Title

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Journal

International Journal of Radiation Oncology • Biology • Physics, 98(2)

ISSN

0360-3016

Authors

Gay, Hiram A
Sanda, Martin G
Liu, Jingxia
et al.

Publication Date

2017-06-01

DOI

10.1016/j.ijrobp.2017.02.019

Peer reviewed

HHS Public Access

Author manuscript

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2017 June 01; 98(2): 304–317. doi:10.1016/j.ijrobp.2017.02.019.

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

Hiram Alberto Gay, M.D.[a], **Martin G. Sanda, M.D.**[b], **Jingxia Liu, Ph.D.**[c], **Ningying Wu, Ph.D.**[c], **Daniel A. Hamstra, M.D., Ph.D.**[d], **John T. Wei, M.D.**[e], **Rodney L. Dunn, M.S.**[e], **Eric A. Klein, M.D.**[f], **Howard M. Sandler, M.D.**[g], **Christopher S. Saigal, M.D., M.P.H.**[h], **Mark S. Litwin, M.D., M.P.H.**[h,h*], **Deborah A. Kuban, M.D.**[i], **Larry Hembroff, Ph.D.**[j], **Meredith M. Regan, ScD**[k], **Peter Chang, M.D.**[l], **the PROSTQA Consortium**[m], and **Jeff M. Michalski, M.D.**[a]

[a]Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO

[b]Department of Urology, Emory University School of Medicine, Atlanta, GA

[c]Division of Public Health Sciences, Washington University School of Medicine, St. Louis, MO

[d]Texas Center for Proton Therapy, Irving, TX

[e]Department of Urology, University of Michigan, Ann Arbor, MI

[f]Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH

[g]Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, CA

[h]Department of Urology, University of California at Los Angeles, Los Angeles, CA

[h*]Health Policy & Management, University of California at Los Angeles, Los Angeles, CA

[i]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

[j]Institute for Public Policy and Social Research, Michigan State University, East Lansing, MI

Corresponding Author: Hiram A. Gay, M.D., Department of Radiation Oncology, Washington University School of Medicine, 4921 Parkview Place, Campus Box 8224, St. Louis, MO 63110, Phone Number: (314)362-8516, Fax: (314)362-8521, hiramgay@wustl.edu.

[m]PROSTQA Consortium:

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

Conflict of Interest: There are no conflicts of interest with this manuscript by any of the authors.

[k]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

[l]Department of Surgery, Beth Israel-Deaconess Medical Center-Harvard Medical School, Boston, MA

Abstract

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 multi-center 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—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 radiation therapy (EBRT) or brachytherapy (BT). HRQOL was measured with the EPIC-26 questionnaire at 2, 6, 12, and 24 months after the initiation of NADT. We used Chi-square or Fisher's Exact test to compare the shift percentages between groups that did or did not receive NADT. Analyses were conducted at the two-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 baseline versus 24 months, 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 to 14%, 13% and 16% in the EBRT group, respectively.

CONCLUSION—Compared to baseline, at 2 years 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, there was no difference in the ability to have an erection, frequency of erections, overall sexual function, hot flashes, breast tenderness/enlargement, feeling depressed, lack of energy or change in body weight. The improved survival in intermediate and high-risk patients receiving ADT and EBRT necessitates pre-treatment counseling of the HRQOL impact of ADT and EBRT.

INTRODUCTION

Androgen deprivation therapy (ADT) strategies play a crucial role in the radiotherapeutic management of men with intermediate and high risk prostate adenocarcinoma. The addition of short-term and long-term ADT to radiation, 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. 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 publication of from the PROST-QA (Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment) consortium focused on the short-term (2 month) effects of neoadjuvant androgen deprivation therapy (NADT) (16). In this study, we compared HRQOL outcomes over time in men receiving external beam radiation therapy (EBRT) or brachytherapy (BT) with or without NADT.

METHODS AND MATERIALS

Centers and Subjects

We analyzed longitudinal cohort data from the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROST-QA) consortium, a multi-institutional prospective study conducted at nine university-affiliated clinical sites across the US. Participants with early stage (T1 or T2) prostate cancer were recruited between 2003 and 2006 (17). The study was approved by the Institutional Review Board and judged compliant with the Health Insurance Portability and Accountability Act (HIPAA) at each center. Participants were ineligible for the study if they had received any prior therapy for prostate cancer. All participants provided signed, informed consent to participate.

In the PROST-QA trial, primary treatment could consist of radical prostatectomy, EBRT or BT. The selection of primary treatment modality was left to the discretion of the treating physician and the participant. At the time of this analysis, 1,201 men with localized prostate cancer had been registered to the PROSTQA study. Of these men, 603 (50.2%) had elected to undergo radical prostatectomy, 5 (0.42%) had more than 12 months NADT duration, 288 (24.0%) had EBRT, 285 (23.7%) had BT, and another 20 (1.7%) participants received a combination of EBRT with a BT boost, ADT, or both.

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

Measures

At registration, pre-treatment demographics, cancer severity, and treatment details were recorded. HRQOL was measured with the EPIC-26 instrument self-reported by computer

assisted telephone interviews prior to NADT, and at 2, 6, 12, and 24 months. The EPIC 26-item questionnaire has been validated (18) and measures prostate cancer-specific HRQOL (19) in men with early and advanced prostate cancer. The questionnaire consists of four summary domains (urinary, bowel, sexual, and vitality/hormonal) as well as two urinary subscales (incontinence and irritative/obstructive). Each summary domain contains function and bother subscales. Participant responses to questions are transformed to a 0–100 scale where higher scores represent better HRQOL. Norman et al. recommend that a clinically meaningful change in function is defined as a change of greater than one half the standard deviation in an HRQOL score (20).

Six questions in the sexual domain and 5 questions in vitality/hormonal domain were analyzed. A previous publication focused on the short-term effects of ADT (21) at 2 months. Instead, we focused on longer-term responses at 6, 12 and 24 months.

Statistical Analysis

The responses to the individual questions were dichotomized as seen in Table 2 and Table 4, thus combining one or more higher-severity items in one category, and one or more items of less severity in another as was done in the original publication (17). For a given treatment modality, responses were further grouped according to NADT or no NADT. Descriptive percentage of responses per group were reported according to treatment modality: EBRT (Table 2 and 4), and BT (Table 3 and 5). There was only a 44.4% power 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%. 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 need be considered. The p-values of the interaction term in the GEE model were estimated to assess whether the percentages at each time point between No NADT and NADT groups were the same. The GEE model does not work for some questions because of the small sample size, and in those cases the Cochran-Mantel-Haenszel test was considered. Missing data was treated as missing at random and excluded from the GEE analysis.

Table 6 shows the baseline vs 24 months, and 6 months vs 24 months as percentage difference for participants who shifted to the worse dichotomized category for a given question. We chose these comparisons because we wanted to compare the baseline with the least symptoms versus the long term or 24 time month time point, and 6 months, where symptoms tend to be worse, versus the long term or 24 time month time point. The Chi-square or Fisher’s Exact test was use 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 two-sided 5% significance level.

RESULTS

Table 1 shows the characteristics of the patients. Patients receiving NADT had a higher overall cancer severity, and consequently had higher PSAs, higher Gleason scores, higher T stages, a higher 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 Table

2 and Table 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” there was a marked statistically significant difference between those who did or did not receive NADT. The vitality/hormonal responses for the EBRT and BT groups are listed in Table 4 and Table 5, respectively. In the hormonal/vitality domain for the EBRT group, patients receiving NADT did statistically worse on the lack of energy question. Figures 1a to 1f show the 6 statistically significant question comparisons, respectively: frequency of erections (Fig. 1a), quality of erections (Fig. 1b), ability to have erection (Fig. 1c), ability to reach an orgasm (Fig. 1d), ability to function sexually (Fig. 1e) and lack of energy (Fig. 1f).

Table 6 compares the baseline vs 24 months, and 6 months vs 24 months percentage difference for participants who shifted to the worse dichotomized category for a given question. When looking at “Your ability to reach orgasm (climax),” 24.4% of EBRT plus NADT participants compared to 13.9% of EBRT participants shifted from “Fair/Good/Very good” at baseline to “Very poor to none/Poor “ at 24 months. There was also a statistically significant shift to the worse dichotomized category for “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?” between the EBRT plus NADT, doing worse, and EBRT groups for the baseline versus 24 month comparison. For the EBRT plus NADT and EBRT group baseline versus 24 month comparison, there was no statistically significant shift for the hormone/vitality questions.

When examining the 6- vs 24-month sexual comparison, when looking at “Your ability to have an erection,” 2.3% of EBRT plus NADT participants and 10.4% of EBRT participants shifted from “Fair/Good/Very good” at 6 months to “Very poor to none/Poor “ in 24 months. There was also a statistically significant shift to the worse dichotomized category for “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 EBRT plus NADT and EBRT group 6- vs 24-month comparison, there was no statistically significant shift for the hormone/vitality questions.

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

DISCUSSION

Patients receiving EBRT plus NADT had worse HRQOL, as measured by frequency of erections, quality of erections, ability to have erections, ability to reach orgasms, ability to function sexually, and lack of energy. However, when comparing baseline versus 24 months, only ability to reach orgasms, quality of erections, and ability to function sexually are significant. It is reassuring that patients were not worse at 24 months for the majority of the sexual and hormone/vitality questions. This is important, because for intermediate-risk disease and high-risk disease patients, the addition of short-term and long-term ADT to

radiation, 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 impact of radical prostatectomy, brachytherapy, or external-beam radiation therapy in prostate cancer participants (17, 22), there is surprisingly little data on the long adverse effects from NADT on men. A recent publication based on the PROST-QA database reported the 2-month QOL outcomes on 71 participants receiving RT and NADT (16). In this study we included men who did not receive NADT for comparison. Specifically, we included 202 men who received EBRT only, 90 EBRT plus NADT, 286 BT only, and 20 BT plus NADT. All available QOL time points up to 24 months were included for a better understanding of the long-term treatment effects of NADT. The Medical Research Council RT01 trial, which delivered 3–6 months of NADT plus 64 Gy or 74 Gy in 2 Gy fractions, addressed the short-term effects of NADT using the UCLA-PCI, the Functional Assessment of Cancer Therapy core questionnaire with its additional prostate subscale, and the Short Form-36 Health Survey questionnaire (23).

Son et al. studied 179 men (72% African-American) who completed the EPIC-26 at 2, 6, 12, 18, and 24 months after IMRT, and found no significant difference in the global score by 24 months with only a statistically significant decline in the frequency of erections (24). These differences in findings are likely secondary to our study's larger sample size and multicenter design leading to a more heterogeneous and generalizable patient population.

EORTC 22991 randomized intermediate and high-risk localized patients to RT or RT and ADT. HRQOL was assessed with the QLQ-C30 and the QLQ-PR25. Hormonal treatment symptoms, sexual activity and functioning scales were clinically significantly impaired at 6 months and 1 year, without any marked difference between the arms from year 2 onward (8).

The current study provides useful insights for clinicians. Tables 2–6 and Figure 1 may be useful when counseling patients on the side effects from the different types of radiation therapy. Comparing baseline versus 24 months, 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 questions compared to 14%, 13% and 16% in the EBRT group, respectively. Comparing 6 months versus 24 months, there was a statistically significant improvement in the ability to have an erection, ability to reach an orgasm, and the frequency of erections which may be helpful for reassuring patients at their 6 month follow-up visit. Since the effects of NADT may be decreasing after 6 months for most patients, these comparisons suggest that NADT has a greater impact on the ability to have an erection and the frequency of erections, that both NADT and EBRT impact the ability to reach an orgasm, and that EBRT has a greater impact on the ability to function sexually.

For the hormone/vitality question regarding lack of energy, compared to participants receiving EBRT, more patients receiving EBRT plus NADT were in a significantly worse dichotomized category. Although the majority of patients received 6 months or less of NADT, these findings were still evident at 2 years. In general, for this question (Figure 1f)

participants who only received EBRT remained stable, while those who received EBRT plus NADT had about a 30% absolute worsening, followed by a 15% absolute improvement at 1 year and a further 5% absolute improvement at 2 years. Interestingly, changes over time were not statistically significant for hot flashes, breast tenderness/enlargement, feeling depressed, and change in body weight. There was only a 44.4% power 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 this study is that the length of NADT was not controlled. However, we limited the length to NADT to 12 months, and most participants received 6 months or less of NADT. The National Comprehensive Cancer Network (NCCN) prostate cancer guidelines suggest considering 4 to 6 months of ADT in intermediate-risk participants undergoing external beam RT, and 2 to 3 years of ADT for high-risk participants undergoing external beam RT (25). This may explain why HRQOL for the entire group reaches a nadir at 6 months.

CONCLUSIONS

Compared to baseline, at 2 years 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, there was no difference in the ability to have an erection, frequency of erections, overall sexual function, hot flashes, breast tenderness/enlargement, feeling depressed, and lack of energy or change in body weight. The improved survival in intermediate and high-risk patients receiving ADT and EBRT necessitates pre-treatment counseling of the HRQOL impact of ADT and EBRT.

Acknowledgments

Supported by NCI Grant 5R01CA095662 and NIH 1RC1CA146596. We acknowledge PROSTQA 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 (Emory University Dept. of Urology, 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 coordinators at each clinical site.

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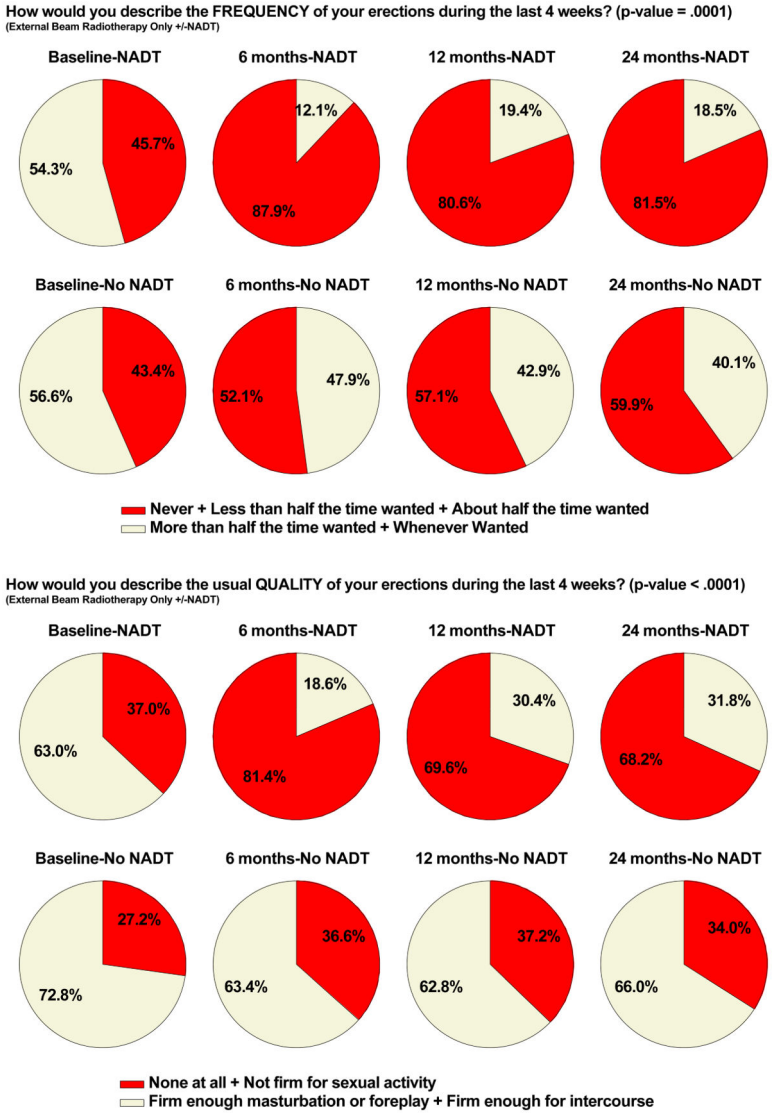
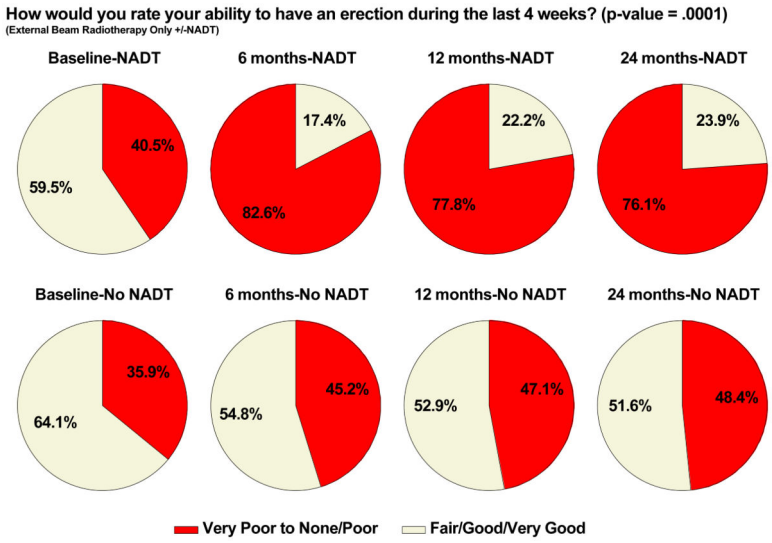
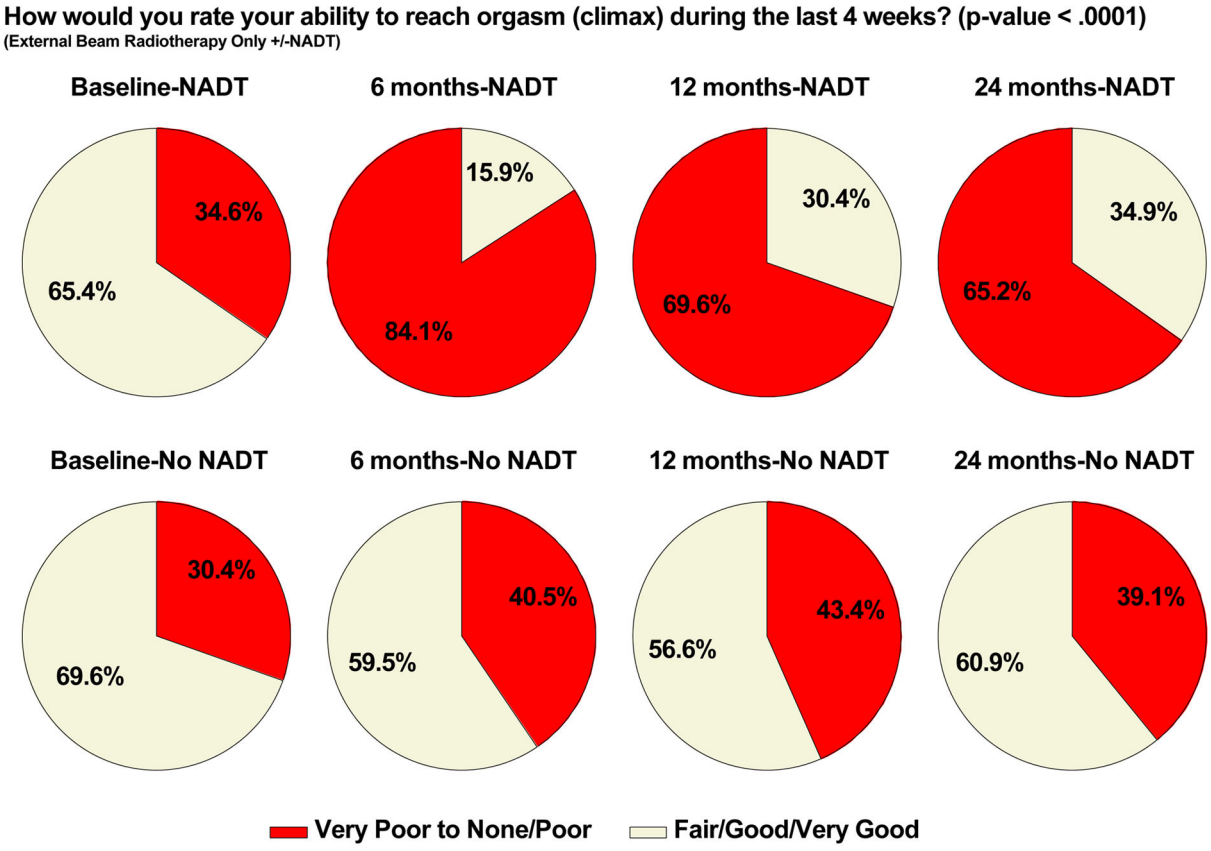
SUMMARY

We evaluated HRQOL for 2 years among 573 participants undergoing EBRT or BT with or without NADT for newly diagnosed, early-stage prostate cancer. At 2 years, participants receiving NADT plus EBRT compared to EBRT had a worse ability to reach an orgasm, erection quality, and ability to function sexually, while the ability to have an erection, frequency of erections, sexual function, hot flashes, breast tenderness, feeling depressed, lack of energy, and body weight did not reach significance.







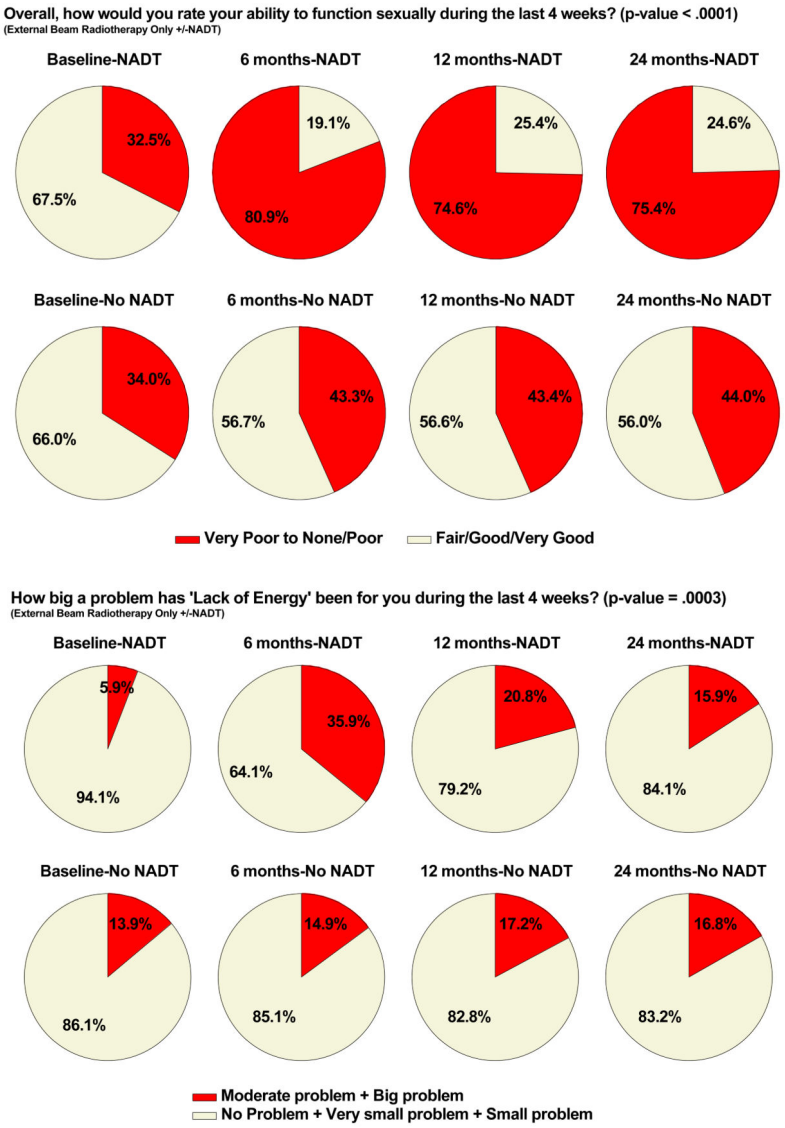


Figure 1.

Figures 1a to 1f show the 6 statistically significant question comparisons, respectively: frequency of erections (Fig. 1a), quality of erections (Fig. 1b), ability to have erection (Fig. 1c), ability to reach orgasm (Fig. 1d), ability to function sexually (Fig. 1e) and lack of energy (Fig. 1f).

Table 1

Patient characteristics.

	External Beam Radiation Therapy		P value*	Brachytherapy		P value*
	No NADT (N=202)	**NADT (N=86)**		**No NADT (n = 271)**	**NADT (n = 14)**	
Age - yr			**0.03**			0.57
Median	69	71		66	67	
Range	45 – 83	50 – 85		45 – 81	52 – 79	
Age group – no. (%)			0.07			0.88
<60	31 (15)	10 (12)		60 (22)	2 (14)	
60–69	88 (44)	28 (32)		130 (48)	7 (50)	
>70	83 (41)	48 (56)		81 (30)	5 (36)	
Race			0.87			0.34
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)	
Mean number of coexisting illnesses	1.5 ± 1.3	1.4 ± 1.2	0.39	1.3 ± 1.1	1.5 ± 1.1	0.37
Mean BMI	28.6 ± 5.3	28.7 ± 5.8	0.80	28.4 ± 4.6	28.9 ± 4.8	0.76
Mean prostate size - mL	48.9 ± 26.0	51.4 ± 34.3	0.83	38.8 ± 17.7	56.7 ± 12.8	**<0.0001**
PSA - ng/mL			**<0.0001**			0.33
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	
Group			**0.0005**			0.15
<4	36 (18)	11 (13)		59 (22)	4 (29)	
4–10	133 (66)	43 (50)		199 (73)	8 (57)	
>10	33 (16)	32 (37)		13 (5)	2 (14)	
Gleason score – no. (%)			**<0.0001**			0.18
<7	123 (61)	7 (8)		210 (77)	8 (57)	
7	77 (38)	42 (49)		58 (22)	6 (43)	

	External Beam Radiation Therapy		P value*	Brachytherapy		P value*
	No NADT (N=202)	NADT (N=86)		No NADT (n = 271)	NADT (n = 14)	
>7	2 (1)	37 (43)		2(1)	0 (0)	
Clinical stage – no. (%)			**<0.0001**			0.47
T1	157 (78)	45 (52)		228 (84)	11 (79)	
T2	45 (22)	41 (48)		42 (16)	3 (21)	
Mean proportion of biopsy cores with cancer - %	0.3 ± 0.2	0.4 ± 0.3	**0.0001**	0.3 ± 0.2	0.2 ± 0.2	0.42
Overall cancer severity — no. (%)			**<0.0001**			0.07
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)			**0.01**	N/A	N/A	
Median	70	73				
Range	48 – 90	41 – 77				
Maximum dose PTV (Gy)			0.79	N/A	N/A	
Median	80	81				
Range	45 – 107	46 –90				
IMRT – no. (%)			0.40	N/A	N/A	
Yes	162 (85)	71 (89)				
No	29 (15)	9 (11)				
Pelvic lymph nodes treated no. (%)			**<0.0001**	N/A	N/A	
Yes	7 (4)	25 (31)				
No	184 (96)	55 (69)				
Prescribed BT dose (Gy)	N/A	N/A				0.77
Median				144	144	
Range				80 – 145	137 – 145	
D90 ETV (Gy)	N/A	N/A				0.51

	External Beam Radiation Therapy		P value*	Brachytherapy		P value*
	No NADT (N=202)	NADT (N=86)		No NADT (n = 271)	NADT (n = 14)	
Median				152	158	
Range				12–346	116–178	
V100 ETV (%)	N/A	N/A				0.60
Median				93	94	
Range				69 – 100	81 – 99	

Abbreviations: ETV = Evaluation Target Volume, Post Implant; PTV = Planning Target Volume; BT =Brachytherapy

Table 2

External Beam Radiation therapy Only +/−NADT Distribution of participant responses to EPIC Sexual HRQOL items at baseline, 6, 12, and 24 months.

	NADT			No NADT			P value*
How would you rate each of the following during the last 4 weeks?	**Very poor to none + Poor**	**Fair + Good + Very good**	**n**	**Very poor to none + Poor**	**Fair + Good + Very good**	**n**	
Your ability to have an erection?							**0.0001**
Baseline:	40.5%	59.5%	84	35.9%	64.1%	198	
6 months:	82.6%	17.4%	69	45.2%	54.8%	177	
12 months:	77.8%	22.2%	72	47.1%	52.9%	170	
24 months:	76.1%	23.9%	67	48.4%	51.6%	157	
How would you describe the usual QUALITY of your erections during the last 4 weeks?	None at all + Not firm for sexual activity	Firm enough masturbation or foreplay + Firm enough for intercourse		None at all + Not firm for sexual activity	Firm enough masturbation or foreplay + Firm enough for intercourse		**<.0001**
Baseline:	37.0%	63.0%	81	27.2%	72.8%	191	
6 months:	81.4%	18.6%	70	36.6%	63.4%	175	
12 months:	69.6%	30.4%	69	37.2%	62.8%	164	
24 months:	68.2%	31.8%	66	34.0%	66.0%	159	
How would you describe the FREQUENCY of your erections during the last 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		**0.0001**
Baseline:	45.7%	54.3%	81	43.4%	56.6%	189	
6 months:	87.9%	12.1%	66	52.1%	47.9%	169	
12 months:	80.6%	19.4%	67	57.1%	42.9%	163	
24 months:	81.5%	18.5%	65	59.9%	40.1%	157	
Your ability to reach orgasm (climax)?							**<.0001**
Baseline:	34.6%	65.4%	81	30.4%	69.6%	194	
6 months:	84.1%	15.9%	69	40.5%	59.5%	173	
12 months:	69.6%	30.4%	69	43.4%	56.6%	166	
24 months:	65.2%	34.9%	66	39.1%	60.9%	156	
Overall, how would you rate your ability to function sexually during the last 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	

	NADT			No NADT			P value*
How would you rate each of the following during the last 4 weeks?	**Very poor to none + Poor**	**Fair + Good + Very good**	**n**	**Very poor to none + Poor**	**Fair + Good + Very good**	**n**	
6 months:	80.9%	19.1%	68	43.3%	56.7%	171	
12 months:	74.6%	25.4%	67	43.4%	56.6%	168	
24 months:	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 last 4 weeks?	Moderate problem + Big problem	No Problem + Very small problem + Small problem		Moderate problem + Big problem	No Problem + Very small problem + Small problem		0. 4622
Baseline:	15.5%	84.5%	84	20.3%	79.7%	197	
6 months:	34.7%	65.3%	72	29.5%	70.5%	173	
12 months:	25.7%	74.3%	70	29.0%	71.0%	169	
24 months:	34.9%	65.2%	66	32.3%	67.7%	161	

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

Table 3

Brachytherapy Distribution only +/−NADT of participant responses to EPIC Sexual HRQOL items at baseline, 6, 12, and 24 months.

	NADT			No NADT			P value*
How would you rate each of the following during the last 4 weeks?	**Very poor to none + Poor**	**Fair + Good + Very good**	**n**	**Very poor to none + Poor**	**Fair + Good + Very good**	**n**	
Your ability to have an erection?							0.9501
Baseline:	35.7%	64.3%	14	30.5%	69.5%	262	
6 months:	61.5%	38.5%	13	49.0%	51.0%	241	
12 months:	50.0%	50.0%	12	46.2%	53.8%	238	
24 months:	58.3%	41.7%	12	49.6%	50.5%	222	
How would you describe the usual QUALITY of your erections during the last 4 weeks?	None at all + Not firm for sexual Activity	Firm enough masturbation or foreplay + Firm enough for intercourse		None at all + Not firm for sexual Activity	Firm enough masturbation or foreplay + Firm enough for intercourse		0.5041
Baseline:	21.4%	78.6%	14	20.5%	79.5%	254	
6 months::	53.9%	46.2%	13	39.4%	60.6%	236	
12 months:	27.3%	72.7%	11	31.9%	68.1%	229	
24 months:	36.4%	63.6%	11	36.4%	63.6%	220	
How would you describe the FREQUENCY of your erections during the last 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		0.3714
Baseline:	35.7%	64.3%	14	36.4%	63.6%	253	
6 months:	76.9%	23.1%	13	56.7%	43.3%	231	
12 months:	58.3%	41.7%	12	53.7%	46.3%	227	
24 months:	66.7%	33.3%	12	62.0%	38.0%	216	
Your ability to reach orgasm (climax)?							0.6923
Baseline:	28.6%	71.4%	14	23.3%	76.7%	253	
6 months:	61.5%	38.5%	13	42.6%	57.5%	235	
12 months:	36.4%	63.6%	11	36.1%	64.0%	233	
24 months:	50.0%	50.0%	12	43.9%	56.1%	221	
Overall, how would you rate your ability to function sexually during the last 4 weeks?	Very poor + Poor	Fair + Good + Very Good		Very poor + Poor	Fair + Good + Very Good		0.5890
Prior to NADT:	35.7%	64.3%	14	26.9%	73.1%	260	

	NADT			No NADT			P value*
How would you rate each of the following during the last 4 weeks?	**Very poor to none + Poor**	**Fair + Good + Very good**	**n**	**Very poor to none + Poor**	**Fair + Good + Very good**	**n**	
6 months:	61.5%	38.5%	13	46.9%	53.1%	239	
12 months:	45.5%	55.6%	11	42.2%	57.8%	237	
24 months:	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 last 4 weeks?	Moderate problem + Big problem	No Problem + Very small problem + Small problem		Moderate problem + Big problem	No Problem + Very small problem + Small problem		0.8713
Baseline:	21.4%	78.6%	14	17.7%	82.3%	260	
6 months:	46.2%	53.9%	13	33.1%	67.0%	239	
12 months:	45.5%	54.6%	11	29.0%	71.0%	238	
24 months:	41.7%	58.3%	12	28.3%	71.8%	223	

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

Table 4

External Beam Radiation therapy Only +/−NADT distribution of participant responses to EPIC Hormone/Vitality HRQOL items at baseline, 6, 12, and 24 months.

	NADT			No NADT			P value*
How big a problem during the last 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**	
Hot flashes							0.0924
Baseline:	1.2%	98.8%	84	1.0%	99.0%	202	
6 months:	33.3%	66.7%	78	2.2%	97.8 %	182	
12 months:	20.8%	79.2%	77	0.5%	99.5%	181	
24 months:	7.3%	92.8 %	69	2.4%	97.6%	166	
Breast tenderness/enlargement[1]							0.8611
Baseline:	0%	100%	85	1.5%	98.5%	201	
6 months:	2.6%	97.4%	78	1.7%	98.3%	181	
12 months:	1.3%	98.7%	77	1.7%	98.3%	181	
24 months:	2.9%	97.1%	69	1.2%	98.8%	167	
Feeling depressed							0.8733
Baseline:	3.5%	96.5%	85	6.9%	93.1%	202	
6 months:	3.9%	96.2%	78	6.1%	93.9%	181	
12 months:	6.5%	93.5%	77	8.3%	91.7%	181	
24 months:	5.8%	94.2%	69	4.8%	95.2%	167	
Lack of energy							**0.0003**
Baseline:	5.9%	94.1%	85	13.9%	86.1%	202	
6 months:	35.9%	64.1%	78	14.9%	85.1%	181	
12 months:	20.8%	79.2%	77	17.2%	82.8%	180	
24 months:	15.9%	84.1%	69	16.8%	83.2%	167	
Change in body weight							0.1251
Baseline:	3.6%	96.4%	84	4.5%	95.5%	202	
6 months:	12.8%	87.2%	78	3.9%	96.1%	181	

	NADT			No NADT			P value*
How big a problem during the last 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**	
12 months:	14.3%	85.7%	77	3.9%	96.1%	179	
24 months:	10.1%	89.9%	69	4.8%	95.2%	167	

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

[1]Cochran-Mantel-Haenszel test

Table 5

Brachytherapy only +/−NADT distribution of participant responses to EPIC Hormone/Vitality HRQOL items at baseline, 6, 12, and 24 months.

	NADT			No NADT			P value*
How big a problem during the last 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**	
Hot flashes[1]							0.1014
Baseline:	0%	100%	14	0.7%	99.3%	270	
6 months:	15.4%	84.6%	13	2.4%	97.6%	253	
12 months:	0%	100%	12	0.8%	99.2%	250	
24 months:	8.3%	91.7%	12	1.3%	98.7%	233	
Breast tenderness/enlargement[1]							0.7551
Baseline:	0%	100%	14	0.7%	99.3%	270	
6 months:	7.7%	92.3%	13	1.2%	98.8%	253	
12 months:	0%	100%	12	0.8%	99.2%	250	
24 months:	0%	100%	12	0.9%	99.1%	233	
Feeling depressed[1]							0.9208
Baseline:	0%	100%	14	4.1%	95.9%	271	
6 months:	15.4%	84.6%	13	4.3%	95.7%	254	
12 months:	16.7%	83.3%	12	3.6%	96.4%	249	
24 months:	0%	100%	12	5.2%	94.9%	233	
Lack of energy							0.3000
Baseline:	7.1%	92.9%	14	6.7%	93.3%	270	
6 months:	30.8%	69.2%	13	15.8%	84.3%	254	
12 months:	8.3%	91.7%	12	14.4%	85.6%	250	
24 months:	8.3%	91.7%	12	11.6%	88.4%	233	
Change in body weight[1]							0.0501
Baseline:	0%	100%	14	3.0%	97.1%	271	
6 months:	30.8%	69.2%	13	5.9%	94.1%	254	
12 months:	16.7%	83.3%	12	7.6%	92.4%	249	

	NADT			No NADT			P value*
How big a problem during the last 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**	
24 months:	8.3%	91.7%	12	6.0%	94.0%	233	

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

[1]Cochran-Mantel-Haenszel test

Int J Radiat Oncol Biol Phys. Author manuscript; available in PMC 2018 June 01.

Table 6

Comparison of the baseline vs. 24 month, and 6 month vs. 24 month for the percentage of participants shifting to the worst dichotomized category for a given question during the time period.

	Baseline vs. 24 mo.						6 mo. vs. 24 mo.					
	External %			Brachytherapy %			External %			Brachytherapy %		
	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	0.07	28.6	19.9	0.49	2.3	10.4	**0.02**	14.3	8.1	0.33
How would you describe the usual QUALITY of your erections during the last 4 weeks?	23.3	12.9	**0.03**	21.4	16.2	0.71	3.5	8.9	0.11	14.3	6.6	0.26
How would you describe the FREQUENCY of your erections during the last 4 weeks?	25.6	20.3	0.32	35.7	21.4	0.20	2.3	11.4	**0.01**	7.1	10.3	>0.99
Your ability to reach orgasm (climax)?	24.4	13.9	**0.03**	28.6	18.8	0.48	1.2	7.9	**0.03**	7.1	8.9	>0.99
Overall, how would you rate your ability to function sexually during the last 4 weeks?	30.2	16.3	**0.01**	14.3	18.1	>0.99	2.3	7.4	0.09	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 last 4 weeks?	18.6	17.8	0.87	28.6	15.9	0.26	11.6	12.4	0.86	14.3	9.6	0.64
Hormone/Vitality:												
Hot flashes	5.8	2.0	0.13	7.1	0.7	0.14	2.3	1.0	0.59	0	1.1	>0.99
Breast tenderness/enlargement	2.3	1.0	0.59	0	0.7	>0.99	1.2	1.0	>0.99	0	0.7	>0.99
Feeling depressed	3.5	3.5	>0.99	0	3.7	>0.99	2.3	2.5	>0.99	0	2.2	>0.99
Lack of energy	9.3	9.4	0.98	0	7.0	0.61	1.2	5.9	0.12	0	4.4	>0.99
Change in body weight	5.8	3.5	0.35	7.1	4.4	0.49	7.0	2.5	0.09	0	4.1	>0.99

*Chi-square or Fisher's Exact test