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Original Article

Effects of Androgen Deprivation Therapy Duration on Health-Related Quality of Life, Physical Activity, Anxiety and Depression Levels in Patients with Intermediate- and High-Risk Prostate Cancer

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ABSTRACT

Objective: Androgen deprivation therapy (ADT) is the common and important treatment for patients with intermediate- or high-risk prostate cancer (PCa). Androgen deprivation therapy can lead to serious side effects in short and long term duration in life of patients. The aim of the study was to investigate the effect of ADT on physical activity, mental health, and quality of life in intermediate- and high-risk PCa patients.

Methods: Seventy-eight patients (34 intermediate risk and 44 high risk) were included in this study. Quality of life was evaulated using the European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-C30), physical activity level using the International Physical Activity Questionnaire (IPAQ), anxiety and depression status using the Hospital Anxiety and Depression Scale (HADS), and quality of life in terms of health using the Nottingham Health Profile.

Results: The duration of ADT use in patients with high-risk and intermediate-risk was mean 24.6 months and 6.3 months, respectively. However, the duration of ADT use did not significantly affect the quality of life, physical activity, anxiety, and depression levels ($P > .05$). Binary logistic regression analysis showed that BMI was negatively associated with moderate PA in unadjusted analysis [odds ratio (OR): 0.87; 95% confidence interval (CI), 0.75-1.00]. According to the results of the adjusted analysis, being moderately physically active was positively associated with the functional subscale of the EORTC-QLQ-C30 (OR: 1.10; CI: 1.01-1.20).

Conclusion: The study revealed that short-term or long-term use of ADT causes similar side effects. The intermediate-risk status of the patients did not result in a significant reduction in ADT side effects.

Keywords: Androgen deprivation therapy, anxiety, depression, prostate cancer, quality of life

Introduction

Prostate cancer (PCa) commonly occurs in men aged 50 years and above. Every year, almost 1.6 million men receive a new Pca diagnosis, and the disease results in 366 000 mortality in men.[1] Prostate cancer incidence has been increasing in the elderly population worldwide.[2] A prostate-specific antigen (PSA) level test from the blood serum is used for clinical diagnosis, and curative treatment is possible in the early stages of the disease. Active surveillance, radical prostatectomy, radical radiotherapy, adjuvant hormonal therapy, or brachytherapy treatment methods are available depending on the patient's risk group.[3]

Prostate cells require androgens for their function, development, and proliferation. If this androgenic stimulus is interrupted, apoptosis occurs in prostate cells. Androgen deprivation therapy (ADT) regulates and suppresses androgenic activity as a treatment approach that enables tumor cells to develop.[4] Androgen deprivation therapy is used in combination with neoadjuvant and adjuvant radiotherapy in patients with moderate- and high-risk PCa. Androgen ablation dramatically reduces serum testosterone levels, producing side effects that can reduce health-related quality of life, such as sexual dysfunction, fatigue, cognitive dysfunction, poor sleep quality, anemia, and psychological exhaustion.[5] Additionally, decreased physical activity (PA) levels disrupt insulin regulation, cause metabolic syndrome, and alter body composition, affecting body weight.[6]

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Patients exposed to longer ADT treatment experience serious side effects as their PCa risk level increases. Reduced bone density and decreased muscle strength are 2 of these side effects, which boost the risk of falls and fractures in PCa patients at high risk.[7] There is a negative relationship between the duration of ADT and bone mineral density. ADT reduces bone mineral density within 12 months, leading to 20% osteoporosis, and low bone mineral density limits physical activity.[8] Furthermore, it has been reported that patients with high-risk PCa patients who use ADT for more than 6 months experience particularly decreased PA levels, and perceive the PA as a potential risk.[9] Physical activity and exercise are the most essential modalities to improve overall musculoskeletal function in PCa patients undergoing ADT, because increased physical activity has been suggested to be associated with reduced PCa mortality.[10] Several mechanisms have been proposed to explain the potential association between physical activity and PCa, including reduced oxidative stress and reduced prostate inflammation in physically active men.[6] Previous studies indicated that men receiving ADT had lower physical performance and self-reported physical functioning than men not receiving ADT.[11] However, the relationship between the PA level and the ADT duration according to PCa risk level is unknown.

Since ADT treatment crosses the blood–brain barrier, it may cause neuropsychiatric problems, such as depression when applied for a long time.[12] Androgen deprivation therapy causes depression with an increased risk of 23%[13] and a large study in elderly patients with PCa reported that ADT increases the risk of anxiety and depression.[14]

All these side effects indicate the need to focus on the multidimensional evaluation of patients and the identification of specific impairments. However, the side effects are general and not specific to patients with intermediate- and high-risk PCa. Our study's main goal was to evaluate the PA, quality of life, anxiety, and depressive symptoms in patients with intermediate and high-risk PCa who were receiving different duration of ADT.

Methods

Study Design and Participants

This cross-sectional study was performed at the University of Health Sciences Prof. Dr. Cemil Taşçıoğlu City Hospital Department of Radiation Oncology between April to October 2022. This study included 78 PCa patients who had received a diagnosis, undergone radiation, and had ADT for at least 6 months. The evaluated patients were divided into 2 groups as high and intermediate risk prostate cancer. The risk level of the patients was determined by a radiation oncologist according to Gleason scoring. In addition, patients who used ADT for a mean of 3-6 months were defined as intermediate risk, and patients who used ADT for more than 6 months were at high risk. ADT-related effects were questioned 6 months after completing hormone treatment. Patients gave their verbal and written consent to participate. The study received the ethics committee's approval (2022-01/18). The Declaration of Helsinki's 2008 guidelines were followed for conducting this study.

The inclusion criteria were histologically proven PCa patients with high or intermediate risk according to D'Amico,[15] completion of radiotherapy before enrollment, having undergone at least 6 months of ADT, and being above 65 years old. Patients were excluded if they had an active metastatic tumor focus, orthopedic or neurological impairments affecting daily life activities, balance, and mobility, or visual, hearing, or mental disorders affecting communication. To avoid confounding, patients who had undergone prostate cancer surgery were also excluded.

Interventions

Hormonotherapy

Androgen deprivation therapy was prescribed as a neoadjuvant hormonotherapy for 3 months before radiotherapy and concomitant during radiotherapy treatment with intermediate and high risk groups of prostate cancer patients. Luteinizing hormone-releasing hormone agonist (leuprolide acetate in every 3 months) was administered for 6 months and 24-36 months duration for intermediate and high risk patients as an adjuvant therapy, respectively. Bicalutamide 50 mg was given as an antiandrogen therapy 15 days before luteinizing hormone-releasing hormone agonist therapy and continued for 30 days totally to avoid the testosterone flare.

Radiotherapy Treatment

Radiotherapy was delivered for whole pelvis 50 Gy/2 Gy/fraction (fx) and prostate with seminal vesicles with a total dose of 78 Gy/2 Gy/fx by a standard fractionation scheme within 39 days with high risk patients. In intermediate group of patients radiotherapy was administered for prostate and base of seminal vesicles with a total dose of 67.5 Gy/2.7 Gy/fx within 25 days by a moderate hypofractionation. All patients were treated using 6 MV photons with arc therapy.

Outcome Measures

Quality of Life

The European Organisation for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-C30) survey was used to assess health-related quality of life, symptom load, and functional health in PCa survivors.[16] It contains 30 items in 3 domains: functional, symptom, and global health status. Global health score includes a 7-point Likert scale. A higher score reflects better quality of life for the functional domain and a higher score reflects a poorer quality of life for the symptom domain.[17]

Physical Activity

The International Physical Activity Questionnaire—Short Form (IPAQ-SF) was used to determine energy expenditure, PA level, and sitting times. The metabolic equivalent of task (MET) is calculated for a reference period of the last 7 days.[18] Patients were classified as inactive (<600 MET-min/week), moderate (600-3000 MET-min/week), and vigorous (>3000 MET-min/week) according to the MET values.[19]

Depression and Anxiety

The Hospital Anxiety and Depression Scale (HADS), a survey which consist of 7 items for anxiety symptoms and 7 items for depression symptoms, was used to assess the patients' levels of anxiety and depression. Each item was scored from 0 to 3 points. A higher score indicates increased anxiety and depression status.[20] As reported in previous studies on the HAD scale, a cut-off score of 10/11 is used for the anxiety subscale (HAD-A), and 7/8 for the depression subscale (HAD-D).[21]

Health-Related Quality of Life

The Nottingham Health Profile (NHP) is a general and self-reported subjective health status questionnaire. There are 2 parts to the NHP: The first part focuses pain, vitality, sleep disorders, physical fitness, emotional response, and social isolation, and the second part focuses work, housework, family life, social life interests, sexual life, and usage of leisure time.[22] The score is from 0 to 100, 0 shows worst health state and 100 shows highest health status, and each item is dichotomized (yes/no). The first part is scored between 0 and 600 points and the second part is scored between 0 and 7 points. A higher score indicates an increase in health problems for both sections.[23]

Statistical Analysis

The Sample size was determined based on the EORTC-QLQ-C30 score.[24] An independent samples *t*-test was used to calculate with an effect size of 0.42 (moderate). The total sample size was found as 78 with an alpha level of 0.05 a power of 0.95. The Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA) was used the statistical analysis. The normal distribution of the data was examined using visual (histogram and probability plots) and analytical (Shapiro–Wilk test) methods. For categorical variables, the chi-squared test and for continuous variables the Mann–Whitney *U*-test or independent *t*-test was used. A binary logistic regression model was constructed, adjusting for BMI, functional quality of life, and cancer risk to explore the PA level-associated factors. The statistical significance was determine at the 0.05 level.

Results

One hundred twenty-five patients were screened, 98 of whom had nonmetastatic PCa. Eighteen patients did not meet the inclusion criteria and 2 patients rejected to participate. The flow chart of the participants is shown in Figure 1. A total of 78 patients over the age of 65 were included in this study. Among them, 44 patients were diagnosed with high-risk PCa and 34 patients were diagnosed with intermediate-risk PCa. All of the patients underwent radiotherapy and had no metastatic tumor focus. Except for the ADT duration, no statistical differences were found between the groups in terms of demographic data at baseline. More than half of the patients had stage IIB tumors. Table 1 shows the demographic and clinical characteristics of PCa patients according to the risk status.

There were no statistically significant differences between the groups in terms of the EORTC-QLQ-C30 total score and its subscale scores, depression, anxiety, and the NHP score. High-risk PCa patients had a higher PA level while intermediate-risk PCa patients had a lower PA level, but there was no statistically significant difference between the groups ($P < .184$) (Table 2).

A binary logistic regression analysis was performed to identify the possible risk factors for being moderately physically active relative to being physically inactive. According to the results of the adjusted analysis, being moderately physically active was positively associated with cancer risk (odds ratio (OR): 3.42; 95% CI, 1.14-10.23] and functional subscale of the EORTC-QLQ-C30 (OR: 1.10; CI: 1.01-1.20). BMI was negatively associated with moderate physical activity in unadjusted analysis [OR: 0.87; 95% CI, 0.75-1.00]. Table 3 shows the adjusted and unadjusted ORs for moderately physically active patients relative to inactive patients.

Table 1. Demographic Variables

Variables	Intermediate-Risk PCa (n = 34) Mean (SD)	High-Risk PCa (n = 44) Mean (SD)	*P*
Age (years)	69.61 ± 6.46	69.70 ± 6.24	.952#
Height (cm)	1.69 ± 0.62	1.67 ± 0.67	.878#
Body weight (kg)	78.67 ± 11.05	80.02 ± 9.90	.579#
BMI (kg/m^2)	27.47 ± 4.27	27.81 ± 3.40	.699#
ADT time (days) (month)	189.58 ± 30.15 6.3	738.93 ± 122 24.6	**.000**#
IPAQ Inactive/middle active	17/17	13/31	.054*
Adjuvant radiotherapy (yes/no)	34	44	
Tumor stage (%)			
IIA	6/34 (17.6)	1/44 (2.2)	
IIB	7/34 (20.5)	3/44 (6.8)	
IIC	17/34 (50)	22/44 (50)	
IIIA	1/34 (2.9)	5/44 (11.3)	
IIIB	2/34 (5.8)	10/44 (22.7)	
IIIC	1/34 (2.9)	3/44 (6.8)	
GS score	6.5	7.74	
Metastasis ratio M_0	34/34	44/44	

P values obtained using the independent samples test; **P* values using from chi-square test; #*P* values obtained using the independent samples test.
BMI, body mass index; GS, Gleason score; IPAQ, International Physical Activity Questionnaire; PCa, prostate cancer.

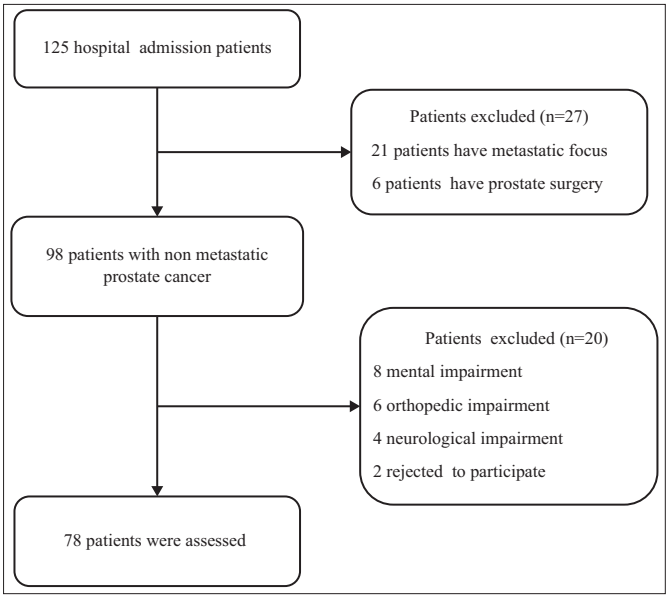

Figure 1. Flowchart of patients.

Discussion

In this study, we compared intermediate- and high-risk PCa patients in terms of anxiety, depression, and health-related quality of life status. We aimed to identify the factors associated with physical activity. Our study found no significant differences in PA, anxiety, or depressive symptom levels among patients based on the duration of ADT. The results indicated a positive effect of functional quality of life on physical activity level and a negative interaction between BMI and physical activity.

Prostate cancer is a hormone-sensitive tumor, and ADT is the keystone of systemic therapy for patients with high or intermediate-risk localized PCa.[25] About 50 % of patients receive ADT during their treatment, and when the risk level of cancer increases, the duration of ADT becomes longer.[26] Androgen deprivation therapy is generally well-tolerated, however, it can cause short and long-term adverse effects, leading to poor quality of life. Some studies have shown metabolic effects after 3 months of ADT, resulting in changes in BMI in patients with PCa. In contrast, Basaria et al. reported that cholesterol levels either decreased or did not change at 6 months of ADT.[27] Side effects may affect physical performance within 1 year.[28] In our study, the intermediate-risk cancer group received ADT for at least 189 days (6 months), while the high-risk cancer group received ADT for an average of 738 (24 months) days. There was no difference between the groups in terms of BMI. Although short-term ADT is often recommended for patients with a diagnosis of intermediate-risk PCa, durations ranging from 4 to 6-8 months have been observed in the literature. In our study, the duration of treatment of the moderate-risk ADT group was compatible with the literature.[29]

Table 2. Patient-Reported Outcomes Between Intermediate-Risk PC and High-Risk PC

	Intermediate-Risk PCa (n = 34)				High-Risk PCa (n = 44)				
Outcomes	**Mean ± SD**	**Median (IQR)**	**Skewness**	**Kurtosis**	**Mean ± SD**	**Median (IQR)**	**Skewness**	**Kurtosis**	***P****
IPAQ (MET)	775 ± 592.63	693 (347-1155)	1.60	3.219	897.77 ± 602.45	693 (503-1328.25)	1.458	2.792	.184
HADS depression	2.44 ± 1.84	2 (1-3.25)	0.437	−0.535	2.84 ± 2.66	2 (0-4)	0.672	−0.688	.763
HADS anxiety	4.23 ± 2.66	4.50 (2-6)	−0.126	−0.668	4.02 ± 2.87	4 (2-6)	1.184	3.450	.549
NHP part 1 total score	104.38 ± 77.06	82.35 (34.21-168.10)	0.366	−1.070	109.41 ± 70.09	104.76 (51.30-166.93)	0.355	−.725	.702
NHP part 2 total score	1.61 ± 1.18	2 (0.75-3)	−0.006	-1.099	1.79 ± 1.35	2 (1-2.75)	0.507	−0.132	.724
EORTC-QLQ (general score)	76.47 ± 20.04	75 (66.66-100)	−0.623	−0.064	75.18 ± 18.28	75 (58.33-91.66)	-0.072	−1.249	.683
EORTC-QLQ (Symptom score)	8.44 ± 6.84	7.69 (2.56-12.82)	0.711	−0.203	10.05 ± 7.72	8.97 (3.03-15.38)	0.760	−0.297	.386
EORTC-QLQ (Function score)	92.09 ± 5.16	93.33 (88.88-95.55)	−0.297	−0.830	90.90 ± 6.77	93.33 (87.22-95.55)	−0.905	0.162	.696

**P* values obtained using Mann–Whitney *U*-test.
EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality of Life questionnaire; HADS, Hospital Anxiety and Depression Scale; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range; NHP, Nottingham Health Profile.

Table 3. Predictor Factors for Physical Activity Status

	Adjusted			Non-adjusted		
	Odds Ratio	**95% CI**	***P***	**Odds Ratio**	**95% CI**	***P***
BMI	0.87	0.75-1.00	.063	0.86	0.75-0.98	**.024**
Cancer risk	3.42	1.14-10.23	**.028**	2.38	0.93-6.06	.068
EORTC-QLQ (Function score)	1.10	1.01-1.20	**.029**	1.09	1.01-1.18	**.026**

Values in bold indicate statistical significance.
BMI, body mass index; CI, confidence interval; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality of Life questionnaire.

The duration of ADT impacts the patients at different levels for improving clinical outcome measures. Radiotherapy and long-term ADT are effective for survival, especially in high-risk PCa patients. However, many studies are investigating strategies to reduce the duration of ADT due to the side effects.[30] Although there is a consensus that ADT provides an overall health benefit, the systemic and clinical effects of short- and long-term ADT may be different. Alternatively, high-risk PCa patients may have to use ADT for life, and ADT side effects may limit the potential oncologic benefit.[31] Bolla et al[32] reported that 18 months and 36 months of ADT made no difference in terms of survival and quality of life; however, the effect of ADT in the first 6 months is not known in the literature. To the best of our knowledge, our study is one of the first studies to investigate the early effects of ADT in PCa patients.

A comparison of the side effects of ADT on PA levels was performed for different treatment algorithms, including ADT only, ADT plus radiotherapy, and ADT before and after surgery.[33] Therefore, the side effects of ADT duration on PA are not clearly described. In the present study, the participants consisted of patients receiving radiotherapy and ADT to avoid possible confounding effects of different treatment processes.

Fatigue, impaired body composition, bone mineral loss, and reduced muscle strength caused by ADT are very common side effects that result in decreased PA and performance levels.[34] In our study, BMI was negatively associated with the level of PA and an increase in cancer risk level induced an increase in the level of PA. Although high risk PCa has been reported as a barrier to PA,[35] we propose that this result may be related to patient education and follow-up time directed by the radiation oncologists and physiotherapists before the ADT application. It has been reported that education and enhanced health services provide the most effective benefit in minimizing the side effects of the ADT process.[36]

Prostate cancer patients who can survive for a long time without any recurrences or a second neoplasm have a good quality of life level and suffer fewer treatment-related side effects.[37] Ferro et al. reported the first section of the NHP score of 105 as a satisfactory quality of life indicator in patients with PCa who survived for a long time.[38] In our study, the NHP score was found to be 104 for patients with intermediate and high-risk PCa. The duration of ADT did not show any significant differences in the quality of life in both groups. Cancer recurrence and metastasis can be primary factors affecting the quality of life.

In individuals diagnosed with urologic cancer, the physical quality of life of patients is significantly impacted by treatment and its side effects. Along with physical side effects include urogenital, sexual, and body image disorders, mental health is also seriously impacted. According to biopsychosocial models, there is a clear relationship between mental and physical health.[39,40]

Anxiety and depression levels of patients with PCa vary depending on the treatment process. Patients receiving radiotherapy had HADS anxiety scores of 5 in the first 3 months, 5.18 at the end of the 6th months, and 5.15 at the end of the 12th months. Depression scores were 5.66 at the end of the 3rd months, 5.32 at the end of the 6th months, and 5.15 at the end of the 12th months.[41] The participants in our study were patients who had completed the radiotherapy process, and the mean anxiety subscale score was 4 and the mean depression subscale score was 2. Our anxiety results were similar to the literature, however, depression levels were lower. In addition, our patients had higher anxiety levels than depression levels which differs from the literature. We think that this may be related to the fact that the worsening genitourinary system side effects in PCa patients causes more anxiety than depression.[42] Also, we would like to emphasize that the mean anxiety and depression scores were under the cutoff values of the HADS questionnaire of the patients in our study. Consequently, similar and higher levels of physical activity and quality of life may be associated with lower anxiety and depression symptoms in patients in the medium- and high-risk groups.

This study has limitations. First, no group used ADT for less than 6 months, which hinders our ability to observe the effects of ADT between 0-3 months. Secondly, this study included a small group of patients recruited from a single center. Future multicenter studies with larger sample sizes may reveal if patient education had any effect on the results. Thirdly, PA level was determined with a self-reported tool. More objective methods should be used to provide clearer results about PA level and physical performance. In future studies, the relationship between physical activity level and cancer risk should be

investigated and it should be considered that BMI may be indirectly associated with cancer risk in a larger sample.

Conclusion

In conclusion, the duration of ADT use increases in high-risk PCa patients and long-lasting ADT negatively affects the quality of life by changing the PA level, emotional status, and body composition. However, the duration of ADT use does not make any difference in the side effects. Although the duration of ADT was shorter in intermediate-risk patients, it had a similar effect in high-risk PCa patients who used it for a longer time. Treatment approaches should be planned multidisciplinary for patients with an intermediate-risk level of PCa receiving ADT.

Ethics Committee Approval: The ethical committee approval for the study was provided by the Acıbadem Mehmet Ali Aydınlar University (ATADEK) ethics committee (Approval no: 2022 01/18, Date: January 1, 2022).

Informed Consent: Written and verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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