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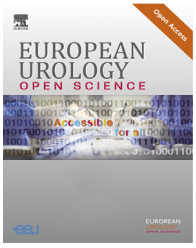

European Association of Urology

Prostate Cancer

Prospective Long-term Health-related Quality of Life Outcomes After Surgery, Radiotherapy, or Active Surveillance for Localized Prostate Cancer

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Abstract

Background: Localized prostate cancer (PCa) treatment is associated with reduced health-related quality of life (HRQoL). Current literature is limited by short-term follow-up.
Objective: To prospectively evaluate the 5-yr HRQoL outcomes in men undergoing radical prostatectomy (RP), external beam radiotherapy (EBRT), or active surveillance (AS).
Design, setting, and participants: We prospectively evaluated HRQoL in patients with low-risk/favorable intermediate-risk PCa enrolled in the Center for Prostate Disease Research multicenter database between 2007 and 2017.
Intervention: Of 1012 patients included in the study, 252 (24.9%) underwent AS, 557 (55.0%) RP, and 203 (20.0%) EBRT. Patients complete the Expanded Prostate Cancer Index Composite and the 36-item Medical Outcomes Study Short Form at baseline and thereafter each year up to 5 yr after treatment.
Outcome measurements and statistical analysis: Temporal changes in HRQoL were compared between treatments and were modeled using linear regression models adjusted for baseline HRQoL, demographic, and clinical characteristics.
Results and limitations: RP showed the least irritative symptoms and worse incontinence in comparison with AS ($p < 0.001$ for both subdomains) or EBRT ($p < 0.001$ for both subdomains) at all time points. RP sexual domain score was worse than the scores of AS (mean difference 22.3 points, 95% confidence interval [CI] 10.5–27.8, $p < 0.001$) and EBRT (mean difference 16.9 points, 95% CI 12.5–20.3, $p < 0.001$) during years 1–3 and not different from that of EBRT (mean difference 2.9 points, 95% CI –4.8 to 8.3, $p = 0.3$) at years 4 and 5. Bowel function and bother were worse for

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EBRT than for AS ($p < 0.001$ for both subdomains) and RP ($p < 0.001$ for both subdomains) at all time points. During the 3–5-yr period, AS demonstrated the worst decline in all mental health domains ($p < 0.001$ in comparison with both EBRT and RP).

Conclusions: RP results in worse long-term urinary function and incontinence, but in less irritative and obstructive symptoms than EBRT and AS. Sexual domain scores were least affected by AS, while RP shows similar scores to EBRT at long term. Long-term HRQoL changes are critical for advising patients.

Patient summary: We evaluated long-term health-related quality of life (HRQoL) in a large US population treated for localized prostate cancer. HRQoL outcomes varied according to treatment modality and time. These changes should inform patients about their expected outcomes following treatment.

1. Introduction

Localized prostate cancer (PCa) accounts for 77% of newly diagnosed PCa cases and is associated with excellent prognosis. The 10-yr relative survival between 2001 and 2016 for treated patients with localized PCa in the USA was 100% [1]. According to the National Comprehensive Cancer Network (NCCN) guidelines, treatment options for patients with localized, low- to intermediate-risk PCa with life expectancy of at least 10 yr include active surveillance (AS), radical prostatectomy (RP), and external beam radiotherapy (EBRT) [2]. The impact of PCa treatment modalities on health-related quality of life (HRQoL) has increasingly been investigated in the past decade using validated patient-reported outcome measurements (PROMs) [3,4]. These questionnaires assess common quality of life (QoL) domains that affect men after PCa diagnosis and treatment, such as urinary, sexual, bowel, and hormonal functions. A PROM assessment can reflect the impact of diagnosis and treatment on the patients' QoL perceptions.

Owing to the excellent survival of these patients, knowledge of the adverse events of different management options is critical for making patient informed treatment decisions. A major discussion point in a patient-centered treatment is the tradeoff between disease progression-free survival and HRQoL. In such a discussion, the benefits and harms of each treatment modality should be weighted, and treatment choice should be customized to the specific patient.

Most studies examining HRQoL metrics in different treatment modalities have reported outcomes after 2–3 yr of follow-up [5–7]. Only a few studies reported on long-term HRQoL outcomes in large cohorts, comparing several treatment modalities, including RP, EBRT, and AS. Patients undergoing AS are of particular interest as the goal of AS is to avoid the impact of definitive treatment on their functional and HRQoL outcomes. Furthermore, only few HRQoL studies included a long-term follow-up of AS patients. Such data comparing patients with localized disease, eligible for all treatment modalities, can contribute to fortifying the level of certainty when advising patients regarding treatment choice.

The objective of this study was to assess the long-term impact of treatment modality on HRQoL in a contemporary, racially diverse cohort of men with localized, low-risk and favorable intermediate-risk PCa. Patients who elected to undergo RP or EBRT were compared with those who were managed with AS over a 5-yr period.

2. Patients and methods

2.1. Study population

All patients were enrolled in the Center for Prostate Disease Research (CPDR) multicenter national database. Sites included Madigan Army Medical Center (Tacoma, WA), Naval Medical Center (San Diego, CA), Virginia Mason (Seattle, WA), and Walter Reed National Military Medical Center (Bethesda, MD). Site participation in the CPDR database was granted by each institutional review board (IRB), with second-tier IRB approval by the Uniformed Services University of the Health Sciences (Bethesda, MD). Prospective collection of HRQoL data was initiated in 2007, and informed consent was obtained at the time of transrectal ultrasound-guided biopsy for a suspicion of PCa, as described previously [8]. All patients enrolled in the database have detailed demographic, clinical, treatment, outcome, and comorbidity data. We compared HRQoL outcomes between patients undergoing AS, RP, or EBRT at different time points during a 5-yr follow-up period. A patient's inclusion criteria for the study were the following: age <75 yr, biopsy confirmed diagnosis of low-risk (grade group 1, prostate-specific antigen [PSA] <10 ng/ml, and cT1–cT2a) or favorable intermediate-risk (grade group 1 or 2, PSA 10–20 ng/ml, or cT2b–cT2c) PCa using the NCCN guidelines [2], completion of a baseline HRQoL survey, at least one completed follow-up survey, and >12 mo of follow-up. The AS cohort was defined as patients who received no definitive treatment within 12 mo of diagnosis and more than one PSA level or repeat biopsy within 18 mo of diagnosis. EBRT patients were treated with intensity-modulated radiotherapy, three-dimensional conformal radiotherapy, or proton-beam therapy within 6 mo of diagnosis. The surgery group was defined as patients undergoing RP within 6 mo of diagnosis.

2.2. QoL survey

HRQoL data were collected using the validated Expanded Prostate Cancer Index Composite (EPIC) and the 36-item Medical Outcomes Study Short Form (SF-36) [4,9]. The SF-36 questionnaire measures general physical and mental health through eight subscales that combine into Physical Component Summary and Mental Component Summary scores. The EPIC questionnaire focuses on evaluating bother in the urinary, bowel, sexual, and hormonal domains during the prior 4 wk. Higher scores indicate better HRQoL (score range, 0–100).

These surveys were administered immediately before or after prostate biopsy as baseline and within 3 mo of diagnosis. Subsequent surveys were administered at 3-mo intervals for the 1st year and at 6-mo intervals thereafter. Survey time points with <50% completion were excluded from the analysis.

2.3. Statistical analysis

Demographic, clinical, and baseline HRQoL characteristics were compared between treatment groups (EBRT, AS, and RP) using analysis of variance tests for continuous variables and chi-square tests for categorical variables. HRQoL scores for all subscales over time were modeled using multivariable linear regression models fitted with generalized estimating equations (GEEs), assuming an autoregressive correlation structure, adjusted for age at diagnosis, clinical stage, race/ethnicity, comorbidities (0, 1, Z2), biopsies before diagnosis (0, Z1), and baseline HRQoL score. Adjusted mean HRQoL scores were calculated for each treatment group and time point. At 12, 24, 36, 48, and 60 mo, the absolute change in HRQoL scores was computed as the follow-up score minus the baseline score. In order to address baseline score differences, a sensitivity analysis was performed by separately analyzing and fitting GEE models for 332 patients with perfect (100) baseline urinary function score, and 750 patients with "good" physical function score (>80). These results were then compared with the results of the entire cohort. All statistical tests were two sided, and p values were adjusted for multiple comparisons using Bonferroni correction with a statistical significance threshold set at 0.05. Analyses were conducted using SAS statistical software (version 9.3; SAS Institute Inc., Cary, NC, USA).

3. Results

Of the 1012 patients who were included in the study, 252 (25%) were enrolled in an AS protocol, 557 (55%) underwent RP, and 203 (20%) underwent EBRT. Patients' demographic and clinical characteristics are presented in Table 1. The mean age at diagnosis was 63.3, 59.6, and 64.8 yr for AS, RP, and EBRT patients, respectively ($p < 0.001$). The average follow-ups were 5.4 yr for the AS group, 5.4 yr for the RP group, and 5.1 yr for the EBRT group ($p = 0.169$). There were significantly more favorable intermediate-risk patients in the EBRT (60.6%) and RP (44.7%) groups than in the AS group (10.3%). Groups were also different regarding tumor stage ($p = 0.036$), ethnicity ($p < 0.001$), and number of comorbidities ($p = 0.003$). Among 203 patients treated with EBRT, only 20 (9.8%) received short-term androgen deprivation therapy (ADT). Overall, 49.4% of patients were followed up for 60 mo, 18.9% for 48 mo, 14.5% for 36 mo, 10.9% for 24 mo, and 6.3% for 12 mo. Table 2 presents the adjusted mean change in EPIC and SF-36 scores, from baseline up to 5 yr of follow-up for the different treatment modalities.

3.1. HRQoL associated with urinary symptoms

In the adjusted urinary function (Fig. 1A) and incontinence (Fig. 1B) domains, RP scored significantly worse at all time points up to 5 yr in comparison with AS and EBRT. In the 3–5-yr period, EBRT scored significantly better in those domains than AS. RP and EBRT showed an initial decline in QoL scores for urinary bother (Fig. 1C) during the 1st year but later improved. In the time period between 3 and 5 yr, however, both RP and EBRT patients reported on increased urinary bother, with RP patients scoring worse than EBRT patients. Urinary irritative scores seem to be initially improved by RP, while remaining stable in AS patients (Fig. 1D). During the 3–5-yr period, both RP and EBRT patients report on increased irritative symptoms with EBRT scoring worse. Globally, urinary function is most affected by RP despite irritative scores being worse in the EBRT group (Fig. 1E). During AS, patients report a significant decline in urinary function.

3.2. HRQoL associated with sexual function

Sexual function (Fig. 1F) and bother (Fig. 1G) in the EPIC survey were greatly affected by EBRT and RP with a continuous modest decline seen in AS. These differences

Table1 – Baseline demographic and clinical characteristics

	AS (N = 252)	RP (N = 557)	EBRT (N = 203)	Total (N = 1012)	p value
Age at diagnosis, mean (SD)	63.3 (7.3)	59.6 (7.3)	64.8 (6.4)	61.6 (7.5)	<0.001
PSA at diagnosis, mean (SD)	5.1 (2.6)	5.2 (2.7)	6.4 (3.6)	5.4 (2.9)	<0.001
Follow-up (yr), mean (SD)	5.4 (2.3)	5.4 (2.2)	5.1 (2.1)	5.3 (2.2)	0.169
Risk group, n (%)					<0.001
Low	226 (89.7)	308 (55.3)	80 (39.4)	614 (60.7)	
Favorable intermediate	26 (10.3)	249 (44.7)	123 (60.6)	398 (39.3)	
Tumor stage, n (%)					0.036
T1a-T1c	203 (80.6)	403 (72.4)	147 (72.4)	753 (74.4)	
T2	49 (19.4)	154 (27.6)	56 (27.6)	259 (25.6)	
Race/ethnicity, n (%)					<0.001
Caucasian	188 (75.5)	404 (72.7)	119 (59.2)	711 (70.7)	
African American	43 (17.3)	111 (20.0)	69 (34.3)	223 (22.2)	
Asian	13 (5.2)	25 (4.5)	10 (5.0)	48 (4.8)	
Other	5 (2.0)	16 (2.9)	3 (1.5)	24 (2.4)	
No. of comorbidities, n (%)					0.003
0	193 (76.6)	467 (83.8)	147 (72.4)	807 (79.7)	
1	48 (19.0)	80 (14.4)	49 (24.1)	177 (17.5)	
2	11 (4.4)	10 (1.8)	7 (3.4)	28 (2.8)	
Type of surveys					
Patient with EPIC	250 (99.2)	553 (99.3)	199 (98.0)	1002 (99.0)	
Patient with SF-36	244 (96.8)	520 (93.4)	188 (92.6)	952 (94.1)	

AS = active surveillance; EBRT = external beam radiotherapy; EPIC = Expanded Prostate Cancer Index Composite; PSA = prostate-specific antigen; RP = radical prostatectomy; SD = standard deviation; SF-36 = 36-item Medical Outcomes Study Short Form.

Table 2 – Adjusted mean change in EPIC and SF-36 scores from baseline to 1-, 2-, 3-, 4-, and 5-yr follow-up for patients treated with active surveillance, radical prostatectomy, or external beam radiation

Treatment and HRQoL domain	1-yr score change		2-yr score change		3-yr score change		4-yr score change		5-yr score change	
	Mean (95% CI)	*p* value	Mean (95% CI)	*p* value	Mean (95% CI)	*p* value	Mean (95% CI)	*p* value	Mean (95% CI)	*p* value
Active surveillance										
Sexual function	−4 (−8, 0)	0.099	−9 (−14, −4)	<0.001	−12 (−18, −7)	<0.001	−13 (−20, −6)	<0.001	−15 (−22, −8)	<0.001
Sexual bother	−5 (−11, 1)	0.967	−7 (−13, 0)	0.118	−11 (−19, −4)	<0.001	−14 (−23, −5)	<0.001	−10 (−19, 0)	0.070
Urinary function	−2 (−5, 1)	1	−5 (−8, −1)	<0.001	−8 (−13, −4)	<0.001	−8 (−12, −4)	<0.001	−8 (−13, −3)	<0.001
Urinary bother	0 (−4, 3)	1	−1 (−5, 2)	1	−2 (−7, 2)	1	−4 (−8, 1)	0.990	−2 (−8, 3)	1
Bowel function	1 (−2, 3)	1	0 (−3, 2)	1	−1 (−4, 2)	1	0 (−3, 2)	1	−1 (−4, 2)	1
Bowel bother	−1 (−3, 1)	1	−1 (−4, 1)	1	−2 (−5, 1)	1	−2 (−6, 2)	1	−4 (−8, 0)	0.141
Hormonal function	−1 (−4, 2)	1	−3 (−7, 1)	1	−3 (−7, 1)	0.520	−3 (−7, 1)	0.728	−3 (−8, 2)	1
Hormonal bother	−2 (−5, 1)	1	−2 (−5, 1)	0.920	−2 (−5, 1)	1	−2 (−6, 1)	1	−2 (−5, 2)	1
PCS	−1 (−2, 0)	0.430	−1 (−3, 0)	0.286	−2 (−4, −1)	<0.001	−2 (−4, 0)	0.015	−3 (−6, −1)	<0.001
MCS	−1 (−2, 1)	1	−1 (−3, 0)	0.633	−1 (−3, 0)	0.498	−2 (−3, 0)	0.143	−2 (−5, 0)	0.021
Radical prostatectomy										
Sexual function	−34 (−38, −30)	<0.001	−28 (−32, −25)	<0.001	−26 (−30, −22)	<0.001	−26 (−30, −21)	<0.001	−26 (−31, −22)	<0.001
Sexual bother	−37 (−43, −32)	<0.001	−30 (−36, −25)	<0.001	−27 (−33, −21)	<0.001	−26 (−32, −20)	<0.001	−25 (−32, −18)	<0.001
Urinary function	−16 (−19, −12)	<0.001	−13 (−16, −10)	<0.001	−15 (−18, −11)	<0.001	−16 (−19, −12)	<0.001	−17 (−20, −13)	<0.001
Urinary bother	−5 (−8, −2)	<0.001	−1 (−4, 2)	1	−2 (−5, 1)	1	−2 (−6, 1)	1	−3 (−7, 1)	0.305
Bowel function	−1 (−2, 1)	1	0 (−1, 2)	1	0 (−2, 2)	1	0 (−2, 2)	1	0 (−2, 2)	1
Bowel bother	−1 (−3, 1)	1	1 (−1, 2)	1	0 (−2, 2)	1	0 (−2, 2)	1	−1 (−3, 2)	1
Hormonal function	−3 (−5, −1)	<0.001	−2 (−4, 0)	0.165	−2 (−5, 0)	0.029	−1 (−3, 1)	1	−2 (−5, 1)	0.636
Hormonal bother	−2 (−4, −1)	<0.001	−2 (−4, 0)	0.004	−2 (−4, 0)	0.027	−2 (−4, 0)	0.480	−2 (−5, 0)	0.184
PCS	−1 (−2, −1)	<0.001	−1 (−2, 0)	<0.001	−2 (−3, −1)	<0.001	−2 (−3, −1)	<0.001	−3 (−4, −1)	<0.001
MCS	−1 (−2, 0)	0.003	−1 (−2, 0)	0.343	−1 (−2, 0)	1	−1 (−2, 0)	0.202	−1 (−2, 0)	0.948
External beam radiation										
Sexual function	−11 (−17, −5)	<0.001	−14 (−20, −7)	<0.001	−12 (−20, −5)	<0.001	−14 (−21, −6)	<0.001	−14 (−21, −6)	<0.001
Sexual bother	−14 (−23, −4)	<0.001	−17 (−27, −7)	<0.001	−12 (−23, −2)	0.005	−16 (−27, −4)	<0.001	−18 (−30, −6)	<0.001
Urinary function	−3 (−7, 0)	0.292	−5 (−9, −1)	<0.001	−4 (−8, 0)	0.017	−5 (−10, −1)	0.006	−6 (−12, −1)	0.013
Urinary bother	−4 (−8, 1)	0.404	−3 (−8, 2)	1	−2 (−6, 3)	1	−2 (−7, 3)	1	−4 (−11, 2)	1
Bowel function	−3 (−6, 0)	0.400	−4 (−7, −1)	0.004	−3 (−6, 0)	0.072	−4 (−8, 0)	0.027	−2 (−6, 1)	0.819
Bowel bother	−3 (−7, 0)	0.013	−5 (−9, −1)	0.001	−5 (−8, −1)	<0.001	−5 (−9, −1)	<0.001	−5 (−9, −1)	0.002
Hormonal function	−7 (−12, −3)	<0.001	−3 (−7, 0)	0.201	−1 (−5, 3)	1	−3 (−8, 2)	1	−1 (−6, 3)	1
Hormonal bother	−4 (−7, −1)	0.002	−3 (−6, 0)	0.061	−2 (−5, 1)	1	−3 (−7, 1)	0.351	−1 (−4, 2)	1
PCS	−1 (−3, 1)	1	−2 (−4, 0)	0.046	−2 (−4, 0)	0.154	−3 (−5, −1)	<0.001	−2 (−5, 0)	0.032
MCS	−1 (−3, 1)	1	−2 (−4, 0)	0.612	−1 (−2, 1)	1	−1 (−3, 1)	1	−1 (−3, 1)	1

CI = confidence interval; EPIC = Expanded Prostate Cancer Index Composite; MCS = mental component summary; PCS = physical component summary; SF-36 = 36-item Medical Outcomes Study Short Form.
Adjusted mean change scores are predicted values from linear regression models fitted with generalized estimating equations adjusted for age, race, major comorbidities, and tumor stage.
The *p* values are adjusted for multiple comparisons using the Bonferroni correction.

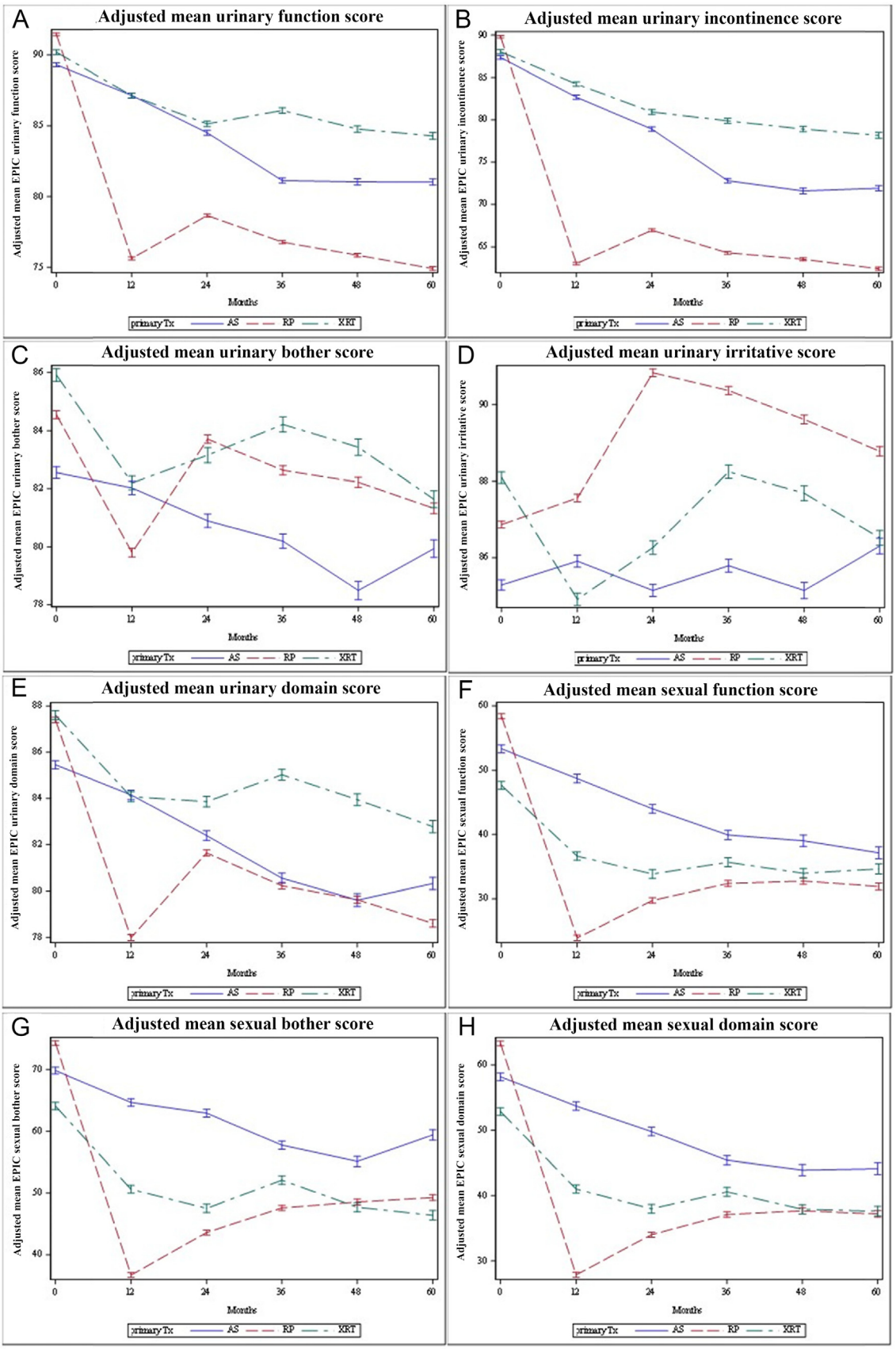

Fig. 1 – Adjusted mean urinary and sexual domain scores. AS = active surveillance; EPIC = Expanded Prostate Cancer Index Composite; RP = radical prostatectomy; Tx = treatment; XRT = radiation therapy.

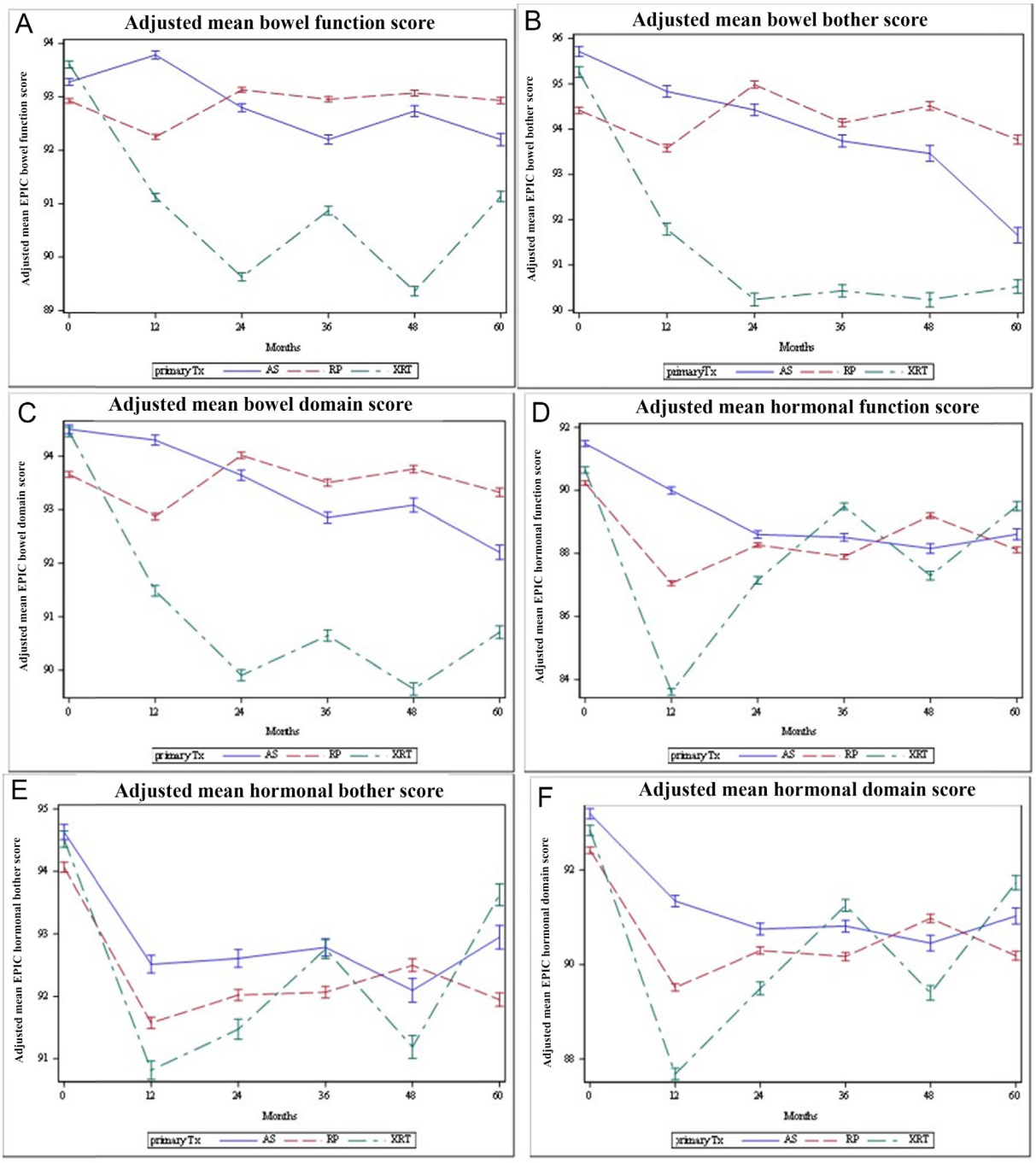

Fig. 2 – Adjusted mean bowel and hormonal domain scores. AS = active surveillance; EPIC = Expanded Prostate Cancer Index Composite; RP = radical prostatectomy; Tx = treatment; XRT = radiation therapy.

were persistent through 5 yr; however, in the time period of 3–5 yr, they were diminished. This pattern is again confirmed in the general sexual domain score (Fig. 1H) where EBRT and RP patients demonstrated significant decline through 5 years. At years 4 and 5 however, no significant difference between RP and EBRT patients in terms of general sexual domain scores were noted.

3.3. *HRQoL associated with bowel symptoms*

Bowel function (Fig. 2A) and bowel bother (Fig. 2B) scores declined significantly over the 5-yr period in the EBRT and AS groups, while minimal changes were observed in RP patients. The bowel domain score demonstrates a similar trend with EBRT and AS showing significant decrease in the associated HRQoL over 5 yr.

3.4. *HRQoL associated with hormonal symptoms*

Similarly to bowel symptoms, hormonal function (Fig. 2D) declined the most after EBRT and during the 1st year of follow-up. Hormonal bother (Fig. 2E), function (Fig. 2D) and general domain (Fig. 2F) all decrease significantly during the 1st year in all treatment groups, however, a signifi-

cant improvement in the EBRT group and a plateau in the RP and AS groups was demonstrated after 2 yr of follow up.

3.5. HRQoL associated with overall satisfaction

Overall satisfaction (Fig. 3A) improved over time in all treatment groups. The greatest improvement at 5 yr was identified in the EBRT cohort. At 12 mo, EBRT and RP had the greatest improvement in overall satisfaction, however, by 5 yr, EBRT demonstrated the greatest improvements.

3.6. HRQoL associated with physical health

In the SF-36 survey, general and physical health declined significantly over time across all treatment modalities. Mean general health (Fig. 3B), physical function (Fig. 3C), and the physical component summary (Fig. 3D) scores, all demonstrate that RP had the least impact on the physical health QoL.

3.7. HRQoL associated with mental health

The adjusted mean energy (Fig. 3E), social functioning (Fig. 3F), emotional health problems (Fig. 3G), and mental component summary (Fig. 3H) scores, all demonstrate similar patterns. Although AS had the least impact on initial scores among all the groups, this advantage disappeared over time. In the 3–5-yr period, AS demonstrated the worst decline in all subdomains displaying the lowest scores at 5 yr among all the modalities. All treatment modalities demonstrated a decline in mental health during the 1st year; however, scores in the RP and EBRT cohorts plateaued or improved somewhat. RP demonstrated the highest scores at 5 yr, outperforming AS in mental health over this time period.

3.8. Sensitivity analysis

When performing a sensitivity analysis comparing results for the entire cohort with results for 332 patients with perfect (100) baseline urinary function score and 750 patients with "good" physical function score (>80), we found that treatment effect changes were consistent in all domains and subscales except one, which was the sexual bother score. This score alone had a statistically significant difference among primary treatment groups with a p value of 0.028 for patients with a perfect urinary function score, which showed no statistically significant change between treatment groups for the entire cohort. The complete patient characteristics and results of the sensitivity analysis are presented in the Supplementary material.

4. Discussion

Currently, in the setting of similar disease control outcomes achieved with different treatment modalities, the urologist is challenged in providing appropriate guidance to the patient with localized PCa. In our previous studies, we examined how HRQoL is affected by AS when compared with RP [10] or EBRT [11] during a 3-yr follow-up. In the current study, we compared HRQoL outcomes in men undergoing AS, RP, or EBRT with updated 5-yr data.

Prior randomized trials have demonstrated that RP has a significant impact on urinary incontinence in comparison with EBRT or AS [12,13]. In the ProtecT trial, which examined patient-reported outcomes during a 6-yr follow-up, patients treated with RP reported significantly worse incontinence than patients undergoing EBRT or observation at all time points. Interestingly, the effect of incontinence on patients' perceived HRQoL was worse in the RP group up to 2 yr, but then became somewhat similar to that reported in the other groups. Similar patterns were demonstrated for other scores that combined incontinence and lower urinary tract symptoms [12]. Although current evidence shows that the global urinary domain scores are less affected by EBRT, specific urinary subscales such as irritative and obstructive symptoms have been shown to be significantly greater than in RP patients [5,6]. Furthermore, in a meta-analysis by Ohri et al. [14], summarizing long-term radiation outcomes in 11 835 men with PCa, a median of 17% and 3% of patients suffered moderate and severe late GU toxicity, respectively. Similarly to prior studies, our results demonstrated that while irritative symptoms were worse in the EBRT group, RP patients suffered more from incontinence. In the global urinary domain assessment, EBRT outperformed RP up to 5 yr despite its worse irritative scores. This may suggest that incontinence is more significant to patients than irritative voiding. Interestingly, the AS group urinary domain scores fall in between RP and EBRT patients for this metric. This may represent an age-dependent continuous decline in urinary function.

In the sexual domain of our study, EBRT patients demonstrated a significant decline in sexual function and bother during the first 2 yr of follow-up, but later improved and plateaued up to 5 yr. This trend could be attributed to concomitant short-term ADT treatment effect or early radiation toxicity, suggesting that the effect of ADT is at least partially temporary. This is supported by prior studies that demonstrated that ADT treatment is associated with sexual dysfunction up to 2 yr after treatment [15,16]. RP patients demonstrated the worse decline in sexual function during the 1st year after surgery, however improved steadily thereafter and converged with EBRT patient scores in the time frame of 3–5 yr. This suggests that during long-term follow-up, patients who undergo RP or EBRT display similar sexual dysfunction. Although patients on AS were least affected in the sexual domain, they displayed a constant age-related decline in sexual function through 5 yr of follow-up.

Several large studies, including the ProtecT trial [12] and observational prospective studies by Resnic et al. [17], Barocas et al. [5], and Chen et al. [6], have shown that EBRT had the largest negative effect on bowel function, particularly during the 1st year of follow-up. Late moderate GI toxicity due to radiation has been reported in 15% of patients and includes tenesmus, frequency of defecation, and rectal bleeding [14]. These effects, however, are durable past the first few years in some studies but not in others. Our study results show that EBRT patients report worse bowel function and bother than RP and AS patients at all time points throughout 5 yr. Interestingly, between years 2–3 and 4–5 of follow-up, EBRT patients report on improved bowel function but same negative bother

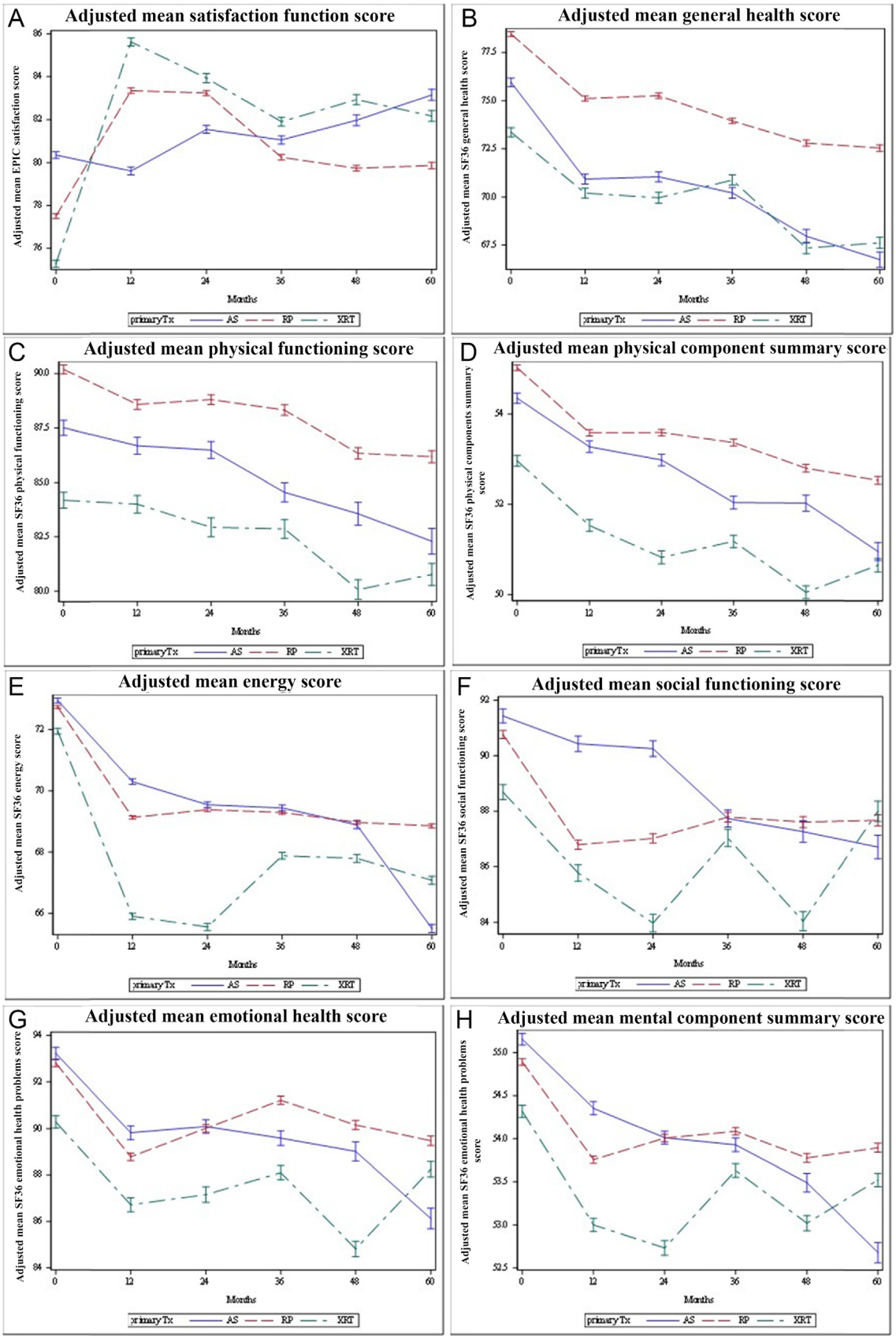

Fig. 3 – Adjusted mean satisfaction, physical, and mental health domain scores. AS = active surveillance; EPIC = Expanded Prostate Cancer Index Composite; RP = radical prostatectomy; SF-36 = 36-item Medical Outcomes Study Short Form; Tx = treatment; XRT = radiation therapy.

scores. This finding may testify to the perceived importance of bowel function in patients' HRQoL.

Several population-based studies have demonstrated that the general and mental health of patients undergoing RP, EBRT, or AS are not differently impacted [5,6,10]. These studies are further bolstered by the PIVOT study, which reported on similar scores for mental health and anxiety between men who underwent RP or observation during a median follow-up of 12.7 yr [13]. Interestingly, our results suggest that while mental health QoL scores decline significantly in the 1st year after definitive treatment with RP or EBRT, these patients adjust to their new state and display either improvement or plateau in the following years. AS patients, on the contrary, report on consistent decline in mental health scores throughout the study period.

In this era of personalized medicine, HRQoL has become a paramount issue when counseling PCa patients. AS, RP, and EBRT are all viable options for disease control, but the choice of treatment needs to be customized individually. In this study, we demonstrated that HRQoL is affected differently according to the treatment modality chosen, different domains, and specific time frame after treatment. The study results can be generalized due to the racially diverse cohort examined and the use of validated assessment tools. Our results demonstrate that for patients treated for localized PCa, HRQoL perceptions continues to change many years after treatment and should be monitored in order to provide the opportunity for intervention and improvement. The findings in this study should inform a patient-centered discussion about the treatment options for localized PCa, reflecting the most likely effect of treatment choice on QoL.

Some limitations of this work are the selection bias and confounding by indication that are inherent to observational cohort studies. For instance, the AS cohort comprised 89.7% low-risk and only 10.3% favorable intermediate-risk patients. To minimize bias, we used models adjusting for baseline characteristics and a wide range of variables associated with treatment selection. Second, HRQoL outcomes are reported up to 5 yr but may change during longer follow-up. Last, the use of published thresholds to interpret clinically significant functional difference may not be generalized to all domains or patients.

5. Conclusions

In this racially diverse cohort of men with localized low- or intermediate-risk PCa, RP resulted in worse long-term urinary function and incontinence, while irritative symptoms were more common in EBRT and AS. Sexual domain scores were least affected by AS, while RP showed similar scores to EBRT at years 4–5. Bowel HRQoL was most impacted by EBRT. AS patients demonstrated a continuous decline in all mental health domains, performing worse than RP or EBRT at 5 yr.

These findings provide a basis for informing patients and clinicians regarding the impact of disease and treatments on QoL, and allow for a better patient-centered discussion.

***Author contributions*:** Eyal Kord 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.

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Drafting of the manuscript: Kord, Jung, Flores, Porter.
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Statistical analysis: Jiang, Elsamanoudi.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.12.006.

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