Survivorship Beyond Convalescence: 48-Month Quality-of-Life Outcomes After Treatment for Localized Prostate Cancer

John L. Gore, Lorna Kwan, Steve P. Lee, Robert E. Reiter, Mark S. Litwin

Decision making for treatment of localized prostate cancer is often guided by therapeutic side-effect profiles. We sought to assess health-related quality-of-life outcomes for patients 48 months after treatment for localized prostate cancer. Men treated for localized prostate cancer (N = 475) were evaluated before treatment and at 11 intervals during the 48 months after intervention. Changes in mean health-related quality-of-life scores and the probability of regaining baseline levels of health-related quality of life were compared between treatment groups. All statistical tests were two-sided. Urinary incontinence was more common after prostatectomy (n = 307) than after brachytherapy (n = 90) or external beam radiation therapy (n = 78) (both P < .001), whereas voiding and storage urinary symptoms were more prevalent after brachytherapy than after prostatectomy (both P < .001). Sexual dysfunction profoundly affected all three treatment groups, with a lower likelihood of regaining baseline function after prostatectomy than after external beam radiation therapy or brachytherapy (P < .001). Bowel dysfunction was more common after either form of radiation therapy than after prostatectomy. These results may guide decision making for treatment selection and clinical management of patients with health-related quality-of-life impairments after treatment for localized prostate cancer.


In 2009, the immense public health burden of prostate cancer perseveres. Because no treatment has proven superiority in prostate cancer control, treatment side-effect profiles often determine treatment choices (1). Prospective studies (2,3) have characterized 2-year health-related quality-of-life outcomes among patients who were treated for clinically localized prostate cancer and have demonstrated treatment-specific impairments in urinary function, sexual function, and bowel function. Patient recovery profiles marked this 2-year period as one of convalescence. We hypothesized that the recovery documented in those prospective assessments would continue for surgical patients. Conversely, we hypothesized that the third and fourth years after radiation therapy would capture the onset of progressive functional decline as a result of cumulative radiation-induced injury. Herein, we describe the health-related quality-of-life outcomes for patients 48 months after treatment for localized prostate cancer.

This analysis expands on previous work (2) that examined 2-year outcomes for patients treated for localized prostate cancer with radical prostatectomy (n = 307), external beam radiation therapy (n = 78), or brachytherapy (n = 90). Participant inclusion and exclusion criteria have been described previously (2). Briefly, subjects completed a comprehensive assessment of generic and prostate cancer–specific health-related quality of life before treatment and completed follow-up questionnaires at 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, and 48 months after treatment to capture maximal fluctuations in functional convalescence. All statistical tests were two-sided. Subjects who completed a 48-month survey were older (mean age ± SD = 63.7 ± 8.1 years) than those who did not (60.2 ± 7.1 years) (P < .001); responders and nonresponders did not differ in other sociodemographic or clinical characteristics. We assessed generic health-related quality of life with the Medical Outcomes Study Short Form-36 (4), from which we derived physical and mental composite summary scores. The physical and mental composite scores measure generic, physical, and mental health and are standardized to the general US population with a normative mean of 50 and standard deviation of 10. Thus, a score of less than 50 denotes physical or mental function that is worse than the US average. We evaluated prostate cancer–specific health-related quality of life with the University of California–Los Angeles (UCLA) Prostate Cancer Index and the American Urological Association Symptom Index (AUASI) (5,6). The Prostate Cancer Index quantifies urinary, sexual, and bowel dysfunction, with a higher score indicating better function. Conversely, higher scores on the AUASI indicate worse storage and voiding urinary symptoms. We examined mean scores over time and the subject’s likelihood of regaining baseline function after treatment, as defined by a score within 10% of the baseline score. We modeled this binary outcome with nonlinear mixed models with random slopes and intercepts to evaluate the association between treatment modality and the likelihood of regaining baseline function. Other covariates were included in the models as fixed effects. In addition, we incorporated an interaction between treatment type and the duration of follow-up and between treatment type and the squared value of the duration of follow-up to control for the time dependence of functional recovery.

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After estimation, we calculated the interval probability of regaining baseline function from the model coefficients and created smoothed probability plots (7). All protocols were approved by the UCLA institutional review board and were compliant with the Health Insurance Portability and Accountability Act. Each participant provided written informed consent.

Patients who underwent prostatectomy were younger, more highly educated, and had fewer comorbid conditions than those who underwent external beam radiation therapy or brachytherapy (Table 1). External beam radiation therapy patients had more aggressive tumor characteristics at baseline, with higher pretreatment mean levels of prostate-specific antigen and a higher prevalence of prostate cancers that were palpable on rectal examination (ie, stage T2 or greater) at presentation.

Although brachytherapy was associated with a lower likelihood of regaining baseline AUASI score than radical prostatectomy, the probability of regaining baseline function improved throughout the 48-month study period. Conversely, subjects who underwent external beam radiation therapy demonstrated progressive worsening of urinary function related to storage and voiding symptoms. Patients treated with either type of radiation therapy experienced minor impairments in urinary control (Figures 1, D, and 2, D); continence was most profoundly affected among prostatectomy patients (P < .001). After prostatectomy, the likelihood of continued functional recovery of continence beyond 30 months was low. Sexual dysfunction profoundly affected all three treatment groups (Figures 1, E, and 2, E). Patients treated with external beam radiation therapy suffered progressive decline in sexual function throughout the 48 months after treatment. Alternatively, patients treated with brachytherapy demonstrated continued, if slight, improvement in sexual function over time. Interpretation of sexual function outcomes among radical prostatectomy patients was confounded by their superior baseline mean scores. Despite better mean scores, the likelihood that prostatectomy patients would regain baseline sexual function remained minimal 4 years after surgery (P < .001). Patients who were treated with either type of radiation therapy reported more bowel dysfunction than prostatectomy patients (Figures 1, F, and 2, F).

Recovery from functional impairments followed a varied trajectory after treatment for clinically localized prostate cancer. Urinary dysfunction varied statistically and clinically significantly by treatment type. Incontinence was more common after surgery, but storage and voiding symptoms were more prevalent after radiation therapy. From initial postoperative trends in prospective assessments, other investigators have projected continued improvement in urinary control beyond 24 months after radical prostatectomy (2,3). However, we found that urinary control recovery

### Table 1. Demographic and clinical characteristics of the study sample (N = 475)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prostatectomy (n = 307)</th>
<th>EBRT (n = 78)</th>
<th>Brachytherapy (n = 90)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (±SD), y</td>
<td>60.1 ± 7.2</td>
<td>70.8 ± 7.3</td>
<td>68.4 ± 6.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race or ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>262 (85.3)</td>
<td>66 (84.6)</td>
<td>71 (78.9)</td>
<td>.34</td>
</tr>
<tr>
<td>Not white</td>
<td>45 (14.7)</td>
<td>12 (15.4)</td>
<td>19 (21.1)</td>
<td></td>
</tr>
<tr>
<td>Married or partnered, No. (%)</td>
<td></td>
<td>256 (83.4)</td>
<td>64 (82.0)</td>
<td>.75</td>
</tr>
<tr>
<td>Education level, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Less than college</td>
<td>80 (26.4)</td>
<td>22 (28.2)</td>
<td>36 (40.4)</td>
<td></td>
</tr>
<tr>
<td>College or more</td>
<td>223 (73.6)</td>
<td>56 (71.8)</td>
<td>53 (59.6)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity count, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td>.60</td>
</tr>
<tr>
<td>0</td>
<td>117 (38.1)</td>
<td>22 (28.2)</td>
<td>31 (34.4)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>109 (35.5)</td>
<td>32 (41.0)</td>
<td>34 (37.8)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>81 (26.4)</td>
<td>24 (30.8)</td>
<td>25 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Mean PSA level (±SD), ng/mL</td>
<td></td>
<td>7.3 ± 6.9</td>
<td>13.6 ± 21.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean biopsy Gleason score (±SD)</td>
<td></td>
<td>6.3 ± 0.9</td>
<td>6.7 ± 1.0</td>
<td>.002</td>
</tr>
<tr>
<td>Tumor stage, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td>.003</td>
</tr>
<tr>
<td>T1</td>
<td>216 (70.4)</td>
<td>42 (53.9)</td>
<td>71 (78.9)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>90 (29.3)</td>
<td>34 (43.6)</td>
<td>17 (18.9)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>1 (0.0)</td>
<td>2 (2.6)</td>
<td>2 (2.2)</td>
<td></td>
</tr>
</tbody>
</table>

* EBRT = external beam radiation therapy; PSA = prostate-specific antigen.
† Categorical variables were compared with χ² analysis and Fisher exact test. Continuous variables were compared with independent samples t tests. All statistical tests were two-sided.

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**From the Editors**

Prior knowledge
In the absence of definitive results from randomized controlled clinical trials, treatment for localized prostate cancer is often selected by use of therapeutic side effects.

Study design
Questionnaire-based study of health-related quality-of-life outcomes for patients 48 months after treatment for localized prostate cancer that included prostatectomy, brachytherapy, or external beam radiation therapy. Questionnaires were completed before treatment and at 11 different times during the 48 months after treatment.

Contribution
Urinary incontinence was more common after prostatectomy. Voiding and storage urinary symptoms were more common after brachytherapy. Sexual dysfunction profoundly affected all three treatment groups, with the lowest likelihood of regaining baseline function after prostatectomy. Bowel dysfunction was more common after either form of radiation therapy.

Implications
Results from this study provide information that can be used to select the best treatments for individual patients with prostate cancer.

Limitations
Patients may have undergone treatments that were discordant with preexisting conditions (eg, subjects treated with radiation therapy had worse bowel function scores at baseline, which grew worse with treatment). Subjects whose cancer recurred were not analyzed separately, which might have biased the results toward poorer outcomes.
indicate better urinary control, sexual function, or bowel function. RP = radical prostatectomy; EBRT = external beam radiation therapy.

Subjects may undergo treatment discordant with preexisting detrainers in their health-related quality of life (eg, brachytherapy in men with severe baseline voiding urinary symptoms). In our sample, external beam radiation therapy subjects had worse bowel function scores at baseline. These preexisting symptoms may have predisposed those who received either radiation modality to more severe bowel dysfunction after treatment. Concomitant with primary therapy, men who receive external beam radiation therapy or brachytherapy may have received androgen deprivation therapy. In our sample, hormone therapy was administered to 59% of subjects who received external beam radiation therapy and 23% of subjects who received brachytherapy. Those with more aggressive tumor characteristics more commonly receive androgen deprivation with radiation, which may impair both generic and disease-specific health-related quality of life (17,18). Similarly, risk-stratified men may undergo brachytherapy with an external beam radiation therapy boost, which is known to confer worse health-related quality of life than either brachytherapy or external beam radiation therapy alone (8,17,19). Furthermore, we did not separately examine subjects whose cancer recurred, which also impacts both general well-being and cancer-specific domains (12,20). Inclusion of these subjects may peaked 30 months after surgery. This finding may guide clinical decision making regarding the optimal timing of secondary therapies. Reassurance may assuage the worries of those with early impairments, but it will not suffice when the dysfunction persists. Depending on the severity of the dysfunction, patients and their clinicians may consider interventions ranging from urethral sling or artificial urinary sphincter. Depending on the severity of the dysfunction, patients and their clinicians may consider interventions ranging from urethral sling or artificial urinary sphincter. These preexisting symptoms may have predisposed those who received either radiation modality to more severe bowel dysfunction after treatment. Concomitant with primary therapy, men who receive external beam radiation therapy or brachytherapy may have received androgen deprivation therapy. In our sample, hormone therapy was administered to 59% of subjects who received external beam radiation therapy and 23% of subjects who received brachytherapy. Those with more aggressive tumor characteristics more commonly receive androgen deprivation with radiation, which may impair both generic and disease-specific health-related quality of life (17,18). Similarly, risk-stratified men may undergo brachytherapy with an external beam radiation therapy boost, which is known to confer worse health-related quality of life than either brachytherapy or external beam radiation therapy alone (8,17,19). Furthermore, we did not separately examine subjects whose cancer recurred, which also impacts both general well-being and cancer-specific domains (12,20). Inclusion of these subjects may
have biased our sample toward worse outcomes. However, we sought to characterize long-term health-related quality of life after treatment for clinically localized prostate cancer, inclusive of factors inherent to the treatment choice. This method of analysis certainly introduces bias, but it also facilitates valid comparison of the expected outcomes of an average subject undergoing treatment for localized prostate cancer.

We have characterized long-term health-related quality-of-life outcomes after treatment for clinically localized prostate cancer. Capturing baseline function before treatment permitted comparison of interval mean scores with pretreatment function. With assessments through 48 months after treatment, we encapsulated both the convalescent period immediately after therapy and the subsequent period characterized by functional improvement, functional plateau, or the onset of functional decline, depending on the primary therapy and the health-related quality-of-life domain assessed. These results may guide decision making for treatment selection and clinical management of patients with health-related quality-of-life impairments after treatment for localized prostate cancer.

References

Figure 2. Smoothed probability plots of the interval likelihood of returning to baseline health-related quality of life as measured by various instruments. A and B) Medical Outcomes Study Short Form-36. C) American Urological Association (AUA) Symptom Index. D–F) University of California–Los Angeles Prostate Cancer Index. RTB = return to baseline; RP = radical prostatectomy; EBRT = external beam radiation therapy.


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