Original Article

Discerning the Survival Advantage Among Patients With Prostate Cancer Who Undergo Radical Prostatectomy or Radiotherapy: The Limitations of Cancer Registry Data

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BACKGROUND: The objective of this study was to compare the overall survival of patients who undergo radical prostatectomy or radiotherapy versus noncancer controls to discern whether there is a survival advantage according to prostate cancer treatment and the impact of selection bias on these results. **METHODS:** A matched cohort study was performed using the Surveillance, Epidemiology, and End Results (SEER)-Medicare–linked database. In total, 34,473 patients ages 66 to 75 years were identified who were without significant comorbidity, were diagnosed with localized prostate cancer, and received treatment treated with surgery or radiotherapy between 2004 and 2011. These patients were matched to a noncancer control cohort. The rates of all-cause mortality that occurred within the study period were compared. Cox proportional hazards regression analysis was used to identify determinants associated with overall survival. **RESULTS:** Of 34,473 patients who were included in the analysis, 21,740 (63%) received radiation therapy, and 12,733 (37%) underwent surgery. There was improved survival in patients who underwent surgery (hazard ratio, 0.35; 95% confidence interval, 0.32-0.38) and in those who received radiotherapy (hazard ratio, 0.72; 95% confidence interval, 0.68-0.75) compared with noncancer controls. Overall survival improved significantly in both treatment groups, with the greatest benefit observed among patients who underwent surgery (log rank $P < .001$). **CONCLUSIONS:** Population-based data indicated that patients with prostate cancer who received treatment with either surgery or radiotherapy had improved overall survival compared with a cohort of matched noncancer controls. Surgery produce longer survival compared with radiation therapy. These results suggest an inherent selection-bias because of unmeasured confounding variables. ***Cancer*** **2017;123:1617-24.** *© 2017 American Cancer Society.*

KEYWORDS: outcomes, prostate cancer, prostatectomy, survival, treatments, utilization.

INTRODUCTION

Prostate cancer remains the most commonly diagnosed solid-organ tumor among US men, with an estimated 220,800 new cases and 27,540 deaths in 2015.[1] Curative treatment options for men with prostate cancer include surgery and radiation.[2,3] Driven by intensive prostate-specific antigen (PSA) screening over the last quarter century, prostate cancer has witnessed a marked stage migration[4] toward a more indolent course in the majority of newly diagnosed patients.[5] Therefore, it has been suggested that active surveillance may be the most appropriate treatment strategy for most newly diagnosed patients who have low-risk disease (clinical tumor classification, T1-T2a; Gleason score, $\leq$6; PSA, $<$10 ng/mL).[6] Despite this recommendation, a significant proportion of men who are eligible for active surveillance receive curative therapy with either surgery or radiation.[7]

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With increased concern regarding the overdiagnosis and overtreatment of prostate cancer, treatment decisions regarding primary therapy are understandably complex. Prior studies have questioned the perceived survival benefit in patients who receive treatment for prostate cancer.[8] In a recent randomized clinical trial assessing men with clinically localized prostate cancer, radical prostatectomy did not reduce prostate cancer-specific or overall mortality compared with observation.[9] In an attempt to ameliorate overtreatment and select patients most likely to benefit from treatment, guidelines have now incorporated life expectancy into the prostate cancer treatment decision-making process.[6]

Despite recent level 1 evidence concluding that there is no significant difference in prostate cancer specific-mortality among men with localized disease who receive treatment versus those who undergo active monitoring,[10] physicians have had to use observational studies to answer clinical questions. Giordano et al examined men treated from 1992 to 1999 with and without androgen deprivation for locally advanced prostate cancer to explore the effect of selection biases in observational studies.[11] Those investigators observed that men who underwent androgen deprivation had higher prostate cancer mortality despite clinical trial evidence that this treatment improves cancer mortality, thus suggesting that outcomes derived from observational studies should be interpreted with caution.[11] Limitations in that study included results derived from historic data (ie, before the year 2000), the results of which may not be applicable to a modern cohort, and a relatively heterogeneous cohort of patients with advanced disease. In an attempt to further explore the impact of selection bias using contemporary observational data in the treatment of prostate cancer, we conducted a population-based, matched cohort study comparing the overall survival of men who underwent radical prostatectomy or received primary prostate radiotherapy for localized prostate cancer with that of noncancer controls. We hypothesize that selection for treatment of localized prostate cancer would lend to improved survival outcomes over noncancer controls, suggesting selection bias for men who undergo those particular treatments.

MATERIALS AND METHODS

Data Sources

We used Surveillance, Epidemiology, and End Results (SEER)–Medicare data for the current analyses. Those data are composed of a linkage of population-based cancer registry data from 18 SEER areas with Medicare administrative data. The SEER program covers approximately 30% of the US population, and the Medicare program provides benefits to 97% of Americans aged $\geq$65 years.[12]

Study Population

Because of baseline differences between patient populations undergoing radiotherapy and surgery, we limited our analysis to include only patients who were expected to be candidates for either surgery or radiotherapy based on age and limited comorbid medical conditions. From the SEER-Medicare–linked database, we identified 34,473 patients who met the following criteria: ages 65 to 75 years, Charlson Comorbidity Index (CCI) scores of 0 or 1, localized prostate cancer (clinical tumor classification, T1/T2), diagnosed with prostate cancer between 2004 and 2011, and received treatment with either radical prostatectomy or radiotherapy. To ensure data completeness and to allow enough follow-up time to evaluate treatment and hospitalization, we included only patients who had full medical insurance coverage provided by Medicare Part A and Part B during the 12 months before and after treatment and who were not Health Maintenance Organization members. Patients who had a diagnosis of any other cancer before or after their prostate cancer diagnosis were excluded.

Control Group

Patient characteristics differ between those who undergo surgery and those who receive radiotherapy, and men who receive radiotherapy are often older and have increased comorbidities. Therefore, we matched each prostate cancer treatment group (surgery and radiotherapy) to noncancer controls by age, race/ethnicity, state, and CCI.[13] Noncancer controls were selected from a 5% random sample of Medicare beneficiaries aged $\geq$66 years and included only men who were without a prior cancer diagnosis at the time of matching.[14]

Patient Demographics, Tumor Characteristics, and Treatments

Patient demographics and tumor characteristics at the time of diagnosis, including age, race/ethnicity, geographic region, census variables (urban/rural, education, poverty level), diagnosis year, grade, and tumor classification (T1/T2), were extracted from the Patient Entitlement and Diagnosis Summary File (PEDSF). Tumor grade was dichotomized into low grade (well differentiated and moderately differentiated) and high grade (poorly differentiated and undifferentiated). Treatment variables, including surgery and radiotherapy, were determined from Medicare claims. Comorbidity was assessed using

TABLE 1. Demographics of Patients Diagnosed With Prostate Cancer

Characteristic	Total No.	Patients With Prostate Cancer							Noncancer Controls		
		Surgery		RT			Total				
		No.	%	No.	%	P[a]	No.	%	Total No.	%	P[b]
Year of diagnosis						<.001					.973
2004	9045	1520	11.9	3003	13.8		4523	13.1	4522	13.1	
2005	8732	1475	11.6	2884	13.3		4359	12.6	4373	12.7	
2006	9442	1609	12.6	3097	14.3		4706	13.7	4736	13.7	
2007	9848	1832	14.4	3094	14.2		4926	14.3	4922	14.3	
2008	9014	1709	13.4	2771	12.8		4480	13	4534	13.2	
2009	8417	1647	12.9	2550	11.7		4197	12.2	4220	12.2	
2010	7860	1592	12.5	2353	10.8		3945	11.4	3915	11.4	
2011	6588	1349	10.6	1988	9.1		3337	9.7	3251	9.4	
Race/ethnicity						<.001					<.001
Non-Hispanic white	58,339	10,985	86.3	17,974	82.7		28,959	84	29,380	85.2	
Non-Hispanic black	5622	773	6.1	2172	10		2945	8.5	2677	7.8	
Hispanics	1624	309	2.4	503	2.3		812	2.4	812	2.4	
Other	3361	666	5.2	1091	5		1757	5.1	1604	4.7	
State						<.001					.892
California	19,047	4427	34.8	5064	23.3		9491	27.5	9556	27.7	
Connecticut	3632	536	4.2	1282	5.9		1818	5.3	1814	5.3	
Georgia	9621	1199	9.4	3651	16.8		4850	14.1	4771	13.8	
Hawaii	831	197	1.6	235	1.1		432	1.3	399	1.2	
Iowa	4208	947	7.4	1168	5.4		2115	6.1	2093	6.1	
Kentucky	4923	921	7.2	1498	6.9		2419	7	2504	7.3	
Louisiana	4691	820	6.4	1546	7.1		2366	6.9	2325	6.7	
Michigan	4243	738	5.8	1391	6.4		2129	6.2	2114	6.1	
New Jersey	9364	1138	8.9	3532	16.3		4670	13.6	4694	13.6	
New Mexico	1571	318	2.5	469	2.2		787	2.3	784	2.3	
Utah	2244	507	4	634	2.9		1141	3.3	1103	3.2	
Washington	4571	985	7.7	1270	5.8		2255	6.5	2316	6.7	
Charlson comorbidity score						<.001					.781
0	52,671	10,306	80.9	16,014	73.7		26,320	76.4	26,351	76.4	
1	16,275	2427	19.1	5726	26.3		8153	23.7	8122	23.6	
Clinical tumor classification						<.001					—
T1	—	7406	58.2	13,865	63.8		21,271	—	—	—	
T2	—	5327	41.8	7875	36.2		13,202	—	—	—	
Tumor grade						<.001					
Low	—	4340	34.1	10,817	49.8		15,157	—	—	—	
High	—	8393	65.9	10,923	50.2		19,316	—	—	—	

Abbreviation: RT, radiotherapy.
[a] P values were determined with chi-square tests between the surgery and RT groups.
[b] P values were determined with chi-square tests between patients with prostate cancer and noncancer controls.

the Klabunde modification of the CCI from the year before diagnosis.[15] The Klabunde modification uses comorbid conditions identified by the CCI and incorporates the diagnostic and procedure data contained in Medicare physician (Part B) claims. The variables were categorized as indicated in Table 1.

The primary exposure was the treatment received within 6 months after diagnosis, as identified from claims data using International Classification of Diseases ninth edition (ICD-9) procedure codes and Current Procedural Terminology (CPT) codes listed in Supporting Table 1 (see online supporting information). The primary outcome of interest was overall survival.

For descriptive purposes, patients were classified into 2 mutually exclusive categories based on the treatment received within this initial period: radical prostatectomy (open, minimally invasive, or perineal) and radiotherapy (external beam, brachytherapy or, both) (Supporting Table 1; see online supporting information). Patients who received both radical prostatectomy and radiotherapy were excluded from analysis. CPT-4 code 55899 (unspecified male genitourinary procedure) may sometimes be used with an open radical prostatectomy administrative code to specify minimally invasive radical prostatectomy with robotic assistance for private health plans, but Medicare does not recognize this coding schema, and very few men had this combination of codes; therefore, this was not used to identify minimally invasive radical prostatectomy.

TABLE 2. Multivariable Cox Proportional Hazards Regression for the Original Cohort and Stratified Analysis by Race/Ethnicity

Variable	HR	95% CI	*P*
Original cohort			
Treatment			
Noncancer controls	1.00		
Surgery	0.35	0.32-0.38	<.001
RT	0.72	0.68-0.75	<.001
Race			
Non-Hispanic white	1.00		
Non-Hispanic black	1.66	1.55-1.78	<.001
Hispanics	0.99	0.84-1.17	.935
Other	0.79	0.70-0.89	.002
Stratified by race/ethnicity			
Non-Hispanic white			
Noncancer controls	1.00		
Surgery	0.34	0.31-0.37	<.001
RT	0.74	0.70-0.78	<.001
Non-Hispanic black			
Noncancer controls	1.00		
Surgery	0.37	0.29-0.48	<.001
RT	0.61	0.53-0.70	<.001
Hispanic			
Noncancer control	1.00		
Surgery	0.42	0.24-0.72	.002
RT	0.61	0.42-0.88	.008
Other			
Noncancer control	1.00		
Surgery	0.36	0.24-0.55	<.001
RT	0.62	0.47-0.81	.001

Abbreviations: CI, confidence interval; HR, hazard ratio; RT, radiotherapy.

Statistical Analysis

For all prostate cancer groups, follow-up began at the date of diagnosis. Follow-up for the noncancer control group began at the pseudo-diagnosis date, which is the date of diagnosis of their matched patients with prostate cancer. The primary outcome measure, overall survival, was calculated from the start of follow-up until the date of death (from the Medicare files) or the last follow-up. Overall survival of each prostate cancer treatment group was compared with that of the noncancer control group.

The chi-square test was used to evaluate whether differences existed between the case and control groups. The Kaplan-Meier method was used to calculate overall survival estimates. Differences were calculated using a log-rank test. Risk stratification into low-risk and high-risk disease was estimated based on clinical stage and tumor grade. Patients were classified with low-risk cancer if they had a T1 tumor and low histologic grade, and high-risk disease included T1 or T2 tumors with high-grade histology. In addition, a multivariable A Cox proportional hazards model was used to assess the influence of treatment type on outcome between the case and control groups. To minimize potential selection bias, we used propensity score-based, 1:1 matching algorithm. In this algorithm, a logistic regression model was performed controlling for all demographic and clinical variables to generate the predicted probability that was used for matching. The purpose of this matching, which was based on existing covariates, was to create a similar case and control cohort that would be used for further analysis. Although our greedy propensity score-matching algorithm matched patients on several key variables, the proportion of cases and controls by race/ethnicity variable was still significant after matching, and that may influence survival outcome. Also, previous studies have reported racial disparities in prostate cancer care; therefore, we further stratified our Cox proportional hazards model base on 4 race/ethnicity groups. *P* values $< .05$ were considered statistically significant. The SAS statistical software program (version 9.4; SAS Institute, Cary, NC) was used to perform all data-management and statistical analyses. This study was deemed exempt by the institutional review boards at The University of Texas MD Anderson Center and the University of Texas Medical Branch.

RESULTS

Of the total 34,473 patients (median age, 66 years; range, 66-75 years) who were included in the analysis, 21,740 (63%) received radiation therapy (median age, 66 years; range, 66-75 years), and 12,733 (37%) underwent surgery (median age, 66 years; range, 66-75 years). The demographics of our prostate cancer study population are summarized in Table 1. The median follow-up was 63 months (range, 1-120 months) for the study cohort: 71 months for men with low D'Amico risk disease and 62 months for those with high D'Amico risk disease.

Compared with noncancer controls (median age, 66 years), there was no significant difference between men in the prostate cancer cohort and those in the noncancer control group with the exception of race/ethnicity ($P < .001$). The prostate cancer cohort had a significantly higher percentage of non-Hispanic blacks (52.4% vs 47.6%) and race/ethnicity defined as other (52.3% vs 47.7%) (Table 1).

In multivariable analysis, improved survival was observed for patients who underwent surgery (hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.32-0.38) and for those who received with radiotherapy (HR, 0.72; 95% CI, 0.68-0.75) compared with the noncancer control group (Table 2). When stratified by race/ethnicity, improved survival persisted among patients regardless of race/ethnicity who received surgery or radiotherapy compared with noncancer controls (all $P < .01$).

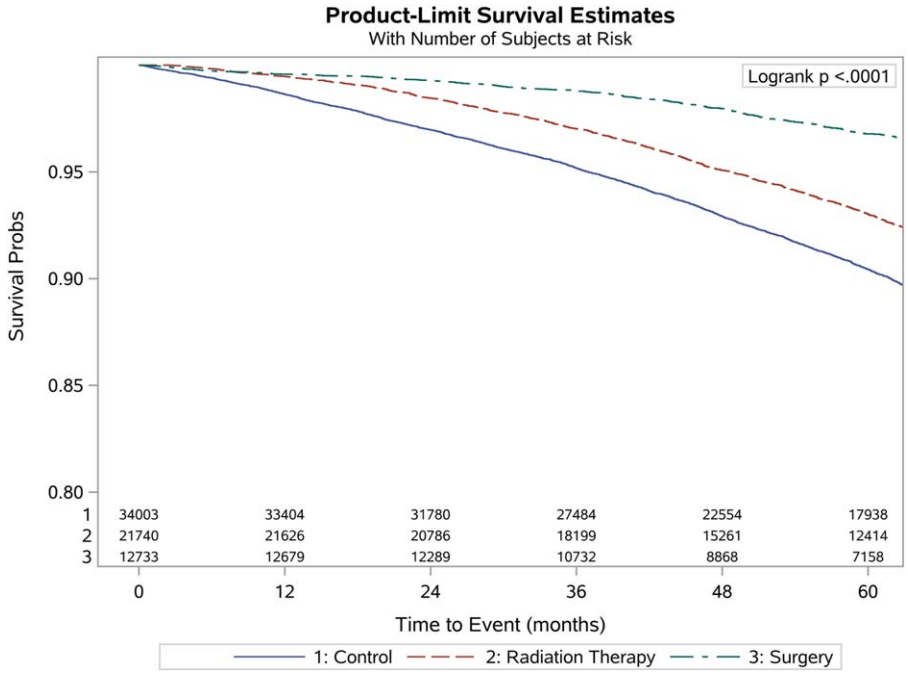

Figure 1. Kaplan-Meier product-limit estimates of survival probabilities (Probs) are illustrated.

There was significantly improved overall survival in both treatment groups, with the most benefit observed among those who underwent surgery (log rank $P < .001$), as illustrated in Figure 1. These findings persisted when patients with prostate cancer were stratified according to low-risk and high-risk disease, as illustrated in Figure 2. Therefore, we expected that patients who received treatment for prostate cancer would have a longer life expectancy. When we compared the rate of other-cause mortality and overall mortality between out prostate cancer cohort and the noncancer control cohort, we observed a significantly increased cumulative incidence of overall mortality in the noncancer controls ($P < .001$) (Supporting Figure 1; see online supporting information).

DISCUSSION

In a cohort of men ages 66 to 75 years identified from SEER-Medicare claims, although the receipt of either surgery or radiotherapy for prostate cancer was associated with improved overall survival, men who underwent surgery had the longest survival compared with men who did not have cancer. Given the matching adjustments, these results suggest that some of the observed improved benefit was likely related to inherent selection bias among men who received treatment for prostate cancer. This bias is most pronounced among men who undergo surgery because of unmeasured, confounding variables.

Despite the difficulty in performing a randomized study between surgery and radiation for localized prostate cancer, because of patient choice and physician bias, a recent trial indicated that prostate cancer-specific mortality was low and that there was no significant difference among men who received treatment (surgery or radiotherapy) versus those who underwent active monitoring.[10] Before that landmark study, patients with localized prostate cancer decided on treatment of their primary tumor with either surgery or radiotherapy based on retrospective and observational data. Although much observational data suggest either a slight advantage, or at least a similar oncologic benefit, with surgical excision, it is important to understand the limitations to this type of data. Given the benefit of treatment observed in those who received treatment for prostate cancer compared with noncancer controls, this study suggests potential limitations of using cancer registry data to compare survival outcomes in otherwise healthy men with prostate cancer.

Our study has several important findings. First, in a cohort of men who theoretically would be candidates for either surgery or radiotherapy because of their age and good overall health, we observed that those who underwent surgery had the greatest overall survival benefit compared with those who received radiation and the noncancer control cohort. Studies using retrospective, population-based cancer registry data have noted similar

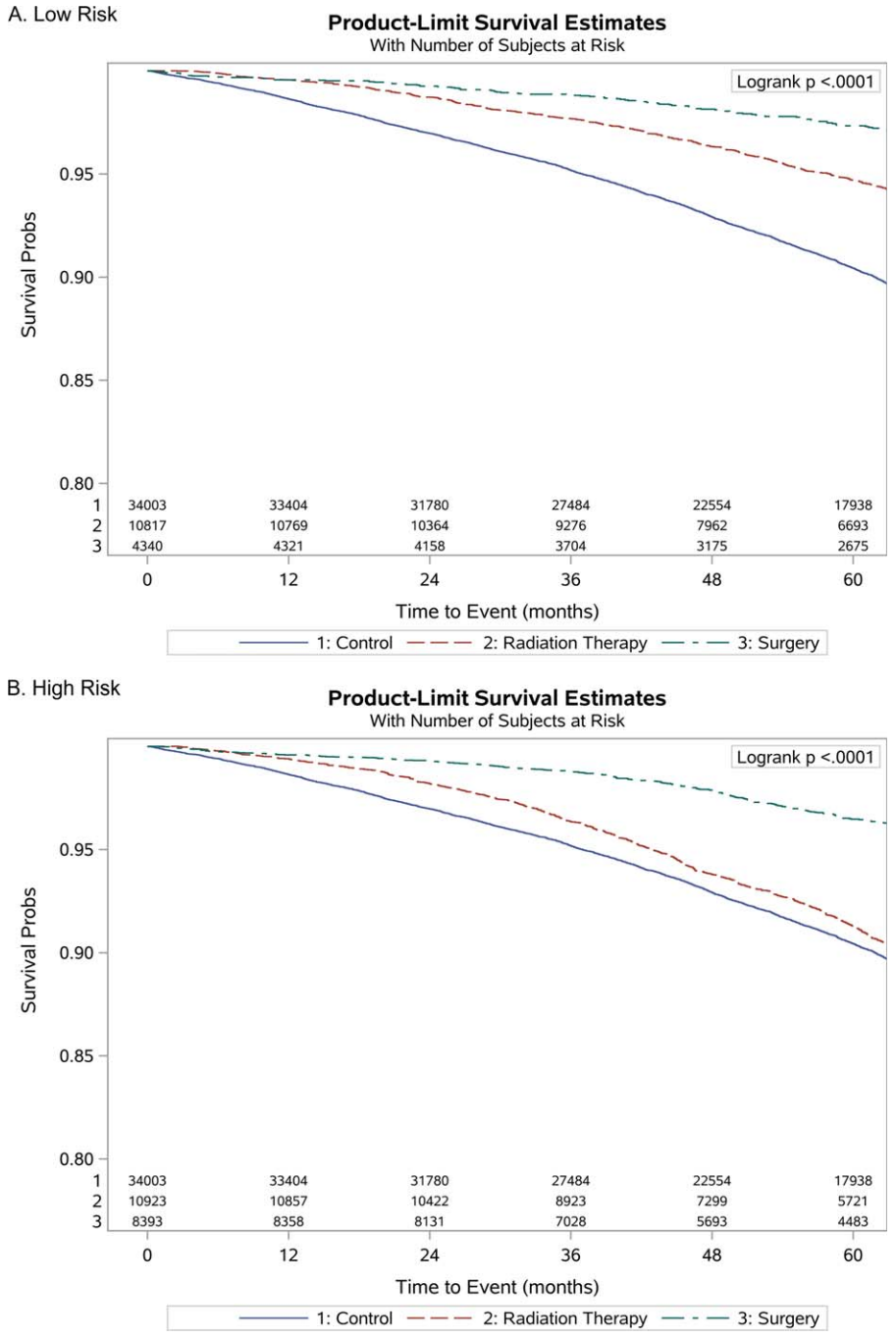

Figure 2. Kaplan-Meier product-limit estimates of survival by probabilities (Probs) are illustrated for (A) low-risk patients and (B) high-risk patients.

selection bias in treating other malignancies.[14] Surgery and radiation for prostate cancer have come under scrutiny, because many of these men have competing risks that may have a greater impact on their overall survival than their underlying prostate cancer.[8] Given the existence of these competing risks and the potential for their impact on physician recommendations, decisions regarding therapy are at risk of selection bias. These unmeasured confounding variables, which are inherent to using cancer registry data, likely account for a portion of the perceived survival benefit.

Second, we observed an improved overall survival benefit independent of race/ethnicity compared with the noncancer control cohort. These results persisted for men

who either underwent surgery or received radiotherapy, with those who underwent surgery having the greatest overall survival benefit. Racial disparities in prostate cancer care have been reported previously; however, to our knowledge, this is the first report of improved overall survival for men with prostate cancer compared with noncancer controls regardless of treatment and independent of race/ethnicity. These findings are relevant given the uncertainty regarding inferior oncologic outcomes, which may be because of increased cancer risk and/or socioeconomic determinants that have been implicated in decreased survival, such as lesser availability and access to primary health care facilities among black patients.[16,17] It appears that the use of big data like that available from SEER-Medicare introduces unmeasured confounders that impact the reporting of survival outcomes regardless of race/ethnicity.

Third, we demonstrated that men who underwent surgery had the greatest overall survival benefit compared with those who underwent radiotherapy or noncancer controls. Men who undergo surgery are often younger and healthier, as depicted in our study. Although we attempted to control for this using a roughly homogeneous group of men who theoretically would be fit to undergo either treatment, we could not control for inherent selection bias, which likely contributed to this observation. Moreover, this unmeasured selection bias more often explains our observation of an improved survival benefit among men who underwent surgery compared with noncancer controls. Prior randomized data suggested an improved overall survival benefit among men who received radiotherapy or underwent surgery for prostate cancer.[18-20] Although clinical trials overcome concerns of internal validity, there are often concerns regarding external validity and generalizability—clinical trial enrollees tend to be younger and healthier than most patients with cancer and often times represent highly selected patient subgroups.[21-23] We caution against ignoring the level 1 evidence suggesting a benefit to treatment for prostate cancer and do not condone abandoning surgery as a treatment option. However, our data do suggest that some of the observed survival benefit to surgery reported in observational studies may be contributed by selection bias. Furthermore, the use of overall survival as a study endpoint and using such data in guideline-based recommendations should be further scrutinized before making treatment recommendations.

It is not clear how this selection bias can be overcome, particularly when using population-based data. Extensive modeling and statistical adjustments do not seem capable of overcoming physician judgment or limit these inherent biases. Although randomized controlled trials are not plausible in this population, there are other potential options for effective comparisons. One option would be to prospectively enroll patients in observational studies of local therapy for prostate cancer by creating narrow inclusion criteria and requiring multispecialty consultation, followed by patient choice for therapy. This would generate a more homogeneous population of men who are better fit for comparison of both oncologic and quality-of-life outcomes. In summary and as previously demonstrated using older observational data, we also conclude that the results from observational studies comparing outcomes of different therapies should be viewed with some skepticism because of inherent selection bias.[11]

Although our findings are relevant to policy, they must be interpreted in the context of the study design. First, SEER-Medicare data are limited to men aged $\geq$65 years, and our results may not be generalizable to younger men diagnosed with prostate cancer. Moreover, this study primarily analyzed healthy men with prostate cancer ages 66 to 70 years (only 0.7% were aged >70 years) and further excluded patients who received both prostatectomy and radiation, who clearly were at increased risk of death. The combination of these 2 factors likely contribute significantly to the results from the survival analyses and account for some of the observed selection bias.[24]

Second, we excluded PSA values in the current study, because a preliminary evaluation of SEER data uncovered problems with the quality and interpretation of the PSA value.[25] Although this questions the validity of large data sets, prior studies have suggested the limited impact PSA may have on disease risk stratification of patients who have tumor characteristics similar to those who have complete data.[26]

Finally, although we attempted to control for known predictors of survival, the findings are hypothesis-generating, and there may be omitted-variable bias. Although we used the CCI, there may have been differences in health status between the surgery and radiotherapy groups that were not reflected in the Charlson comorbidity scores. However, observational studies reflect practice patterns; and, compared with the results from well conducted, randomized controlled trials, they do not appear to differ qualitatively or to overestimate treatment effects.[21,22]

Conclusions

In a large, population-based registry, we demonstrated that treatment of localized prostate cancer, with either surgery or radiotherapy, was associated with an improved overall survival benefit compared with noncancer controls. Although the cohorts were matched, men who

underwent surgery appeared to have the greatest overall survival benefit. These results suggest an inherent selection-bias because of unmeasured, confounding variables.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Stephen B. Williams: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, project administration, and funding acquisition. **Jinhai Huo**: Conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, visualization, and project administration. **Karim Chamie**: Conceptualization, methodology, investigation, writing–original draft, and writing–review and editing. **Marc C. Smaldone**: Conceptualization, methodology, investigation, writing–original draft, and writing–review and editing. **Christopher M. Kosarek**: Conceptualization, methodology, investigation, writing–original draft, and writing–review and editing. **Justin E. Fang**: Conceptualization, methodology, investigation, writing–original draft, and writing–review and editing. **Leslie A. Ynalvez**: Conceptualization, methodology, investigation, writing–original draft, and writing–review and editing. **Simon P. Kim**: Conceptualization, methodology, investigation, writing–original draft, and writing–review and editing. **Karen E. Hoffman**: Conceptualization, methodology, investigation, writing–original draft, and writing–review and editing. **Sharon H. Giordano**: Conceptualization, methodology, investigation, resources, writing–original draft, writing–review and editing, supervision, project administration, and funding acquisition. **Brian F. Chapin**: Conceptualization, methodology, investigation, resources, writing–original draft, writing–review and editing, supervision, and project administration.

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