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Prostate Cancer

Patient-reported Quality of Life Following Stereotactic Body Radiotherapy and Conventionally Fractionated External Beam Radiotherapy Compared with Active Surveillance Among Men with Localized Prostate Cancer

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Abstract

Background: Evidence supporting the efficacy of stereotactic body radiotherapy (SBRT) for localized prostate cancer is accumulating, but comparative studies of patient-reported quality of life (QOL) following SBRT versus conventionally fractionated external beam radiotherapy (EBRT) or active surveillance (AS) are limited.
Objective: To compare QOL of patients pursuing SBRT and EBRT versus AS.
Design, setting, and participants: A population-based cohort of 680 men with newly diagnosed localized prostate cancer was prospectively enrolled from 2011 to 2013.
Intervention: SBRT, EBRT without androgen deprivation therapy, or AS.
Outcome measurements and statistical analysis: QOL was prospectively assessed before treatment (baseline), and at 3, 12, and 24 mo after treatment using the validated Prostate Cancer Symptom Indices, which contain four domains: sexual dysfunction, urinary obstruction/irritation, urinary incontinence, and bowel problems. Propensity weighting via logistic regression models was used to balance baseline characteristics, and the mean QOL scores of EBRT and SBRT patients were compared against AS patients as the control group.
Results and limitations: Compared with AS patients, EBRT patients had worse urinary obstructive/irritative symptoms and sexual dysfunction at 3 mo, and worse bowel symptoms at 3 and 24 mo. SBRT patients had similar scores as AS patients in all domains and across all time points; however, due to small sample size, worse sexual function and urinary incontinence in SBRT patients cannot be ruled out. Further research is needed to assess long-term outcomes.
Conclusions: In a nonrandomized cohort of men with localized prostate cancer, SBRT appeared to result in favorable QOL results through 2 yr of follow-up, but worse sexual function and urinary incontinence compared with AS cannot be ruled out completely. Larger studies with longer follow-up are needed to confirm these findings.
Patient summary: Stereotactic body radiotherapy (SBRT) and active surveillance appear to have similar quality of life outcomes through 2 yr, although worse sexual function and urinary incontinence from SBRT cannot be ruled out completely.

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1. Introduction

Patients with localized prostate cancer often have excellent survival outcomes. As a result, quality of life (QOL) is an important factor in the patient's decision-making process concerning treatment options. One option is active surveillance (AS), which is surveillance without immediate treatment and delays treatment-related adverse effects without compromising long-term survival in select patients [1]. For patients receiving radiotherapy (RT), it is most commonly delivered using small daily doses of RT over several weeks (termed "conventional fractionation"). Continued technological developments have more recently allowed the use of stereotactic body RT (SBRT) to deliver extremely hypofractionated treatment using large daily doses and completing RT within five treatments.

As an evolving treatment option, SBRT comparative outcomes versus other modalities are limited but of substantial clinical interest. While some studies have reported that SBRT is safe and effective [2,3], others have raised concerns regarding its toxicity profile. A phase I trial of dose escalation from 45 to 50 Gy in five fractions reported 18% and 31% of ≥grade 2 gastrointestinal and genitourinary (GU) toxicity, respectively [4]; another dose escalation study reported 10% ≥grade 3 rectal toxicity in the 50 Gy cohort, with many requiring a diverting colostomy [5]. A claims data-based analysis suggested increased GU toxicity following SBRT compared with intensity-modulated radiotherapy (IMRT) at 6 and 24 mo [6]. It is well recognized that in prostate cancer, patient-reported QOL provides valid and more comprehensive data regarding treatment-related side effects than physician assessments and claims data [7,8]. To inform patients and physicians about treatment-related side effects related to SBRT, the goal of this study was to compare QOL of SBRT patients versus QOL of those who received conventional fractionation RT and AS.

2. Patients and methods

2.1. Patient cohort

A population-based prospective cohort of patients with newly diagnosed prostate cancer was enrolled in collaboration with the Rapid Case Ascertainment system of the North Carolina Central Cancer Registry. From January 2011 to June 2013, patients with newly diagnosed localized prostate cancer were identified from across all 100 counties of North Carolina by the Cancer Registry within a median of 1–2 wk of diagnosis and contacted by the study team for enrollment in a prospective observational cohort. Patient enrollment details were described previously [9]. All patients were enrolled and baseline data collected prior to any treatment.

As SBRT was a newer modality with relatively lower use, this study also collaborated with three institutions outside of North Carolina to enroll additional patients receiving SBRT to enrich this cohort. Eligibility criteria and study methodology were identical between North Carolina patients and additional SBRT patients in this study. SBRT patients were treated with the Accuray CyberKnife system.

This study was approved by the University of North Carolina institutional review board. All patients enrolled in the study provided written informed consent.

2.2. Data collection

Patient's demographic information, including age, race, health insurance status, education level, household income, and marital status, was collected by patient report at baseline. Medical records were collected from all patients and abstracted to determine treatment received; if medical record was not available, cancer registry data were used to determine treatment.

2.3. QOL assessment

QOL was assessed prospectively using the validated Prostate Cancer Symptom Indices (PCSIs) [10]. PCSIs assess four domains, including sexual dysfunction, urinary obstruction and irritation, urinary incontinence, and bowel problems, with each domain scored from 0 to 100, where a higher score represents *worse* dysfunction. All surveys were conducted by telephone in a process similar to that previously described [11] at baseline (pretreatment), and at 3, 12, and 24 mo after completion of treatment. For patients on AS, timing of follow-up surveys was calculated from an anchor date of 3 mo after initial diagnosis.

2.4. Statistical analysis

The primary goal of this study was to compare patients who received SBRT and conventionally fractionated RT with those who pursued AS as the "control" group. None of the SBRT patients received androgen deprivation therapy (ADT), and therefore only external beam radiotherapy (EBRT) patients who did not receive ADT were included. Among EBRT patients, 79% received IMRT.

In order to adjust for potential differences in baseline characteristics, propensity score weighting was used as previously described [12], contrasting AS against each of the RT groups. In brief, propensity scores were estimated using logistic regression models incorporating age, race, health insurance status, education level, household income, marital status, year of diagnosis, baseline 12-item Short Form QOL, and baseline PCSI domain scores. Propensity score odds were used to assign weights relative to AS to balance potential confounders [13], and standardized differences [14] were calculated to assess and verify whether the balancing was adequate. Missing data were multiply imputed using the fully conditional specification approach as previously described [12]. The imputation model included as many relevant baseline characteristics as possible (including age, race, education, household income, health insurance, employment status, and QOL scores at baseline or at the preceding time point) in order to make the data most likely to satisfy the missing at random assumption [15].

Propensity score-weighted PCSI domain scores were calculated for each time point, and the mean difference of each of the RT groups was assessed in comparison with the AS group. More specifically, the PCSI domain score of a treatment group was compared with that of the AS group by conducting a simple regression, in which the treatment type was entered as a binary indicator. In these regression analyses, inverse probability of treatment-weighted estimates were used for the respective treatment types, and robust standard errors were used for the computation of confidence intervals (CIs).

In addition to the primary analysis described above, we also report PCSI scores without imputation or propensity weighting, in order to examine consistency in results and our overall conclusions.

All tests used two-sided $p < 0.05$ for statistical significance. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline characteristics

The cohort includes 387 patients who pursued AS, 189 patients who received EBRT without ADT, and 104 patients who underwent SBRT. The median age was 65–66 yr in all three groups comprising a total of 680 patients, and 72–82% of them were married (Table 1). Propensity score weighting was used to balance baseline patient characteristics. A majority of patients on AS had low-risk disease (76%), while 57% of EBRT patients and 41% of SBRT patients had intermediate-risk disease (Supplementary Table 1). Characteristics of patients who reported data only at baseline and those who reported follow-up data are summarized in Supplementary Table 6. In the AS and EBRT groups, there appear to be more missing data in racial minority patients; there are also more missing data in unmarried patients within the EBRT group.

3.2. Sexual dysfunction

Propensity score-weighted mean QOL domain scores of each group and the mean difference score versus AS are shown in Table 2. For the sexual dysfunction domain, patients on AS had a baseline mean score of 44.7 (standard deviation [SD] 38.0) with gradual worsening to 56.7 (SD 38.1) by 24 mo. At 3 mo, patients who received EBRT without ADT had statistically significantly worse sexual dysfunction compared with those on AS with a mean difference of 8.0 (95% CI 0.5–15.6). Otherwise, there was no statistically significant difference at baseline, 12 mo, or 24 mo between the two groups. For patients who received SBRT, there was no statistically significant difference in sexual dysfunction scores compared with those on AS at all time points of follow-up. However, with an upper bound of the 95% CI ranging from 8.0 to 14.2, the possibility of SBRT resulting in worse sexual dysfunction compared with AS cannot be ruled out completely. We performed a subgroup analysis of EBRT patients who received IMRT in comparison with those electing for AS, which is summarized in Supplementary Table 2.

3.3. Urinary obstruction and irritation

For the urinary obstruction and irritation domain, patients on AS had a baseline mean score of 23.4 (SD 14.0), which remained relatively stable throughout the 24-mo follow-up. Patients who received EBRT had worse urinary obstruction and irritation at 3 mo compared with those on AS with a

Table 1 – Patient demographics and baseline characteristics across different treatment groups

	Before propensity weighting, no. (%)			After propensity weighting[a] (%)		
	Active surveillance (n = 387)	EBRT without ADT (n = 189)	SBRT (n = 104)	Active surveillance	EBRT without ADT	SBRT
Age at diagnosis, mean (SD)	66 (7.5)	66 (6.9)	65 (6.8)	66 (7.5)	67 (7.2)	65 (7.8)
Race						
White	286 (74)	124 (66)	100 (96)	74	75	72
Black/other	101 (26)	65 (34)	4 (4)	26	25	28
Health insurance						
Medicare	187 (48)	98 (52)	52 (50)	48	48	44
Private	123 (32)	51 (27)	45 (43)	32	32	39
Medicaid/none	77 (20)	40 (21)	7 (7)	20	20	16
Education						
≤High school	126 (33)	70 (37)	9 (9)	33	32	29
Some college	103 (27)	53 (28)	30 (29)	27	28	24
College graduate	158 (41)	66 (35)	65 (63)	41	40	46
Household income ($/yr)						
<40 000	164 (42)	92 (49)	19 (18)	42	41	51
40 000–70 000	97 (25)	47 (25)	22 (21)	25	27	16
70 001–90 000	49 (13)	19 (10)	18 (17)	13	13	13
>90 000	77 (20)	31 (16)	45 (43)	20	20	21
Marital status						
Married	313 (81)	136 (72)	85 (82)	81	80	87
Not married	74 (19)	53 (28)	19 (18)	19	20	13
Baseline QOL scores						
SF-12, mean (SD)						
Physical	47.7 (11.3)	47.6 (11.4)	52.1 (8.4)	47.7 (11.3)	47.8 (11.6)	49.9 (11.8)
Mental	54.6 (8.4)	53.6 (9.3)	53.2 (7.6)	54.6 (8.4)	54.8 (8.4)	55.1 (6.2)
PCSI, mean (SD)						
Sexual dysfunction	44.7 (38.0)	49.9 (39.1)	42.0 (38.0)	44.7 (38.0)	43.6 (39.2)	52.0 (39.5)
Urinary obstruction/irritation	23.4 (14.0)	22.6 (14.7)	22.9 (13.2)	23.4 (14.0)	22.9 (15.2)	20.9 (12.9)
Urinary incontinence	11.1 (20.7)	12.5 (22.3)	8.3 (16.3)	11.1 (20.7)	10.7 (21.1)	12.0 (18.2)
Bowel problems	6.1 (8.3)	6.9 (10.2)	5.5 (6.9)	6.1 (8.3)	5.8 (8.6)	4.4 (6.7)

ADT = androgen deprivation therapy; EBRT = external beam radiation treatment; PCSI = Prostate Cancer Symptom Indices; QOL = quality of life; SBRT = stereotactic body radiotherapy; SD = standard deviation; SF-12 = 12-item Short Form.

[a] Sample sizes after propensity weighting are not provided because they often involve decimal points (nonwhole numbers).

Table 2 – Propensity-weighted Prostate Cancer Symptom Indices scores for sexual, urinary, and bowel symptoms across different treatment groups at baseline, and at 3, 12, and 24 mo

	Active surveillance		EBRT without ADT			SBRT		
	No. of patients	Mean score (SD)	No. of patients	Mean score (SD)	Mean difference score vs active surveillance (95% CI)	No. of patients	Mean score (SD)	Mean difference score vs active surveillance (95% CI)
Sexual dysfunction								
Baseline	382	44.7 (38.0)	182	43.6 (55.6)	−1.0 (−8.1, 6.1)	100	44.2[a] (67.3)	−0.5 (−12.1, 11.1)
3 mo	299	45.5 (38.9)	134	53.5 (55.2)	8.0[b] (0.5, 15.6)	95	43.2[a] (65.7)	−2.2 (−13.6, 9.1)
12 mo	272	48.3 (37.5)	128	51.3 (52.9)	3.0 (−4.3, 10.3)	92	51.2[a] (65.2)	2.8 (−8.5, 14.2)
24 mo	233	56.7 (38.1)	117	55.5 (52.4)	−1.2 (−8.7, 6.3)	74	52.9[a] (62.5)	−3.9 (−15.7, 8.0)
Urinary obstruction/irritation								
Baseline	379	23.4 (14.0)	182	22.9 (21.5)	−0.5 (−3.4, 2.3)	102	20.9 (23.9)	−2.5 (−6.7, 1.6)
3 mo	298	23.6 (13.1)	140	34.4 (27.3)	10.8[b] (7.5, 14.2)	95	20.5 (33.0)	−3.1 (−7.1, 1.0)
12 mo	278	26.6 (15.5)	129	24.5 (20.3)	−2.0 (−5.0, 0.9)	94	26.1 (38.6)	−0.4 (−5.9, 5.1)
24 mo	225	25.7 (14.3)	120	24.4 (21.4)	−1.3 (−4.6, 2.1)	78	25.6 (28.0)	0 (−6.6, 6.5)
Urinary incontinence								
Baseline	379	11.1 (20.7)	182	10.7 (29.9)	−0.3 (−4.0, 3.3)	102	12.0 (33.9)	1.0 (−5.4, 7.4)
3 mo	301	12.6 (20.8)	136	16.7 (34.5)	4.0 (−0.5, 8.6)	95	12.3 (31.3)	−0.4 (−5.5, 4.8)
12 mo	276	14.5 (22.6)	130	15.1 (33.8)	0.7 (−4.2, 5.5)	94	17.3 (43.6)	2.8 (−5.3, 11.0)
24 mo	230	17.8 (23.8)	120	17.8 (35.0)	−0.1 (−5.2, 5.1)	79	11.9 (36.9)	−5.9 (−12.5, 0.7)
Bowel problems								
Baseline	387	6.1 (8.3)	182	5.8 (12.1)	−0.3 (−1.8, 1.1)	102	4.4 (12.5)	−1.7 (−3.8, 0.4)
3 mo	302	7.3 (9.8)	140	11.9 (21.2)	4.6[b] (2.0, 7.3)	97	4.9 (11.8)	−2.4[b] (−4.4, −0.5)
12 mo	279	7.5 (10.4)	130	9.5 (19.0)	2.0 (−0.5, 4.5)	95	4.7 (13.5)	−2.8[b] (−5.1,−0.5)
24 mo	233	6.5 (7.2)	120	9.7 (21.4)	3.2[b] (0.2, 6.2)	79	4.0 (9.3)	−2.5[b] (−4.3, −0.7)

ADT = androgen deprivation therapy; CI = confidence interval; EBRT = external beam radiation therapy; SBRT = stereotactic body radiotherapy; SD = standard deviation.
Domain scores range from 0 to 100, with higher score indicating worse symptoms.
[a] Analysis of the sexual dysfunction score for SBRT patients excluded two outliers who required very high propensity weights if included in the analysis.
[b] Statistically significant difference versus active surveillance.

mean difference of 10.8 (95% CI 7.5–14.2; Table 2 and Fig. 1B). Otherwise, there was no difference at baseline, 12 mo, or 24 mo between the two groups. For patients who received SBRT, there was no difference in urinary obstruction and irritation score compared with those on AS at all time points.

3.4. Urinary incontinence

Patients on AS had a baseline mean score of 11.1 (SD 20.7) in the urinary incontinence domain, with an increase over time to 17.8 (SD 23.8) by 24 mo. Patients receiving EBRT without ADT and SBRT had no statistically significant difference in urinary incontinence at all time points assessed compared with those on AS. However, with an upper bound of the 95% CI as high as 11.0, the possibility of SBRT resulting in worse urinary incontinence compared with AS cannot be ruled out completely.

3.5. Bowel problems

Overall, bowel problems at baseline were minimal, with mean scores of 6.1 (SD 8.3), 5.8 (SD 12.1), and 4.4 (SD 12.5) for patients on AS, EBRT without ADT, and SBRT, respectively. Compared with AS, those who received EBRT had statistically significantly worse bowel scores at 3 mo with a mean difference score of 4.6 (95% CI 2.0–7.3), and at 24 mo with a mean difference score of 3.2 (95% CI 0.2-6.2). Patients who received SBRT had statistically lower (better) bowel problem scores at 3, 12, and 24 mo than those on AS, although the magnitudes of these score differences are small.

3.6. Sensitivity analysis

Supplementary Table 4 summarizes QOL scores without propensity score weighting or imputation for patients with complete data throughout all assessment time points. Supplementary Table 5 summarizes QOL scores without propensity score weighting or imputation for all patients with completed data at each time point. These results are consistent with the data reported in Table 2.

4. Discussion

There is intense research interest in shortening the RT course in prostate cancer due to the improved patient convenience of fewer treatments, associated cost savings, and potential radiobiological advantages of delivering high doses per fraction [16]. Nine randomized trials have been published comparing conventionally fractionated RT (8–9 wk) with moderately hypofractionated RT (4–5 wk), demonstrating similar cancer-control outcomes, although some trials have shown increased toxicity from hypofractionation [17]. Now, multiple ongoing trials are comparing longer-duration RT with extreme hypofractionation (1–2 wk), including HYPO-RT-PC

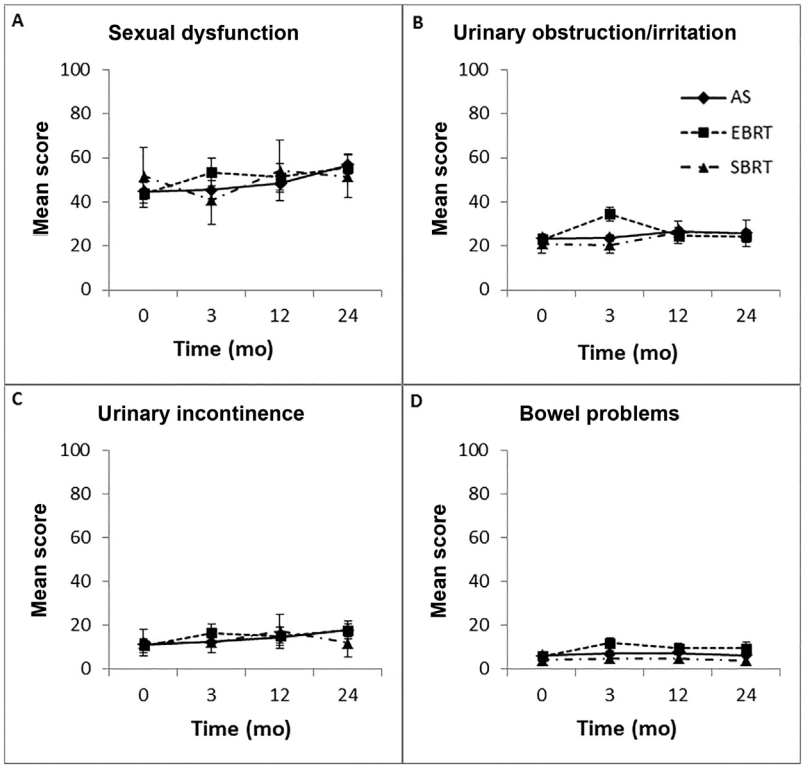

Fig. 1 – Patient-reported quality of life (with 95% confidence intervals) over time for (A) sexual dysfunction, (B) urinary obstruction/irritation, (C) urinary incontinence, and (D) bowel problems. AS = active surveillance; EBRT = external-beam radiotherapy; SBRT = stereotactic body radiotherapy.

(ISRCTN45905321), HEAT (NCT01794403), NRG-GU005 (NCT03367702), and PACE (NCT01584258). Results of the Scandinavian noninferiority phase III trial (HYPO-RT-PC) randomizing 1200 patients with intermediate-risk disease to 42.7 Gy in seven fractions versus 78 Gy in 39 fractions were recently reported, showing noninferior freedom from biochemical or clinical failure at 5 yr with hypofractionation (83.7% vs 83.8%) [18]. In addition, a large pooled analysis of multiple phase II trials including 1100 patients receiving 35–40 Gy in four to five fractions showed 5-yr biochemical relapse-free survival rates of 95% and 84% for low- and intermediate-risk patients, respectively [19]. As published evidence accumulates demonstrating the efficacy of extreme hypofractionation including SBRT (five or fewer fractions), its use has continued to increase [20,21], with demand driven by the convenience of 1–2 wk treatment compared with a conventional 8–9-wk course.

On the contrary, some published studies have raised concerns about SBRT delivering large doses of RT with each treatment. A Medicare claims-based study reported higher rates of GU toxicity (as determined by diagnoses and diagnostic procedures performed) with SBRT versus IMRT [6], while a phase I/II trial reported six cases of ≥grade 3 rectal toxicity among 61 patients treated at 50 Gy in five-fraction dose level, two of whom suffered a severe rectourethral fistula and five required a diverting colostomy [5]. However, the limitations of using claims data as surrogates for treatment-related toxicity is well recognized [22,23], and the toxicity observed in a dose escalation trial is likely explained by the dose-finding nature of that study. To date, there is a paucity of studies comparing QOL for patients receiving SBRT versus those receiving conventionally fractionated EBRT or on AS. This is important information in the patient's decision-making process.

To fulfill this knowledge gap, we prospectively enrolled patients with newly diagnosed prostate cancer to assess QOL changes from before to after treatment. To our knowledge, this is the first comparative study between SBRT, EBRT, and AS. AS patients serve as an important "control" group often lacking in previous studies. A prior study by Evans et al. [24] assessed QOL using the Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaire in 381 SBRT patients, 160 IMRT patients, and 262 brachytherapy patients. This study showed better bowel QOL for SBRT patients than for IMRT patients. Another study by Johnson et al. [25] compared QOL between SBRT and moderately hypofractionated RT in 912 men. The latter had worse urinary symptoms, and there was no difference in bowel or sexual domains. Our results are consistent with the results of these prior studies in which EBRT caused worse urinary and bowel QOL compared with AS, but SBRT was not worse than AS. These findings require further validation through randomized studies, and multiple ongoing trials including HYPO-RT-PC, HEAT, NRG-GU005, and PACE are collecting QOL data. However, it may take several years for these data to be reported, and again, these randomized studies do not have an AS arm for comparison.

Improved QOL for SBRT compared with EBRT may stem from underlying radiobiology. Prostate cancer has a relatively low alpha-beta ratio (α/β) compared with other

malignancies, and even in relation to dose-limiting adjacent normal tissues including rectum and bladder [17]. This suggests that the therapeutic ratio can be augmented with larger doses per fraction, that is, prostate cancer cells are more sensitive to hypofractionation than the surrounding organs at risk. In addition, SBRT by definition uses higher-precision patient immobilization, organ motion tracking, and radiation targeting than conventional RT [26], which may be translating to a clinical QOL benefit.

This study has several strengths and limitations. The population-based cohort is a strength. However, because patient recruitment was statewide, details of specific RT dosimetry such as total dose, fractionation, and seminal vesicle coverage were not available. Further, we did not assess QOL of patients who received moderately hypofractionated RT, as this was not commonly used during 2011–2013 when patients were enrolled. Although we used propensity score weighting to account for potential differences in baseline characteristics, the study is not randomized and cannot account for uncontrolled confounders. Further, missing data are a limitation and appeared to occur more often in racial minority (AS and EBRT) and unmarried (EBRT) patients, which can introduce a bias. Another strength is that all data were collected prospectively (including all baseline QOL data collected prior to treatment); to our knowledge, this is the only population-based prostate cancer cohort for which this is true. However, individual patients received treatment as deemed appropriate by the radiation oncologist and/or urologist, and it is not possible to distinguish the role of the natural course of radiation effects versus symptom-directed therapy in QOL in this study. Finally, while we report QOL results through 2 yr after treatment, long-term outcomes may differ and require further research. However, prior studies have demonstrated little QOL change after 2 yr for EBRT [27] and SBRT [28]. Specifically, a single-institutional cohort of 230 patients treated with SBRT demonstrated that urinary and bowel QOL assessed by the EPIC questionnaire changed little from 1 to 8 yr [28]. More studies are needed to confirm these findings.

5. Conclusions

In a prospective, nonrandomized cohort of men with prostate cancer, patients treated with conventionally fractionated EBRT experienced worse sexual dysfunction and urinary obstruction/irritation compared with those on AS at 3 mo. They also experienced worse bowel symptoms at 3 and 24 mo, although the magnitudes of differences in the bowel domain were small. Patients who received SBRT appeared to have favorable outcomes similar to those on AS in all domains and across all time points through 2 yr, although a difference in sexual dysfunction and urinary incontinence cannot be ruled out completely. Larger studies with longer follow-up are needed to confirm these findings.

Author contributions: Ronald C. Chen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Godley, Chen, Usinger, Basak.
Acquisition of data: Dickerson, Morris, Perman, Usinger, Lim, Wibbelsman, Chang, Crawford, Broughman.
Analysis and interpretation of data: Moon, Basak, Chen.
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Critical revision of the manuscript for important intellectual content: Moon, Basak, Dickerson, Morris, Perman, Chen.
Statistical analysis: Basak.
Obtaining funding: Chen.
Administrative, technical, or material support: Usinger, Lim, Wibbelsman, Chang, Crawford, Broughman.
Supervision: Godley, Chen.
Other: Patient enrollment: Dickerson, Morris, Perman, Chen.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.02.026.

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