

## Role of Androgen Deprivation Therapy for Node-Positive Prostate Cancer

Yu-Ning Wong, Stephen Freedland, Brian Egleston, Gary Hudes, J. Sanford Schwartz, and Katrina Armstrong

### ABSTRACT

#### Purpose

To determine the impact of adjuvant androgen deprivation therapy (ADT) for patients who have node-positive prostate cancer in the prostate-specific antigen (PSA) era.

#### Patients and Methods

We used linked Surveillance, Epidemiology and End Results-Medicare data to construct a cohort of men who underwent radical prostatectomy (RP) between 1991 and 1999 and who had positive regional lymph nodes. We classified men as receiving adjuvant ADT if they received ADT within 120 days of RP, and we compared them to the men who had not received adjuvant ADT. We used propensity scores to balance potential confounders of receiving adjuvant ADT (ie, tumor characteristics, extent of nodal disease, demographics, receipt of radiation therapy) and Cox proportional hazard methods to measure the impact of adjuvant ADT on overall survival (OS), stratified by propensity score quintile. We conducted a sensitivity analysis that used 90, 150, 180, and 365 days as the definition for adjuvant ADT.

#### Results

A total of 731 men were identified, 209 of whom received ADT within 120 days of RP. There was no statistically significant difference in OS between the adjuvant ADT and non-ADT group (HR, 0.97; 95% CI, 0.71 to 1.27). There was no statistically significant survival difference with 90, 150, 180, and 365 days as the adjuvant ADT definition.

#### Conclusion

Deferring immediate ADT in men with positive lymph nodes after RP may not significantly compromise survival. Because observational studies should be considered hypothesis-generating studies, these results should be validated in a prospective fashion in a similar patient population.

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### INTRODUCTION

Although androgen deprivation therapy (ADT) has a well-defined role in patients who have metastatic disease<sup>1</sup> or high-risk, localized disease and who are undergoing radiotherapy,<sup>2</sup> its role in patients who have node-positive disease after radical prostatectomy (RP) is controversial. Messing et al<sup>3,4</sup> reported the results of a randomized, controlled clinical trial of men who had node-positive prostate cancer after RP that compared life-long adjuvant ADT that was started immediately after RP with ADT that was initiated at the time of metastatic disease. The study reported a significant advantage in progression-free survival (PFS) and overall survival (OS) that favored adjuvant ADT.<sup>3,4</sup> However, development of clinical metastases, rather than biochemical recurrence, was the indication for treatment in the delayed arm in this study. This is in contrast to the contemporary

practice post-operative prostate-specific antigen (PSA) surveillance to detect biochemical recurrence (BCR). Because BCR occurs at a median of 8 years before the onset of radiologic and other evidence of metastatic disease,<sup>5</sup> this long interval allows physicians the opportunity to initiate therapy before the onset of metastatic disease on the basis of an assessment of patients' risks for disease progression and prostate cancer-specific mortality (PCSM).

Therefore, the benefit of adjuvant ADT in contemporary node-positive patients is unclear. Given the potential for long-term adverse effects associated with ADT, such as osteoporosis,<sup>6</sup> cardiovascular disease, diabetes,<sup>7</sup> and mood disorders,<sup>8</sup> it is important to understand the impact of adjuvant ADT on OS. If adjuvant ADT is not associated with an improvement in OS compared with treatment at BCR, or sometime thereafter, then delaying the initiation of ADT until BCR may spare patients significant treatment-related toxicities.

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This study used the linked Surveillance, Epidemiology, and End Results-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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To better characterize the role of adjuvant ADT on OS in this setting, we examined a population-based sample of men who had node-positive prostate cancer after RP.

## PATIENTS AND METHODS

### Data Source

We used data from the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database. SEER is a population-based cancer registry that encompasses approximately 14% of the US population and that is administered by the National Cancer Institute. SEER includes information on tumor histology, size, and grade.<sup>9</sup> Approximately 97% of individuals in SEER who were 65 years and older were successfully linked to their Medicare claims.

The original study population included 111,640 men between 65 and 80 years of age who had an incident prostate cancer diagnosis between 1991 and 1999. Men were excluded if they were diagnosed at autopsy or death or had Medicare entitlement on the basis of end-stage renal disease. Because Medicare does not contain complete claims information for individuals in managed care, men were excluded if they were enrolled on a health maintenance organization from 90 days before diagnosis to 180 days after diagnosis; this represented approximately 21% of the original cohort. The project was approved by the institutional review boards at the Fox Chase Cancer Center and the University of Pennsylvania.

### Variable Definitions

SEER-reported tumor grades were well differentiated (Gleason score of 2 to 4), moderately differentiated (Gleason score of 5 to 7) or poorly differentiated (Gleason Score of 8 to 10), anaplastic or unknown. Twenty-one patients who were classified as having anaplastic or unknown tumors were included in the poorly differentiated group.

### Tumor Stage

We used clinical extension information provided by SEER to determine tumor stage for patients who were diagnosed from 1991 to 1995. In this category, operative/pathology information is given priority over clinical information in determining stage. In 1995, SEER began to report pathologic information separately, and this pathologic extension category was used to determine tumor stage for patients who were diagnosed from 1995 to 1999. For patients whose pathologic extension was categorized as unknown, we used the corresponding clinical extension. We categorized patients as T2c or less, T3a, or T3b to T4. We included 12 patients who had unknown clinical stage in the T3b to T4 category, and we excluded nine patients who had metastatic disease.

### Definition of Node-Positive Disease

Only patients who had positive regional lymph nodes were included in this analysis. SEER described regional lymph nodes as N1 (single node < 2 cm), N2 (single node 2 to 5 cm or multiple nodes, none > 5 cm), N3 (single or multiple lymph nodes, at least one of which is > 5 cm), or regional nodes NOS. Five patients in our data set were described as having at least one lymph node greater than 5 cm; they were included in the regional nodes NOS in this analysis. Patients with distant lymph nodes, lymph nodes NOS, or unknown were excluded.

### Covariates

**Comorbid disease.** Comorbidities were identified by searching Medicare inpatient and outpatient claims and Part B claims during the 90 days before diagnosis. Comorbidities were identified by using a modification of the methods described by Elixhauser.<sup>10</sup> In this analysis, cancer was not considered a comorbidity; however, stroke and coronary heart disease were included on the basis of their relatively high prevalence. In our propensity score models, we calculated the odds of receiving ADT on the basis of the number of comorbidities.

**Demographics.** Age, marital status, ethnicity, 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 of fewer than 20,000 residents; the remaining patients were classified as living in an urban area. Because SEER does not provide individual patient level socioeconomic status (SES), we used median household income per census tract and percent census tract with a four-year college education as proxies for SES. Eighteen patients did not have SES data. However, these characteristics were balanced between the adjuvant ADT and no-ADT arms in the baseline analysis (Table 1). The analyses with and without SES had similar results, so we did not use SES in our final models.

### Treatment

Treatment was determined by searching Medicare files for the appropriate International Classification of Diseases-9 and Healthcare Common Procedure Coding System codes for RP and radiation therapy during the 6 months after the date of diagnosis. Codes for ADT were assessed for the first 3 years past diagnosis. Because SEER provides the month of diagnosis only, we assumed that all patients were diagnosed on the 15th of the month, and we included an additional 15 days in the treatment time windows. Medicare files included the inpatient claims (Part A), the carrier or physician file (Part B) and the outpatient claims file.

### Definition of Adjuvant ADT

The indication for ADT (adjuvant *v* salvage) was not available in Medicare claims. Therefore, in our primary analysis, we used receipt of ADT within 120 days after surgery as our definition of adjuvant ADT. This is less stringent than the time frame used in the study (12 weeks) by Messing et al,<sup>3,4</sup> but it may better reflect practice patterns in a nonclinical trial population. All other patients, including those who received ADT after 120 days or those who never received ADT, were included in the no-ADT group. We tested various definitions of adjuvant ADT, which ranged between 90 to 365 days, in our sensitivity analysis.

### Survival

OS was defined as the interval from the date of RP to the date of death according to Medicare. Patients who were alive at the end of the study period (December 30, 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. Prostate cancer-specific survival was determined by using cause-of-death information provided by SEER.

### Statistical Analysis

Summary statistics were constructed by using frequencies and proportions for categorical variables and means and medians for continuous variables. We used propensity scores to balance observed covariates between the adjuvant ADT and no-ADT arms.

Propensity scores are the probability that a patient received adjuvant ADT on the basis of his observed covariates. We calculated propensity scores by using multivariable logistic regression. Receipt of adjuvant ADT was the outcome of interest; age, SEER site, year of diagnosis, stage, tumor grade, marital status, receipt of radiation, and comorbidities were independent variables. Propensity scores then were used to group patients into quintiles, and we used  $\chi^2$  tests and *t* tests to determine that the covariates were balanced within quintiles.

We measured the impact of receiving ADT on with using a Cox Proportional Hazards regression and prostate cancer-specific survival with a Competing Risk Proportional Hazards Regression.<sup>11</sup> In both models, we controlled for propensity score as the only independent variable using a restricted cubic spline with five knots. Restricted cubic splines are flexible functions that allow for nonlinear relationships in models.<sup>12</sup> The propensity score was not statistically significant (*P* = .93). 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.

To test our definition of adjuvant therapy, we performed sensitivity analyses by using alternate time periods to define receipt of adjuvant ADT: 90, 150, 180, and 365 days OS. The statistics were performed with STATA 8.0

Table 1. Patient Characteristics

Characteristic	No Adjuvant Treatment		Adjuvant Treatment		P*
	No.	%	No.	%	
No. of patients	522		209		
Median age at diagnosis		69.9		69.5	.161
Year of diagnosis				.061	
1991-1993	319	61.11	120	57.42	
1994-1996	134	25.67	47	22.49	
1997-1999	69	13.22	42	20.10	
Ethnicity					.544
White	477	91.38	186	89.00	
African-American	26	4.98	12	5.74	
Other	19	3.64	11	5.26	
Marital status					.127
Single/other	83	15.90	24	11.48	
Married	439	84.10	185	88.52	
SEER site					< .005
San Francisco	67	12.84	20	9.57	
Connecticut	30	5.75	8	3.83	
Detroit	53	10.15	19	9.09	
Hawaii	8	1.53	7	3.35	
Iowa	63	12.07	40	19.14	
New Mexico	40	7.66	9	4.31	
Seattle	80	15.33	27	12.92	
Utah	70	13.41	13	6.22	
Atlanta	15	2.87	15	7.18	
San Jose-Monterey	31	5.94	7	3.35	
Los Angeles	65	12.45	44	21.05	
Comorbidities					.011
0	257	51.3	94	40.87	
1	135	26.95	71	30.87	
2	60	58.82	42	18.26	
≥ 3	49	9.78	23	10	
Tumor size					.437
≤ T2c	156	29.89	53	25.36	
T3a	119	22.80	48	22.97	
T3b-T4 or unknown	247	47.32	108	51.67	
Tumor grade					.009
Well differentiated	11	2.11	< 5	< 2.4	
Moderately differentiated	259	49.62	78	37.32	
Poorly differentiated	252	48.28	127	60.77	
Nodal status					< .005
Single node < 2 cm	153	29.31	31	14.83	
Single node 2-5 cm or multiple nodes	67	12.84	75	35.89	
Regional nodes NOS	302	57.85	103	49.28	
Receipt of radiation	77	14.75	18	8.61	.026
Median income, \$†	40,654		39,058		.3563
% with college education†		26.65		26.5	.922
Residence					.458
Metropolitan	404	77.39	167	79.90	
Nonmetropolitan	118	22.61	42	20.10	

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; NOS, not otherwise specified.

\*P values are for  $\chi^2$  tests for all variables, with the exception of age, median income, and percent with college education. The t-test was used for those covariates.

†Households, by census tracts: eighteen participants did not have information about median income or college education available. These variables were not included in the final model.

(STATA Corp, College Station, TX) and R version 2.5.1. (R Foundation for Statistical Computing; <http://www.r-project.org>).

## RESULTS

A total of 23,545 patients were identified as having undergone RP between 1991 and 1999. A total of 819 (3.5%) had regional lymph

node metastasis at the time of surgery. We excluded patients who received ADT before RP (n = 50), patients who had metastatic disease (n = 9), and patients without available RP dates (n = 29). The final cohort for analysis was 731 patients.

In our primary analysis of 120 days from RP as the definition of adjuvant ADT, 188 (25.7%) of patients received ADT. Baseline characteristics are listed in Table 1. Use of adjuvant ADT varied by year of

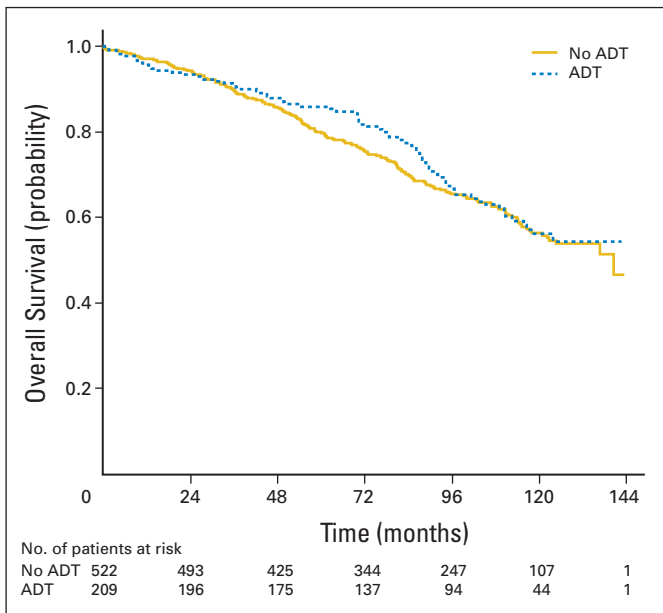


Fig 1. Overall survival (Kaplan-Meier). ADT, androgen deprivation therapy.

diagnosis, SEER site, number of comorbidities, grade, nodal status, and receipt of radiation therapy within 6 months of diagnosis. There was no statistically significant difference in the use of ADT by ethnicity, marital status, tumor stage, SES, or place of residence.

At the end of the study period, 269 patients (36.8%) had died. Seventy-one patients (9.7%) had died as a result of prostate cancer. Ten-year OS and PCSM were similar in both groups (Figs 1 and 2) After adjustment of the propensity score, there was no statistically significant difference in OS (HR, 0.95; 95% CI, 0.71 to 1.27; Table 2).

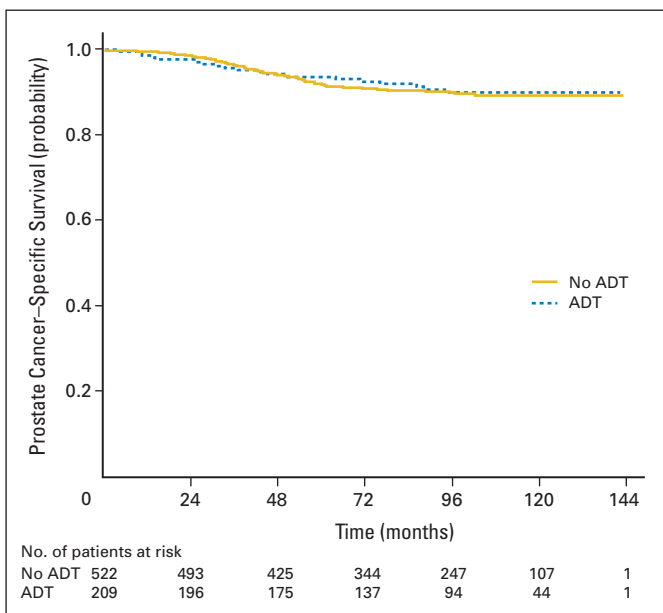


Fig 2. Prostate cancer-specific survival estimated from cumulative incidence. ADT, androgen deprivation therapy.

Table 2. Overall Survival According to Alternate Definitions for Adjuvant ADT

Survival (days)	Adjuvant ADT Use		HR for Death in Adjuvant ADT Group	95% CI
	No. of Patients With No Adjuvant ADT	No. of Patients With Adjuvant ADT		
90	543	188	0.97	0.72 to 1.32
120	522	209	0.95	0.71 to 1.27
150	511	220	1.02	0.77 to 1.36
180	501	230	1.06	0.81 to 1.41
365	473	258	1.18	0.90 to 1.54

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio.

In addition, there was no statistically significant difference in PCSM (subdistribution HR, 0.97; 95% CI, 0.56 to 1.68).

We then performed sensitivity analysis by repeating the analyses with various definitions of adjuvant ADT: 90, 150, 180, and 365 days. The propensity score adjusted results are listed in Tables 2 and 3. As listed, there was no significant OS difference with 90, 150, 180, and 365 days as the adjuvant ADT definition. There was no difference in prostate cancer-specific survival using 90, 150, and 180 days. However, the use of 365 days as the adjuvant ADT definition resulted in a higher risk of prostate cancer-specific death in the adjuvant arm (HR, 1.96; 95% CI, 1.16 to 3.29).

## DISCUSSION

The role of ADT in patients with node-positive prostate cancer after RP is controversial. Messing et al<sup>3,4</sup> found significant improvements in both PCSM and OS in the adjuvant ADT arm.<sup>3,4</sup> However, Schroeder et al<sup>13</sup> recently reported the results of EORTC 30846, which examined the role of immediate versus delayed ADT in patients who had node-positive disease and who did not undergo RP. There was no difference in OS between the early and deferred ADT arms. Whether the difference was a result of the removal of the primary tumor in the study by Messing et al<sup>3,4</sup> or the higher rate of clinical T3 disease in the study by Schroeder et al<sup>13</sup> is not known. Given these conflicting results, the 2006 American Society of Clinical Oncology Practice Guidelines do not give firm recommendations regarding the role of ADT in patients with node-positive

Table 3. Prostate-Cancer Specific Survival According to Alternate Definitions for ADT

Survival (days)	Adjuvant ADT Use		Subdistribution HR for Death in Adjuvant ADT Group	95% CI
	No. of Patients With No Adjuvant ADT	No. of Patients With Adjuvant ADT		
90	543	188	1.22	0.69 to 2.16
120	522	209	0.97	0.56 to 1.68
150	511	220	1.15	0.67 to 1.97
180	501	230	1.53	0.90 to 2.61
365	473	258	1.96	1.16 to 3.29

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio.



disease, and they note that any benefit in prostate cancer–specific survival may be offset by an increase in non-PCSM.<sup>14</sup>

Observational studies can be helpful to provide clinical guidance when clinical trial data is limited or equivocal. These results suggest that the delay of ADT in patients who have node-positive prostate cancer after RP may not adversely impact OS. We believe that these results add to the currently available data and should help treatment decisions, especially in patients who are concerned about ADT-associated toxicity.

Our results may differ from those of Messing et al<sup>3,4</sup> for several reasons. The most likely is the difference in indication for initiation of ADT in the groups that were initially observed. In the study by Messing et al,<sup>3,4</sup> patients were only started on ADT if they developed clinical metastases, which are associated with a high risk of both cancer-specific and overall mortality.<sup>5,15</sup> However, in the early 1990s, routine post-RP monitoring of PSA became routine, and patients in our series likely were followed for BCR. If treatment with ADT at the time of BCR is successful in the treatment of micrometastatic disease and in the prevention of the onset of metastatic disease and subsequent death from prostate cancer, it is possible that earlier detection and treatment of BCR may have led to the improved outcomes in the delayed arm in our series.

Even among patients with BCR, outcomes vary significantly. Risk factors for PCSM (ie, PSA recurrence within 3 years, Gleason score  $\geq$  8, PSA doubling time  $<$  9 months)<sup>16</sup> may guide clinicians in the selection of patients for treatment with ADT; others with indolent disease may elect to be observed. Therefore, even among patients with node-positive disease, it may be possible to defer adjuvant therapy and to spare some the toxicities associated with ADT.

Our results also may be different from those reported by Messing et al<sup>3,4</sup> because of baseline differences between the two study populations. The group in our study is older than those enrolled on the trial by Messing et al (median age, 69 v 65.6 years). In addition, clinical trial participants tend to be healthier than the general population.<sup>17</sup> Therefore, if ADT-associated toxicities, such as osteoporosis, metabolic syndrome, and cardiovascular disease, have greater effects on patients who are older or sicker, the benefits of ADT on PCSM may be offset by an increased non-cancer-specific mortality. Therefore, any possible benefit of ADT must be balanced against the known long-term toxicities of ADT.<sup>14</sup>

Our results also may have differed from those reported by Messing et al<sup>3,4</sup> because they were diagnosed during the 1990s, when PSA screening increased in use. This length-time bias may have resulted in patients who had earlier-stage, lower-volume disease than those seen in the study by Messing et al. Therefore, our cohort may better represent contemporary patients diagnosed the PSA era, when patients are more likely to have early-stage disease and, consequently, a lower chance of micrometastatic disease. This would result in a smaller benefit from adjuvant ADT than those in the study by Messing et al.

Our study has several strengths. Our population-based estimates of the prevalence of node-positive disease after RP are similar to prior reports of between 0.87% and 10%.<sup>18,19</sup> We are able to report OS, rather than to rely on intermediate markers of survival, such as BCR, which may not correlate well with OS. However, patients diagnosed during the later portion of our study had shorter follow-up; given the long natural history of prostate cancer,

it will be important to follow these patients to determine if their outcomes differ from earlier patients.

Our study highlights the significant uncertainty that surrounds the role of adjuvant therapy for men with high-risk, localized prostate cancer. Although ADT has a well-defined role for patients who have locally advanced prostate cancer and who are undergoing definitive radiation therapy,<sup>2,20</sup> it has not been effective in the neoadjuvant setting before RP.<sup>21,22</sup> This apparent dichotomy may support an interaction between radiation therapy and ADT that is not present in patients who undergo RP and who receive neoadjuvant ADT.<sup>23</sup> This may also explain the lack of benefit of adjuvant ADT seen in this study.

This study has several limitations. SEER-Medicare does not provide information about the indication for ADT. Patients who received salvage ADT for biochemical, local, or distant recurrence likely will have worse clinical outcomes than those who received ADT in the adjuvant setting. On the other hand, patients who did not receive ADT during the first 3 years after diagnosis likely had less aggressive disease and would be expected to have longer survival. We have attempted to address this limitation by analyzing the data as an intention-to-treat design, in which patients who received adjuvant ADT (within 120 days of RP) were compared with all other patients in the cohort. We then tested our definition of adjuvant therapy by performing sensitivity analyses with 90, 150, 180, and 365 days; we found no statistically significant difference in OS when we used any of the examined definitions. This supports our a priori cutoff of 120 days as the definition of adjuvant ADT. Similar results were seen for prostate cancer–specific survival, in which there was no significant difference with 90, 150, and 180 days. However, when we extended the definition to 365 days, the adjuvant arm did worse (HR for PCSM, 1.96; 95% CI, 1.16 to 3.29). This probably occurred because, according to this extended definition, some of these patients likely had early relapse and were treated with the salvage regimen. Therefore, they were likely at a higher risk of PCSM than those who did not receive ADT. This may reflect a benefit in PCSM, because treatment for early relapse is offset by ADT-related toxicity, which resulted in no difference in OS.

Although we have attempted to control for known confounders, it is impossible to adjust for unmeasured confounders, such as performance status or patient preferences, in an observational study such as this. However, all men are presumably healthy enough to undergo RP, which reduces the possibility that unmeasured imbalances in performance status alone explained our results. It is possible that patients who received adjuvant ADT may have been more motivated to seek out aggressive care; however, despite this potential bias, there was no evidence of improved survival in the group that received adjuvant ADT. In addition, our cohort did not include patients who were enrolled in health maintenance organizations. If outcomes for prostate cancer vary by insurance status, it is possible that our results may not be generalizable to patients covered by managed care.

In conclusion, this study suggests that OS in men with node-positive prostate cancer after RP may not be significantly harmed by delaying the initiation of ADT. As with an observational study, these results should be considered hypothesis generating and

should be confirmed in prospective clinical trials in a similar patient population, which should include treatment at the time of BCR in the delayed treatment arm rather than at the onset of metastases.

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Employment or Leadership Position:** None **Consultant or Advisory Role:** Stephen J. Freedland, AstraZeneca (C), GTx Inc (C); J. Sanford

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**Administrative support:** Katrina Armstrong

**Provision of study materials or patients:** Katrina Armstrong

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**Data analysis and interpretation:** Yu-Ning Wong, Stephen J. Freedland, Brian L. Egleston, Gary R. Hudes, Katrina Armstrong

**Manuscript writing:** Yu-Ning Wong, Stephen J. Freedland, Gary R. Hudes, Katrina Armstrong

**Final approval of manuscript:** Yu-Ning Wong, Stephen J. Freedland, Brian L. Egleston, Gary R. Hudes, J. Sanford Schwartz, Katrina Armstrong

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