

# Survival of Men With Clinically Localized Prostate Cancer Treated With Prostatectomy, Brachytherapy, or No Definitive Treatment

## *Impact of Age at Diagnosis*

Jonathan D. Tward, MD, PhD<sup>1</sup>  
 Christopher M. Lee, MD<sup>1</sup>  
 Lisa M. Pappas, MS<sup>2</sup>  
 Aniko Szabo, PhD<sup>2</sup>  
 David K. Gaffney, MD, PhD<sup>1</sup>  
 Dennis C. Shrieve, MD, PhD<sup>1</sup>

<sup>1</sup> Department of Radiation Oncology, Huntsman Cancer Hospital, University of Utah, Salt Lake City, Utah.

<sup>2</sup> Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah.

Jonathan Tward 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.

Address for reprints: Jonathan D. Tward, M.D., Ph.D., Department of Radiation Oncology, Huntsman Cancer Hospital, University of Utah, 1950 Circle of Hope, Salt Lake City, Utah 84112-5560; Fax: (801) 585-2666; E-mail: Jonathan.Tward@hci.utah.edu

Received June 23, 2006; revision received August 1, 2006; accepted August 21, 2006.

**BACKGROUND.** The optimal treatment for men with early stage prostate cancer remains undefined. Survival of such patients after surgery, brachytherapy, or no definitive therapy was investigated specifically to determine the impact of age at diagnosis.

**METHODS.** In all, 60,290 men diagnosed with organ-confined, low and moderate grade prostate cancer between 1988 and 2002 were retrospectively identified from centers participating in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Prostate cancer-specific mortality (PCSM) and any-cause mortality (ACM) were determined. Outcomes for patients treated by brachytherapy, surgery, or receiving no definitive treatment were compared using the Wilcoxon test, stratified by T-stage and grade, and using multivariate analysis.

**RESULTS.** The median follow-up time was 46 months (range, 0–189 months). For men under age 60 at diagnosis, PCSM at 10 years was 1.3%, 0.5%, and 3.7% for surgery, brachytherapy, and no definitive therapy, respectively. For men age 60 and older the PCSM was 3.8%, 5.3%, and 8.4%, respectively. On univariate and multivariate analysis, surgery and brachytherapy resulted in statistically equivalent PCSM and ACM, and both had a significantly lower PCSM and ACM versus no definitive therapy.

**CONCLUSIONS.** A better survival was observed in men treated with a definitive therapy. The magnitude of the benefit on PCSM or ACM was similar for both definitive therapies irrespective of age. *Cancer* 2006;107:2392–400.

© 2006 American Cancer Society.

**KEYWORDS:** prostate cancer, brachytherapy, prostatectomy, survival, effect of age.

In 2005, an estimated 232,090 men were diagnosed with, and 30,350 men died of, cancer of the prostate.<sup>1</sup> Among newly diagnosed cases, the majority of men will have clinically localized disease.<sup>2</sup>

Men with localized prostate cancer are often presented with the difficult choice among treatment options including radical surgery, radiation treatment, or active surveillance. But in the absence of prospectively randomized trials, the most appropriate therapy for men with clinically localized prostate cancer remains uncertain. Those with a life expectancy predicted to be greater than 10 years from diagnosis are often counseled to undergo a definitive therapy.

Both radical prostatectomy and brachytherapy are commonly used to treat localized prostate cancer. A 1999 survey of American urologists and radiation oncologists revealed that 93% of urologists felt that prostatectomy was a better treatment than external beam

radiation for clinically localized prostate cancer in men with a life expectancy greater than 10 years, whereas 75% of radiation oncologists felt external beam radiation was equivalent to, or better than, surgery. Among the radiation oncologists, 74% felt that brachytherapy was the same or better than external beam therapy.<sup>3</sup> In a Canadian study, men younger than 60 years of age at the time of diagnosis were found more likely to be referred for surgical therapy than for radiation treatment.<sup>4</sup>

The aim of the current study was to determine prostate cancer-specific mortality (PCSM) and any-cause mortality (ACM, overall survival) for men treated by surgery, brachytherapy, or receiving no definitive therapy. These outcomes were compared using age as a continuous variable, as well as by discrete age cohorts of men younger or older than age 60 at the time of diagnosis for clinical utility.

## MATERIALS AND METHODS

### Data and Study Population

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the US National Cancer Institute (NCI) using the SEER 13-Registries dataset (November 2004 edition).<sup>5</sup> The SEER database is composed of a set of geographically defined, population-based, central cancer registries in the US (data from Connecticut, Iowa, Hawaii, New Mexico, Utah, metropolitan areas of Atlanta, Detroit, Los Angeles, Oakland, San Francisco, San Jose-Monterey, Seattle-Puget Sound, and Alaska Native populations) and is operated by local nonprofit organizations under contract with the NCI. Serial registry data are submitted electronically without personal identifiers (deidentified) to the NCI on a biannual basis and the NCI thereafter makes the data available to the public for research purposes.<sup>5</sup> Because all SEER database information remains deidentified, approval by an ethics committee and informed consent by the study participants were not necessary to perform the analyses. The case ascertainment rate from the SEER registries has been reported to be 97.5%. The SEER database is the authoritative source of population-based information on cancer incidence and survival in the US. In general, the populations covered by SEER are known to be representative of the whole US.<sup>6</sup>

The analyzed study population included men diagnosed with 1997 American Joint Committee on Cancer Stage II, T1c-T2b prostate adenocarcinoma who underwent either surgery, brachytherapy monotherapy, or no definitive treatment. Histological classification was based on the *International Classification of Diseases for Oncology* codes (ICD 8140).<sup>7</sup> Patients

were included who were diagnosed between January 1, 1988, and December 31, 2002, and for whom complete datasets were available. The prognostic factors included in the analysis were: age, race, stage, grade, therapy, and year of diagnosis. Information on race was used as entered in the SEER database. This information was analyzed to evaluate known differences in prognosis according to race.<sup>8</sup> The causes for patient exclusion from the analysis were: any nonbrachytherapy form of radiation therapy, whether combined with brachytherapy or as definitive treatment; clinically staged nodal involvement (N1 disease); clinically staged distant spread (M1 disease); high-grade pathology; lack of staging information; and cases with missing variables. There were 60,290 men who met the above criteria and served as the patient population for our study. All participants in the SEER program routinely link patient files with vital records (i.e., death certificates) in their respective areas of coverage to identify patients with cancer who have died (regardless of cause of death); therefore, death certificates are the source for information regarding underlying cause of death as recorded in the SEER program database. Furthermore, the National Center for Health Statistics conducts routine reviews of death certificates to ensure quality of data.<sup>6</sup>

### Statistical Analysis

Surgery was specifically compared with brachytherapy because these definitive treatment choices remain controversial for men with a good performance status. High-grade pathology was excluded because brachytherapy monotherapy is not indicated for high-grade disease. Cause-specific mortality was analyzed using methods that adjusted for the competing risks of mortality as implemented in the *cmprsk* 2.1–5 software package in R.<sup>9–12</sup> The possible causes of death were combined as “prostate cancer,” “diseases of the heart,” and “all other causes.” Heart disease was separated from the other causes because it occurred more often than the cause of main interest—death from prostate cancer. The cumulative incidence of death due to each of these 3 causes was estimated using the methods of Gaynor et al.<sup>11</sup> The cumulative incidence of death from any cause is the sum of the cause-specific incidences; it also equals to 1-KM, where KM is the Kaplan-Meier estimate for overall survival. Using cohorts of men under age 60 and 60 and older, the cumulative incidence curves were compared via a stratified Wilcoxon-type test proposed by Gray.<sup>12</sup> The stratification was according to stage and grade. The same test was used for pairwise comparisons. The cumulative incidence curves

**TABLE 1**  
Demographics of Study Population

	Men aged <60 y						Men aged ≥60 y					
	14,503 Men. Median follow-up: 43 m						45,787 Men. Median follow-up: 46 m					
	Brachytherapy		Surgery		No definitive therapy		Brachytherapy		Surgery		No definitive therapy	
	n	%	n	%	n	%	n	%	n	%	n	%
No. of men	1233		11,566		1704		5404		23,192		17,191	
Median age at Dx	56		55		56		69		66		75	
Deaths from prostate cancer	1		48		23		35		381		596	
Deaths from any cause	19		313		144		336		2864		4660	
T-Stage (1997 AJCC)												
T1C-elevated psa	831	67.4	6919	59.8	1062	62.3	3372	62.4	11,800	50.9	8858	51.5
T2A-one lobe	300	24.3	3290	28.4	447	26.2	1581	29.3	8827	38.1	5944	34.6
T2B-both lobes	102	8.3	1357	11.7	195	11.4	451	8.3	2565	11.1	2389	13.9
Grade												
Well differentiated; grade I	98	7.9	649	5.6	250	14.7	432	8.0	2057	8.9	2650	15.4
Moderately differentiated; grade II	1135	92.1	10,917	94.4	1454	85.3	4972	92.0	21,135	91.1	14,541	84.6
Race												
American Indian/Alaska Native	5	0.4	39	0.3	9	0.5	11	0.2	62	0.3	52	0.3
Asian or Pacific Islander	40	3.2	378	3.3	52	3.1	207	3.8	1041	4.5	1023	6.0
Black	152	12.3	1534	13.3	353	20.7	353	6.5	2067	8.9	2095	12.2
Unknown	22	1.8	86	0.7	140	8.2	60	1.1	94	0.4	999	5.8
White	1014	82.2	9529	82.4	1150	67.5	4773	88.3	19,928	85.9	13,022	75.7
Reason surgery was not performed												
Contraindicated due to other conditions	5	0.4	NA		19	1.1	51	0.9	NA		431	2.5
Refused	138	11.2	NA		209	12.3	379	7.0	NA		1149	6.7
Surgery not recommended	595	48.3	NA		520	30.5	2807	51.9	NA		6882	40.0
Unknown	495	40.1	NA		956	56.1	2167	40.1	NA		8729	50.8

for death from any cause were compared via a stratified Wilcoxon test.

We modeled the cumulative incidence of prostate cancer survival via a proportional hazard model that accounts for the competing risks of death as described by Fine and Gray.<sup>10</sup> First, grade, stage, race, and therapy were entered into the model as categorical variables, whereas year and age at diagnosis were modeled continuously with natural cubic splines. Testing for interactions revealed that the effect of age varied by therapy, so this interaction was added to the model. No further interactions were identified. We examined the assumption of proportional hazards via residual plots and found no substantial deviations. An examination of the fitted splines for year and age at diagnosis showed that the effect of the diagnosis year was approximately linear, whereas the effect of age at diagnosis was constant up to about age 60 and increasing for higher ages. Thus, we replaced the splines in the model with a linear term for diagnosis year and a piecewise linear combination of a constant followed by a linear increase after 60 for age at diagnosis (we have not performed optimization for the change-point). This

resulted in only a slight decrease in the likelihood, while enhancing the interpretability of the model.

SEER\*Stat software v. 6.1.4 (Surveillance Research Program, NCI, Bethesda, MD) was used to extract case level data from the SEER Cancer Public-Use Database 1973–1999, November 2003 Submission. R v. 2.2.1 was used for statistical analyses.<sup>5</sup> We defined  $P < .05$  to be statistically significant.

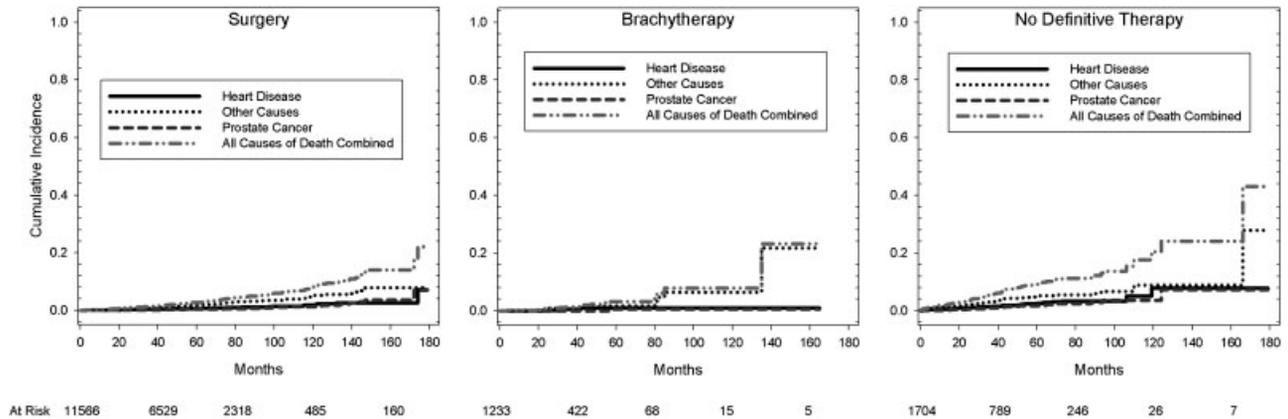
**RESULTS**

The median observation period for the entire study population was 46 months (range, 0–179 months). Patient demographic information and clinical characteristics are listed in Table 1.

The distributions of cause of death, stratified by the therapy received, are shown in Table 2. To standardize the follow-up and provide more accurate comparison of competing causes of death among the different therapies, the results are expressed as number of deaths per 1000 person-years of follow-up. The total numbers of deaths from all causes per 1000 person-years of follow-up for surgery, brachytherapy, or no definitive treatment were 19.33, 36.09, and 66.65 respectively.

**TABLE 2**  
Causes of Death

	Surgery 34,758 men 163,557 person-y		Brachytherapy 6637 men 19,647 person-y		Neither 18,895 men 71,339 person-y	
	No. of deaths	Deaths/1000-person-y	No. of deaths	Deaths/1000-person-y	No. of deaths	Deaths/1000-person-y
Prostate cancer	429	2.62	36	1.83	619	8.68
Nonprostate malignancy	855	5.23	77	3.92	891	12.49
Diseases of heart	800	4.89	111	5.65	1440	20.19
Cerebrovascular diseases	176	1.08	13	0.66	313	4.39
Respiratory disease	133	0.81	13	0.66	274	3.84
Accidents and adverse effects	65	0.40	7	0.36	78	1.09
Diabetes mellitus	57	0.35	8	0.41	95	1.33
Pneumonia and influenza	78	0.48	10	0.51	167	2.34
Alzheimers	29	0.18	5	0.25	37	0.52
Other benign illness	540	3.30	429	21.84	841	11.79
Total	3162	19.33	709	36.09	4755	66.65



**FIGURE 1.** Cumulative incidence of death by cause for men <60 years at diagnosis.

The cumulative incidence curves for competing causes of death and death from any cause are shown in Figures 1 and 2 for men under age 60 at diagnosis and 60 and older, respectively. Fewer than 6% of those treated with brachytherapy or surgery died of prostate cancer within 10 years of their diagnosis (Table 3). In a univariate Wilcoxon analysis (stratified by T-stage and grade), there was no statistical difference in either PCSM or ACM for men treated by surgery versus brachytherapy, irrespective of age cohort. Patients in both age groups undergoing surgery or brachytherapy demonstrated a significantly lower PCSM or ACM compared with men undergoing no definitive therapy ( $P < .002$ ). Men age 60 and over at diagnosis who underwent brachytherapy were significantly more likely to die of heart disease than those undergoing surgery ( $P = .048$ ), but the increased risk was not apparent until approximately 8 years after diagnosis (Fig. 2).

In the multivariate model, the effect of brachytherapy and surgery were also statistically indistin-

guishable for PCSM (likelihood ratio test  $P = .16$ ). Lower stage and grade of disease, more recent year of diagnosis, and nonblack ethnicity resulted in a significantly improved PCSM (Table 4). When analyzing age as a continuous variable, age less than 60 years at diagnosis did not alter the hazard ratio for prostate cancer death. However, after age 60 at diagnosis the risk of dying from prostate cancer starts rising and this rise is the highest for patients treated with surgery.

Utilization rates of the different therapies over the study interval by date of diagnosis quartile are shown in Table 5. The relative use of surgery to brachytherapy has declined 7-fold from the earliest (1988–1991) to the latest quartile (2000–2002).

**DISCUSSION**

Despite the frequency of diagnosis, the most appropriate treatment for men with newly diagnosed, clini-

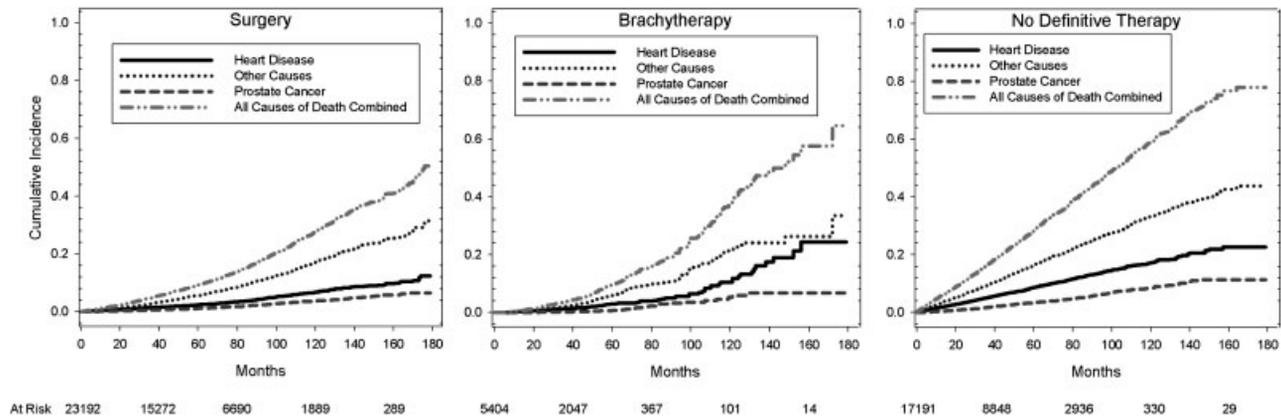


FIGURE 2. Cumulative incidence of death by cause for men ≥60 years at diagnosis.

TABLE 3  
Univariate Analysis

	Men <60 y at Dx	Men ≥60 y at Dx
Death from prostate cancer (10 y)*		
Surgery	1.3%	3.8%
Brachytherapy	0.5%	5.3%
No definitive therapy	3.7%	8.4%
Death from any cause (10 y)*		
Surgery	7.8%	27.4%
Brachytherapy	7.9%	37.1%
No definitive therapy	20.5%	58.7%
Comparison of death from prostate cancer <sup>†</sup>	<i>P</i>	<i>P</i>
Surgery vs brachytherapy	.380	.595
Surgery vs no definitive therapy	<.001	<.001
Brachytherapy vs no definitive therapy	.002	<.001
Comparison of death from any cause <sup>‡</sup>		
Surgery vs brachytherapy	.908	.625
Surgery vs no definitive therapy	<.001	<.001
Brachytherapy vs no definitive therapy	<.001	<.001

\* Cumulative incidence estimates by the method of Gaynor. For "Death from any cause," it is equivalent to 1 minus the Kaplan-Meier estimate.

<sup>†</sup> Stratified Wilcoxon-type test stratified by the method of Gray et al.<sup>12</sup>

<sup>‡</sup> Wilcoxon test stratified by T-stage and grade.

TABLE 4  
Prostate Cancer-Specific Survival

	RR	95% CI	<i>P</i>
Grade			
grade 1	1	Reference	
grade 2	1.85	1.54-2.22	<.001
Stage			
stage Ic	1	Reference	
stage IIa	0.99	0.83-1.17	.87
stage IIb	2.16	1.80-1.69	<.001
Year of Diagnosis			
per decade	0.22	0.17-0.29	<.001
Race			
Other	1	Reference	
African American	1.25	1.04-1.51	.018
Therapy			
Surgery	1	Reference	
Brachytherapy	1.77	0.99-3.15	.054
No definitive therapy	4.34	3.34-5.63	<.001
Age >60			
per decade, surgery	2.96	2.61-3.36	<.001
per decade, brachytherapy	1.52	0.97-2.39	.066
per decade, no def. tx.	1.55	1.38-1.74	<.001
<60 y	No effect		

cally localized prostate cancer is controversial. With 60,290 men, this study represents the largest population-based analysis to date revealing the cause-specific and overall mortality for brachytherapy, surgery, or no definitive treatment for clinically localized prostate cancer. A recently published Scandinavian prospective randomized trial revealed a survival benefit for prostatectomy versus "Watchful Waiting."<sup>13</sup> Our patient population is similar to those in that trial in that 1) we "enrolled" men from 1988 versus 1989, respectively, onward; 2) in neither study were prostate-specific antigen (PSA) data used for stratification; 3) T-staging encompassed both T1 and T2 disease; and 4) a grading system of well-differentiated and

moderately differentiated tumors was used as entry criteria and stratification instead of Gleason scoring. The studies differed in that the Scandinavian trial was prospectively randomized, included diagnoses made after a TURP procedure, and excluded men whose baseline PSA values were >50 ng/mL. In our study PSA data was unavailable. Although the grading system used by the SEER database to classify tumors as well or moderately differentiated is based on Gleason scoring, the Scandinavian trial tumor grading was based on the World Health Organization definition.<sup>14</sup> Therefore, the SEER grades and the grades used in the Scandinavian trial cannot be reliably compared.

**TABLE 5**  
Utilization Rates of Competing Therapies Over the Study Interval

Year of diagnosis	Surgery	Brachytherapy	No definitive therapy	Grand total	Surgery: brachytherapy ratio
1988-1991	2329	116	641	3086	20.1
1992-1995	6834	329	4004	11,167	20.8
1996-1999	15,124	2461	7851	25,436	6.1
2000-2002	10,471	3731	6399	20,601	2.8
Grand total	34,758	6637	18,895	60,290	

No completed randomized trial has directly compared brachytherapy to surgery. The American College of Physicians and Surgeons (ACOSOG) opened a prospectively randomized trial comparing brachytherapy to prostatectomy in 2000, but unfortunately the study was prematurely closed in April 2004 after only accruing 56 of the planned 1980 patients needed. Given the strong biases among both patients and health care providers regarding the relative risks and merits of these treatments, it is unlikely that such a trial will be initiated within the near future. Although not a prospectively randomized trial, this study is the first to evaluate these 3 treatment choices with actual mortality as an endpoint.

There have been several retrospective studies, usually single-institutional or regional experiences, which have compared various outcomes of surgery to brachytherapy.<sup>15-18</sup> In most, surrogate endpoints for disease progression are used based on various interpretations of PSA failure, PSA velocity, or time to PSA progression.<sup>19-24</sup> Nevertheless, the role of post-therapy PSA monitoring and its impact on clinical outcome remains controversial.<sup>25</sup> These data clearly demonstrate that both brachytherapy and surgery can prevent prostate cancer death, and the magnitude of the effect was similar for both cohorts. One may argue that because the SEER database encodes the underlying cause of death from the death certificate, this information could be unreliable. However, Albertsen et al.<sup>26</sup> and Penson et al.<sup>27</sup> have determined through 2 independent validation studies that prostate cancer mortality can be classified reliably, with concordance rates of 87% to 96% with medical record review. Surgery or brachytherapy resulted in similar survival for both the young men (under 60) as well as those who were older at diagnosis.

The American Cancer Society currently recommends PSA screening for prostate cancer beginning at age 50 (age 45 if high risk), and the National Comprehensive Cancer Center (NCCN) guidelines recommend a baseline PSA evaluation at age 40.<sup>28-30</sup> As a result, numerous men under the age of 60 are being diagnosed with early and localized prostate cancer. According to Albertsen et al.,<sup>31</sup> counseling men who

have moderately differentiated disease (the vast majority of men in this study) and a life expectancy of more than 15 years "poses the greatest challenge." In the absence of randomized Phase III trial data, physicians have been unsure of the most appropriate treatment course for this group of men with a long life expectancy. Reflecting the uncertainty, the NCCN treatment guidelines recommend that men with low-risk, clinically localized prostate cancer with a greater than 10 year life expectancy have either expectant management, radiotherapy (3D conformal external beam or brachytherapy), or radical prostatectomy with or without pelvic lymph node dissection.<sup>28</sup> Earlier surveys have revealed that 93% of American urologists felt that prostatectomy was a superior therapy to radiation treatment, in sharp contrast to the 75% of radiation oncologists who felt radiation therapy was equivalent or better.<sup>3</sup> Despite the lack of any definitive survival data to support the use of surgery over brachytherapy, Walsh<sup>32</sup> has argued that radical prostatectomy should be the gold standard for treatment of localized prostate cancer. Our findings demonstrate that brachytherapy is also an excellent treatment choice for men of all ages, with PCSM outcomes similar to those after surgery. The increased utilization rates of brachytherapy relative to surgery over the study period reflect the increasing acceptance of brachytherapy as a definitive alternative to surgery; this trend has been reported in other large prospectively gathered databases.<sup>33</sup>

This study is the first to demonstrate an apparent overall survival advantage for brachytherapy compared with no definitive treatment, and validates prior reports that document a survival advantage for surgery.<sup>34</sup> Without treatment, only a small proportion of men diagnosed with clinically localized prostate cancer will die of their disease within 10-20 years.<sup>31,35-38</sup> Given that both surgery and brachytherapy are invasive procedures with possible lifetime side-effects, the debate over which men with a long life expectancy should be treated with a definitive therapy continues to be relevant.

The observed number of deaths from any cause, adjusted by person-years of follow-up, was lowest for

the surgery group and highest for the neither therapy group (Table 2). A reason other than “unknown” for not undergoing surgery was encoded in the database for 3875 of the men who had brachytherapy. Of these men, surgery was encoded as “not recommended” 86% of the time. One possible interpretation of these observations is that the healthiest men were selected for surgery, whereas those with more underlying medical comorbidities were directed to brachytherapy or neither treatment. This assumption was supported by the competing risk of mortality analysis (Figs. 1, 2, Table 2). Death from heart disease, the greatest single cause of death in the study population, was significantly greater in the men over 60 cohort undergoing brachytherapy compared with surgery. The shape of this mortality curve is interesting: the brachytherapy curve is virtually indistinguishable from the surgery curve until approximately year 8 after diagnosis. Then a dramatic relative rise in heart-disease death in the brachytherapy group becomes evident. One possible explanation for this observation is that these men had known medical comorbidities at diagnosis, making major surgery more risky, yet judged to have a  $\geq 10$ -year life expectancy and decent performance status still allowing for brachytherapy. The relative rise in heart disease death after 8 years may therefore reflect sound clinical prognostication. Alternatively, the increased cardiac mortality seen in the brachytherapy cohort of men over 60 may reflect an increased utilization of androgen deprivation therapy (ADT) in this group relative to the other groups. Androgen deprivation therapy has been linked to dyslipidemia and high cardiac mortality.<sup>39</sup> If true, ADT would delay disease progression and would skew the PCSM survival estimates to a more favorable profile. A more rigorous analysis of this hypothesis would require a more robust database that encodes medical history and ADT use (which the SEER database does not do) and is beyond the scope of this work.

Although there is a reported 97.5% case ascertainment rate at the participating SEER sites, these sites only comprise approximately 10% of the US population.<sup>6</sup> In addition, specific clinical and pathological data known to be of prognostic significance are not readily available, including information regarding PSA, Gleason scoring, androgen ablation therapy, specifics of brachytherapy, such as radiation dose, dose rate, and isotope used, or the type of prostatectomy performed.<sup>5</sup> Quality assurance and provider volume measures for the definitive therapy providers are also important clinical factors that can also influence outcome.<sup>40,41</sup> We were unable to adjust for these factors in our analyses. In addition, the SEER

database does not record history of treatment failure (whether local-regional or distant spread) or time of recurrence. The lack of these data prevents SEER population analyses from containing an event-free survival component.

On both univariate and multivariate analysis, brachytherapy was found to yield a statistically equivalent PCSM compared with surgery. Likewise, both definitive therapies appeared statistically superior to the no definitive therapy group. Nevertheless, we cannot confidently conclude that brachytherapy and surgery are equivalent therapies, nor that either was superior to the no definitive therapy group, because we could not control for the distribution of Gleason scoring, androgen deprivation therapy use, and PSA values in these 3 treatment cohorts. The SEER program code manual, used by registrars to encode information into the SEER database, instructs registrars to encode Gleason 2, 3, and 4 as Grade I, and Gleason 5, 6, and 7 as Grade II.<sup>42</sup> Although these grades were used in the analysis, the Grade II group encompasses 3 distinct Gleason risk groups:  $3 + 3 = 6$  and lower,  $3 + 4 = 7$ , and  $4 + 3 = 7$ . Each of these Gleason scores is associated with different risks of failure.<sup>43-45</sup> In addition, contemporary prostate brachytherapy techniques were just beginning to gain acceptance in the US in the late 1980s. Grimm et al.<sup>46</sup> reported poorer biochemical control in men implanted at the Seattle Prostate Institute between 1986-1987 versus those implanted between 1988 to 1990, which suggested that a “learning curve” to the brachytherapy technique may be important to outcome. In the current study, the men with the longest follow-up times were treated in that era. Likewise, surgical techniques continue to evolve. Therefore, our long-term PCSM survival estimates for both definitive therapy groups may not accurately reflect risk for men treated in the 21st century.

Despite these shortcomings, this analysis remains pertinent; the SEER database reflects practice patterns in the US and is directly applicable to a man seeking therapy in America. Even though treatment guidelines recommend brachytherapy monotherapy only for men with T1c-T2a, PSA  $< 10$  ng/mL, in our study we found men with 1997 AJCC T2b (both lobes) disease who were also implanted, reflecting variability in adherence to guidelines.

Factors other than survival, such as the risks, side effect profiles, and quality of life after an intervention weigh heavily on men deciding to undergo treatment for this disease, which is unlikely to claim their life. For this reason, the best treatment for localized prostate cancer will continue to be debated and should be individualized for each patient. These find-

ings do, however, reveal that within a large US population with data collected over a period of 15 years, both brachytherapy and surgery can prevent prostate cancer death for men with localized, low to moderate grade disease at presentation. For men seeking a definitive treatment, both younger and older men should be counseled that either surgery or brachytherapy is appropriate.

## REFERENCES

- Ries LAG EM, Kosary CL, Hankey BF, et al. (eds.). SEER Cancer Statistics Review, 1975–2002. Bethesda, MD: National Cancer Institute, 2005.
- Cooperberg MR, Lubeck DP, Mehta SS, Carroll PR. Time trends in clinical risk stratification for prostate cancer: implications for outcomes (data from CaPSURE). *J Urol*. 2003;170(6 Pt 2):S21–25; discussion S26–27.
- Fowler FJ Jr, McNaughton Collins M, Albertsen PC, Zietman A, Elliott DB, Barry MJ. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. *JAMA*. 2000;283:3217–3222.
- Alibhai SM, Krahn MD, Cohen MM, Fleshner NE, Tomlinson GA, Naglie G. Is there age bias in the treatment of localized prostate carcinoma? *Cancer*. 2004;100:72–81.
- Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER\*Stat Database: Incidence — SEER 13 Regs Public-Use, Nov 2004 Sub (1973–2002 varying), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.
- Surveillance, Epidemiology, and End Results (SEER) Program Web site. Data quality. Available at: <http://seer.cancer.gov/about/quality.html>. Accessed May 6, 2005.
- Piercy C VHV, Muir C. International classification of diseases for oncology, 2nd ed. Geneva: World Health Organization, 1990.
- Tewari A, Horninger W, Pelzer AE, et al. Factors contributing to the racial differences in prostate cancer mortality. *BJU Int*. 2005;96:1247–1252.
- R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2005.
- Fine JP, Gray RJ. A proportional hazards model for the sub-distribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
- Gaynor JJ, Feuer EJ, Tan CC, et al. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. *J Am Stat Assoc*. 1993;88:400–409.
- Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16:1141–1154.
- Bill-Axelsson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2005;352:1977–1984.
- Mostofi FK, Sesterhenn I, Sobin LH. Histological typing of prostate tumours. Geneva: World Health Organization, 1980.
- Alexianu M, Weiss GH. Radical prostatectomy versus brachytherapy for early-stage prostate cancer. *J Endourol*. 2000;14:325–328.
- Jo Y, Junichi H, Tomohiro F, Yoshinari I, Masato F. Radical prostatectomy versus high-dose rate brachytherapy for prostate cancer: effects on health-related quality of life. *BJU Int*. 2005;96:43–47.
- Sharkey J, Cantor A, Solc Z, et al. Brachytherapy versus radical prostatectomy in patients with clinically localized prostate cancer. *Curr Urol Rep*. 2002;3:250–257.
- Sharkey J, Cantor A, Solc Z, et al. 103Pd brachytherapy versus radical prostatectomy in patients with clinically localized prostate cancer: a 12-year experience from a single group practice. *Brachytherapy*. 2005;4:34–44.
- Horwitz EM, Thames HD, Kuban DA, et al. Definitions of biochemical failure that best predict clinical failure in patients with prostate cancer treated with external beam radiation alone: a multi-institutional pooled analysis. *J Urol*. 2005;173:797–802.
- Horwitz EM, Vicini FA, Ziaja EL, Dmichowski CF, Stromberg JS, Martinez AA. The correlation between the ASTRO Consensus Panel definition of biochemical failure and clinical outcome for patients with prostate cancer treated with external beam irradiation. American Society of Therapeutic Radiology and Oncology. *Int J Radiat Oncol Biol Phys*. 1998;41:267–272.
- Kuban D, Thames H, Levy L, et al. Failure definition-dependent differences in outcome following radiation for localized prostate cancer: can one size fit all? *Int J Radiat Oncol Biol Phys*. 2005;61:409–414.
- Ray ME, Thames HD, Levy LB, et al. PSA nadir predicts biochemical and distant failures after external beam radiotherapy for prostate cancer: a multi-institutional analysis. *Int J Radiat Oncol Biol Phys*. 2006;64:1140–1150.
- Thames H, Kuban D, Levy L, et al. Comparison of alternative biochemical failure definitions based on clinical outcome in 4839 prostate cancer patients treated by external beam radiotherapy between 1986 and 1995. *Int J Radiat Oncol Biol Phys*. 2003;57:929–943.
- Zelevsky MJ, Ben-Porat L, Scher HI, et al. Outcome predictors for the increasing PSA state after definitive external-beam radiotherapy for prostate cancer. *J Clin Oncol*. 2005;23:826–831.
- Vicini FA, Vargas C, Abner A, Kestin L, Horwitz E, Martinez A. Limitations in the use of serum prostate specific antigen levels to monitor patients after treatment for prostate cancer. *J Urol*. 2005;173:1456–1462.
- Albertsen PC, Walters S, Hanley JA. A comparison of cause of death determination in men previously diagnosed with prostate cancer who died in 1985 or 1995. *J Urol*. 2000;163:519–523.
- Penson DE, Albertsen PC, Nelson PS, Barry M, Stanford JL. Determining cause of death in prostate cancer: are death certificates valid? *J Natl Cancer Inst*. 2001;93:1822–1823.
- National Comprehensive Cancer Network (NCCN). Prostate Cancer Early Detection. v. 2.2005. Jenkintown, PA: National Comprehensive Cancer Network, 2005.
- Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2005. *CA Cancer J Clin*. 2005;55:31–44; quiz 55–36.
- Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2006. *CA Cancer J Clin*. 2006;56:11–25.
- Albertsen PC, Hanley JA, Fine J. 20-Year outcomes following conservative management of clinically localized prostate cancer. *JAMA*. 2005;293:2095–2101.
- Walsh PC. Radical prostatectomy for localized prostate cancer provides durable cancer control with excellent quality of life: a structured debate. *J Urol*. 2000;163:1802–1807.

33. Cooperberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol.* 2004;22:2141-2149.
34. Alibhai SM, Klotz LH. A systematic review of randomized trials in localized prostate cancer. *Can J Urol.* 2004;11:2110-2117.
35. Adolfsson J, Steineck G, Hedlund PO. Deferred treatment of clinically localized low-grade prostate cancer: actual 10-year and projected 15-year follow-up of the Karolinska series. *Urology.* 1997;50:722-726.
36. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med.* 1994;330:242-248.
37. Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. *JAMA.* 2004;291:2713-2719.
38. Johansson JE, Holmberg L, Johansson S, Bergstrom R, Adami HO. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. *JAMA.* 1997;277:467-471.
39. Braga-Basaria M, Muller DC, Carducci MA, Dobs AS, Basaria S. Lipoprotein profile in men with prostate cancer undergoing androgen deprivation therapy. *Int J Impot Res.* 2006;18:494-498.
40. Joudi FN, Konety BR. The impact of provider volume on outcomes from urological cancer therapy. *J Urol.* 2005;174:432-438.
41. Spencer BA, Steinberg M, Malin J, Adams J, Litwin MS. Quality-of-care indicators for early-stage prostate cancer. *J Clin Oncol.* 2003;21:1928-1936.
42. Cancer Statistics Branch SP. Bethesda, MD: SEER Program Code Manual, 1998.
43. Chan TY, Partin AW, Walsh PC, Epstein JI. Prognostic significance of Gleason score 3+4 versus Gleason score 4+3 tumor at radical prostatectomy. *Urology.* 2000;56:823-827.
44. D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen M-H. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol.* 2003; 21:2163-2172.
45. Merrick GS, Butler WM, Galbreath RW, Lief JH, Adamovich E. Biochemical outcome for hormone-naive patients with Gleason score 3+4 versus 4+3 prostate cancer undergoing permanent prostate brachytherapy. *Urology.* 2002;60:98-103.
46. Grimm PD, Blasko JC, Sylvester JE, Meier RM, Cavanagh W. 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. *Int J Radiat Oncol Biol Phys.* 2001;51:31-40.