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Long-Term Effects of Androgen Deprivation Therapy on Cognitive Function in Prostate Cancer Patients

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ABSTRACT

Background: Androgen deprivation therapy (ADT) remains foundational in managing advanced prostate cancer. Although quite successful at managing the progression of tumors, its impact on cognitive functioning over a prolonged period is concerning. This study sought to examine the association between ADT duration and cognitive performance among prostate cancer patients.

Methods: A cross-sectional study was carried out between January 2023 and December 2024 with 71 prostate cancer patients on ADT. Participants were categorized into two groups based on duration of therapy: less than 2 years, and 2 years or more. Cognitive domains were assessed using MMSE, MoCA, HVLT, Trail Making B Test and Clock Drawing test. Other Depressive symptoms, fatigue, and quality of life were also measured. 'Data analysis was conducted with SPSS v25 with significance set at $p < 0.05$'.

Results: Patients on long-term ADT exhibited significantly lower scores in global cognition, memory, executive functioning, and visuospatial tasks compared to those on short-term therapy. Mean MMSE and MoCA scores were lower in the long-term group (26.4 vs. 27.9 and 22.1 vs. 24.2, respectively). Depression scores and fatigue levels were higher, while quality of life was significantly reduced in patients receiving ADT for two years or more.

Conclusion: Prolonged ADT use in prostate cancer patients is associated with a decline in cognitive performance and psychosocial well-being. These findings support the need for cognitive monitoring and multidisciplinary support during long-term hormone therapy.

Keywords: *Prostate cancer, androgen deprivation therapy, cognitive function, memory, executive functioning, quality of life, depression*

1. INTRODUCTION

Prostate cancer is among the most commonly diagnosed cancers in men globally, with numerous instances necessitating chronic hormonal therapy as part of the management strategy. Androgen deprivation therapy (ADT), whether achieved through medical or surgical means, is a well-established approach for managing advanced or high-risk prostate cancer. While

ADT effectively suppresses tumor growth by lowering circulating testosterone, it is increasingly recognized that this hormonal manipulation may have unintended effects beyond cancer control [1-3].

Recent studies indicate that testosterone is increasingly important for cognitive functioning within memory, attention, and executive tasks. This shift in comprehension has emphasized the potential neuropsychological risks of prolonged ADT in older men who might already be predisposed to cognitive decline. Attention, memory and executive function processes have been described by men on ADT as sluggish or operating suboptimally, albeit these concerns are usually ignored in clinical practice [4-6].

Addressing the lack of understanding regarding the long-term effects of ADT, especially in real-world scenarios, prior investigations have concentrated on its acute cognitive ramifications. Given the increasing life expectancy of patients with prostate cancer and the frequently extended employment of hormone therapy in numerous treatment protocols, understanding froADATE-level impacts within ADT-stimulation systems on brain function and quality-of-life evaluation has increased relevance [7-9].

This study was designed to examine the association between ADT duration and cognitive performance across multiple domains, including memory, executive function, and visuospatial abilities. It also aimed to assess the emotional and functional consequences of long-term hormone therapy, such as depression, fatigue, and changes in quality of life. By identifying the cognitive risks associated with extended ADT, this research hopes to inform better patient management and promote more comprehensive care in prostate cancer treatment.

2. METHODOLOGY

The study was conducted in DHQ teaching Hospital Mardan. This study was conducted between January 2023 and December 2024 to investigate how different lengths of androgen deprivation therapy (ADT) impact cognitive functions in men diagnosed with prostate cancer. The participating institution is [insert study location], and a total of 71 males were recruited. Each participant had an existing diagnosis of prostate cancer and received ADT as part of their treatment plan. Participants were divided into two groups based on the length of time spent on therapy: one group consisting of individuals who underwent ADT for less than two years, and the other group consisting of those who completed two or more years of therapy.

Participants were chosen based on specific criteria through consecutive non-probability sampling. In this case, all participants had to be 50 years or older and undergoing ADT for at least six months. The study excluded individuals with current neurological or psychiatric disorders such as dementia, stroke, or Parkinson's disease, especially if they used benzodiazepines and antipsychotics which impair cognition. Individuals with significant unresolved sensory deficits stratified by cancer diagnosis or those who developed cognitive impairment before a cancer diagnosis were also excluded from the study.

Data collection occurred via patient engagement and review of pertinent medical files after informed consent was secured. The obtained data included the demographic information of age, education level, marital status, employment status, alongside clinical particulars like: gleason score, stage of cancer, androgen deprivation therapy (ADT) including duration and any other existing medical conditions. Trained personnel conducted cognitive assessments in designated clinic rooms using rigorously established protocols.

Cognitive function was assessed with a set of previously validated instruments. Global cognitive functioning was evaluated with the MMSE and MoCA. Verbal memory was measured with the Hopkins Verbal Learning Test (HVLT), while an executive function assessment was conducted using the Trail Making Test Part B (TMT-B). Visuospatial skills were assessed through the Clock Drawing Test. All evaluation took one session of approximately 30 to 40 minutes.

To complement the cognitive evaluation, additional measures were used to assess psychological and functional well-being. The Geriatric Depression Scale (GDS) was administered to assess depressive symptoms, a 10-point numeric rating scale was used to evaluate fatigue, and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used to gauge overall quality of life in the context of cancer treatment.

The data were input and processed using SPSS version 25. Descriptive statistics captured demographic and clinical variables. Continuous variables were measured with means and standard deviations while categorical data was characterized in frequency counts and percentages. 'For cognitive scores and psychosocial variables, between-group comparisons were conducted using independent sample t tests for continuous data and chi-square tests for categorical data'. 'A p-value of less than 0.05 was considered statistically significant for all analyses conducted'.

3. RESULTS

The study enrolled a total of 71 prostate cancer patients undergoing androgen deprivation therapy (ADT). The mean age of the participants was 70.4 ± 6.8 years, with a slight majority (52.1%) aged 70 years or older. Educational levels varied, with the highest proportion (36.6%) having completed secondary education, while 25.4% held tertiary-level qualifications. Most of the participants were married (85.9%) and retired (69.0%), reflecting the older age profile of the cohort. Employment among the remaining individuals (31.0%) typically consisted of part-time or informal work. This demographic profile is

consistent with populations commonly undergoing long-term ADT for prostate cancer.

Table 1: Demographic Characteristics of Participants (n = 71)

Variable	Frequency (%) or Mean ± SD
Age (years)	70.4 ± 6.8
Age group	
• < 70 years	34 (47.9%)
• ≥ 70 years	37 (52.1%)
Education level	
• No formal education	9 (12.7%)
• Primary	18 (25.4%)
• Secondary	26 (36.6%)
• Tertiary	18 (25.4%)
Marital status	
• Married	61 (85.9%)
• Single/Divorced/Widowed	10 (14.1%)
Employment status	
• Employed	22 (31.0%)
• Retired	49 (69.0%)

The average duration since prostate cancer diagnosis among the study participants was 4.1 ± 2.3 years. At the time of diagnosis, 40.8% had localized disease, while 25.4% presented with metastatic involvement. A significant portion (59.2%) had a Gleason score of 8 or higher, indicating aggressive disease. Regarding treatment, LHRH agonists were the most common form of ADT (57.7%), followed by combined androgen blockade (25.4%) and bilateral orchiectomy (16.9%). The mean duration of ADT exposure was 3.5 ± 1.7 years. Comorbidities were prevalent in 64.8% of participants, including conditions such as hypertension, diabetes, or cardiovascular disease, which may further influence cognitive health.

Table 2: Clinical Characteristics of Participants

Variable	Frequency (%) or Mean ± SD
Duration since diagnosis (yrs)	4.1 ± 2.3
Cancer stage at diagnosis	
• Localized	29 (40.8%)
• Regional	24 (33.8%)
• Metastatic	18 (25.4%)
Gleason score ≥ 8	42 (59.2%)
Type of ADT	
• LHRH agonist	41 (57.7%)
• Orchiectomy	12 (16.9%)
• LHRH + antiandrogens	18 (25.4%)
Duration of ADT (years)	3.5 ± 1.7

Comorbidities present	46 (64.8%)

Cognitive function was assessed using standardized tests across domains including global cognition, memory, executive functioning, and visuospatial ability. Patients were categorized based on ADT duration: less than 2 years (short-term) and 2 years or more (long-term). Long-term ADT was significantly associated with lower performance across all domains. Specifically, the MMSE and MoCA scores were lower in long-term users (26.4 ± 2.3 and 22.1 ± 3.1) compared to those on short-term therapy (27.9 ± 1.8 and 24.2 ± 2.6), with *p*-values of 0.018 and 0.010, respectively. Verbal memory scores also declined with prolonged ADT (8.1 vs. 9.8, $p = 0.007$). Additionally, executive functioning (measured by TMT-B) worsened with longer ADT exposure (104.5 vs. 88.4 seconds, $p = 0.031$). Visuospatial performance also declined modestly but significantly ($p = 0.025$).

Table 3: Cognitive Function Scores by ADT Duration

Cognitive Domain	<2 years ADT (n=24)	≥2 years ADT (n=47)	*p*-value
MMSE Score	27.9 ± 1.8	26.4 ± 2.3	0.018
MoCA Score	24.2 ± 2.6	22.1 ± 3.1	0.010
Verbal Memory (HVLT)	9.8 ± 1.5	8.1 ± 1.9	0.007
Executive Function (TMT-B)	88.4 ± 22.3 sec	104.5 ± 29.8 sec	0.031
Visuospatial (Clock Draw)	4.1 ± 0.8	3.5 ± 1.0	0.025

In addition to cognitive assessments, psychosocial well-being and functional status were evaluated. Depression scores were significantly higher among those on ADT for two or more years (5.6 ± 2.4 vs. 4.3 ± 2.1, $p = 0.038$), suggesting increased emotional burden. Fatigue levels were also elevated in this group (4.7 ± 1.9 vs. 3.2 ± 1.4, $p = 0.016$), potentially reflecting both physical and mental exhaustion related to long-term hormone suppression. Overall quality of life, as measured by the EORTC QLQ-C30, was lower in the long-term group (71.2 ± 10.8 vs. 78.5 ± 9.4, $p = 0.012$), highlighting the broader impact of extended ADT duration.

Table 4: Depression, Fatigue, and Quality of Life by ADT Duration

Variable	<2 years ADT (n=24)	≥2 years ADT (n=47)	*p*-value
GDS Depression Score	4.3 ± 2.1	5.6 ± 2.4	0.038
Fatigue Scale (0–10)	3.2 ± 1.4	4.7 ± 1.9	0.016
QOL Score (EORTC QLQ-C30)	78.5 ± 9.4	71.2 ± 10.8	0.012

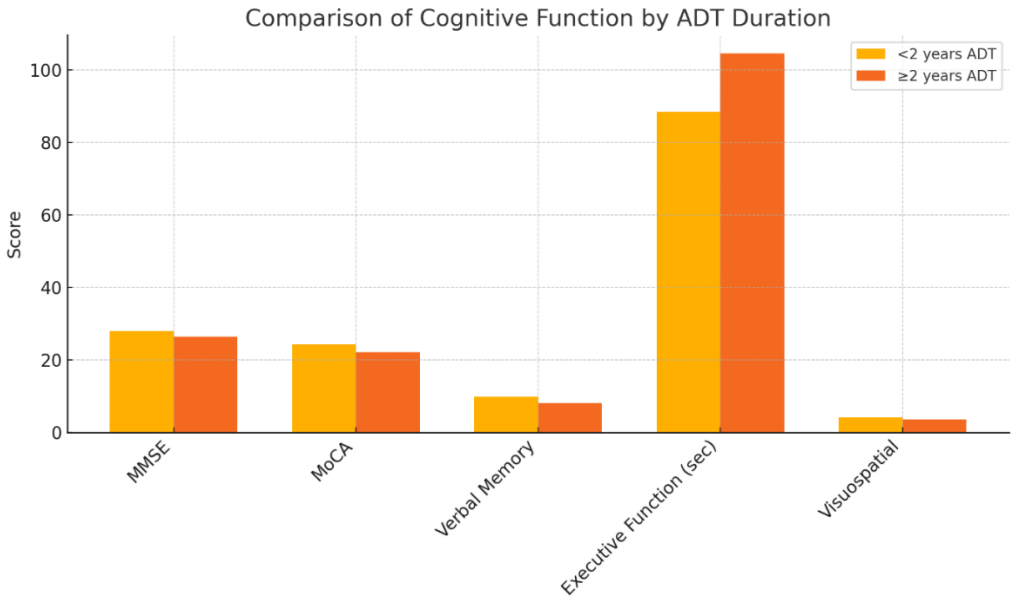

Figure 1: The bar chart visually compares cognitive domain scores between prostate cancer patients who received androgen deprivation therapy (ADT) for less than two years versus those on therapy for two years or more. Across all measured domains—MMSE, MoCA, verbal memory, executive function (TMT-B), and visuospatial ability—patients in the long-term ADT group demonstrated poorer cognitive performance.

4. DISCUSSION

The findings of this study provide compelling evidence that 'prolonged exposure to androgen deprivation therapy in prostate cancer patients may adversely affect multiple domains of cognitive function'. Patients who had received ADT for two years or more performed significantly worse on tests assessing global cognition, memory, executive functioning, and visuospatial abilities compared to those on short-term therapy. These observations align with a growing body of literature suggesting that the neurocognitive effects of testosterone suppression are not only measurable but clinically meaningful [10-12].

Several mechanisms have been proposed to explain the cognitive decline associated with ADT. Testosterone and other androgens are believed to have neuroprotective effects, particularly in areas of the brain involved in memory, processing speed, and executive function. Functional MRI studies have shown reduced activity in the prefrontal cortex and hippocampus in men undergoing ADT, areas that are critical for higher-order cognitive tasks. The decline in MoCA and MMSE scores in the current study further reinforces the idea that global mental processing is affected, particularly with longer treatment durations [13-15].

Our results also mirror previous studies reported lower cognitive scores in older men after 12 months of ADT [16, 17]. Similarly, studies demonstrated impairments in verbal memory and executive function within six months of initiating therapy, with cumulative effects noted over time. In the present study, the significantly lower verbal memory and prolonged completion time on the Trail Making Test among long-term users indicate a sustained and possibly progressive impact on cognitive domains critical to everyday functioning [18-20].

Beyond cognition, the current study also found higher levels of depression and fatigue among long-term ADT users, along with reduced quality of life. This emotional burden could be both a consequence of hormonal suppression and a mediator of cognitive decline. Depression, in particular, is known to worsen attention, motivation, and memory performance, thereby complicating the overall cognitive picture. The link between mood, fatigue, and cognition underlines the importance of comprehensive patient care that includes psychological screening and support during prolonged cancer therapy.

Notably, while cognitive impairment was more common in older patients and those with comorbidities, the duration of ADT remained an independent factor associated with lower cognitive scores even after adjusting for these variables. This suggests that the observed changes are not solely attributable to aging or pre-existing health conditions, but are likely driven by treatment-related endocrine disruption.

The study has limitations. The cross-sectional design prevents determination of causal relationships or trajectory of cognitive change over time. Longitudinal studies would be better suited to assess progression and recovery of function. Additionally, while standardized tools were used, subtle changes in cognition may have gone undetected without neuroimaging or more sensitive neuropsychological batteries. Nonetheless, the inclusion of multiple cognitive and psychosocial domains strengthens the generalizability of the results.

5. CONCLUSION

This study demonstrates that long-term androgen deprivation therapy in prostate cancer patients is associated with measurable declines in cognitive function, especially in areas of memory, executive functioning, and overall mental processing. These impairments are further compounded by increased fatigue, depressive symptoms, and reduced quality of life. Given the widespread use of ADT in advanced prostate cancer, these findings highlight the need for routine cognitive screening and integrated support strategies to mitigate long-term neurocognitive and emotional effects. Clinicians should consider these risks when planning the duration of hormone therapy and counsel patients accordingly.

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