidity status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson comorbidity score 0-1</td>
<td>7446 (94.7)</td>
<td>10 664 (93.5)</td>
</tr>
<tr>
<td>Charlson comorbidity score ≥2</td>
<td>421 (5.3)</td>
<td>740 (6.5)</td>
</tr>
<tr>
<td>Year of cancer diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1992-1997</td>
<td>2876 (36.6)</td>
<td>5348 (46.9)</td>
</tr>
<tr>
<td>1998-2002</td>
<td>4991 (63.4)</td>
<td>6056 (53.1)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; PADT, primary androgen deprivation therapy; SEER, Surveillance, Epidemiology, and End Results.

a Data are presented as No. (%) unless otherwise specified. Race was self-determined by the patients. For cancer grade, a Gleason score of 2 to 4, 5 to 7, and 8 to 10 corresponded to well-differentiated, moderately differentiated, and poorly differentiated disease, respectively. Clinical extension information provided by SEER was used to determine cancer stage (T1, T2). Charlson comorbidity score was derived from Medicare claims during the year before prostate cancer diagnosis by using a validated algorithm.[6,11]

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

Survival Outcomes

There were 1560 prostate cancer deaths and 11 045 deaths from all causes in the study cohort. Unadjusted and adjusted prostate cancer-specific survival and overall survival were worse for patients treated with PADT when analyses were conducted using a traditional Cox multivariate model (Table 3). The Cox proportional hazards regression model 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 IVA was used (Table 3, Table 4, Table 5, and Figure), PADT was still associated with increased unadjusted and adjusted prostate cancer-specific mortality (hazard ratio [HR], 1.17; 95% CI, 1.03-1.33), but there was no significant 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 preplanned analyses by cancer grade, PADT was associated with either no effect or an adverse effect on prostate cancer–specific survival and overall survival for poorly differentiated or moderately differentiated cancer, respectively, in unadjusted and adjusted Cox proportional hazards regression model 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 and Figure), although the associated effect on median overall survival was not significant (57 months; 95% CI, 56-61 months vs 54 months; 95% CI, 53-57 months, respectively). Similar patterns were observed for 5- and 10-year prostate cancer–specific survival and overall survival (Table 4). The marginal effect of PADT on prostate cancer–specific survival was 15.1% (95% CI, 0%-30.5%) at 5 years and 24.5% (95% CI, 0.1%-49.6%) 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 1 month of treatment; whereas, 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 5826 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, 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 survival and overall survival in men who did not initially receive definitive therapy (eg, surgery or radiation) for localized prostate cancer.

Using IVA 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 proportional hazards regression model that adjusts only for measured confounding factors differed from those

**Table 3. Risk of Mortality According to Cancer Grade and Treatment for the Conventional Cox Multivariate and Instrumental Variable Analysis Results**

<table>
<thead>
<tr>
<th>Cancer Grade</th>
<th>PADT</th>
<th>Conservative Management</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/Person-Year</td>
<td>Rate per 100</td>
<td>Events/Person-Year</td>
<td>Rate per 100</td>
</tr>
<tr>
<td><strong>Prostate cancer–specific mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>867/32,744</td>
<td>2.6</td>
<td>693/55,424</td>
<td>1.3</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>381/22,181</td>
<td>1.7</td>
<td>389/46,992</td>
<td>0.8</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>483/10,196</td>
<td>4.7</td>
<td>284/6848</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Overall mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>4729/39,767</td>
<td>11.9</td>
<td>6316/66,567</td>
<td>9.5</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>2832/27,251</td>
<td>10.4</td>
<td>4989/56,938</td>
<td>8.8</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>1849/12,115</td>
<td>15.3</td>
<td>1145/7903</td>
<td>14.4</td>
</tr>
</tbody>
</table>

**Table 4. Instrumental Variable Analysis Results**

<table>
<thead>
<tr>
<th>Cancer Grade</th>
<th>Prostate cancer–specific mortality</th>
<th>Events/Person-Year</th>
<th>Rate per 100</th>
<th>Events/Person-Year</th>
<th>Rate per 100</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>504/25,911</td>
<td>1.9</td>
<td>581/33,578</td>
<td>1.7</td>
<td>1.12 (1.00-1.27)</td>
<td>1.17 (1.03-1.33)</td>
<td></td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>245/17,568</td>
<td>1.4</td>
<td>315/29,937</td>
<td>1.1</td>
<td>1.33 (1.12-1.57)</td>
<td>1.43 (1.20-1.70)</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>238/5557</td>
<td>4.3</td>
<td>299/5835</td>
<td>5.1</td>
<td>0.84 (0.71-0.99)</td>
<td>0.84 (0.70-1.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>3360/32,393</td>
<td>10.4</td>
<td>4202/39,075</td>
<td>10.8</td>
<td>0.96 (0.92-1.01)</td>
<td>1.00 (0.96-1.05)</td>
<td></td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>2098/22,332</td>
<td>9.4</td>
<td>3425/35,397</td>
<td>9.7</td>
<td>0.97 (0.92-1.03)</td>
<td>1.01 (0.95-1.07)</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>976/6601</td>
<td>14.8</td>
<td>1084/6745</td>
<td>16.1</td>
<td>0.92 (0.84-1.00)</td>
<td>0.92 (0.84-1.01)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; PADT, primary androgen deprivation therapy.

a Covariates included age, race, comorbidity status, cancer stage, cancer grade, income quartiles, urban residence, SEER (Surveillance, Epidemiology, and End Results) region, marital status, and year of diagnosis. SEER region was not included in the instrumental variable analysis.

b P < .05.
with the NA approach. These observations suggest that there is significant unaccounted residual bias associated with traditional analytical methods in this setting and that the NA approach may be particularly advantageous. In addition, 1 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.

In our study, cancer-specific survival but not overall survival appeared worse for men with lower risk cancer treated with PADT. This observation has been previously documented in a randomized controlled study of PADT in men with T0-T4 disease. The authors suggested several possible explanations for this finding, including competing causes of death, misclassification, and statistical variation. 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 observed in preclinical models) that increase the probability of death due to prostate cancer instead of a competing cause of death. As shown in the Figure, 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 or older; therefore, the results could differ for younger men. The SEER-Medicare database does not capture information on antiandrogen use.

### Table 4. Adjusted Percentage Overall and Prostate Cancer–Specific Survival in High-Use and Low-Use Areas

<table>
<thead>
<tr>
<th>Cancer Grade</th>
<th>High-PADT Use</th>
<th>Low-PADT Use</th>
<th>High vs Low Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths/Person-Year</td>
<td>Adjusted Survival,%</td>
<td>Deaths/Person-Year</td>
</tr>
<tr>
<td>Prostate cancer–specific survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-y all grades</td>
<td>378/21757</td>
<td>91.6</td>
<td>408/25386</td>
</tr>
<tr>
<td>5-y moderately</td>
<td>180/14759</td>
<td>93.8</td>
<td>196/22689</td>
</tr>
<tr>
<td>5-y poorly</td>
<td>190/4782</td>
<td>79.2</td>
<td>248/4863</td>
</tr>
<tr>
<td>10-y all grades</td>
<td>500/25709</td>
<td>80.1</td>
<td>570/3322</td>
</tr>
<tr>
<td>10-y moderately</td>
<td>242/17430</td>
<td>83.1</td>
<td>308/29456</td>
</tr>
<tr>
<td>10-y poorly</td>
<td>237/5529</td>
<td>59.8</td>
<td>298/5783</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-y all grades</td>
<td>2349/2544</td>
<td>62.0</td>
<td>2632/26987</td>
</tr>
<tr>
<td>5-y moderately</td>
<td>1456/17558</td>
<td>65.5</td>
<td>2085/24459</td>
</tr>
<tr>
<td>5-y poorly</td>
<td>717/5376</td>
<td>47.3</td>
<td>823/5281</td>
</tr>
<tr>
<td>10-y all grades</td>
<td>3238/31770</td>
<td>30.2</td>
<td>3949/37499</td>
</tr>
<tr>
<td>10-y moderately</td>
<td>2012/21914</td>
<td>33.9</td>
<td>3211/33971</td>
</tr>
<tr>
<td>10-y poorly</td>
<td>953/6518</td>
<td>17.3</td>
<td>1054/6598</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PADT, primary androgen deprivation therapy.

### Table 5. Marginal Effect of PADT on Overall and Prostate Cancer–Specific Survival in High-Use and Low-Use Areas

<table>
<thead>
<tr>
<th>Cancer Grade</th>
<th>5-Year Survival</th>
<th>10-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk Difference, %</td>
<td>Difference in PADT Use, %</td>
</tr>
<tr>
<td>Prostate cancer–specific survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All localized</td>
<td>-1.1</td>
<td>21.9</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>-1.9</td>
<td>22.6</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>3.4</td>
<td>22.6</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All localized</td>
<td>-0.1</td>
<td>21.9</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>-0.3</td>
<td>22.6</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>2.4</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PADT, primary androgen deprivation therapy.

### Notes
- Analyses used 95% bootstrapped CIs. Marginal effect is the risk difference (obtained from Table 4) divided by the difference in PADT use (obtained from Table 2).
Therefore, patients using antiandrogens only might be misclassified into the conservative management cohort and, because a previous study 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) showed that the use of antiandrogens as sole treatment for localized prostate cancer is relatively uncommon (approximately 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, prostate-specific antigen levels, family history, diet, body mass) depends on finding a suitable, partly random, varying factor (instrumental variable) that can be used to balance treatment groups. Our instrumental

**Figure.** Adjusted Prostate Cancer–Specific Survival and Overall Survival in High-Use and Low-Use Health Service Areas by Cancer Grade

<table>
<thead>
<tr>
<th>Health Service Area</th>
<th>PADT Use</th>
<th>Prostate Cancer–Specific Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-PADT use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-PADT use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-PADT use</td>
<td>1478</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>High-PADT use</td>
<td>1433</td>
<td>0.82</td>
<td>0.82</td>
</tr>
</tbody>
</table>

**Table 6.** Adjusted HRs for Overall and Cancer-Specific Mortality Among 5826 Patients With PADT Surviving at Least 3 Years

<table>
<thead>
<tr>
<th>Cancer Grade</th>
<th>Duration of PADT</th>
<th>Cancer-Specific Mortality Rate per 100 (Deaths/Person-Year)</th>
<th>Adjusted HR (95% CI)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>0.39 (16/4056)</td>
<td>1.24 (199/16031)</td>
<td>2.22 (1.32-3.74)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>0.72 (7/969)</td>
<td>2.32 (179/7700)</td>
<td>2.44 (1.14-5.23)</td>
</tr>
<tr>
<td>All localized</td>
<td>0.45 (23/5103)</td>
<td>1.58 (379/23988)</td>
<td>2.42 (1.58-3.72)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer Grade</th>
<th>Duration of PADT</th>
<th>Overall Mortality Rate per 100 (Deaths/Person-Year)</th>
<th>Adjusted HR (95% CI)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>4.40 (242/5498)</td>
<td>7.43 (1457/19613)</td>
<td>1.32 (1.14-1.52)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>5.42 (73/1347)</td>
<td>9.70 (895/9227)</td>
<td>1.46 (1.14-1.86)</td>
</tr>
<tr>
<td>All localized</td>
<td>4.61 (320/6934)</td>
<td>8.18 (2381/29119)</td>
<td>1.36 (1.20-1.53)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; PADT, primary androgen deprivation therapy.

* covariates included age, race, comorbidity status, cancer stage, cancer grade, income quintiles, urban residence, SEER (Surveillance, Epidemiology, and End Results) region, marital status, and year of diagnosis.
variable (high- and low-PADT use HSAs) had excellent properties. However, as in randomized studies, it is possible that some unmeasured factors still may have been imbalanced between groups. Nonetheless, sensitivity analyses, using various geographic-based instruments and removing patients with other cancers or comorbidity scores of more than 0, yielded similar results and suggested that the analyses were robust. However, it is still possible that the use of an NA approach in this setting does not adequately control for unknown confounding variables; therefore, if possible, a randomized trial should be considered.

There are 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 increased in this population by 2- to 3-fold in recent years. Published studies have generally not provided data specific for localized (T1-T2) disease and have had limited sample sizes. The largest published study describing PADT use among patients with T1-T2 disease was descriptive, noncomparative, and had limited follow-up. The randomized Early Prostate Cancer trial had a large subset of patients with T1-T2 disease but a nontraditional form of PADT (bicalutamide) was used. Results from this trial revealed a trend toward decreased overall survival in patients treated with PADT. The Veterans Administration Co-operative Urological Research Group study also used a nonconventional form of PADT (diethylnitrostenol). 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 trial 30891, which included patients with both localized and advanced disease (eg, T0-4, N0-2), 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. Studies by the Medical Research Council, the European Organization for Research and Treatment of Cancer trial 30846, and the Swiss Group for Clinical Cancer Research focused on patients with more advanced disease. In general, although 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 conclusion, our analyses suggest that PADT is not associated with improved survival among the majority of elderly men with T1-T2 prostate cancer. The significant adverse effects and costs associated with PADT, along with our finding of a lack of overall survival benefit, suggest that clinicians should carefully consider the rationale for initiating PADT in elderly patients with T1-T2 prostate cancer.

Author Contributions: Dr Lu-Yao had full access to all of 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: Lu-Yao, Albertson, Yao. Acquisition of data: Lu-Yao. Analysis and interpretation of data: Lu-Yao, Albertson, Moore, Shih, Lin, DiPaola, Yao. Drafting of the manuscript: Lu-Yao, Lin, Yao. Critical revision of the manuscript for important intellectual content: Lu-Yao, Albertson, Moore, Shih, Lin, DiPaola, Yao. Statistical analysis: Lu-Yao, Moore, Shih, Lin, Yao. Obtained funding: Lu-Yao. Administrative, technical, or material support: Lu-Yao, Albertson. Study supervision: Lu-Yao, Shih, DiPaola.

Financial Disclosures: None reported.

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Disclaimers: This study used the Linked SEER-Medicare Database. The interpretation and reporting of these data are the sole responsibility of the authors. The content of the information does not necessarily reflect the position or the policy of the US Government, and no official endorsement should be inferred.

Additional Contributions: We thank the Applied Research Branch, Division of Cancer Prevention and Population Science, National Cancer Institute; Office of Information Services and Office of Strategic Planning, Centers for Medicare & Medicaid Services; Information Management Services Inc; the SEER program tumor registries in the creation of the SEER-Medicare database. Thanusha Puvananayagam, MPH (Cancer Institute of New Jersey assistant staff) provided outstanding administrative technical assistance. Ms Puvananayagam did not receive any compensation.

REFERENCES


HORMONAL THERAPY USE FOR LOCALIZED PROSTATE CANCER
Primary Androgen Deprivation Therapy in Men With Prostate Cancer

To the Editor: The analysis of prostate cancer–specific and overall survival by Dr Lu-Yao and colleagues concluded that primary androgen deprivation therapy (PADT) offered no benefit compared with conservative management in elderly men with localized prostate cancer. Since their comparison was based on epidemiologic data rather than those obtained in a prospective randomized trial, there is a possibility that confounding variables may have influenced patient outcomes.

Serum prostate-specific antigen (PSA) has been shown to be an independent predictor of outcome in newly diagnosed patients and may often be used by clinicians to choose recommended therapy. It seems likely that men with higher PSA levels (and thus worse prognoses) were those who were given PADT. However, the study by Lu-Yao et al does not include an analysis of PSA data and their possible influence on treatment recommendations. In the absence of this information, it is not possible to conclude that PADT confers no benefit, especially to a high–PSA-level subpopulation of patients.

Leslie Laufman, MD
llaufman@columbus.rr.com
Columbus, Ohio

Financial Disclosures: None reported.

In Reply: As noted in our article, an important limitation of nonrandomized studies is the potential for biases associated with unmeasured confounding variables. Traditional statistical methods have been limited in the ability to adjust for unmeasured or unknown biases.

Instrumental variable analytic (IVA) methods, like the one we used, have been used to better overcome these challenges and limitations. Previous studies have shown that IVA methods can very effectively adjust for unmeasured or unknown imbalances, such as might have occurred with PSA values. Although we could not unequivocally document balance in PSA values, examination of other factors, such as age, comorbidity, stage, and grade, demonstrated balance in the comparison groups, suggesting that the IVA method accomplished its goal. In addition, the results of our study were consistent with other similar studies further suggesting that the results are likely valid.

Nonetheless, it is still possible that there could have been some residual imbalance, much like that which sporadically occurs when many baseline variables are examined at the completion of a randomized study. As we recommended in our discussion, it would thus be best to conduct a large randomized trial, although there could be considerable difficulty in doing so because of existing patient and clinician beliefs, as well as the resources and length of follow-up required for such a study. Absent such a trial, we hope our study provides some reasonable data for physicians and their patients as they make important personal clinical decisions.

Grace L. Lu-Yao, PhD
Weichung Shih, PhD
Siu-Long Yao, MD
syao@aya.yale.edu
Cancer Institute of New Jersey
New Brunswick

Financial Disclosures: Dr Siu-Long Yao reported that during the last 5 years he has been employed by Sanofi-Aventis and Schering-Plough in the area of clinical cancer research. Dr Grace Lu-Yao reported having received clinical research funding from the New Jersey Commission on Cancer Research and the Agency for Healthcare Research and Quality and employment with HealthStat. Dr Shih reported having received clinical research funding from Myriad.


Failure to Report Financial Disclosure Information

To the Editor: We would like to apologize to the readers and editors of JAMA for a difference in understanding of the JAMA policy for reporting financial disclosures and resultant failure to report our disclosure information in our article. The basis of our omission of financial information was that we did not foresee a reasonable likelihood of financial gain or bias as a consequence of our activities or employment in other areas of the fields of prostate cancer or cancer research that were separate from our study in early stage prostate cancer and, therefore, did not believe that there were additional relevant disclosures.

In the interest of full transparency and to avoid any potential misunderstanding, we hereby report that during the past 5 years, including during the time the study was conducted and the manuscript was submitted to JAMA, Dr Siu-Long Yao has been employed by Sanofi-Aventis and Schering-Plough in the area of clinical cancer research. Sanofi-Aventis and Schering-Plough contributed no funding and played no role whatsoever in the design, interpretation, or
drafting of our study or manuscript. In addition, during the past 5 years, the following authors have received financial support and maintained affiliations as follows: Dr Lu-Yao has received clinical research funding from the New Jersey Commission on Cancer Research and the Agency for Healthcare Research and Quality and employment with HealthStat; Dr Peter Albertsen has received clinical research funding from Sanofi-Aventis and consultation fees from Blue Cross/Blue Shield; and Dr Weichung Shih has received clinical research funding from Myriad. None of these entities contributed funding or played any role whatsoever in the design, interpretation, or drafting of our study or manuscript. We regret any misunderstanding that resulted from the omission of these disclosures.

Grace Lu-Yao, MPH, PhD
Robert Wood Johnson Medical School
New Brunswick, New Jersey

Peter Albertsen, MD
University of Connecticut
Farmington

Weichung Shih, PhD
University of Medicine and Dentistry of New Jersey
Piscataway

Siu-Long Yao, MD
syao@aya.yale.edu
Robert Wood Johnson Medical School
New Brunswick

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RESEARCH LETTER

Respirator Tolerance in Health Care Workers

To the Editor: Anticipated respirator intolerance and supply shortages during future influenza pandemics prompted the Institute of Medicine to review respirator use in health care workers1 and consider whether disposable models could be reused or modified for reuse.2 One option involves placing a medical mask over a disposable respirator to diminish contamination and attrition.1 However, little is known about the workplace tolerability of respirators commonly worn by health care workers, who may be called on to wear respiratory protection for the duration of their work shifts for several consecutive weeks during a pandemic.3,4 We estimated the length of time health care workers would tolerate wearing commonly used respirators while performing their typical occupational duties.

Methods. Participants were 27 volunteers (mean [SD] age, 48 [11] years; range, 25-65 years; 15 women) among approximately 225 health care workers employed by the local Veterans Health System who were approached. The inclusion criterion was having worn a respirator in the context of duties at least once; all participants were accustomed to wearing N95 respirators (filters ≥95% of particles approximately 0.3 µm in size) for brief periods. Exclusion criteria included systemic disease or pregnancy. The sample comprised 16 nurses, 2 nurse practitioners, 4 nurse technicians, 2 telemetry technicians, 2 respiratory therapists, and 1 clerical assistant from the intensive care unit (n=13), emergency department (n=6), and medical/surgical ward (n=6). Each provided written informed consent, underwent a prestudy examination, and was fit-tested for each respirator. The study was approved by the local institutional review board.

In this unblinded multiple crossover study, before each work shift (intersession interval, ≥1 day) each participant was randomly assigned a respirator ensemble (TABLE 1) to wear as long as he or she was “willing to tolerate” the effects while performing typical occupational duties, not including interposed break periods (15 minutes at 2 and 6 hours; 30 minutes at 4 hours). Those who experienced intolerance before 8 hours reported up to 3 reasons for premature discontinuation.

Sample size was chosen to achieve power of 0.8 or greater to detect a difference of 2 hours in median tolerance times. Kaplan-Meier estimates of survival were used for descriptive purposes. Tolerance time for the cup-shaped N95 was compared with a medical mask and with the N95 with an exhalation valve. The 2 respirators that had a medical mask placed over the respirator surface to protect against contamination were compared with the same respirators without a mask. An extended Cox model,7 which accounted for correlation between repeated measures within participant, was used to compare the time to doff among respirators by controlling for the effects of sex and age. SAS 9.1 (SAS Institute, Cary, North Carolina) was used for the analyses. The Bonferroni step-down method8 was used to adjust the P values for 2-sided tests to account for multiple tests.

Results. Each participant wore all 8 respirators except 1 who failed the duckbill N95 fit test. No sequence or period effects were found. Tolerance time varied by respirator model (Table 1). Women were significantly more likely than men to experience intolerance before 8 hours (hazard ratio, 1.97; 95% confidence interval, 1.02-3.75; P = .04). Participants discontinued wearing the respirator ensembles before 8 hours in 126 of 215 total sessions (59%), reporting a variety of reasons for intolerance, including communication interference (TABLE 2).

Comment. A large percentage of participants were unwilling to wear the respirator ensembles for the entire 8-hour work shift, even with interposed break periods. No respirator was ideal: users of disposable models frequently experienced facial heat and pressure, and users of...
Author Contributions: Dr Radonovich had full access to all of 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: Radonovich, Cheng, Shenal, Hodgson, Bender.

Acquisition of data: Radonovich.

Analysis and interpretation of data: Radonovich, Cheng, Hodgson, Bender.

Drafting of the manuscript: Radonovich, Cheng, Hodgson.

Critical revision of the manuscript for important intellectual content: Radonovich, Cheng, Shenal, Hodgson, Bender.

Statistical analysis: Cheng.

Obtained funding: Radonovich, Shenal.

Administrative, technical, or material support: Radonovich.

Study supervision: Radonovich, Bender.

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Disclaimer: The views, opinions, and findings contained in this report are those of the authors and do not necessarily represent the official position or policy of the North Florida/South Georgia Veterans Health System, the Office of Public Health and Environmental Hazards, the US Department of Veterans Affairs, or the University of Florida or other employers or affiliates.

Additional Contributions: Helen Dunn, MSN, Malcom Randall VA Medical Center, and Elizabeth Franco, RN, Malcom Randall VA Medical Center, coordinated the study and received compensation. Parker Small, MD, University of Florida, provided review and guidance and did not receive compensation.


CORRECTION

Unreported Financial Disclosures: In the Original Contribution titled “Survival Following Primary Androgen Deprivation Therapy Among Men With Localized Prostate Cancer,” published in the July 9, 2008, issue of JAMA (2008;300[2]:173-181), the authors failed to report financial disclosures on page 180. The financial disclosures should have read, “Dr Siu-Long Yao reported that during the last 5 years he has been employed by Sanofi-Aventis and Schering-Plough in the area of clinical cancer research. Dr Grace Lu-Yao reported having received clinical research funding from the New Jersey Commission on Cancer Research and the Agency for Healthcare Research and Quality and employment with HealthStat. Dr Albertson reported having received clinical research funding from Sanofi-Aventis and consultation fees from Blue Cross/Blue Shield. Dr Shih reported having received clinical research funding from Myriad.”