Five-Year Outcomes After Prostatectomy or Radiotherapy for Prostate Cancer: The Prostate Cancer Outcomes Study

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Background: **Men treated for clinically localized prostate cancer with either radical prostatectomy or external beam radiotherapy usually survive many years with the side effects of these treatments. We present treatment-specific quality-of-life outcomes for prostate cancer patients 5 years after initial diagnosis.** ***Methods:*** **The cohort consisted of men aged 55–74 years who were newly diagnosed with clinically localized prostate cancer in 1994–1995 and were treated with radical prostatectomy (n = 901) or external beam radiotherapy (n = 286). We used clinical and quality-of-life data previously collected at the time of diagnosis (i.e., baseline) and at the 2-year follow-up and data newly collected at 5 years after diagnosis to compare urinary, bowel, and sexual function and to examine temporal changes in those functions. Odds ratios (ORs) and adjusted percentages were calculated by logistic regression. All statistical tests were two-sided.** ***Results:*** **At 5 years after diagnosis, overall sexual function declined in both groups to approximately the same level. However, at 5 years after diagnosis, erectile dysfunction was more prevalent in the radical prostatectomy group than in the external beam radiotherapy group (79.3% versus 63.5%; OR = 2.5, 95% confidence interval [CI] = 1.6 to 3.8). Approximately 14%–16% of radical prostatectomy and 4% of external beam radiotherapy patients were incontinent at 5 years (OR = 4.4, 95% CI = 2.2 to 8.6). Bowel urgency and painful hemorrhoids were more common in the external beam radiotherapy group than in the radical prostatectomy group. All of these differences remained statistically significant after adjustment for confounders and for differences between treatment groups in some baseline characteristics.** ***Conclusions:*** **At 5 years after diagnosis, men treated with radical prostatectomy for localized prostate cancer continue to experience worse urinary incontinence than men treated with external beam radiotherapy. However, the two treatment groups were more similar to each other with respect to overall sexual function, mostly because of a continuing decline in erectile function among the external beam radiotherapy patients between years 2 and 5. [J Natl Cancer Inst 2004; 96:1358–67]**

Men who are diagnosed with localized prostate cancer live many years with the sequelae of the treatments they receive *(1,2).* Given this reality, it is important that men and their clinicians understand the long-term consequences of various treatments on health-related quality of life.

The main treatment choices for men with clinically localized prostate cancer are radical prostatectomy, external beam radiotherapy, radioactive seed implants (i.e., brachytherapy), and conservative management. However, because there are few direct comparisons of these treatments, there is continuing disagreement and uncertainty about the relative efficacy of these forms of disease management *(3–5).* Results of a large, randomized clinical trial suggested that, compared with "watchful waiting," radical prostatectomy reduced disease-specific mortality but had statistically significantly greater adverse impacts on sexual and urinary incontinence and no effect on overall survival *(6,7).* Presently, there are no completed trials that directly compare the long-term survival of men treated with surgery versus radiotherapy, leaving the question of survival benefit unanswered. In the absence of such survival comparisons, understanding the risks of adverse health-related quality-of-life side effects up to 5 years after treatment may help men better decide between surgery and radiotherapy.

Two recent reviews have summarized the existing literature on the most common sequelae of radical prostatectomy and external beam radiotherapy, which include urinary, bowel, and sexual dysfunction *(8,9).* Many of the studies that have examined the side effects of prostate cancer treatments enrolled volunteers or had nonrepresentative samples of patients, used cross-sectional rather than longitudinal designs, or failed to adjust for key variables that were likely to confound the relationship between treatment and outcomes.

The Prostate Cancer Outcomes Study (PCOS) was designed to address these limitations by prospectively assessing the long-term health-related quality-of-life outcomes for a large, diverse, population-based sample of men who were diagnosed with prostate cancer in 1994 or 1995 and treated in a community-based setting *(10).* The PCOS assembled an extensive dataset of clin-

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ical and sociodemographic variables by using patient self-reports as well as reviews of inpatient and ambulatory medical records. Several previous reports have used PCOS data to provide detailed information on the 2-year experiences of men with clinically localized cancer who underwent radical prostatectomy, external beam radiotherapy, or androgen deprivation therapy *(11–14)*. In this study, we compared treatment-specific and general health outcomes among men who were initially treated with radical prostatectomy or external beam radiotherapy and completed the 5-year survey, adjusting the estimated differences between the two groups for multiple clinical prognostic factors, pretreatment disease-related function and comorbidity, and demographic and socioeconomic variables.

Subjects and Methods

Patients

The PCOS enrolled patients from six geographic regions (Connecticut, Utah, New Mexico, and the metropolitan areas of Atlanta [GA], Los Angeles County [CA], and Seattle–Puget Sound [WA]) for a longitudinal assessment of prostate cancer practice patterns and patient outcomes. Details of the rationale, objectives, and methods of the PCOS have been reported previously *(10,11)*.

All six Surveillance, Epidemiology, and End Results (SEER[1]) registries participating in the PCOS obtained institutional review board approval. The registries identified and contacted eligible patients within 4–6 months of diagnosis. Eligible patients had biopsy-proven primary invasive carcinoma of the prostate that was diagnosed during the period from October 1, 1994, through October 31, 1995. All men aged 39–89 years were eligible except those who resided in King County (WA), where eligibility was limited to men aged 60–89 years. The PCOS oversampled men younger than 60 years, Hispanic men in Los Angeles and New Mexico, and black men in Atlanta and Los Angeles.

Details of the original selection of cases for this comparison of treatment outcomes are provided in our earlier report on 2-year outcomes *(11)*. The PCOS sampled 5672 eligible men, of whom 3533 (62%) participated by completing a 6- and/or a 12-month survey. Among the 3533 PCOS participants, 2047 men aged 55–74 years at the time of initial diagnosis had clinically localized disease. We excluded 444 men who received neither radical prostatectomy nor external beam radiotherapy as initial therapy. We selected an age range of 55–74 years because in our cohort, radiotherapy was uncommon among men younger than 55 years (8%) and radical prostatectomy was infrequent among men older than 74 years (7%). Other exclusions yielded a study sample of 1591 patients aged 55–74 years with clinically localized prostate cancer who received either radical prostatectomy or external beam radiotherapy as primary therapy within 1 year of cancer diagnosis. These men were members of the cohort analyzed for our report of 2-year outcomes *(11)*.

Data Collection

The procedure we used to collect the 5-year survey data was similar to that used for all earlier PCOS surveys. We used a mailed self-administered survey to obtain information about general and disease-specific measures of health-related quality of life, comorbidity, the patient's perception of his disease progression or recurrence, and current treatments used for his prostate cancer. The disease-specific outcomes were urinary incontinence, bowel dysfunction, and sexual dysfunction. We analyzed the individual items that made up these domains, as well as summary measures of each domain. On the 5-year survey, several new items relative to earlier surveys were added to comprehensively assess men's evaluations of the extent of distress, or "bother," posed by the presence of urinary, bowel, and sexual dysfunction. These bother items were derived from prior surveys *(15,16)*. We also used the Medical Outcomes Study (MOS) SF-36 instrument to assess general quality of life *(17)*. Additional demographic and socioeconomic status data included age, race, marital status, education level, and income. We also included variables in this analysis that were collected from medical record reviews conducted 1–2 years after initial diagnosis. Variables collected from medical records included clinical details on prognostic factors such as grade, stage, and prostate-specific antigen values and all initial treatments.

Statistical Methods

We explicitly addressed the presence of selection bias by incorporating estimated propensity scores in our analyses *(18,19)*. The propensity score was defined as the probability of a case subject receiving a radical prostatectomy on the basis of his pretreatment characteristics. These characteristics included detailed clinical prognostic factors, individual demographic and socioeconomic characteristics, comorbidities, and pretreatment urinary, bowel, and sexual function variables. Propensity scores were used to analyze the 2-year outcome data to assess whether there was sufficient overlap of covariates between the two treatment groups to justify comparing patient outcomes *(11)*. To estimate the propensity score for this study, PCOS investigators specified, *a priori*, multiple baseline variables thought to be predictive of the use of radical prostatectomy versus external beam radiotherapy for the treatment of clinically localized prostate cancer *(11)*. Multiple logistic regression modeling, with baseline variables as covariates, used treatment as the outcome variable to produce the propensity scores. The modeling revealed substantial differences in the likelihood of receiving radical prostatectomy according to age at diagnosis, symptoms, prostate-specific antigen levels, and baseline urinary and sexual function *(11)*.

If there is sufficient overlap on model covariates, the association of the outcomes with treatment can be evaluated and adjusted for the propensity score to partly account for selection bias. To assess whether the propensity score could be used to help achieve better balance in the covariates, we tested for differences in the covariates between treatment groups within each propensity score quintile in the analysis of 2-year outcomes. We found no statistically significant differences between the radical prostatectomy and external beam radiotherapy groups for any of the clinical or sociodemographic covariates after adjustment for the propensity score quintile *(11)*. These results demonstrated that the measured covariates overlapped sufficiently for these two treatment groups to be compared. The estimated propensity score was therefore included as an adjustment variable in all subsequent regression models assessing health-related quality-of-life outcomes at 2 years *(11)* and, for

the present analysis, at 5 years, to explicitly account for baseline differences by treatment group.

We performed two analyses: a cross-sectional comparison of complications and a longitudinal analysis comparing effects over time. The cross-sectional analysis compared individual urinary, bowel, and sexual outcomes between treatment groups among the 5-year survey responders. Each outcome was summarized as a binary measure from the three to five original item response categories. The choice of cut points was based on empirical assessments plus the investigators' judgments of clinical relevance.

We used logistic regression models that included the binary response variables for the outcomes to assess differences in the individual function and bother items and in general quality of life at 5 years after diagnosis. Covariates included in all these models were as follows: treatment (radical prostatectomy versus external beam radiotherapy), treatment propensity score, age at diagnosis, race/ethnicity, education level, comorbidity score (based on self-report of 12 distinct chronic conditions ascertained via survey), and the baseline value of the outcome measure. These regression models were used to predict the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) as well as the probability of experiencing complications for each treatment group. The adjusted percentages of men in each treatment group experiencing complications were then standardized directly to the distribution of the covariates among the entire weighted sample *(20)*.

We compared differences in disease-specific outcomes longitudinally by treatment group by modeling the change in the multi-item summary scale scores for the urinary, bowel, and sexual domains from baseline to the 24- and 60-month surveys. Summary scores for the urinary incontinence, bowel, and sexual function domains were derived by averaging the individual item scores (except the bother items) and then standardizing the averaged score on a scale of 0–100, with 100 representing best or normal function. Generalized estimating equations linear models were used to compare the radical prostatectomy and external beam radiotherapy case subjects over the 5-year time period to account for the correlated nature of the repeated observations. For three separate models, corresponding to urinary incontinence, bowel, and sexual function scale scores, the change in the 0–100 standardized scale score from baseline to the 2- and 5-year survey data for each scale were the dependent variables. The same set of independent variables used in the cross-sectional models was included in the longitudinal models. We examined interactions between treatment group and age, baseline function, education, comorbidity, and propensity scores. We graphed the summary scores stratifying by high versus low baseline scores because of statistically significant interactions between baseline function scores, treatment group, and temporal changes. Our choice of cut points to distinguish the high (or normal) baseline versus lower baseline function groups was based on empirical analysis of distributions of baseline scores and clinical judgment.

Because of the high attrition rate in the study between the 2- and 5-year surveys, we assessed the possibility of bias due to differential nonresponse according to treatment group. We compared responders to the 5-year follow-up survey with nonresponders by treatment group with regard to clinical and sociodemographic and socioeconomic variables, using both frequency tables and logistic regression models. In addition, we assessed the sensitivity of our results to missing data by performing an analysis that used the last data available for nonrespondents.

All cross-sectional and longitudinal models were implemented with the use of the Survey Data Analysis (SUDAAN) statistical computer package (Research Triangle Institute, Research Triangle Park, NC). The Horvitz–Thompson weight, which is the inverse of the sampling proportion for each sampling stratum (defined by age, race/ethnicity, and study area), was used to obtain unbiased estimates of the regression parameters for all eligible prostate cancer patients in the PCOS study areas. A more detailed description of the sampling strata used and the calculation of sampling weights is provided elsewhere *(10)*. All estimates (percentages) presented in tables, the text, and graphs are weighted to this population. Wald-type F statistics using the robust variance estimator were used to assess statistical significance of estimated regression coefficients. All P values were two-sided, and P values less than .05 were considered statistically significant.

RESULTS

A total of 1591 men aged 55–74 who initially received either radical prostatectomy (n = 1156) or external beam radiotherapy (n = 435) for clinically localized prostate cancer were previously analyzed 2 years after diagnosis *(11)*. In the present analysis, we report on the 1187 men who also completed the 5-year follow-up survey. We analyzed data from 901 (79%) of the men who initially received a radical prostatectomy and 286 (67%) of the men who initially received external beam radiotherapy. In the original cohort of 1591 men, we found that, after adjustment for propensity scores, the two treatment groups were not statistically significantly different with respect to multiple clinical, sociodemographic, and economic variables *(11)*. This similarity between the two treatment groups persisted among the men who completed the 5-year survey.

Urinary Incontinence

Table 1 shows unadjusted percentages along with adjusted odds ratios and adjusted percentages from logistic regression models for urinary incontinence outcomes among responders to the 5-year survey. Men who initially underwent radical prostatectomy continued to report more urinary incontinence than men who initially underwent radiotherapy. For example, 15.3% of radical prostatectomy patients were incontinent (defined as having no control or frequently leaking urine) at 5 years versus 4.1% of radiotherapy patients, after adjustment for confounders. These differences were fairly similar to those observed at 2 years; the percentages of men reporting incontinence and overall bother due to incontinence were consistently approximately 4–6 times higher in the radical prostatectomy group than in the external beam radiotherapy group.

Figure 1 shows the results of a temporal analysis of the summary incontinence scores through 5 years after diagnosis. Our cross-sectional analyses revealed that, overall, more men in the external beam radiotherapy group than in the radical prostatectomy group had pretreatment incontinence *(11)*. Mean function scores are shown for patients without any incontinence at baseline (mean score = 100) and for patients with some symptoms of incontinence at baseline (mean score = 79). Figure 1 illustrates slight declines in the summary scores in all groups

Table 1. Comparison of 5-year PCOS survey responders on individual urinary, bowel, and sexual domain items*

Domain	RP† (n = 901)	EBRT† (n = 286)	OR (95% CI)
Urinary			
No control or frequent leaks vs. total control or occasional leaks	14.4 (15.3)	4.9 (4.1)	4.4 (2.2 to 8.6)
Leaks ≥2 times per day‡	15.6 (16.1)	4.1 (3.6)	5.3 (2.6 to 10.8)
Wears any pads to stay dry‡	28.6 (28.6)	4.2 (4.2)	9.4 (4.7 to 18.9)
Frequent urination more than half the time‡	10.6 (10.1)	8.9 (9.3)	1.1 (0.6 to 1.9)
Bothered by dripping or leaking urine§	13.9 (14.3)	3.0 (2.6)	6.5 (2.7 to 15.6)
Bowel‖			
Diarrhea‡	23.3 (23.9)	28.8 (26.7)	0.84 (0.55 to 1.26)
Painful bowel movements‡	10.4 (11.5)	12.2 (9.4)	1.31 (0.73 to 2.35)
Bowel urgency‡	17.7 (19.3)	33.4 (28.5)	0.56 (0.36 to 0.87)
Wetness in rectal area‡	13.8 (14.8)	20.6 (18.3)	0.75 (0.47 to 1.20)
Painful hemorrhoids‡	11.0 (10.2)	15.7 (19.6)	0.43 (0.25 to 0.74)
Bothered by frequent bowel movement to pain, or urgency§	4.3 (4.8)	5.0 (4.0)	1.23 (0.52 to 2.89)
Sexual			
No/little vs. some/a lot of interest in sexual activity	46.5 (48.9)	55.2 (47.4)	1.1 (0.73 to 1.6)
No sexual activity vs. any sexual activity	48.9 (50.7)	51.3 (43.9)	1.4 (0.93 to 2.0)
Erection insufficient for intercourse‡	76.9 (79.3)	73.1 (63.5)	2.5 (1.6 to 3.8)
Bothered by sexual dysfunction§	47.4 (46.7)	42.0 (44.6)	1.1 (0.75 to 1.6)

*Model-based odds ratios (with external beam radiotherapy patients as referent group) and adjusted percentages are from separate logistic regression models (for each row) each adjusting for treatment propensity score, age at diagnosis, baseline function, race/ethnicity, comorbidity, and educational level. All estimates were weighted to total eligible cases. PCOS = Prostate Cancer Outcomes Study; RP = radical prostatectomy; EBRT = external beam radiotherapy; OR = odds ratio; CI = confidence interval.

†Values in columns are unadjusted percentages (adjusted percentages).

‡Percentages and odds ratio for yes versus no/none.

§For bother items, percentages refer to patients reporting a large or moderate problem versus a small or no problem.

‖For the five bowel function items, percentages refer to patients reporting having the problem every day or some days versus rarely or never.

over the 5-year period. However, after adjustment for propensity score, age, comorbidity, education level, and race/ethnicity, there were no statistically significant differences in the changes in urinary incontinence from year 2 to year 5 after diagnosis between men in the radical prostatectomy and men in the external beam radiotherapy groups, regardless of their baseline function.

Table 2 shows the extent to which the men in this cohort were bothered by urinary incontinence, according to six individual measures of bother that were newly added to the 5-year follow-up survey. At 5 years after diagnosis, the cohort had a high level of distress due to urinary dysfunction. A substantial percentage of men in each treatment group continued to be bothered "a lot" or "somewhat" by symptoms such as urinary frequency and nocturia. However, only 11.6% of radical prostatectomy patients versus 22.9% of radiotherapy patients were bothered by slow or difficult urination.

Men who received external beam radiotherapy (and thus retained their prostate glands) showed evidence of increased difficulty with obstructive symptoms, reporting statistically significantly greater bother with slow urination and a statistically nonsignificantly greater bother with urinary urgency than men

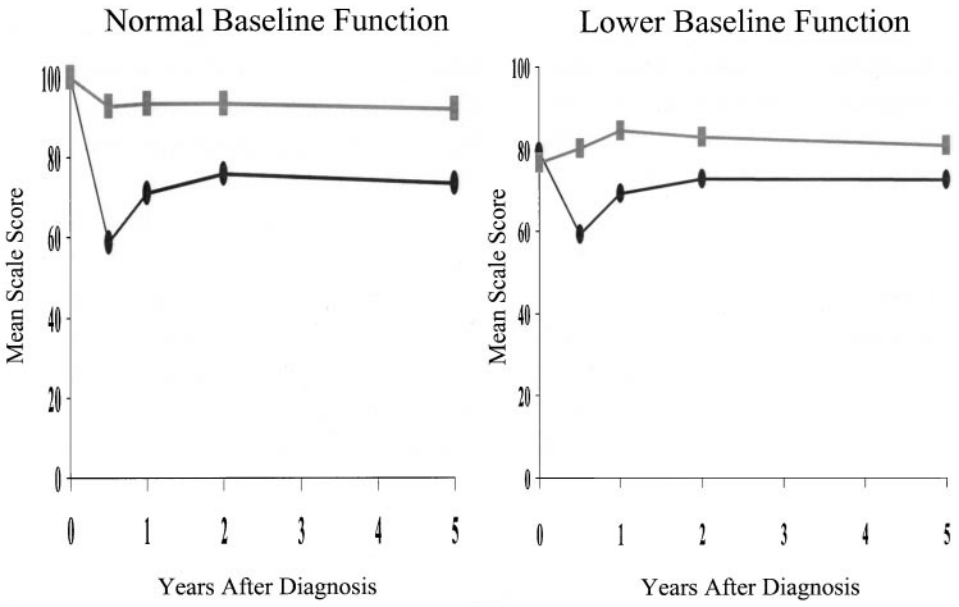

Fig. 1. Average multi-item incontinence summary scores (on a 0–100 scale) plotted as a function of time for radical prostatectomy and external beam radiotherapy patients with normal baseline function (i.e., continent at baseline) and lower baseline function (i.e., some symptoms of incontinence). Baseline function score was measured from retrospective recall of prediagnostic function ascertained on the 6-month survey and is plotted at time zero. There were 635 radical prostatectomy patients and 174 external beam radiotherapy patients with normal baseline function (mean score = 100) who responded to the initial 6-month survey and 521 radical prostatectomy and 261 external beam radiotherapy patients with lower baseline function (mean score = 79) who responded to the same survey. Cumulative loss to follow-up from baseline was 21% of radical prostatectomy patients and 33% of external beam radiotherapy patients. All mean scores are weighted for the sampling design. Average scores for radical prostatectomy patients are indicated by **closed ovals**; average scores for external beam radiotherapy patients are indicated by **closed rectangles**. Average scores are plotted as a function of years since initial diagnosis. The 95% confidence intervals at time zero for both treatment groups with normal baseline function are 99.93 to 100; 95% confidence intervals for the remaining scores are ±2-3 points.

Table 2. Comparison of 5-year PCOS survey responders reporting bother on urinary, bowel, and sexual domain items*

Domain	RP†	EBRT†	OR (95% CI)
Urinary bother‡			
Too far from bathroom	22.1 (24.0)	30.1 (24.9)	0.95 (0.64 to 1.41)
Embarrassment about going to bathroom often	14.7 (15.2)	13.3 (11.9)	1.32 (0.83 to 2.13)
Frequent urination	30.6 (31.6)	34.3 (31.3)	1.01 (0.68 to 1.51)
Urination at night	41.6 (43.2)	51.9 (47.2)	0.84 (0.58 to 1.22)
Urgency in urination	32.7 (34.2)	44.6 (39.9)	0.78 (0.53 to 1.12)
Slow or difficult urination	11.4 (11.6)	23.9 (22.9)	0.43 (0.27 to 0.66)
Bowel bother‡			
Diarrhea	11.2 (11.5)	16.6 (15.3)	0.70 (0.41 to 1.22)
Tenderness during bowel movements	6.8 (7.3)	9.7 (8.4)	0.85 (0.46 to 1.56)
Bleeding with bowel movements	7.5 (8.0)	14.7 (13.0)	0.58 (0.31 to 1.06)
Passing mucus from rectum	5.1 (5.4)	14.4 (13.1)	0.36 (0.20 to 0.66)
Sexual bother§			
Lack of sexual interest	42.7 (41.7)	40.6 (43.8)	0.92 (0.63 to 1.32)
Lack of sexual enjoyment	53.1 (52.2)	45.5 (48.9)	1.14 (0.80 to 1.64)
Inability to satisfy spouse or partner	57.5 (56.4)	46.1 (50.3)	1.28 (0.88 to 1.86)
Orgasm difficulty	47.8 (47.2)	43.4 (46.0)	1.05 (0.73 to 1.51)
Orgasm satisfying	43.4 (42.4)	38.2 (41.4)	1.04 (0.72 to 1.51)
Erectile difficulties	63.4 (62.0)	56.5 (61.2)	1.03 (0.71 to 1.49)

*Model-based odds ratios (with external beam radiotherapy patients as referent group) and adjusted percentages are from separate logistic regression models (for each row) each adjusting for treatment propensity score, age at diagnosis, baseline function, race/ethnicity, comorbidity, and educational level. All estimates were weighted to total eligible cases. PCOS = Prostate Cancer Outcomes Study; RP = radical prostatectomy; EBRT = external beam radiotherapy; OR = odds ratio; CI = confidence interval.

†Values in columns are unadjusted percentages (adjusted percentages).

‡Percentages and odds ratios refer to patients reporting item bother on item of somewhat/a lot versus not at all.

§Percentages and odds ratios refer to patients reporting item bother of a lot versus somewhat/not at all.

who underwent surgery to remove their prostate (data not shown). We examined these symptoms among only continent men to avoid including symptoms reported by men with voiding problems due to incontinence. In this subset of men, we observed statistically significantly worse measures of bother due to both slow urination or difficulty in urination and urgency in external beam radiotherapy patients compared with radical prostatectomy patients.

Bowel Function

Overall, there was very little change in bowel function from year 2 to year 5 after diagnosis. In cross-sectional estimates of bowel dysfunction at 5 years (Table 1), men who received external beam radiotherapy had worse outcomes at 5 years than men who received radical prostatectomy. However, only two measures, bowel urgency and painful hemorrhoids, were statistically significantly worse in external beam radiotherapy patients (29% and 20%, respectively) compared with radical prostatectomy patients (19% and 10%, respectively) at 5 years.

Figure 2 illustrates the convergence of the two treatment groups with respect to bowel function among those with high baseline bowel function. Mean function scores are shown separately for patients with normal baseline function (mean score = 100) and for patients with some baseline dysfunction (mean score = 81). There was an apparent improvement in overall bowel function after the 6-month survey among men who received external beam radiotherapy, regardless of their baseline function. However, there was a slight decline in function from year 2 to year 5 among the radical prostatectomy patients who had normal baseline function. This decline in bowel function was not statistically significantly different from the change in function among men who received external beam radiotherapy and had normal baseline function, after adjustments for propensity scores and other covariates.

Table 2 shows individual measures of bother due to bowel dysfunction, which was not very common in either treatment group. Although there was a pattern of less bother in the radical prostatectomy group than in the external beam radiotherapy group, one problem (passing mucus) was statistically significantly less bothersome in the radical prostatectomy group (5.4%) compared with the external beam radiotherapy group (13.1%).

Sexual Function

As shown in Table 1, both treatment groups reported substantial decrements in sexual function at 5 years after diagnosis. After adjustment for covariates, we found no statistically significant difference between treatment groups regarding interest, frequency of any sexual activity, or the extent of bother due to sexual dysfunction. The between–treatment group difference in impotence, defined as the inability to achieve an erection sufficient for intercourse, was much smaller at 5 years after diagnosis than it was at 2 years after diagnosis. At 2 years, the adjusted percentages of men reporting impotence were 82.1% in the radical prostatectomy group versus 50.3% in the external beam radiotherapy group, whereas at 5 years the adjusted percentages were 79.3% versus 63.5%, respectively.

To further explore the reasons for this change in the difference in sexual function at 5 years by treatment group, we added several variables to the logistic regression models. As we expected, the use of androgen deprivation therapy (defined as current use of hormonal injections or previous orchiectomy) was strongly associated with impotence at 5 years after diagnosis (adjusted OR = 5.2; 95% CI = 2.1 to 13.1). However, the use of different therapies for sexual dysfunction (including sildenafil citrate [Viagra]), self-reported prostate cancer recurrence or metastatic spread, and the perception of being "cancer free" were not statistically significantly associated with impotence at 5

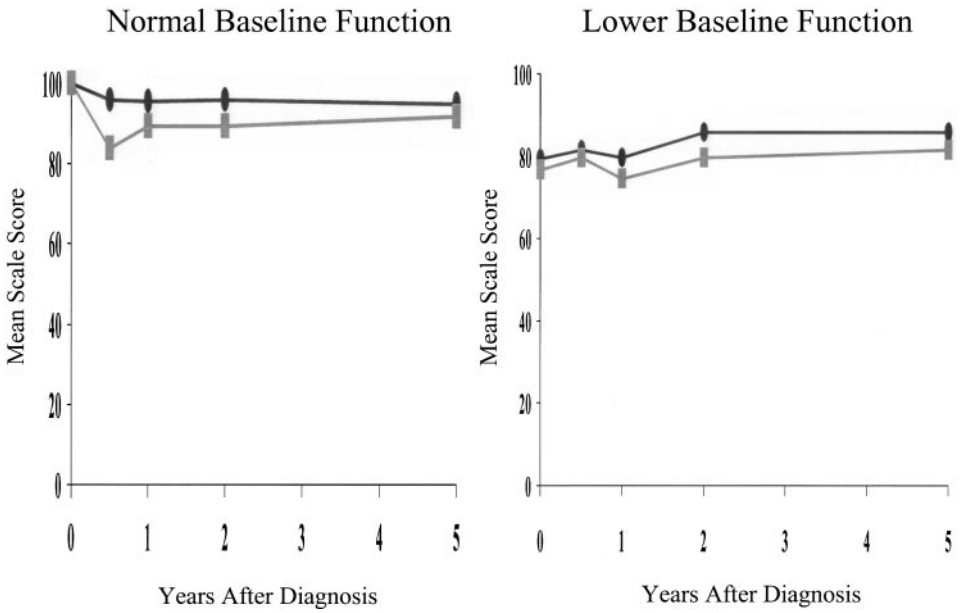

Fig. 2. Average multi-item bowel summary scores (on a 0–100 scale) plotted as a function of time for radical prostatectomy and external beam radiotherapy patients with normal (mean score = 100) and lower (mean score = 81) baseline bowel function. Baseline function score was measured from retrospective recall of prediagnostic function ascertained on 6-month survey and is plotted at time zero. There were 667 radical prostatectomy patients and 224 external beam radiotherapy patients with normal baseline function (mean score = 100) who responded to the initial 6-month survey and 489 radical prostatectomy and 211 external beam radiotherapy patients with lower baseline function (mean score = 81) who responded to the same survey. Cumulative loss to follow-up was 21% of radical prostatectomy patients and 33% of external beam radiotherapy patients. All mean scores are weighted for the sampling design. Average scores for radical prostatectomy patients are indicated by **closed ovals**; average scores for external beam radiotherapy patients are indicated by **closed rectangles**. Average scores are plotted as a function of years since initial diagnosis. The 95% confidence intervals at time zero for both treatment groups with normal baseline function are 99.93 to 100. For the remaining scores, 95% confidence intervals are ±1–2 points for the radical prostatectomy group and ±2–4 points for the external beam radiotherapy group.

years after diagnosis, and adjustment for these factors did not materially alter the differences in sexual function observed between the treatment groups.

We found a statistically significantly different temporal trend in sexual domain summary scale scores by treatment group. Figure 3 shows longitudinal analyses of sexual domain scores, which were derived from the four individual items in Table 1 on achieving and maintaining erections, frequency of sexual activity, and sexual interest, among men in the two treatment groups stratified by baseline function. Mean function scores are shown separately for patients with higher reported baseline sexual scale scores (mean score = 91) and patients with lower baseline scores (mean score = 52). We previously reported that most of the radical prostatectomy patients had slight improvements in their sexual function scale scores at 2 years after diagnosis compared with their scores at 6 months after diagnosis, whereas the scores for the external beam radiotherapy patients showed slight declines *(11)*. However, as shown in Fig. 3, between years 2 and 5 after diagnosis, there was a large, statistically significant difference in the change in the sexual function scale scores between the radical prostatectomy and external beam radiotherapy groups, in both the higher baseline ($P = .003$) and lower baseline ($P < .05$) function groups. In both baseline function groups, men who received external beam radiotherapy experi-

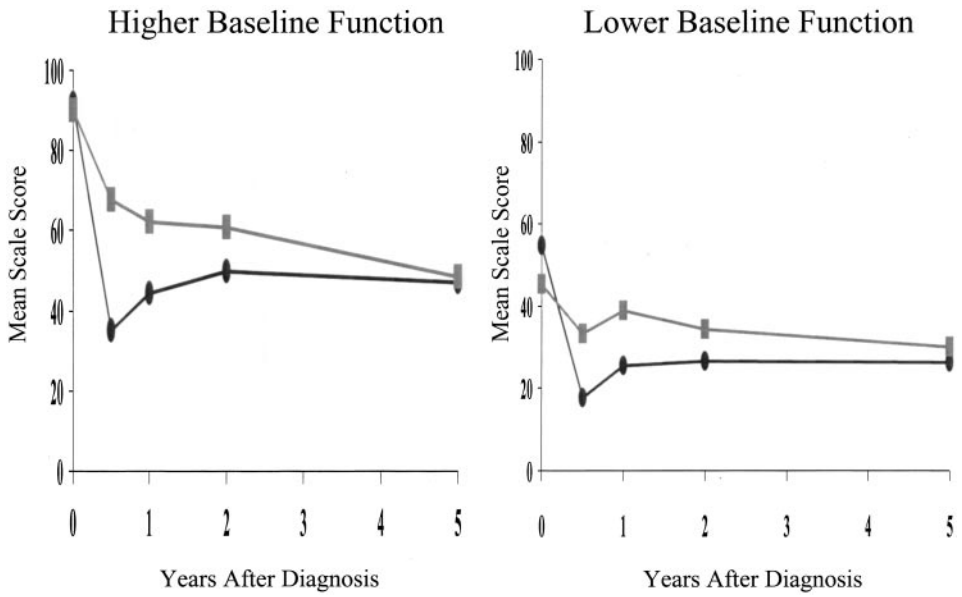

Fig. 3. Average multi-item sexual domain summary scores (on a 0–100 scale) plotted as a function of treatment for radical prostatectomy and external beam radiotherapy patients with higher and lower baseline function. Baseline score was measured from retrospective recall of prediagnostic function ascertained on 6-month survey and is plotted at time zero. There were 478 radical prostatectomy patients and 128 external beam radiotherapy patients with higher baseline scores (mean score = 91) who responded to the initial 6-month survey and 678 radical prostatectomy and 307 external beam radiotherapy patients with lower baseline scores (mean score = 52) who responded to the same survey. Cumulative loss to follow-up was 21% of radical prostatectomy patients and 33% of external beam radiotherapy patients. All mean scores are weighted for the sampling design. Average scores for radical prostatectomy patients are indicated by **closed ovals**; average scores for external beam radiotherapy patients are indicated by **closed rectangles**. Average scores are plotted as a function of years since initial diagnosis. The 95% confidence intervals at time zero among those with higher baseline scores are 91.0 to 92.6 for the radical prostatectomy group and 88.9 to 91.3 for the external beam radiotherapy group. The 95% confidence intervals for the remaining scores are ±2–3 points for the radical prostatectomy group (both higher and lower baseline function), ±5 points for the higher baseline external beam radiotherapy group, and ±2 points for the lower baseline external beam radiotherapy group.

enced large declines in sexual function between years 2 and 5, whereas men who received radical prostatectomy experienced only small declines in sexual function scale scores during that same period. We detected no statistically significant interactions for treatment by age group, comorbidity, or race/ethnicity that could account for the observed decline in sexual function in the external beam radiotherapy group relative to that in the radical prostatectomy group.

Because the use of androgen deprivation therapy had such a substantial effect on erectile function after adjustment for other confounding variables in our cross-sectional model of impotence shown in Table 1, we examined whether changes in the prevalence of androgen deprivation therapy use by treatment group contributed to the temporal trends in overall sexual scale scores shown in Fig. 3. At 2 years after diagnosis, 6% of radical prostatectomy and 3% of external beam radiotherapy groups were on androgen deprivation therapy at the time they completed a survey, but at 5 years after initial diagnosis, the use of androgen deprivation therapy had increased to 8% and 10%, respectively, suggesting a larger increase in androgen deprivation therapy use among the external beam radiotherapy group than in the radical prostatectomy group. We tested for, but did not find, a statistically significant effect of modification of androgen deprivation therapy use on treatment group with respect to the time course of sexual scale scores over 5 years. However, adjustment for androgen deprivation therapy use in our model modified the differences in trends observed from 2 to 5 years such that, among men in the lower baseline function group, the strength of the association between treatment and outcome without the androgen deprivation therapy variable ($P = .05$) became weaker when the androgen deprivation therapy variable was included ($P = .08$) (data not shown).

Table 2 lists the six separate measures of bother due to sexual dysfunction that we examined. There were no statistically significant differences between treatment groups for any of these measures. However, overall sexual function was problematic for men in both treatment groups: approximately 41%–62% (based on the adjusted percentages in Table 2) of the entire study cohort reported being bothered by various aspects of their sexual function. The highest concerns reported were for achieving or maintaining an erection, satisfying one's spouse or partner, and the lack of sexual enjoyment.

We compared general health outcomes for the two treatment groups by using the MOS SF-36 survey (data not shown). As was the case at 2 years after diagnosis, no differences were observed between the radical prostatectomy and external beam radiotherapy groups for the five domains of the SF-36 (i.e., mental health, physical role, emotional role, pain, and vitality) after adjustment for treatment propensity, age, race/ethnicity, education level, and comorbidity. Adding variables representing baseline incontinence, bowel, and sexual dysfunction did not alter these results.

Analysis of Missing Data

Table 3 shows the reasons for nonresponse to the 5-year survey by treatment group. Overall, statistically significantly fewer men in the external beam radiotherapy group than in the radical prostatectomy group completed the 5-year survey ($P = .003$). However, differences between treatment groups in the specific reasons for nonresponse were relatively small; for example, 7% of radical prostatectomy patients had died compared with 11% of external beam radiotherapy patients. Refusal was the leading reason for nonresponse.

Table 3. Reasons for nonresponse to 5-year PCOS survey*

Reason for nonresponse	RP (n = 1156)	EBRT (n = 435)
Died (%)	73 (7%)	52 (11%)
From prostate cancer	8	7
From other cancer	29	15
From non-cancer causes	31	26
From unknown causes	6	4
Active refusal to participate in 2-year PCOS survey (%)	34 (3%)	16 (3%)
Lost to follow-up (%)	37 (3%)	21 (6%)
Refusal (%)	110 (9%)	60 (13%)
Completed 5-year survey† (%)	901 (79%)	286 (67%)

*All estimated percentages were weighted to total eligible cases. PCOS = Prostate Cancer Outcomes Study; RP = radical prostatectomy; EBRT = external beam radiotherapy.

†Difference in the percentage of those who completed the 5-year surveys (RP versus EBRT) was statistically significant ($P = .003$, χ^2 test).

We assessed the extent to which nonresponse might differ by treatment group and thus potentially bias our comparisons, by comparing differences between treatment groups in the level of nonresponse for each of the variables associated with nonresponse. Table 4 shows the distribution of nonresponders according to treatment group and selected demographic and clinical variables. There was a statistically significant difference between treatment groups in nonresponse according to age at diagnosis. Among younger men but not older men we found a statistically significantly higher level of nonresponse in the external beam radiotherapy group than in the radical prostatectomy group after adjustment for all other variables in the table ($P = .009$). This difference was attributable primarily to men who were 60–64 years old at diagnosis; in this group, the nonresponse rates were 47% for men in the external beam radiotherapy group and 17% for men in the radical prostatectomy group. We found no other statistically significant differences between treatment groups with respect to nonresponse rates.

We further evaluated the possible effects of differential response levels by age at diagnosis on our reported outcomes by performing a "last value forward" analysis on urinary, bowel, sexual, and general health outcomes. We used data from the 2-year survey (when available) or from the 12- or 6-month surveys (when necessary) to estimate outcomes at 5 years after diagnosis. The impact of estimating outcomes on the reported comparisons was negligible.

Discussion

There is continuing uncertainty about the superiority of any single treatment strategy for clinically localized prostate cancers, which account for most prostate cancer cases. Results of decision models have demonstrated that patient preferences for outcomes among competing treatment strategies may be an important factor that drives treatment decisions *(21,22)*. Aside from the desire for cure, the possibility of lingering effects on urinary and sexual function may be of greatest concern to men facing the difficult choices surrounding both screening and treatment *(23)*.

This study extends a previous report on outcomes among the PCOS cohort through the first 2 years after diagnosis *(11)*. Our

Table 4. Percentage of enrolled men in the PCOS who were 5-year survey nonresponders, according to treatment group and selected sociodemographic and clinical characteristics*

Characteristic	RP, % (n = 255)	EBRT, % (n = 149)	Adjusted *P*†
Age at diagnosis, y			
55–59	20	31	
60–64	17	47	
65–69	24	31	
70–74	27	29	.009
Race/ethnicity			
Hispanic	22	40	
Black (non-Hispanic)	33	41	
White (non-Hispanic)	20	31	.33
No. of comorbid conditions			
0	25	35	
1	16	33	
2	24	37	
≥3	22	29	.51
Educational attainment			
Advanced degree	14	23	
College graduate	15	23	
Some college	23	32	
<High school	32	53	.80
PSA level at diagnosis, ng/mL			
≤4	17	41	
>4–10	19	30	
>10–20	30	29	
>20	26	45	.10
Gleason score at biopsy or transurethral resection			
2–6	21	32	
7	21	40	
8–10	29	21	.06

*Row percentages are unadjusted and weighted to total eligible men. Column percentages may not add to 100% due to rounding or missing values. PCOS = Prostate Cancer Outcomes Study; RP = radical prostatectomy; EBRT = external beam radiotherapy; PSA = prostate-specific antigen.

†*P* values test differences in distributions between treatment groups and are from Wald tests of the β coefficients for interaction terms included in a logistic regression model (with survey response versus nonresponse as the dependent variable) for treatment (RP versus EBRT) by each of the row (independent) variables.

findings add to the previous literature describing outcomes following radical prostatectomy or external beam radiotherapy for localized prostate cancer by providing new information through 5 years of post-treatment follow-up. Results of large, cross-sectional studies that compared radical prostatectomy patients with external beam radiotherapy patients several years after treatment have further shown that disease-specific function and general health-related quality of life are worse among prostate cancer patients than among age-matched controls *(24)* and that most men do not regain pretreatment sexual function *(25)*. Results of another longitudinal study demonstrated that, in the second year after treatment, men in the external beam radiotherapy group began to show declining sexual function, while men in the radical prostatectomy group did not *(26)*. Other prospective studies *(27,28)* have reported that men treated with radical prostatectomy have different types of sexual impairment compared with men treated with external beam radiotherapy, similar to our findings, and that pretreatment sexual function and the type of therapy predict the time course of sexual dysfunction *(28)*. These studies monitored patients for either 12 or 24 months after initial treatment. To our knowledge, ours is the first study to compare outcomes prospectively by treatment group for 5 years after diagnosis among men sampled from population-based registries and who thus received their care in diverse health care settings.

We report several important new findings. The known adverse effects of radical prostatectomy relative to external beam radiotherapy for clinically localized prostate cancer on urinary continence appeared to remain essentially constant from the second to the fifth year after treatment. There was little recovery in urinary control following either treatment in this cohort. However, subset analysis revealed that, among continent men, external beam radiotherapy patients had greater bother at 5 years due to both slow urination or difficulty in urination and urinary urgency compared with radical prostatectomy patients.

With respect to bowel function, we observed, not unexpectedly, that men in the external beam radiotherapy group continued to have more bowel urgency and painful hemorrhoids than men in the radical prostatectomy group at 5 years after diagnosis. Other differences in individual bowel items became smaller over time between the treatment groups. However, among the external beam radiotherapy patients who had declines in bowel function in the first 6 months after treatment, there was some improvement in overall bowel function at 5 years that was nearly to the level of that among the radical prostatectomy patients, who would be expected to have only very small treatment-related decrements in bowel function. This recovery of bowel function among external beam radiotherapy patients is encouraging. The persistence of low levels of bowel dysfunction in the radical prostatectomy group at 5 years after diagnosis probably reflects the prevalence of bowel problems in the general population rather than complications resulting from the use of external beam radiotherapy following radical prostatectomy, which was uncommon in this cohort.

In the third key domain affected by treatment, we observed a larger decline in the sexual domain scores for the external beam radiotherapy patients than in the sexual domain scores for the radical prostatectomy patients, a finding not previously reported in the literature. Much of the decline in overall sexual function can be attributed to the increased prevalence of impotence, which is just one of the four components used to derive overall sexual function, among the external beam radiotherapy group relative to the radical prostatectomy group. It is possible that the long-term physiologic effects of external beam radiotherapy on erectile function are fundamentally different from those of radical prostatectomy. These effects could cause some external beam radiotherapy patients to experience declines in erectile function much later after therapy than radical prostatectomy patients, who typically experience more acute effects of their treatment on sexual function. Some evidence in the literature suggests that external beam radiotherapy for prostate cancer can cause long-term inflammatory microvessel and neural injuries *(29)*. Results of one study suggested that sexual function may continue to decline for 4 years after radiotherapy *(30)*. Although we attempted to account for the fact that external beam radiotherapy patients tend to be older and have worse baseline sexual function than radical prostatectomy patients, it is possible that the effects of age on sexual function were greater for the external beam radiotherapy patients during the period that they were enrolled in our study than for the (relatively younger) radical prostatectomy patients. Controlling for the use of erectile aids, including Viagra, and the use of androgen deprivation therapy

explained little of the differences in sexual function we observed between the two treatment groups.

Another notable finding was the observation that distress or bother due to sexual dysfunction was prevalent at 5 years in both treatment groups. Prevalences of approximately 40%–60% were found for six items relating to sexual bother in both treatment groups, although differences by treatment group were not found. The lack of differences between treatment groups in sexual bother is consistent with our finding that overall differences in sexual dysfunction were also declining between the two treatment groups over time.

Several potential limitations of this study should be considered when interpreting these results. Foremost is the possibility of bias due to differential loss to follow-up by treatment group. Our analysis of attrition revealed that there was differential nonresponse by age across treatment groups. Most nonresponse was due to survey refusal rather than to illness or death. However, a greater nonresponse level among younger external beam radiotherapy patients could, in theory, bias our estimates (higher than "truth") of dysfunction in all three domains within that group, if one assumes that older patients tend to have systematically worse function than younger patients. Because we could not directly confirm this possibility, we assessed its likelihood by analyzing the "last value available" in responders versus nonresponders according to treatment group for the main outcomes. Results of this analysis did not materially change our results, suggesting that differential nonresponse was probably not the most important reason for our observed results.

Other limitations of the PCOS design have been discussed previously, particularly the reliance on patient recall of pretreatment disease-specific function *(31).* However, this limitation is not important for the temporal analysis of changes from 2–5 years after diagnosis. Although we used propensity scores to statistically adjust for the major identifiable factors related to treatment choice, residual selection bias from unobserved confounders may have remained, which could have potentially influenced the reported estimates of differences. However, we measured and incorporated every known major clinical, demographic, and socioeconomic confounding factor in our study. Furthermore, treatment effects on health outcomes were generally quite large, consistent with results of earlier studies, and clinically plausible.

Treatment for clinically localized prostate cancer has changed since 1994–1995, when our cohort was initially diagnosed and treated. Improvements in surgical and beam radiotherapy techniques and dissemination of newer treatments, such as brachytherapy and androgen deprivation therapy, may produce health outcomes that differ from those we observed. Compared with surgery, brachytherapy may be associated with lower rates of incontinence but greater transient problems with urinary obstruction and irritation while having similar long-term effects on sexual and bowel function *(28,32).* Androgen deprivation therapy is also becoming more commonly used as primary therapy for clinically localized disease *(33–35)* but has substantial adverse effects on sexual function and on general health-related quality-of-life domains *(35,36).* In addition, the long-term use of androgen deprivation therapy has been associated with obesity and a decrease in bone density *(37).* Updated prospective studies among patients from community-based settings that compare complications from all of the available treatment options for men with clinically localized disease are needed.

In conclusion, we found that decrements in urinary, bowel, and sexual function following curative therapy for clinically localized prostate cancer persist 5 years after diagnosis. The most dramatic change was in sexual function: External beam radiotherapy patients declined in function from 2 to 5 years nearly to the level of radical prostatectomy patients, who experienced little or no change. These estimates are from a large population-based sample of patients treated in the full spectrum of health care settings. In the absence of more definitive information from randomized trials comparing treatment groups, these 5-year updates from our earlier report of 2-year outcomes provide new information about the long-term complications of two common treatments for clinically localized prostate cancer to help guide treatment decisions.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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