2017

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Hiram A. Gay
Washington University School of Medicine in St. Louis

Jiangxia Liu
Washington University School of Medicine in St. Louis

Ningying Wu
Washington University School of Medicine in St. Louis

Jeff M. Michalski
Washington University School of Medicine in St. Louis

et al

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

External Beam Radiation Therapy or Brachytherapy With or Without Short-course Neoadjuvant Androgen Deprivation Therapy: Results of a Multicenter, Prospective Study of Quality of Life

Hiram A. Gay, MD,[*] Martin G. Sanda, MD,[†] Jingxia Liu, PhD,[‡] Ningying Wu, PhD,[‡] Daniel A. Hamstra, MD, PhD,[§] John T. Wei, MD,[‖] Rodney L. Dunn, MS,[‖] Eric A. Klein, MD,[¶] Howard M. Sandler, MD,[#] Christopher S. Saigal, MD, MPH,[**] Mark S. Litwin, MD, MPH,[,††] Deborah A. Kuban, MD,[‡‡] Larry Hembroff, PhD,[§§] Meredith M. Regan, ScD,[‖‖] Peter Chang, MD,[¶¶] the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment Consortium, and Jeff M. Michalski, MD[*]**

Department of Radiation Oncology, and [‡]Division of Public Health Sciences, Washington University School of Medicine, St. Louis, Missouri; [†]Department of Urology, Emory University School of Medicine, Atlanta, Georgia; [§]Texas Center for Proton Therapy, Irving, Texas; [‖]Department of Urology, University of Michigan, Ann Arbor, Michigan; [¶]Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio; [#]Department of Radiation Oncology, Cedars-Sinai Medical Center; **Department of Urology, and [††]Health Policy and Management, University of California at Los Angeles, Los Angeles, California; [‡‡]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [§§]Institute for Public Policy and Social Research, Michigan State University, East Lansing, Michigan; and [‖‖]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, and [¶¶]Department of Surgery, Beth Israel-Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Received Nov 2, 2016, and in revised form Feb 7, 2017. Accepted for publication Feb 13, 2017.

Reprint requests to: Hiram A. Gay, MD, Department of Radiation Oncology, Washington University School of Medicine, 4921 Parkview Place, Campus Box 8224, St. Louis, MO 63110. Tel: (314) 362-8516; E-mail: hiramgay@wustl.edu

The present study was supported by National Cancer Institute grant 5R01CA095662 and National Institutes of Health grant 1RC1CA146596.

Conflict of interest: none.

The Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment Consortium: the PROST-QA Consortium includes contributions in cohort design, participant accrual, and follow-up from the following investigators: Meredith Regan (Dana Farber Cancer Institute, Boston, Massachusetts); Larry Hembroff (Michigan State University, East Lansing, Michigan); John T. Wei, Dan Hamstra, Rodney Dunn, Laurel Northouse, and David Wood (University of Michigan, Ann Arbor, Michigan); Eric A. Klein and Jay Ciezki (Cleveland Clinic, Cleveland, Ohio); Jeff Michalski and Gerald Andriole (Washington University, St. Louis, Missouri); Mark S. Litwin and Christopher Saigal (University of California, Los Angeles, Los Angeles, California); Thomas Greenfield, PhD (Berkeley, California), Louis Pisters and Deborah Kuban (MD Anderson Cancer Center, Houston, Texas); Howard Sandler (Cedars Sinai Medical Center, Los Angeles, California); Jim Hu and Adam Kibel (Brigham and Women's Hospital, Boston, Massachusetts); Douglas Dahl and Anthony Zietman (Massachusetts General Hospital, Boston, Massachusetts); Peter Chang, Irving Kaplan, and Andrew Wagner (Beth Israel Deaconess Medical Center, Boston, Massachusetts), and Martin G. Sanda (Emory University, Atlanta, Georgia).

Acknowledgments—We acknowledge the PROST-QA Data Coordinating Center; project management by Jill Hardy, MS (Michigan State University, East Lansing, MI), Erin Najuch and Jonathan Chipman (Dana Farber Cancer Institute, Boston, MA), Dattatraya Patil, MBBS, MPH (Department of Urology, Emory University, Atlanta, GA), and Catrina Crociani, MPH (Beth Israel Deaconess Medical Center, Boston, MA); grant administration by Beth Doiron, BA (Beth Israel Deaconess Medical Center, Boston, MA); and technical support from the coordinators at each clinical site.

Int J Radiation Oncol Biol Phys, Vol. 98, No. 2, pp. 304–317, 2017

http://dx.doi.org/10.1016/j.ijrobp.2017.02.019

Summary

We evaluated health-related quality of life for 2 years among 573 participants undergoing external beam radiation therapy (EBRT) or brachytherapy, with or without neoadjuvant androgen deprivation therapy for newly diagnosed, early-stage prostate cancer. At 2 years, participants receiving neoadjuvant androgen deprivation therapy plus EBRT compared with EBRT alone had a worse ability to reach an orgasm, erection quality, and ability to function sexually. However, differences in the ability to have an erection, frequency of erections, sexual function, hot flashes, breast tenderness, depression, lack of energy, and body weight did not reach statistical significance.

Purpose: The long-term effects of neoadjuvant androgen deprivation therapy (NADT) with radiation therapy on participant-reported health-related quality of life (HRQOL) have not been characterized in prospective multicenter studies. We evaluated HRQOL for 2 years among participants undergoing radiation therapy (RT) with or without NADT for newly diagnosed, early-stage prostate cancer.

Methods and Materials: We analyzed longitudinal cohort data from the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment Consortium to ascertain the HRQOL trajectory of men receiving NADT with external beam RT (EBRT) or brachytherapy. HRQOL was measured using the expanded prostate cancer index composite 26-item questionnaire at 2, 6, 12, and 24 months after the initiation of NADT. We used the χ^2 or Fisher exact test to compare the shift in percentages between groups that did or did not receive NADT. Analyses were conducted at the 2-sided 5% significance level.

Results: For subjects receiving EBRT, questions regarding the ability to have an erection, ability to reach an orgasm, quality of erections, frequency of erections, ability to function sexually, and lack of energy were in a significantly worse dichotomized category for the patients receiving NADT. Comparing the baseline versus 24-month outcomes, 24%, 23%, and 30% of participants receiving EBRT plus NADT shifted to the worse dichotomized category for the ability to reach an orgasm, quality of erections, and ability to function sexually compared with 14%, 13%, and 16% in the EBRT group, respectively.

Conclusions: Compared with baseline, at 2 years, participants receiving NADT plus EBRT compared with EBRT alone had worse HRQOL, as measured by the ability to reach orgasm, quality of erections, and ability to function sexually. However, no difference was found in the ability to have an erection, frequency of erections, overall sexual function, hot flashes, breast tenderness/enlargement, depression, lack of energy, or change in body weight. The improved survival in intermediate- and high-risk patients receiving NADT and EBRT necessitates pretreatment counseling of the HRQOL effect of NADT and EBRT.

Introduction

Androgen deprivation therapy (ADT) strategies play a crucial role in the radiotherapeutic management of intermediate- and high-risk prostate adenocarcinoma. The addition of short-term and long-term ADT to radiation therapy (RT), respectively, has improved overall and cancer-specific survival in multiple randomized trials (1-8). Despite its benefits, ADT has a number of potential side effects, including sexual dysfunction (9), osteoporosis and bone fractures (10), vasomotor symptoms (hot flashes) (11), decreased muscle and increased fat (12), fatigue (13), anemia (14), and thromboembolic events (15), among others. However, a systematic evaluation of health-related quality of life (HRQOL) has not been a component of most of these trials.

The time course and severity of ADT side effects in men receiving definitive RT for prostate cancer has not been extensively characterized using validated, participant-reported HRQOL instruments. A recent report from the PROST-QA (Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment) consortium focused on the short-term (2-month) effects of neoadjuvant ADT (NADT) (16). In the present study, we compared the HRQOL outcomes over time in men receiving external beam RT (EBRT) or brachytherapy (BT) with or without NADT.

Methods and Materials

Centers and subjects

We analyzed the longitudinal cohort data from the PROST-QA consortium, a multi-institutional prospective study conducted at 9 university-affiliated clinical sites across the United States. Participants with early-stage (stage T1 or T2) prostate cancer were recruited from 2003 to 2006 (17). The institutional review boards approved the study, which was judged compliant with the Health Insurance Portability and Accountability Act at each center. Participants were ineligible for the study if they had received any previous therapy for prostate cancer. All participants provided written, informed consent to participate.

In the PROST-QA trial, primary treatment could consist of radical prostatectomy, EBRT, or BT. The selection of the primary treatment modality was left to the discretion of the

treating physician and the participant. At the present analysis, 1201 men with localized prostate cancer had been registered to the PROST-QA study. Of these 1201 men, 603 (50.2%) had elected to undergo radical prostatectomy, 5 (0.42%) had undergone >12 months of NADT, 288 (24.0%) had received EBRT, 285 (23.7%) had received BT, and another 20 (1.7%) had received a combination of EBRT with a BT boost or ADT, or both.

The decision to administer NADT was left to the treating physician and typically started 2 months before the initiation of RT. We decided to focus the present analysis on the participants who had undergone definitive EBRT or BT monotherapy with or without NADT for ≤12 months. In the BT plus NADT group, the median ADT duration was 4 months (range 1-8), and in the EBRT plus NADT group, the median ADT duration was 3 months (range 1-12). Specifically, 202 participants received EBRT only, 86 received EBRT plus NADT, 271 received BT only, and 14 received BT plus NADT. NADT consisted of luteinizing hormone-releasing hormone agonists and/or antiandrogens. Two patients in the EBRT plus NADT group and four in the BT plus NADT group received antiandrogens only. Of the patients receiving EBRT plus NADT or BT plus NADT, 79% and 91% had received <6 months of NADT, respectively.

Measures

At registration, the pretreatment demographics, cancer severity, and treatment details were recorded. HRQOL was measured using the expanded prostate cancer index composite 26-item (EPIC-26) instrument self-reported by computer-assisted telephone interviews before NADT and at 2, 6, 12, and 24 months after NADT. The EPIC 26-item questionnaire has been validated (18) and measures prostate cancer-specific HRQOL (19) in men with early- and advanced-stage prostate cancer. The questionnaire consists of 4 summary domains (urinary, bowel, sexual, and vitality/hormonal) and 2 urinary subscales (incontinence and irritative/obstructive). Each summary domain contains function and bother subscales. The participants' responses to questions are transformed to a 0 to 100 scale, for which higher scores represent better HRQOL. Norman et al (20) defined a clinically meaningful change in function as a change of greater than one half the standard deviation in an HRQOL score.

Six questions in the sexual domain and five in vitality/hormonal domain were analyzed. A previous study focused on the short-term effects of ADT (16) at 2 months. In the present study, we focused on the longer term responses at 6, 12, and 24 months.

Statistical analysis

The responses to the individual questions were dichotomized (see Tables 2 and 4), thus combining ≥1 higher severity items in 1 category and ≥1 items of less severity in another the same as in the original report (17). For a given treatment modality, the responses were further grouped according to NADT or no NADT. The descriptive percentages of responses per group were reported according to treatment modality: EBRT (see Tables 2 and 4) and BT (see Tables 3 and 5). The power to detect an effect size of 0.5 using the sample size of 14 participants in the BT plus NADT group and 271 participants in the BT group was only 44.4%, with a type I error of 5%. The generalized estimating equation (GEE) model was used to analyze the longitudinal data, in which the correlation among the repeated measures from the same participant are considered. The *P* values of the interaction term in the GEE model were estimated to assess whether the percentages at each measurement point between the no-NADT and NADT groups were the same. The GEE model did not work for some questions because of the small sample size; in those cases, the Cochran-Mantel-Haenszel test was used. Missing data were treated as missing at random and excluded from the GEE analysis.

The percentage of difference for the participants who shifted to the worse dichotomized category for a given question was calculated for the baseline versus 24-month and 6-month versus 24-month values (see Table 6). We chose these comparisons because we sought to compare the baseline values with the least symptoms versus the long-term or 24-month point and at 6 months, when symptoms tend to be worse, versus the long-term or 24-month point. The χ^2 or Fisher exact test was used to compare the percentages of shift between the no-NADT and NADT groups. All analyses were conducted using SAS (SAS Institute, Cary, NC) at the 2-sided 5% significance level.

Results

The patient characteristics are listed in Table 1. Patients receiving NADT had worse overall cancer severity and, consequently, had higher prostate-specific antigen levels, higher Gleason scores, higher T stages, a greater proportion of biopsy cores with cancer, and higher rates of pelvic lymph nodes treated. The sexual domain responses for the EBRT and BT groups are listed in Tables 2 and 3, respectively. In the sexual domain for the EBRT group, for all questions, except for "how big a problem has your sexual function or lack of sexual function been," a marked statistically significant difference was found between those who did or did not receive NADT. The vitality/hormonal responses for the EBRT and BT groups are listed in Tables 4 and 5, respectively. In the hormonal/vitality domain for the EBRT group, patients receiving NADT reported significantly worse responses statistically for the lack of energy question. Figure 1 shows the 6 statistically significant question comparisons: frequency of erections, quality of erections, ability to have an erection, ability to

Table 1 Patient characteristics

Characteristic	EBRT			BT		
	No NADT (n=202)	NADT (n=86)	*P* value	No NADT (n=271)	NADT (n=14)	*P* value
Age (y)			.03*			.57
Median	69	71		66	67	
Range	45-83	50-85		45-81	52-79	
Age group			.07			.88
<60 y	31 (15)	10 (12)		60 (22)	2 (14)	
60-69 y	88 (44)	28 (32)		130 (48)	7 (50)	
>70 y	83 (41)	48 (56)		81 (30)	5 (36)	
Race			.87			.34
White	162 (81)	71 (85)		235 (88)	11 (7)	
Black	35 (18)	13 (15)		27 (10)	3 (21)	
Other	2 (1)	0 (0)		4 (2)	0 (0)	
Coexisting illnesses	1.5 ± 1.3	1.4 ± 1.2	.39	1.3 ± 1.1	1.5 ± 1.1	.37
BMI (kg/m^2)	28.6 ± 5.3	28.7 ± 5.8	.80	28.4 ± 4.6	28.9 ± 4.8	.76
Prostate size (cm^3)	48.9 ± 26.0	51.4 ± 34.3	.83	38.8 ± 17.7	56.7 ± 12.8	<.0001*
PSA (ng/mL)			<.0001*			.33
Median	5.9	9.1		5.0	6.5	
Range	0.5-25.8	1.6-99.3		0.6-26.4	2.1-44	
PSA group			.0005*			.15
<4 ng/mL	36 (18)	11 (13)		59 (22)	4 (29)	
4-10 ng/mL	133 (66)	43 (50)		199 (73)	8 (57)	
>10 ng/mL	33 (16)	32 (37)		13 (5)	2 (14)	
Gleason score			<.0001*			.18
<7	123 (61)	7 (8)		210 (77)	8 (57)	
7	77 (38)	42 (49)		58 (22)	6 (43)	
>7	2 (1)	37 (43)		2 (1)	0 (0)	
Clinical stage			<.0001*			.47
T1	157 (78)	45 (52)		228 (84)	11 (79)	
T2	45 (22)	41 (48)		42 (16)	3 (21)	
Biopsy cores with cancer (%)	0.3 ± 0.2	0.4 ± 0.3	.0001*	0.3 ± 0.2	0.2 ± 0.2	.42
Overall cancer severity			<.0001*			.07
Low risk	99 (49)	2 (2)		196 (73)	7 (50)	
Intermediate risk	97 (48)	33 (39)		70 (26)	6 (43)	
High risk	6 (3)	51 (59)		4 (1)	1 (7)	
Minimum dose PTV (Gy)			.01*	NA	NA	
Median	70	73				
Range	48-90	41-77				
Maximum dose PTV (Gy)			.79	NA	NA	
Median	80	81				
Range	45-107	46-90				
IMRT			.40	NA	NA	
Yes	162 (85)	71 (89)				
No	29 (15)	9 (11)				
Pelvic lymph nodes treated			<.0001*	NA	NA	
Yes	7 (4)	25 (31)				
No	184 (96)	55 (69)				
Prescribed BT dose (Gy)	NA	NA				.77
Median				144	144	
Range				80-145	137-145	
D90 ETV (Gy)	NA	NA				.51
Median				152	158	
Range				12-346	116-178	
V100 ETV (%)	NA	NA				.60
Median				93	94	
Range				69-100	81-99	

Abbreviations: BMI = body mass index; BT = brachytherapy; D90 = radiation dose delivered to 90% of organ; EBRT = external beam radiation therapy; ETV = evaluation target volume, after implantation; IMRT = intensity modulated radiation therapy; NA = not applicable; NADT = neoadjuvant androgen deprivation therapy; PSA = prostate-specific antigen; PTV = planning target volume; V100 = volume receiving 100% of prescription dose.

Data presented as median and range, n (%), or mean ± standard deviation.

* Statistically significant.

Table 2 External beam radiation therapy only with or without NADT: distribution of participant responses to EPIC sexual HRQOL items at baseline and 6, 12, and 24 months

How would you rate each of the following during the past 4 weeks?	NADT		n	No NADT		n	*P* value*
Your ability to have an erection?	Very poor to none + poor	Fair + good + very good		Very poor to none + poor	Fair + good + very good		.0001†
Baseline	40.5	59.5	84	35.9	64.1	198	
6 mo	82.6	17.4	69	45.2	54.8	177	
12 mo	77.8	22.2	72	47.1	52.9	170	
24 mo	76.1	23.9	67	48.4	51.6	157	
How would you describe the usual quality of your erections during the past 4 weeks?	None at all + not firm enough for sexual activity	Firm enough for masturbation or foreplay + firm enough for intercourse		None at all + not firm enough for sexual activity	Firm enough for masturbation or foreplay + firm enough for intercourse		<.0001†
Baseline	37.0	63.0	81	27.2	72.8	191	
6 mo	81.4	18.6	70	36.6	63.4	175	
12 mo	69.6	30.4	69	37.2	62.8	164	
24 mo	68.2	31.8	66	34.0	66.0	159	
How would you describe the frequency of your erections during the past 4 weeks?	Never + less than half the time wanted + about half the time wanted	More than half the time wanted + whenever wanted		Never + less than half the time wanted + about half the time wanted	More than half the time wanted + whenever wanted		.0001†
Baseline	45.7	54.3	81	43.4	56.6	189	
6 mo	87.9	12.1	66	52.1	47.9	169	
12 mo	80.6	19.4	67	57.1	42.9	163	
24 mo	81.5	18.5	65	59.9	40.1	157	
Your ability to reach orgasm (climax)?	Very poor to none + poor	Fair+ good + very good		Very poor to none + poor	Fair+ good + very good		<.0001†
Baseline	34.6	65.4	81	30.4	69.6	194	
6 mo	84.1	15.9	69	40.5	59.5	173	
12 mo	69.6	30.4	69	43.4	56.6	166	
24 mo	65.2	34.9	66	39.1	60.9	156	
Overall, how would you rate your ability to function sexually during the past 4 weeks?	Very poor + poor	Fair + good + very good		Very poor + poor	Fair + good + very good		<.0001†
Baseline	32.5	67.5	83	34.0	66.0	194	
6 mo	80.9	19.1	68	43.3	56.7	171	
12 mo	74.6	25.4	67	43.4	56.6	168	
24 mo	75.4	24.6	65	44.0	56.0	159	
Overall, how big a problem has your sexual function or lack of sexual function been for you during the past 4 weeks?	Moderate problem + big problem	No problem + very small problem + small problem		Moderate problem + big problem	No problem + very small problem + small problem		.4622
Baseline	15.5	84.5	84	20.3	79.7	197	
6 mo	34.7	65.3	72	29.5	70.5	173	
12 mo	25.7	74.3	70	29.0	71.0	169	
24 mo	34.9	65.2	66	32.3	67.7	161	

Abbreviations: EPIC = extended prostate cancer index composite; HRQOL = health-related quality of life; NADT = neoadjuvant androgen deprivation therapy.

Data presented as percentages, unless otherwise noted.

* *P* value reflects a test of the interaction term between group and the time points in linear generalized estimating equations.

† Statistically significant.

reach an orgasm, ability to function sexually, and lack of energy.

The results of the comparison of the baseline versus 24-month and 6-month versus 24-month percentage of differences for participants who shifted to a worse dichotomized category for a given question are listed in Table 6. When studying the question, "your ability to reach orgasm (climax)," 24.4% of the EBRT plus NADT participants

Table 3 Brachytherapy distribution only with or without NADT of participant responses to EPIC sexual HRQOL items at baseline and 6, 12, and 24 months

How would you rate each of the following during the past 4 weeks?	NADT		n	No NADT		n	*P* value*
Your ability to have an erection?	Very poor to none + poor	Fair + good + very good		Very poor to none + poor	Fair + good + very good		.9501
Baseline	35.7	64.3	14	30.5	69.5	262	
6 mo	61.5	38.5	13	49.0	51.0	241	
12 mo	50.0	50.0	12	46.2	53.8	238	
24 mo	58.3	41.7	12	49.6	50.5	222	
How would you describe the usual quality of your erections during the past 4 weeks?	None at all + not firm enough for sexual activity	Firm enough for masturbation or foreplay + firm enough for intercourse		None at all + not firm enough for sexual activity	Firm enough masturbation or foreplay + firm enough for intercourse		.5041
Baseline	21.4	78.6	14	20.5	79.5	254	
6 mo	53.9	46.2	13	39.4	60.6	236	
12 mo	27.3	72.7	11	31.9	68.1	229	
24 mo	36.4	63.6	11	36.4	63.6	220	
How would you describe the frequency of your erections during the past 4 weeks?	Never + less than half the time wanted + about half the time wanted	More than half the time wanted + whenever wanted		Never + less than half the time wanted + about half the time wanted	More than half the time wanted + whenever wanted		.3714
Baseline	35.7	64.3	14	36.4	63.6	253	
6 mo	76.9	23.1	13	56.7	43.3	231	
12 mo	58.3	41.7	12	53.7	46.3	227	
24 mo	66.7	33.3	12	62.0	38.0	216	
Your ability to reach orgasm (climax)?	Very poor to none + poor	Fair+ good + very good		Very poor to none + poor	Fair+ good + very good		.6923
Baseline	28.6	71.4	14	23.3	76.7	253	
6 mo	61.5	38.5	13	42.6	57.5	235	
12 mo	36.4	63.6	11	36.1	64.0	233	
24 mo	50.0	50.0	12	43.9	56.1	221	
Overall, how would you rate your ability to function sexually during the past 4 weeks?	Very poor + poor	Fair + good + very good		Very poor + poor	Fair + good + very good		.5890
Before NADT	35.7	64.3	14	26.9	73.1	260	
6 mo	61.5	38.5	13	46.9	53.1	239	
12 mo	45.5	55.6	11	42.2	57.8	237	
24 mo	41.7	58.3	12	46.1	53.9	219	
Overall, how big a problem has your sexual function or lack of sexual function been for you during the past 4 weeks?	Moderate problem + big problem	No problem + very small problem + small problem		Moderate problem + big problem	No problem + very small problem + small problem		.8713
Baseline	21.4	78.6	14	17.7	82.3	260	
6 mo	46.2	53.9	13	33.1	67.0	239	
12 mo	45.5	54.6	11	29.0	71.0	238	
24 mo	41.7	58.3	12	28.3	71.8	223	

Abbreviations: EPIC = extended prostate cancer index composite; HRQOL = health-related quality of life; NADT = neoadjuvant androgen deprivation therapy.

Data presented as percentages, unless otherwise noted.

* *P* value reflects a test of the interaction term between group and the time points in linear generalized estimating equations.

compared with 13.9% of the EBRT participants shifted from "fair/good/very good" at baseline to "very poor to none/poor" at 24 months. Also, a statistically significant shift to the worse dichotomized category for the question, "how would you describe the usual quality of your erections during the last 4 weeks?" and "overall, how would you rate your ability to function sexually during the last 4 weeks?" was found between the EBRT plus NADT group (doing worse) and the EBRT groups for the baseline versus 24-month comparison. For the baseline versus 24-

Table 4 External beam radiation therapy only with or without NADT: distribution of participant responses to EPIC hormone/vitality HRQOL items at baseline and 6, 12, and 24 months

Question	NADT			No NADT			
How big a problem during the past 4 weeks, if any, has each of the following been for you?	Moderate problem + big problem	No problem + very small problem + small problem	n	Moderate problem + big problem	No problem + very small problem + small problem	n	*P* value*
Hot flashes							.0924
Baseline	1.2	98.8	84	1.0	99.0	202	
6 mo	33.3	66.7	78	2.2	97.8	182	
12 mo	20.8	79.2	77	0.5	99.5	181	
24 mo	7.3	92.8	69	2.4	97.6	166	
Breast tenderness or enlargement†							.8611
Baseline	0	100	85	1.5	98.5	201	
6 mo	2.6	97.4	78	1.7	98.3	181	
12 mo	1.3	98.7	77	1.7	98.3	181	
24 mo	2.9	97.1	69	1.2	98.8	167	
Depression							.8733
Baseline	3.5	96.5	85	6.9	93.1	202	
6 mo	3.9	96.2	78	6.1	93.9	181	
12 mo	6.5	93.5	77	8.3	91.7	181	
24 mo	5.8	94.2	69	4.8	95.2	167	
Lack of energy							.0003‡
Baseline	5.9	94.1	85	13.9	86.1	202	
6 mo	35.9	64.1	78	14.9	85.1	181	
12 mo	20.8	79.2	77	17.2	82.8	180	
24 mo	15.9	84.1	69	16.8	83.2	167	
Change in body weight							.1251
Baseline	3.6	96.4	84	4.5	95.5	202	
6 mo	12.8	87.2	78	3.9	96.1	181	
12 mo	14.3	85.7	77	3.9	96.1	179	
24 mo	10.1	89.9	69	4.8	95.2	167	

Abbreviations: EPIC = extended prostate cancer index composite; HRQOL = health-related quality of life; NADT = neoadjuvant androgen deprivation therapy.

Data presented as percentages, unless otherwise noted.

* *P* value reflects a test of the interaction term between group and the time points in linear generalized estimating equations.

† Cochran-Mantel-Haenszel test.

‡ Statistically significant.

month comparison for the EBRT plus NADT and EBRT alone groups, no statistically significant shift was found for the hormone/vitality questions.

When examining the 6- versus 24-month sexual comparison (the question, "your ability to have an erection"), 2.3% of the EBRT plus NADT participants and 10.4% of the EBRT participants shifted from "fair/good/very good" at 6 months to "very poor to none/poor" at 24 months. Also, a statistically significant shift was found to the worse dichotomized category for the questions, "your ability to reach orgasm (climax)" and "how would you describe the frequency of your erections during the last 4 weeks" between the EBRT (doing worse) and EBRT plus NADT groups for the baseline versus 24-month comparison. For the 6- versus 24-month comparison for the EBRT plus NADT and EBRT groups, no statistically significant shift was found for the hormone/vitality questions.

For both the baseline versus 24-month and the 6- versus 24-month BT plus NADT versus BT alone comparison, no statistically significant shift was noted for any of the sexual or hormone/vitality questions. However, the numbers in the BT plus NADT group were small and insufficient to reach any meaningful conclusions compared with the BT alone group.

Discussion

Patients receiving EBRT plus NADT had worse HRQOL, as measured by the frequency of erections, quality of erections, ability to have erections, ability to reach orgasm, ability to function sexually, and lack of energy. However, when comparing the baseline versus 24-month outcomes, only the differences in the ability to reach orgasms, quality

Table 5 Brachytherapy only with or without NADT: distribution of participant responses to EPIC hormone/vitality HRQOL items at baseline and 6, 12, and 24 months

Question	NADT			No NADT			
How big a problem during the past 4 weeks, if any, has each of the following been for you?	Moderate problem + big problem	No problem + very small problem + small problem	n	Moderate problem + big problem	No problem + very small problem + small problem	n	*P* value*
Hot flashes†							.1014
Baseline	0	100	14	0.7	99.3	270	
6 mo	15.4	84.6	13	2.4	97.6	253	
12 mo	0	100	12	0.8	99.2	250	
24 mo	8.3	91.7	12	1.3	98.7	233	
Breast tenderness or enlargement†							.7551
Baseline	0	100	14	0.7	99.3	270	
6 mo	7.7	92.3	13	1.2	98.8	253	
12 mo	0	100	12	0.8	99.2	250	
24 mo	0	100	12	0.9	99.1	233	
Depression†							.9208
Baseline	0	100	14	4.1	95.9	271	
6 mo	15.4	84.6	13	4.3	95.7	254	
12 mo	16.7	83.3	12	3.6	96.4	249	
24 mo	0	100	12	5.2	94.9	233	
Lack of energy							.3000
Baseline	7.1	92.9	14	6.7	93.3	270	
6 mo	30.8	69.2	13	15.8	84.3	254	
12 mo	8.3	91.7	12	14.4	85.6	250	
24 mo	8.3	91.7	12	11.6	88.4	233	
Change in body weight†							.0501
Baseline	0	100	14	3.0	97.1	271	
6 mo	30.8	69.2	13	5.9	94.1	254	
12 mo	16.7	83.3	12	7.6	92.4	249	
24 mo	8.3	91.7	12	6.0	94.0	233	

Abbreviations: EPIC = extended prostate cancer index composite; HRQOL = health-related quality of life; NADT = neoadjuvant androgen deprivation therapy.

Data presented as percentages, unless otherwise noted.

* *P* value reflects a test of the interaction term between group and the time points in linear generalized estimating equations.

† Cochran-Mantel-Haenszel test.

of erections, and ability to function sexually were significant. It is reassuring that patients were not experiencing worse symptoms at 24 months for most of the sexual and hormone/vitality questions. This is important, because for intermediate-risk disease and high-risk disease patients, the addition of short- and long-term ADT to RT, respectively, has improved overall and cancer-specific survival in multiple randomized trials (1-8).

Although the initial report from the PROST-QA trial provided valuable insights into the HRQOL effect of radical prostatectomy, BT, or EBRT in prostate cancer participants (17, 21), surprisingly few data are available on the long-term adverse effects from NADT on men. A recent report based on the PROST-QA database reported the 2-month QOL outcomes for 71 participants receiving RT and NADT (16). In the present study, we included men who had not received NADT for comparison. Specifically, we included 202 men who had received EBRT only, 90 who had received EBRT plus NADT, 286 who had received BT only, and 20 who had received BT plus NADT. All available QOL measurement points $\leq$24 months were included for a better understanding of the long-term treatment effects of NADT. The Medical Research Council RT01 trial, which delivered 3 to 6 months of NADT plus 64 Gy or 74 Gy in 2-Gy fractions, addressed the short-term effects of NADT using the University of California, Los Angeles, Prostate Cancer Index, the Functional Assessment of Cancer Therapy core questionnaire with its additional prostate subscale, and the Short-Form 36-item Health Survey questionnaire (22).

Son et al (23) studied 179 men (72% black) who completed the EPIC-26 questionnaire at 2, 6, 12, 18, and 24 months after intensity modulated RT and found no significant differences in the global score by 24 months, with

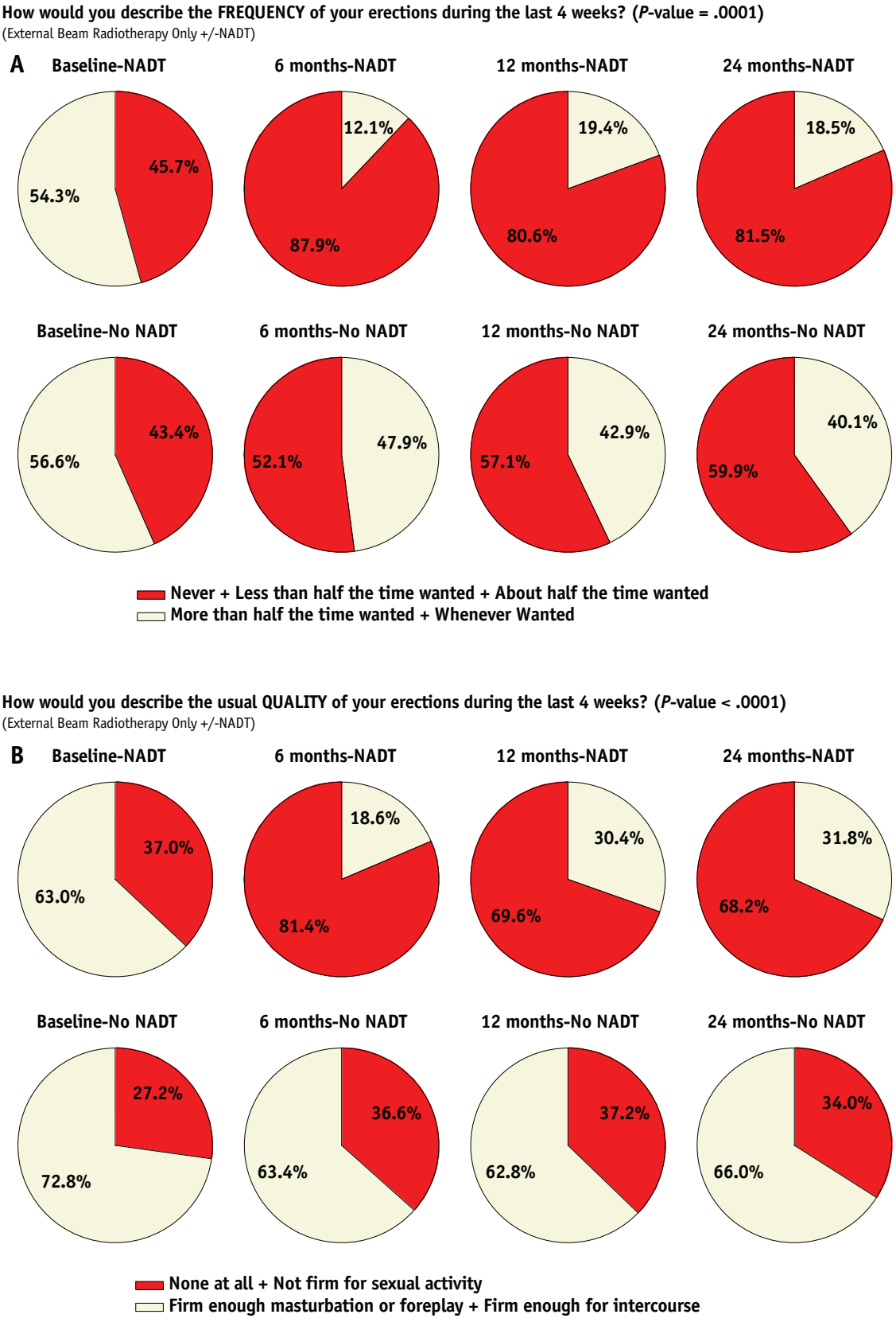
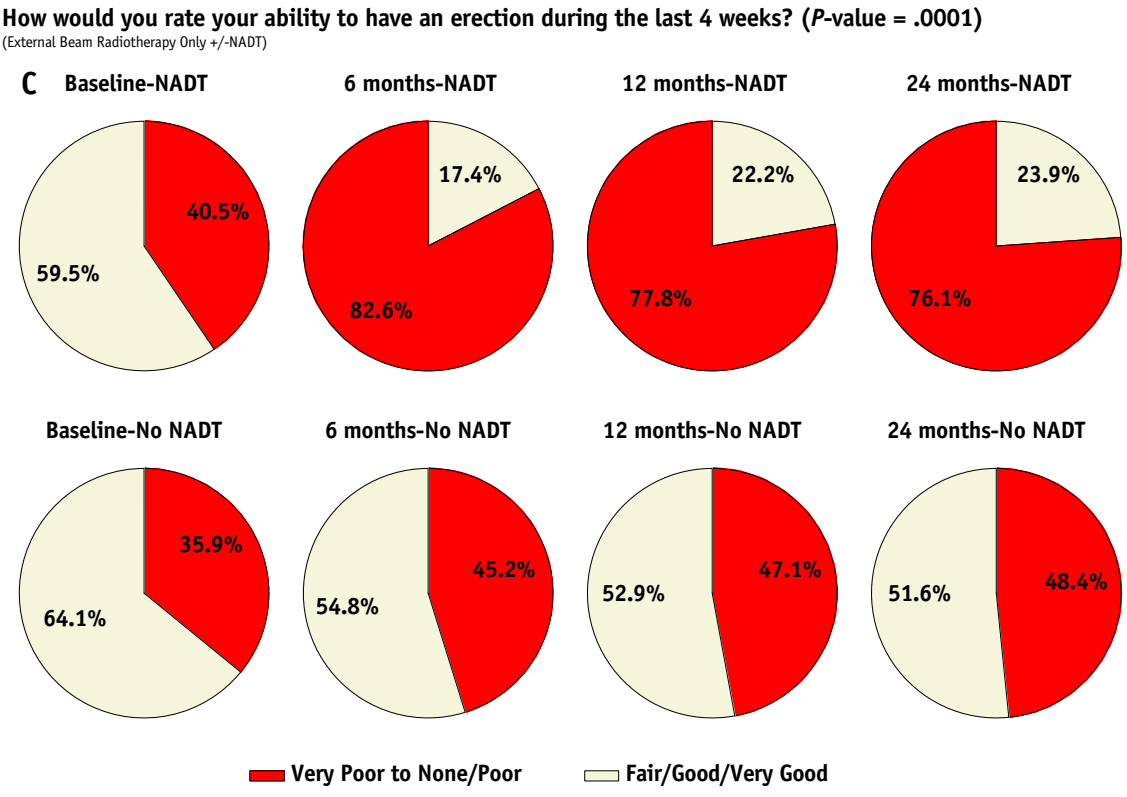


Fig. 1. The 6 statistically significant question comparisons: (A) frequency of erections, (B) quality of erections, (C) ability to have an erection, (D) ability to reach an orgasm, (E) ability to function sexually, and (F) lack of energy. *Abbreviation:* NADT = neoadjuvant androgen deprivation therapy.



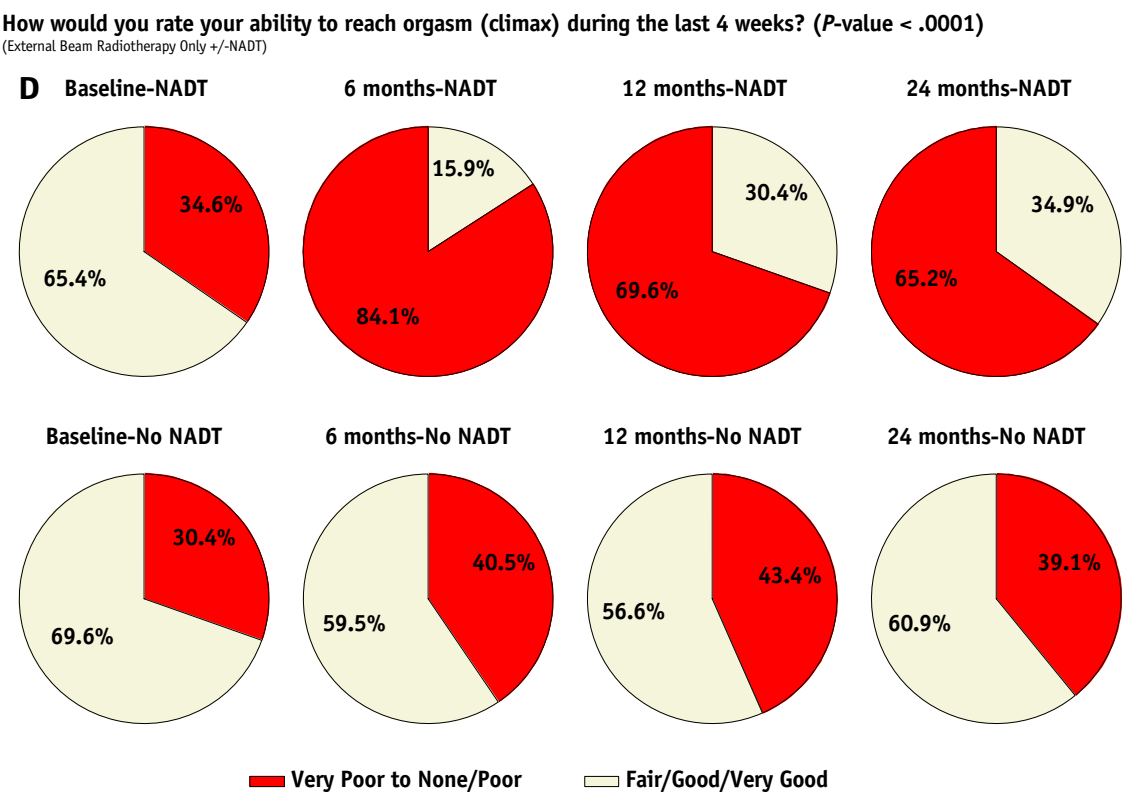
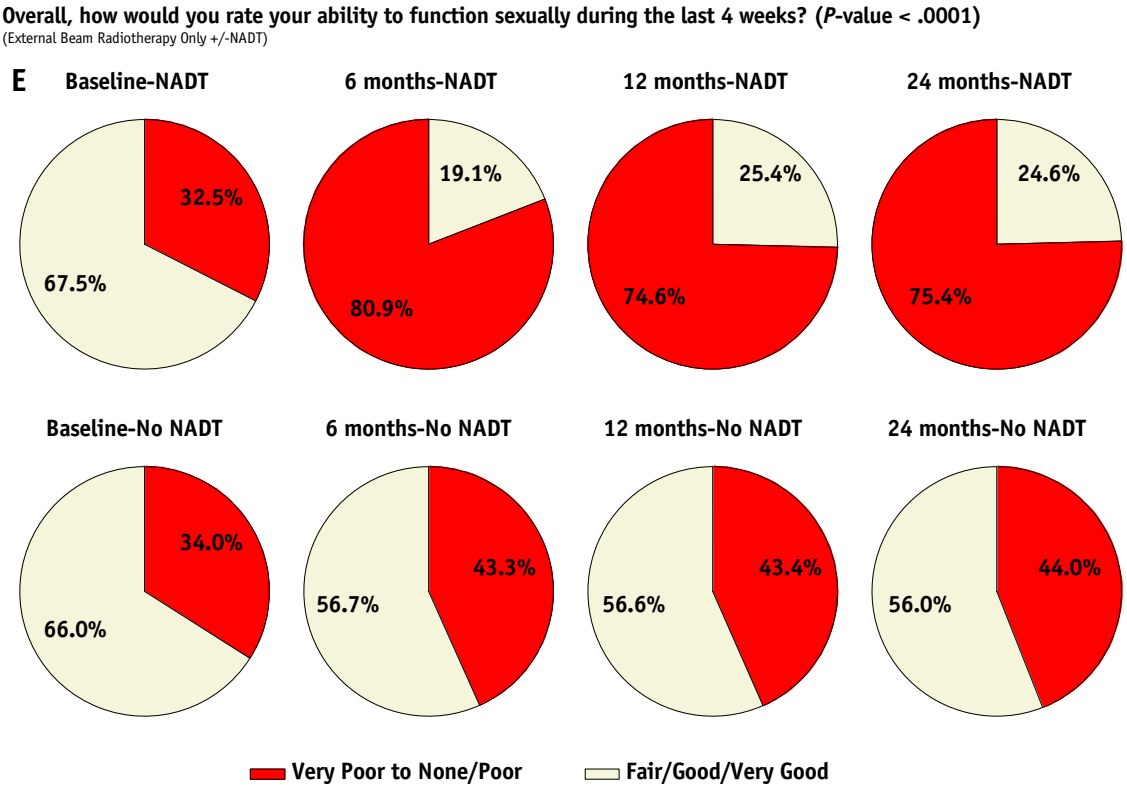


Fig. 1. (*Continued*).



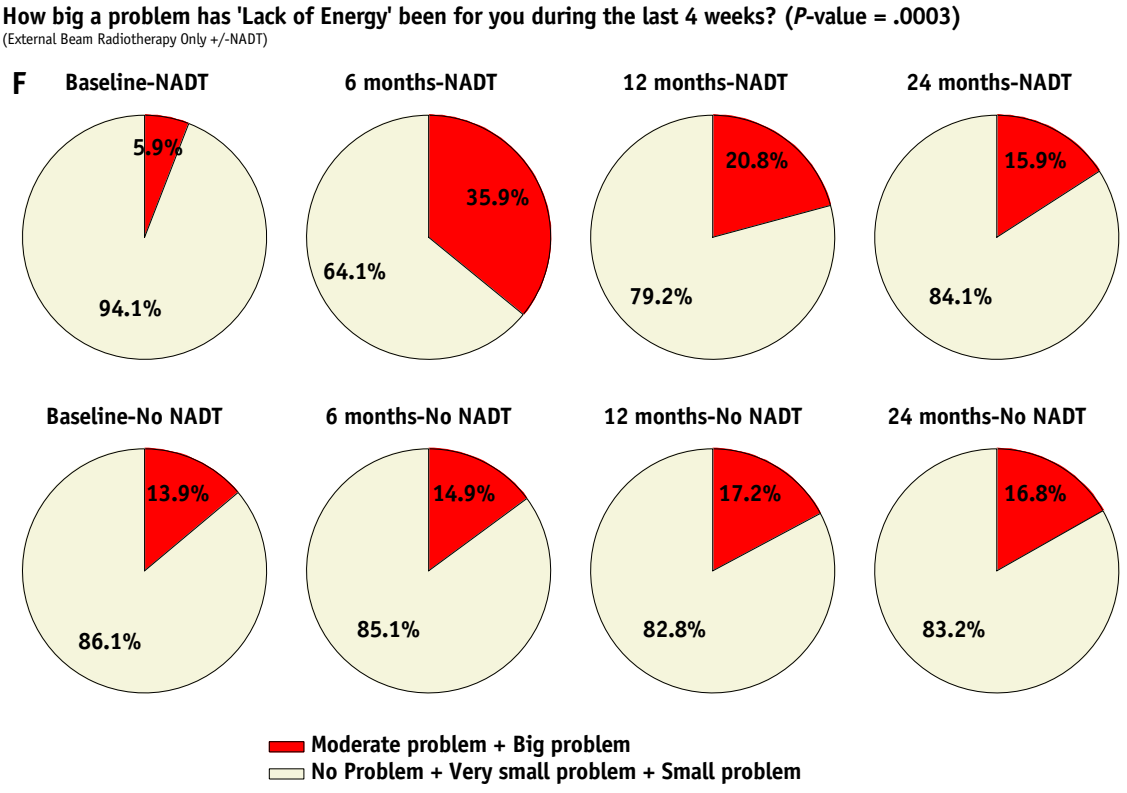


Fig. 1. (*Continued*).

Table 6 Comparison of baseline versus 24 months and 6 months versus 24 months for the percentage of participants shifting to the worst dichotomized category for a given question during the study period

	Baseline vs 24 mo						6 mo vs 24 mo					
	EBRT			BT			EBRT			BT		
Variable	NADT	No NADT	*P* value*	NADT	No NADT	*P* value*	NADT	No NADT	*P* value*	NADT	No NADT	*P* value*
Sexual												
Your ability to have an erection?	26.7	17.3	.07	28.6	19.9	.49	2.3	10.4	.02†	14.3	8.1	.33
How would you describe the usual quality of your erections during the last 4 weeks?	23.3	12.9	.03†	21.4	16.2	.71	3.5	8.9	.11	14.3	6.6	.26
How would you describe the frequency of your erections during the past 4 weeks?	25.6	20.3	.32	35.7	21.4	.20	2.3	11.4	.01†	7.1	10.3	>.99
Your ability to reach orgasm (climax)?	24.4	13.9	.03†	28.6	18.8	.48	1.2	7.9	.03†	7.1	8.9	>.99
Overall, how would you rate your ability to function sexually during the past 4 weeks?	30.2	16.3	.01†	14.3	18.1	>.99	2.3	7.4	.09	7.1	8.1	>0.99
Overall, how big a problem has your sexual function or lack of sexual function been for you during the past 4 weeks?	18.6	17.8	.87	28.6	15.9	.26	11.6	12.4	.86	14.3	9.6	.64
Hormone/vitality												
Hot flashes	5.8	2.0	.13	7.1	0.7	.14	2.3	1.0	.59	0	1.1	>.99
Breast tenderness/ enlargement	2.3	1.0	.59	0	0.7	>.99	1.2	1.0	>.99	0	0.7	>.99
Depression	3.5	3.5	>.99	0	3.7	>.99	2.3	2.5	>.99	0	2.2	>.99
Lack of energy	9.3	9.4	.98	0	7.0	.61	1.2	5.9	.12	0	4.4	>.99
Change in body weight	5.8	3.5	.35	7.1	4.4	.49	7.0	2.5	.09	0	4.1	>.99

Abbreviations: BT = brachytherapy; EBRT = external beam radiation therapy; NADT = neoadjuvant androgen deprivation therapy.
Data presented as percentages, unless otherwise noted.
* χ^2 or Fisher's exact test.
† Statistically significant.

only a statistically significant decline in the frequency of erections. These differences in findings were likely secondary to our study's larger sample size and multicenter design, leading to a more heterogeneous and generalizable patient population.

In the European Organization for Research and Treatment of Cancer 22991 trial, randomized intermediate- and high-risk localized patients to RT or RT and ADT. HRQOL was assessed with the QLQ-C30 and the QLQ-PR25. The hormonal treatment symptoms, sexual activity, and functioning scales were clinically significantly impaired at 6 months and 1 year, without any marked difference between the treatment arms from year 2 onward (8).

The results of the present study provide useful insights for clinicians. Tables 2–6 and Figure 1 could be useful when counseling patients regarding the side effects from the different types of RT. Comparing the baseline versus 24-month outcomes, 24%, 23%, and 30% of participants receiving EBRT plus NADT shifted to the worse dichotomized category for the ability to reach an orgasm, quality of erections, and ability to function sexually compared with 14%, 13%, and 16% in the EBRT group, respectively. Comparing 6 months versus 24 months, a

statistically significant improvement was found in the ability to have an erection, ability to reach an orgasm, and the frequency of erections, which could be helpful for reassuring patients at their 6-month follow-up visit. Because the effects of NADT might be decreasing after 6 months for most patients, these comparisons suggest that NADT has a greater effect on the ability to have an erection and the frequency of erections, that both NADT and EBRT affect the ability to reach an orgasm, and that EBRT has a greater effect on the ability to function sexually.

For the hormone/vitality question regarding the lack of energy, compared with participants receiving EBRT, more patients receiving EBRT plus NADT were in a significantly worse dichotomized category. Although most patients received $\leq$6 months of NADT, these findings were still evident at 2 years. In general, for this question (Fig. 1F), the participants who had only received EBRT remained stable, but those who had received EBRT plus NADT experienced about a 30% absolute worsening, followed by a 15% absolute improvement at 1 year and a further 5% absolute improvement at 2 years. The changes over time were not statistically significant for hot flashes, breast tenderness/enlargement, depression, or change in body weight. The power was only 44.4% to detect an effect size of 0.5 using the sample sizes of 14 participants in the BT plus NADT group and 271 participants in the BT group with a type I error of 5%.

One of the potential confounding factors in the present study was that the length of NADT was not controlled. However, we limited the length of NADT to 12 months, and most participants had received $\leq$6 months of NADT. The National Comprehensive Cancer Network prostate cancer guidelines have suggested considering 4 to 6 months of ADT for intermediate-risk participants undergoing EBRT and 2 to 3 years of ADT for high-risk participants undergoing EBRT (24). This might explain why the HRQOL for the entire group reached a nadir at 6 months.

Conclusions

Compared with baseline, at 2 years, the participants receiving NADT plus EBRT compared with EBRT alone had worse HRQOL, as measured by the ability to reach orgasms, quality of erections, and ability to function sexually. However, no difference was found in the ability to have an erection, frequency of erections, overall sexual function, hot flashes, breast tenderness/enlargement, depression, lack of energy, and change in body weight. The improved survival in intermediate- and high-risk patients receiving ADT and EBRT necessitates pretreatment counseling of the HRQOL effects of ADT and EBRT.

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