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Association between treatment for localized prostate cancer and mental health outcomes

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Abstract

Purpose: We aim to compare patient-reported mental health outcomes for men undergoing treatment for localized prostate cancer, longitudinally over 5 years.

Materials & Methods: We conducted a prospective population-based analysis using the Comparative Effectiveness Analysis of Surgery and Radiation study (CEASAR) study. Patient-reported depressive symptoms (Centers for Epidemiologic Studies Depression, CES-D) and domains of the Medical Outcomes Study 36-item short form survey evaluating emotional well-being and energy/fatigue, were assessed through 5 years after treatment with surgery, radiotherapy (with or without androgen deprivation therapy) and active surveillance. Regression models were adjusted for outcome-specific baseline function, demographic and clinicopathologic characteristics, and treatment approach.

Results: 2742 men (median [quartiles] age 64 [59–70]) met inclusion criteria. Baseline depressive symptoms, as measured by the CES-D, were low (median 4, quartiles 1–8) without differences between groups. We found no effect of treatment modality on depressive symptoms (p= 0.78), though older age, poorer health, being unmarried, and baseline CES-D score were associated with declines in mental health. There was no clinically meaningful association between treatment modality and scores for either emotional well-being (p=0.81) or energy/fatigue (p=0.054).

Conclusions: This prospective, population-based cohort study of men with localized prostate cancer showed no clinically important differences in mental health outcomes including depressive symptoms, emotional well-being, and energy/fatigue according to the treatment received (surgery, radiotherapy, or surveillance). However, we identified a number of characteristics associated with worse mental health outcomes including: older age, poorer health, being unmarried, and baseline CES-D score which may allow for early identification of patients most at risk of these outcomes following treatment.

Keywords

prostate cancer; mental health; quality of life

Introduction

For patients diagnosed with localized prostate cancer, guideline-recommended treatment options include active surveillance, radical prostatectomy, and radiotherapy, based on risk-stratification. Absolute differences in cancer-specific and overall mortality between these approaches are small[1,2], thus, treatment-related morbidity is paramount in treatment decision making. While health-related quality of life outcomes following prostate cancer treatments such as urinary symptoms, erectile dysfunction, and bowel symptoms are well reported[3–6] and the burden of other interventions to manage treatment-related complications

is increasingly recognized[7–10], less attention has been paid to the association between treatment for localized prostate cancer and mental health outcomes.

While mental health outcomes of treatment have been poorly explored among patients with prostate cancer, one small (n=368) cross-sectional study of Black men with prostate cancer found a relatively high prevalence of major depressive symptoms (33%), with an increased likelihood among those who underwent radiotherapy (odds ratio 2.38, 95% confidence interval 1.02–5.51). However, these data are limited by the lack of generalizability, difficulties with causation with a cross-sectional study design, and the need for reproducibility[11]. In contrast, the association between treatment and mental health outcomes is better established in both breast cancer and colorectal cancer[12,13], in which sexual dysfunction and body image concerns contribute to emotional distress and worsening psychosocial function over time.

In this context, we evaluated the association between prostate cancer treatment and patient-reported depression and emotional well-being over time applying previously validated Centers for Epidemiologic Studies Depression (CES-D) and Medical Outcomes Study 36–item Short Form survey (SF-36) scores to data from the prospective population-based Comparative Effectiveness Analysis of Surgery and Radiation study (CEASAR) study.

Materials & Methods

Study Population

The CEASAR study enrolled men with clinically localized prostate cancer (cT1-cT2, PSA<50ng/dL) from 5 population-based Surveillance, Epidemiology and End Results (SEER) Program registries and the observational Cancer of the Prostate Strategic Urologic Research Endeavor prostate cancer registry from 2011–2012, as previously described[14,15]. Institutional review board approval was obtained from Vanderbilt University Medical Center (coordinating center) and from each participating site.

Participants completed surveys at baseline, 6 months and 1-, 3-, and 5-years following enrollment (with the final survey being completed in September 2017). Data regarding tumor characteristics, treatment choice, and treatment dates were obtained from medical chart abstraction 1 year after enrollment[14,15]. Any treatment received after 1 year was based on patient report. Survival was determined from vital status follow-up data obtained from the SEER and Prostate Strategic Urologic Research Endeavor registries.

Exposure

The exposure of interest was the primary treatment modality, categorized as active surveillance, surgery, radiation with androgen deprivation therapy (ADT), and radiation without ADT. Treatment modality was determined primarily based on 1-year chart abstraction, supplemented by patient report.

Outcomes

Depressive symptoms were assessed by using a 10-question version of the previously validated Centers for Epidemiologic Studies Depression scale (CES-D).[16,17] The CES-D10

has been validated across diverse populations[18,19]. To reduce respondent burden, the CES-D was modified to a nine question version. We adjusted the overall CES-D score to reflect this difference (from a standard score of 30 points to 27 points.) Domain scores ranged from 0–27, where 27 indicated more severe depressive symptoms. Notably, to our knowledge, a clinically meaningful difference on this scale has not been described though scores above 19 have strong specificity and positive predictive value for major depression.

The validated Medical Outcome Study 36-item Short Form Survey (SF-36) was used to evaluate emotional well-being and energy and fatigue[20,21]. For the SF-36, domain scores range from 0–100 with 100 indicating the best function. The results of these domain scores were analyzed over time for each treatment modality. We interpreted results based on previously determined minimally clinical important differences of 6 and 9 for emotional well-being and energy and fatigue, respectively[22,23].

Statistical Analysis

Clinical and sociodemographic characteristics were evaluated by treatment modality, categorized as active surveillance, surgery, radiation with ADT, and radiation without ADT. Treatment group differences were assessed using Kruskal-Wallis tests and χ^2 tests for continuous and categorical variables, respectively.

The study endpoints of CES-D score and SF-36 domain scores for emotional well-being and energy and vitality were reported as adjusted mean score differences (with 95% confidence intervals). To further evaluate the associations between treatments and measures of mental health over time, using the longitudinal survey data, we fit multivariable longitudinal linear regression models for CES-D, emotional well-being and energy and vitality adjusting for time since treatment (continuous, restricted cubic splines using 4 knots), age at diagnosis (continuous, restricted cubic splines using 3 knots), race (White, Black, Hispanic, Asian, other), education (less than high school, high school graduate, some college, college graduate, graduate/professional school), marital status (not married, married), comorbidity as measured with total burden index for prostate cancer - TIBI-CaP[24] (categorical: 0–2, 3–4, 5 or more), income (less than $30,000, $30,001-$50,000, $50,001-$100,000, more than $100,000), insurance status (Medicare; private or HMO; and VA, military, Medicaid, other, or uninsured), D'Amico risk category (low, intermediate, high), site (Utah, Atlanta, Los Angeles, Louisiana, NJ, CaPSURE), baseline physical functioning (continuous, linear), baseline general health (continuous, linear), baseline social support (continuous, linear), baseline participatory decision-making scale (continuous, linear), baseline sexual function score (continuous, linear), time-varying sexual function scores (at 6 months, 1, 3, and 5 years, continuous, linear) and corresponding baseline value of the outcome (continuous, restricted cubic splines using 3 knots). Covariates were obtained from patient-reported surveys and chart abstraction, as appropriate.

Comparing between treatment modalities, we utilized active surveillance as the referent. To allow for variable estimation of treatment effect at different time points, we included the interaction terms between treatment and time since treatment in the models. In all models, to account for the correlation due to repeated measures obtained on the same subjects from multiple time points, the Huber-White method[25,26] was implemented by *robcov* function in

rms R package to estimate the variance-covariance matrices. The results of models were reported as mean differences between treatment groups and the associated 95% confidence intervals (CI). All missing covariate values were imputed 10 times using the MICE (multiple imputation using chained equations) implemented by *aregImpute* function in *rms* R package. The EPIC-26 sexual function score was missing at 4, 9, 10, 20, 28% at each time point, respectively. Income was missing in 11%; however, all other variables had less than 5% missing. To graphically represent the trends in CES-D and SF-36 scores, we fit simpler models that included time since treatment start and treatment modality, along with their interaction terms. Statistical significance was considered for all two-sided p values < 5%. All analyses were conducted using R version 4.0.2.

Results

Among 2,742 patients included in the analysis, 372 (13.7%) underwent active surveillance, 1,419 (51.8%) underwent surgery, 630 (23.0%) underwent radiation therapy without ADT and 321 (11.7%) underwent radiation with ADT (Figure 1). Differences in baseline characteristics across the treatment groups are in keeping with prior reports: men who underwent surgery as their primary treatment type were younger, with fewer comorbidities while men undergoing active surveillance were more likely to have low risk disease characteristics, including lower PSA, clinical stage T1, and a low D'Amico risk category. Men with features of high-risk disease (Gleason 8, 9, 10, T2, high D'Amico risk category) were more likely to undergo radiation therapy with ADT (Table 1). Baseline urinary function, urinary incontinence, and bowel function domain scores were similar across all treatment groups. In contrast, baseline sexual function domain scores were higher for men treated with radical prostatectomy compared to those treated with radiation or active surveillance (Table 1).

At baseline, the median CES-D score in this cohort was 4 (interquartile range 1–8), indicating a low prevalence of depressive symptoms (Table 1). We found no evidence of a clinically meaningful treatment-related effect on longitudinal assessments of depressive symptoms measured with the CES-D score, whether assessed continuously or dichotomized at 9 (Table 2). In addition to higher baseline CES-D score ($p<0.001$), on multivariable analysis, significant predictors of decline in CES-D score were older age ($p=0.001$), higher comorbidity ($p<0.001$), poorer overall health ($p=0.001$) and physical function ($p=0.008$), being unmarried ($p=0.02$), lower income ($p=0.002$), and lower baseline participatory decision-making score ($p=0.003$). Interestingly, social support ($p=0.39$) and education ($p=0.12$) were not associated with worsening CES-D scores, nor were race ($p=0.38$), insurance status ($p=0.95$), D'Amico risk group ($p=0.99$), or registry site ($p=0.11$).

Assessing emotional well-being and energy/fatigue domains of the SF-36, we found that, while baseline scores were overall quite high, lower scores were reported among those undergoing radiotherapy (with or without ADT), a difference which persisted over time (Figure 2). However, on adjusted and unadjusted analysis, treatment type was not associated with a clinically significant difference in longitudinal assessments of SF-36 emotional well-being or energy/fatigue scores at 6 months or 1-, 3-, or 5-years following treatment initiation, despite statistically significant differences (Table 2, Supplementary

Table 1). Minor declines in SF-36 energy/fatigue scores at 6 and 12 months among those treated with radiation and ADT (Figure 2) are unlikely to be clinically meaningful and were not statistically significant (Table 2). Notably, there was a statistically significant difference in the SF-36 energy/fatigue domain between patients who underwent surgery compared to radiotherapy though this failed to meet the threshold for a clinically important difference and, also, diminished with time. Further pairwise testing between surgery and radiotherapy, and between radiotherapy with and without ADT demonstrated no clinically meaningful differences in the captured mental health related outcomes (Supplementary Table 2). In addition to baseline SF-36 emotional well-being ($p<0.001$), significant predictors of decline in SF-36 emotion well-being scores were older age ($p<0.001$), higher comorbidity ($p<0.001$), lower income ($p=0.004$), general health ($p=0.02$) and physical function ($p<0.001$), social support ($p=0.001$), and baseline participatory decision making scores ($p=0.002$) Notably, unlike for changes in CES-D score, marital status was not associated with changes in emotional well-being measured by SF-36 ($p=0.17$), nor was race ($p=0.26$), insurance status ($p=0.88$), D'Amico risk group ($p=0.62$), registry site ($p=0.24$)

Discussion

In this population-based, prospective cohort study of men with localized prostate cancer, we found no clinically meaningful association between treatment approach (including active surveillance, radical prostatectomy and radiotherapy) and measures of mental health including depressive symptoms (captured using the validated CES-D) and emotional well-being and energy/fatigue (captured as domains of the validated SF-36). These findings were consistent with our hypothesis, that treatment type would not impact overall mental health outcomes in men with localized prostate cancer. However, on multivariable analysis, we did identify baseline characteristics associated with declining emotional well-being following prostate cancer treatment including older age, poor overall health, unmarried status, and worse baseline depression and emotional well-being symptoms. These characteristics may allow clinicians to identify patients most at risk of declines in mental health following prostate cancer diagnosis and treatment to target interventions to address these issues.

To our knowledge, this is the first prospective evaluation of mental health outcomes in men with localized prostate cancer. While previous work has demonstrated an increased utilization of anti-depressants following diagnosis for patients who received surgery or radiotherapy, but not active surveillance, this relied on administrative records and prescriptions as a proxy for symptoms[27]. In contrast, and in keeping with our findings, there does not appear to be an increased risk of suicide amongst patients diagnosed with prostate cancer, whereas there are increased risks of suicide amongst patients with other malignancies[28].

Although we did not demonstrate a relationship between treatment type and mental health outcomes in men with localized prostate cancer, we did find several factors predictive of declining mental health outcomes. Consistent with research in other malignancies, older, unmarried patients had declining emotional well-being in our analysis. In the bladder cancer population, prior research has demonstrated those at risk for suicidal death were typically elderly, unmarried men[29]. An additional vulnerable population we identified was

those with poor depression and poor emotional well-being symptoms prior to treatment. It is imperative that urologists seize available opportunities to identify and intervene in patients with mental health concerns both at the time of diagnosis and during follow-up. In addition to the importance of addressing patient distress and morbidity associated with these symptoms, prior work has demonstrated that significant mental health care utilization is independently associated with worse cancer specific and all-cause mortality[30]. While psychologic interventions are beyond the scope of most clinicians treating prostate cancer, we ought to appropriately screen and subsequently refer those at risk.

Our findings should be considered in the context of several limitations. First, as this is an observational study, treatment choice is non-random and thus there is the potential for confounding by indication. However, given the baseline similarities between groups and the longitudinal nature of assessment, and control for clinical factors, it is unlikely that this explains the findings. Second, due to the nature of the survey employed, we utilized a modified CES-D 10 with patients completing only nine questions rather than ten questions on the recommendation of our psychometrician in order to reduce respondent burden as other included instruments captured overlapping concepts. We adjusted the overall CES-D score to reflect this difference (from a standard score of 30 points to 27 points.) Similarly, the SF-36 and CES-D have been validated in a general population, but may not detect minute differences in our population of overall healthy men, and should not be used in isolation for diagnosing depression or mental health changes. Third, in the context of a finding of no significant differences, we must consider the potential for type II error. However, given the small differences noted which did not meet established threshold for clinically meaningful differences, increases in sample size are unlikely to change study conclusions. Additionally, many patients with low-risk disease in the CEASAR study received active intervention which, while common at the time, is not reflective of current practice patterns which now favor active surveillance in this cohort. Finally, we must not underestimate the mental health burden of being diagnosed with prostate cancer including for those who choose active surveillance as their primary treatment strategy. Thus using the active surveillance group as the referent group may contribute to the limited impact of treatment modality on mental health outcomes. Perhaps a more appropriate referent group, and consideration for future work, would be a group of healthy age-matched men without a cancer diagnosis.

These limitations notwithstanding, in this population-based, prospective cohort study of men with localized prostate cancer, we found no clinically meaningful association between treatment approach (including active surveillance, radical prostatectomy and radiotherapy) and measures of mental health including depressive symptoms (captured using the validated CES-D) and emotional well-being and energy/fatigue (captured as domains of the validated SF-36). We further identified characteristics of patients with a higher likelihood of declining mental health following prostate cancer diagnosis, independent of treatment approach, including older age, being unmarried, worse overall health and worse baseline mental health.

Conclusions

Careful evaluation of patients at risk for adverse mental health outcomes is warranted among all treatment groups, and appropriate psychiatric assistance should be provided to these patients to optimize the comprehensive care we provide to prostate cancer patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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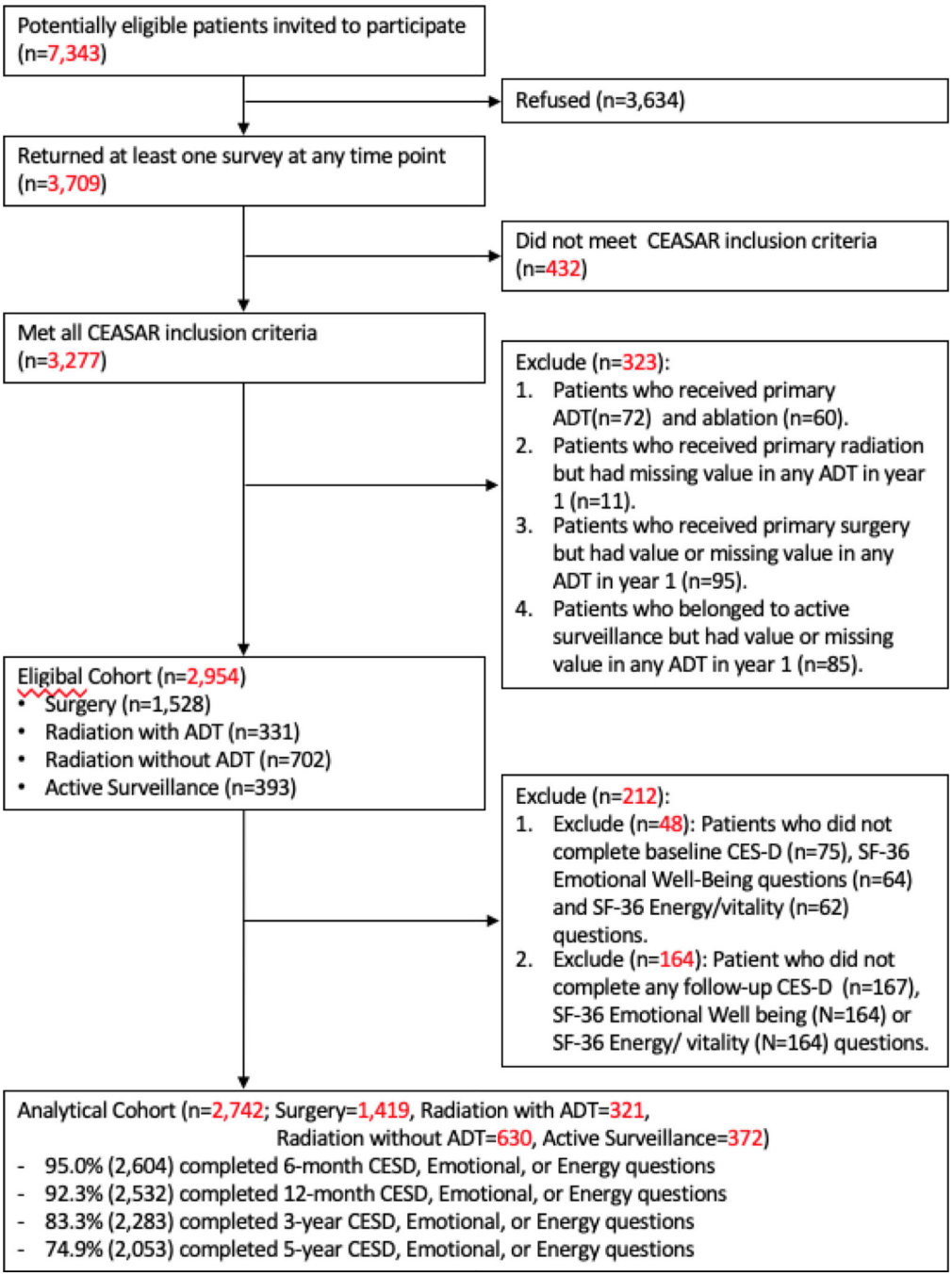

Figure 1:

Diagram of the Assembly of the Comparative Effectiveness Analyses of Surgery and Radiation (CEASAR) Study Cohort and Final Analytic Cohort (CES-D10, Emotional Well-Being, Energy/Vitality cohort)

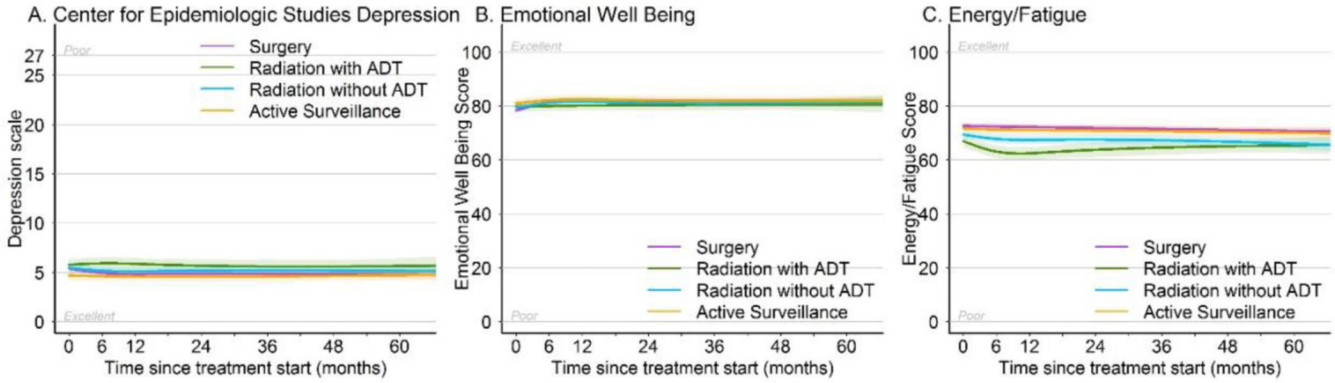

Figure 2:
Trend in unadjusted CES-D and SF-36 scores by treatment modality over time

Table 1:

Baseline demographic, socioeconomic, and disease characteristics by treatment type

	Active Surveillance	Surgery	Radiation with ADT	Radiation without ADT	p-value
	N=372	N=1419	N=321	N=630	
Age at diagnosis, median (IQR)	67 (62–72)	62 (57–66)	70 (65–74)	67(62–72)	<0.001
Race, no (%)					
White	296 (80)	1069 (76)	220 (69)	481 (76)	0.001
Black	39 (11)	165 (12)	56 (18)	103 (16)	
Hispanic	22 (6)	113 (8)	25 (8)	27 (4)	
Asian	9 (2)	40 (3)	13 (4)	10 (2)	
Other	5 (1)	21 (1)	4 (1)	8 (1)	
TIBI-CaP categories, no (%)					
0--2	95 (26)	452 (34)	49 (16)	133 (22)	<0.001
3--4	142 (39)	586 (44)	114 (37)	253 (43)	
5 or more	126 (35)	307 (23)	147 (47)	206 (35)	
Income, no (%)					
<$30,000	63 (18)	211 (17)	101 (36)	124 (22)	<0.001
$30,001–50,000	79 (23)	213 (17)	67 (24)	129 (23)	
$50,001–100,000	105 (31)	422 (33)	67 (24)	174 (31)	
>$100,000	97 (28)	422 (33)	47 (17)	126 (23)	
Education, no (%)					
Less than high school	25 (7)	113 (8)	52 (17)	59 (10)	<0.001
High school graduate	66 (18)	271 (20)	67 (22)	121 (21)	
Some college	77 (21)	298 (22)	68 (22)	145 (25)	
College graduate	91 (25)	324 (24)	57 (19)	135 (23)	
Graduate/professional school	104 (29)	332 (25)	62 (20)	129 (22)	
Marital status, no (%)					
Not married	67 (19)	216 (16)	70 (23)	153 (26)	<0.001
Married	294 (81)	1120 (84)	235 (77)	437 (74)	
Employment Status, no (%)					
Full time	160 (43)	876 (62)	80 (25)	250 (40)	<0.001
Retired/part time/unemployed	210 (57)	530 (38)	235 (75)	371 (60)	
Insurance Status, no (%)					
Medicare	214 (58)	464 (33)	221 (69)	388 (62)	<0.001
Private/HMO	142 (38)	884 (62)	78 (24)	211 (34)	
VA/military/medicaid/none	16 (4)	68 (5)	22 (7)	29 (5)	
PSA at diagnosis, corrected, median (IQR)	5.2 (3.9–7.0)	5.1 (4.2–6.8)	7.0 (4.9–11.3)	5.5 (4.3–7.3)	<0.001
Clinical tumor stage					
T1	309 (84)	1069 (75)	218 (68)	491 (78)	<0.001

	Active Surveillance	Surgery	Radiation with ADT	Radiation without ADT	p-value
	N=372	N=1419	N=321	N=630	
T2	57 (16)	347 (25)	103 (32)	138 (22)	
Biopsy gleason score					
6 or less	330 (89)	717 (51)	44 (14)	334 (53)	<0.001
3 + 4	33 (9)	437 (31)	113 (35)	197 (32)	
4 + 3	6 (2)	147 (10)	57 (18)	58 (9)	
8,9,10	1 (0)	114 (8)	107 (33)	36 (6)	
D'Amico risk category					
Low risk	293 (79)	614 (43)	28 (9)	305 (49)	<0.001
Intermediate risk	67 (18)	598 (42)	144 (45)	261 (42)	
High risk	10 (3)	205 (14)	149 (46)	60 (10)	
Site					
Utah	56 (15)	119 (8)	24 (7)	52 (8)	<0.001
Atlanta	47 (13)	189 (13)	25 (8)	188 (30)	
Los Angeles	116 (31)	409 (29)	76 (24)	100 (16)	
Lousiana	93 (25)	356 (25)	141 (44)	143 (23)	
New Jersey	28 (8)	241 (17)	36 (11)	128 (20)	
CaPSURE	32 (9)	105 (7)	19 (6)	19 (3)	
SF-36 Physical function, median (IQR)	95 (80–100)	100 (85–100)	90 (65–100)	90 (75–100)	<0.001
SF-36 Emotional Well-Being, median (IQR)	88 (72–92)	84 (68–92)	88 (72–92)	84 (72–92)	0.008
SF-36 Energy & Fatigue, median (IQR)	75 (60–85)	75 (60–85)	70 (55–85)	75 (58–85)	<0.001
Depression (CES-D10) Score, median (IQR)	3 (1–6)	4 (1–8)	4 (2–8)	4 (1–8)	0.05
Social support, median (IQR)	95 (75–100)	95 (75–100)	95 (75–100)	95 (70–100)	0.046
Participatory decision making, median (IQR)	86 (68–96)	86 (71–93)	79 (64–89)	79 (68–92)	<0.001
Prostate cancer specific burden, baseline, median (IQR)	14.3 (0.0–37.1)	22.9 (8.6–45.7)	22.9 (5.7–42.9)	20 (5.7–42.9)	<0.001
EPIC-26 sexual function, baseline, median (IQR)	75 (42–89)	80 (38–95)	50 (12–80)	65 (32–85)	<0.001
EPIC-26 urinary incontinence, baseline, median (IQR)	100 (85–100)	100 (79–100)	100 (79–100)	100 (85–100)	0.2
EPIC-26 urinary irritative, baseline, median (IQR)	88 (75–94)	88 (75–100)	88 (75–94)	88 (75–100)	0.011
EPIC-26 bowel function, baseline, median (IQR)	100 (92–100)	100 (96–100)	100 (92–100)	100 (92–100)	0.012
EPIC-26 hormonal domain score at baseline, median (IQR)	95 (85–100)	95 (85–100)	90 (75–95)	95 (85–100)	<0.001

Table 2:

The effect of treatment modality on longitudinal assessment of CES-D and SF-36 emotional well-being and energy/fatigue scores at 6 months and 1-, 3-, and 5-years following index, adjusted for the effect of patient demographic, tumor, and baseline functional characteristics.

	Time	Surgery vs. AS*			Radiation (+ ADT) vs. AS			Radiation (no ADT) vs. AS		
		Effect	95% CI	P-value	Effect	95% CI	P-value	Effect	95% CI	P-value
CESD10										
	0.5	−0.1	[−0.8, 0.5]	0.669	0.2	[−0.5, 1.0]	0.5	0.4	[−0.3, 1.0]	0.264
	1	−0.5	[−0.9, −0.1]	0.024	−0.3	[−0.9, 0.3]	0.351	0	[−0.5, 0.4]	0.881
	3	−0.3	[−0.7, 0.2]	0.316	0.1	[−0.6, 0.9]	0.713	0	[−0.6, 0.5]	0.873
	5	−0.5	[−1.0, 0.0]	0.067	−0.1	[−0.9, 0.7]	0.78	0	[−0.6, 0.6]	0.959
Emotional Well Being										
	0.5	1.9	[−0.1, 4.0]	0.065	0.6	[−17, 3.0]	0.598	0.4	[−17, 2.5]	0.721
	1	2.4	[1.0, 3.8]	<0.001	1.8	[−0.3, 3.9]	0.094	0.6	[−0.9, 2.2]	0.432
	3	1.7	[0.0, 3.3]	0.044	0	[−2.4, 2.4]	0.988	0.8	[−10, 2.6]	0.376
	5	1.2	[−0.6, 3.0]	0.187	0.4	[−2.4, 3.2]	0.769	0.6	[−1.4, 2.6]	0.562
Energy/Fatigue										
	0.5	4.7	[2.2, 7.2]	<0.001	−1	[−4.0, 2.0]	0.528	0.3	[−2.3, 2.9]	0.84
	1	3	[1.4, 4.6]	<0.001	−0.9	[−3.3, 1.5]	0.455	−1.5	[−3.3, 0.2]	0.085
	3	2.1	[0.3, 3.9]	0.023	−2.2	[−5.0, 0.5]	0.113	−0.2	[−2.2, 1.8]	0.845
	5	1.5	[−0.4, 3.4]	0.134	−1.1	[−4.0, 1.8]	0.455	−1.8	[−4.0, 0.5]	0.128
CESD>9 (binary)		Odds Ratio (95% CI)			Odds Ratio (95% CI)			Odds Ratio (95% CI)		
	0.5	0.9	[0.6, 1.6]	0.829	1.3	[0.7, 2.2]	0.448	1.4	[0.8, 2.5]	0.181
	1	0.9	[0.6, 1.3]	0.556	1	[0.6, 1.5]	0.858	1.1	[0.8, 1.6]	0.528
	3	0.8	[0.6, 1.3]	0.404	1.4	[0.8, 2.3]	0.236	0.9	[0.5, 1.3]	0.484
	5	0.8	[0.6, 1.2]	0.364	1	[0.6, 1.8]	0.983	1.3	[0.8, 2.0]	0.323

*AS=Active Surveillance