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ARTICLE

Clinical Research

Sexual function outcomes of radiation and androgen deprivation therapy for localized prostate cancer in men with good baseline function

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Abstract

Background Sexual dysfunction, including erectile dysfunction and loss of libido, are common among men undergoing treatment for localized prostate cancer. Both local treatments and systemic androgen deprivation therapy may contribute to these outcomes and are differentially indicated based on disease characteristics. We sought to compare sexual function through 5 years after radiation treatment with and without androgen deprivation therapy in men with good baseline sexual function to better understand long-term effects in this understudied subset of patients.

Methods We retrospectively reviewed a prospectively assembled population-based cohort of men who underwent radiation with and without androgen deprivation therapy for intermediate or high-risk localized prostate cancer. Sexual function was assessed longitudinally over 5 years. Men with erections sufficient for intercourse at baseline were selected for inclusion.

Results Out of 167 patients included, 73 underwent radiation alone and 94 received androgen deprivation therapy plus radiation (51 with intermediate and 43 with high-risk disease). Androgen deprivation therapy use was associated with worse sexual function through 1 year regardless of disease risk. This difference was no longer statistically significant at 3 years in the intermediate-risk group. Compared to radiation alone, androgen deprivation therapy in high-risk disease was associated with worse sexual function at 3 years (effect: −20.3 points, CI [−31.8, −8.8], $p < 0.001$) but not at 5 years (effect: −3.4, CI [−17.2, 10.5], $p = 0.63$).

Conclusions Androgen deprivation therapy plus radiation is associated with worse sexual function through 3-years follow-up in men with high-risk prostate cancer compared to radiation alone. The addition of androgen deprivation therapy in the treatment of intermediate-risk disease does not appear to result in worse sexual function at 3 or 5-year follow-up compared to radiation alone.

Introduction

Management of prostate cancer presents unique challenges given the variety of treatment modalities available with comparable oncologic outcomes but varying effects on functional outcomes and quality of life. Androgen deprivation therapy (ADT) is commonly used in combination with external beam radiation treatment (EBRT) of localized prostate cancer (typically 4–6 months for intermediate-risk and 1–3 years for high-risk disease) and further complicates the comparison of functional outcome tradeoffs [1, 2].

The impact on sexual function associated with ADT has been well described with rates of erectile dysfunction

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ranging between 70 and 90% [1]. Multiple mechanisms for ADT-associated sexual dysfunction have been proposed including diminished libido, nerve degeneration, impairment of smooth muscle, decreased penile size, and psychological effects [3–6]. Additionally, longer durations of ADT appear to result in more persistent dysfunction [7]. However, the bulk of studies addressing the sexual effects of ADT focus on antiquated long-term treatment regimens for recurrent or metastatic disease or include a study population consisting predominantly of men with poor baseline sexual function. Compared to surgical extirpation, EBRT likely has more delayed deleterious effects on sexual function and, as such, is often more appealing to men with good baseline sexual function. Unfortunately, existing studies offer little help in counseling such men on the long-term expectations of sexual side effects associated with limited-term ADT use associated with EBRT of localized disease.

In this study, we sought to compare sexual function outcomes in a contemporary population-based cohort of men with intermediate- and high-risk prostate cancer and good baseline sexual function undergoing EBRT with and without the addition of ADT. Secondary objectives included identifying patient-level predictors of sexual function recovery and influencers of ADT use. Understanding the impact of ADT use in this setting may help better individualize decision-making for treatment of localized prostate cancer and sexual dysfunction as well as improve patients' expectations for sexual dysfunction duration and the chance of recovery.

Materials/subjects and methods

Men with newly diagnosed localized prostate cancer between January 2011 and February 2012 were enrolled from 5 Surveillance, Epidemiology, and End Results (SEER) registries and the Cancer of the Prostate Strategic Urologic Research Endeavor registry as previously described as part of the prospective population-based Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study [8, 9]. We retrospectively reviewed all men with D'Amico intermediate- or high-risk prostate cancer who underwent EBRT with or without ADT and reported erections sufficient for intercourse at baseline. Those patients who continued to receive ADT at 5-year follow-up were excluded given our objective to compare the recovery of sexual function following cessation of ADT for localized prostate cancer (Fig. 1).

Patient-reported functional outcomes were evaluated using the validated 26-item Expanded Prostate Index Composite (EPIC-26) questionnaire [10]. Sexual and hormonal function domain scores range from 0 to 100 with higher scores representing better function. Adequate baseline sexual function was defined as describing the usual quality of erections as firm enough for intercourse within the last 4 weeks. Surveys were administered within 6 months of the initial diagnosis (baseline) and at 6, 12, 36, and 60 months thereafter. In addition to evaluating the likelihood of retaining sexual function at each time point, we were also interested in those men who experience loss of sexual function followed by meaningful recovery. Recovery of sexual function was defined as a loss of erections sufficient for intercourse at any time during follow-up with subsequent return of erections sufficient for intercourse.

Self-reported patient demographic data included age, race, education level, and marital status. The Total Illness Burden Index for Prostate Cancer (TIBI-CaP) was used to quantify comorbidities with higher scores representing greater disease burden [11]. Disease-specific and treatment data were obtained from medical records at 1 year following enrollment. The use of ADT concurrent with EBRT was determined from the medical records and supplemented with patient-reported information.

Patients were subdivided into three groups for comparative analysis: EBRT alone (either intermediate- or high-risk disease), EBRT plus ADT for intermediate-risk disease, and EBRT plus ADT for high-risk disease. Although the exact duration of hormone therapy was not known on a per-patient basis, these groups were selected to capture and compare real-world ADT regimen differences between intermediate and high-risk diseases.

Statistical analysis

Patients' demographic and baseline characteristics were summarized with median and interquartile range (IQR, continuous variables) or frequency and percentage (categorical variables) by treatment groups and receipt of ADT. Differences among groups were assessed with Kruskal–Wallis, Wilcoxon rank-sum, or χ^2 tests. We fit multivariable linear regression models to evaluate the associations between the treatment groups and the EPIC sexual domain scores over time. In all models, the robust variance-covariance matrices were estimated using the Huber–White method to account for the correlation due to repeated measurements [12]. In order to allow for variable estimation of treatment effect on the sexual domain score at different time points following initial EBRT, we included the interaction terms between the treatment and time from initial EBRT, while adjusting for the following potential confounders: age, baseline sexual domain score, and TIBI-CaP category. To assess the associations between the treatment groups and the recovery of sexual function and receipt of ADT we fit multivariable logistic regression

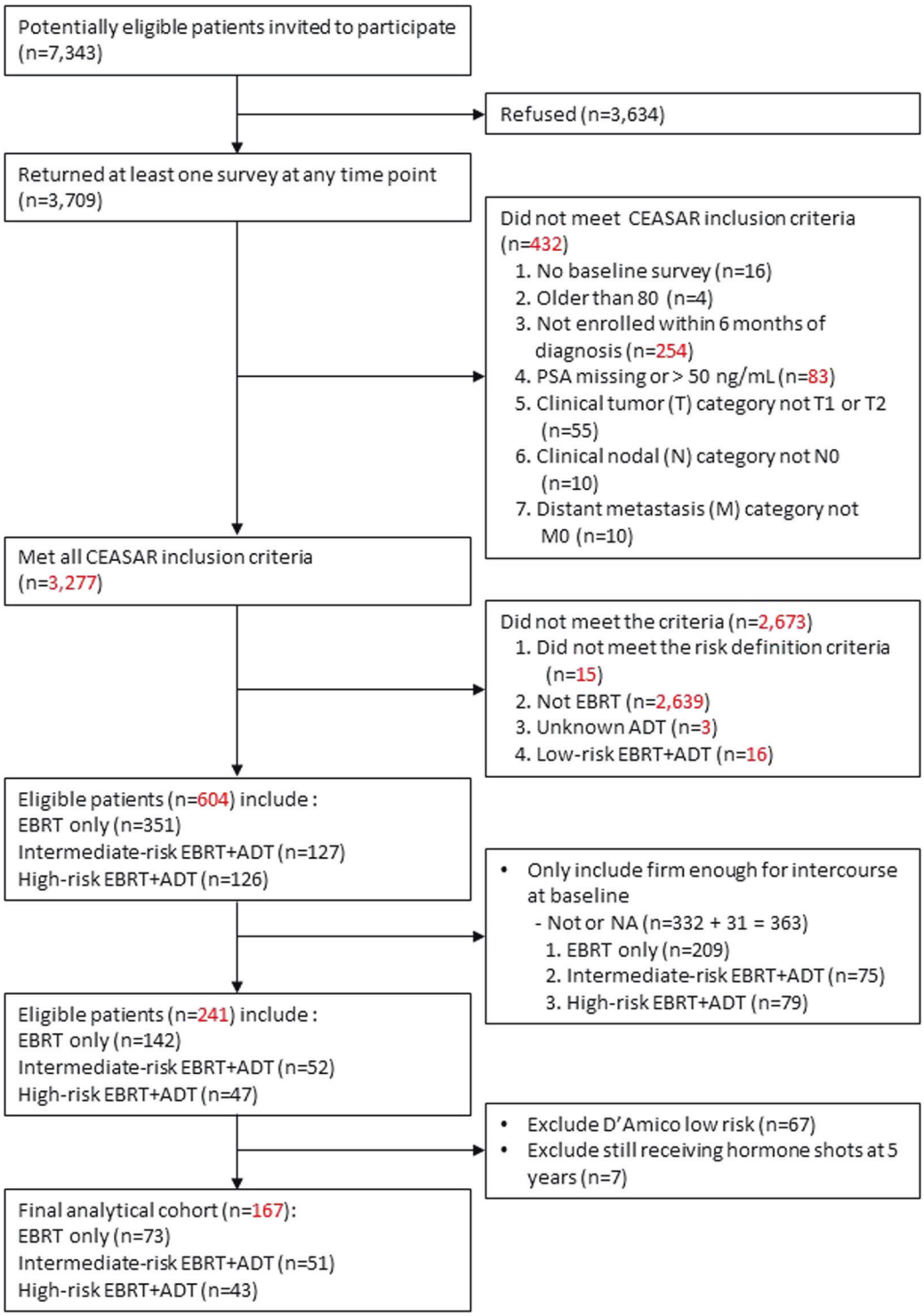

Fig. 1 Patient selection criteria. flow of participants in the CEASAR study with good baseline sexual function undergoing radiation with and without ADT.

models adjusting for age, baseline sexual domain score, and TIBI-CaP. For the receipt of ADT analysis, clinical tumor stage (T1 vs. T2), PSA level, and cardiopulmonary score were further included in the model. Odds ratios and associated 95% CIs were estimated. All missing covariates values were imputed using the Multiple Imputation using Chained Equations (MICE) implemented by aregImpute function in rms R package. Statistical significance was considered for all two-sided p-values <5%. All analyses were conducted using R version 3.6 [13].

Results

Of 604 EBRT patients enrolled, 167 (28%) met inclusion criteria of erections sufficient for intercourse at baseline and intermediate or high-risk disease. Among these, 73 (44%) underwent EBRT alone and 51 (30%) intermediate-risk disease, and 43 (26%) high-risk disease patients received EBRT plus ADT (Fig. 1). Patient demographics did not differ significantly between treatment groups. Of those patients who received EBRT alone, 63 (86%) had an intermediate-risk disease and 10 (14%) had the high-risk disease (Table 1). The dose specifications and type of radiation utilized in each treatment group are detailed in Table 2. Erectile dysfunction treatment use at each follow-up period is described in the Supplemental Table.

Patient characteristics, including age, marital status, and cardiopulmonary disease, were similar between those who received ADT and those who did not. Patients managed with EBRT alone had lower biopsy Gleason scores than those who received ADT and consequently were more common in the intermediate D'Amico risk category rather than the high-risk category. Fifty percent of men with intact baseline sexual function reported erections sufficient for intercourse at 5 years, reflecting an overall decline in sexual function over time regardless of ADT use.

Sexual function by treatment group

Unadjusted sexual and hormonal function scores over time in each treatment group are shown in Fig. 2. Both Fig. 2 and Table 3 demonstrate sexual function decline over time, whether defined by erections sufficient for intercourse or EPIC-26 sexual domain score, in all treatment groups. Sexual function differed between groups on univariate analysis at 6-months ($p < 0.001$), 1-year ($p = 0.002$), and 3-years ($p = 0.02$) follow-up; however, by 5 years no statistical difference was observed ($p = 0.67$). These differences remained significant in multivariable analysis, with worse sexual function observed at 6 months and 1 year in both intermediate- and high-risk EBRT plus ADT cohorts compared to EBRT alone (Table 3). High-risk EBRT plus ADT was also associated with worse sexual function through 3 years when compared to EBRT alone; however, by 5 years these differences were no longer statistically significant. When compared directly to intermediate-risk patients, high-risk patients treated with EBRT plus ADT had a worse sexual function at 1 and 3 years but not at 5 years.

Sexual function recovery

In those men with loss of erections sufficient for intercourse during or after EBRT and ADT, the subsequent recovery of function by 3 years ($n = 74$) and 5 years ($n = 68$) was less likely in men with the high-risk disease compared to those with intermediate-risk disease (Table 3). Age at diagnosis did not appear to influence the recovery of erections at 3-year (OR 1.27, 95% CI 0.69–2.34) or 5-year (OR 0.75, 95% CI 0.37–1.50) follow-up when adjusting for covariates. Better baseline sexual function was associated with recovery by 3 years (OR 2.78, 95% CI 1.40–5.53) but was not statistically significant at 5 years (OR 1.92, 95% CI 0.90–3.74).

Discussion

In this study, we observed significant declines in sexual function among men with baseline erections sufficient for sexual intercourse who underwent EBRT of localized prostate cancer, regardless of disease characteristics and treatment approach. Overall, 50% of men retained or recovered erections firm enough for intercourse at 5-year follow-up. Steeper declines through the first year of follow-up were observed in those men receiving ADT regardless of D'Amico risk category. When compared to the other treatment groups, men who received ADT and EBRT for the high-risk disease had worse sexual function through 3 years but showed no difference at 5 years follow-up. Men with the intermediate-risk disease were the most likely to regain sexual function by 5 years post-EBRT. To our knowledge, this is the first study to specifically describe the sexual side effects of contemporary ADT and EBRT regimens in men with good baseline sexual function.

Adding ADT to EBRT in men with intermediate- and high-risk prostate cancer is now the standard of care following the results of multiple randomized control trials showing both overall and cancer-specific survival advantages [14–16]. Based on the Dana Farber Cancer Institute 95096 and Radiation Therapy Oncology Group 9408 trials, shorter-duration ADT (typically 4–6 months) is employed in intermediate-risk disease [16, 17]. In contrast, more favorable oncologic outcomes appear to be associated with longer-term use (2–3 years) in high-risk diseases [18, 19].

The duration and severity of sexual dysfunction secondary to ADT vary in the literature. One older study evaluating men with poor baseline sexual function undergoing EBRT found no impact of ADT on sexual function at 1 year and questioned whether reported findings of worse sexual function secondary to ADT were, therefore, a result of selection bias [20]. Teloken et al. assessed response to sildenafil in men with good baseline function who underwent either EBRT or brachytherapy. Sexual function recovery was significantly less common in those treated with ADT at each time point with a 3-year follow-up and a mean ADT duration of 3.8 months [21]. Another study randomized patients undergoing EBRT to either 4 or

Table 1 Comparison of demographics, sexual function, and disease characteristics between treatment groups.

	EBRT only ($N = 73$)	Intermediate-risk EBRT + ADT ($N = 51$)	High-risk EBRT + ADT ($N = 43$)	Combined ($N = 167$)	*p*-value
Age at diagnosis	66.0 (62.0, 72.0)	68.0 (63.0, 73.0)	68.0 (64.0, 72.5)	68.0 (62.0, 72.0)	0.32
Race					
White	48 (66%)	41 (80%)	28 (65%)	117 (70%)	0.621
Black	19 (26%)	7 (14%)	12 (28%)	38 (23%)	
Hispanic	4 (5%)	3 (6%)	2 (5%)	9 (5%)	
Asian	1 (1%)	0 (0%)	1 (2%)	2 (1%)	
Other	1 (1%)	0 (0%)	0 (0%)	1 (1%)	
Education					
Less than high school	7 (11%)	4 (8%)	6 (15%)	17 (11%)	0.621
High school graduate	11 (17%)	9 (18%)	5 (12%)	25 (16%)	
Some college	15 (24%)	12 (24%)	15 (38%)	42 (27%)	
College graduate	17 (27%)	12 (24%)	5 (12%)	34 (22%)	
Graduate/ professional	13 (21%)	13 (26%)	9 (22%)	35 (23%)	
Marital status					
Not married	21 (33%)	9 (18%)	13 (33%)	43 (28%)	0.143
Married	42 (67%)	41 (82%)	26 (67%)	109 (72%)	
TIBI-CaP score					
0–2	14 (22%)	7 (14%)	13 (32%)	34 (22%)	0.167
4-Mar	31 (49%)	22 (44%)	13 (32%)	66 (43%)	
5 or more	18 (29%)	21 (42%)	14 (35%)	53 (35%)	
PSA at diagnosis	6.2 (5.0, 8.0)	6.7 (5.1, 10.6)	6.6 (4.4, 14.7)	6.4 (4.9, 10.1)	0.56
Clinical tumor stage					
T1	56 (77%)	41 (80%)	22 (51%)	119 (71%)	0.003
T2	17 (23%)	10 (20%)	21 (49%)	48 (29%)	
Biopsy Gleason score					
6 or less	5 (7%)	2 (4%)	2 (5%)	9 (5%)	<0.001
3 + 4	48 (66%)	32 (63%)	6 (14%)	86 (51%)	
4 + 3	16 (22%)	17 (33%)	6 (14%)	39 (23%)	
8, 9, 10	4 (5%)	0 (0%)	29 (67%)	33 (20%)	
D'Amico risk category					
Intermediate risk	63 (86%)	51 (100%)	0 (0%)	114 (68%)	<0.001
High risk	10 (14%)	0 (0%)	43 (100%)	53 (32%)	
Cardiopulmonary score					
0	52 (85%)	41 (84%)	28 (70%)	121 (81%)	0.194
1	8 (13%)	6 (12%)	12 (30%)	26 (17%)	
2	1 (2%)	1 (2%)	0 (0%)	2 (1%)	
3	0 (0%)	1 (2%)	0 (0%)	1 (1%)	
Vacuum erection device					
Yes	0 (0%)	1 (2%)	0 (0%)	1 (1%)	0.333
No	68 (100%)	48 (98%)	39 (100%)	155 (99%)	
PDE-I—oral medications					
Yes	25 (34%)	12 (24%)	10 (23%)	47 (28%)	0.303
No	48 (66%)	39 (76%)	33 (77%)	120 (72%)	

Table 1 (continued)

	EBRT only ($N = 73$)	Intermediate-risk EBRT + ADT ($N = 51$)	High-risk EBRT + ADT ($N = 43$)	Combined ($N = 167$)	*p*-value
MUSE—urethral pellets					
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	n/a
No	68 (100%)	49 (100%)	39 (100%)	156 (100%)	
Penile prosthesis					
Yes	1 (1%)	1 (2%)	1 (3%)	3 (2%)	0.919
No	66 (99%)	48 (98%)	37 (97%)	151 (98%)	
Penile injections					
Yes	0 (0%)	1 (2%)	0 (0%)	1 (1%)	0.326
No	68 (100%)	47 (98%)	39 (100%)	154 (99%)	
Sexual function score at baseline	85.0 (70.0, 90.0)	80.0 (70.0, 85.0)	81.2 (75.0, 90.0)	81.2 (70.0, 90.0)	0.218

Table 2 Dose (in centigray) and type of radiation by treatment group.

	EBRT only ($N = 73$)	Intermediate-risk EBRT + ADT ($N = 51$)	High-risk EBRT + ADT ($N = 43$)	Combined ($N = 167$)
Intensity-modulated radiation therapy				
No	12 (19%)	6 (12%)	4 (9%)	22 (14%)
Yes	50 (81%)	45 (88%)	39 (91%)	134 (86%)
Proton beam radiation therapy				
No	56 (95%)	46 (92%)	41 (100%)	143 (95%)
Yes	3 (5%)	4 (8%)	0 (0%)	7 (5%)
Image-guided radiation therapy				
No	6 (10%)	4 (8%)	5 (12%)	15 (10%)
Yes	52 (90%)	46 (92%)	37 (88%)	135 (90%)
Radiation dose—(median, lower/upper quartile)	7920 (7600, 7920)	7860 (7740, 8055)	7920 (7740, 7920)	7920 (7600, 7920)
Radiation dose ≥ 7500				
No	9 (15%)	4 (8%)	2 (5%)	15 (10%)
Yes	52 (85%)	46 (92%)	41 (95%)	139 (90%)
Radiation dose per fraction—(median, lower/upper quartile)	180 (180, 200)	180 (180, 180)	180 (180, 180)	180 (180, 182.5)
Radiation dose per fraction > 200?				
No	54 (92%)	49 (98%)	41 (98%)	144 (95%)
Yes	5 (8%)	1 (2%)	1 (2%)	7 (5%)
Treatment of pelvic lymph nodes?				
No	56 (92%)	45 (88%)	23 (53%)	124 (80%)
Yes	5 (8%)	6 (12%)	20 (47%)	31 (20%)

8 months of ADT and observed the most significant reduction in sexual function within the first year and no difference identified at 5 years [22]. Similar results were reported in a study evaluating men undergoing contemporary dose-escalated intensity-modulated radiation therapy (IMRT) with or without ADT. Men in the ADT cohort had worse sexual function during the 2–6 month follow-up period; however, only sexual activity differed at 2 years [23]. Unfortunately, generalization of these findings is challenging given the lack of stratification based on disease characteristics and duration of ADT, unknown baseline function, inclusion of a large number of patients with poor baseline function, varying definitions of adequate sexual function, and follow-up limited to 2 years or less [24–26]. Interestingly, Alemozaffar et al. attempted to predict sexual function through 2 years after prostate cancer treatment

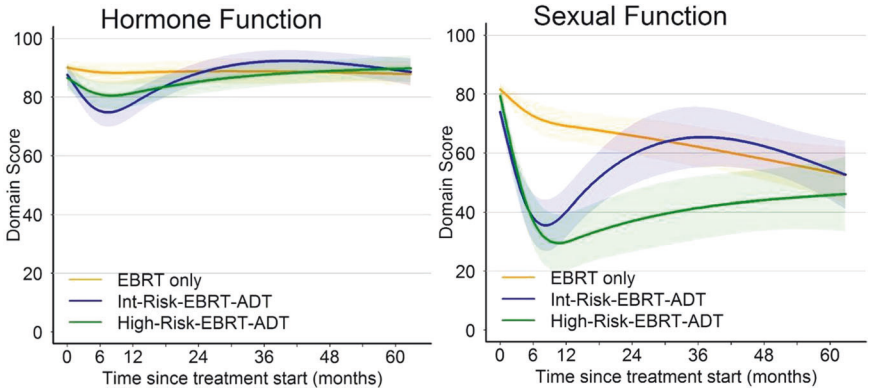

Fig. 2 Hormone and Sexual Function Outcomes. Comparison of unadjusted EPIC-26 sexual and hormone function scores between treatment groups over time.

using a community-based cohort and found probabilities of erections sufficient for intercourse after EBRT varied widely from 16 to 92% depending on the use of ADT, baseline sexual function, and pretreatment PSA values [27]. These studies suggest that sexual function is likely affected during short-term follow-up while patients are still receiving ADT. Indeed, our findings would support this, as worse sexual function through 1 and 3 years was observed in men treated with ADT and EBRT for intermediate- and high-risk disease respectively. Unlike these prior studies, we were able to follow men longer and found no difference in sexual function at 5 years regardless of disease severity and treatment differences. Additionally, we intentionally chose to evaluate men with good sexual function prior to treatment in order to avoid the pitfalls of previous studies that were limited by study populations with poor baseline sexual function.

While we present one of the largest series in the current literature evaluating sexual side effects of ADT and EBRT (and the only study to solely assess men with good baseline sexual function), our study does possess several limitations. The exact duration of ADT use was not known for each patient, so we assumed the standard of care duration of ADT use (typically 4–6 months for intermediate-risk and 12–36 months for high-risk disease). Despite this limitation of the data, our findings reflect real-world clinical practice and are important for inclusion in the discussion of expected functional outcomes associated with common ADT and EBRT regimens. Additionally, testosterone levels were unknown throughout follow-up which limits our ability to understand the persistence of hormone depletion following cessation of ADT as well as observe hormonal decline secondary to normal aging. Nevertheless, we were able to observe hormonal domain scores over time which assess clinical effects of ADT such as hot flashes, low energy, weight change, and gynecomastia. One strength of our study is the inclusion of modern EBRT practices, such as IMRT, which better target cancer sites while limiting side effects secondary to radiation of surrounding structures. Despite these practices, higher radiation threshold doses to the penile bulb may be unavoidable and have been associated with higher rates of impotence [28]. While Table 2 details the type and dose of radiation included in our analysis, dosimetry to the penile bulb was not specifically evaluated. Finally, follow-up was limited to distinct intervals which may miss important sexual effects of treatment that occur between these times; however, continuous monitoring of function in these individuals would be challenging.

Sexual function preservation represents an especially important factor for the majority of men when making prostate cancer management decisions [29]. Better quantifying the chance of sexual function recovery following treatment with ADT is important given the many erectile dysfunction management options with varying levels of invasiveness. Our findings offer more clear expectations for men with good baseline sexual function regarding their chances and timing of recovery following ADT and EBRT, which may affect the aggressiveness of which sexual dysfunction treatment is pursued and limit regret associated with localized treatment decision-making.

Conclusions

We present comparative sexual function through 5 years in men with good baseline sexual function who were treated with EBRT for intermediate- and high-risk prostate cancer. Declines in sexual function over 5 years were noted in all groups, regardless of ADT use. Patients treated with ADT experienced worse sexual function through 1 year compared to EBRT alone; however, these differences attenuated by 3 years in the intermediate-risk group and by 5 years in the high-risk group. Men with intermediate-risk disease, who tend to receive shorter-duration ADT, were more likely to recover sexual function when compared to men with high-risk disease. These findings may help better inform prostate cancer shared decision-making and guide interventions to address sexual dysfunction following EBRT for intermediate- and high-risk disease.

Table 3 Comparison of sexual function between treatment groups.

		EBRT only	Intermediate-risk EBRT + ADT	High-risk EBRT + ADT	Intermediate-risk EBRT + ADT vs. EBRT only			High-risk EBRT + ADT vs. EBRT only			High-risk EBRT + ADT vs. Intermediate-risk EBRT + ADT		
	N	(*N* = 73)	(*N* = 51)	(*N* = 43)	Effect	CI	*p*-value	Effect	CI	*p*-value	Effect	CI	*p*-value
Domain													
Sexual function - EPIC-26													
		Unadjusted median (IQR) domain score			Adjusted linear model; effect size = point difference between groups								
Baseline	166	85.0 (70.0, 90.0)	80.0 (70.0, 85.0)	81.2 (75.0, 90.0)									
6 months	148	75.0 (60.0, 85.0)	11.7 (0.0, 68.3)	21.7 (0.0, 75.0)	−30.5	[−40.5, −20.5]	<0.001	−34.9	[−45.1, −24.7]	<0.001	−4.4	[−16.5, 7.7]	0.478
1 year	146	80.0 (45.0, 90.0)	55.0 (24.2, 77.5)	26.7 (0.0, 60.6)	−18.3	[−26.2, −10.4]	<0.001	−32.8	[−42.0, −23.7]	<0.001	−14.5	[−25.1, −4.0]	0.007
3 years	129	69.4 (43.3, 84.6)	70.0 (42.1, 81.2)	28.3 (7.5, 70.0)	6.1	[−4.3, 16.5]	0.248	−20.3	[−31.8, −8.8]	<0.001	−26.4	[−39.9, −13.0]	<0.001
5 years	112	65.0 (26.7, 82.5)	65.0 (38.3, 80.0)	43.8 (21.7, 70.0)	5.3	[−7.1, 17.7]	0.398	−3.4	[−17.2, 10.5]	0.633	−8.7	[−23.3, 5.9]	0.243
Individual items													
Erections sufficient for intercourse													
		Unadjusted number (%)			Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	167	73 (100%)	51 (100%)	43 (100%)									
6 months	149	48 (77%)	14 (28%)	15 (41%)	0.2	[0.1, 0.4]	<0.001	0.2	[0.1, 0.5]	<0.001	1.2	[0.5, 2.9]	0.731
1 year	146	40 (66%)	20 (43%)	12 (31%)	0.4	[0.2, 0.7]	0.003	0.2	[0.1, 0.4]	<0.001	0.5	[0.2, 1.0]	0.061
3 years	130	33 (57%)	23 (62%)	11 (31%)	1.7	[0.7, 4.0]	0.198	0.3	[0.1, 0.8]	0.010	0.2	[0.1, 0.5]	<0.001
5 years	113	23 (45%)	18 (55%)	15 (52%)	1.5	[0.6, 3.9]	0.401	1.6	[0.6, 4.1]	0.376	1	[0.3, 3.0]	0.960
Individual items													
Initial loss followed by recovery of erections sufficient for intercourse													
		Unadjusted number (%)			Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Recovery by 3 years	74	9 (45%)	19 (68%)	6 (23%)	3.5	[1.3, 9.1]	0.011	0.5	[0.2, 1.4]	0.203	0.1	[0.0, 0.5]	0.002
Recovery by 5 years	68	12 (63%)	21 (75%)	9 (43%)	2.0	[0.6, 6.4]	0.261	0.6	[0.2, 1.7]	0.38	0.3	[0.1, 1.0]	0.044

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Competing interests The authors declare no competing interests.

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