

ORIGINAL ARTICLE

Long-Term Functional Outcomes after Treatment for Localized Prostate Cancer

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ABSTRACT

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BACKGROUND

The purpose of this analysis was to compare long-term urinary, bowel, and sexual function after radical prostatectomy or external-beam radiation therapy.

METHODS

The Prostate Cancer Outcomes Study (PCOS) enrolled 3533 men in whom prostate cancer had been diagnosed in 1994 or 1995. The current cohort comprised 1655 men in whom localized prostate cancer had been diagnosed between the ages of 55 and 74 years and who had undergone either surgery (1164 men) or radiotherapy (491 men). Functional status was assessed at baseline and at 2, 5, and 15 years after diagnosis. We used multivariable propensity scoring to compare functional outcomes according to treatment.

RESULTS

Patients undergoing prostatectomy were more likely to have urinary incontinence than were those undergoing radiotherapy at 2 years (odds ratio, 6.22; 95% confidence interval [CI], 1.92 to 20.29) and 5 years (odds ratio, 5.10; 95% CI, 2.29 to 11.36). However, no significant between-group difference in the odds of urinary incontinence was noted at 15 years. Similarly, although patients undergoing prostatectomy were more likely to have erectile dysfunction at 2 years (odds ratio, 3.46; 95% CI, 1.93 to 6.17) and 5 years (odds ratio, 1.96; 95% CI, 1.05 to 3.63), no significant between-group difference was noted at 15 years. Patients undergoing prostatectomy were less likely to have bowel urgency at 2 years (odds ratio, 0.39; 95% CI, 0.22 to 0.68) and 5 years (odds ratio, 0.47; 95% CI, 0.26 to 0.84), again with no significant between-group difference in the odds of bowel urgency at 15 years.

CONCLUSIONS

At 15 years, no significant relative differences in disease-specific functional outcomes were observed among men undergoing prostatectomy or radiotherapy. Nonetheless, men treated for localized prostate cancer commonly had declines in all functional domains during 15 years of follow-up. (Funded by the National Cancer Institute.)

PATIENTS WITH CLINICALLY LOCALIZED prostate cancer have a favorable long-term overall and cancer-specific rate of survival regardless of treatment choice.¹⁻³ There are currently no completed prospective, randomized trials that evaluate differences in survival outcomes between radical prostatectomy and external-beam radiation therapy. Consequently, predicted functional outcomes have become essential components of treatment decision making.^{4,5} Although studies with short-term follow-up (1 to 3 years) and intermediate-term follow-up (4 to 5 years) have identified incremental differences in functional outcomes between patients undergoing prostatectomy and those undergoing radiotherapy, longer-term outcomes remain largely unknown. Since the median life expectancy after treatment for prostate cancer is 13.8 years,⁶ a careful evaluation of long-term functional outcomes is critical to an understanding of the comprehensive experience of men living with a diagnosis of prostate cancer.

The goal of this study was to compare urinary, bowel, and sexual function and the extent to which men were bothered by declines in function 15 years after prostatectomy or radiotherapy for clinically localized prostate cancer. We used data from the Prostate Cancer Outcomes Study (PCOS), a population-based cohort of men in whom prostate cancer had been diagnosed in the mid-1990s and who had been followed prospectively for 15 years.

METHODS

PATIENTS

From October 1, 1994, through October 31, 1995, PCOS investigators enrolled patients with incident prostate cancer from six participating Surveillance, Epidemiology, and End Results (SEER) sites: Connecticut, Utah, New Mexico, and the metropolitan areas of Atlanta, Los Angeles, and Seattle–Puget Sound. The institutional review board at each participating site approved the study and accepted a completed survey as implied consent (standard operating procedure in 1995). Details of the objectives and methods of the PCOS have been reported previously.⁷⁻⁹

In the PCOS, investigators sampled 5672 of the 11,137 eligible cases, with intentional oversampling of cases of men under the age of 60 years and Hispanic and black men in specific

registries. The final cohort included 3533 men (62.3% of those sampled) who completed a survey at 6 months, 12 months, or both after diagnosis. For the current analysis, we limited the cohort to men in whom clinically localized prostate cancer had been diagnosed between the ages of 55 and 74 years, who had completed either a 2-year or 5-year follow-up survey, and who underwent either prostatectomy or radiotherapy as primary treatment (with or without androgen-deprivation therapy) within 1 year after diagnosis. We identified 1655 men who met these inclusion criteria, of whom 1164 (70.3%) had undergone prostatectomy and 491 (29.7%) had undergone radiotherapy.

DATA COLLECTION

At the time of enrollment, eligible men were asked to complete a self-administered survey that included items on clinical and sociodemographic issues, coexisting medical conditions,^{8,9} and disease-specific health-related quality of life. Because of the practical limitation of interviewing participants before diagnosis, baseline assessment was conducted at 6 months, at which time participants were asked to recall prediagnostic urinary, sexual, and bowel function. Previous validation work within the PCOS had shown agreement between baseline and 6-month estimates of these measures.¹⁰ Men were contacted again at 1, 2, 5, and 15 years after diagnosis and asked to complete a survey containing items on clinical outcomes and disease-specific health-related quality of life.

We measured disease-specific health-related quality of life using items adapted from previously validated and reliable instruments.¹¹⁻¹⁴ Multi-item rating scales were summarized as a binary measure to facilitate clinical interpretation regarding urinary incontinence, bowel function, and sexual function.¹⁵ Each domain-specific summary scale was scored from 0 to 100, with 100 representing better function.

STUDY OVERSIGHT

The study was designed and the data gathered by the PCOS investigators. The Vanderbilt University authors performed the data analysis. All the authors contributed to the writing and review of the manuscript, and no additional uncredited persons were involved. All the authors assume responsibility for the integrity and completeness of the data.

STATISTICAL ANALYSIS

All analyses were adjusted for sampling weights. Comparisons of baseline characteristics were performed with the use of logistic-regression analysis with and without adjustment for propensity scoring. We used propensity-scoring methods to control for nonrandom treatment assignments.^{16,17} We identified, a priori, baseline characteristics of patients that were thought to predict the type of surgical treatment and estimated the propensity score for undergoing prostatectomy by including these characteristics in a multivariable logistic-regression model with treatment as the response variable. We tested for between-group differences in covariates within quintiles of propensity scores and found no significant differences for any of the clinical or sociodemographic covariates within propensity-score quintiles.⁸

We conducted cross-sectional analysis of responses to individual items at each study time point and longitudinal assessment of domain-specific summary scores from baseline through year 15. We used logistic-regression models to compare responses to individual items according to study group. Model covariates included sampling weight, age at diagnosis, race or ethnic group, education level, comorbidity score, propensity score, and baseline responses to the specific item of interest. Adjusted odds ratios and 95% confidence intervals for each individual item were calculated. All P values are two-sided, and P values of less than 0.05 are considered to indicate statistical significance. R software, version 2.13.0¹⁸ with the survey package,^{19,20} was used for all statistical analyses.

We used a multilevel approach to handle missing data. In cases in which a patient did not respond to the entire survey at a given time point, we estimated the missing domain-specific summary score using a linear mixed-effects model that included the patient's baseline characteristics and various interaction terms. In the event that a patient did not respond to an entire survey, individual items were not imputed and the patient was not included in the logistic-regression analysis for that time point. When a patient responded to a particular survey but did not respond to one or two items within a scale, we used a hot-deck imputation approach, in which we randomly selected responses to the item from a pool of patients with identical responses on the remaining questions for the functional score in

consideration. If fewer than 10 such patients were available, a random sample was taken from the entire data set. Data imputation was performed only for men who were known to be alive at the time of the survey of interest.

RESULTS**PATIENTS**

Relevant baseline demographic, clinical, and pathological data are presented in Table 1 (with additional baseline data provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). At the time of the 15-year survey, 322 of the 1164 men in the prostatectomy group (27.7%) and 247 of the 491 men in the radiotherapy group (50.3%) had died. Survey response rates among living patients were 87.5% at 2 years after diagnosis, 83.3% at 5 years, and 60.3% at 15 years. There was a difference of 12.2 percentage points in response to the 15-year survey between the prostatectomy group and the radiotherapy group (63.2% and 51.0%, respectively). The longitudinal evaluation of summary scores was conducted both before and after data imputation, and no differences were identified (data not shown).

URINARY INCONTINENCE

Men in the prostatectomy group were significantly more likely than those in the radiotherapy group to report urinary leakage at 2 years (odds ratio, 6.22; 95% confidence interval [CI], 1.92 to 20.29) and 5 years (odds ratio, 5.10; 95% CI, 2.29 to 11.36). However, despite absolute differences in the prevalence of urinary incontinence between the two study groups at 15 years (18.3% and 9.4%, respectively), we observed no significant difference in the adjusted odds of urinary incontinence (odds ratio, 2.34; 95% CI, 0.88 to 6.23) (Table 2). Nonetheless, patients in the prostatectomy group were more likely to wear incontinence pads at all study time points (Table S2 in the Supplementary Appendix). Although both the absolute likelihood and the relative likelihood of being bothered by urinary incontinence was significantly higher among men in the prostatectomy group at 2 and 5 years, no significant differences were apparent 15 years after diagnosis.

Figure 1 shows the longitudinal evaluation of summary scores for urinary incontinence among men in the two study groups. Patients were strati-

Table 1. Selected Clinical and Sociodemographic Characteristics of the Patients at Baseline.*

Variable	Prostatectomy (N=1164)	Radiotherapy (N=491)	P Value†	
			Unadjusted	Adjusted
Median age (interquartile range) — yr	64 (59–68)	69 (64–71)	<0.001	0.75
Race or ethnic group — no. (%)‡				
Non-Hispanic white	806 (75.9)	370 (82.0)	<0.001	0.83
Non-Hispanic black	170 (11.7)	65 (10.4)		
Hispanic	188 (12.4)	56 (7.7)		
Baseline prostate-specific antigen level — no. (%)			0.35	0.74
<4.0 ng/ml	122 (9.8)	43 (9.4)		
4.0–10.0 ng/ml	703 (61.0)	252 (55.9)		
>10.0 ng/ml	339 (29.2)	196 (34.7)		
Gleason score — no. (%)§			<0.001	0.94
2–4	743 (63.9)	292 (59.3)		
5–7	216 (18.2)	110 (22.1)		
8–10	73 (6.5)	46 (9.6)		
Unknown	132 (11.4)	43 (8.9)		
No. of coexisting illnesses — no. (%)			<0.001	0.64
0	513 (42.5)	159 (33.3)		
1	368 (33.7)	160 (33.1)		
2	179 (15.2)	93 (16.9)		
≥3	104 (8.4)	79 (16.7)		

* All percentages were adjusted for sampling weight and thus were not calculated by dividing the numerator by the denominator.

† P values were calculated with and without adjustment for propensity scores.

‡ Race or ethnic group was self-reported.

§ The Gleason score ranges from 2 to 10, with higher scores indicating more aggressive disease.

fied according to baseline urinary function. Normal urinary function was defined as a summary score of 100, whereas a score of less than 100 at baseline was considered to indicate lower urinary function. After initial larger changes, there were slight declines in summary scores for urinary function over time in both groups, regardless of treatment.

SEXUAL FUNCTION

Men in the prostatectomy group were significantly more likely than those in the radiotherapy group to report having erections insufficient for intercourse at 2 years (odds ratio, 3.46; 95% CI, 1.93 to 6.17) and 5 years (odds ratio, 1.96; 95% CI, 1.05 to 3.63) (Table 2). Erectile dysfunction was nearly universal at 15 years, with 87.0% of those in the prostatectomy group and 93.9% of those in

the radiotherapy group reporting an inability to achieve an erection sufficient for intercourse. There was no significant between-group difference in the adjusted odds for erectile dysfunction at 15 years (odds ratio, 0.38; 95% CI, 0.12 to 1.22). Despite modest absolute between-group differences in the number of men who reported being bothered by sexual dysfunction, no significant relative differences were identified at any study time point.

Patients were stratified into two groups on the basis of sexual function at baseline. The cutoff point of 80 was chosen because it had previously been used in the 2- and 5-year PCOS reports of functional outcomes.^{8,9} This threshold was originally chosen on the basis of empirical assessment and the investigators' judgment of clinical relevance. Patients with a baseline score

Table 2. Survey Responses on Selected Items Regarding Urinary, Bowel, and Sexual Function.*

Outcome	Prostatectomy	Radiotherapy	Adjusted Odds Ratio (95% CI)†
	<i>percent</i>		
Urinary incontinence			
No control or frequent urinary leakage			
2 yr	9.6	3.2	6.22 (1.92–20.29)
5 yr	13.4	4.4	5.10 (2.29–11.36)
15 yr	18.3	9.4	2.34 (0.88–6.23)
Bothered by dripping or leaking urine‡			
2 yr	10.6	2.4	5.86 (1.93–17.64)
5 yr	12.9	2.9	7.66 (2.97–19.89)
15 yr	17.1	18.4	0.87 (0.41–1.80)
Sexual function			
Erection insufficient for intercourse			
2 yr	78.8	60.8	3.46 (1.93–6.17)
5 yr	75.7	71.9	1.96 (1.05–3.63)
15 yr	87.0	93.9	0.38 (0.12–1.22)
Bothered by sexual dysfunction‡			
2 yr	55.5	48.2	1.19 (0.77–1.86)
5 yr	46.7	39.7	1.48 (0.92–2.39)
15 yr	43.5	37.7	1.33 (0.58–3.03)
Bowel function			
Bowel urgency			
2 yr	13.6	34.0	0.39 (0.22–0.68)
5 yr	16.3	31.3	0.47 (0.26–0.84)
15 yr	21.9	35.8	0.98 (0.45–2.14)
Bothered by frequent bowel movements, pain, or urgency‡			
2 yr	2.9	7.9	0.37 (0.14–0.96)
5 yr	4.4	5.8	0.93 (0.27–3.22)
15 yr	5.2	16.0	0.29 (0.11–0.78)

* All percentages were adjusted for sampling weight.

† Odds ratios are for the prostatectomy group as compared with the radiotherapy group. Odds ratios have been adjusted for registry, age, baseline function, race or ethnic group, tumor grade, number of coexisting illnesses, education level, and propensity score.

‡ Survey respondents described being bothered as either a “moderate problem” or “big problem.”

of 80 or more were considered to have higher sexual function (mean, 91.8), whereas those with a baseline score of 79 or less were defined as having lower sexual function (mean, 49.9). Longitudinal analysis of sexual-function outcomes revealed declines in the mean summary score for sexual function over time in the two study groups (Fig. 2). This trend was consistent among patients with higher or lower baseline sexual function. Despite early- and intermediate-term

data revealing treatment-dependent differences in patterns of sexual dysfunction, after 5 years both treatment groups had a gradual decline in sexual function.

BOWEL FUNCTION

Men in the radiotherapy group reported significantly higher rates of bowel urgency than did those in the prostatectomy group at 2 years (odds ratio, 0.39; 95% CI, 0.22 to 0.68) and 5 years

Figure 1. Urinary Function over 15 Years.

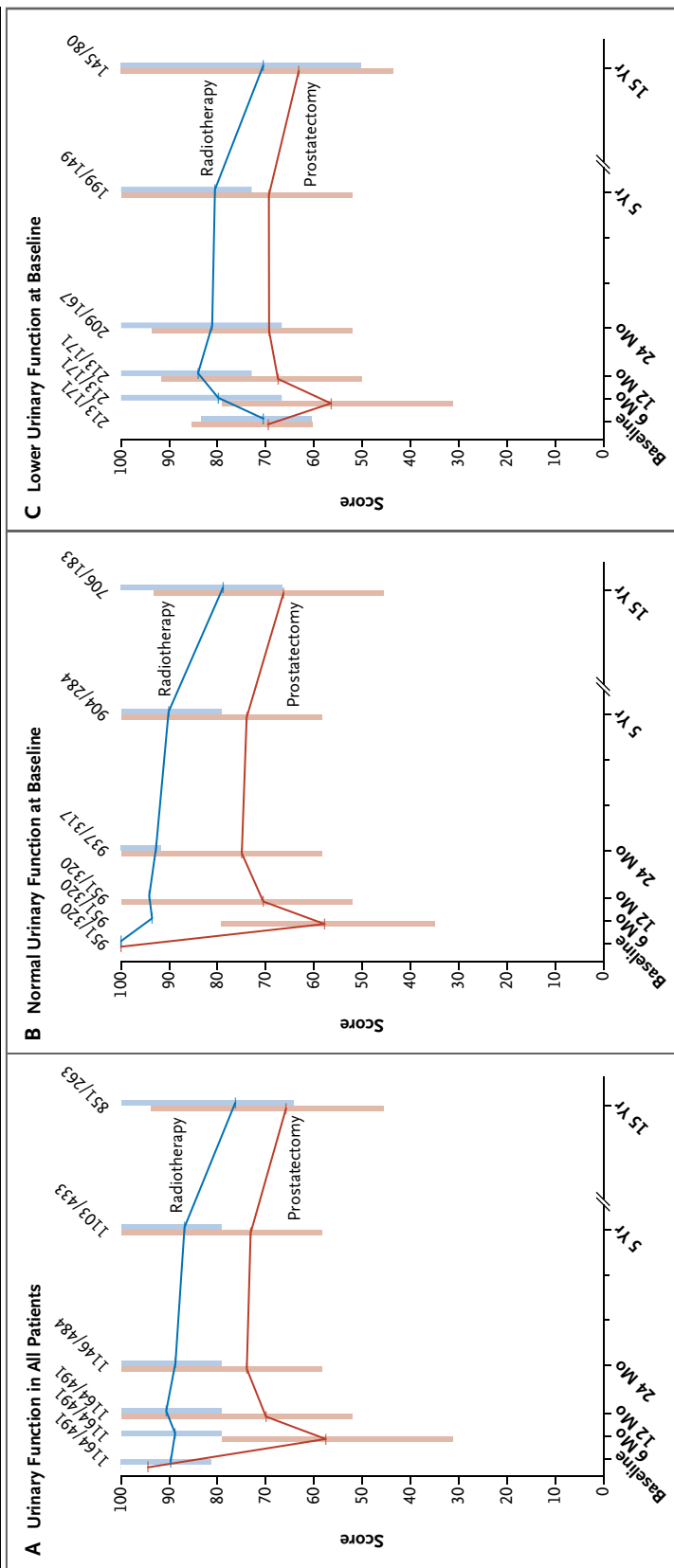
Shown is a longitudinal evaluation of mean unadjusted summary scores for urinary function in the overall cohort (Panel A), in a subgroup of men with normal urinary function at baseline (summary score, 100) (Panel B), and in a subgroup of men with lower urinary function at baseline (summary score, <100) (Panel C), according to whether they underwent either prostatectomy or radiotherapy for prostate cancer. Bars represent interquartile ranges. The numbers of patients who were evaluated in the prostatectomy group and the radiotherapy group, respectively, are listed for each time point.

(odds ratio, 0.47; 95% CI, 0.26 to 0.84) (Table 2). However, at 15 years, despite absolute differences in the prevalence of bowel urgency between the prostatectomy group and the radiotherapy group (21.9% vs. 35.8%), we observed no significant difference in the adjusted odds of bowel urgency (odds ratio, 0.98; 95% CI, 0.45 to 2.14). Patients who received radiotherapy reported being significantly more bothered by bowel symptoms at both the 2-year and 15-year time points. Although small absolute differences in the likelihood of painful bowel movements were observed throughout the study, we observed no significant relative difference in the likelihood of painful bowel movements at any time point (Table S2 in the Supplementary Appendix).

Figure 3 illustrates the temporal changes in overall bowel function. Patients with a baseline summary score for bowel function of less than 100 were considered to have lower baseline bowel dysfunction. Patients had a slight decline in the overall mean summary score for bowel function from 5 to 15 years, regardless of study group or baseline function. Mean bowel-function scores were lower for men who had undergone radiotherapy at each time point.

DISCUSSION

Disease-specific health-related outcomes regarding quality of life are essential components of decision making for any man with prostate cancer.²¹⁻²³ However, the literature largely reports only outcomes that are short-term (1 to 3 years) or intermediate-term (4 to 5 years), which may not reflect the long-term experience of men undergoing treatment for prostate cancer. We have previously reported short- and intermediate-term functional outcomes after prostatectomy or ra-



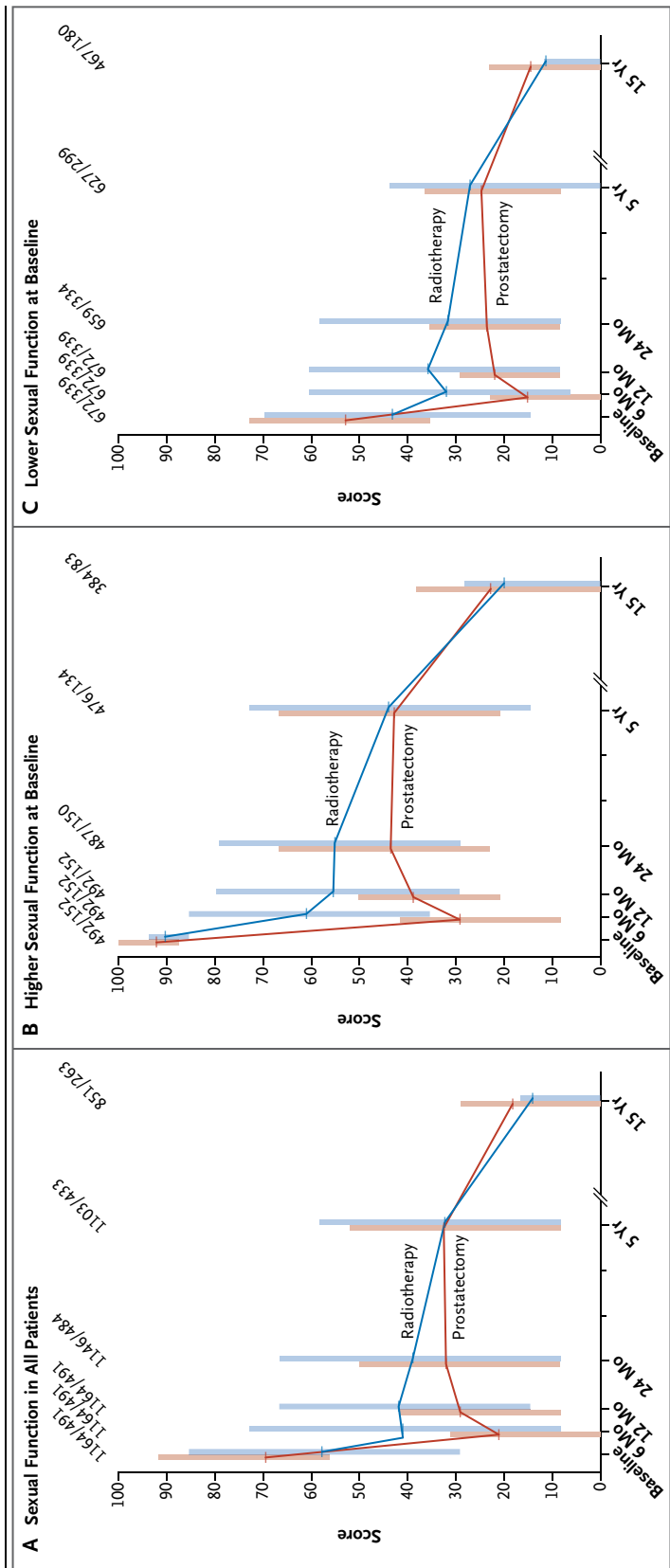


Figure 2. Sexual Function over 15 Years.
 Shown is a longitudinal evaluation of mean unadjusted summary scores for sexual function in the overall cohort (Panel A), in a subgroup of men with higher sexual function at baseline (summary score, ≥ 80) (Panel B), and in a subgroup of men with lower sexual function at baseline (summary score, < 80) (Panel C). The range of possible scores is from 0 to 100, with higher scores indicating better function. Bars represent interquartile ranges. The numbers of patients who were evaluated in the prostatectomy group and the radiotherapy group, respectively, are listed for each time point.

diotherapy for localized prostate cancer in the PCOS.⁷⁻⁹ This report of 15-year outcomes represents a mature portrait of patient-reported, disease-specific health-related quality-of-life outcomes in a population-based longitudinal cohort.

Assessment of 5-year outcomes in the current study revealed numerous differences between the two study groups. Specifically, men who underwent prostatectomy were five times as likely as those who underwent radiotherapy to have urinary incontinence and twice as likely to have erectile dysfunction. Furthermore, at 5 years, men in the prostatectomy group were more likely to be bothered by urinary incontinence than were those in the radiotherapy group (odds ratio, 7.66; 95% CI, 2.90 to 19.89). Despite these differences, we observed no significant differences in the adjusted odds of urinary incontinence or erectile dysfunction between the two study groups at 15 years.

Our study has a number of important findings. At 15 years, the prevalence of erectile dysfunction was nearly universal, affecting 87.0% of men in the prostatectomy group and 93.9% of those in the radiotherapy group. Nonetheless, only 43.5% of men in the prostatectomy group and 37.7% of those in the radiotherapy group reported being bothered with respect to sexual symptoms. The possible reasons for the second finding include declining sexual interest with age, acceptance of sexual dysfunction over time, or both. Despite some evidence of stabilization or improvement of urinary and sexual symptoms from 2 to 5 years, long-term follow-up reveals consistent functional declines after 5 years. It remains unknown whether this continued decline is due to prostate cancer and its treatment, the normal aging process, or a combination of factors.

Multiple reports have detailed significant

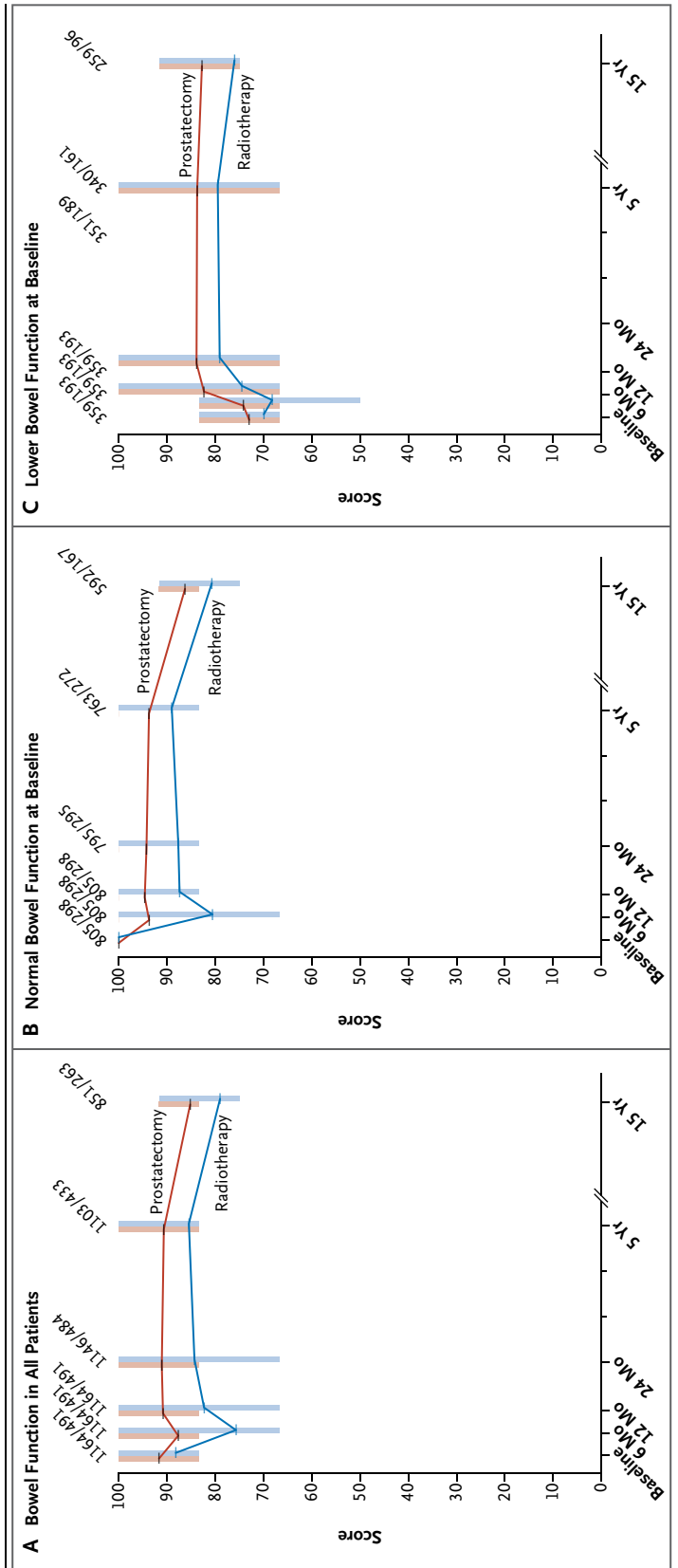
Figure 3. Bowel Function over 15 Years.

Shown is a longitudinal evaluation of mean unadjusted summary scores for bowel function in the overall cohort (Panel A), in a subgroup of men with normal bowel function at baseline (summary score, 100) (Panel B), and in a subgroup of men with lower bowel function at baseline (summary score, <100) (Panel C). Bars represent interquartile ranges. The numbers of patients who were evaluated in the prostatectomy group and the radiotherapy group, respectively, are listed for each time point.

functional declines after either prostatectomy or radiotherapy for prostate cancer. Sanda et al.²⁴ found that 58% of men who had undergone prostatectomy and 60% of those who had undergone radiotherapy had poor-quality erections 2 years after treatment. Furthermore, 14% of men who had undergone prostatectomy and 7% of those who had undergone radiotherapy had urinary incontinence.²⁴ Various investigators have reported similar short- and medium-term declines in diverse populations within different health care systems.²⁵⁻²⁹

The Scandinavian Prostate Cancer Group 4 (SPCG-4) trial,³⁰ in which men were randomly assigned to undergo prostatectomy or monitoring only (“watchful waiting”), recently reported quality-of-life outcomes at a median follow-up of 12.2 years. Similar to long-term data from the PCOS, erectile dysfunction (84%) and sexual distress (48%) were common among men who had undergone prostatectomy. They were also more likely to have daily urinary incontinence than were those assigned to watchful waiting. Unlike the results from the PCOS, which revealed some recovery in erectile function up to 5 years, longitudinal outcomes from the SPCG-4 trial did not show the same trends with respect to the risk of erectile dysfunction, with rates of 80% at 2 to 3 years, 78% at 4 to 5 years, and 83% at 6 to 8 years.³⁰ Certainly, differences in time-dependent rates of sexual dysfunction may be related to differences in clinical and disease characteristics between the two study populations.

Regardless of treatment, patients in the PCOS had significant declines in sexual and urinary function over the duration of the study. The causes of these declines probably include both advancing age and additional cancer treatments. Indeed, patients without prostate cancer have age-related urinary and sexual dysfunction. Litwin,³¹ who administered the University of California Los



Angeles Prostate Cancer Index (UCLA-PCI) to a population of 598 men (median age, 73 years) without prostate cancer, found that 50% were unable to achieve an erection sufficient for intercourse and 32% were unable to achieve an erection sufficient for any sexual activity. Urinary incontinence was reported in 31% of men, with at least weekly urinary incontinence reported in 18%. In their report on 5-year functional outcomes in men with localized prostate cancer and matched controls, Hoffman et al.³² found a decline in sexual function among controls, although the magnitude of this change was far less than that of men treated for prostate cancer. Furthermore, although urinary and bowel function remained stable in the control group, men with prostate cancer had declines in both urinary and bowel function. A recent cross-sectional report from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial reported similar findings at 10 years.³³ Despite these data, the longitudinal evolution of these changes from 5 years to 15 years in men without prostate cancer remains unknown.

Several limitations of this study must be considered when interpreting these results. At the time of the long-term survey, there were between-group differences in rates of questionnaire nonresponse that were largely the result of differential death rates according to treatment. Although data imputation minimizes bias associated with differential nonresponse, nonrandom loss to follow-up may introduce systematic bias. Furthermore, both death and loss to follow-up result in a sample-size reduction that may have limited our ability to detect small differences between the two study groups. This may explain the observed absolute differences in functional outcomes in the absence of significant relative differences. Although an analysis of propensity scoring addresses known confounding, it cannot control for confounding because of unmeasured charac-

teristics. Like all other PCOS analyses, measures of baseline function were ascertained 6 months after diagnosis. Retrospective recall of baseline function may differ from prospective assessment, though data suggest that recall is likely to have a small effect on estimates of change over time.¹⁰ In addition, although this analysis evaluated urinary incontinence, only the 15-year survey included irritative voiding dysfunction, thereby limiting the longitudinal evaluation of this domain. Finally, although we evaluated the comparative harms of prostatectomy and radiotherapy, the precise contribution of prostate-cancer treatment to age-dependent changes in urinary, sexual, and bowel function remains unknown, given the absence of an untreated, age-matched control cohort.

In conclusion, men undergoing prostatectomy or radiotherapy for localized prostate cancer had declines in all functional outcomes throughout early, intermediate, and long-term follow-up. Whereas short- and intermediate-term data reveal differences in functional profiles among men undergoing prostatectomy and radiotherapy, at 15 years we observed no significant relative between-group differences. Considering the often long duration of survival after treatment for prostate cancer, these data may be used to counsel men considering treatment for localized disease.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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