RESEARCH PAPER

Impact of Androgen Deprivation Therapy on Cognitive Function and Quality of Life in Men with Prostate Cancer

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ABSTRACT

Background: Androgen deprivation therapy (ADT) is a mainstay in the management of prostate cancer, particularly advanced disease. Notwithstanding this, there have been concerns about its long-term psychological, cognitive, and quality of life (QoL) effects. Prolonged use of ADT in prostate cancer patients led to significantly elevated depression and anxiety scores, degraded cognitive function, and declining scores in quality-of-life measures tied to hormonal and bowel health.

Methodology: In this analysis we ran an 18-month prospective cohort study evaluating 120 men with prostate cancer. Group A (n=60) received continuous ADT, and Group B (n=60) received alternative treatment without long-term ADT. Standardized questionnaires using BDI-II, TMAS, CFQ, and EORTC QLQ-PR25 were done to measure the outcomes.

Results: Group A had higher depression and anxiety scores, impaired cognitive function (CFQ median 10 to 25, $p<0.0001$), and deterioration of hormonal and bowel symptoms. Urinary symptoms in both groups improved over time. Group B had no change in any measure.

Conclusion: The findings demonstrate the complex burden of long-term ADT and the value of routine psychological assessment and integrative support interventions in prostate cancer survivorship care.

Keywords: Androgen deprivation therapy; prostate cancer; cognitive function; central nervous system; quality of life.

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INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide, with 1.4 million cases in 2020 and an estimated 375,000 deaths related to it (1). Androgen deprivation therapy (ADT) is still a mainstay treatment of localized and metastatic prostate cancer. Although it yields significant oncologic benefit, ADT has been linked to a broad spectrum of side effects, ranging from sarcopenia, gynecomastia, and anemia to metabolic syndrome and elevated cardiovascular risk (2).

Of special concern in recent years has been the possible effect of long-term ADT on CNS function, including cognitive impairment, mood regulation, and general quality of life (QoL). Androgen receptors are densely located in brain regions that are involved in emotional and memory processing, i.e., hippocampus and amygdala. Disruption of androgen action in such neural networks has been postulated to be a likely mediator of the neuropsychiatric side effects seen in the clinical setting (3).

Incidental evidence points towards the possible association of the length of ADT treatment with enhanced risks of depression, anxiety, and cognitive impairment. Literature has documented the enhanced incidence of depressive symptoms among men who are under long-term hormonal therapy for prostate cancer, with some even reporting impaired memory and reduced executive function (4). Second-generation anti-androgens such as enzalutamide and apalutamide have also been shown to cross the blood-brain barrier and might further exacerbate these CNS-related side effects (5).

Notwithstanding increasing clinical interest, the association between ADT and cognitive impairment is contentious. Although some studies have reported an association between long-term ADT and cognitive impairment across attention, visuospatial function, and verbal memory (6), others have been unable to reproduce these results (7). Confounding variables such as prior psychiatric history, age-related hormonal deficiency, and comorbidity may explain these discrepancies (8).

The objective of this prospective study is to assess the long-term impact of ADT on cognitive function, psychological status, and quality of life in prostate cancer patients. We use proven assessment tools to contrast continuous ADT patients with non-ADT modality patients in an 18-month follow-up.

PATIENTS AND METHODS

Study design and setting

This prospective cohort study took place in Cairo University Clinical Oncology Department in collaboration

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with the Psychiatry Department. Patient recruitment took place between July 2021 and January 2023. Ethical clearance was granted by the institutional review board, and written informed consent was taken from all the participants.

Participants and grouping

The analysis comprised 120 male adult patients with histologically confirmed prostate adenocarcinoma. Patients were stratified into two groups according to the modality of their treatment. Group A (n=60) consisted of patients who were on continuous ADT for >18 months, with or without adjunct psychotherapy. Group B (n=60) consisted of patients treated with other modalities like radical prostatectomy, radiotherapy, active surveillance, or watchful waiting. The latter group had no or a maximum of short-term ADT (6 months or less) as part of their initial local treatment.

Inclusion criteria

Age >18 years; Histologically proven prostate adenocarcinoma; ECOG performance status 0-2.

Exclusion criteria

History of chronic psychiatric illness; Severe baseline depression or anxiety (as rated by BDI-II and TMAS) requiring referral; ECOG performance status >2; Visceral crisis or non-controlled metastatic disease.

Assessment tools

Assessment of psychological, cognitive, and quality of life was undertaken at baseline and again after 18 months on the following validated instruments:

Beck Depression Inventory-II (BDI-II): Measures symptoms of depression with 0-63 scores.

Taylor Manifest Anxiety Scale (TMAS): Assesses trait anxiety using a 50-item validated Arabic version.

Cognitive Failures Questionnaire (CFQ): Measures cognitive lapses in attention, memory, and motor skills.

EORTC QLQ-PR25: A prostate cancer-specific quality of life questionnaire assessing urinary, bowel, sexual, and hormonal symptoms.

All of the tools were provided in Arabic-translated and locally validated versions. Patients were administered under supervision to determine accuracy and understanding.

Statistical analysis

SPSS software version 28 was used for analysis. Non-parametric continuous variables between groups were compared using the Mann-Whitney U test. Categorical variables were compared using Fisher's exact test or the Chi-square test. Paired group comparisons were performed using the Wilcoxon signed-rank test. Statistical significance was determined using a value of $p < 0.05$. Missing values were not replaced and were not included in patients who had missing follow-up in paired comparisons.

RESULTS

Baseline characteristics

The demographic and clinical characteristics of the 120 patients recruited are presented in Table 1.

Group A (ADT group) consisted of considerably more high-risk disease patients (95% vs. 0%, $p < 0.001$) and a higher median Gleason sum (8 vs. 6, $p < 0.001$) compared to Group B. Radical radiotherapy was administered most commonly to Group A patients (86.7%), whereas 65% of Group B patients underwent radical prostatectomy ($p < 0.001$). ECOG performance status was a little lower in Group A, but not statistically significant.

These baseline imbalances mirror real practice, wherein ADT would be initiated more often in poorer Gleason grades and poorer prognostic profiles. This selection bias can explain, at least in part, variability in later patient-reported outcomes. According to more recent registry data (8), ADT-treated men were more likely to have extensive tumor burden and concomitant comorbidities than surgery-alone-treated men, leading to stratified analysis in clinical reporting.

Psychological outcomes

The two groups were also similar on the Beck Depression Inventory-II (BDI-II) and Taylor Manifest Anxiety Scale (TMAS) tests at baseline. By 18 months after baseline, Group A had increased depression and anxiety scores. BDI-II went from a median of 15 (IQR 9-17) to 18 (IQR 12-18), and TMAS went from 19 (IQR 15-20) to 20 (IQR 18-22), and both were statistically significant ($p < 0.0001$; Table 2). No significant alteration was observed in Group B over the same duration ($p = 1.000$ for both tools), indicating an excellent correlation between long-term ADT and psychological burden (9).

These findings concur with earlier studies that have documented higher prevalence of depressive symptoms and emotional lability in men on ADT (10) (11).

Quality of life outcomes (EORTC QLQ-PR25)

Urinary symptom scores decreased significantly in both groups, presumably due to therapeutic control of disease. In Group A, urinary symptom scores decreased from a median of 37.5 to 20.8 ($p < 0.001$). This benefit was offset by an equally significant worsening in bowel symptoms (median increased from 8.3 to 20.8, $p < 0.001$), hormonal-related symptoms (16.7 to 38.9, $p < 0.001$), and reduction in sexual activity (25 to 16.7, $p < 0.001$). Sexual function was statistically unaltered.

This pattern suggests that even as sexual activity - measured in terms of frequency and desire - consistently declined, functional ability was preserved to some extent, perhaps because of the adjunctive administration of phosphodiesterase inhibitors or pelvic rehabilitation in some individuals.

Conversely, Group B had a mild reduction in sexual function (66.7 to 58.3, $p = 0.045$) without any significant differences in bowel, hormonal, or sexual activity domains (Table 3) (12) (13).

These results are also in line with Adam et al. and Donovan et al., who found that ADT-treated patients did have increased hormonal burden and decreased sexual satisfaction and overall quality of life (14).

Cognitive function outcomes (CFQ scores)

Group A demonstrated statistically significant worsening in all sections of the Cognitive Failures Questionnaire (CFQ). For forgetfulness, the score increased from a median of 5 to 11, distractibility from 1 to 6, and false triggering from 2 to

5 - all with $p < 0.0001$. The CFQ total score increased from 10 to 25 ($p < 0.0001$; Table 4).

Group B, however, had consistent cognitive scores across all areas, with no statistically significant difference in the overall CFQ score (7 to 6, $p = 0.130$; Table 4) (15).

The declining performance observed in Group A is consistent with earlier reported neurocognitive consequences of long-term ADT therapy, as described in Araujo et al. and Hong et al., which associated ADT exposure with increased risk of memory impairment, decreased attention span, and executive dysfunction (16) (Figure 1).

Table 1. *Baseline Demographic and Clinical Characteristics*

Variable		Group A (ADT, n=60)	Group B (No ADT, n=60)	P value
Median age (range)		65.37 (48-80)	63.63 (54-80)	0.161
ECOG PS 0/1/2				
	0	44	25	<0.001
	1	6	35	
	2	10	0	
Comorbidities		26 (43.3%)	29 (48.3%)	0.583
Gleason score, median (IQR)		8 (7-9)	6 (6-7)	<0.001
Risk group:				
	High	57	0	<0.001
	Intermediate	3	41	
	Low	0	19	
Surgery		6 (10%)	39 (65%)	<0.001
Radiotherapy		52 (86.7%)	21 (35%)	<0.001

Table 2. *BDI-II and TMAS Scores at Baseline and 18 Months*

Measure	Group A Baseline Median (IQR)	Group A 18 Months Median (IQR)	P	Group B Baseline Median (IQR)	Group B 18 Months Median (IQR)	P
BDI-II	15 (9-17)	18 (12-18)	<0.0001	16 (12-17)	16 (12-18)	1.000
TMAS	19 (15-20)	20 (18-22)	<0.0001	15 (11-17)	15 (11-17)	1.000

Table 3. *EORTC QLQ-PR25 Scores – at baseline and after 18 months*

Group A (ADT)	Domain	Baseline Median (IQR)	18 Months Median (IQR)	P
	Urinary Symptoms	37.5 (33.33-45.83)	20.83 (16.67-25)	<0.0001
	Bowel Symptoms	8.33 (8.33-16.67)	20.83 (16.67-25)	<0.0001
	Hormonal Symptoms	16.67 (11.11-19.44)	38.89 (33.33-44.44)	<0.0001
	Sexual Activity	25 (0-50)	16.67 (0-41.67)	0.001
	Sexual Function	58.33 (41.67-66.67)	16.67 (8.33-25)	0.180
Group B (No ADT)				
	Urinary Symptoms	29.17 (25-37.5)	6.25 (4.17-16.67)	<0.0001
	Bowel Symptoms	8.33 (0-8.33)	8.33 (0-8.33)	0.739
	Hormonal Symptoms	5.56 (5.56-11.11)	11.11 (5.56-11.11)	0.206
	Sexual Activity	33.33 (16.67-66.67)	33.33 (16.67-50)	0.23
	Sexual Function	66.67 (66.67-66.67)	58.33 (50-75)	0.045

Table 4. *CFQ Scores – at baseline and after 18 months*

Group A (ADT)	Domain	Baseline Median (IQR)	18 Months Median (IQR)	P
	Forgetfulness	5 (3.5-6)	11 (8.5-13)	<0.0001
	Distractibility	1 (1-3)	6 (5-8)	<0.0001
	False Triggering	2 (1-3)	5 (4-7)	<0.0001
	Total Score	10 (8-13)	25 (20-31.5)	<0.0001
Group B (No ADT)				
	Forgetfulness	3 (3-4)	3 (3-5)	0.300
	Distractibility	1 (0-1)	1 (0-2)	0.893
	False Triggering	2 (1-2)	1 (1-2)	0.080
	Total Score	7 (6-9)	6 (5-8)	0.130

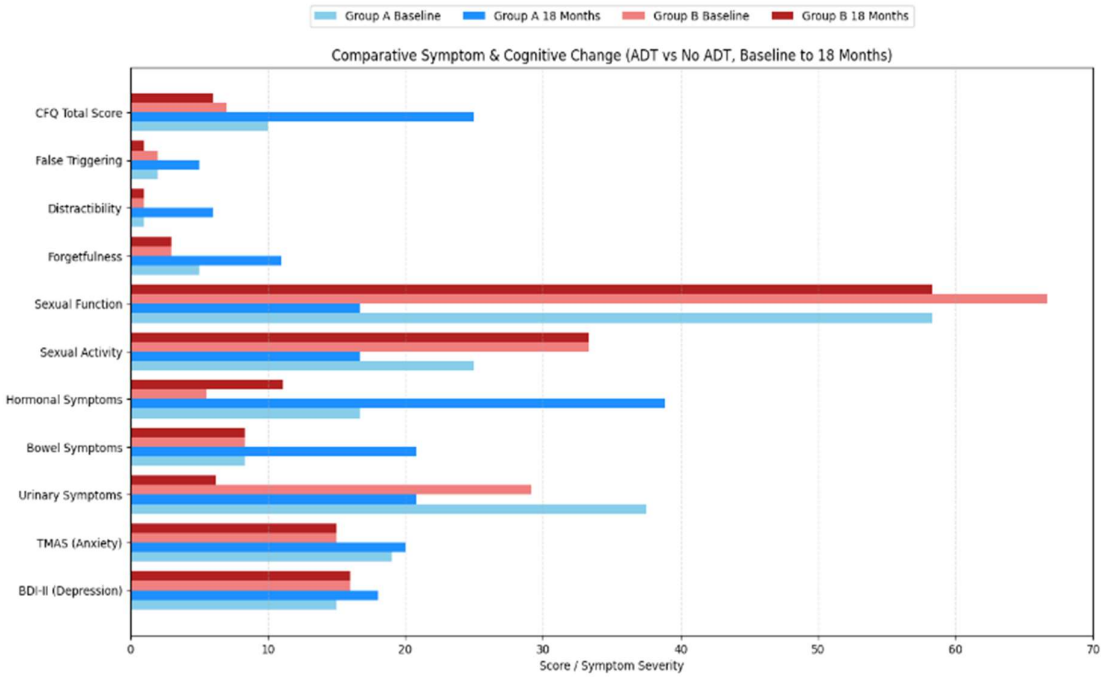

Figure 1. *Comparative change (ADT vs No ADT, Baseline to 18 Months)*

DISCUSSION

The toxicities of androgen deprivation therapy (ADT), however, are well established. But its neuropsychiatric effects, i.e., cognitive impairment and mood change, are contentious. Our prospective cohort study aimed to clarify the long-term psychological, cognitive, and quality-of-life effects of long-term ADT therapy in men with prostate cancer. The results confirm increasing clinical concern: long-term ADT exposure (>18 months) correlated with statistically significant and clinically relevant decreases in psychological well-being, cognitive function, and several patient-reported domains of quality of life (9).

Psychological impact

Group A, ADT-treated patients, demonstrated substantial increases in depressive and anxiety symptoms over time, with BDI-II scores increasing from median 15 to 18, and TMAS from 19 to 20 ($p < 0.0001$). These were not seen among the non-ADT group (Group B), and are therefore a specific psychological penalty of long-term androgen suppression (10).

These results are consistent with previously documented correlations between ADT and mood disorders. Cherrier et al., for example, reported mood changes and cognitive symptoms among intermittently treated men on ADT, while Siebert et al. and Deka et al. reaffirmed increased risks of depression and anxiety among ADT-treated patients compared to controls (17).

Dinh et al. furthered these observations in two seminal studies linking ADT to increased rates of depression and anxiety among large cohorts of prostate cancer (18).

Consistent with these results, Tsao et al. (2022) revealed, among 66,000 men with prostate cancer, among the ADT recipients, there was a 38% increased risk of developing depression or anxiety during the first year of treatment (10.6% vs. 7.7%, $p < 0.01$) (11). Alarmingly, almost half (48%) of the patients diagnosed did not undergo formal psychiatric treatment. This disparity in psychological management highlights the necessity for more active screening and interventions among ADT recipients.

Similarly, Siebert et al. (2020) revealed a 51% elevated risk of depression and a 45% increase in dementia in the long-term users of ADT.

Cognitive function

This research proved that patients in Group A had seriously deteriorated CFQ scores for all cognitive subdomains - forgetfulness, distractibility, and false triggering - following 18 months of uninterrupted ADT. Group B did not undergo significant changes, which suggests long-term ADT is the reason for progressive cognitive impairment (19). Araujo et al. in the NEON-PC study also documented the same: cognitive impairment was more frequent in the ADT group based on MoCA-derived thresholds (14).

Tae et al.'s large retrospective study also corroborated this correlation with a hazard ratio of 1.17 ($p = 0.002$) for cognitive dysfunction in patients treated with ADT based on Cox regression models (16). It is pertinent that a meta-analysis of 28 studies and over 2.2 million patients reported significantly higher hazard ratios for dementia (HR 1.20), Alzheimer's disease (HR 1.26), depression (HR 1.66), and Parkinson's disease (HR 1.57) in ADT recipients.

Most recently, Hinojosa-Gonzalez et al. (2024), in a meta-analysis of over 2.2 million patients, identified ADT as having strong association with higher hazard ratios for depression (HR 1.66, $p < 0.00001$) and Parkinson's disease (HR 1.57, $p < 0.00001$), thereby connecting neuroendocrine disruption to mood and motor neurocognitive outcomes (20). Such broader implications require multidisciplinary treatment of ADT-exposed patients beyond oncology boundaries.

In addition, Araujo et al. (2022) (14) discovered that continuous ADT patients had 6.8-fold greater odds of measurable impairment on the MoCA scale at 18 months, representing not only statistically but also clinically relevant cognitive decline. Tae et al. (2018) corroborated these findings using Cox proportional hazards models with a hazard ratio of 1.17 for cognitive dysfunction in a large Korean series (16).

These replicative findings in different populations establish the neurotoxicity of androgen suppression.

Quality of life

While urinary symptom scores were better in both groups - suggesting disease control to some extent - the ADT group had significant decreases in bowel and hormonal symptom scores and a dramatic drop in sexual activity and satisfaction (16). These results are similar to those of Donovan et al., who determined poorer sexual function and more sexual bother in ADT patients than in prostatectomy-only groups (20).

Strengths and limitations

The strengths of our study include prospective design, employment of validated Arabic-translated questionnaires, and 18-month follow-up. There are weaknesses, however. Firstly, the non-randomised design renders possible selection bias, although the baseline characteristics were mostly similar except for cancer severity. Secondly, confounding factors like subclinical depression or baseline cognitive reserve have not been adjusted for formally by multivariable modelling. Thirdly, the generalizability of our findings can be confined to comparable health care settings.

CONCLUSIONS

This prospective cohort study adds to the accumulating evidence that long-term treatment with androgen deprivation therapy (ADT) in patients with prostate cancer is a critical determinant of decline in psychological well-being, cognitive function, and overall quality of life. ADT-treated patients for 18 months or more had statistically significant elevations in depression and anxiety scores, declines in several domains of cognitive function - e.g., memory and attention - and deterioration in hormonal- and bowel-related quality of life symptoms.

The neuropsychiatric effects seen in this current study align with previous work by Cherrier et al., Araujo et al., and Tae et al., which found that ADT disrupts neural processing and results in memory impairment, distractibility, and declining executive function over time. While urinary function improved in both cohorts, other areas like sexual activity and endocrine health significantly worsened on ADT - consistent with findings by Donovan et al. and Adam et al., which highlight the multi-dimensional QOL cost of hormone suppression.

Based on these results, we recommend regular monitoring of psychological and cognitive measures in men undergoing long-term ADT. Addition of psychiatric consultation services and active symptom monitoring should be part of standard treatment for these men. In addition, our findings emphasize the importance of investigation into pharmacologic, behavioral, or cognitive training interventions that can minimize the negative neuro-psychologic consequences of ADT, and future studies should seek to identify modifiable risk factors and longitudinal recovery or continued decline patterns after receiving or stopping ADT.

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Ethical Statement

Institutional review board approval of this research was obtained at Cairo University. Written informed consent was obtained from all participants before study enrollment according to the Declaration of Helsinki.

Conflicts of Interest

All the authors of the paper have completed the ICMJE uniform disclosure form. There are no competing interests, according to the authors' declaration, for this research.

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