

NEOADJUVANT HORMONAL THERAPY AND OLDER AGE ARE ASSOCIATED WITH ADVERSE SEXUAL HEALTH-RELATED QUALITY-OF-LIFE OUTCOME AFTER PROSTATE BRACHYTHERAPY

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ABSTRACT

Objectives. Brachytherapy is increasingly used as a treatment for localized prostate cancer but information regarding long-term, postimplantation, patient-reported sexual health-related quality-of-life (HRQOL) is scant. Neoadjuvant hormonal therapy is commonly administered with brachytherapy, yet its potentially adverse effects on subsequent sexual health have not been described using a validated HRQOL instrument. We used a validated HRQOL survey to characterize the significance of neoadjuvant hormonal therapy and other baseline factors on postimplantation sexual function and impairment.

Methods. A cross-sectional survey using the expanded prostate cancer index composite HRQOL instrument was administered to all 114 localized prostate cancer patients who underwent ultrasound-guided, transperineal brachytherapy during a 4-year period and to 142 age-matched control men. Multivariable models measured the association of baseline factors and covariates with postimplantation sexual HRQOL.

Results. Older age ($P = 0.01$) and neoadjuvant hormonal therapy ($P = 0.009$) were independently associated with diminished sexual HRQOL after prostate brachytherapy. Among patients younger than 69 years old, 33% reported at least fair sexual function after brachytherapy alone compared with 19% of men after brachytherapy with neoadjuvant hormonal therapy. Of the age-matched control men younger than 69 years old, 78% reported at least fair sexual function. Among patients older than 69 years, 26% reported at least fair sexual function after brachytherapy alone compared with 5% after brachytherapy with neoadjuvant hormonal therapy, and 61% of age-matched controls reported at least fair sexual function.

Conclusions. Patient age and neoadjuvant hormonal therapy are independent, significant determinants of sexual HRQOL after prostate brachytherapy. These factors should be taken into consideration when counseling patients with localized prostate cancer regarding the expected, postimplantation sexual HRQOL outcome. UROLOGY 59: 480–484, 2002. © 2002, Elsevier Science Inc.

Physician-reported outcomes from select series have suggested that brachytherapy may have less morbidity than historical results with conventional therapies.^{1,2} Indeed, untoward effects on erectile function early after implantation may be modest.³ However, longer follow-up at leading

brachytherapy centers has shown a substantial prevalence of later onset erectile dysfunction.^{3–5}

Validated instruments are pivotal for accurately detecting health-related quality-of-life (HRQOL) outcomes from an unbiased patient perspective.⁶ However, patient-reported data regarding long-term brachytherapy effects on sexual HRQOL have been sparse.^{7–9} Consequently, factors affecting postimplantation sexual functioning have not been fully characterized. With prospective data not yet available, cross-sectional studies provide a unique resource for evaluating such factors.¹⁰ To address the hypothesis that baseline clinical factors can affect long-term, postbrachytherapy sexual HRQOL, factors affecting sexual HRQOL were analyzed in a

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cross-sectional study of brachytherapy patients and age-matched controls.

MATERIAL AND METHODS

SUBJECTS

Patients who underwent brachytherapy as primary prostate cancer therapy between June 1995 and May 1999 (n = 114) and 142 age-matched men without prostate cancer were eligible for an institutional review board-approved cross-sectional HRQOL survey after various prostate cancer therapies.^{11,12} The control group was identified from the Pepper Center Subjects Registry at the University of Michigan. Enrollees in this registry are community-dwelling older adults who have agreed to be interviewed for research studies and to provide demographic and health status information. Preliminary screening of the registry data identified a cancer and surgery-free sample that was frequency matched to the treatment group by decade of age. Of the eligible patients and controls, 74% and 78%, respectively, participated. The current analysis focused on sexual HRQOL reported by brachytherapy subjects from among the broader participating cohort.¹² The median age was 68.5 years, median preimplantation prostate-specific antigen (PSA) level was 6.3 ng/mL, median Gleason score was 6, and median time since seed implantation was 1.6 years; 51% received neoadjuvant hormonal therapy.

Prostate brachytherapy was performed as previously described,¹² using transrectal ultrasound guidance to guide delivery of 160 Gy by iodine-125 implants for patients treated with brachytherapy alone and 80 Gy by iodine-125 for patients undergoing brachytherapy combined with external beam radiation. Neoadjuvant hormonal therapy (luteinizing hormone-releasing hormone agonist) was administered to 43 men for a median duration of 3 months. External radiation without hormonal neoadjuvant was administered in 15 patients; hormonal neoadjuvant was administered without external radiation in 23 patients; external radiation and hormonal adjuvant were both administered in 20 patients; and neither was administered in 26 patients. Indications for neoadjuvant hormonal therapy included either the presence of high-risk cancer or large prostate size, and the indication for external radiation was moderate risk or worse cancer.

MEASURES

The 13-item expanded prostate cancer index composite (EPIC)-sexual HRQOL domain augments the 9-item University of California, Los Angeles-Prostate Cancer Index sexual domain with items regarding orgasm and a multi-item set regarding bother.^{6,11} The EPIC-sexual item set contains two conceptually distinct types of questions that reflect either sexual symptom severity (measured by the function subscale) or patient value regarding these symptoms (the bother subscale). These subscales are scored on a scale from 0 to 100, with higher scores representing a better health state.

STATISTICAL ANALYSIS

Analysis of covariance was used to determine the association of baseline and demographic characteristics with the postimplantation sexual HRQOL. The comorbidities evaluated in the model included age, time since seed implantation, baseline PSA, Gleason score, clinical stage, use of neoadjuvant external radiation therapy, and use of neoadjuvant hormonal therapy. Analyses were performed at the 5% significance level and conducted using Statistical Analysis System software (SAS Institute, Cary, NC).

TABLE I. Results of a multivariable regression model evaluating baseline determinants of postbrachytherapy sexual HRQOL outcome*

Variable	Effect Size (Parameter Estimate)	P Value
Age	-0.93	0.013
Neoadjuvant hormonal therapy	-14.36	0.009

KEY: HRQOL = health-related quality-of-life; EPIC = expanded prostate cancer index composite; PSA = prostate-specific antigen.

* Sexual HRQOL outcome measured by EPIC-sexual summary score; variables included in the multivariable regression included age, time since seed implantation, baseline PSA, Gleason score, clinical stage, use of neoadjuvant external radiation therapy, and use of neoadjuvant hormonal therapy. Criteria for removing variables from the analysis included P > 0.10 until the final model (shown) was generated. Forcing nonsignificant variables into the model did not reduce the significance of age or neoadjuvant hormonal therapy.

RESULTS

Analyses relating pretherapy clinical factors with postimplantation sexual HRQOL indicated that neoadjuvant hormonal therapy and increasing age were each independently associated with worse sexual health at an average of 22 months after prostate brachytherapy (Table I). The significance of age and neoadjuvant hormonal therapy was retained even when Gleason score and baseline PSA were forced into the model. These effects are illustrated in the observed mean EPIC-sexual summary and subscale scores stratified by age and neoadjuvant hormonal therapy (Table II). The EPIC-sexual summary and subscale scores from age-matched control men provide a context that shows the clinical relevance of the average long-term sexual HRQOL outcome after prostate brachytherapy. Another context for interpreting these HRQOL score differences is that one half the standard deviation of an HRQOL score is considered a threshold for a clinically meaningful difference. This threshold equals 12 for the EPIC-sexual summary score or function subscale and 15 for the bother subscale. The HRQOL differences between the groups in Table II generally exceeded these thresholds.

To demonstrate the untoward effects that age and neoadjuvant hormonal therapy have on sexual functioning after prostate brachytherapy, patient responses to specific EPIC-sexual questions were stratified by these factors (Table III). The adverse practical implications of neoadjuvant hormone therapy and age older than 69 years could be seen across a spectrum of sexual function characteristics. The responses by age-matched controls also provided a practical context of expected sexual function, although such controls may not reflect how cancer itself may affect sexuality.

To examine the effects of time elapsed after pros-

TABLE II. Sexual HRQOL scores for brachytherapy patients and age-matched control men as a function of age and neoadjuvant hormonal therapy

Sexual Index Score	Age <69 yr*			Age ≥69 yr		
	BT Only (n = 20)	BT with NHT (n = 22)	Control Men (n = 44)	BT Only (n = 21)	BT with NHT (n = 21)	Control Men (n = 67)
Summary	43 (28–58)	29 (17–41)	67 (61–72)	33 (21–44)	18 (11–25)	54 (47–61)
Function	38 (24–52)	27 (15–38)	62 (56–67)	25 (13–37)	12 (6–18)	48 (40–55)
Bother	46 (30–62)	34 (21–47)	78 (71–84)	40 (26–55)	26 (13–39)	69 (60–78)

KEY: BT = brachytherapy; NHT = neoadjuvant hormonal therapy.

Numbers in parentheses are 95% confidence intervals.

* 69 years was the median age of the BT cohort.

TABLE III. Distribution of responses by brachytherapy patients and age-matched control men to specific items from the EPIC instrument

Response to EPIC Question	Age <69 yr*			Age ≥69 yr		
	BT Only	BT with NHT	Control Men	BT Only	BT with NHT	Control Men
Sufficiently firm erection for intercourse	28%	23%	74%	32%	10%	55%
Achieve erections >50% of time desired	28%	19%	74%	28%	0%	56%
At least fair sexual function	33%	19%	78%	26%	5%	61%
Small or no sexual impairment	40%	41%	87%	50%	26%	79%

Abbreviations as in Tables I and II.

* Represents median age of BT cohort.

TABLE IV. Sexual HRQOL in brachytherapy patients as a function of time since interstitial seed implant

Sexual Index Score	Interval After Brachytherapy			Age-Matched Controls (n = 111)
	4–12 months (n = 23)	12–24 months (n = 34)	>24 months* (n = 27)	
Summary	38 (23–54)	29 (20–38)	26 (18–34)	61 (57–66)
Function	32 (18–47)	24 (16–32)	20 (12–28)	56 (51–60)
Bother	45 (27–63)	36 (26–46)	31 (20–42)	74 (69–80)

KEY: HRQOL = health-related quality of life.

Numbers in parentheses are 95% confidence intervals.

* Median time since treatment for patients in the >24-month group was 33 months (range 24–48).

tate implantation on sexual health, the mean EPIC-sexual summary and subscale scores were stratified by the number of years since implantation (Table IV). The deterioration of the observed mean postbrachytherapy sexual HRQOL appeared to continue beyond 24 months after prostate implantation. Less than 15% of subjects had follow-up longer than 36 months, and the possibility of additional changes with longer follow-up cannot be excluded.

COMMENT

Information regarding the prognostic factors affecting postbrachytherapy sexual functioning has been sparse. This may in part be explained by the

paucity of postbrachytherapy sexual outcome data measured by valid HRQOL instruments. In addition to providing information from the patient's perspective, the ability of validated HRQOL instruments to quantify sexual function renders these tools ideally suited for characterizing HRQOL prognostic factors. Validated instruments can measure HRQOL outcome by a continuous scale, thereby allowing concurrent assessment of several items contributing to an HRQOL domain, while also allowing greater power in detecting effects at smaller sample size.¹³

In this context, we detected an adverse association between sexual function after prostate brachytherapy and older age or use of neoadjuvant hor-

monal therapy. Of several prior studies, only one recent study has found an association of these two factors (age and neoadjuvant hormonal therapy) with sexual function outcome after brachytherapy.^{2-4,14,15} However, this preceding study did not use patient-report methods with a validated HRQOL instrument, and so our findings using a validated instrument can be considered as complementary to those of Potters *et al.*¹⁵ Two possible explanations for why some studies of physician-reported data did not detect the adverse prognostic effects of these factors include that neoadjuvant hormonal therapy prevalence and age distribution may have been lower in prior studies and that physician-report data typically reported sexual function as a dichotomized variable. Moreover, prior studies using valid HRQOL measures of sexual function after brachytherapy focused on early follow-up, before radiation has had its full effect on pelvic tissues.⁷ A long-term physician report study showed a median time to impotence after prostate brachytherapy of 17 months.⁴ Of interest, we did not detect an independent adverse effect of external radiation given with brachytherapy, but this may have been because of the small sample size, which precludes definitive conclusions regarding the independent effects of concurrent external radiation. Our observations confirmed that sexual function can continue to decline beyond the first year after implantation, and our age-matched control data suggest that this decline is more than would be expected from age alone. Sexual HRQOL measured in only the first year after prostate brachytherapy therefore would not be expected to measure the full impact of brachytherapy on long-term sexual functioning adequately.

The limitations of this study include a single institution setting and a cross-sectional design. However, the utility of cross-sectional studies in identifying factors pivotal for eventual long-term outcome is well established.¹⁰ The use of age-matched controls to provide a context for our findings also addresses the limitations of a cross-sectional study, such as the lack of baseline HRQOL measures. Nevertheless, the possibility of selection bias does indicate a need for prospective evaluation of age, neoadjuvant hormonal therapy, and other HRQOL prognostic factors.^{10,13} For example, the nonrandomized use of neoadjuvant hormonal therapy or external radiation in conjunction with prostate brachytherapy reflects a selection bias regarding these factors in our study. The adjustment for comorbidities in the present study was limited to multivariable analysis of covariance that included age, cancer stage, grade, baseline PSA, time since therapy, use of external radiation, and neoadjuvant hormonal therapy; other comorbidities

were not measured. Although our study was conducted at a single institution, the observed sexual HRQOL outcomes for young men (less than 69 years old) who did not receive neoadjuvant hormonal therapy in this cohort were not dissimilar from that of prior reports with long-term follow-up.^{4,5,9}

CONCLUSIONS

Information regarding the association of patient baseline and treatment characteristics with post-brachytherapy sexual health has been limited. Patients who undergo brachytherapy for localized prostate cancer may retain better postbrachytherapy sexual health when treated at a younger age or if neoadjuvant hormonal therapy is avoided.

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