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Impact of Androgen Deprivation Therapy on Mental and Emotional Well-Being in Men with Prostate Cancer: Analysis from the CaPSURE™ Registry

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

EBRT = external beam radiation therapy

LHRH = luteinizing hormone-releasing hormone

MH = mental health

PADT = primary androgen deprivation therapy

QoL = quality of life

RE = role emotional

SO = social function

VT = vitality

Purpose: While androgen deprivation therapy can delay cancer progression and reduce tumor burden, its use can be limited by adverse side effects. We evaluated the effect of androgen deprivation therapy on mental and emotional well-being in men with nonmetastatic prostate cancer.

Materials and Methods: Participants were enrolled in the national CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) registry, and treated with radical prostatectomy, external beam radiation therapy or brachytherapy with no androgen deprivation therapy (local); local with androgen deprivation therapy (combination); or primary androgen deprivation therapy. Emotional quality of life was evaluated by SF-36® social function, role emotional, vitality and mental health subscales before and up to 24 months after treatment. Subscales were assessed as continuous scores and as clinically meaningful declines of at least half a standard deviation since pretreatment. Associations between treatment and quality of life changes over time were evaluated with mixed modeling. Quality of life declines were evaluated with logistic regression.

Results: Among 3,068 men the combination and primary androgen deprivation therapy groups were older, single, with less education and higher clinical CAPRA (Cancer of the Prostate Risk Assessment) score risk than the local group (all values $p < 0.01$). Androgen deprivation therapy exposure was associated with significant changes with time in adjusted role emotional (-8.4 points, $p = 0.01$) and vitality (-9.2 points, $p = 0.02$) scores. Treatment group was not associated

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with any clinically meaningful quality of life declines. A potential limitation is the observational nature of the study.

Conclusions: Use of androgen deprivation therapy was associated with changes in mental and emotional well-being but did not result in clinically meaningful declines at 24 months. Patients must be counseled on possible quality of life changes related to androgen deprivation therapy as well as interventions to attenuate these effects before receiving treatment for prostate cancer.

Key Words: androgens, personal satisfaction, prostatic neoplasms, quality of life

In 2013, 238,590 new cases of prostate cancer were estimated to arise in the United States with 29,720 projected deaths for the year.[1] Some patients with prostate cancer are more likely to experience morbidity and mortality from treatment related complications and noncancer comorbidities than from prostate cancer itself. Therefore, it is important to weigh the risks and benefits of all relevant prostate cancer treatment options as various modalities may have adverse side effects that affect well-being and survivorship.[2]

Androgen deprivation therapy, which suppresses the production of testicular androgen by medical or surgical castration, remains the gold standard treatment modality for advanced prostate cancer, either alone or combined with EBRT.[3,4] Demonstrated benefits of ADT include reduction of tumor burden, delayed cancer progression and overall improvement in survival in some cases.[5] However, the use of ADT may have a number of adverse physical side effects including hot flashes, decreased libido, fatigue, decreased bone and muscle mass, increased total body fat content[5,6] and possible harmful cardiovascular effects.[7,8]

Prior studies have suggested negative outcomes with regard to cognitive and affective symptoms after ADT,[9] particularly in the elderly.[10] Emotional upset (tearfulness, irritability and anger),[11] decreased motivation, hopelessness,[12,13] and cognitive interruptions in attention, memory and visual processing[14,15] have been reported. Some studies have linked depression to ADT use, although it is unclear whether such effects are a direct consequence of ADT itself[16] or perhaps associated with age, comorbidities,[17,18] or hot flashes, fatigue and insomnia.[9,19] To be sure, the detrimental effects of ADT on mental and depressive symptoms are controversial. Timilshina et al recently reported that ADT use was not associated with depressive symptoms in patients with nonmetastatic prostate cancer in a study which included a healthy control arm without cancer.[20] In this study we evaluate the effects of ADT on mental and emotional well-being in men with localized prostate cancer from largely community based practices across the United States.

METHODS

The CaPSURE database is a longitudinal, observational registry of men with biopsy proven prostate cancer.[21] Since 1995 patients have been enrolled at 36 community based, 3 academic and 4 veteran's urological practices nationwide under central institutional review board supervision. Participating urologists recruit patients consecutively at diagnosis and treat according to usual practices. Followup data are collected at subsequent office visits and on patient questionnaires. Patients are followed until death or study withdrawal.

The current study focused on men newly diagnosed with localized (nonmetastatic) prostate cancer in 1995 to 2011 and treated with radical prostatectomy, brachytherapy, EBRT or PADT with LHRH agonist and/or antiandrogen medications. Clinical risk at diagnosis was classified using the CAPRA as low (0 to 2), intermediate (3 to 5) or high (6 to 10).[22] Treatment types were categorized based on exposure to ADT as radical prostatectomy, EBRT or brachytherapy with no ADT (local); local with adjuvant and/or neoadjuvant ADT (combination); or primary ADT.

At diagnosis patients completed a checklist of general symptoms including fever, fatigue, weight fluctuations, edema, hot flashes and several emotional well-being items. Men who reported depression, insomnia, confusion, poor concentration, sleep disturbances, nervousness or poor memory were identified as a group who indicated some mental impairment at diagnosis. Patients also reported their emotional QoL using the RAND 36-Item Short-Form Health Survey subscales measuring social function (limitation in normal social activities), role emotional (limitation due to emotional problems), vitality (energy/fatigue) and mental health (psychological distress) subscales.[23] Scores range from 0 to 100 with higher scores representing better QoL. All patients completed a pretreatment survey plus at least 1 survey at 6, 12, 18 or 24 months after primary treatment. QoL outcomes assessed were change and decline in these scores. Continuous change in MH, VT, SO and RE scores was measured from before treatment to 6 months after and to 24 months after primary treatment. Clinically meaningful decline at posttreatment assessment was defined as a decrease of at least half a standard deviation from the pretreatment mean score.[24]

Demographics, clinical characteristics, symptoms, comorbid conditions and QoL scores at diagnosis were compared among local, combination and PADT groups using frequency tables and chi-square test for categorical variables, and means and ANOVA for continuous

variables. Posttreatment QoL scores at 6 and 24 months after primary treatment were also compared among the groups. Associations between treatment group and QoL change scores over time were evaluated with repeated measures mixed modeling. Models were adjusted for diagnostic features (mental impairment, clinical CAPRA risk, age, number of comorbidities, education, relationship status), type of clinical site and time since treatment. A sensitivity analysis was also performed using only those 1,180 patients who completed questionnaires at all points during the study. Multivariate logistic regression models were used to evaluate the association between treatment group and QoL decline adjusted for the same covariates in the mixed models.[24] Model covariates were selected a priori and assessed for inter-item correlations. A $p < 0.05$ was considered significant. All analysis was completed using SAS® 9.2 for Windows®.

RESULTS

As of 2013, 14,521 patients were recruited to CaPSURE. Of those patients 7,609 enrolled within 6 months of diagnosis and were treated with local or combination therapy or PADT for nonmetastatic disease. Not all patients were able to provide pretreatment and posttreatment QoL data due to interruptions in enrollment and followup. Therefore, the study cohort comprised a subset of 3,068 men who completed a pretreatment and at least 1 posttreatment QoL assessment (fig. 1). Patients lacking QoL data who were excluded from analysis had the same mean age (65 years) and year of diagnosis (2002) but reported less overall mental impairment (9% vs 36%) at diagnosis and a shorter followup (53 vs 76 months) (both $p < 0.01$).

Mean age (years) varied significantly among local (63), combination (68) and PADT (73) groups ($p < 0.01$). Men exposed to ADT were less educated ($p < 0.01$), single ($p < 0.01$) and of nonCaucasian race ($p = 0.04$). Clinically patients in the combination and PADT groups were classified as 40% to 42% intermediate and 20% high CAPRA risk while 68% of the local group was low risk ($p < 0.01$, see supplementary table, http://jurology.com/).

Of men included in the study 75% were treated with local therapy, 20% had combination treatment and 5% received PADT. Among men in the PADT group 84% were treated with LHRH agonist monotherapy and 16% received combined androgen blockade. Median duration of ADT was 5 months (IQR 3–9) in the PADT group and 4 months (IQR 3–7) in the combination group ($p < 0.01$).

Approximately 36% of patients reported some type of mental impairment at pretreatment evaluation including depression, insomnia, confusion, poor concentration, sleep disturbances, nervousness or poor memory. There were no overall differences in rates of mental health symptoms at diagnosis among treatment groups, although 18% of the PADT group reported poorer memory compared to 12% of the local group and 15% of the combination group ($p = 0.02$).

Unadjusted pretreatment QoL scores differed among treatment groups with men in the PADT group reporting lower VT scores (mean 61 ± 21.1) than men in the local (69 ± 18.4) and combination (66 ± 19.7) groups ($p < 0.01$, table 1). Pretreatment SO scores also differed among PADT (85 ± 21.5), combination (87 ± 20.0) and local (90 ± 17.8) groups ($p < 0.01$). With time the effect of ADT on emotional scores varied. At 6 months after treatment 18% of the PADT group and 20% of the combination group had clinically significant RE declines compared to 14% of the local group ($p = 0.02$). By 24 months 27% of the PADT group reported declines in VT vs 14% of the local group and 18% of the combination group ($p = 0.01$). MH scores at 24 months also declined for 13% of the PADT group vs 5% of the local group and 6% of the combination group ($p = 0.04$, table 1).

Multivariate repeated measures analysis demonstrated that ADT exposure was associated with significant changes in RE and VT adjusted for diagnostic features, type of clinical site and time

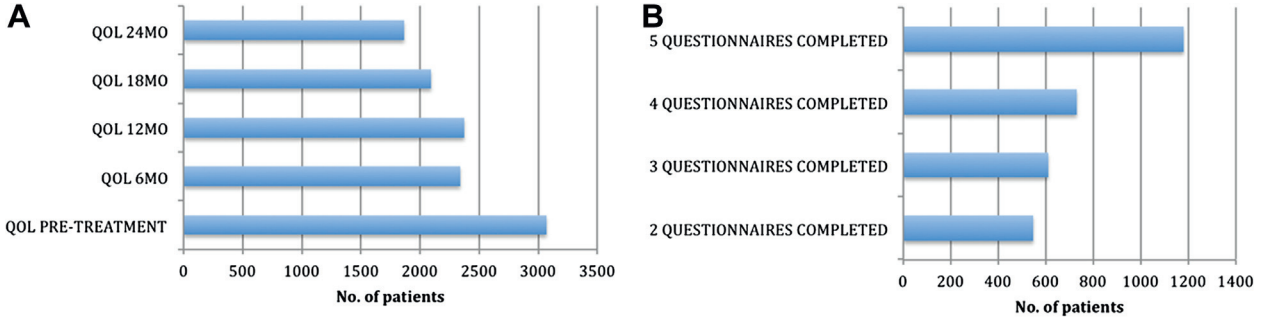

Figure 1. Distribution of QoL questionnaires at each specified time (*A*) and completed QoL questionnaires (*B*) during 24-month followup.

Table 1. *Unadjusted pretreatment health related QoL scores by treatment group*

SF-36 QoL Subscale	Local Treatment	Combination Treatment	PADT	p Value
Mental health:				
Mean pretreatment score (SD)	78.7 (15.6)	80.1 (15.6)	79.4 (16.9)	0.15
No. decline at 6 mos (%)	106 (6)	44 (9)	7 (6)	0.20
No. decline at 24 mos (%)	73 (5)	21 (6)	8 (13)	0.04
Role emotional:				
Mean pretreatment score (SD)	85.0 (30.5)	84.1 (30.8)	78.7 (36.7)	0.06
No. decline at 6 mos (%)	235 (14)	97 (20)	20 (18)	0.02
No. decline at 24 mos (%)	137 (10)	38 (10)	13 (20)	0.08
Social function:				
Mean pretreatment score (SD)	89.6 (17.8)	86.7 (20.0)	84.8 (21.5)	<0.01
No. decline at 6 mos (%)	405 (24)	104 (21)	18 (16)	0.23
No. decline at 24 mos (%)	164 (12)	45 (13)	14 (23)	0.09
Vitality:				
Mean pretreatment score (SD)	68.8 (18.4)	65.5 (19.7)	60.8 (21.1)	<0.01
No. decline at 6 mos (%)	304 (18)	111 (22)	19 (17)	0.07
No. decline at 24 mos (%)	192 (14)	65 (18)	17 (27)	0.01

Decline defined as decrease of at least half a standard deviation since baseline.

since treatment. Men in the PADT group experienced the largest decreases of −8.4 for RE and −9.2 for VT (table 2). QoL change with time was not statistically significant among treatment groups for MH, RE or SO but was borderline for VT ($p = 0.05$, fig. 2). The sensitivity analysis of 1,180 patients who completed questionnaires at every point yielded results similar to those of the full model of the entire cohort of 3,068 patients and, thus, was not reported.

Among mixed model covariates mental health symptoms at diagnosis, a greater number of comorbidities and lower education level were associated with changes in all 4 domains (all $p \leq 0.03$). Age at diagnosis was associated with changes in mental health ($p < 0.01$) but not role emotional, social function or vitality, while type of clinical site ($p < 0.01$) was associated with all domains but MH. Greater clinical risk was significantly associated with declines in RE and SO only (both $p < 0.01$).

The multivariate logistic regression analysis evaluating the association between ADT exposure and QoL decline at 24 months did not demonstrate any statistically significant findings. The strongest association, although not significant, was between treatment type and MH ($p = 0.13$), where the combination group (OR 0.43, 95% CI 0.16–1.12) and local group (0.39, 95% CI 0.16–0.97) had lower odds of decline in QoL than the PADT group.

Table 2. *Repeated measures analysis with mixed modeling evaluating association between treatment type and change in emotional well-being scores from pretreatment through 24 months after treatment*

SF-36 QoL Subscale	Combination Treatment Estimate (SE)	PADT Estimate (SE)	Change p Value	Decline p Value*
Mental health	+0.55 (1.05)	−3.68 (2.33)	0.85	0.13
Role emotional	−0.23 (2.11)	−8.35 (4.73)	0.01	0.43
Social function	−1.30 (1.42)	−3.54 (3.17)	0.91	0.62
Vitality	−1.92 (1.42)	−9.19 (3.15)	0.02	0.83

Fully adjusted models included age at diagnosis, education level, relationship status, CAPRA score, time since treatment, baseline mental health symptoms, number of comorbid conditions, type of clinical site, and an interaction term between treatment group and time since treatment.
All values for local treatment estimate (SE) were 0.00 (reference).
* For the results from multivariate logistic regression models of association between treatment group and clinically meaningful decline in QOL score of at least half a standard deviation from baseline.

DISCUSSION

We evaluated the effects of ADT on mental and emotional well-being over time in men with prostate cancer using longitudinal observational data from the CaPSURE registry. Multivariate mixed model analysis demonstrated that exposure to ADT was associated with significant changes in RE and VT scores. However, there were no clinically meaningful declines in any domains at 24 months associated with exposure to ADT in the multivariate logistic regression model. The attenuation of ADT effects at 24 months represented in figure 2 was interesting in that men in the ADT group could be adapting to their symptoms over time and, thus, reporting improved scores. The phenomenon is supported in the literature.[25,26]

The most pronounced effect of ADT was on VT, suggesting a tendency toward disturbances in energy in our cohort. This result corroborates other studies documenting fatigue among the most commonly reported side effects of ADT.[19,27] However, it remains unclear whether the fatigue is a direct effect of ADT or secondary to the physical side effects of ADT such as sleep disturbances or hot flashes.[16,19] In a survey of 327 patients treated with prostatectomy Savard et al reported that approximately a third of participants experienced sleep disturbances, for which ADT was identified as an independent risk factor.[19] Despite our findings it is unclear how well the instrument used (ie RAND SF-36 scale) fully measures the mental and

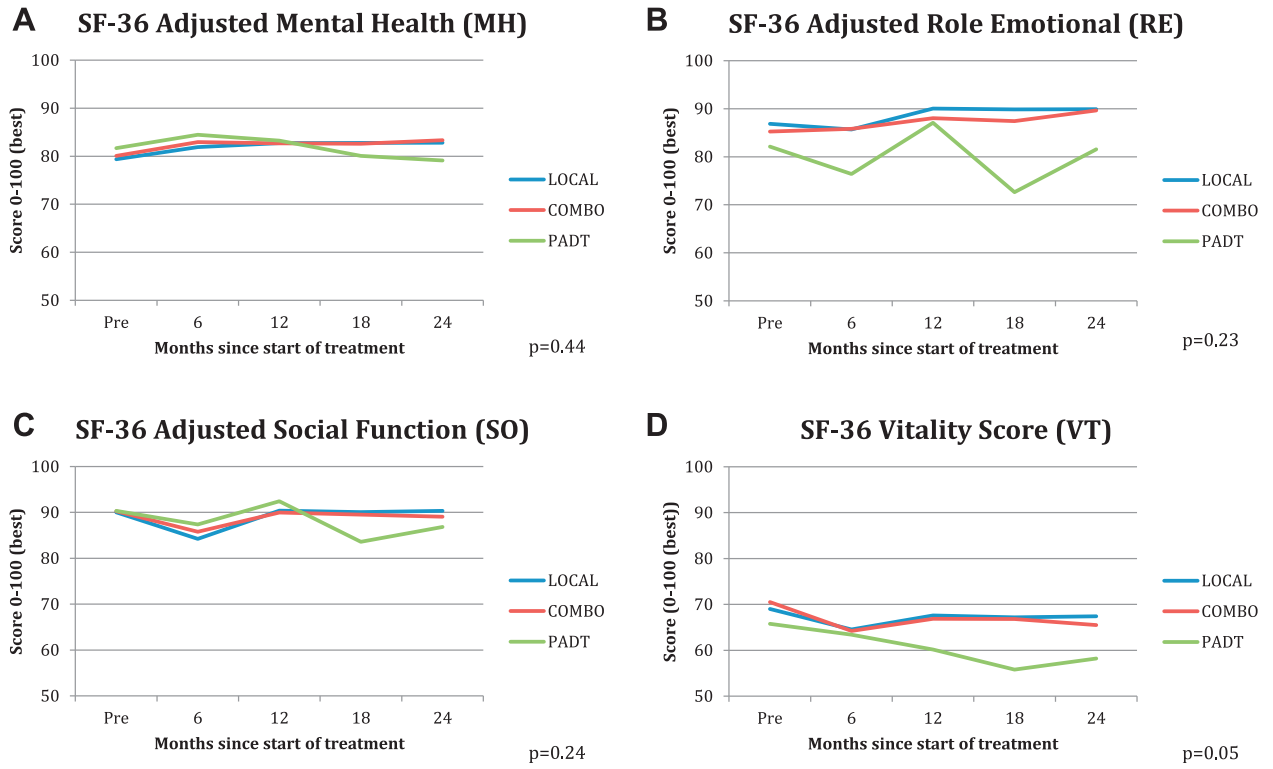

Figure 2. Longitudinal changes in mental health (*A*), role emotional (*B*), social function (*C*) and vitality (*D*) QoL scores from pretreatment to 24-month followup by treatment group.

emotional effects of ADT. Other validated questionnaires for depression, anxiety and distress such as the PHQ-9 (Patient Health Questionnaire), GAD-7 (General Anxiety Disorder 7-item scale) and DT (Distress Thermometer) may have been better tools. Nevertheless, the SF-36 scale is widely used and validated in health related QoL studies.

In a study of QoL in 20 men undergoing ADT for prostate cancer by Ng et al participants reported emotional lability including tearfulness, increased irritability and anger.[11] In interviews with 15 Israeli patients receiving hormonal therapy for advanced prostate cancer, Navon and Morag likewise documented the psychosocial effects experienced by patients on ADT.[12,13] In accordance with our results they reported decreased motivation and excitement overall, along with feelings of hopelessness and discouragement related to physical and sexual effects of ADT. While these studies were limited by small numbers of participants without pretreatment and followup data, their results suggest that mental and emotional decreases may be compounded by effects of ADT on physical well-being, as previously documented by Sadetsky et al.[28]

Reports of depression in patients on ADT are less consistent. In a case-control study of more than 100,000 men with and without prostate cancer, Shahinian et al reported the development of at least 1 clinical diagnosis of depression, cognitive impairment or constitutional symptoms in 31.3% of men on ADT vs 23.7% in those not on ADT.[17] Notably the cohort in the study by Shahinian et al was drawn from Medicare data, restricting representation to men older than 65 years. In another prospective study of 52 men with locally advanced prostate cancer receiving ADT Pirl et al reported that hormonal therapy was not associated with clinically significant changes in depression during a 12-month followup period,[18] but fatigue increased significantly during this period, and a nonADT control group was not included in this study.

Given the known adverse effects of ADT (eg muscle mass loss, cognitive decline), interventions to improve or maintain physical and emotional well-being would be beneficial in this patient population. Randomized clinical trials involving resistance and aerobic exercise have shown beneficial results in patients with prostate cancer initiating ADT. Two randomized trials have shown that an exercise program for men on ADT decreased fatigue, improved muscular fitness and improved general health compared to men on ADT in the control arm.[29,30]

Furthermore, our results demonstrate that lower educational levels are independently associated with changes in all 4 cognitive domains in the

setting of ADT. While all patients should be well-informed about the potential adverse effects of ADT, interventions to improve mental and emotional health such as exercise programs and dietary/lifestyle changes could be of particular importance for less educated men.[29,30]

Several limitations should be noted in the present study. Our inclusion criteria involved only men with localized prostate cancer at diagnosis, while indications for ADT often include more advanced stages of disease. The observational nature of CaPSURE and patient reported data may also introduce selection and recall bias. Not all patients were able to provide pretreatment and posttreatment QoL data due to interruptions in enrollment and followup. The actual duration of ADT may be longer than described due to potential inaccuracies in reporting and variable duration of testosterone suppression after LHRH therapy in older men. Other than SF-36 scores, there were no detailed assessments of psychosocial well-being potentially associated with ADT effects or comprehensive data on the use of antidepressant and anxiolytic medications. CaPSURE does not record whether ADT was given as continuous vs intermittent treatment, which limits our ability to evaluate dose-response relationships.

Despite these limitations there are several notable strengths of the present study. The CaPSURE cohort reflects a sizable, geographically diverse population of patients drawn largely from community based practices, thus reflecting usual patterns of care across the nation in a demographically representative sample. Moreover the RAND 36-Item Short-Form Health Survey is a validated widely used questionnaire that yields reliable information in the mental and emotional domains. The availability of pretreatment and longitudinal followup measures of health related QoL allows for a unique, comprehensive evaluation of patients with prostate cancer.

CONCLUSIONS

We found that ADT was associated with changes in the mental and emotional well-being of men with prostate cancer. However, these changes did not result in clinically meaningful declines in QoL at 24 months. Patients must be counseled on the possibility of QoL changes associated with ADT as well as interventions to attenuate these effects before initiating treatment to allow for an informed decision process regarding hormonal therapy for prostate cancer.

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