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Basic Original Report

Effect of Exercise Adjunct to Radiation and Androgen Deprivation Therapy on Patient-Reported Treatment Toxicity in Men With Prostate Cancer: A Secondary Analysis of 2 Randomized Controlled Trials

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Abstract

Purpose: Physical inactivity, in addition to clinical factors, has been associated with higher levels of late pelvic symptoms in patients with prostate cancer (PCa) after radiation therapy. The aim of this study was to investigate the effect of a structured multicomponent exercise program comprised of aerobic and resistance training as well as impact loading on the prevalence and severity of symptoms commonly resulting from androgen deprivation therapy (ADT) and pelvic radiation therapy.

Methods and Materials: We performed a secondary analysis of pooled data from 2 randomized controlled trials that investigated the role of exercise on treatment-related side effects in patients with PCa receiving ADT. Patients were included in the analysis if they had undergone radiation therapy during the intervention in addition to ADT. Patient-reported quality of life and functional and symptom scales were assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 and PR25 before and after 6 months of exercise or usual care (UC).

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Data sharing statement: Research data are not available at this time.

Note—An online CME test for this article can be taken at https://academy.astro.org.

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Results: One-hundred and fifteen patients with PCa receiving ADT, aged 47 to 84 years, who also underwent radiation therapy were included in the analysis (exercise, n = 72; UC, n = 43). There was a significant reduction in physical functioning ($P = .019$) and increased fatigue ($P = .007$) in the control group, with no change observed in the exercise group. Similarly, there was a trend toward reduced sexual activity in the control group ($P = .064$), with a mean adjusted change of -7.1 points. Furthermore, the prevalence of clinically important pain at 6 months was lower in the exercise group compared with UC (18.1 vs 37.2%, $P = .022$). No between-group differences were found for urinary ($P = .473$) or hormonal treatment-related symptoms ($P = .552$).
Conclusions: Exercise during concomitant hormone and radiation treatment for men with PCa may mitigate some adverse changes in patient-reported fatigue, physical functioning, and possibly sexual activity. The promotion and provision of exercise to counter a range of treatment-related adverse effects in patients with PCa undergoing radiation therapy and ADT should be actively encouraged.

Introduction

Prostate cancer is among the most prevalent cancers globally and the second most commonly diagnosed cancer in males after lung cancer.[1] In 2018, an estimated 1,276,106 new cases of prostate cancer were diagnosed and 358,989 deaths were recorded.[1] Approximately 37% to 42% of patients with prostate cancer aged 65 years and older receive radiation therapy as their initial treatment.[2] Based on the severity of the disease, some patients may receive radiation therapy in combination with androgen deprivation therapy (ADT).[3] Over the past few decades, technological advances and improved treatment regimens have led to increased tumor control and a dramatic reduction in radiation therapy toxicity.[4] However, despite modern treatment techniques, some patients still experience adverse effects from radiation therapy.[4] Although patients are surviving longer, health-related quality of life is negatively affected as a result of long-term consequences of radiation therapy as well as late treatment-associated toxicity.[4]

Adverse effects associated with pelvic radiation therapy of the prostate commonly encompass urinary and bowel symptoms, including rectal toxicity, as well as reduced sexual function. Symptoms exacerbate over the course of treatment, are most severe immediately after radiation therapy, and generally improve thereafter.[5,6] Furthermore, clinical factors such as a higher prescribed radiation dose, preexisting bladder and bowel symptoms, as well as older age have been associated with increased late-onset toxicity after pelvic radiation therapy in men with prostate cancer.[6,7] Lifestyle factors including cigarette smoking as well as being overweight or obese have also been associated with increased toxicity after treatment in this patient group.[8-10] In addition, physical inactivity during and after radiation therapy has been associated with more severe late pelvic symptoms.[10] Conversely, increasing bowel symptoms have been associated with a reduced likelihood of being physically active (ie, exercising 2 or more times per week) following treatment.[11]

Exercise has been shown to reduce treatment-related adverse effects such as loss of muscle and bone mass, fatigue, and decline in physical function associated with ADT in men with prostate cancer.[12-15] Moreover, pelvic floor training programs have been effective in reducing the duration of incontinence after radical prostatectomy.[16] In contrast, relatively few studies have investigated the effect of concomitant exercise during treatment on acute radiation-induced toxicity in men with prostate cancer. Kapur et al[17] performed a retrospective analysis of acute radiation toxicity in 65 men with localized prostate cancer who had participated in a randomized controlled trial of aerobic exercise (ie, home-based continuous walking for 30 minutes at least 3 days a week at a moderate intensity; n = 32) during 4 weeks of radiation therapy. Although rectal toxicity was not significantly different between groups at weekly assessment time points during treatment, the mean rectal toxicity scores over the 4-week treatment period were significantly lower in the exercise group.[17] Furthermore, mean bladder toxicity scores were significantly lower in the exercise group at 4 weeks post radiation therapy completion.[17] There can be hesitancy among clinicians to recommend exercise,[18,19] in particular resistance or impact training, due to concerns about exacerbating urinary and bowel issues; however, this has not been reported in the scientific literature and appears anecdotal.

Given the paucity of current evidence regarding the influence of exercise training on radiation-induced toxicity in men with prostate cancer, we performed a secondary analysis of 2 randomized controlled trials and investigated the effect of a structured multicomponent exercise program that contained aerobic and resistance training as well as impact loading on the prevalence and severity of symptoms commonly resulting from radiation therapy and ADT in men with prostate cancer.

Methods and Materials

We performed a secondary analysis on pooled data from 2 randomized controlled trials that investigated the consequence of exercise on treatment-related side effects in men with prostate cancer receiving ADT with or without

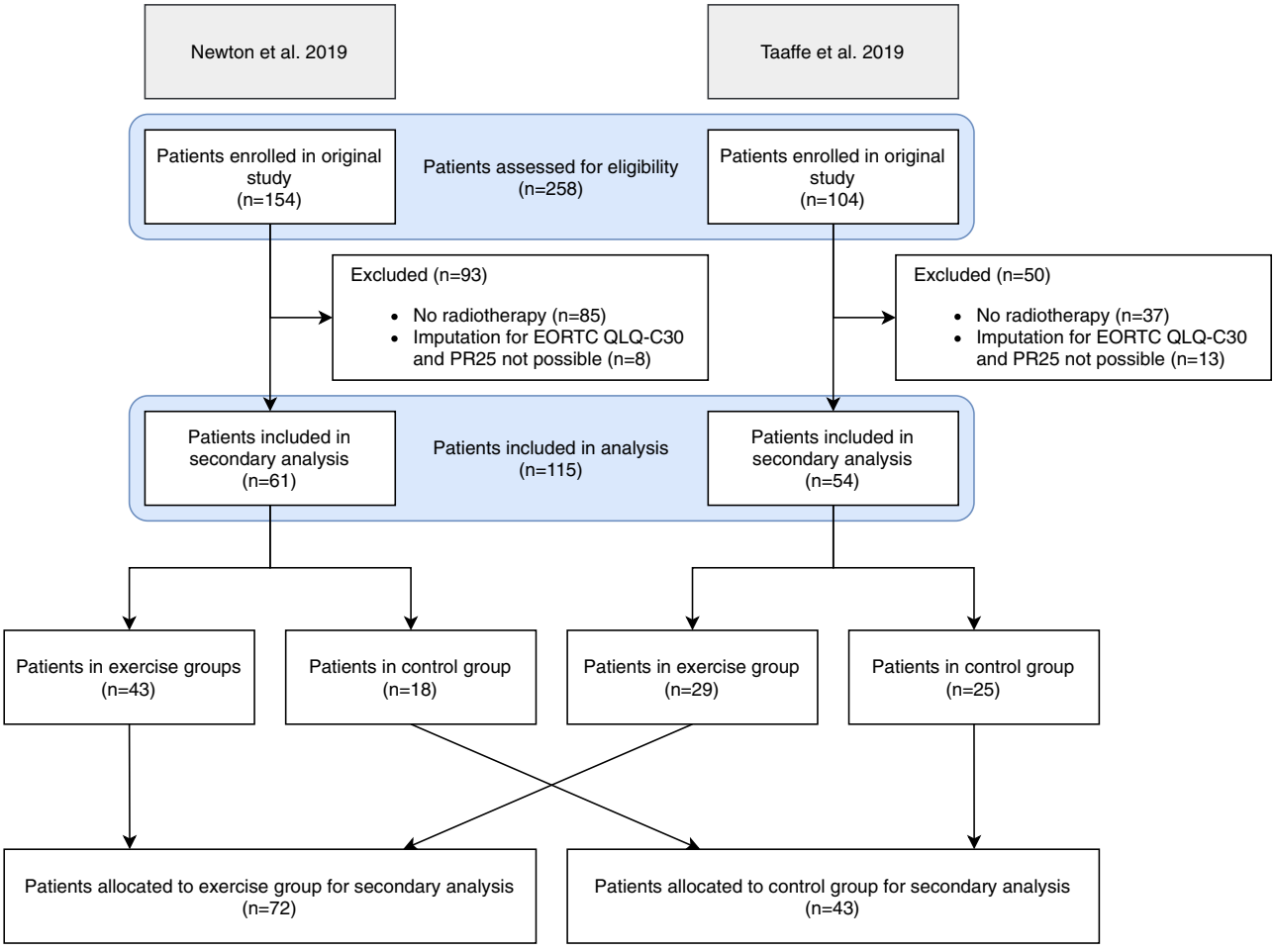

Figure 1 Study flow diagram.

concurrent radiation therapy.[14,15] In short, a total of 258 men undergoing treatment for prostate cancer were recruited across both studies by referral from their treating urologist or radiation oncologist in Perth, Western Australia. Detailed inclusion and exclusion criteria for these studies are described elsewhere.[14,15] For the current analysis, patients were included if they had commenced radiation therapy during the course of the initial 6 months of the intervention and had complete questionnaire response rate (ie, it was possible to calculate scales/scores after imputing missing items) at baseline and after 6 months of the exercise intervention or usual care (Fig 1). Both studies were approved by the Human Research Ethics Committee at Edith Cowan University and all participants provided written informed consent (Clinical Trial Registry Number: ACTRN12609000200280 and ACTRN12612000097842).

Study design

In Newton et al,[14] patients were randomly allocated to 1 of 3 groups: (1) impact loading + resistance training, (2) aerobic exercise + resistance training, or (3) usual care + delayed exercise. Group (3) acted as a control group and commenced aerobic exercise after 6 months of the intervention. In Taaffe et al,[15] patients were randomized to either an immediate exercise group that undertook a multicomponent exercise program consisting of aerobic, resistance, and impact-loading exercises for 6 months or a delayed exercise group that received usual care for the initial 6 months of the intervention (control) followed by 6 months of the identical exercise program as the immediate exercise group. The studies by Newton et al[14] and Taaffe et al[15] were both yearlong trials; however, for the purpose of the current analysis, patients were grouped into exercise versus usual care (control) based on whether they engaged in the structured exercise program during the initial 6 months of the intervention. Accordingly, only study outcome measures reported at baseline and at 6 months were assessed in this analysis.

Exercise program

A detailed description of the exercise interventions of both source data sets has been published elsewhere.[14,15]

Briefly, exercise was undertaken 2 to 3 days per week in small groups of up to 10 patients in an exercise clinic setting with supervision by accredited exercise physiologists and performed at a moderate to high intensity. Specifically, resistance training consisted of 6 primary exercises targeting the major upper and lower body muscles (ie, chest press, seated row, shoulder press, leg press, leg extension, and leg curl) that were supplemented with the lat pull down, biceps curl, triceps extension, and seated calf raise. Exercises were performed for 2 to 4 sets each at an intensity of 6- to 12-repetition maximum (RM) with a 1 to 2 minute rest period between sets. Aerobic exercise was performed for 20 to 40 minutes at an intensity of 60% to 85% of maximal heart rate (HR_{max}) and consisted of different exercise modes, including walking/jogging on a treadmill and cycling or rowing on a stationary ergometer. Exercise intensity was monitored using individual HR monitors with a chest strap (Polar Electro Oy, Kempele, Finland) and adjusted to maintain HR within the target range. At later stages of the program, some sessions included interval training with intensities up to 85% of HR_{max} to reduce potential boredom. Impact loading consisted of 2 to 4 rotations of skipping (30 seconds), bounding over soft hurdles (13-30 cm), drop jumps (10-20 cm), and hopping/leaping (10 repetitions per set). In addition to clinic-based training, patients in the impact loading + resistance training group performed home-based exercises consisting of 2 to 4 rotations of skipping (30 seconds), hopping, leaping, and drop jumping (10 repetitions each) 2 days/week. Patients in the aerobic exercise + resistance training group were encouraged to accumulate an additional 150 minutes/week of home-based aerobic activity. Similarly, patients who undertook the multicomponent exercise program consisting of aerobic exercise, resistance training, and impact-loading were encouraged to perform additional twice weekly home-based aerobic exercise activities such as walking or cycling and a modified version of the impact loading program. All clinic-based sessions commenced with a warm-up consisting of low intensity aerobic exercise and ended with a cool-down comprised of stretching exercises.

Primary endpoints

Quality of life and functional and symptom scales were assessed at baseline and after 6 months of exercise or usual medical care using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire core (QLQ-C30) and prostate cancer (PR25) module.[20,21] Scores for each scale are calculated based on either a single or multiple items of the questionnaire, where higher scores indicate better functioning or more symptom burden and lower scores indicate worse functioning or less symptom burden. Missing items (ie, 1 or more missing answers to questions within a questionnaire) from multi-item scales were imputed if at least half of the items from the scale had been answered. Specifically, it was assumed that the missing items had values equal to the average of those items that were present for that respondent.[22] To calculate the prevalence of clinically important problems/symptoms for each EORTC QLQ-C30 scale, we used the thresholds for clinical importance determined by Giesinger et al.[23]

Other measures

Demographic and clinical patient data were collected by self-report and extracted from medical records, respectively. Height and weight were assessed using a stadiometer and electronic scale, respectively, to subsequently calculate body mass index (BMI) as kg/m^2. Physical activity levels were assessed using the Godin leisure-time exercise questionnaire.[24] Prostate-specific antigen and testosterone were measured by an Australian National Association of Testing Authorities laboratory (Pathwest Diagnostics, Perth, WA, Australia). A physical performance battery consisting of 400-meter walk, repeated chair rise test, and backward 6-meter walk was used to assess walking endurance, lower body strength, and dynamic balance, respectively.[25] In addition, 1RM muscle strength testing was performed for the chest press, leg press, and seated row exercises.[25]

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY). For continuous variables, normality of the distribution was assessed using the Shapiro-Wilk test. Patient characteristics at baseline were analyzed using independent t tests or Mann-Whitney U tests, as appropriate, for continuous data and χ^2 tests for categorical data to assess any between-group differences. Generalized linear mixed models were performed for each EORTC QLQ-C30 and PR25 scale as well as for physical performance variables with patient as random effect and BMI, hypertension status (ie, yes or no), time (ie, baseline or 6 months), and group (ie, exercise or control) as fixed effects. For post hoc pairwise contrasts the sequential Bonferroni adjusted significance level was 0.05. Between-group differences for prevalence rates of clinically important problems/symptoms for each EORTC QLQ-C30 scale at baseline and 6 months were analyzed using χ^2 tests. All tests were 2-tailed and statistical significance was set at an α level of 0.05 for all analyses.

Results

Patient demographic and clinical characteristics for the 115 men included in the analyses are shown in

Table 1 Demographic and clinical characteristics of patients in the exercise and control group at baseline

	Exercise group (n = 72)*	Control group (n = 43)*	*P* value
Age (years), mean (SD)	67.9 (7.8)	67.8 (7.5)	.937
Height (cm), mean (SD)	172.9 (6.4)	171.6 (5.7)	.275
Weight (kg), median (IQR)	80.5 (71.4-92.2)	83.1 (75.3-95.2)	.094
BMI (kg/m^2), median (IQR)	26.9 (24.7-29.5)	28.6 (25.9-33.2)	.012
Married, n (%)	58 (81.7)†	37 (86.0)	.545
Currently employed, n (%)	26 (36.1)	19 (44.2)	.391
Tertiary education, n (%)	22 (31.0)†	9 (20.9)	.242
Current smoker, n (%)	4 (5.6)	2 (4.7)	.833
Gleason score, median (IQR)	7.0 (7.0-8.5)‡	7.0 (7.0-8.0)§	.666
PSA (ng/mL), median (IQR)	0.5 (0.0-2.3)‖	0.7 (0.1-2.9)¶	.256
Testosterone (nmol/L), median (IQR)	1.1 (0.0-3.1)‖	1.7 (0.7-4.4)¶	.179
Godin leisure-time activity score, median (IQR)	24.0 (13.0-36.0)†	25.5 (17.3-45.0)¶	.490
Cardiovascular disease, n (%)	6 (8.3)	6 (14.0)	.340
Hypertension, n (%)	24 (33.8)†	23 (54.8)¶	.029
Dyslipidemia, n (%)	19 (26.4)	18 (42.9)¶	.070
Diabetes, n (%)	10 (13.9)	9 (20.9)	.325
EBRT completed within 6-month intervention (days#), median (IQR)	47.0 (39.5-53.0)‖	44.5 (35.0-51.3)¶	.410
Total EBRT completed (days#), median (IQR)	50.0 (41.8-53.0)‖	50.0 (42.0-52.3)¶	.864
Baseline to start of radiation therapy (days), median (IQR)	98.0 (69.0-129.0)†	97.0 (71.0-132.0)	.981
End of radiation therapy to follow-up**†† (days), median (IQR)	42.0 (8.5-88.8)‖	33.0 (0.0-74.0)	.213
Brachytherapy, n (%)	16 (22.2)	9 (20.9)	.871

Abbreviations: BMI = body mass index; EBRT = external beam radiation therapy; IQR = interquartile range; PSA = prostate-specific antigen; SD = standard deviation.

* Unless indicated otherwise.

† n = 71

‡ n = 61

§ n = 39

‖ n = 70

¶ n = 42

Days ≠ fractions.

** If radiotherapy ended after the 6-month (ie, follow-up) assessment was completed, the value was set to 0 days difference for that patient.

†† If patient received brachytherapy in addition to EBRT, the date of brachytherapy seed insertion was used as the end of radiotherapy.

Table 1. There were no significant differences between the exercise (n = 72) and control group (n = 43) in baseline characteristics, except for BMI and hypertension, with patients in the control group having a higher BMI and a higher prevalence of hypertension compared with the exercise group. Men were aged 47 to 84 years and had a median Gleason score of 7. The median duration of radiation therapy that was completed within the 6-month intervention was 45.5 days, and patients commenced radiation therapy treatment a median of 98 days after their baseline assessments. Two men had an interruption of their radiation therapy treatment. There were no major exercise-related adverse events in either exercise trial.

Physical performance outcome

Exercise had the desired effect, with a significant difference between the exercise and control groups in walking endurance as assessed by 400-meter walk time (P = .039), with an adjusted mean difference of -10.2 seconds (Table 2). Furthermore, significant between-group differences in 1RM strength were observed for the chest press ($P < .001$), leg press ($P < .001$), and seated row (P = .002), with all strength measures increasing in the exercise group from baseline to 6 months while decreasing in the control group. There were no between-group differences for the repeated chair rise time and the backward 6-meter walk time.

Table 2 Physical performance measures at baseline and after 6 months of exercise or usual care (control)

	Baseline	6 months	Estimated mean change from baseline to 6 months		Adjusted between-group difference in mean change from baseline to 6 months*		
	Mean (SD)	Mean (SD)	Mean (95% CI)	*P* value†	Coefficient	95% CI	*P* value
400-meter walk time (s)					−10.2	−19.9 to −0.5	.039
Exercise (n = 70)	254.2 (38.6)	243.3 (30.5)	−10.8 (−16.7 to −5.0)	<.001			
Control (n = 40)	256.6 (38.0)	257.4 (40.6)	−0.7 (−8.4 to 7.1)	.866			
Repeated chair rise time (s)					−0.4	−1.1 to 0.3	.232
Exercise (n = 70)	11.9 (2.4)	11.0 (2.4)	−0.9 (−1.3 to −0.9)	<.001			
Control (n = 40)	12.0 (2.7)	11.6 (2.2)	−0.5 (−1.0 to 0.04)	.072			
Backward 6-meter walk time (s)					−1.3	−3.2 to 0.6	.190
Exercise (n = 70)	16.0 (5.9)	14.7 (4.8)	−1.3 (−2.4 to −0.1)	.035			
Control (n = 41)	16.0 (5.7)	16.0 (7.3)	0.03 (−1.5 to 1.6)	.971			
Chest press 1RM (kg)					5.0	3.0-7.0	<.001
Exercise (n = 67)	39.6 (11.2)	41.9 (11.3)	2.2 (0.9-3.4)	.001			
Control (n = 40)	45.6 (14.4)	42.7 (12.5)	−2.9 (−4.4 to −1.3)	.001			
Leg press 1RM (kg)					29.1	18.0-40.3	<.001
Exercise (n = 69)	128.5 (47.0)	157.4 (54.1)	28.9 (22.2-35.5)	<.001			
Control (n = 38)	138.2 (52.9)	137.6 (47.1)	−0.3 (−9.2 to 8.7)	.955			
Seated row 1RM (kg)					6.7	3.6-9.7	<.001
Exercise (n = 68)	72.3 (14.0)	75.9 (14.0)	3.5 (1.7-5.4)	<.001			
Control (n = 40)	75.2 (14.4)	72.0 (11.1)	−3.2 (−5.6 to −0.7)	.011			

Abbreviations: BMI = body mass index; CI = confidence interval; RM = repetition maximum; SD = standard deviation.

* Generalized linear mixed model analysis adjusted for BMI and hypertension status.

† Estimated mean change and corresponding *P* values are based on adjusted mixed model analysis using a sequential Bonferroni adjusted significance level of 0.05.

Quality of life outcomes

There were no significant between-group differences for any of the functional and symptoms scales of the EORTC QLQ-C30 after exercise (Table 3). However, there was a significant reduction in physical functioning ($P = .019$) as well as increased fatigue ($P = .007$) in the control group. In addition, diarrhea significantly increased only in the exercise group ($P < .001$) compared with a nonsignificant increase in the control group ($P = .084$). The prevalence rates of clinically important problems/symptoms ranged from 1.4% (appetite loss) to 39.5% (dyspnoea) across all scales (Table 4). There was a significant between-group difference for clinically important pain at 6 months that was not observed at baseline, with pain being more prevalent in the control group compared with the exercise group (37.2% vs 18.1%, $P = .022$). Similarly, the prevalence of clinically important dyspnoea increased by ~12% in the control group, whereas it increased by only ~1% in the exercise group ($P = .070$ for between-group difference at 6 months).

Urinary and bowel toxicity

Scores for urinary, bowel, and hormonal treatment-related symptoms increased (ie, worsened) from baseline to 6 months in both groups, with no significant difference between exercise and control (Table 5). However, there was a trend for exercise to reduce any problems associated with wearing an incontinence aid compared with the control group ($P = .056$), with an adjusted mean difference of −21.7 points.

Sexual activity and function

There was no significant difference between groups in sexual activity, but exercise seemed to ameliorate the decline in sexual activity that was seen in the control group ($P = .064$), resulting in a mean adjusted within-group change of -7.1 points (Table 5). No significant between-group change was observed in sexual functioning between the exercise and control group.

Discussion

We investigated the effects of 6 months of supervised multicomponent exercise programs on patient-reported treatment toxicity in men with prostate cancer undergoing concomitant radiation and ADT. As such, this study produced 3 important findings: (1) exercise mitigated some adverse effects of treatment on fatigue, physical functioning, and possibly sexual activity; (2) the prevalence of clinically important pain at 6 months was lower in the exercise group compared with the usual care control

Table 3 EORTC QLQ-C30 global health status and functional and symptoms scales at baseline and after 6 months of exercise or usual care (control)

	Baseline	6 months	Estimated mean change from baseline to 6 months		Adjusted between-group difference in mean change from baseline to 6 months*		
	Mean (SD)	Mean (SD)	Mean (95% CI)	*P* value†	Coefficient	95% CI	*P* value
Global health status					3.8	−1.6 to 9.3	.169
Exercise	78.6 (16.8)	79.5 (15.4)	1.1 (−2.3 to 4.4)	.533			
Control	73.8 (18.1)	70.7 (21.5)	−2.8 (−7.1 to 1.6)	.208			
Physical functioning					2.7	−0.8 to 6.2	.124
Exercise	94.4 (9.2)	94.0 (10.2)	−0.6 (−2.7 to 1.5)	.589			
Control	89.1 (13.4)	85.3 (17.8)	−3.3 (−6.1 to −0.6)	.019			
Role functioning					−4.8	−12.1 to 2.5	.196
Exercise	92.1 (15.1)	89.4 (17.1)	−2.8 (−7.3 to 1.6)	.213			
Control	83.3 (24.7)	85.3 (21.6)	2.0 (−3.8 to 7.8)	.499			
Emotional functioning					4.1	−1.5 to 9.8	.149
Exercise	88.1 (15.7)	89.8 (14.1)	2.0 (−1.5 to 5.4)	.263			
Control	84.4 (16.1)	82.4 (20.4)	−2.2 (−6.6 to 2.3)	.337			
Cognitive functioning					2.1	−2.9 to 7.0	.411
Exercise	87.5 (14.7)	87.0 (14.9)	−0.7 (−3.7 to 2.3)	.646			
Control	82.2 (16.8)	79.1 (17.9)	−2.8 (−6.7 to 1.2)	.165			
Social functioning					−2.3	−10.0 to 5.3	.548
Exercise	88.9 (18.8)	86.1 (19.2)	−2.3 (−7.0 to 2.3)	.325			
Control	79.5 (21.8)	79.5 (24.9)	−0.00 (−6.1 to 6.1)	1.000			
Fatigue					−5.5	−12.3 to 1.3	.111
Exercise	21.6 (18.9)	23.5 (18.4)	1.9 (−2.3 to 6.0)	.374			
Control	24.8 (21.1)	32.0 (24.8)	7.4 (2.0-12.8)	.007			
Nausea and vomiting					−0.7	−3.9 to 2.4	.660
Exercise	2.1 (7.4)	1.4 (5.4)	−0.7 (−2.6 to 1.2)	.470			
Control	2.3 (5.8)	2.3 (6.9)	−0.00 (−2.5 to 2.5)	1.000			
Pain					−2.8	−9.8 to 4.2	.430
Exercise	8.8 (13.7)	10.6 (17.8)	2.3 (−1.9 to 6.6)	.280			
Control	13.6 (18.6)	18.6 (19.7)	5.2 (−0.4 to 10.7)	.069			
Dyspnoea					−3.5	−10.9 to 3.9	.354
Exercise	7.9 (15.3)	8.8 (17.7)	0.5 (−4.1 to 5.0)	.838			
Control	11.6 (20.4)	17.1 (23.4)	4.0 (−1.9 to 9.9)	.185			
Insomnia					−2.1	−11.9 to 7.6	.668
Exercise	21.3 (25.2)	25.9 (29.2)	4.2 (−1.7 to 10.2)	.162			
Control	21.7 (24.0)	27.9 (29.9)	6.3 (−1.4 to 14.1)	.106			
Appetite loss					0.9	−5.5 to 7.4	.773
Exercise	2.3 (10.2)	3.7 (14.3)	0.9 (−3.0 to 4.9)	.637			
Control	3.9 (13.0)	3.9 (13.0)	−0.00 (−5.1 to 5.1)	1.000			
Constipation					2.1	−5.9 to 10.0	.611
Exercise	6.9 (16.7)	7.4 (17.0)	0.5 (−4.4 to 5.3)	.849			
Control	11.6 (25.1)	9.3 (21.0)	−1.6 (−7.9 to 4.7)	.620			
Diarrhea					4.6	−2.2 to 11.4	.182
Exercise	2.3 (10.2)	12.0 (20.4)	9.4 (5.2-13.5)	<.001			
Control	5.4 (17.7)	10.1 (20.0)	4.8 (−0.6 to 10.2)	.084			
Financial difficulties					0.3	−6.5 to 7.2	.926
Exercise	7.9 (16.3)	8.3 (19.2)	−0.5 (−4.7 to 3.7)	.825			
Control	13.2 (25.3)	12.4 (25.2)	−0.8 (−6.2 to 4.6)	.774			

Abbreviations: BMI = body mass index; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core; SD = standard deviation.

Exercise group n = 72, control group n = 43.

* Generalised linear mixed model analysis adjusted for BMI and hypertension status.

† Estimated mean change and corresponding *P* values are based on adjusted mixed model analysis using a sequential Bonferroni adjusted significance level of 0.05.

Table 4 Prevalence of clinically important problems/symptoms for each EORTC QLQ-C30 scale at baseline and after 6 months of exercise or usual care (control)

	Baseline, n (%)			6 months, n (%)		
	Exercise group	Control group	*P* value	Exercise group	Control group	*P* value
Functioning scales						
Physical functioning	7 (9.7%)	11 (25.6%)	.024	7 (9.7%)	12 (27.9%)	.011
Role functioning	3 (4.2%)	5 (11.6%)	.128	5 (6.9%)	5 (11.6%)	.388
Emotional functioning	9 (12.5%)	11 (25.6%)	.073	8 (11.1%)	7 (16.3%)	.426
Cognitive functioning	11 (15.3%)	14 (32.6%)	.030	11 (15.3%)	15 (34.9%)	.015
Social functioning	4 (5.6%)	7 (16.3%)	.059	3 (4.2%)	4 (9.3%)	.265
Symptom scales						
Fatigue	9 (12.5%)	8 (18.6%)	.372	10 (13.9%)	10 (23.3%)	.200
Nausea and vomiting	6 (8.3%)	6 (14.0%)	.340	5 (6.9%)	5 (11.6%)	.388
Pain	13 (18.1%)	10 (23.3%)	.500	13 (18.1%)	16 (37.2%)	.022
Dyspnoea	16 (22.2%)	12 (27.9%)	.492	17 (23.6%)	17 (39.5%)	.070
Insomnia	10 (13.9%)	6 (14.0%)	.992	15 (20.8%)	8 (18.6%)	.773
Appetite loss	1 (1.4%)	1 (2.3%)	.710	1 (1.4%)	1 (2.3%)	.710
Constipation	3 (4.2%)	5 (11.6%)	.128	3 (4.2%)	4 (9.3%)	.265
Diarrhea	4 (5.6%)	5 (11.6%)	.241	21 (29.2%)	10 (23.3%)	.489
Financial difficulties	15 (20.8%)	11 (25.6%)	.556	14 (19.4%)	10 (23.3%)	.627

Abbreviation: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core.
Smaller values indicate lower prevalence of clinically important problems (ie, functional impairment) or symptoms.
Exercise group (n = 72); control group (n = 43).

Table 5 EORTC QLQ-PR25 symptom and functional scales at baseline and after 6 months of exercise or usual care (control)

	Baseline	6 months	Estimated mean change from baseline to 6 months		Adjusted between-group difference in mean change from baseline to 6 months*		
	Mean (SD)	Mean (SD)	Mean (95% CI)	*P* value†	Coefficient	95% CI	*P* value
Urinary symptoms					−2.2	−8.4 to 3.9	.473
Exercise	14.5 (12.8)	21.3 (18.8)	6.9 (3.2-10.6)	<.001			
Control	17.2 (16.3)	26.1 (18.9)	9.1 (4.3-14.0)	<.001			
Incontinence aid					−21.7	−44.0 to 0.6	.056
Exercise (n = 5)	13.3 (18.3)	0.0 (0.0)	−8.3 (−22.5 to 5.9)	.240			
Control (n = 4)	25.0 (31.9)	41.7 (16.7)	13.4 (−3.7 to 30.4)	.119			
Bowel symptoms					0.5	−3.5 to 4.5	.801
Exercise	2.2 (5.4)	5.9 (9.6)	3.8 (1.3-6.2)	.003			
Control	4.4 (8.0)	7.6 (10.6)	3.2 (0.1-6.4)	.046			
Hormonal treatment-related symptoms					1.1	−2.6 to 4.9	.552
Exercise	9.4 (9.9)	16.9 (13.8)	6.9 (4.6-9.1)	<.001			
Control	10.3 (9.9)	15.9 (12.4)	5.7 (2.8-8.7)	<.001			
Sexual activity					4.8	−4.7 to 14.3	.323
Exercise	22.2 (24.4)	20.1 (20.5)	−2.3 (−8.2 to 3.5)	.427			
Control	19.0 (21.7)	12.0 (21.0)	−7.1 (−14.7 to 0.42)	.064			
Sexual functioning					10.0	−20.4 to 40.3	.512
Exercise (n = 10)	51.9 (27.3)	50.8 (21.3)	−9.2 (−25.6 to 7.2)	.265			
Control (n = 3)	72.2 (34.7)	63.9 (34.7)	−19.2 (−44.7 to 6.3)	.137			

Abbreviations: BMI = body mass index; CI = confidence interval; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire prostate cancer module; SD = standard deviation.
Exercise group n = 72, control group n = 43, unless indicated otherwise.

* Generalised linear mixed model analysis adjusted for BMI and hypertension status.

† Estimated mean change and corresponding *P* values are based on adjusted mixed model analysis using a sequential Bonferroni adjusted significance level of 0.05.

group; and (3) the exercise intervention did not appear to exacerbate prostate cancer-specific, patient-reported health outcomes of urinary and bowel symptoms overall compared with the control group, although increased reporting of diarrhea was statistically significant only in the exercise but not the control group.

Prostate cancer treatment is associated with a range of side effects that can affect a patient's quality of life. In men with prostate cancer undergoing radiation therapy with or without ADT, common side effects include unfavorable body composition changes, fatigue, urinary and bowel symptoms, and sexual problems.[26-28] It has been previously demonstrated that exercise can be an effective treatment to counteract some of these side effects.[14,15,25,29] For example, from the previous studies on patients included in this secondary analysis we reported that combining resistance training and impact loading attenuated bone loss and preserved muscle mass in patients undergoing ADT.[14,15] However, less information is available for patients with prostate cancer treated specifically with radiation therapy alone or in combination with ADT. To date, the largest randomized controlled trial of patients with prostate cancer initiating radiation therapy with or without ADT has been conducted by Segal et al.[30] They investigated the effect of 24 weeks of aerobic or resistance exercise in 121 patients with prostate cancer on fatigue (primary outcome), quality of life, and physical fitness among other outcomes. Both exercise interventions mitigated fatigue compared with a usual care control group, and resistance training also improved quality of life.[30] In line with these results, the exercise intervention of the present study resulted in improved physical performance and maintenance of fatigue levels in the exercise group, whereas fatigue was significantly increased in the control group at 6 months compared with baseline values. Furthermore, the adjusted mean change of 7.4 points in the control group is clinically important, although modest.[31]

Interestingly, a substantial increase in the prevalence of clinically important pain was observed in the control group at 6 months (ie, after the intervention), which was not seen in the exercise group. Furthermore, although not statistically significant between groups, the within-group mean change of 5.2 points in the pain score in the control group is clinically important, albeit a modest change. Unfortunately, the EORTC QLQ-C30 does not specify the type or location of pain but assesses pain in general and whether it interferes with daily activities. Thus, identifying how exercise might have affected pain in the present study was not possible. Griffith et al[32] also assessed pain in a mixed cancer cohort (55.6% prostate cancer) randomized to either a home-based walking program or usual care. Although an increased exercise dose was associated with decreased pain in their study, there was no significant difference in the change of pain scores between the 2 groups.[32] More research is required to determine whether exercise significantly affects pain and what specific exercise prescription is most appropriate.

In contrast to previous studies,[17,33] the multicomponent exercise program did not prevent or improve treatment-related urinary and bowel toxicities, but there was a trend for use of incontinence aids to be less of a problem for men in the exercise group. However, only a limited number of patients reported wearing an incontinence aid, which may have affected the results. One possible explanation for the nonsignificant effect of exercise in our study for urinary and bowel symptoms could be that outcomes were assessed by patient self-report using validated questionnaires as opposed to clinician assessment at weekly treatment review as in the study by Kapur et al.[17] However, Dieperink et al[33] also used a self-report questionnaire to assess treatment-related adverse effects in patients with prostate cancer in a multidisciplinary rehabilitation program and found that exercise resulted in improvements in urinary scores compared with a usual care control group. It is important to note, however, that the study by Dieperink et al[33] was conducted postradiation and, thus, patients may have presented with a different toxicity profile compared with the present analysis. It is also noteworthy that urinary and bowel problems overall were not reported by patients in the exercise group as being worse than in the control group, except for diarrhea, which, despite increasing in both groups, was only significant in the exercise group. This provides early evidence to counter the perception[18,19] that exercise, in particular resistance and impact training, may exacerbate urinary and bowel issues and requires further targeted research.

Erectile dysfunction is a common problem after treatment in men with prostate cancer.[34] In a study comparing sexual function in men with localized prostate cancer on active surveillance with patients receiving radical therapy, 56% to 60% of men who received radiation therapy were sexually inactive as a result of erectile dysfunction.[35] Furthermore, among patients in the radiation therapy group who were sexually active, 73% to 76% had problems achieving or maintaining an erection.[35] It has previously been shown that exercise maintains sexual activity in men with prostate cancer undergoing ADT.[36] However, in this previous trial,[36] less than 30% of men received concomitant radiation, limiting the ability to detect a compounding effect of ADT and radiation on sexual activity and function. Despite all patients in the current trial receiving ADT and radiation, sexual activity was approximately the same before and after the intervention in the exercise group compared with the usual care control group that showed a trend for a decrease in sexual activity. Dahn et al[37] evaluated the relationship between physical activity and sexual functioning in men with localized prostate cancer who had undergone radiation therapy in the previous 18 months and observed that increased physical activity was significantly associated

with better sexual functioning. In the present analysis, there was, however, no significant difference between groups in sexual functioning, although the sexual functioning score decreased by 8.3 points (unadjusted within-group difference of mean scores) in the control group compared with similar pre- and postintervention scores in the exercise group. However, owing to the structure of the questionnaire we used in this analysis, which requires patients to answer questions related to sexual functioning only if they had been sexually active within the last 4 weeks of answering the questionnaire, data were only available for 13 patients (11%).

As expected, the exercise intervention had a significant effect on multiple indices of upper and lower body muscle strength and aerobic capacity. These improvements included increased physical performance in the 400-meter walk as well as 1RM strength in several muscle groups of the upper and lower body, specifically the legs, back, and chest. Preserving, or improving, physical function and performance is important given its association with patient outcomes and survival. For example, slower 400-meter walk was associated with increased mortality, incident cardiovascular disease, mobility limitation, and disability in a cohort study of 3075 community-dwelling older adults.[38] Furthermore, in a systematic review of studies of patients with cancer, poorer physical performance was associated with treatment-related complications and decreased survival.[39] Hence, engaging in exercise and physical activity should be recommended to patients with cancer commencing treatment, particularly if patients already present with decreased performance and ability to perform daily tasks.

The present study has several strengths and limitations that are worth mentioning. Our study reports on a large sample of 115 men diagnosed with prostate cancer undergoing both radiation therapy and ADT. Moreover, patients followed a well-supervised clinic-based exercise program ensuring appropriate training progression to facilitate optimal training outcomes over the 6-month intervention period. A limitation of this study is that the thresholds for clinical importance used in the present analysis to calculate the prevalence rates of clinically important problems/symptoms are not prostate cancer-specific. However, the cancer patient population in the study by Giesinger et al[23] upon which the thresholds are based nevertheless consisted of 9.7% patients with prostate cancer.

Conclusions

Exercise during concomitant hormone and radiation treatment for men with prostate cancer may mitigate some adverse changes in patient-reported fatigue, physical functioning, and possibly sexual activity. In addition, the prevalence of clinically important pain was lower in the exercise group at 6 months compared with the control group. Although there was no mediating effect on patient-reported urinary, bowel, or hormonal treatment-related symptoms overall, exercise did not exacerbate these issues, with the exception of diarrhea. Given that exercise appears to be an effective countermeasure to several treatment-related adverse effects, patients undergoing radiation therapy and ADT should be encouraged by their oncologist to engage in physical exercise during treatment.

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