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Quality of life for men with metastatic castrate-resistant prostate cancer participating in an aerobic and resistance exercise pilot intervention

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Abstract

Background: Following a prostate cancer diagnosis, disease and treatment-related symptoms may result in diminished quality of life (QoL). Whether exercise improves QoL in men with metastatic castrate-resistant prostate cancer (mCRPC) is not fully understood.

Methods: We conducted a 3-arm pilot randomized controlled trial to assess the feasibility, acceptability, safety, and efficacy of a 12-week remotely monitored exercise program among men with mCRPC. Here we report qualitative changes in QoL, consistent with the guidelines for pilot trials. Men were randomized to control, aerobic exercise, or resistance exercise. Exercise prescriptions were based on baseline cardiorespiratory and strength assessments. QoL outcomes were evaluated using self-reported questionnaires (e.g., QLQ-C30, PROMIS Fatigue, Pittsburgh Sleep Quality Index (PSQI), EPIC-26) collected at baseline and 12 weeks.

Results: A total of 25 men were randomized (10 control, 8 aerobic, 7 resistance). Men were predominately white (76%) with a median age of 71 years (range: 51−84) and 10.5 years (range: 0.9−26.3) post prostate cancer diagnosis. The men reported poor sleep quality and high levels of fatigue at enrollment. Other baseline QoL metrics were relatively high. Compared to the controls at 12 weeks, the resistance arm reported some improvements in social function and urinary irritative/obstruction symptoms while the aerobic arm reported some improvements in social function and urinary incontinence, yet worsening nausea/vomiting. Compared to the resistance arm, the aerobic arm reported worse urinary irritative/obstruction symptoms and self-rated QoL, yet some improvements in emotional function, insomnia, and diarrhea.

Conclusions: The 3-month exercise intervention pilot appeared to have modest effects on QoL among mCRPC survivors on ADT. Given the feasibility, acceptability, and safety demonstrated in prior analyses, evaluation of the effect of the intervention on QoL in a larger sample and for extended duration may still be warranted.

Keywords: Behavioral intervention: Physical activity; Remote; Strength training

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1. Introduction

Prostate cancer is the most common non-cutaneous malignancy in men, with 248,530 new diagnoses estimated to occur in the United States in 2021 [1]. Approximately 10−20% of these malignancies will advance to metastatic castrate-resistant prostate cancer (mCRPC) [2]. Fortunately, metastatic prostate cancer has the highest 5-year survival rate of any major cancer type [1] due in part to the advances in systemic treatment approaches [3−7]. Given these improvements in survival, there has been a practical shift to thinking about the long term effects of treatment, including an interest in sustaining quality of life (QoL) for men living with mCRPC [8].

Standard treatment for metastatic prostate cancer is lifelong androgen deprivation therapy (ADT) which is associated with declines in cognitive function and negative impacts on cardiovascular, sexual, muscular, and bone health [8−10]. Newer androgen signaling inhibitors (ASIs; Abiraterone, Enzalutamide) are frequently added to ADT and have also been shown to increase patient fatigue [11−13], hot flashes [11,14], falls [11,12,15], dizziness [11], and decrease appetite [11]. Given these treatment side effects, coupled with the emotional stress and financial burden of coping with a terminal illness [16] and the complications of concomitant comorbidities common among men with prostate cancer [17,18], men with mCRPC are at increased risk of diminished QoL [8].

Substantial evidence from observational and randomized clinical trials demonstrates the benefits of physical activity in improving outcomes and QoL among prostate cancer survivors [19−22]. However, few studies have examined this relationship among men with metastatic prostate cancer. We developed the **C**linical trial of **H**igh-intensity **A**erobic and resistance exercise for **M**etastatic **P**rostate cancer (CHAMP) study to address this gap in research. Recent results demonstrated the intervention was not only feasible and acceptable, but also safe [23]. Here, we report on secondary outcomes of the CHAMP trial: to assess the effect of the intervention on QoL among men with mCRPC.

2. Methods

2.1. Study population

We conducted a randomized phase II, 3-arm pilot trial comparing two 12-week exercise interventions to standard of care among men (≥18 years old) with mCRPC between 2016 and 2020. Men actively on ADT with a gonadotropin-releasing hormone agonist/antagonist or prior bilateral orchiectomy, an Eastern Cooperative Oncology Group (ECOG) status of 0 to 1, and English-speaking were eligible to participate (clinicaltrials.gov NCT02613273). Additional treatments (e.g., Abiraterone, Enzalutamide, chemotherapy, immunotherapy) were allowed. Men living within a 3-hour drive of the University of California, San Francisco (UCSF) were recruited through physician referral and patient lists. The focus on proximity to UCSF was to accommodate onsite exercise participation. The original protocol was changed from solely allowing on-site exercise to optional remote supervised exercise to improve recruitment. The pilot study also planned to enroll 39 participants but was stopped early due to the COVID-19 pandemic and the closure of gyms. Physician consent to participant in vigorous aerobic or resistance exercise and completion of a steep ramp test to determine maximal power output and heart rate were required to participate. Men with a contraindication to exercise, spinal cord instability, moderate or severe bone pain, and those with uncontrolled hypertension were not eligible. We further excluded men who self-reported ≥75 minutes/week of vigorous aerobic exercise or ≥3 sessions/week of resistance exercise at enrollment. All participants provided written consent and all study-related activities were done in accordance with the Declaration of Helsinki and under the supervision of the local Institutional Review Board.

2.2. Interventions

Participants were block (size 1-2) randomized 1:1:1 to aerobic exercise, resistance exercise, or usual care using the *blockrand* package in R [24]. Randomization was stratified based on whether men were on active treatment (other than ADT) at the time of enrollment. Study personnel assigning participants were blinded to allocation sequences. Allocation sequences were uploaded to the Research Electronic Data Capture (REDCap) [25] and schema were concealed from the coordinator who assigned study participants.

Detailed information about the interventions was reported previously [23]. Briefly, participants randomized to the aerobic exercise arm engaged in 3 aerobic exercise sessions per week for 12 weeks using a cycle ergometer. The program was mostly vigorous, and the moderate exercise was added to balance out exertion levels over the duration of the program, given the age of the study population and limitations. Two sessions were high-intensity interval training workouts and one was a continuous moderate-intensity workout. The resistance exercise arm consisted of 3 resistance exercise sessions per week for 12 weeks that included 8 exercises for the upper and lower body. One session was focused on high load and light volume, 1 session on light load and high volume, and the third on moderate load and moderate volume. Sessions progressed from 1 to 4 sets of 4 to 14 repetitions. The usual care arm was instructed to follow their typical exercise routine. Exercise prescriptions were tailored to each participant's baseline cardiorespiratory and strength assessments (Steep Ramp test, 1 Repetition Maximum chest press, leg press, leg extension, seated row) and based on clearance guidance from treating medical physicians. Given the nature of the intervention, participant blinding was not feasible.

Men visited UCSF at baseline and at 12 weeks. During the baseline visit, participants were provided with a Polar heart rate (HR) strap, which enabled remote monitoring by the exercise physiologist of the HR data in the Polar accounts each week. Participants were instructed to wear the HR monitor for all prescribed exercise sessions and to complete an online exercise survey via REDCap following each workout. Aerobic exercise participants reported whether they performed the aerobic exercise as prescribed; if not, they were asked to report more time/exceeded heart rate or less time/did not hit heart rate. Resistance exercise participants reported whether they performed the resistance exercise as prescribed; if not, they were asked to report how they changed the amount of sets, repetitions, and/or weight. Surveys were reviewed by the exercise physiologist to assess adherence and adverse events. Weekly check-ins (phone or email) were utilized to ensure compliance and address any concerns. The exercise physiologist discussed the surveys and Polar data with the participants on weekly calls and made a final adherence assessment. All study-related exercise was completed at an exercise facility near each participant's residence. Study personnel were available to aid participants in identifying a workout facility close to their residence and a 3-month membership was supported from the study budget.

2.3. Outcome assessments

We evaluated 8 secondary QoL outcomes specified *a priori*. Participants completed surveys at baseline and end of intervention (12 weeks). Participants were emailed a secure link to complete the surveys electronically.

QLQ-C30. The European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire − Core 30 (QLQ-C30) is a 30-item questionnaire used to measure cancer-specific health-related QoL [26]. QLQ-C30 includes 5 function scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, pain, nausea and vomiting), 6 symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global health status/QoL scale. Each scale ranges in score from 0 to 100 points. A higher score on the symptom scales or items reflects higher symptom burden, while a higher score for global QoL and functioning reflect better QoL or functioning. The QLQ-C30 scoring manual was used to calculate the scores [27]. Participants who responded to less than half of the scale components did not have a score calculated for that scale (i.e., treated as missing; n=4 for all sub-scores except diarrhea (n=5) and financial difficulties (n=6)). We used published guidelines for interpreting changes in QoL to quantify meaningful changes (see Table 4 in Cocks et al [28], which expanded on the 1998 published guidelines [29]).

EQ-5D. The EuroQol 5-dimensional (EQ-5D) questionnaire is used to assess health status [30,31]. We employed the newest version, the EQ-5D-5L, which asks respondents to report their difficulty on a 5-level scale (no problems, slight problems, moderate problems, severe problems, extreme problems) to each of 5 domains (mobility, self-care, usual activity, pain and discomfort, anxiety and depression) [32,33]. Additionally, respondents were asked to report overall health on a scale of 0 (worst health imaginable) to 100 (best health imaginable). The EQ-5D-5L User Guide was used to calculate the scores [34]. Participants who failed to respond to the questionnaire did not have a score calculated (i.e., treated as missing; n=5 for the 5 domains and n=7 for overall health).

EPIC-26. The Expanded Prostate Cancer Index Composite − 26 (EPIC-26) is a 26-item questionnaire used to assess prostate cancer-specific QoL. The EPIC-26 includes 5 domains (urinary incontinence, urinary irritative/obstructive, bowel, sexual, hormonal). Each domain ranges in score from 0-100, with a higher score reflecting better QoL. The EPIC-26 scoring manual was used to calculate the scores [35]; participants who failed to respond to at least 80% of the items contributing to any domain did not have a score calculated for that domain (i.e., treated as missing; n=4 for incontinence, n=5 or irritative/obstructive, n=6 for bowel; n=20 for sexual; n=8 for hormonal). The minimally important differences differ by domain: 6 to 9 for incontinence, 5 to 7 for irritative/obstructive, 4 to 6 for bowel, and 4 to 6 for hormonal [36]. We do not report on the sexual domain given that only 9 men provided a response at either baseline or 12 weeks.

FACIT-Fatigue. The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (version 4) is a 13-item validated self-reported questionnaire used to assess fatigue among older adults [37]. The FACIT-Fatigue score ranges from 0 to 52, with a higher score reflecting less fatigue burden; the mean value in the general population is 40.1 [37]. Consistent with the scoring guidelines, participants who failed to respond to at least 50% of the items did not have a score calculated (n=4).

FACT-G Social/Family Well-Being The Functional Assessment of Cancer Therapy − General (FACT-G) can be used to assess 4 different health-related QoL domains [37]. We used the Social/Family Well-Being (SFWB) domain of the FACT-G questionnaire to assess participants social and family well-being. FACT-G SFWB scores range from 0 to 28, with a higher score reflecting better social and familial well-being; the mean value for SFWB in the general population is 19.9 [37]. Consistent with the scoring guidelines, participants who failed to respond to at least 50% of the items did not have a score calculated (n=4).

STAI. State-Trait Anxiety Inventory (STAI) was used to measure participant anxiety. STAI consists of 2 sub-scales (Trait, State), each comprised of a 20-item assessment. The Trait subscale quantifies an individual's anxiety traits and is thus a relatively constant measure. Subsequently, the Trait assessment was only administered at study baseline. The State sub-scale measures an individual's current state of anxiety and was administered at enrollment and 12 weeks.

We used the State assessment to assess change in anxiety over the study period. Both the Trait and State scores range from 20 to 80, with higher scores reflecting greater anxiety. Participants who failed to respond to at least 80% of the items for either assessment did not have a score calculated for that assessment (i.e., treated as missing; n=4 for State).

CES-D. The Center for Epidemiological Studies Depression Scale (CES-D) is a 20-item questionnaire. Participants are asked to rate the frequency of depressive symptoms over the prior week from 0 (rarely or none of the time) to 3 (most or almost all of the time). Total scores range from 0 to 60 with higher scores indicating greater depressive symptoms. A score of 16 or higher identifies individuals at risk of clinical depression [38]. Participants who did not complete the questionnaire did not have a score calculated for that assessment (i.e., treated as missing; n=9). Prior research suggests an 11 point change reflects a minimally importance or clinically relevant change, though notably these assessments were made on prior versions of the CES-D [39].

PSQI. Sleep quality was assessed using the validated Pittsburgh Sleep Quality Index (PSQI) questionnaire [40,41]. The PSQI consists of 7 component scores summarizing potential sleep problems (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, daytime dysfunction). Component scores range from 0 (no difficulty) to 3 (severe difficulty) and are summed to generate a global PSQI score ranging from 0 (no difficulty) to 21 (severe difficulty in all areas). A global score <5 reflects good sleep quality [40]. Participants who did not complete the questionnaire did not have a score calculated (i.e., treated as missing; n=8).

2.4. Statistical analysis

Descriptive statistics of participants' sociodemographic and clinical characteristics are provided for each of the main QoL outcomes. Two-sample t-tests were used to compare mean change in patient-reported QoL measures from enrollment and 12-weeks among the 3 arms. Results are reported as mean change and 95% confidence intervals (CI). To compare the changes in QoL measure at 12-week to baseline QoL within arm, paired t-tests were used. We assessed for normality by visual assessment of smoothed density plots and quantile-quantile plots of the change scores, separately by combinations of arm and outcome.

As pre-planned secondary trial outcomes, all QoL analyses were conducted among men with complete follow-up data for the given metric. Consistent with guidelines for pilot trials, we focus on the patterns of change rather than statistical significance [42]. All analyses were conducted in R version 3.6.3.

3. Results

Of the 333 men screened with mCRPC, 25 were enrolled and randomized to remote aerobic exercise intervention (N=8), remote resistance exercise intervention (N=7), or were allocated to the control group (N=10). Primary reasons for exclusion were provider's discretion (e.g., comorbidities, new heart condition; n=88) and not meeting other inclusion criteria (n=123). Additional details, including all reasons for exclusion, were detailed in a prior publication [23]. Patients reported prior systemic therapies (non-mutually exclusive categories), including LHRH analog/antagonist (100%), abiraterone (56%), enzalutamide (28%), other antiandrogen treatments (92%), chemotherapy (20%), and Sipuleucel-T (48%). Full treatment history was reported previously [23]. Men were predominately white (76%) with a median age of 71 years (range: 51−84) and 10.5 years (range: 0.9-26.3) post prostate cancer diagnosis. Mean scores by various demographic and clinical characteristics are presented in Table 1. Men ≥71 years of age (vs. <71), men identifying as a race other than white (vs. white), and men within 10.5 years since initial diagnosis (vs. ≥10.5 years) reported worse QoL. By chance, men assigned to the control arm generally had higher QoL at baseline and those assigned to the aerobic arm generally had lower QoL [Table 1]. However, baseline QoL metrics were relatively high across all study arms, with 2 notable exceptions: sleep quality was poor (PSQI >5) and fatigue burden was high [37] [Tables 1−3].

The change (SD) between baseline and 12 weeks within each arm is shown in Tables 2 and 3. After the 12-week intervention, there was relatively little change from baseline within any of the study arms and no discernable trends emerged. For men randomized to resistance exercise, there was worsening of QoL on some of the subscales of the QLQ-C30 metric (role, emotional, and cognitive function; pain, insomnia, and diarrhea symptom burden), reflecting small-medium meaningful changes for all but role, but these did not result in a change in global QLQ-C30. There was also a minor decline in sleep quality (PSQI). Conversely, those in the resistance group showed some clinically meaningful improvement on EPIC-26 urinary irritative/obstruction domain and minor improvement in social and family well-being. For men randomized to aerobic exercise, there was again worsening of QoL on some of the subscales of the QLQ-C30 metric (physical, role, and cognitive function; appetite loss and constipation symptom burden), reflecting a small meaningful change for both appetite and constipation. There were clinically meaningful improvements (bowel) and declines (urinary irritative/obstruction) across domains of EPIC-26. Men in the aerobic exercise group also reported some improvements in sleep quality (PSQI) and non-meaningful depressive symptoms (CES-D) within the 12-week intervention. On an individual level, while most participants experienced improvement in depressive symptoms (declines in CES-D score) (Fig. 1), these were likely not clinically meaningful changes.

Comparisons in mean change (95% CI) over the study period between each study arm are shown in Tables 2 and 3. There was relatively little between arm changes for any of

Table 1
Mean (SD) baseline scorea by demographic and clinical characteristics of 25 men with metastatic castrate-resistant prostate cancer participating in a resistance or aerobic exercise pilot randomized clinical trial

Characteristic	*N* (%)[b]	QLQ-C30 Global Health Status[c]	EQ-5D-5L Overall Health (VAS)[c]	EPIC-26 Incontinence[c]	FACT-G Social/ Family Well Being[c]	FACIT-Fatigue[c]	PSQI[d]	STAI Trait[d]	CES-D[d]
Randomization Group									
Control	10 (40)	81.7 (13.5)	80.7 (7.9)	69.2 (11.3)	22.5 (4.7)	7.0 (8.4)	10.1 (3.2)	28.2 (7.4)	6.2 (5.5)
Aerobic	8 (32)	66.7 (26.0)	60.0 (20.7)	66.7 (11.9)	19.9 (3.9)	19.5 (12.5)	12.0 (2.8)	34.4 (11.4)	14.0 (9.8)
Resistance	7 (28)	80.6 (6.8)	57.0 (12.1)	72.9 (11.7)	19.5 (4.0)	8.3 (8.4)	9.0 (2.8)	25.9 (4.1)	5.3 (6.9)
Age									
≥71	14 (56)	71.8 (22.2)	65.0 (21.7)	65.1 (13.9)	20.5 (5.1)	11.7 (13.1)	10.8 (3.1)	29.4 (9.2)	7.8 (8.5)
<71	11 (44)	81.8 (11.1)	74.3 (11.2)	74.2 (3.8)	21.4 (3.4)	11.2 (8.9)	10.1 (3.2)	29.7 (8.3)	8.4 (7.3)
Race									
White	19 (76)	77.8 (17.4)	71.2 (18.1)	70.1 (10.1)	21.1 (4.4)	9.8 (9.9)	10.7 (3.2)	28.4 (8.4)	6.6 (6.7)
Other	6 (24)	72.2 (22.2)	63.8 (17.3)	66.7 (15.4)	20.2 (4.4)	16.4 (14.1)	10.0 (3.0)	33.0 (9.5)	12.2 (9.6)
Education									
≤ 4-Yr College	12 (48)	76.5 (17.0)	68.7 (18.1)	73.7 (4.4)	22.9 (3.4)	10.5 (8.4)	10.2 (3.4)	30.4 (10.8)	8.5 (8.1)
Grad/Prof School	13 (52)	76.3 (20.1)	70.2 (18.3)	65.5 (14.1)	19.2 (4.4)	12.3 (13.3)	10.7 (2.9)	28.7 (6.4)	7.8 (7.9)
Time Since DX									
≥10.5 yrs	13 (52)	79.5 (13.0)	70.2 (13.5)	66.3 (14.1)	21.6 (3.8)	10.3 (11.2)	10.1 (3.2)	25.8 (5.1)	5.4 (5.4)
<10.5 yrs	12 (48)	72.7 (23.3)	68.7 (21.6)	72.7 (5.8)	20.1 (4.9)	12.8 (11.5)	10.9 (3.1)	33.6 (10.0)	10.8 (9.0)
PSA Level at DX									
≥10 ng/mL	13 (52)	73.6 (20.4)	70.4 (19.1)	72.0 (6.7)	21.8 (5.1)	13.6 (11.8)	11.1 (3.2)	31.8 (10.0)	10.0 (8.9)
<10 ng/mL	12 (48)	79.2 (16.5)	68.1 (16.8)	66.5 (14.4)	19.9 (3.3)	9.4 (10.5)	9.9 (3.0)	27.1 (6.5)	6.5 (6.7)
Most recent PSA									
≥3.9 ng/mL	13 (52)	75.6 (18.8)	68.8 (17.8)	66.7 (13.0)	21.3 (4.1)	9.9 (12.8)	9.5 (2.4)	27.8 (7.0)	5.5 (5.9)
<3.9 ng/mL	12 (48)	77.3 (18.7)	70.3 (18.7)	72.3 (8.6)	20.5 (4.8)	13.3 (9.1)	11.6 (3.5)	31.4 (10.1)	11.2 (8.9)

Abbreviations: CES-D = Center for Epidemiological Studies Depression Scale; DX = diagnosis; EPIC = Expanded Prostate Cancer Index Composite; FACIT = Functional Assessment of Chronic Illness Therapy; FACT-G = Functional Assessment of Cancer Therapy-General; PSA = prostate specific antigen; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; STAI = State-Trait Anxiety Inventory; VAS = visual analogue scale; Yr = year.

[a] Mean scores are reported among participants who completed the baseline questionnaire; number of participants with incomplete baseline scores included: 1 for QLQ-C30, 4 for EQ-5D-5L VAS, 1 for EPIC-26 incontinence, 1 for FACT-G, 1 for FACIT Fatigue, 4 for PSQI, and 3 for CES-D.

[b] Reflects total men with each characteristic. See footnote a for information on item non-response.

[c] Higher score reflects better quality of life for the given measure.

[d] Higher score reflect worse quality of life for the given measure.

Table 2
Mean change in quality of life (QLQ-C30) observed among men with metastatic castrate-resistant prostate cancer participating in a resistance or aerobic exercise pilot randomized trial.

	Control (n=10)			Resistance (n=7)				Aerobic (n=8)				
	n[a]	Baseline (SD)	Within (SD)[b]	n[a]	Baseline (SD)	Within (SD)[b]	Versus control (CI)[c]	n[a]	Baseline (SD)	Within (SD)[b]	Versus control (CI)[c]	Versus resistance (CI)[d]
Global Health[e]	10	81.7 (13.5)	0.8 (6.1)	6	80.6 (6.8)	-1.4 (3.4)	-2.2 (-7.3, 2.9)	5	66.7 (26.0)	-5.0 (11.2)	-5.8 (-19.4, 7.8)	-3.6 (-17.3, 10.1)
Physical Function[e]	10	93.3 (9.9)	-6.0 (8.6)	6	96.7 (5.6)	-1.1 (5.0)	4.9 (-2.4, 12.2)	5	91.7 (5.9)	-1.3 (9.9)	4.7 (-7.6, 16.9)	-0.2 (-12.3, 11.9)
Role Function[e]	10	90.0 (16.1)	1.7 (16.6)	6	97.2 (6.8)	-5.6 (22.8)	-7.2 (-31.7, 17.3)	5	85.4 (20.8)	-3.3 (7.5)	-5.0 (-18.4, 8.4)	2.2 (-21.7, 26.2)
Emotional Function[e]	10	93.3 (15.6)	0.8 (4.7)	6	100.0 (0.0)	-5.6 (6.8)	-6.4 (-13.7, 0.9)	5	84.4 (20.1)	0.0 (5.9)	-0.8 (-8.1, 6.4)	5.6 (-3.1, 14.2)
Cognitive Function[e]	10	88.3 (20.9)	-5.0 (11.2)	6	94.4 (8.6)	-8.3 (17.5)	-3.3 (-21.9, 15.3)	5	87.5 (17.3)	-3.3 (7.5)	1.7 (-9.0, 12.3)	5.0 (-13.6, 23.6)
Social Function[e]	10	95.0 (11.2)	-13.3 (17.2)	6	97.2 (6.8)	0.0 (10.5)	13.3 (-1.6, 28.2)	5	77.1 (26.6)	0.0 (0.0)	13.3 (1.0, 25.6)	0.0 (-11.1, 11.1)
Fatigue[f]	10	24.4 (20.2)	-2.2 (12.6)	6	16.7 (18.3)	0.0 (17.2)	2.2 (-16.3, 20.8)	5	36.1 (27.1)	4.4 (6.1)	6.7 (-3.8, 17.1)	4.4 (-13.7, 22.6)
Nausea/Vomiting[f]	10	6.7 (16.1)	-6.7 (16.1)	6	0.0 (0.0)	0.0 (0.0)	6.7 (-4.9, 18.2)	5	0.0 (0.0)	3.3 (7.5)	10.0 (-3.1, 23.1)	3.3 (-5.9, 12.6)
Pain[f]	10	5.0 (11.2)	10.0 (16.1)	6	16.7 (21.1)	8.3 (13.9)	-1.7 (-18.3, 15.0)	5	29.2 (14.8)	3.3 (13.9)	-6.7 (-24.8, 11.5)	-5.0 (-24.2, 14.2)
Dyspnea[f]	10	6.7 (14.1)	3.3 (18.9)	6	5.6 (13.6)	-5.6 (13.6)	-8.9 (-26.5, 8.7)	5	8.3 (15.4)	-6.7 (14.9)	-10.0 (-29.9, 9.9)	-1.1 (-21.0, 18.8)
Insomnia[f]	10	23.3 (27.4)	3.3 (18.9)	6	0.0 (0.0)	16.7 (27.9)	13.3 (-16.5, 43.1)	5	29.2 (37.5)	0.0 (23.6)	-3.3 (-32.3, 25.6)	-16.7 (-51.8, 18.4)
Appetite loss[f]	10	6.7 (14.1)	0.0 (15.7)	6	0.0 (0.0)	0.0 (0.0)	0.0 (-11.2, 11.2)	5	4.2 (11.8)	13.3 (18.3)	13.3 (-9.2, 35.9)	13.3 (-9.3, 36.0)
Constipation[f]	10	10.0 (22.5)	-3.3 (29.2)	6	11.1 (27.2)	0.0 (0.0)	3.3 (-17.5, 24.2)	5	12.5 (17.3)	6.7 (14.9)	10.0 (-14.6, 34.6)	6.7 (-11.8, 25.2)
Diarrhea[f]	10	3.3 (10.5)	-3.3 (10.5)	6	0.0 (0.0)	11.1 (27.2)	14.4 (-14.0, 42.9)	4	16.7 (25.2)	-8.3 (16.7)	-5.0 (-29.9, 19.9)	-19.4 (-51.5, 12.6)
Financial Difficulty[f]	8	11.1 (23.6)	0.0 (17.8)	6	11.1 (27.2)	0.0 (0.0)	0.0 (-14.9, 14.9)	5	29.2 (27.8)	0.0 (23.6)	0.0 (-29.2, 29.2)	0.0 (-29.3, 29.3)

Abbreviations: CI = 95% Confidence Interval; SD = standard deviation.

[a] Reflects the number of men who responded to relevant questions at baseline and 12 weeks and, thus, could be included in the change analyses. There were 2 (financial difficulty) or 1 (all others) non-responses at baseline. There were 4 (diarrhea), 6 (financial difficulty), or 3 (all others) non-responses at 12-weeks.

[b] Comparison of the change between baseline and 12 weeks within study arm.

[c] Comparison of the baseline to 12-week change between the treatment arm compared to control arm.

[d] Comparison of the baseline to 12-week change between aerobic arm and resistance arm.

[e] Higher score reflects better quality of life for the given measure; thus, a positive change score reflects improvement.

[f] Higher score reflects worse quality of life for the given measure; thus, a negative change score reflects improvement.

Table 3
Change in health-related quality of life measures observed among men with metastatic castrate-resistant prostate cancer participating in a resistance or aerobic exercise pilot randomized trial.

	Control (n=10)			Resistance (n=7)				Aerobic (n=8)				
	n[a]	Baseline (SD)	Within (SD)[b]	n[a]	Baseline (SD)	Within (SD)[b]	Versus control (CI)[c]	n[a]	Baseline (SD)	Within (SD)[b]	Versus control (CI)[c]	Versus resistance (CI)[d]
EQ-5D-5L[e]												
Index	10	0.9 (0.1)	0.0 (0.1)	6	0.9 (0.1)	0.0 (0.1)	0.0 (-0.1, 0.0)	4	0.8 (0.1)	0.0 (0.0)	0.0 (0.0, 0.1)	0.1 (0.0, 0.1)
VAS	10	80.7 (7.9)	2.3 (9.6)	3	57.0 (12.1)	19.3 (13.7)	17.0 (-12.1, 46.2)	5	60.0 (20.7)	2.6 (15.2)	0.3 (-18.2, 18.8)	-16.7 (-43.9, 10.4)
EPIC-26[e]												
Urinary Incontinence	10	69.2 (11.3)	-3.1 (8.9)	6	72.9 (11.7)	-1.0 (11.1)	2.1 (-10.0, 14.2)	5	66.7 (11.9)	3.3 (7.0)	6.5 (-2.9, 15.8)	4.4 (-8.2, 16.9)
Irritative/Obstruction	10	91.2 (7.9)	-1.9 (6.6)	5	81.2 (23.0)	11.2 (13.5)	13.1 (-3.4, 29.6)	5	87.5 (11.6)	-8.8 (13.0)	-6.9 (-22.6, 8.9)	-20.0 (-39.3, -0.7)
Bowel	9	97.7 (2.2)	0.0 (5.1)	5	95.8 (5.9)	2.5 (3.7)	2.5 (-2.8, 7.8)	5	83.9 (23.9)	6.7 (17.8)	6.7 (-15.2, 28.6)	4.2 (-17.7, 26.1)
Vitality/Hormone	7	88.5 (12.5)	-5.0 (13.8)	5	81.7 (15.7)	4.0 (12.4)	9.0 (-8.2, 26.2)	5	66.9 (20.3)	-1.0 (4.2)	4.0 (-9.0, 17.0)	-5.0 (-20.2, 10.2)
FACT-G SFWB[e]	10	22.5 (4.7)	0.6 (3.7)	6	19.5 (4.0)	1.8 (2.7)	1.3 (-2.2, 4.7)	5	19.9 (3.9)	2.0 (2.1)	1.4 (-1.8, 4.7)	0.2 (-3.1, 3.5)
FACIT-Fatigue[e]	10	7.0 (8.4)	1.0 (3.7)	6	8.3 (8.4)	1.1 (5.0)	0.1 (-5.3, 5.5)	5	19.5 (12.5)	-1.4 (4.7)	-2.5 (-8.2, 3.3)	-2.5 (-9.2, 4.2)
PSQI[f]	9	10.1 (3.2)	0.2 (2.1)	4	9.0 (2.8)	1.0 (1.6)	0.8 (-1.7, 3.3)	4	12.0 (2.8)	-1.5 (3.7)	-1.7 (-7.3, 3.8)	-2.5 (-8.0, 3.0)
STAI State[f]	10	24.4 (5.2)	0.6 (3.4)	6	22.4 (3.4)	0.6 (2.4)	-0.1 (-3.2, 3.1)	5	33.9 (13.3)	1.4 (11.9)	0.8 (-13.8, 15.4)	0.8 (-13.8, 15.5)
CES-D[f]	8	6.2 (5.5)	-1.0 (4.6)	4	5.3 (6.9)	0.8 (2.2)	1.8 (-2.7, 6.2)	4	14.0 (9.8)	-2.2 (2.5)	-1.2 (-5.9, 3.4)	-3.0 (-7.1, 1.1)

Abbreviations: CES-D = Center for Epidemiological Studies Depression scale; CI = 95% Confidence Interval; EPIC = Expanded Prostate Cancer Index Composite; FACIT = Functional Assessment of Chronic Illness Therapy; FACT-G = Functional Assessment of Cancer Therapy-General; PSQI = Pittsburgh Sleep Quality Index; SD = Standard Deviation; SFWB = Social/Family Wellbeing; STAI = State-Trait Anxiety Inventory; VAS = visual analogue scale.

[a] Reflects the number of men who responded to relevant questions at baseline and 12 weeks and, thus, could be included in the change analyses. EQ-5D-5L: there were 2 (index) and 4 (VAS) non-responses at baseline and 3 (index) and 4 (VAS) at 12 weeks. EPIC-26: there were 1 (incontinence, hormonal), 2 (irritative), and 3 (bowel), non-responses at baseline. There were 3 (incontinence, irritative, bowel), and 8 (hormonal), non-responses at 12 weeks. FACT-G: there was 1 non-response at baseline and 3 at 12 weeks. FACIT: there was 1 non-response at baseline and 4 at 12 weeks. STAI (State): there was 1 non-response at baseline and 3 at 12 weeks. PSQI: there were 4 non-responses at baseline and 6 at 12 weeks. CES-D: there were 3 non-responses at baseline and 9 at 12 weeks.

[b] Comparison of the change between baseline and 12 weeks within study arm.

[c] Comparison of the baseline to 12-week change between the treatment arm compared to control arm.

[d] Comparison of the baseline to 12-week change between aerobic arm and resistance arm.

[e] Higher score reflects better quality of life for the given measure; thus, a positive change score reflects improvement.

[f] Higher score reflects worse quality of life for the given measure; thus, a negative change score reflects improvement.

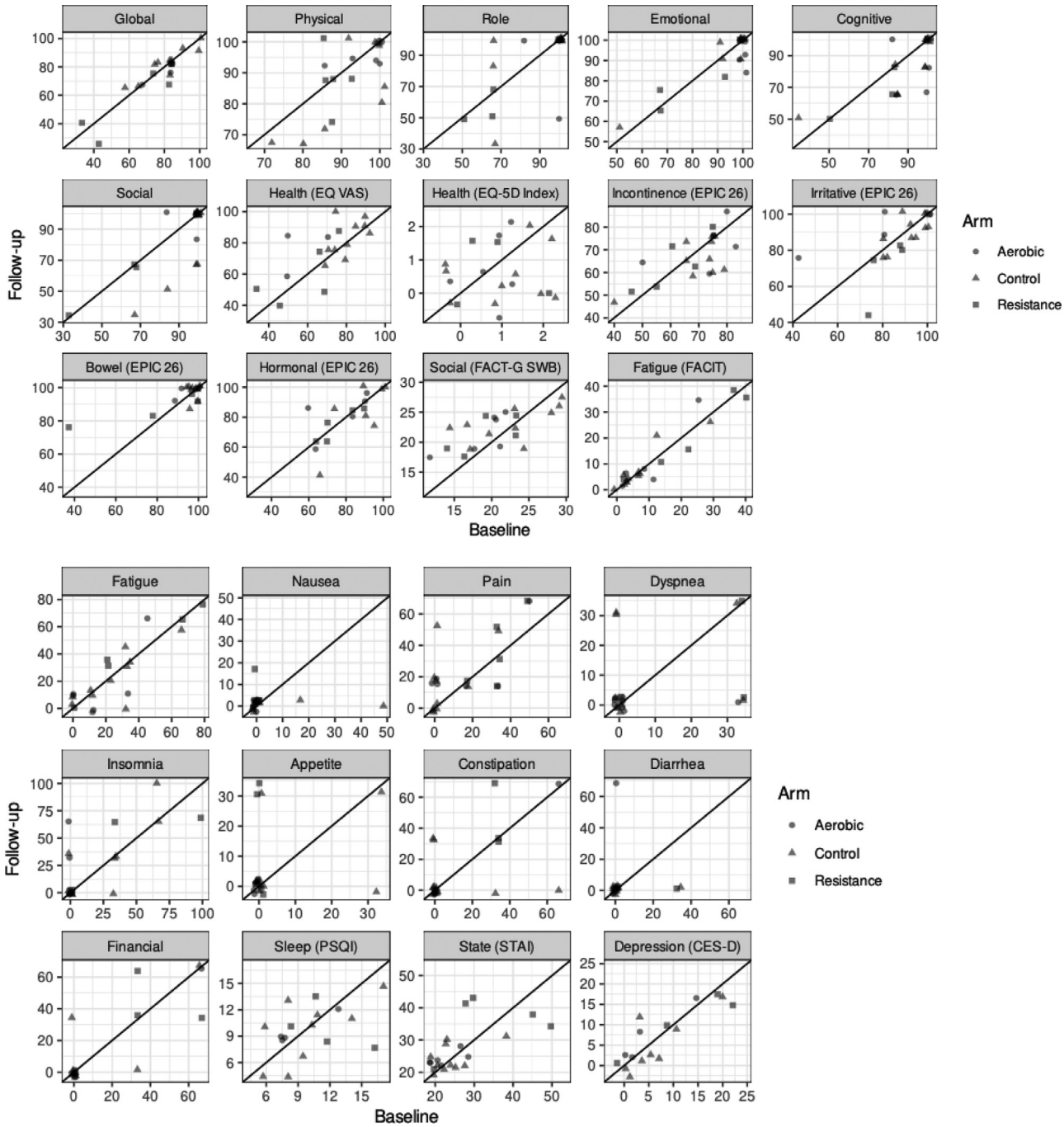

Fig. 1. Baseline and 12-week score for men with metastatic prostate cancer participating in a resistance or aerobic exercise pilot randomized trial Figure plots the baseline and 12-week (follow-up) score for each individual participant. Points on the diagonal reflect scores that did not change (exactly equal) between baseline and follow-up. Figure 1A (top panel) includes quality of life metrics where a higher score reflects better quality of life. Thus, points above the diagonal line reflect improvements in quality of life between baseline and 12 weeks. Figure 1B (bottom panel) includes quality of life metrics where a lower score reflects better quality of life. Thus, points below the diagonal line reflect improvements in quality of life between baseline and 12 weeks.

the study arms. Compared to the control arm, the resistance group reported some (meaningful) improvements in QoL (EQ-5D-5L; EPIC-26 Urinary Irritative/Obstruction), while the aerobic group reported some improvements in urinary incontinence (non-meaningful) and a small, meaningful worsening of nausea/vomiting. Compared to the control group, both active groups also reported improvements in social function (QLQ-C30). Compared to the resistance exercise group, the aerobic exercise group experienced meaningfully worse urinary irritative/obstruction symptoms (EPIC-26) and declines in self-rated QoL (EQ-5D-5L visual analogue scale) yet some small-medium meaningful improvements in emotional function, insomnia, and diarrhea (QLQ-C30). No other notable changes were observed.

4. Discussion

We observed little change in QoL outcomes among men with mCRPC participating in a pilot, 12-week, remotely monitored aerobic or resistance exercise intervention. There are several plausible reasons for these results. First, this is a small pilot study designed to assess the feasibility, acceptability, and safety of the exercise interventions and it is possible that the small sample size precluded observing modest differences. Alternatively, it is possible that these physical activity interventions may not be effective at changing QoL among men with mCRPC or that the duration of the intervention was not sufficient to observe any potential effects. A 2012 review of 21 supervised and non-supervised clinical exercise studies (aerobic, resistance, endurance, and/or pelvic strengthening) among men with prostate cancer reported that more than half of them were longer than 12 weeks, and most of those were 6 months or longer [21]. Among the 7 studies that evaluated changes in QoL following a 12 week or less exercise intervention, 4 found improvement and 3 reported no change. However, among the 11 studies that evaluated changes in QoL following exercise interventions longer than 12 weeks, 8 reported improvements while 3 reported no change. Studies that reported improved QoL included resistance or endurance training whereas those that reported no change utilized home-based walking programs.

Despite the well-documented effects of mCRPC treatment on diminished QoL [8−15], men in this study had markedly high QoL at baseline on most measures except sleep quality and fatigue. This might be because men who volunteer to participate in research studies, and in particular for exercise intervention trials, tend to be among the healthiest of the sick. These high baseline values could create a ceiling effect that may explain the limited influence of the intervention on QOL. If true, then results of this pilot trial may not inform the potential effects of exercise interventions among the general mCRPC population. Subsequently, future studies focused on QoL as a primary endpoint would benefit from limiting enrollment to men with lower baseline QoL. The fact that the intervention was shown to be feasible, acceptable, and, safe should ease concerns about encouraging such interventions in men with mCRPC [23]. This safety profile is consistent with 2 recent exercise trials among men with bone metastases [43,44]. Another consideration for future studies is to enroll men with metastatic prostate cancer who are ADT naive, in whom ADT treatment effects may be more pronounced, and therefore potentially subject to greater benefit from exercise.

Only 9 men completed the sexual function questions at baseline or end of study, so we were unable to report these data. Future studies should consider ways to remedy missingness on highly sensitive questions and consider non-response rates when performing sample size and power calculations.

Interestingly, the patterns of the between arm comparisons in this study suggest that resistance exercise may provide some additional benefit to improving QoL over aerobic exercise. This would be consistent with a study that compared the effects of a 24-week intervention of either resistance or aerobic exercise vs usual care among men with prostate cancer undergoing radiation therapy [45]. The study found that men in both exercise groups reported improvements in QoL at 12 weeks, but the effect was only sustained at 24 weeks for men who participated in resistance exercise. The resistance exercise intervention was similar to that used in this study: 3 sessions per week with 2 sets of 8 to 12 repetitions of 10 exercises. Further study is necessary to determine if there is truly a benefit of resistance over aerobic exercise for QoL among men with mCRPC rather than a chance observation.

There are additional limitations to consider. This pilot trial was not powered to detect differences for these secondary outcomes. There were also slight differences in baseline QoL measures across groups, which occurred by chance due to the small sample size. Relatedly, there is some overlap in the health domains that were examined across surveys, which complicates the interpretation. Unless a specific instrument is of interest, future studies should consider using QLQ-C30, EQ-5D-5L, and EPIC-26 to limit participant burden. Finally, most patients were primarily white, married, and highly educated. Black/African-American men bear a greater burden of prostate cancer morbidity and mortality and are under-represented in behavioral intervention trials [19,46,47]. Future studies should strive to reach more diverse populations.

This pilot randomized control trial of 2 12-week remotely monitored exercise interventions did not appear to have a meaningful impact on QoL metrics among men with mCRPC. However, given the relatively high baseline QoL of this study population, investigations into the potential of this approach to improve QoL among the general mCRPC population may still be warranted. Further integration of participants' fatigue and sleep reporting within the intervention may help to improve these metrics. Given the safety profile of this intervention [23], future exercise studies are warranted. And considering a change to the decentralized gym and the use of electronic surveys, the intervention employed in this trial is scalable. An important goal of pilot trials is to improve future research; future studies might consider the following recommendations: a) attempt to limit enrollment to men with self-reported poor QoL in addition to poor exercise habits; b) consider enrolling men who are about to embark on ADT; c) expand the intervention's focus and evaluate QoL metrics as primary outcomes; d) use a limited number of QoL surveys to minimize patient burden, e) focus on enrolling racially/ethnically and socioeconomically diverse populations; and f) increase the duration of the exercise intervention. The INTERVAL trial (NCT04507698), an ongoing phase III 2-year trial of exercise in men with mCRPC and mHSPC, is well-suited to address these questions in future analyses [48].

Ethics Approval & Consent

All participants provided written consent and all study-related activities were done in accordance with the Declaration of Helsinki and under the supervision of the local Institutional Review Board.

Availability of Data & Materials

Data are available for bona fide researchers who request it from the authors.

Contributions

Conceptualization: SAK, EVB, CJR, LZ, RUN, AL, and JMC. Data curation: SAK, NP, ASB, EL, NP. Formal analysis: YHC. Methodology: CSL, YHC, SAK. Project administration: SAK. Writing − Original: CSL. Writing − review and editing: All authors.

Conflicts of Interest

None related to the research.

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