

Effects of a six-month supervised physical exercise program on physical and cardio-metabolic profile and quality of life in patients with prostate cancer on androgen deprivation therapy: a pilot and feasibility study

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Introduction To evaluate the effect of a six-month supervised physical exercise program on the physical and cardio-metabolic profile and quality of life in patients with prostate cancer on androgen deprivation therapy.

Material and methods Twenty-seven patients with prostate cancer on androgen deprivation therapy were included in a physical exercise program. The program consisted of supervised physical exercises during a six-month period (two hours, twice a week). The exercise program contained moderate to high intensity aerobic and resistance exercises: cycling, walking or jogging for 45 minutes at an intensity of $\pm 80\%$ of the individual maximum heart rate, followed by resistance exercises targeting the major lower and upper body muscles. All patients were assessed prior to the exercise program, including anthropometrical parameters, blood analysis, quality of life and physical fitness. Blood analysis was repeated at a three-month follow-up. Anthropometrical parameters, physical fitness and quality of life were recorded at a three-, six- and nine-month follow-up.

Results A positive effect on physical performance, muscular strength and quality of life was seen. The applied physical exercise program was well tolerated and characterized by a high satisfaction rate. An alarming issue of remarkably unfavorable baseline cardio-metabolic profile was revealed within our study population.

Conclusions Our data indicates that a six-month supervised physical exercise program can be beneficial in preventing androgen deprivation therapy-related side effects in patients with prostate cancer. We emphasize the importance of screening for cardio-metabolic risk factors in patients who are treated with androgen deprivation therapy.

Key Words: quality of life ↔ prostate cancer ↔ physical exercise ↔ androgen deprivation therapy

INTRODUCTION

Prostate cancer is the second most common cancer diagnosed in men worldwide [1]. A growing awareness of prostate cancer stimulated develop-

ment of different treatment modalities, resulting in an increasing overall survival [1, 2]. Despite a good overall survival, patients with prostate cancer often have a high rate of morbidity [3]. Particularly androgen deprivation therapy has been shown

to cause significant side effects including unfavorable changes in body composition (decreased muscle and bone mass, increased body fat), fatigue, sexual dysfunction and a reduced health-related quality of life [4]. Several studies suggest that early initiated physical training is beneficial in preventing androgen deprivation therapy-related side effects [5, 6, 7]. Furthermore, different authors have demonstrated significant gains in fitness and quality of life as a result of physical exercise in this population [3, 8].

The primary aim of this pilot study is to describe the influence of a six-month supervised physical exercise program on the physical and cardio-metabolic profile in patients with prostate cancer on androgen deprivation therapy. Furthermore, we wanted to evaluate if the expected effect persists three months after training cessation. The secondary goal was to determine the effect of the supervised physical exercise program on quality of life.

MATERIAL AND METHODS

With this pilot study, we want to present the data from a six-month supervised physical exercise program at the Antwerp University Hospital, which combined a range of aerobic and resistance exercises and evaluated the benefit of physical exercise regarding the general health status, physical function and quality of life in men with prostate cancer undergoing androgen deprivation therapy.

After approval by the Ethics Committee (n° 13/40/384), a total of 70 patients were invited to participate in our pilot study between October 2014 and March 2016. The physical exercise program was established in cooperation with the Multidisciplinary Oncological Center of Antwerp, the department of Urology and the department of Physical Medicine and Rehabilitation (Antwerp University Hospital, Edegem, Belgium).

Inclusion criteria was age ≥ 50 years, histological diagnosis of prostate cancer with or without metastasis and an androgen deprivation therapy-exposure of \geq six months. Exclusion criteria were previous diagnosis of any cancer other than prostate cancer and pre-existing cardiovascular or metabolic disease. Our final study-population consisted of 27 patients. The main reasons for declining the invitation was lack of interest or inability to reach the hospital on a regular basis due to transportation problems and fear of injuries. All included patients provided a written informed consent.

Pre-training assessment included an anthropometrical assessment (body mass index, abdominal circumference and blood pressure), physical fitness and a fasting blood sample containing a lipid profile (total

cholesterol, triglycerides, low-density lipoproteins and high-density lipoproteins) and a glucose profile (HbA1c and glycaemia). An EORTC-C30 (European Organization for Research and Treatment of Cancer) questionnaire V.3 was used to assess the baseline quality of life in all patients. This questionnaire incorporates 15 multi-item scales: Global health status / quality of life scale, five functional scales (Physical, Role, Emotional, Cognitive and Social) and nine symptom scales (Fatigue, Nausea or Vomiting, Pain, Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea and Financial difficulties) [9]. Physical fitness was assessed by isometric muscle strength measurements (joint angle of 90° for knee and elbow flexion, and 45° for knee extension) using a Primus RS dynamometer (BTE Technologies Inc., Hanover, MD, USA).

A 30-seconds single leg balance test was carried out, i.e. the number of attempts needed to accumulate a total stable balance time of 30 seconds while standing on one foot with closed eyes. Blood analysis was repeated at three-month follow-up. Anthropometrical parameters, physical fitness and quality of life were recorded at the three-month, six-month and nine-month follow-up (Table 1).

The 27 patients were divided into four groups of six to eight patients. Prior to the physical exercise program, a Conconi test (relationship between running speed and individual heart rate) was performed to identify the individual aerobic threshold. The exercises were adjusted to this heart rate, targeting the best training outcome.

The patients had supervised training sessions of two hours for a six-month period (twice weekly for three months, followed by once weekly for another three months). The training sessions were conducted at the department of Physical Medicine and Rehabilitation of the Antwerp University Hospital, according to the "General Sports Medicine Guidelines for Cancer Survivors" [10]. Each training session included moderate to high intensity aerobic and resistance exercises. The 45-minute aerobic section of the program was modified for each patient according to their individual interest or capacity, varying between intervals of cycling, walking or jogging at $\pm 80\%$ of their maximum heart rate. The resistance exercises consisted of leg extensions, leg presses, leg curls, chest presses, seated presses, triceps flexes and triceps extensions.

SPSS V.21 (IBM Corp, Armonk, NY, USA) was used to perform statistical analysis. A p-value ≤ 0.05 was considered statistically significant. A Shapiro-Wilk test ($p > 0.05$) and a visual inspection of their histograms, normal Q-Q plots showed that our variables were approximately normally distributed for

Table 1. Summary of the measurements and time points

Measure/Domain	T0	T3	T6	T9
General information				
Date of birth	X			
Tumor-stage	X			
Gleason score	X			
Androgen deprivation therapy duration (months)	X			
Previous prostate cancer treatment	X			
Anthropometricals				
Weight (kg)				
Length (m)	X	X	X	X
Body mass index (kg/m ²)	X	X	X	X
Abdominal circumference (cm)	X	X	X	X
Blood pressure :				
Systolic (mmHg)	X	X	X	X
Diastolic (mmHg)				
Resting heart rate (bps)				
Biologicals				
Glucose (mg/dl)	X	X		
HbA1c (mg/dl)	X	X		
Cholesterol (mg/dl)	X	X		
(total cholesterol, high-density lipoproteins, low-density lipoproteins, triglycerides)				
Physical Fitness				
Balance 30sec	X	X	X	X
Power (Nm)	X	X	X	X
Flexion knee (right/left)	X	X	X	X
Extension knee (right/left)	X	X	X	X
Flexion elbow (right/left)	X	X	X	X
EORTC-C30 score				
Functional scale (%)	X	X	X	X
Symptom scale (%)	X	X	X	X
Quality of Life scale (%)	X	X	X	X

different time measurements (T0 – T3 – T6 – T9). A one-way repeated measures ANOVA was used to compare means. Post-hoc analyses were used in case of significant differences in measurements, with a significance level of 0.05 and a confidence interval of 95%. We represent the p-value of adjusted group difference in mean change over several months (Bonferroni test).

RESULTS

Baseline (Table 2)

Twenty-seven patients were included in this pilot study. Mean age was 71.4 ± 6.2 years. The largest part of the group consisted of patients with localized prostate cancer (80%) and radiation was the major treatment prior to androgen deprivation therapy (88%). The mean duration of androgen deprivation therapy before entering the study was 30.96 months. Around 62.5% of the study-population used goserelin acetate long-acting implants in monotherapy, where 33.3% used goserelin acetate long-acting implants

Table 2. Baseline characteristics

	N = 27	
	Mean	SD
Age (y)	71.4	6.2
Cancer stage		
Recurrent localized (%)		80%
Nodal metastases (%)		8%
Bone metastases (%)		12%
Gleason score	7	1.2
Previous radiation (%)		88%
Previous prostatectomy (%)		28%
Height (cm)	173	5
Weight (kg)	86.2	9.3
Body mass index (kg/m ²)		
Underweight (<18.5)	29	3
Normal weight (18.5–24.9)		0%
Overweight (25–29.9)		4%
Obese (≥30)		64%
Obese (≥30)		32%
Abdominal circumference (cm)	106.7	8.9
≥102 cm		68%
Known diabetes		
yes		19%
no		81%
Systolic blood pressure (mmHg)		
Normal blood pressure (<120 mmHg)	144	20
Pre-hypertension (120–139 mmHg)		8%
Stage 1 hypertension (140–159 mmHg)		28%
Stage 2 hypertension (≥160 mmHg)		48%
Stage 2 hypertension (≥160 mmHg)		16%
Diastolic blood pressure (mmHg)		
Normal blood pressure (<80 mmHg)	76	9
Pre-hypertension (80–89 mmHg)		64%
Stage 1 hypertension (90–99 mmHg)		16%
Stage 1 hypertension (90–99 mmHg)		8%
Stage 2 hypertension (≥100 mmHg)		0%
Blood sample		
Fasting glucose		
Normal (70 to 100 mg/dl)		56%
Pre-diabetes (101 to 126 mg/dl)		16%
Diabetes (>126 mg/dl)		28%
HbA1c		
Increased risk of diabetes (5.7–6.4%)		56%
Diabetes (>6.5%)		28%
Cholesterol		
Total cholesterol ≥200 mg/dl		36%
Low-density lipoproteins ≥130 mg/dl		36%
High-density lipoproteins ≤40 mg/dl		40%
Triglycerides ≥200 mg/dl		32%
EORTC-C30		
Functional scale (%)	79%	13%
Symptom scale (%)	17%	10%
Quality of life scale (%)	66%	15%

in combination with either bicalutamide 50 mg (16%), abiraterone acetate 1000 mg and prednisolone 10 mg (8.7%) or cyproterone acetate 50 mg (8.6%). Finally, 4.2% of our study-population used degarelix 80 mg once monthly.

We noticed a mean body mass index of 29 ± 3 kg/m², which indicates that the majority of our study-population was overweight (64%) or obese (32%).

As a consequence, 68% of the study-population had an abdominal circumference ≥ 102 cm, indicating a higher risk for cardiovascular diseases and type two diabetes mellitus. Prior to inclusion, only five patients (18.5%) were known to have diabetes. However, based on our blood sample values (HbA1c), 28% were categorized in the diabetes group, while 56% were at increased risk to develop diabetes. 36% of our study-population had a total cholesterol ≥ 200 mg/dl, low-density lipoproteins ≥ 130 mg/dl, high-density lipoproteins ≤ 40 mg/dl and triglycerides ≥ 200 mg/dl. The mean systolic blood pressure was 144 ± 20 mmHg and the mean diastolic blood pressure was 76 ± 9 mmHg. Concerning the systolic blood pressure, 64% of the patients had hypertension (48% had stage 1 hypertension and 16% had stage 2 hypertension). The average self-reported quality of life was 66%. The average scores for the functional scale and symptom scale were 79% and 17%, respectively.

Drop-out rate

Seven patients left the training program after six months because of different factors and did not return for the nine-month follow-up assessment. The major reasons for leaving the study-protocol were a lack of interest and disease progression. We emphasize that only two third of the patients (18/27) returned for the nine-month follow-up as-

essment. No adverse events occurred during the training program.

Evolution in metabolic profile (Table 3)

The baseline mean body mass index and mean abdominal circumference were 29.1 kg/m^2 (range 22.4–35.2) and 106.7 cm (range 93.0–125.0), respectively. We notice a statistically significant decrease in mean body mass index (28.7 kg/m^2 (range 21.9–35.4); $p < 0.001$) and mean abdominal circumference (104.3 cm (range 91.0–123.0); $p < 0.001$) at the three-month follow-up. Based on these results, it seems that further training continues to improve those parameters. However, because of a high nine-month follow-up dropout rate, these findings could not be supported on a statistic level.

Blood samples at the three-month follow-up showed no statistically significant changes. Baseline mean total cholesterol, mean low-density lipoproteins, mean high-density lipoproteins and mean triglycerides were 189.7 mg/dl (range 121.0–293.0), 116.9 mg/dl (range 50.0–250.0), 49.9 mg/dl (range 27.0–79.0) and 178.2 mg/dl (range 46.0–428.0), respectively. Whereas at the three-month follow-up we found a mean total cholesterol of 193.4 mg/dl (range 105.0–313.0; $p = 0.55$), mean low-density lipoproteins of 121.0 mg/dl (range 17.0–226.0; $p = 0.54$), mean high-density lipoproteins of 49.9 mg/dl (range 27.0–95.0; $p = 0.36$) and mean triglycerides of 129.7 mg/dl

Table 3. Evolution in metabolic profile after 6 month of exercise training

	T0 Mean [min–max]	T3 Mean [min–max]	T6 Mean [min–max]	T9 Mean [min–max]	Group difference in mean change T0 \geq T3 (p value)	Group difference in mean change T3 \geq T6 (p value)	Group difference in mean change T6 \geq T9 (p value)
Body mass index (kg/m ²)	29.1 [22.4–35.2]	28.7 [21.9–35.4]	27.9 [21.8–34.4]	27.9 [22.1–33.7]	<0.001	1.00	1.00
Abdominal circumference (cm)	106.7 [93.0–125.0]	104.3 [91.0–123.0]	101.5 [91.0–114.0]	102.1 [90.0–116.0]	<0.001	0.78	1.00
Lipid profile (mg/dl)							
Total cholesterol	189.7 [121.0–293.0]	193.4 [105.0–313.0]			0.55		
Low-density lipoproteins	116.9 [50.0–250.0]	121.0 [17.0–226.0]			0.54		
High-density lipoproteins	49.9 [27.0–79.0]	51.5 [27.0–95.0]			0.36		
Triglycerides	178.2 [46.0–428.0]	129.7 [58.0–322.0]			0.19		
Fasting glucose (mg/dl)	116.6 [80.0–255.0]	115.8 [83.0–224.0]			0.91		
HbA1c (mg/dl)	6.3 [5.5–10.0]	6.1 [4.6–8.3]			0.07		

Table 4. Evolution of physical performance and fitness after 6 month of exercise training

	T0 Mean [min–max]	T3 Mean [min–max]	T6 Mean [min–max]	T9 Mean [min–max]	Group difference in mean change T0 ≥ T3 (p value)	Group difference in mean change T3 ≥ T6 (p value)	Group difference in mean change T6 ≥ T9 (p value)
Resting heart rate (bpm)	76 [50–112]	75 [58–102]	73 [51–104]	69 [48–98]	0.03	1.00	0.48
30-sec Balance test	11 [1–16]	6 [0–13]	8 [1–18]	7 [1–11]	0.04	0.67	1.00
Power (Nm)	103 [60–150]	120 [80–60]	121 [60–180]	114 [60–180]	0.01	1.00	0.32
Flexion knee							
Right (Nm)	63 [39–97]	80 [38–149]	80 [35–128]	75 [40–100]	0.99	1.00	1.00
Left (Nm)	62 [42–95]	78 [33–137]	84 [43–157]	76 [35–101]	1.00	0.56	1.00
Extension knee							
Right (Nm)	130 [66–208]	128 [42–223]	125 [58–225]	138 [72–225]	1.00	1.00	0.23
Left (Nm)	130 [69–207]	123 [57–226]	120 [63–209]	140 [90–210]	1.00	1.00	1.00
Flexion elbow							
Right (Nm)	49 [28–67]	47 [27–84]	52 [27–86]	52 [33–82]	1.00	0.89	1.00
Left (Nm)	46 [24–72]	46 [27–76]	47 [30–69]	52 [31–76]	1.00	1.00	1.00

(range 58.0–322.0; $p = 0.19$). Similar results were found for the glucose profile. Fasting glucose ($p = 0.91$) was 116.6 (range 80.0–255.0) and 115.8 (range 83.0–224.0) and HbA1c ($p = 0.07$) was 6.3 mg/dl (range 5.5–10.0) and 6.1 mg/dl (range 4.6–8.3) at baseline and three-month follow-up, respectively. Yet some remarkably high values were observed (fasting glucose of 224 mg/dl, total cholesterol of 313 mg/dl and triglycerides of 428 mg/dl), indicating a poorly controlled metabolic profile in some individuals.

Evolution in physical performance and fitness (Table 4)

Resting heart rate (baseline: 76 bps; range 50–112), muscle strength (baseline 103 Nm; range 60–150) and 30-second balance test (baseline 11; range 1–16) improved significantly at the three-month follow-up

(75 bps (range 58–102); $p = 0.03$, 120 (range 80–160); $p = 0.01$ and 6 (0–13); $p = 0.04$, respectively). No significant difference was found at six-month follow-up or nine-month follow-up. Furthermore, no statistical significant differences were found for flexion and extension test results at three, six or nine-month follow-up, nor any significant differences in left versus right performance.

Evolution in self-reported score regarding quality of life, functional and symptomatic scale [EORTC – C30] (Table 5)

Self-reported general functional performance showed statistically significant improvements. This improvement persisted up to the last assessment at the nine-month follow-up ($p = 0.01$, $p = 0.02$ and $p = 0.04$ at three, six and nine-month follow-up, respectively). Self-reported symptom scale improved

Table 5. Evolution in quality of life regarding self-reported score

	T0 Mean [min–max]	T3 Mean [min–max]	T6 Mean [min–max]	T9 Mean [min–max]	Group difference in mean change T0 ≥ T3 (p value)	Group difference in mean change T3 ≥ T6 (p value)	Group difference in mean change T6 ≥ T9 (p value)
Functional scale	79.8 [51.3–100]	83.1 [38.5–100]	85.8 [69.2–100]	85.1 [41.0–100]	0.01	0.02	0.04
Symptom scale	17.6 [1.2–35.9]	13.5 [0–35.9]	11.6 [2.6–26.7]	16.7 [5.1–38.5]	0.20	0.45	0.58
Quality of life scale	66.1 [25.0–100]	74.0 [33.3–100]	74.6 [41.7–91.7]	73.9 [33.3–91.7]	0.01	1.00	1.00

at the three (13.5, range 0–35.9) and six-month follow-up (11.6, range 2.6–26.7), however, not significantly ($p = 0.20$ and $p = 0.45$ at three and six-month follow-up, respectively). There was a non-significant ($p = 0.58$) deterioration at the nine-month follow-up (16.7, range 5.1–38.5). The self-reported quality of life at three-month follow-up improved significantly (74.0 (range 25.0–100), $p = 0.01$) and maintained a steady state at the six (74.6, range 41.7–91.7) and nine-month (73.9, range 33.3–91.7) follow-up with no statistical significance ($p = 1.00$ at six and nine-month follow-up).

DISCUSSION

Prostate cancer is the second most common cancer in men worldwide and the most common in developed countries, where the mortality rate reaches 14.5 per 100,000 patients [1]. The highest incidence is recorded in Europe, North America and Oceania, largely because of the increased awareness and a wide availability and use of prostate-specific antigen [1, 11].

A significant remission of prostate cancer is seen after castration, which remains the cornerstone of treatment of advanced prostate cancer. Castration can be accomplished surgically (orchidectomy) or medically (androgen deprivation therapy) [12, 13]. Androgen deprivation therapy is used in approximately 45% of prostate cancer patients. It slows down tumor progression and improves the survival rate [14, 15].

Several adverse effects may occur in men with prostate cancer undergoing androgen deprivation therapy [16]. Those effects are mostly related to the unfavorable cardio-metabolic profile of androgen deprivation therapy and the concomitant hypoandrogenic status [17, 18]. On short term, it causes changes in the lipid and glucose-profile, leading to hyperinsulinemia, increased cholesterol, elevated total body fat and development of abdominal adiposity [19]. Furthermore, androgen deprivation therapy accelerates the bone and muscle loss and causes osteoporosis and fractures on the long-term [4, 20, 21]. Men on androgen deprivation therapy have a hypotestosterone level resulting in sexual dysfunction, gynecomastia, hot flushes and fatigue [22, 23]. These side effects reduce the quality of life, including mood and cognition [24].

Prevention of androgen deprivation therapy-related side effects is a topic of increasing interest [14]. Physical exercise has been suggested to be the most beneficial, safe and cost-effective method to improve body composition in these patients [3, 16, 25, 26]. A combination of supervised resistance and aerobic training leads to an increase in lean mass and mus-

cle strength [27]. A reduction of body fat was seen, as well as improvement in insulin sensitivity [5]. A systematic review by Gardner et al. shows that exercising improves physical performance and cardiorespiratory status, which – on the long term – contributes to preserving the patient's capacity for independent living [8].

Based on the pre-training assessment, we could state that the majority of the patients had an unfavorable cardio-metabolic profile, with hypercholesterolemia, hypertension, diabetes and obesity all present before the start of the training program. This unfavorable cardio-metabolic profile could lead to an underestimation of the cardio-vascular risk factors in patients with prostate cancer on androgen deprivation therapy. Considering that patients in a better general condition might be more motivated to participate in this program, the prevalence of cardio-vascular risk factors in this population could be even higher than our study shows. Since androgen deprivation therapy is associated with both cardiovascular disease and mortality [28], we emphasize the importance of screening and closer monitoring of cardio-vascular risk factors before and periodically after starting androgen deprivation therapy. Due to our small study-population, we were unable to demonstrate a statistically significant long term effect of exercise on the metabolic profile. However, several authors have shown a beneficial effect of physical training on multiple adverse effects of androgen deprivation therapy [6, 29, 30]. We expect to reach similar results by increasing the number of patients in this study in the future.

This pilot study shows that supervised physical exercise program positively improves physical performance in the short-term, particularly concerning muscular strength and balance. Galvão et al. and Beydoun et al. have shown similar findings in a larger series [31, 32]. Additionally, Gardner et al. describes comparable effects in their systematic review [8]. Despite the lack of a statistically significant effect of the training program on muscular strength, our data suggests a clinically meaningful effect of training, which could contribute to preserving a patient's capacity for independent living.

A positive effect of physical exercise related changes in self-reported quality of life was found in our study-population. Teleni et al. described comparable results, advocating that physical performance may contribute to an improved well-being [33]. These findings may motivate caretakers to give more attention to the overall impact of exercise on androgen deprivation therapy-related side effects in the future. Our supervised physical exercise program was well tolerated by the study-population. No adverse events

occurred during the study-period. Due to a close contact with our patients, we were able to collect useful feedback which revealed a very high satisfaction rate within the group.

We found that a supervised physical exercise program in small groups of six to eight patients might be more effective than an individual physical exercise program. We believe that social stimulation is extremely valuable, as it increases individual compliance and encourages maintaining a healthy lifestyle. These results are consistent with the findings of Galvão et al. [34]. Furthermore, Keogh et al. showed a better outcome for group-based supervised training in contrast to independent training and suggested that exercise counseling should be included in the daily care of patients with prostate cancer on androgen deprivation therapy [3].

The major limitations of our study lie within the small number of included patients and the lack of an age-matched control group with similar cardiovascular profiles, yet without androgen deprivation therapy, to compare with our study-population. Due to the low number of patients, several positive changes could not reach a statistically significant level. Furthermore, the control group could validate our results and thus the positive impact of physical exercise on the adverse influence of androgen deprivation therapy. However, the aim of this pilot-study was to check the feasibility of our study-design and a multicenter randomized controlled trial based on this study-design is therefore recommended in the future.

This pilot study used body mass index and abdominal circumference and was therefore only able to estimate a general body fat distribution (particularly truncal). To determine the exact change in body composition (fat versus lean mass), accurate measurements using a dual-energy X-ray absorptiometry or bio-impedance spectroscopy are needed [35]. How-

ever, those techniques are expensive and complex, and therefore not suitable for use on a daily basis.

Our pilot study assessed the health-related quality of life in patients with prostate cancer using only the EORTC-C30. To reach more qualitative results and clinical validity, a disease-specific module, such as the EORTC QLQ-PR25 (Prostate Cancer Module for QLQ-C30), should be added [36].

Finally, a future training program should include a general lifestyle intervention targeting a healthy individualized dietary behavior as an extra support [37].

CONCLUSIONS

This pilot study revealed a remarkably unfavorable cardio-metabolic profile in patients with prostate cancer on androgen deprivation therapy. It is our belief that these risk factors are underdiagnosed in these patients. Therefore, we want to raise the awareness of clinicians for a metabolic risk assessment before starting androgen deprivation therapy and periodically thereafter. Furthermore, our study showed both statistically and clinically significant benefits of supervised physical exercise program in patients with prostate cancer on androgen deprivation therapy. This pilot study demonstrated that a supervised physical exercise program can reduce several androgen deprivation therapy-related side effects, improving general health status, self-reported as well as observed physical function and quality of life. We therefore recommend incorporating a supervised physical exercise program in the treatment of patients with prostate cancer on androgen deprivation therapy. A multi-center randomized controlled trial based on this pilot study design is therefore to confirm our findings.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics. *CA Cancer J Clin.* 2015; 65: 87-108.
2. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS. Global Surveillance of Cancer Survival 1995-2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet.* 2015; 385: 977-1010.
3. Keogh JW, MacLeod RD. Body Composition, Physical Fitness, Functional Performance, Quality of Life, and Fatigue Benefits of Exercise for Prostate Cancer Patients: A Systematic Review. *J Pain Symptom Manage.* 2012; 43: 96-110.
4. Allan CA, Collins VR, Frydenberg M, McLachlan RI, Matthiesson KL. Androgen Deprivation Therapy Complications, Thematic Review. *Endocr Relat Cancer.* 2014; 21: 119-129.
5. Hvid T, Winding K, Rinnov A, Dejgaard T, Thomsen C, Iverson P. Endurance Training Improves Insulin Sensitivity and Body Composition in Prostate Cancer Patients Treated With Androgen Deprivation Therapy. *Endocr Relat Cancer.* 2013; 20: 621-632.
6. Culos-Reed SN, Robinson JW, Lau H, Stephenson L, Keats M, Norris S. Physical Activity for Men Receiving Androgen Deprivation Therapy for Prostate Cancer: Benefits From a 16-week Intervention. *Support Care Cancer.* 2010; 18: 591-599.
7. Cormie P, Galvao DA, Spry N, Joseph D, Chee R, Taaffe DR. Can Supervised Exercise Prevent Treatment Toxicity in Patients with Prostate Cancer Initiation

- Androgen-Deprivation Therapy: A Randomised Controlled Trial. *BJU Int* 2015; 115: 256-266.
8. Gardner JR, Livingston PM, Fraser SF; Effects of Exercise on Treatment-Related Adverse Effects for Patients With Prostate Cancer Receiving Androgen-Deprivation Therapy: A Systemic Review. *J Clin Oncol*. 2014; 32: 335-346.
 9. Scott NW, Fayers PM, Aaronson NK, et al. The European Organization for Research and Treatment of Cancer (EORTC): Quality of Life Department 2013; Belgium: EORTC Quality of Life; ©1995, 1999, 2001 [cited 2013 Nov 1]. Available from: <http://www.eortc.be/qol/files/SCManualQLQ-C30.pdf>
 10. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sport Medicine Roundtable on Exercise Guidelines for Cancer Survivors. *Med Sci Sports Exerc*. 2010; 42: 1409-1426.
 11. Center MM, Jemal A, Lortet-Tieulent J, et al. International Variation in Prostate Cancer Incidence and Mortality Rates. *Eur Urol*. 2012; 61: 1072-1092.
 12. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU Guidelines on Prostate Cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2014; 65: 124-137.
 13. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU Guidelines on Prostate Cancer. Part 2: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer. *Eur Urol*. 2014; 65: 467-479.
 14. Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS. Increasing Use of Gonadotropin-Releasing Hormone Agonists for the Treatment of Localized Prostate Carcinoma. *Cancer*. 2005; 103: 1615-1624.
 15. Cooperberg MR, Grossfeld GD, MD, Lubeck DP, Carroll PR. National Practice Patterns and Time Trends in Androgen Ablation for Localized Prostate Cancer. *J Natl Cancer Inst*. 2003; 95: 981-989.
 16. Nguyen PL, Alibi SMH, Basaria S, et al Adverse Effects of Androgen Deprivation Therapy and Strategies to Mitigate Them. *Eur Urol*. 2015; 67: 825-836.
 17. Tivesten A, Pinthus JH, Clarke N, Duivenvoorden W, Nilsson J. Cardiovascular Risk with Androgen Deprivation Therapy for Prostate: Potential Mechanisms. *Urol Oncol*. 2015; 33: 464-475.
 18. Choi SM, Kam SC. Metabolic Effects of Androgen Deprivation Therapy. *Korean J Urol*. 2015; 56: 12-18.
 19. Nishiyama T, Ishizaki F, Anraku T, Shimura H, Takahashi K. The Influence of Androgen Deprivation Therapy on Metabolism in Patients with Prostate Cancer. *J Clin Endocrinol Metab*. 2005; 90: 657-660.
 20. Alibhai SMH, Gogov S, Allibhai Z. Long-term Side Effects of Androgen Deprivation Therapy in Men With Non-Metastatic Prostate Cancer: A Systematic Literature Review. *Crit Rev Oncol Hematol*. 2006; 60: 201-215.
 21. Galvao DA, Taaffe DR, Spry N, Joseph D, Turner D, Newton RU. Reduced Muscle Strength and Functional Performance in Men with Prostate Cancer Undergoing Androgen Suppression: A Comprehensive Cross-Sectional Investigation. *Prostate Cancer Prostatic Dis*. 2009; 12: 198-203.
 22. Jones JS, Kohli M, Loprinzi CL. Androgen Deprivation Therapy-Associated Vasomotor Symptoms. *Asian J Androl*. 2012; 14: 193-197.
 23. Walker LM, Tran S, Robinson JW. Luteinizing Hormone-Releasing Hormone Agonists: A Quick Reference for Prevalence Rates of Potential Adverse Effects. *Clin Genitourin Cancer*. 2013; 11: 375-384.
 24. Ahmadi H, Daneshmand S. Androgen Deprivation Therapy for Prostate Cancer: Long-Term Safety and Patient Outcomes. *Patient Relat Outcome Meas*. 2014; 5: 63-70.
 25. Alibhai SMH, Mina DS, Ritvo P, et al. A phase II RCT and economic analysis of three exercise delivery methods in men with prostate cancer on androgen deprivation therapy. *BMC Cancer*. 2015; 15: 312.
 26. Segal R. Physical Functioning for Prostate Health. *Can Urol Assoc J*. 2014; 8: 162-163.
 27. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined Resistance and Aerobic Exercise Program Reverses Muscle Loss in Men undergoing Androgen Suppression Therapy for Prostate Cancer Without Bone Metastasis: A Randomized Controlled Trial. *J Clin Oncol*. 2010; 28: 340-347.
 28. Zhao J, Zhu S, Sun L, et al. Androgen Deprivation Therapy for Prostate Cancer Is Associated with Cardiovascular Morbidity and Mortality: a Meta-Analysis of Population-Based Observational Studies. *Plos One*. 2014; 9: 1-9.
 29. Winters-Stone KM, Beer TM. Review of exercise Studies in Prostate Cancer Survivors Receiving Androgen Deprivation Therapy Calls for an Aggressive Research Agenda to General High-Quality Evidence and Guidance for Exercise As Standard of Care. *J Clin Oncol*. 2014; 32: 2518-2519.
 30. Winters-Stone KM, Dobek JC, Bennett JA, et al. Resistance Training Reduces Disability in Prostate Cancer Survivors on Androgen Deprivation Therapy: Evidence From a Randomised Controlled Trial. *Arch Phys Med Rehabil*. 2015; 96: 7-14.
 31. Galvao DA, Spry N, Denham J, et al. A Multicentre Year-long Randomised Controlled Trial of Exercise Training Targeting Physical Functioning in Men with Prostate Cancer Previously Treated with Androgen Suppression and Radiation from TROG 03.04 RADAR. *Eur Urol*. 2014; 65: 856-864.
 32. Beydoun N, Bucci JA, Chin YS, Spry N, Newton R, Galvao DA. Prospective Study of Exercise Intervention in Prostate Cancer Patients on Androgen Deprivation Therapy. *J Med Imaging Radiat Oncol*. 2014; 58: 369-376.
 33. Teleni L, Chan RJ, Chan A, et al. Exercise Improves Quality of Life in ADT-treated Prostate Cancer: Systemic Review of RCT's. *Endocr Relat Cancer*. 2016; 23: 101-112.
 34. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Cardiovascular and Metabolic Complications during Androgen Deprivation: Exercise as a Potential Countermeasure. *Prostate Cancer Prostatic Dis*. 2009; 12: 233-240.
 35. Berruti A, Dogliotti C, Terrone C, et al. Changes in Bone Mineral Density, Lean Body Mass and Fat Content as Measured by Dual Energy X-Ray Absorptiometry in Patients With Prostate Cancer Without Apparent Bone Metastases Given Androgen Deprivation Therapy. *J Urol*. 2002; 167: 2361-2367.
 36. van Andel G, Bottomley A, Fossa SD, et al. An International Field Study of the EORTC QLQ-PR25: a Questionnaire for Assessing the Health-Related Quality of Life in Patients with Prostate Cancer. *Eur J Cancer*. 2008; 44: 2418-2424.
 37. Bourke L, Doll H, Crank H, Daley A, Rosario D, Saxton JM. Lifestyle Intervention in Men with Advanced Prostate Cancer Receiving Androgen Suppression Therapy: A Feasibility Study. *Cancer Epidemiol Biomarkers Prev*. 2011; 20: 647-657. ■