Support Care Cancer (2014) 22:1537–1548
DOI 10.1007/s00520-013-2103-1

ORIGINAL ARTICLE

Functional benefits are sustained after a program of supervised resistance exercise in cancer patients with bone metastases: longitudinal results of a pilot study

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Received: 9 July 2013 / Accepted: 12 December 2013 / Published online: 15 January 2014

Abstract
Introduction Exercise may represent an effective adjunct therapy to current medical management strategies for maintaining functional independence and improving quality of life in cancer patients with bone metastatic disease. However, it has yet to be determined if there are any sustained effects following the completion of an exercise program by patients with bone metastases.
Purpose The aim of this study is to determine whether a 3-month supervised resistance exercise program results in any sustained functional benefits in prostate and breast cancer patients with bone metastatic disease.
Methods Twenty men and women with bone metastatic disease secondary to prostate or breast cancer completed a 3-month supervised resistance exercise program followed by a 6-month observation period. Outcomes were assessed at baseline, post-exercise, and 6-month follow-up.
Results Fourteen participants completed the follow-up observation period. Significant improvements in physical function (4–6 %), physical activity levels (~160 min/week), lean mass (3–4 %), and quality of life (5–7 %) were observed at the completion of the exercise program. At the 6-month follow-up, significant improvements in ambulation (4 %), physical activity level (~105 min/week), whole body lean mass (2 %), and quality of life (13 %) remained.
Conclusions An appropriately designed and supervised 3-month resistance exercise program may lead to significant improvements in functional ability, physical activity level, lean mass, and quality of life that remain 6 months after completion of the program in cancer patients with bone metastases. Future trials involving larger sample sizes are required to expand these preliminary findings.

Keywords Bone metastases · Physical activity · Advanced cancer · Physical function

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Introduction

Bone metastases are most prevalent in patients with prostate and breast cancer, with these two primary cancer sites estimated to account for 80 % of all bone metastatic disease cases [5]. Autopsy data suggests the incidence of bone metastases to be approximately 65–75 % in prostate and breast cancer patients [5]. Skeletal complications resulting from bone metastatic disease commonly include bone pain, fractures, spinal cord compressions, and, although rare in prostate cancer patients, hypercalcemia [33]. These complications are a major cause of morbidity which has a profound impact on quality of life (QoL) as well as considerable economic cost for the patient and health care system [16, 35, 44]. Given the relatively long clinical course of bone metastatic disease (5-year survival rate of prostate and breast cancer patients with bone lesions are 46 and 64 %, respectively [5]), strategies to decrease the morbidity of bone metastatic disease are vitally important.

In the absence of bone-targeted therapy, the annual rate of skeletal-related events (SREs; i.e., radiotherapy to bone, pathological fracture, surgery to bone, spinal cord compression) is approximately 1.5 and 4.0 per person in prostate and breast cancer patients, respectively [23, 25]. SREs result in significant reductions in functional ability and QoL [16, 23, 35, 44], further accentuating the already reduced capacity resulting from accumulated cancer treatments in these advanced patients. Of concern, pathological fractures have been associated with a significantly increased risk of death in patients with bone metastatic disease [34]. Current therapy for bone metastatic disease centers on reducing the incidence and associated morbidity of SREs in an attempt to maintain and/or increase functional ability, QoL, and survival [6, 26, 37, 46]. Given these goals, exercise may represent an important adjunct therapy to current medical management strategies.

Exercise has established efficacy for counteracting many adverse side effects of cancer treatment, including leading to improved functional ability and QoL [8, 32, 38]. Furthermore, emerging observational evidence indicates that physical activity is associated with a significant reduction in relative risk of mortality in both prostate and breast cancer patients [8, 18, 22]. Apart from initial recommendations to alter exercise intensity, duration, and mode and avoid impact-loading activities, no exercise prescription guidelines exist for patients with bone metastases given their heightened risk of SREs [32, 38] and conservative advice is to avoid exercise [11, 14, 39, 40], despite well-established health risks of such a strategy [13, 35]. Our team recently published the first randomized controlled trial of a resistance exercise program specifically designed for prostate cancer patients with bone metastatic disease [7]. This trial established that appropriately designed and supervised resistance exercise targeting skeletal regions not affected by bone lesions may be safe and well tolerated by prostate cancer patients with bone metastatic disease and can lead to improved physical function, physical activity levels, and lean muscle mass [7]. Such changes are expected to alleviate morbidity and promote prolonged independence, providing initial evidence of the potential role of exercise in the effective management of bone metastatic disease.

However, it has yet to be determined if there are any sustained effects following the completion of an exercise program that could counteract the progressive morbidity and diminished QoL experienced by patients with bone metastases. Here, we investigate whether a 3-month supervised resistance exercise program results in sustained functional benefits, enhanced QoL, and body composition in prostate and breast cancer patients with bone metastatic disease. If established as safe and efficacious for longer-term benefit, such exercise medicine could have significant impact in alleviating suffering and preserving QoL for these patients with little cost and no additional toxicity burden. Furthermore, emerging research involving animal models suggests that the mechanical loading of bone involved with exercise may inhibit osteolytic capability and formation of metastatic tumors. Although loading did not induce tumor cell death per se, these findings indicate the exciting possibility of prescribing exercise to attenuate the progression of bone metastatic disease [27].

Methods

Participants

Oncologists and urologists in Perth, Western Australia referred 30 people with bone metastatic disease secondary to prostate or breast cancer from July 2011 through August 2012 and screened for participation in the study (Fig. 1). Inclusion criteria were (1) a histological diagnosis of prostate or breast cancer, (2) established bone metastatic disease as determined by a whole body bone scan, and (3) medical clearance obtained from the participant's physician. Exclusion criteria were (1) moderate-severe bone pain that limited activities of daily living (i.e., National Cancer Institute's Common Terminology Criteria for Adverse Events grade 2–3 bone pain [29]), and (2) musculoskeletal, cardiovascular, and/or neurological disorders that could inhibit participants from exercising. This protocol was approved by the University Human Research Ethics Committee and all participants provided written informed consent.

Experimental design

This study involved a single-group (uncontrolled) longitudinal design. Participants completed a 3-month resistance exercise program specifically designed for patients with bone metastatic disease followed by an observation period of 6 months. No formal advice or instruction was provided to participants during the observation period.

Outcome measures

Outcome measures were assessed at baseline (0 months), post-exercise intervention (3 months), and 6-month follow-up

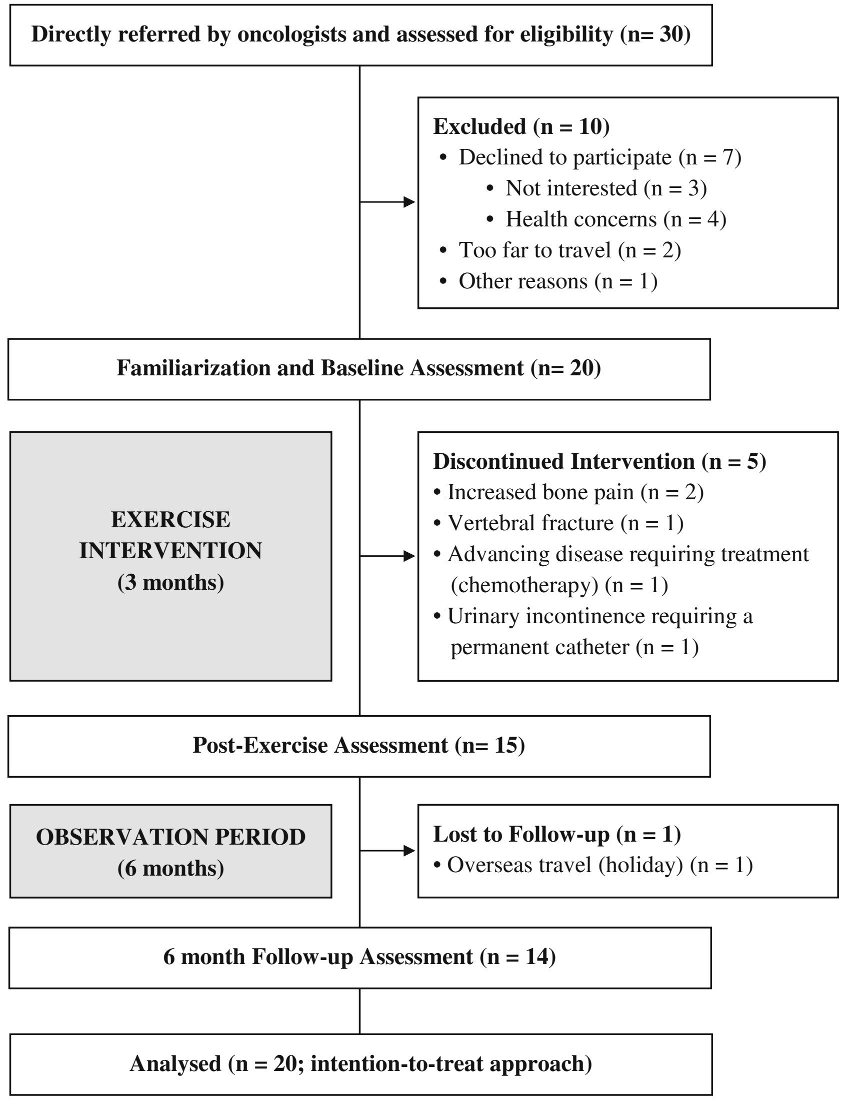

Fig. 1 Flow of participants throughout trial

(9 months). Participants completed a familiarization session 7–10 days prior to baseline testing involving all physical function assessments.

Safety and tolerability of exercise The safety and tolerability of the exercise program was evaluated using a series of measures. The incidence and severity of any adverse events and skeletal complications [5] were recorded throughout the intervention and follow-up periods using a detailed log. Bone pain was assessed using the Functional Assessment of Cancer Therapy Bone Pain questionnaire (FACT-BP; higher scores representing lesser bone pain and/or better QoL) [30] and a visual analogue scale (VAS) [31], including severity ratings from no pain (0) to very severe pain (10). Serial assessments of bone pain were also recorded prior to the start of each exercise session using the VAS. The location of any bone pain and whether this pain affected their ability to undertake usual activities of daily living since the previous exercise training session was also recorded. Exercise session attendance was tracked and compliance to the prescribed exercise program was assessed as the rate of successfully completed exercise sessions compared to the number of sessions attended. Non-compliance to an exercise session was considered as any deviation from the prescribed number of exercises, sets, or repetitions. Session rating of perceived exertion (RPE) was recorded immediately after the completion of each exercise session to assess the perceived intensity of the exercise [4]. Perceived tolerance of the exercise session was also assessed using a 7-point Likert scale administered after the completion of each exercise session [7].

Physical function and physical activity levels A series of standard tests were used to assess the following physical function [14]: (1) one repetition maximum (1 RM) in leg extension, (2) 400-m walk, (3) usual and fast pace 6-m walk, (4) timed up and go, and (5) the sensory organization test performed on the NeuroCom Smart Balance Master (NeuroCom, OR, USA). To minimize the potential risk of skeletal complications, participants with bone metastases affecting the femur did not perform the leg extension 1 RM and 400-m walk assessments (n=6) given that these activities place high musculoskeletal demands on the lower body. The Activities-Specific Balance Confidence scale assessed falls self-efficacy with higher score representing greater balance confidence [28]. Self-reported physical activity was assessed by the Godin Leisure-Time Exercise Questionnaire [21].

Body composition Regional and whole body bone mineral-free lean mass and fat mass were derived from whole body dual-energy X-ray absorptiometry scans (DXA; Hologic Discovery A, Waltham, MA). Appendicular lean mass, trunk adiposity, and visceral fat mass were assessed using standard procedures. Bone mineral density (BMD, in grams per square centimeter) of the total hip was also assessed using DXA. Patients with bone lesions in the proximal femur region were scanned on the non-affected side.

Patient-reported outcomes A series of questionnaires with sound psychometric properties were utilized to assess QoL (Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36]) [43], psychological distress (Brief Symptom Inventory-18 [BSI]) [47], and cancer-related fatigue (Multidimensional Fatigue Symptom Inventory-Short Form [MFSI-SF]) [41].

Exercise intervention

The exercise program has been described previously [7]. Briefly, participants completed twice weekly resistance exercise sessions, undertaken in small groups of up to five participants for approximately 60 min per session, under the supervision of an accredited exercise physiologist. Eight exercises that targeted the major muscle groups were performed with the specific selection based on a modular approach (Table 1) so that affected regions were not loaded and mechanical force on these structures minimized [7]. Exercises were performed at a set cadence of 1–2 s for both eccentric and concentric phases in order to minimize peak forces transmitted to the skeleton, and progressed from 12 to 8 RM with two to four sets per exercise [14, 38]. The participant's response to the exercise program was monitored using defined procedures to track bone pain at every exercise session. If increases in the severity and/or location of pain were observed, the exercise program was modified and referral for appropriate specialist care was provided if necessary (i.e., severity of pain increased dramatically, an increase in pain was sustained over consecutive exercise sessions and/or the pain negatively impacted ability to perform activities of daily living). In addition to the resistance exercise sessions, participants were encouraged to undertake home-based aerobic exercise sessions of walking and/or stationary cycling, with the aim of accumulating a total of 150 min of moderate intensity aerobic exercise each week [32, 38].

Table 1 The systematic approach to selecting resistance exercises for prostate and breast cancer patients with bone metastatic disease based on the location of the bone lesions

Metastases site	Body region to target		
	Upper body	Trunk	Lower body
Pelvis	√	√	√**
Lumbar spine	√	–	√
Thoracic spine and/or ribs	√*	–	√
Femur	√	√	√**
Humerus	√*	√	√
All regions	√*	–	√**

√=target exercise region; *=exclusion of shoulder flexion/extension/abduction/adduction—inclusion of elbow flexion/extension; **=exclusion of hip extension/flexion—inclusion of knee extension/flexion

Statistical analyses

Data were analyzed using SPSS Statistics 20. Analyses including standard descriptive statistics and repeated measures analysis of variance. Measures of bone pain were adjusted for use of pain medication. An intention-to-treat approach was utilized for all analyses using maximum likelihood imputation of missing values (expectation maximization). All tests were two-tailed with statistical significance set at an alpha level of 0.05. Results are presented as mean±standard deviation or number of participants (percentage of participants) for frequency data. With an alpha level of 0.05 and a sample of 20 patients, we achieved 92 % statistical power to detect a moderate-large standardized effect (d=0.8) in outcomes.

Results

Despite differences between prostate and breast cancer patients at baseline in bone pain (women reported greater pain levels, p=0.011–0.031) and body composition measures, the response to the exercise intervention and observation period was similar between sexes. As such, analyses for the prostate and breast cancer patients were performed together.

Participant characteristics Participant characteristics are outlined in Table 2. Enrolled participants had significant bone metastatic disease load with 65 % presenting with two or more affected skeletal regions and 30 % of participants regularly using prescribed pain medication. Five male participants discontinued the resistance exercise program due to increased bone pain (n=1, related to events outside of the intervention, completed 3 exercise sessions; n=1, increase in preexisting pain level requiring radiation therapy, completed 12 exercise sessions), vertebral fracture (n=1, preexisting pain in thoracic spine increased leading to referral to clinician and confirmation of fracture, completed five exercise sessions), advancing disease requiring treatment with chemotherapy (n=1, completed nine exercise sessions), and unrelated health complication (n=1, urinary incontinence requiring a permanent catheter which the participant was not comfortable continuing to exercise with, completed seven exercise sessions). Participants who did not complete the exercise intervention had a significantly longer time since cancer diagnosis (withdrew=6.2±4.7 years vs. completed=2.8±2.5 years, p=0.050) as well as a trend towards higher Gleason score (withdrew=8.8±0.8 vs. completed=8.0±0.9, p=0.082). There were no other demographic or clinical differences between those who did and did not complete the intervention. One participant was lost to follow-up due to overseas travel (holiday).

Safety of the resistance exercise intervention No adverse events occurred during the supervised resistance exercise sessions (Table 3). However, three participants experienced a SRE requiring them to withdraw from the program (described above), and there were two falls reported outside of the supervised exercise sessions. One fall occurred while a participant was dressing at home which resulted in a fractured rib and the other occurred during a participant's walk around her neighborhood (no skeletal complications occurred). Both participants were able to continue the exercise intervention with clinician approval and appropriate modifications in exercise prescription. There was one fall reported during the observation period which occurred during an external exercise program that the participant pursued personally but did not cause any skeletal complications. There were no significant changes in bone pain between baseline, post-exercise, and 6-month follow-up assessment points, although there was a trend towards increased perception of pain determined by the VAS (Table 4). Three participants received radiation to the bone during the exercise intervention, two of which continued to receive radiation during the observation period. One of these participants was prescribed pain medications during the exercise intervention for increasing pain in a region of preexisting pain, which was continued

Table 2 Baseline characteristics of participants

Characteristic	n (%) or mean ± SD
Gender – Male	17 (85)
– Female	3 (15)
Age (years)	70.0±9.8
Height (cm)	171.4±9.3
Weight (kg)	83.9±13.9
BMI (kg/m^2)	28.5±3.5
Number of comorbidities[a]	1.6±1.1
Number of medications	4.1±2.1
Tertiary education	5 (25)
Married	16 (80)
Current smoker	0 (0)
Self-rated health[b]	3.0±0.9
Cancer type - prostate	17 (85)
- Breast	3 (15)
Time since cancer diagnosis (years)	3.6±3.4
Time since bone metastatic disease diagnosis (years)	1.1±1.0
Location of bone lesions	
Pelvis	15 (75)
Lumbar spine	12 (60)
Ribs/thoracic spine	14 (70)
Femur	6 (30)
Humerus	4 (20)
Other	7 (35)
Severity of bone metastatic disease	
Minor (1 region affected)	7 (35)
Moderate (2 regions affected)	4 (20)
Major (>2 regions affected)	9 (45)
Number of regions affected	2.9±1.9
Using pain medication	6 (30)
Bone pain (VAS)	0.9±1.7
Previous hormone therapy	19 (95)
Previous radiation	11 (55)
Previous chemotherapy	4 (20)
Previous surgery (primary tumor)	4 (20)

Results presented as mean±SD or number of participants (percentage of participants)

BMI body mass index

[a] Cardiovascular disease, hypertension, diabetes, osteoporosis, and dyslipidemia

[b] Self-rated health *1* excellent, *2* very good, *3* good, *4* fair, *5* poor; *VAS* visual analogue scale

Table 3 Indicators of the safety and tolerability of the exercise intervention assessed during every exercise session

Measure	Result
Adverse events during the exercise sessions	0
Attendance (out of 24 sessions)	20.4±6.9
Compliance (% of successfully completed sessions out of number of sessions attended)	88.7±12.2
Perceived exercise intensity (session RPE)	13.7±1.2
Perceived exercise tolerance (0=intolerable; 7=highly tolerable)	6.1±0.7
Severity of bone pain at the start of each session (VAS; 0=no pain; 10=very severe pain)	
Average of all sessions	0.7±1.0
Maximum across all sessions	1.8±1.9
Range across all sessions	1.7±1.9
Incidence of bone pain negatively affecting the ability to undertake usual activities of daily living between exercise sessions[a]	7

Results presented as number of incidents or mean±SD

RPE rating of perceived exertion (target range for cancer survivors is 12–16 which is equivalent to descriptors of between "light and somewhat hard" to between "hard (heavy) and very hard"); *VAS* visual analogue scale

[a] These seven incidences occurred in three participants

throughout the observation period. No other changes in pain medication were reported.

The supervised exercise program was well attended with an average attendance rate of 85 % (~20 out of a possible 24 sessions; Table 3). Compliance to the exercise prescription was high (~89 % of attended sessions were successfully completed in full adherence with the prescribed program; Table 3). Deviations from the prescribed program commonly involved not completing all the required sets for an exercise or not performing an exercise during the session. Participants were able to exercise at an intensity within the target range for cancer survivors (i.e., moderate-high intensity; RPE=12–16 [38]) with an average perceived intensity of 13.7±1.2 on the RPE scale. Participants perceived the exercise sessions to be tolerable with an average perceived tolerance score of 6.1±0.7 out of a possible rating of 7 (Table 3). The severity of bone pain reported at each exercise session was low with an average of 0.7±1.0 on a scale of 0 (no pain) to 10 (very severe pain) and a maximum of 1.8±1.9 across all sessions (Table 3). The highest level of perceived bone pain recorded by any participant throughout the exercise program was 5.0 out of 10, with the average range for participants across all exercise sessions being 1.7±1.9 (Table 3). There were seven incidences across three participants where a change in bone pain since the previous exercise session adversely affected the ability to undertake normal daily activities (Table 3; two of which were receiving radiation to bone and pain medication). Additionally, there were five other incidences in which bone pain impacted activities of daily living that resulted from actions external to the exercise program. These incidences occurred in the three participants who received radiation to bone during the exercise program and most commonly the incidences were reported after bouts of gardening.

Physical function and physical activity levels Statistically, significant improvements were observed pre to post the resistance exercise intervention in physical function (Table 4). Specifically, muscle strength (4 % increase in leg extension 1 RM), aerobic capacity (3 % decrease in 400-m walk time), and ambulation (6 and 5 % decrease in 6-m usual and fast pace walk time) improved significantly. There were also trends towards improvement in timed up and go time (4 %) and balance confidence (5 %). Only the significant improvement in ambulation was maintained 6 months after the completion of the supervised exercise program (4 % improvement from baseline in 6-m usual pace walk). The resistance exercise intervention elicited significant improvements in physical activity levels (Table 4). The Godin leisure score index and the amount of weekly resistance exercise increased significantly when assessed immediately post the intervention, with a trend towards increased mild intensity exercise also observed (p=0.095). The significant improvement from baseline in weekly minutes of resistance exercise remained following the 6-month observation period, but the magnitude of improvement was approximately halved. Additionally, mild intensity weekly activity was significantly higher at the follow-up assessment 9 months after baseline.

Body composition and bone mineral density Whole body lean mass and appendicular lean mass increased significantly following the exercise program, with increases of 3 and 4 %, respectively (Table 4). The significant increase in whole body lean mass was still apparent 6 months after completion of the resistance exercise program (1.5 % increase from baseline). There were no changes in any of the measures of fat mass at post-exercise or 6-month follow-up. A significant increase in BMD at the hip was observed 6 months after the exercise intervention equating to a 2 % improvement since baseline.

Quality of life, psychological distress, and cancer-related fatigue The social functioning QoL subscale increased significantly following the program (7 %; Table 5). Additionally, trends towards improvement were observed in the physical functioning (5 %; p=0.095), role–physical (6 %; p=0.118),

Table 4 Bone pain, physical function, physical activity levels, and body composition values and change over the duration of the study

Measure	Baseline (*n*=20)		Post-exercise (*n*=15)		6 month follow-up (*n*=14)		Difference between baseline and post-exercise[a]				Difference between baseline and 6 month follow-up[a]			
	Mean	SD	Mean	SD	Mean	SD	Mean	95 % CI		p	Mean	95 % CI		p
Bone pain														
FACT-bone pain (score)[b]	50.9	8.9	51.5	7.6	50.6	6.9	0.7	−2.2	3.6	0.614	−0.3	−3.1	2.5	0.834
Bone pain-VAS (cm)[b]	1.0	1.9	1.5	2.1	0.6	0.6	0.5	0.0	1.0	0.060	−0.4	−1.3	0.6	0.450
Physical function														
Leg extension 1RM (kg)	70.8	18.8	73.5	18.9	68.6	18.5	2.7	1.0	4.5	0.005	−2.2	−6.7	2.2	0.291
400-m walk (seconds)	262.6	43.6	255.4	43.4	266.4	53.5	−7.2	−12.0	−2.3	0.007	3.9	−7.7	15.4	0.481
6-m walk - usual pace (seconds)	4.59	0.45	4.32	0.37	4.40	0.51	−0.27	−0.39	−0.15	<0.001	−0.19	−0.38	0.00	0.046
6-m walk - fast pace (seconds)	3.29	0.46	3.12	0.44	3.25	0.67	−0.17	−0.27	−0.07	0.002	−0.03	−0.19	0.12	0.651
Timed up and go (seconds)	7.18	1.33	6.92	1.27	7.21	1.91	−0.26	−0.62	0.10	0.147	0.03	−0.55	0.61	0.915
Balance - SOT (score)	75.5	8.0	76.3	7.9	75.9	9.2	0.8	−1.3	3.0	0.437	0.5	−0.9	1.9	0.484
Balance confidence (ABC score)	79.6	23.7	83.3	19.7	79.7	20	3.7	−0.7	8.2	0.095	0.1	−3.3	3.6	0.939
Body composition														
Whole body lean mass (kg)	52.9	9.9	54.4	9.4	53.6	9.7	1.5	0.1	2.9	0.039	0.8	0.1	1.5	0.039
Appendicular lean mass (kg)	22.0	4.7	22.9	4.5	22.2	4.5	0.9	0.2	1.6	0.016	0.2	−0.1	0.5	0.208
Whole body fat mass (kg)	28.5	6.9	28.8	6.5	28.3	7.1	0.3	−0.3	1.0	0.303	−0.1	−1.1	0.9	0.833
Trunk fat mass (kg)	14.9	3.7	15.1	3.5	14.8	3.7	0.2	−0.3	0.6	0.390	−0.1	−0.6	0.4	0.692
Whole body percent fat (%)	34.0	6.0	33.6	6.1	33.6	5.8	−0.3	−0.8	0.2	0.170	−0.4	−1.4	0.7	0.445
Visceral fat mass (kg)	0.83	0.24	0.84	0.24	0.82	0.26	0.01	−0.02	0.00	0.568	−0.01	−0.05	0.01	0.421
Bone mineral density														
Hip BMD (g/cm^2)	0.808	0.123	0.808	0.128	0.824	0.126	0.000	−0.012	0.012	0.977	0.016	0.008	0.025	0.001
Physical activity level														
Godin leisure score index	18.6	14.7	30.5	22.1	21.6	14.8	12.0	5.6	18.3	0.001	3.1	−2.7	8.8	0.277
Mild exercise (mins/week)	68.5	94.7	137.5	213.0	145.3	133.3	69.0	−13.2	151.2	0.095	76.8	1.9	151.8	0.045
Moderate exercise (mins/week)	88.8	179.8	84.0	87.8	56.0	68.1	−4.8	−66.0	56.4	0.872	−32.7	−99.1	33.7	0.315
Vigorous exercise (mins/week)	14.4	38.1	9.6	47.4	23.3	62.0	-4.8	−16.6	7.1	0.411	9.0	−4.0	21.9	0.164
Resistance exercise (mins/week)	11.3	28.9	118.6	71.2	63.2	83.0	107.4	83.8	130.9	<0.001	51.9	19.7	84.2	0.003

[a] Repeated measures ANOVA

[b] Includes adjustment for use of pain medication, *FACT* functional assessment of cancer therapy, *VAS* visual analogue scale, *1RM* one repetition maximum, *SOT* sensory organization test, *ABC* activities specific balance confidence, *DXA* dual energy X-ray absorptiometry, *BMD* bone mineral density

and physical health composite (5 %; p=0.095) subscales of the SF-36. Despite a trend towards sustained improvement, the significant change in social function was not maintained after the 6-month observation period, likely due to increased variability at this time point (9 %; p=0.111). However, a significant improvement in role–physical QoL was observed at follow-up (13 %; p=0.035). There was also a trend towards improvement in the bodily pain QoL domain after the 6-month observation period (5 %; p=0.116). No changes occurred throughout the study period in any of the psychological distress domains measured (Table 5). Improvements in cancer-related fatigue approached statistical significance for total (p=0.090) and general (p=0.056) fatigue domains at post-exercise (Table 5). A significant reduction in physical fatigue was observed 6 months following the completion of the exercise program compared to baseline (Table 6).

Discussion

The range of symptoms and complications associated with bone metastatic disease contribute to significant physiological and function declines which compromise physical and mental well-being [35, 44]. This is the first study to examine whether resistance exercise can elicit sustained benefits for cancer patients with bone metastatic disease. The major finding of this study was that exercise-induced improvements in physical function, physical activity level, lean mass, BMD, and QoL were apparent 6 months after the completion of a resistance exercise program in cancer patients with bone metastases. Additionally, these preliminary findings indicate that appropriately designed and supervised resistance exercise may be safe and well tolerated by prostate

Table 5 Quality of life, fatigue, and psychological distress values and change over the duration of the study

Measure	Baseline (n=20)		Post-exercise (n=15)		6 month follow-up (n=14)		Difference between baseline and post-exercise*				Difference between baseline and 6 month follow-up[a]			
	Mean	SD	Mean	SD	Mean	SD	Mean	95 % CI		p	Mean	95 % CI		p
Quality of life (SF-36)														
Physical functioning (NBS)	44.2	9.4	46.2	7.8	44.9	8.4	2.0	−0.4	4.3	0.095	0.7	−1.6	3.0	0.543
Role physical (NBS)	40.8	10.8	43.2	9.1	45.9	8.9	2.5	−0.7	5.6	0.118	5.1	1.2	8.9	0.035
Bodily pain (NBS)	46.9	8.9	46.7	9.9	49.1	8.5	−0.2	−3.6	3.2	0.913	2.2	−0.6	5.1	0.116
General health (NBS)	43.8	9.7	44.8	9.2	43.6	8.8	1.0	−1.5	3.5	0.396	−0.2	−3.4	3.0	0.986
Vitality (NBS)	43.7	10.2	45.8	8.3	47.3	8.4	2.1	−1.8	6.1	0.275	3.6	−0.7	8.0	0.096
Social functioning (NBS)	39.0	10.5	41.8	6.9	42.7	7.5	2.9	0.4	5.3	0.023	3.7	−0.9	8.4	0.111
Role emotional (NBS)	37.1	10.0	35.5	9.8	39.6	5.7	−1.6	−5.7	2.6	0.436	2.5	−1.5	6.6	0.209
Mental health (NBS)	50.4	11.8	51.5	7.8	52.0	5.0	1.1	−2.1	4.3	0.482	1.5	−3.5	6.6	0.537
Physical health composite	44.1	10.1	46.1	9.0	46.0	8.3	2.1	−0.4	4.5	0.095	1.9	−0.9	4.8	0.166
Mental health composite	43.0	11.5	43.3	9.1	45.7	6.6	0.3	−3.1	3.8	0.836	2.7	−2.3	7.7	0.276
Psychological distress (BSI)														
Depression (score)	3.2	4.8	2.9	5.2	1.7	2.1	−0.3	−1.1	0.5	0.498	−1.5	−3.4	0.5	0.129
Anxiety (score)	2.4	3.8	2.1	2.8	1.7	2.2	−0.2	−1.5	1	0.675	−0.6	−2.4	1.2	0.491
Somatisation (score)	2.8	2.9	3.1	2.8	2.3	2.4	0.3	−1.1	1.6	0.696	−0.5	−1.2	0.3	0.360
Global severity index (score)	8.3	9.5	8.1	9.8	5.8	5.9	−0.2	−2.8	2.3	0.849	−2.5	−6.0	0.9	0.143
Fatigue (MFSI-SF)														
Total (score)	9.5	20.1	5.4	14.2	6.0	15.0	−4.0	−8.7	0.7	0.090	−3.5	−9.1	2.2	0.213
General (score)	8.9	6.8	7.0	4.7	7.7	5.7	−1.9	−3.9	0.1	0.056	−1.2	−2.8	0.5	0.151
Physical (score)	3.6	2.8	3.0	2.5	2.4	2.1	−0.5	−1.8	0.8	0.406	−1.9	−1.9	−0.5	0.001
Emotional (score)	4.0	5.2	3.3	3.2	3.8	3.0	−0.6	−2.2	0.9	0.415	−0.2	−2.5	2.1	0.881
Mental (score)	5.3	4.7	4.9	2.8	4.3	3.3	−0.3	−1.8	1.2	0.678	−0.9	−2.8	1.0	0.312
Vigor (score)	12.2	5.1	12.7	4.7	12.4	4.5	0.5	−0.7	1.8	0.377	0.2	−1.1	1.6	0.736

[a] Repeated measures ANOVA; SF-36—medical outcomes study 36-Item short-form health survey; *NBS* norm based score, *BSI-18* brief symptom inventory, *MFSI-SF* multidimensional fatigue symptom inventory-short form

and breast cancer patients with bone lesions. Due to the considerable patient and societal burden associated with bone metastatic disease, therapies that prolong time to first and/or subsequent SREs as well as maintain or improve functional ability and QoL after SREs have a high degree of clinical importance in the management of the patient with bone metastatic disease [6, 23, 26, 37, 46]. Findings from this initial study suggest that exercise may be an important therapy in the management of bone metastatic disease.

The 3-month resistance exercise program elicited physiological and functional changes in patients with bone metastases that are associated with reduced risk of falls and the risk of sustaining fall-related fractures [15, 42]. In healthy adults, muscular strength and walking speed have been established as independent risk factors of falls [36, 45]. The resistance exercise program in this study significantly improved both strength and 6-m walk speed in patients with bone metastatic disease. Notably, the magnitudes of improvement are comparable to patients with localized disease [11, 14], indicating that this patient group can respond to and benefit from exercise. Not only are these changes believed to have a significant impact on general mobility and everyday functional ability, but may have also contributed to a 5 % improvement in balance confidence (p= 0.095). While the improvement in strength was not maintained after the completion of the program, improvements in ambulation were still apparent after the 6-month observation period. The sustained improvement in mobility may confer a long-term protective effect against falls and fall-related fractures [36, 45]. While fractures (or other SREs) are not exclusively associated with falls in patients with bone metastatic disease, the sustained risk reduction of falls and fall-related fracture conferred by exercise may contribute to the delay/prevention of some SREs. Furthermore, improvements in strength, fitness, and ambulation may reduce the severity of impairment associated with SREs and/or aid in maintaining/recovering function following the occurrence of SREs.

The observation that a relatively short resistance exercise program prompts favorable physical activity behavior change over an extended period of time in patients with bone metastatic disease has a high degree of clinical relevance. Specifically, the increase in objectively measured durations of mild activity is likely reflective of patients increased capacity to be more functional and active in their everyday life. Thus, the exercise intervention may have prompted a sustained ability to regain a more "normal" lifestyle, less encumbered by the physical consequences of advanced cancer [10]. Superior physical activity levels are associated with an array of beneficial health outcomes including improved disease, physical and psychosocial outcomes in various cancer survivor populations [2, 8]. Furthermore, emerging observational evidence indicates that prostate and breast cancer patients who participate in higher levels of physical activity have significantly reduced risk of disease recurrence as well as both cancer-specific and all-cause mortality [8, 18, 22]. However, this evidence arises from samples of patients with primarily localized disease thus the same protective effect may not apply to patients with established metastatic disease.

The improvement observed in lean mass and BMD 6 months after the completion of the exercise program provides further evidence of the beneficial role of exercise in the management of bone metastatic disease. From the age of ~40–50 years, lean mass and BMD decreases at an annual rate of approximately 0.5–2.0 % [1, 17], but this decline is significantly accelerated by cancer treatments common to prostate and breast cancer [12, 17, 20, 38]. For example, previous reports indicate a reduction of 0.5 % (1.4 kg) in lean mass over a 9-month period in prostate cancer patients with localized disease receiving ADT [12]. Loss of lean mass contributes to sarcopenia while BMD loss leads to osteoporosis, both of which may contribute to an increased risk for fracture [9, 17, 42]. The current findings demonstrate that patients with bone metastatic disease can perform resistance exercise at an intensity required to elicit improvements in lean mass and BMD. Notably, significant improvements were apparent after the 6-month observation period (0.8 kg) even in the absence of a formal intervention. Thus, resistance exercise may be an effective countermeasure to declines in lean muscle mass, BMD, and the resulting functional impairments in patients with bone metastases, changes that may aid in the prevention and management of SREs.

Given the advanced stage of disease, therapies that help preserve QoL in patients with bone metastatic disease are clearly important. The 3-month supervised resistance exercise program improved various domains of QoL which were sustained 6 months after completion of the program. Improvements of a clinically significant magnitude (i.e. >3 norm based scoring points [3]) were observed in role-physical, vitality, and social functioning domains of quality of life at follow-up. While improvements in physical domains are somewhat expected, improvement in the social functioning domain highlights the comprehensive nature of benefits provided by the formal exercise program. The interaction amongst patients sharing the same condition and the rapport developed with the exercise physiologists may have provided patients with an additional avenue for support and social interaction. Furthermore, the capacity of resistance exercise to alleviate fatigue in this patient population is significant, especially given that fatigue is a common impairment experienced by patients with bone metastatic disease [19, 24, 26].

There are several limitations associated with this study that should be considered when interpreting the findings. The study lacked a control group, involved a relatively small sample size (mostly men with prostate cancer), and a relatively short follow-up observation period. Furthermore, participants were relatively well functioning patients who were mostly motivated to undertake the exercise study. However, this trial involved older, advanced cancer patients with high disease load, a group that is very difficult to recruit and can be reluctant to enroll in a 9-month exercise study. Furthermore, this is the first study to examine the long-term impact of exercise in patients with bone metastases and among a relatively small number of supervised exercise trials involving cancer survivors to incorporate a follow-up assessment point. Future study involving larger sample sizes, a randomized controlled design with extended follow-up are warranted to determine the efficacy of exercise on risk of SREs and disease burden in patients with bone metastatic disease.

In conclusion, initial evidence from this small longitudinal trial suggests that an appropriately designed and supervised 3-month resistance exercise program may lead to significant improvements in functional ability, physical activity level, lean mass, and QoL that are apparent 6 months after the completion of the program in cancer patients with bone metastases. Such improvements have a high degree of clinical significance given their potential to reduce disease burden associated with bone metastatic disease. This initial evidence demonstrates the exciting promise of targeted exercise prescription in attenuating the expected physiological and functional declines associated with bone metastatic disease. Future trials involving larger sample sizes are required to expand these preliminary findings.

Acknowledgments This study was funded by Cancer Council of Western Australia through the Early Career Investigator research grants program. PC is supported by the Cancer Council Western Australia Postdoctoral Research Fellowship. DAG is funded by a Movember New Directions Development Award obtained through Prostate Cancer Foundation of Australia's Research Program.

Conflict of interest The authors have no conflicts of interest to disclose.

Appendix

Table 6 Example of common resistance exercises selected based on the location of bone metastatic disease

Metastases site	Body region to target		
	Upper body	Trunk	Lower body
Pelvis	Chest press, lat pulldown, seated row, bicep curl, triceps extension	Abdominal crunch, back extension	Leg extension, leg curl, calf raise
Lumbar spine	Chest press, lat pulldown, seated row, bicep curl, triceps extension	–	Leg Press, leg extension, leg curl, calf raise
Thoracic spine and/or ribs	Bicep curl, triceps extension, lateral raise	–	Leg press, leg extension, leg curl, calf raise
Femur	Chest press, lat pulldown, seated row, bicep curl, triceps extension	Abdominal crunch, back extension	Leg extension, leg curl, calf raise
Humerus	Bicep curl, triceps extension	Abdominal crunch, back extension	Leg Press, leg extension, leg curl, calf raise
All regions	Case by case basis	–	Case by case basis

As many patients will have bone lesions at various sites, the selection of exercises was individualized on a case by case basis and carefully monitored throughout an exercise program

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