Impact of Brachytherapy on Regional, Racial, Marital Status, and Age-Related Patterns of Definitive Treatment for Clinically Localized Prostate Carcinoma

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BACKGROUND. The impact of the increased use of permanent prostate brachytherapy compared with other treatment modalities (such as radical prostatectomy and external-beam radiation therapy [EBRT]) for the treatment of clinically localized prostate carcinoma, and the previously reported regional, racial, and age-related variations in prostate carcinoma treatment, have not been well characterized to date. Therefore, the authors evaluated the impact of permanent prostate brachytherapy on the relative rates of the use of specific prostate carcinoma treatment modalities over time.

METHODS. Surveillance, Epidemiology, and End Results (SEER) cancer registry data from 1995 to 2000 were analyzed in a longitudinal, observational study utilizing bivariate and multivariate techniques.

RESULTS. Differential changes in the use of specific definitive treatment modalities were noted by region, age group, racial/ethnic group, and marital status. Increasing use of permanent prostate brachytherapy, with and without concomitant EBRT, was proportional to the decreasing use of radical prostatectomy alone and EBRT alone over time.

CONCLUSIONS. The current study revealed that permanent prostate brachytherapy appears to be replacing other treatment modalities in increasing numbers of clinically localized prostate carcinoma cases. Persistent regional, racial/ethnic, marital status, and age-related differences in the use of permanent prostate brachytherapy merit further investigation. Cancer 2005;104:1372–80. © 2004 American Cancer Society.

KEYWORDS: permanent prostate brachytherapy, radical prostatectomy, external-beam radiation therapy, prostate carcinoma.

Prostate carcinoma is the most prevalent noncutaneous malignancy diagnosed in men in the U.S. There were projected to be 232,090 incident cases of prostate carcinoma and 30,350 deaths in the U.S. in 2005, accounting for 33% of all newly diagnosed cancers in men.1 In contrast to watchful waiting (no immediate intervention), “definitive” treatment options for early-stage prostate carcinoma include radical prostatectomy, external-beam radiation therapy (EBRT), and permanent prostate brachytherapy. Without a randomized clinical trial, the optimal therapy for clinically localized prostate carcinoma cannot be defined. Therefore, treatment decisions are subject to the provider’s clinical opinion and a patient’s priorities. Variations in the use of specific definitive therapies for the treatment of clinically localized prostate carcinoma are expected and have been previously reported. The region of the country, race, marital status, and age at which the disease was diagnosed have all been reported to influence
the rates of use of specific definitive treatment modalities for the treatment of clinically localized prostate carcinoma.²⁻⁷

Permanent prostate brachytherapy, as a treatment modality for clinically localized prostate carcinoma, is recommended as monotherapy for patients with T1–T2a disease, with a prostate-specific antigen (PSA) level ≤ 10 ng/mL, and with a Gleason score ≤ 6. Permanent prostate brachytherapy is also recommended with supplemental EBRT for patients with higher-risk features.⁸⁻¹⁰ In the last decade, and possibly related to excellent outcome comparable to prostatectomy and EBRT,¹¹⁻¹³ there has been an increased interest in treating early-stage prostate carcinoma with permanent prostate brachytherapy.¹⁴,¹⁵ The impact of the increased use of this treatment modality for clinically localized prostate carcinoma on the overall use of other definitive modalities (such as radical prostatectomy and EBRT), and of the previously reported regional, racial, marital status, and age-related variations in prostate carcinoma treatment, has not been well characterized. Therefore, we evaluated the relative rates of the use of specific definitive prostate carcinoma treatment modalities over time. Using the national Surveillance, Epidemiology, and End Results (SEER) registry data on men diagnosed between 1995–2000, we sought to determine whether relative rates of radical prostatectomy and EBRT declined while rates of permanent prostate brachytherapy increased. We also sought to determine whether this phenomenon was consistent throughout variations in geographic region, race/ethnicity, marital status, and age.

MATERIALS AND METHODS

The National Cancer Institute developed and maintains the SEER 12 registries, a population-based cancer registry system, to collect data regarding cancer incidence, treatment, and mortality. SEER 12 records data from 12 geographic sites including 6 states (Connecticut, Iowa, New Mexico, Utah, Alaska, and Hawaii) and 6 metropolitan areas (metropolitan Atlanta, metropolitan Detroit, Seattle/Puget Sound, Los Angeles, San Francisco, and San Jose/Monterey). The populations in these areas are generally representative of the national population. Data sources are predominantly hospitals and hospital-based outpatient clinics.¹⁶

Localized/regional stage prostate carcinoma cases (International Classification of Diseases–9th revision [ICD-9] code 185, and International Classification of Diseases for Oncology [ICD-O]-2 codes 8140) that were diagnosed between 1995 and 2000 were evaluated. Because the goal was to evaluate differences among specific definitive therapies, those cases whose treatment was watchful waiting (n = 40,112) were eliminated, resulting in a sample of 83,631 cases. Cases with missing data regarding treatment (n = 2,009 [2.4%]) or race (n = 842 [1.0%]) were excluded to achieve a final sample size of 80,780 cases. The analyzed treatment modalities were EBRT, permanent prostate brachytherapy, combined permanent prostate-brachytherapy and EBRT, radical prostatectomy, and radical prostatectomy with postoperative EBRT.

Analysis

Univariate frequencies described the variables of interest, all of which were ordinal or categorical. The weighted case counts were cross-tabulated and graphed. A partitioned Pearson chi-square test for ordered columns was used for the unadjusted model of year and treatment. In the multivariate analysis, a multinomial logistic regression approach was employed to predict the type of treatment from year of treatment and demographic and clinical covariates, using 1995 as the base year and radical prostatectomy as the reference treatment category. The covariates included the following: marital status (married and nonmarried); age (4 categories: young [ages 40–55 yrs], middle-aged [ages 56–65 yrs], younger-old [ages 66–75 yrs], and older-old [ages > 75 yrs]), race (white, black, Hispanic, other); region (West [San Francisco, New Mexico, Utah, San Jose-Monterey, and Los Angeles], Northwest [Seattle/Puget Sound, Hawaii, and Alaska], Midwest [metropolitan Detroit and Iowa], and East [Connecticut and metropolitan Atlanta]); entire state versus metropolitan SEER location; and tumor grade (well differentiated, moderately differentiated, and poorly differentiated/undifferentiated). The reference groups were marital status (nonmarried [single, separated, divorced, widowed, and unknown]); age (middle-aged [ages 56–65 yrs]); race (white); region (West); location type (metropolitan area); year (1995); and tumor grade (moderately differentiated). Similar to the use of odds ratios (OR) in logistic regression, multinomial logistic regression estimates the relative risk ratios (RRR). The RRRs for each factor, relative to the base condition, can be interpreted much in the same way as OR. RRR values are presented with their 95% confidence intervals (95% CIs) as a measure of their precision. Stata 8 software (StataCorp, College Station, TX) was used for the data analyses.

RESULTS

In the current study cohort of 80,780 cases, 76.3% were white, 11.7% were black, 6.4% were Hispanic, and 5.6% were other (Table 1). Ninety percent of these men were ages 40–75 years, 77.7% were married, and 44.8% were from the western portion of the U.S. Approximately 74% were diagnosed with moderately dif-
FERENT PROSTATE BRACHYTHERAPY INFLUENCED THE USE OF THE
EXTERNAL-BEAM RADIATION THERAPY (EBRT) INCREASED YEARLY (P < 0.0001), WHEREAS THERE IS A PROPORTIONAL INCREASE
IN THE USE OF PERMANENT PROSTATE BRACHYTHERAPY BOTH
ALONE AND IN COMBINATION WITH EBRT (P < 0.0001).

Figure 2 illustrates the impact of permanent prostate
brachytherapy on regional variations in the use of
specific treatment modalities. The greatest decline in
the use of radical prostatectomy and EBRT, in con-
junction with the greatest increase in the use of per-
manent prostate brachytherapy alone and in combi-
nation with EBRT, was noted in the Eastern and
Northwestern portions of the U.S. (Figs. 2A, 2C). In the
West, which comprises nearly as many cases as the
other three regions combined, the use of EBRT ap-
peared to be more stable over time (Fig. 2D) (all Ps
< 0.01). Also within the West, the trade-off over time
between radical prostatectomy decreasing and perma-
nent prostate brachytherapy (with or without EBRT)
increasing is evident (Fig. 2D). The Midwest appears
to show a relatively smaller decline in the use of rad-
ical prostatectomy over time (Fig. 2B).

Figure 3 illustrates the impact of the increasing
use of permanent prostate brachytherapy on age vari-
ations among specific treatment modalities. Among
those in the cohort who were diagnosed between the
ages of 40–55 years and 56–65 years, radical prosta-
tectomy was the most common treatment modality
received. Among those who were diagnosed between
the ages of 66–75 years demonstrated the greatest trade-
offs between specific treatment modalities, with EBRT
and radical prostatectomy decreasing and permanent
prostate brachytherapy alone or in combination with
EBRT increasing over time (P < 0.0001).

The impact of the use of permanent prostate
brachytherapy on racial/ethnic variations in the use of
specific treatment modalities is illustrated in Figure 4.
In general, a relatively higher use of EBRT was noted
among the black and other racial/ethnic categories
compared with the white and Hispanic categories (P
< 0.0001). Among the four racial/ethnic categories,
the use of permanent prostate brachytherapy alone
and in combination with EBRT increased over time (P
< 0.0001). White men demonstrated the greatest use

| Table 1: Characteristics of Cases with Localized Prostate Carcinoma
SEER-12 1995–2000 (n = 80,780) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>No. of cases</td>
<td>%</td>
</tr>
<tr>
<td>Age yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–55</td>
<td>9557</td>
<td>11.8</td>
</tr>
<tr>
<td>56–65</td>
<td>27,758</td>
<td>34.4</td>
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<td>66–75</td>
<td>35,234</td>
<td>43.6</td>
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<tr>
<td>&gt; 75</td>
<td>8231</td>
<td>10.2</td>
</tr>
<tr>
<td>Race</td>
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<td></td>
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<tr>
<td>Black</td>
<td>9408</td>
<td>11.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5178</td>
<td>6.4</td>
</tr>
<tr>
<td>White</td>
<td>61,644</td>
<td>76.3</td>
</tr>
<tr>
<td>Other</td>
<td>4550</td>
<td>5.6</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>18,025</td>
<td>22.3</td>
</tr>
<tr>
<td>Married</td>
<td>62,755</td>
<td>77.7</td>
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<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East</td>
<td>13,746</td>
<td>17.0</td>
</tr>
<tr>
<td>Midwest</td>
<td>18,334</td>
<td>22.7</td>
</tr>
<tr>
<td>Northwest</td>
<td>12,543</td>
<td>15.5</td>
</tr>
<tr>
<td>West</td>
<td>36,157</td>
<td>44.8</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated (Gleason score 2–4)</td>
<td>4515</td>
<td>5.6</td>
</tr>
<tr>
<td>Moderately differentiated (Gleason score 5–7)</td>
<td>59,827</td>
<td>74.1</td>
</tr>
<tr>
<td>Poorly differentiated/undifferentiated (Gleason score 8–10)</td>
<td>16,438</td>
<td>20.4</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>38,940</td>
<td>48.2</td>
</tr>
<tr>
<td>EBRT</td>
<td>27,207</td>
<td>33.7</td>
</tr>
<tr>
<td>Prostate brachytherapy</td>
<td>6451</td>
<td>8.0</td>
</tr>
<tr>
<td>Radical prostatectomy with radiation</td>
<td>2240</td>
<td>2.8</td>
</tr>
<tr>
<td>Prostate brachytherapy with EBRT</td>
<td>5942</td>
<td>7.4</td>
</tr>
</tbody>
</table>

SEER: Surveillance, Epidemiology, and End Results program; EBRT: external-beam radiation therapy.
of permanent prostate brachytherapy (with and without EBRT) as well as the greatest trade-offs over time between specific treatment modalities, with EBRT and radical prostatectomy decreasing and permanent prostate brachytherapy alone or in combination with EBRT increasing (Fig. 4C).

Figure 5 illustrates the use of specific treatment modalities stratified by marital status (married vs. nonmarried). Compared with other treatment options, married men more commonly received a radical prostatectomy ($P < 0.0001$). Nonmarried men received EBRT and radical prostatectomy with approximately equal frequency, although the relative use of radical prostatectomy and EBRT declined over the treatment period for both married and unmarried men ($P < 0.0001$). The decline in the use of radical prostatectomy and EBRT appears to be proportional to the increase in the use of permanent prostate brachytherapy with and without EBRT. However, the decline in the use of radical prostatectomy for married men appears to have plateaued in 1998.

The RRRs for the specific treatment modalities shown in Figure 6 were obtained from the multivariable model, which was adjusted for age, race/ethnicity, marital status, region of the country, metropolitan SEER site, and tumor grade. The RRRs describe relative increases in other specific definitive therapies in a given year compared with radical prostatectomy. Higher RRRs do not describe absolute differences in the use of treatment modalities. Compared with the baseline year of 1995, the risk of receiving permanent prostate brachytherapy, alone or in combination with EBRT, relative to receiving radical prostatectomy increased significantly over time. The RRR of receiving permanent prostate brachytherapy rather than radical prostatectomy increased yearly to reach 7.4 ($P < 0.0001$; 95% CI, 6.50–8.45) in the year 2000. The RRR of receiving permanent prostate brachytherapy in combination with EBRT rather than radical prostatectomy increased yearly to reach 6.2 ($P < 0.0001$; 95% CI, 5.41–7.16) in the year 2000. No significant change over time was noted for the RR of receiving a radical prostatectomy in combination with EBRT over the RR of receiving radical prostatectomy alone ($P > 0.05$). The RRR of receiving EBRT alone increased slightly to reach 1.16 (95% CI, 1.1–1.2) in 2000.

Racial/ethnic and regional variations in the RR of receiving permanent prostate brachytherapy over a radical prostatectomy also were noted. Compared with whites, nonwhites (blacks, Hispanics, and other) were somewhat more likely to receive EBRT and somewhat less likely to receive permanent prostate brachytherapy. Hispanic men were significantly less likely to receive permanent prostate brachytherapy over a radical prostatectomy, either alone (RRR = 0.52; 95% CI, 0.44–0.61) or in combination with EBRT (RRR = 0.51; 95% CI, 0.43–0.60). Compared with unmarried men, married men were less likely to receive permanent prostate brachytherapy (RRR = 0.69; 95% CI, 0.65–0.74), EBRT (RRR = 0.57; 95% CI, 0.55–0.59), or the 2 therapies combined (RRR = 0.78; 95% CI, 0.73–0.84) relative to radical prostatectomy. Compared with the West, the RR of receiving permanent prostate brachytherapy alone (RRR = 4.7; 95% CI, 4.3–5.1) or in

<p>| Table 2: Unadjusted Model of Use of Specific Treatment Modalities over Time (1995–2000) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>1995 (%)</th>
<th>1996 (%)</th>
<th>1997 (%)</th>
<th>1998 (%)</th>
<th>1999 (%)</th>
<th>2000 (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP</td>
<td>6210 (54.4)</td>
<td>6290 (52.1)</td>
<td>6445 (49.3)</td>
<td>6319 (45.5)</td>
<td>6572 (45.9)</td>
<td>6704 (44.3)</td>
<td>38,940 (48.2)</td>
</tr>
<tr>
<td>EBRT</td>
<td>4281 (37.5)</td>
<td>4345 (36.0)</td>
<td>4405 (33.7)</td>
<td>4616 (33.2)</td>
<td>4866 (32.0)</td>
<td>4694 (31.0)</td>
<td>27,207 (33.7)</td>
</tr>
<tr>
<td>RP + radiation</td>
<td>368 (3.2)</td>
<td>375 (3.1)</td>
<td>383 (2.9)</td>
<td>378 (2.7)</td>
<td>371 (2.4)</td>
<td>365 (2.4)</td>
<td>19,075 (2.4)</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>296 (2.6)</td>
<td>535 (4.4)</td>
<td>932 (7.1)</td>
<td>1267 (9.1)</td>
<td>1524 (10.0)</td>
<td>1897 (12.5)</td>
<td>5942 (7.4)</td>
</tr>
<tr>
<td>Brachytherapy + EBRT</td>
<td>256 (2.2)</td>
<td>521 (4.3)</td>
<td>916 (7.0)</td>
<td>1311 (9.4)</td>
<td>1455 (9.6)</td>
<td>1483 (9.8)</td>
<td>5942 (7.4)</td>
</tr>
<tr>
<td>Total</td>
<td>11,411</td>
<td>12,066</td>
<td>13,081</td>
<td>13,891</td>
<td>15,188</td>
<td>15,143</td>
<td>80,780</td>
</tr>
</tbody>
</table>

RP: radical prostatectomy; EBRT: external-beam radiation therapy.

*The distribution of cases receiving different specific treatment modalities varied significantly over time (chi-square partition for dispersion = 99.72 on 4 degrees of freedom [$P < 0.0001$]).
FIGURE 2. (A, B) Weighted counts of cases with prostate carcinoma, diagnosed in the East and Midwest, receiving five different treatment modalities from 1995 to 2000. The counts were weighted to calendar year 2000 levels for each region. (C, D) Weighted counts of cases with prostate carcinoma, diagnosed in the Northwest and West, receiving five different treatment modalities from 1995 to 2000. The counts were weighted to calendar year 2000 levels for each region.

FIGURE 3. (A, B) Weighted counts of cases with prostate carcinoma receiving 5 different treatment modalities from 1995 to 2000, stratified by age group: ages 40–55 years and ages 56–65 years. The counts were weighted to calendar year 2000 levels for each age group. (C, D) Weighted counts of cases with prostate carcinoma receiving 5 different treatment modalities from 1995 to 2000, stratified by age group: ages 66–75 years and age > 75 years. The counts were weighted to calendar year 2000 levels for each age group.
combination with EBRT (RRR = 4.7; 95% CI, 4.3–5.1) over a radical prostatectomy was greater in the East. Compared with the West, in the Midwest the RRR of receiving permanent prostate brachytherapy alone was 1.8 (95% CI, 1.6–1.9) and was 1.7 (95% CI, 1.6–1.8) in combination with EBRT, compared with radical prostatectomy. Compared with the West, in the Northwest, the RRR of receiving permanent prostate brachytherapy alone was 3.8 (95% CI, 3.5–4.1) and was 1.9 (95% CI, 1.7–2.1) in combination with EBRT over a radical prostatectomy.

DISCUSSION
The results of the current study demonstrate that the use of radical prostatectomy and EBRT declined from 1995 to 2000, whereas the use of permanent prostate brachytherapy increased. These results suggest a significant shift in treatment approach to clinically localized prostate carcinoma over the study period. Although the benefits of permanent prostate brachytherapy as a monotherapy may not extend to all clinical status T1–T2a cases, those with a higher PSA level (> 10 ng/mL) and higher Gleason scores (> 6) have been reported to respond favorably.13 It is unknown whether these findings are the result of an overall increase in the patients’ desires for less invasive procedures or are the result of providers’ increased use of new technology. Over the last two decades, other minimally invasive procedures (i.e., laparoscopic and robotic surgery) also have increased in popularity.17–20 Placed in this context, the increased use of permanent prostate brachytherapy may be the result of men who desire treatments that are less invasive and therefore less intrusive on their quality of life (QOL). In this regard, further research is required to understand why this phenomenon of an overall decline in the use of radical prostatectomy and EBRT with increased permanent prostate brachytherapy is present.

Racial/Ethnic Treatment Trends
Racial variations in the use of specific treatment modalities for clinically localized/regional prostate carcinoma have been reported.2,7 In the current study, racial variations in treatment approaches were still apparent, such that nonwhite men were less likely to receive permanent prostate brachytherapy relative to white men after controlling for age, marital status, urbanicity, region, and tumor grade. Although the optimal treatment modality for localized/regional prostate carcinoma has not been determined and is subject to a physician’s clinical opinion and a patient’s...
priorities, it is possible that persistent racial variations in the use of specific treatment modalities signal inequities in health care access, in education regarding treatment options, or in health care delivery. Therefore, these data underscore the importance of understanding how men with prostate carcinoma make treatment decisions. Our observed trends warrant continued monitoring for future shifts, and further research to ensure the appropriate and timely treatment for all men, particularly with respect to cultural/racial/ethnic differences.

Regional Treatment Trends
Regional variations in the use of radical prostatectomy and EBRT have been previously reported. However, to our knowledge little is known concerning regional variations in the use of permanent prostate brachytherapy. The observed regional variations suggest that the adoption of permanent prostate brachytherapy as a treatment approach for clinically localized prostate carcinoma occurred most quickly in the East, spreading in other regions of the country more slowly. Despite the rapidity with which information and innovative techniques may be disseminated, it is noteworthy that this definite regional effect, which is unlikely to be due to a case-mix or patient characteristics, and more likely to be a reflection of regional variations in provider expertise or practice style.

Age-Related Treatment Trends
For all age categories, the use of permanent prostate brachytherapy alone or in combination with EBRT increased over time, whereas the use of other treatment modalities (radical prostatectomy and EBRT) decreased. This finding was greatest among men who were diagnosed between the ages of 66 and 75 years. This finding is consistent with that of Bubolz et al. who reported that the use of permanent prostate brachytherapy increased with age. Those authors also reported that permanent prostate brachytherapy is a substitute for radical prostatectomy in older men. This finding of an increase in the use of permanent prostate brachytherapy may be the result of controversy over the benefits of the aggressive treatment of prostate carcinoma in older men, including many urologists who recommend a conservative treatment approach for older men and men who are unwilling to accept a worse QOL to achieve a potential increased survival over time. It is possible that older men consider permanent prostate brachytherapy as a treatment modality that may provide the best of both worlds: increased survival with the least impact on QOL. However, further research is required in this area to determine the factors related to this observation.

Marital Status-Related Treatment Trends
In addition, we found differences in the impact of brachytherapy by marital status. Overall, married men...
more commonly received a radical prostatectomy, whereas nonmarried men received EBRT and radical prostatectomy equally. This finding may be a reflection of different values regarding the trade-off between quantity of life and QOL between married and nonmarried men. Volk et al.24 reported that wives were more willing to trade off QOL for quantity of their husbands’ lives. Compared with their wives, men valued the risks of treatment side effects (impotence and incontinence) to a greater extent and were willing to trade off quantity of life for QOL. The greater use of radical prostatectomy in married men may be a reflection of the impact of spouses on the treatment decision.

Study Limitations
In determining the significance of our findings, some limitations should be considered. Within SEER, socioeconomic data (i.e., income, education, and insurance status) are not included. Therefore, our findings may in part be the result of variations in income, education, and insurance status. Although socioeconomic factors have been suggested as a possible cause for the racial/ethnic variations in prostate carcinoma treatment observed, to the best of our knowledge these factors have not been found to influence overall age and regional variations in the use of specific treatment modalities for prostate carcinoma. Also, within SEER, comorbid disease status is not reported. This is important because choice of treatment may be influenced by comorbid disease status. Permanent prostate brachytherapy is suggested as a kindler and gentler treatment compared with radical prostatectomy.25 Therefore, one would expect a greater use of permanent prostate brachytherapy among men with high comorbidity. Further research is required to determine the significance of the relation between socioeconomic factors and comorbid disease status with regard to our findings of region, age, marital status, and racial variations in the use of permanent prostate brachytherapy.

Permanent prostate brachytherapy as a treatment modality for clinically localized prostate carcinoma continues to gain popularity over other treatment modalities. If the trend toward greater utilization of prostate brachytherapy continues, it may lead to a fundamental shift toward more conservative approaches in the management of prostate carcinoma.

REFERENCES


