Comprehensive Comparison of Health-Related Quality of Life After Contemporary Therapies for Localized Prostate Cancer

By John T. Wei, Rodney L. Dunn, Howard M. Sandler, P. William McLaughlin, James E. Montie, Mark S. Litwin, Linda Nyquist, and Martin G. Sanda

Purpose: Health-related quality-of-life (HRQOL) concerns are pivotal in choosing prostate cancer therapy. However, concurrent HRQOL comparison between brachytherapy, external radiation, radical prostatectomy, and controls is hitherto lacking. HRQOL effects of hormonal adjuvants and of cancer control after therapy also lack prior characterization.

Patients and Methods: A cross-sectional survey was administered to patients who underwent brachytherapy, external-beam radiation, or radical prostatectomy during 4 years at an academic medical center and to age-matched controls. HRQOL among controls was compared with therapy groups. Comparison between therapy groups was performed using regression models to control covariates. HRQOL effects of cancer progression were evaluated.

Results: One thousand fourteen subjects participated. Compared with controls, each therapy group reported bothersome sexual dysfunction; radical prostatectomy was associated with adverse urinary HRQOL; external-beam radiation was associated with adverse bowel HRQOL; and brachytherapy was associated with adverse urinary, bowel, and sexual HRQOL ($P < .0002$ for each). Hormonal adjuvant symptoms were associated with significant impairment ($P < .002$). More than 1 year after therapy, several HRQOL outcomes were less favorable among subjects after brachytherapy than after external radiation or radical prostatectomy. Progression-free subjects reported better sexual and hormonal HRQOL than subjects with increasing prostate-specific antigen ($P < .0001$).

Conclusion: Long-term HRQOL after prostate brachytherapy showed no benefit relative to radical prostatectomy or external-beam radiation and may be less favorable in some domains. Hormonal adjuvants can be associated with significant impairment. Progression-free survival is associated with HRQOL benefits. These findings facilitate patient counseling regarding HRQOL expectations and highlight the need for prospective studies sensitive to urinary irritative and hormonal concerns in addition to incontinence, sexual, and bowel HRQOL domains.


Health-related quality-of-life (HRQOL) outcomes after therapy is a pivotal concern among localized prostate cancer patients and their physicians. The need to re-evaluate comparative HRQOL expectations has been fueled by contemporary refinement of standard local therapies, such as the evolution of anatomic prostatectomy and development of three-dimensional (3D) conformal radiation, and by concurrent development of ultrasound-guided, transperineal prostate brachytherapy. Despite paucity of published data that directly compares patient-reported HRQOL after prostate brachytherapy with contemporary radical prostatectomy or external-beam radiation, brachytherapy has been increasingly used and is marketed with largely unsubstantiated claims regarding superior HRQOL.1-2 There have been few studies to describe patient-reported HRQOL after brachytherapy.3-5 However, a comparison of the three most common contemporary therapies for localized prostate cancer (brachytherapy, external-beam radiation, and radical prostatectomy) has not been previously reported in a large cohort. Such data are necessary to inform patients fully about treatment options and to address individual patient preferences for the various possible outcomes.5

Other pivotal components of expected HRQOL outcomes after localized prostate cancer therapies are also in need of refined assessment. Prior evaluations that compared HRQOL after radical prostatectomy and radiation therapy found significant differences in prostate-related HRQOL.

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domains, including urinary incontinence, bowel function, and sexual function. However, these reports did not assess either urinary function components other than incontinence (such as urinary obstruction and irritative voiding) or symptoms related to hormonal therapy, which is increasingly used as a primary therapy adjunct. Finally, possible HRQOL effects of localized prostate cancer control compared with treatment failure have not been previously described. These concerns warrant evaluation to facilitate patient counseling in regard to HRQOL outcome expectations after contemporary therapy.

We hypothesized that long-term, durable HRQOL outcomes differ after brachytherapy, external-beam radiation, or radical prostatectomy for localized prostate cancer, and that cancer control after these therapies has different HRQOL than prostate cancer progression. To test these hypotheses, we performed a cross-sectional HRQOL assessment in patients who had undergone brachytherapy, external-beam radiation, or radical prostatectomy for localized prostate cancer during a 4-year period at an institution with expertise in each of these therapies. Our findings provide a framework for informing patients with regard to HRQOL expectations after contemporary therapies for localized prostate cancer and identify urinary irritative symptoms and androgen-deprivation concerns as hitherto underappreciated, yet significant, prostate cancer HRQOL components.

PATIENTS AND METHODS

Subjects

All patients who had undergone either brachytherapy, external-beam radiation, or radical prostatectomy as primary therapy for localized prostate cancer during a 4-year period (June 1, 1995, to May 31, 1999) at the University of Michigan, Departments of Radiation Oncology and Urology-Surgery, were offered participation in this institutional review board–approved cross-sectional survey. This time interval was selected to ensure pre-established technical expertise in each of the three interventions. At least 20 procedures per year were performed in each treatment group during this interval, and more than 30 procedures had been performed during the 3-year period preceding this interval. Eligible cohorts in this time interval included 114 consecutive patients who underwent brachytherapy, 203 consecutive patients who underwent external-beam radiation, and 896 consecutive patients who underwent radical prostatectomy. Patients treated for prostate neoplasms other than adenocarcinoma and patients who received external-beam radiation for metastatic disease were excluded. A control group that consisted of 142 male volunteers was identified from the Pepper Center Subjects Registry at the University of Michigan Geriatric Center; the number of available registrants in the Pepper Center Registry restricted control group size. Enrollees in this registry are community-dwelling older adults who had agreed to be contracted for research studies and provide demographic and health status information, including history of prostate cancer and surgery. Preliminary screening of the registry data was conducted to identify a cancer-free and surgery-free sample that was frequency matched to the treatment group by decade of age. Each eligible patient and control was mailed a letter of introduction from the study investigators, an institutional review board–approved consent form, a five-dollar cash incentive, and a composite survey that comprised the RAND 36-Item Health Survey 1.0 (RAND SF-36), the Functional Assessment of Cancer Therapy–General (FACT-G), Functional Assessment of Cancer Therapy–Prostate (FACT-P) cancer subscale, and the Expanded Prostate cancer Index Composite (EPIC), an expanded version of the University of California, Los Angeles prostate cancer index (UCLA-PCI).

Techniques of Primary Therapy

External-beam radiation was accomplished using a 3D conformal technique, as described previously. Briefly, patients were immobilized with customized foam devices and underwent a planning computed tomographic (CT) imaging scan in the treatment position. The CT data were entered into a 3D treatment-planning system, and various structures, including the prostate, seminal vesicles, bladder, rectum, and regional lymphatics, were identified and outlined on each slice by the physician. Custom blocking with cerrobend blocks or multileaf collimators was designed using beam’s eye view, and margins were adjusted to provide a minimum dose of 95% to the planning target volume. Treatments were delivered with 1.8-to-2.0-Gy daily fractions, 5 days a week, and varied from 55 Gy to 80 Gy, depending on the stage of disease and the level of pretreatment prostate-specific antigen (PSA).

Prostate brachytherapy was performed via a transperineal approach using transrectal ultrasound guidance as previously described and reflecting the modality presently in widespread use. Briefly, a preimplant prostate ultrasound was obtained to develop a custom treatment plan; a 160-Gy dose by iodine-125 implants was scheduled for each patient who was treated primarily with brachytherapy, and an 80-Gy dose by iodine-125 was scheduled for a subset of patients who underwent brachytherapy and adjuvant external-beam radiation (these subjects were considered to have undergone brachytherapy as primary therapy). Two to 4 weeks after an implant, a CT scan was obtained to allow accurate calculation of dose to prostate volume, and, when possible, full-dose delivery was evaluated by dosimetry after implantation.

Radical prostatectomy was performed using the technique described by Walsh. Briefly, after induction of general or epidural anesthesia, the prostate was removed entirely, with the seminal vesicles, via a lower midline incision, with extent of nerve preservation performed on the basis of intraoperative judgment, and an indwelling foley catheter was used to stent the urethrovessical anastomosis for 1 to 3 weeks after surgery.

Measures and Data Collection

To obtain a comprehensive assessment of HRQOL, five validated survey instruments were used to assess function and bother across a broad range of possible health states. These instruments were chosen because they had been developed to evaluate the varied and complementary health states encountered after therapy for localized prostate cancer. General HRQOL was evaluated with the RAND SF-36; general cancer-related quality of life (QOL) was assessed using FACT-G (version 4.0); and general prostate cancer–related QOL was measured using the FACT-P (version 4.0). Responses to the RAND SF-36 were summarized into two scales: the mental component summary and the physical component summary. These two scales are standardized to the United States population normative values, with a mean score of 50 and a SD of 10. Version 4 of FACT-G has 27 items, with a possible score range of 0 to 108, and the FACT-P has 12 items, with a possible score range of 0 to 48. Instruments for measuring health domains specifically relevant to localized prostate cancer disease and therapy
included the American Urological Association (AUA) Symptom Index to assess urinary obstruction; and the EPIC (a modified expansion of the UCLA-PCI) to measure urinary continence/irritation, bowel, sexual, and hormonal (androgen-deprivation) function as well as related bother. The EPIC instrument (50 items) was constructed by modifying the previously described UCLA-PCI (20 items) with the addition of items in regard to irritative urinary symptoms, irritative bowel symptoms, symptoms related to androgen deprivation, and items expanding the assessment of function-specific bother in each domain (to complement the existing domains of urinary, bowel, and sexual function). This expansion of the UCLA index was undertaken to expand the scope of the original UCLA-PCI into these areas after content analysis by an expert panel of three radiation oncologists, two prostate cancer nurses, two urological oncology surgeons, a survey researcher, and by prostate cancer patients. Painful or difficult urination, hot flashes, and rectal or urinary bleeding are examples of symptoms commonly encountered by prostate cancer patients that are not measured by UCLA-PCI but are assessed by EPIC. Complete reliability and validity evaluations were conducted for EPIC and have been described previously.

**Table 1. Demographic Data and Characteristics of Control Men and Localized Prostate Cancer Patients Stratified by Primary Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Brachytherapy</th>
<th>External-Beam Radiation</th>
<th>Radical Prostatectomy</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate, %</strong></td>
<td>73.7</td>
<td>72.4</td>
<td>74.9</td>
<td>78.9</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>67.2†</td>
<td>70.9†#‡</td>
<td>63.5*#</td>
<td>64.8‡</td>
</tr>
<tr>
<td>SD</td>
<td>7.3</td>
<td>7.2</td>
<td>7.8</td>
<td>8.6</td>
</tr>
<tr>
<td><strong>White, %</strong></td>
<td>91.5</td>
<td>93.8</td>
<td>94.3</td>
<td>95.5</td>
</tr>
<tr>
<td><strong>Currently married, %</strong></td>
<td>89.2</td>
<td>87.5</td>
<td>86.2</td>
<td>78.2</td>
</tr>
<tr>
<td><strong>Currently involved in a relationship, %</strong></td>
<td>94.0</td>
<td>94.5</td>
<td>93.9</td>
<td>90.0</td>
</tr>
<tr>
<td><strong>High-school education, %</strong></td>
<td>89.2*</td>
<td>95.0</td>
<td>92.9†</td>
<td>99.1*†</td>
</tr>
<tr>
<td><strong>Time since primary therapy, months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>21†</td>
<td>29*</td>
<td>30†</td>
<td>NA</td>
</tr>
<tr>
<td>Range</td>
<td>4-52</td>
<td>4-52</td>
<td>4-53</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Adjuvant/neoadjuvant hormone therapy, %</strong></td>
<td>51†</td>
<td>33*</td>
<td>28†</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Pretreatment serum PSA, ng/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>9.7</td>
<td>9.1</td>
<td>7.3</td>
<td>NA</td>
</tr>
<tr>
<td>SD</td>
<td>14.9</td>
<td>12.7</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td><strong>Biopsy gleason score distribution, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-6</td>
<td>68.3*</td>
<td>43.1*</td>
<td>59.6*</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>23.2</td>
<td>47.9</td>
<td>37.3</td>
<td></td>
</tr>
<tr>
<td>8-10</td>
<td>8.5</td>
<td>9.0</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical T-stage distribution, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>35.7*</td>
<td>35.8†</td>
<td>62.2*†</td>
<td>NA</td>
</tr>
<tr>
<td>T2</td>
<td>59.5</td>
<td>57.1</td>
<td>37.4</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>4.8</td>
<td>7.1</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
*†#‡Mean values or percent distributions that share a common symbol [in a single row corresponding to a single variable] are significantly different from each other (P < .01).

**Statistical Analysis**

Pair-wise comparisons were used to test for differences in demographic characteristics between each of the three treatment groups and the control group. Fisher’s exact test was used to test for differences between the groups for categorical variables, including response rate, race (white v nonwhite), marital status (currently married v not currently married), relationship status (currently involved in a relationship v not currently in relationship), education (high school graduate v test-retest reliability (product-moment correlations > 0.80), as did subscale scores that subdivided each domain into symptom severity measures (function subscales) and impairment measures (bother subscales). All eligible subjects were mailed a one-time survey packet that contained SF-36, FACT-G, FACT-P, EPIC, and AUA-SI and demographic questions in September 1999. Telephone reminders were used for patients who did not respond within 1 month of the initial survey mailing. Information in regard to prostate cancer severity before primary therapy (clinical tumor stage, Gleason grade, serum PSA), use of adjuvant therapy (eg, androgen deprivation), and subsequent recurrence-free survival was ascertained from hospital and outpatient office records (cancer recurrence status at time of survey was ascertainable in 96% of subjects). PSA progression was defined by American Society for Therapeutic Radiation Oncology criteria for external radiation or brachytherapy patients and by serum PSA of more than 0.2 ng/mL for radical prostatectomy patients. Accrual to the study was closed on December 1, 1999.
Higher scores are indicative of more severe obstructive voiding symptoms. Non-high school graduate); treatment groups were also evaluated for differences in Gleason sum (< 7, 7, and > 7), clinical tumor stage (T1, T2, and T3), and exposure to androgen deprivation by Fisher’s exact test (Table 1). Age differences between the control group and each treatment group were tested using the Student’s t test. Treatment differences for duration of follow-up and pretreatment PSA were evaluated using analysis of variance. An attempt was made to address the large number of comparisons by setting a more conservative level for alpha at 0.01.

The primary study analysis entailed comparing the HRQOL domain scores of controls to each treatment group (brachytherapy, external-beam radiation, and radical prostatectomy) using analysis of covariance, adjusting for age. Significance was set at alpha = 0.005 for this analysis (Table 2) because 10 different HRQOL domain scores were compared in this manner. In addition, Bonferroni adjustment was used (multiplying the unadjusted P value by three to yield the reported, Bonferroni-adjusted P value) to accommodate the three pair-wise comparisons of each HRQOL score (one for each of three therapy groups). The Bonferroni method was used in this comparison (of therapy groups to controls) because it has preferable characteristics to the other multiple comparison methods when only a subset of all possible pair-wise comparisons are to be considered.23

Subsequent analyses included the comparison of HRQOL between therapy groups (Table 3) and the comparison between PSA progression-free survivors with patients without progression (Table 4). These analyses focused on the six prostate cancer–specific HRQOL scores (FACT-P and five EPIC domains), each of which had been significant in comparison to controls in the age-adjusted analysis. Therefore, significance was set at alpha = 0.008 for these (Tables 3 and 4) analyses. A model-building process was used to test for differences between therapy groups while controlling for the significant effects of age, cancer severity (Gleason score, T-stage, and baseline PSA), time since intervention, and indicator of hormone therapy use. Each of these variables was treated as a possible explanatory variable in the model-building process, which was performed separately for each of the six evaluated HRQOL domains as follows. First, the optimal functional form for each explanatory variable was determined. Evaluated forms included linear, quadratic, and cubic versions, along with other forms that may have been suggested from the scatter plots and indicator models (eg, natural log transformation). Models with higher-level terms (quadratic and cubic) were examined using the test statistic for the highest-level term to determine whether this term was making a significant contribution. For comparisons between models with the same number of explanatory variables (eg, linear vs natural log), the coefficients of determination of the respective models were compared with the form that best fit the data. After the optimal functional form was identified, the Cook’s distance diagnostic values were analyzed to determine if one or a few values were having an undue influence on this form of the explanatory variable. In cases where an extremely influential observation was found, the models were rerun, excluding the influential observation to determine whether another functional form might have been more appropriate. Finally, an interaction between the explanatory variable and the cohort groups was inserted into the model. When significant, this interaction term was also included in the model-building process.

After the correct functional forms of each explanatory variable were found, they were included in a backward-selection model building process. The 5% significance level was used as the cutoff for inclusion into the model. For variables with higher-level terms included (eg, quadratic and cubic interactions), only the higher-level terms were evaluated for dismissal from the model. If these higher-level terms were targeted for dismissal, they were removed, despite the fact that they were significant in the bivariate functional form checking step. After the final models were developed, predicted means and associated 99% confidence intervals were calculated on the basis of population characteristics using equal weights for each of the three treatment groups. Cohort differences were explored using the Tukey-Kramer multiple adjustment method to adjust for the multiple between-therapy group comparisons performed. The Tukey-Kramer method was chosen to adjust for comparison between treatment groups because, in contrast to the comparison of controls to therapy groups in...
was evident in hormonal functioning between ERT and BT subjects over the time period studied. Differences (between therapy groups) in FACT-P and EPIC HRQOL domains did not change over time following the first year after therapy, with the exception of hormonal HRQOL (see below).

Table 3. Comparison of Long-Term HRQOL More Than 1 Year After Different Localized Prostate Cancer Therapies, Controlling for Age, Time Since Therapy, and Pretreatment Cancer Severity

<table>
<thead>
<tr>
<th>HRQOL Domain</th>
<th>Brachytherapy (n = 41)</th>
<th>External-Beam Radiation (n = 127)</th>
<th>Radical Prostatectomy (n = 570)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General prostate cancer HRQOL</td>
<td>FACT-P prostate component subscale</td>
<td>Mean 99% CI Mean 99% CI Mean 99% CI</td>
<td>32.4*† 30.1-34.8 36.4* 34.7-38.2 36.9† 35.8-38.2</td>
</tr>
<tr>
<td>Domain-specific prostate cancer HRQOL: EPIC summary scores</td>
<td>Urinary irritative</td>
<td>71.5† 67.4-75.5 84.2# 81.2-87.2 89.6# 88.3-91.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence</td>
<td>82.1 74.8-89.9 92.8* 87.1-98.5 77.5* 75.0-80.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel</td>
<td>76.0† 72.2-79.8 85.2# 82.5-87.8 93.2† 92.0-94.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual</td>
<td>26.9* 18.2-35.6 38.8* 32.3-45.3 33.9 29.6-38.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hormonal‡</td>
<td>83.7 79.4-88.0 87.2 84.4-89.9 90.9 89.5-92.3</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Mean HRQOL scale score values are shown that have been adjusted by multivariable modelling controlling for effects of age, time since therapy, pretreatment Gleason score, clinical T stage, pretreatment serum PSA, and use of hormonal therapy, with 99% confidence intervals in parentheses. Only those HRQOL measures which have been validated in prostate cancer subjects (EPIC, FACT-P) are included in this analysis. The model-adjusted scores for each domain are shown at the arbitrary mean follow-up of subjects included in this analysis (mean follow-up = 2.5 years after therapy for all subjects who were at least one year after therapy). Differences (between therapy groups) in FACT-P and EPIC HRQOL domains did not change over time following the first year after therapy, with the exception of hormonal HRQOL (see below).

*†#Mean values that share a common symbol are significantly different from each other in a pairwise comparison (significance set at alpha = 0.008 after Tukey adjustment for comparisons between three groups). For each of the significant differences noted, the observed P < .0005 after Tukey adjustment for multiple comparisons, except for the sexual HRQOL difference between ERT and BT, for which P = .007.

†Therapy group effect on EPIC hormonal domain was found to have a significant interaction with the duration of follow-up, even among subjects more than 1 year after therapy. Therefore, hormonal HRQOL differences between therapy groups varied over time of follow up: ERT subjects had worse hormonal functioning than RP subjects from 1 to 2.3 years after therapy but not thereafter, whereas BT patients had worse hormonal functioning than RP after 1.9 years. No difference was evident in hormonal functioning between ERT and BT subjects over the time period studied.

NOTE. Mean HRQOL scale score values adjusted for age and time since therapy by two-way analysis of covariance. Only those HRQOL measures that have been validated in prostate cancer subjects (EPIC, FACT-P) are tabulated.

<table>
<thead>
<tr>
<th>HRQOL Domain</th>
<th>Progression-Free (n = 779)</th>
<th>Increasing PSA (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General prostate cancer HRQOL</td>
<td>FACT-P prostate component subscale</td>
<td>Mean 99% CI Mean 99% CI</td>
</tr>
<tr>
<td>Domain-specific prostate cancer HRQOL, EPIC summary scores</td>
<td>Urinary irritative</td>
<td>87.4 86.1-88.6 85.6 81.8-89.4</td>
</tr>
<tr>
<td></td>
<td>Urinary incontinence</td>
<td>80.9 78.6-83.1 76.9 70.0-83.8</td>
</tr>
<tr>
<td></td>
<td>Bowel</td>
<td>90.9 89.8-92.0 90.2 88.6-93.7</td>
</tr>
<tr>
<td></td>
<td>Sexual</td>
<td>37.1 34.9-39.3* 26.7 20.1-33.3</td>
</tr>
<tr>
<td></td>
<td>Hormonal</td>
<td>90.3 89.2-91.4* 84.7 81.4-88.0</td>
</tr>
</tbody>
</table>

NOTE. Mean HRQOL scale score values adjusted for age and time since therapy by two-way analysis of covariance. Only those HRQOL measures that have been validated in prostate cancer subjects (EPIC, FACT-P) are tabulated.

*Denotes statistically significant differences in a given HRQOL domain between progression-free patients and those patients who had a PSA recurrence (significance set at alpha = 0.008). For each of the significant differences noted, the observed P ≤ .0001.

RESULTS

The survey population comprised all patients who underwent brachytherapy, external-beam radiation, or radical prostatectomy for localized prostate cancer at the University...
of Michigan radiation oncology and urology programs during 4 years (1995 to 1999) and age-matched controls without known prostate cancer. Of the 1,355 eligible subjects, 1,014 consented to participate and completed assessable questionnaires (response rate, 74.8%). Among nonparticipants, 20 either lacked a forwarding address or had died, and 321 patients did not return either a completed survey or signed consent. Baseline demographic and cancer-specific variables are summarized in Table 1. Prevalence of hormonal therapy use in this table refers to adjuvant or neoadjuvant hormonal therapy initiated as part of the primary therapy, not as salvage therapy for treatment failure.

HRQOL scores were stratified by cohort. Means and confidence intervals of unadjusted raw scores are reported in Table 2. Higher values for any measure represent more favorable HRQOL (except AUA-SI, for which higher scores indicate more severe obstructive urinary symptoms). HRQOL scores from each therapy group were first compared with the age-appropriate control group. Consistent with prior studies,5,7 general HRQOL measures (RAND SF-36 and FACT-G) did not detect significant differences between therapy groups and controls. In contrast, EPIC urinary, sexual, bowel, and hormonal HRQOL domains consistently detected differences in one or more of the therapy groups compared with controls (as did FACT-P and AUA-SI) (Table 2). As expected, radical prostatectomy was associated only with worse urinary incontinence \( (P < .0001) \) and sexual HRQOL \( (P < .0001) \) than controls, although external-beam radiation was associated only with worse bowel \( (P < .0001) \) and sexual \( (P < .0001) \) HRQOL than controls. In contrast, brachytherapy was associated with significantly worse urinary irritation and obstruction and bowel HRQOL, as well as worse sexual HRQOL, than controls \( (P < .0001 \) in each of these comparisons) (Table 2), and also showed marginal adverse urinary incontinence \( (P = .01) \).

To measure the clinical relevance of these differences, EPIC has bother subscales that measure impairment related to each prostate-specific HRQOL domain summary score.17 Urinary, bowel, and sexual domains were each significantly bothersome for brachytherapy patients \( (P < .0001) \); whereas only bowel and sexual effects were bothersome for external-beam radiation patients \( (P < .0001) \); and only sexual functioning was bothersome for radical prostatectomy patients \( (P < .0001) \). To illustrate these observed differences in urinary, bowel, and sexual impairment, the distribution of answers to the three bother questions are shown in Fig 1.

The EPIC survey instrument also includes questions about symptoms and impairment associated with androgen deprivation. EPIC hormonal function scores associated significantly with use of hormonal therapy administered as adjuvant or neoadjuvant with the primary therapy (mean
hormonal function scale among patients who had hormonal therapy, 83.7; for those without hormonal therapy, 88.0; \( P = .0004 \) ), whereas more general HRQOL measures were not sensitive to the use of adjuvant or neoadjuvant androgen deprivation administered as a part of the primary intervention. Hormonal HRQOL was worse among either external-radiation or brachytherapy patients compared with controls \( (P < .0001) \), and these hormonal symptoms were significantly bothersome \( (P < .002 \) for EPIC hormonal bother subscale differences; data not shown). This may in part be caused by higher prevalence of hormonal therapy among brachytherapy patients than external-beam or radical-prostatectomy patients \( (51\%, 33\%, \text{and } 28\% \) , respectively; Fisher’s exact test \( P < .0001 \) ).

Direct comparison of durable, long-term HRQOL between the therapy groups was undertaken next. This analysis focused on the prostate cancer-specific EPIC and FACT-P HRQOL measures among subjects at least 1 year after therapy (Table 3). Model-building using linear regression techniques was used to adjust for differences between the cohorts in the distribution of age, pretreatment cancer severity, use of hormonal therapy, and time since therapy. It should be noted, however, that unmeasured baseline factors may nevertheless contribute to differences in such a cross-sectional comparison.\(^{23} \) There was no long-term difference in urinary incontinence between radical prostatectomy and brachytherapy patients, although the prostatectomy patients had more incontinence than the external radiation group. Urinary irritative symptoms and impairment were worst among brachytherapy patients, as was bowel HRQOL. Sexual HRQOL was worse after brachytherapy than after external radiation. To determine if the adverse HRQOL profile of brachytherapy was related to use of external radiation boost after brachytherapy in a subset of the brachytherapy subjects, these comparative analyses were repeated, excluding such cases. After excluding such ostensibly less favorable cases, sexual HRQOL after brachytherapy was not worse than after external-beam radiation, although all other adverse HRQOL domain outcomes of brachytherapy compared with external radiation or radical prostatectomy were conserved.

The HRQOL effects of prostate cancer progression after primary therapy were then evaluated. Overall PSA progression-free survival after therapy for prostate cancer in this cohort was 89.9%. This overall rate of progression was too small for conclusive comparisons of progression-free survival between treatment groups, and, consistent with the low observed rate of PSA progression in the entire cohort, no significant differences in PSA progression were observed between the therapy groups. Progression-free patients reported marginally better general HRQOL than those with increasing PSA (FACT-P \( P = .023 \) ), although this general HRQOL score difference met neither the significance threshold for this analysis of alpha = 0.008 nor a previously proposed threshold for clinical relevance \( (0.5 \text{ SD of HRQOL score}) \).\(^{6} \) However, significantly better sexual and hormonal HRQOL was observed among progression-free patients than those with increasing PSA \( (P < .0001 \) for each) (Table 4). The sexual and hormonal HRQOL benefits of PSA progression-free survival were independent of primary therapy group and are likely to be clinically significant, given that the observed differences also exceed 0.5 SD.\(^{6} \) These findings suggest that PSA progression-free survival after prostate cancer therapy may have HRQOL benefits relative to disease progression.

**DISCUSSION**

Decision-making in regard to localized prostate cancer therapy is hindered by a paucity of data that directly compares the three most common local therapies for prostate cancer: brachytherapy, external-beam radiation, and radical prostatectomy. Contributing to this uncertainty is the lack of completed or active randomized clinical trials to compare these therapies. In the absence of such trials, observational studies that compare outcomes can provide useful information. Because widely applied measures of prostate cancer severity can be used to partially control baseline differences, prostate cancer is particularly amenable to observational assessments of patients who self-select different therapies.\(^{24-26} \) In this setting, a direct comparison of HRQOL between the current three most common local therapies for prostate cancer can provide much needed information in regard to related HRQOL outcomes.

Prior studies have shown the importance of focusing prostate cancer HRQOL assessment on patient-reported outcomes, measured using validated, prostate-specific HRQOL domain scores, when comparing different prostate cancer therapies.\(^{7-11,27-31} \) HRQOL after brachytherapy, however, has not been previously characterized by concurrent comparison to controls and to patients who underwent radical prostatectomy or external-beam radiation. The short-term convenience of brachytherapy as an outpatient operation seems favorable to the 2-to-3-day hospitalization with 2 weeks of urinary catheterization after surgery, or the 7-week course of daily visits needed for external-beam radiation. However, our findings suggest that the durable HRQOL effects of brachytherapy cannot be dismissed as insignificant. Indeed, HRQOL after brachytherapy was significantly less favorable than after either radical prostatectomy or external radiation in several HRQOL domains, and brachytherapy showed no advantage in any measured long-term HRQOL outcome.
It could be argued that the adverse HRQOL effects after brachytherapy may be unique in a single-institution study. However, the HRQOL effects we observed are consistent with the limited available patient-reported data from leading brachytherapy series, and rigorous treatment dose planning with postimplantation dosimetry confirmation was generally applied in our cases. The single preceding study that measured FACT-P and AUA-SI scores in brachytherapy patients observed HRQOL scores (mean FACT-P, 35.4; AUA-SI, 15.4) similar to those observed in our cohort (mean FACT-P, 33.2; AUA-SI, 12.6). With respect to diarrhea, rectal urgency and bleeding, incontinence, and the quality of erections, our findings also were similar to recent observations in other contemporary prostate brachytherapy series of postbrachytherapy, patient-reported HRQOL that reported such data. Therefore, our findings did not represent an aberration from expected outcomes but instead corroborated the severity of brachytherapy-associated HRQOL effects and uniquely provided the context of normal controls and subjects who underwent external-beam radiation or surgery administered by refined, contemporary techniques. Despite providing evidence regarding outcome at an average of 2 years after primary therapy, this duration of follow-up may still not be long enough to determine stable complication rates (especially for sexual function, known to change for several years after treatment) and differences in follow-up duration between groups can compound this problem. In addition, it is possible that radiation dose reduction and refined patient selection may lead to future improvements in brachytherapy-associated HRQOL.

HRQOL assessment in our study also extends prior work in two aspects of survey content: assessment of hormonal symptoms and assessment of urinary irritation/obstruction. Neoadjuvant and salvage therapy with androgen ablation are now commonplace in the management of localized prostate cancer, yet consequent HRQOL effects have not been previously evaluated using patient-reported data. With a comprehensive instrument sensitive to hormonal symptoms, such as hot flashes, fatigue, and breast tenderness, we found that some patients reported significant impairment related to androgen deprivation. Patients should be informed of the potential for adjuvant androgen-deprivation therapy to affect their QOL.

In the assessment of urinary function and bother, prior and ongoing studies of localized prostate cancer HRQOL have largely focused on only one aspect of urinary function: urinary incontinence. However, bladder outlet obstruction and urethral irritation (related to complications of therapy, local cancer persistence or progression, or underlying benign prostatic hyperplasia) are commonly encountered after radical prostatectomy, external radiation, or brachytherapy for prostate cancer. The EPIC survey provides a unique tool for concurrently measuring urinary incontinence versus urinary irritative HRQOL effects, and this study shows that each of these can be associated with significant impairment. In this cohort, long-term urinary incontinence was more common among radical prostatectomy patients than among external radiation patients, whereas brachytherapy patients were also marginally affected by incontinence. In contrast, long-term urinary irritative and obstructive symptoms were most severe after brachytherapy but also significantly worse after external radiation compared with radical prostatectomy (Table 3). The combined long-term prevalence after brachytherapy of both significant urinary irritation/obstruction, as well as of marginal urinary incontinence, provides a possible explanation for the marked overall urinary impairment encountered among brachytherapy patients, in contrast to that encountered after either radical prostatectomy or external-beam radiation (Fig 1).

The clinical relevance of the observed HRQOL differences is in part reflected by the distribution of EPIC domain-specific impairment (Fig 1). Additionally, each EPIC HRQOL domain score (urinary-incontinence; urinary-irritative/obstructive; bowel; sexual; hormonal) showed a significant difference between at least one of the prostate cancer–patient therapy groups compared with control men, suggesting that each of these domains are clinically relevant. Moreover, patient-reported impairment in these domains was significant, as evidenced by observed differences in bother subscale scores. Finally, the observed EPIC domain score differences reported herein generally exceeded a previously advocated threshold (0.5 SD of a Likert-transformed of HRQOL score, such as EPIC).

Serum PSA measurements are widely used as a measure of cancer control after primary therapy for localized cancer. However, the highly variable relationship of PSA increase and subsequent prostate cancer mortality, which may occur many years, if at all, after PSA increase, prompts a need to characterize HRQOL effects associated with PSA progression after local-regional therapy. We found that PSA progression after localized prostate cancer therapy was associated with significantly bothersome effects with regard to sexual and hormonal function, whereas effects on more general HRQOL were marginal. The observed HRQOL effects associated with PSA increase, however, may be caused by salvage or secondary therapies rather than representing a direct consequence of increasing PSA itself. The extent to which indirect HRQOL effects of secondary therapy and direct HRQOL effects (symptoms caused by the prostate cancer itself) contribute to such adverse HRQOL is in need of further study.
In this study, pretreatment measures of HRQOL were unavailable. Hence, unmeasured baseline HRQOL differences may contribute to differences observed after treatment. Another limitation of the comparative analyses herein is that a subset of the sample had been used to validate EPIC. Subjects in our study also chose their own therapy, so selection bias cannot be excluded. We controlled the comparative analysis for covariates, including age and cancer severity, in an effort to limit effects of possible baseline differences. Moreover, baseline factors, such as age and cancer severity, were more favorable in the brachytherapy group than in patients who underwent external radiation, yet the brachytherapy group showed worse HRQOL than external radiation in bowel, urinary, and general prostate cancer (FACT-P) domains. The selection bias problem is nevertheless inherent and not fully correctable in any cross-sectional study, including this one. Controlling, in multivariable models, for such differences on the basis of selection biases is notoriously incomplete. A longitudinal study to evaluate these concerns is needed because baseline HRQOL scores could better control for the HRQOL prognostic differences between patient groups. Conversely, these data may be more easily generalized than data from randomized clinical trials, which typically have narrow inclusion and exclusion criteria. The finding that HRQOL scores remain significantly lower even after an attempt to control covariates are contrary to the popular albeit unsubstantiated notion that brachytherapy is less morbid in the long-term than external-beam radiation or radical prostatectomy.

Without a randomized clinical trial to compare prostatectomy, external-beam radiation, and brachytherapy, comparative observational outcomes can help guide appropriate HRQOL expectations. Our comprehensive assessment of prostate cancer HRQOL, at an average of nearly 2 years after therapy, suggests that brachytherapy may not be as free from long-term morbidity as often suggested and broadly advertised. The assessment of a broader range of bothersome prostate-related symptoms than undertaken previously revealed that irritative urinary symptoms can be as bothersome as urinary incontinence and that the HRQOL effects of androgen-deprivation therapy can cause significant impairment. Finally, our data suggest that recurrence-free survival is associated with better HRQOL than prostate cancer recurrence, suggesting that a PSA recurrence-free outcome may represent a distinct health state. These findings provide a basis for counseling patients in regard to long-term HRQOL expectations after primary prostate cancer therapy and demonstrate that urinary irritative and hormonal concerns are significant elements of localized prostate cancer HRQOL.

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