Critical Reviews in Oncology / Hematology 166 (2021) 103433

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Exercise for individuals with bone metastases: A systematic review

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ARTICLE INFO

Keywords:
neoplasm metastasis
bone neoplasms
neoplasms
rehabilitation
exercise
sports
systematic review

ABSTRACT

Background: Exercise has the potential to improve physical function and quality of life in individuals with bone metastases but is often avoided due to safety concerns. This systematic review summarizes the safety, feasibility and efficacy of exercise in controlled trials that include individuals with bone metastases.
Methods: MEDLINE, Embase, Pubmed, CINAHL, PEDro and CENTRAL databases were searched to July 16, 2020.
Results: A total of 17 trials were included incorporating aerobic exercise, resistance exercise or soccer interventions. Few (n = 4, 0.5%) serious adverse events were attributed to exercise participation, with none related to bone metastases. Mixed efficacy results were found, with exercise eliciting positive changes or no change. The majority of trials included an element of supervised exercise instruction (n = 16, 94%) and were delivered by qualified exercise professionals (n = 13, 76%).
Conclusions: Exercise appears safe and feasible for individuals with bone metastases when it includes an element of supervised exercise instruction.

1. Introduction

Preservation of physical function is a key objective of cancer rehabilitation in patients with advanced cancer (Cheville et al., 2016; Padgett et al., 2018). The presence of bone metastases can lead to abrupt and clinically significant declines in physical function and overall performance status, which has been associated with increased healthcare utilization, reduced quality of life and fewer treatment options (Silver et al., 2013; Kurtz et al., 2005; Ten Tusscher et al., 2019; Maltser et al., 2017). Regular exercise (e.g. aerobic and resistance exercise) has been shown to improve measures of physical function in cancer patients and is recommended as an effective supportive care strategy (Campbell et al., 2019; Hayes et al., 2019; Cormie et al., 2018; Support, 2018). However, exercise is often underutilized by medical professionals for patients with bone metastases due to uncertainties around safety and the overall risk of skeletal-related events (SREs) associated with bone metastases, including pathological fracture and spinal cord compression (Cheville et al., 2011; Silver et al., 2018; Sheill et al., 2018a; Ten Tusscher et al., 2020). In contrast, patients with bone metastases have expressed interest in receiving exercise information and participating in exercise programs, highlighting the need for evidence-informed guidance on exercise as a therapeutic intervention in this setting (Ten Tusscher et al., 2019; Delrieu

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https://doi.org/10.1016/j.critrevonc.2021.103433
Received 8 November 2020; Received in revised form 26 March 2021; Accepted 28 July 2021
Available online 3 August 2021

et al., 2019; Lowe et al., 2010; Sheill et al., 2018b).

Previous systematic reviews on exercise in people with advanced cancer exist, yet to our knowledge, none have primarily focused on participants with bone metastases (Heywood et al., 2018; Nadler et al., 2019; Beaton et al., 2009; Dittus et al., 2017; Lowe et al., 2009; Titz et al., 2016; Salakari et al., 2015). A meta-analysis by Nadler et al. evaluating exercise interventions in individuals with advanced cancer included a sub-group analysis from six trials that included some participants with bone metastases and concluded that exercise was likely safe if it was supervised and individually tailored (Nadler et al., 2019). The authors note that the appropriateness and safety of unsupervised exercise is currently unclear due to lack of randomized controlled trials (RCTs) that include participants with bone metastases in exercise interventions (Nadler et al., 2019).

Given the risk of SREs associated with bone metastases and the negative consequences elicited by poor physical function, it is important to establish the safety and efficacy of exercise specific to individuals with bone metastases across supervised and unsupervised settings (Sturgeon et al., 2019; Coleman, 2006; Healey and Brown, 2000). To effectively design and implement exercise within clinical settings, it is also critical to understand exercise feasibility (El-Kotob and Giangregorio, 2018). To address this gap in the knowledgebase, we conducted a systematic review to summarize and qualitatively assess the safety, feasibility and efficacy of exercise in controlled trials that include individuals with bone metastases.

2. Methods

2.1. Literature Search

Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (Moher et al., 2009) reporting guidelines were followed and registration with PROSPERO (CRD42019121958). Electronic databases (MEDLINE, Embase, Pubmed, CINAHL, PEDro and CENTRAL) were searched from inception to 16 July 2020, using a search strategy developed in consultation with a university librarian. Additionally, grey literature and reference lists of eligible papers were searched. The search included subject headings or keywords for “cancer” and “bone metastases or advanced cancer” and “exercise” (eSupplement eTable 1). Limits included human participants and publication in English.

2.2. Eligibility Criteria

Inclusion criteria were: 1) design: RCT or controlled clinical trial; 2) population: 18-years or older with a diagnosis of cancer; sample included participants with metastatic bone disease (with confirmed number of participants with bone metastases); 3) intervention: any exercise intervention comprising more than one session of structured exercise; 4) comparator group: usual care, control or comparator interventions; and 5) outcome: at least one outcome related to efficacy on physical function (e.g., sit to stand), functional capacity (e.g., cardiopulmonary exercise test), muscular strength (e.g., one repetition maximum) or treatment side effect (e.g., fatigue). Exercise was operationally defined as aerobic, resistance or flexibility exercise, sports-specific training (e.g., soccer), yoga, tai chi, Pilates or a combination of any of these modalities. Structured exercise refers to an exercise prescription given to be performed in a supervised or unsupervised setting.

2.3. Trial Selection, Data Extraction and Synthesis

Citations yielded from the search were exported to Endnote (Clarivate Analytics, Philadelphia, PA) and duplicates were removed (Bramer et al., 2016). Title and abstract screening was performed by two review teams (SW and SM; KAB and NHH). Two reviewers (SW and NHH) independently performed full-text screenings. Data was extracted using a standard form that included sample and intervention characteristics (age, presence of bone metastases, exercise prescription, supervision characteristics), safety (adverse events, exclusion criteria, exercise modifications), feasibility (recruitment, attendance, study retention, adherence), and efficacy outcomes (between group mean differences, 95% confidence intervals and p-values). Two reviewers (SW and NHH) independently assessed risk of bias using Cochrane Risk of Bias 2.0 for RCTs and Risk of Bias In Non-Randomized Studies of Interventions, identifying “high risk”, “some concerns” and “low risk” of bias of each trial (Sterne et al., 2019; Sterne et al., 2016). Disagreements were discussed and resolved. Corresponding authors of included trials were contacted when additional information was required.

Descriptive statistics including mean, standard deviation (SD) & range were generated with SPSS v25 (IBM Corporation; Chicago, IL, USA) to summarize data from eligible trials. A separate descriptive analysis was conducted for trials that only included individuals with bone metastases. For trials that included individuals with and without bone metastases, results of the total sample are presented.

3. Results

3.1. Overview

A total of 12,781 records were identified through the database search and 24 publications met the eligibility criteria, representing 17 trials (eSupplement, eFig. 1). Of the excluded trials, 11 did not record the number of participants who had bone metastases and were therefore excluded. Of the included trials, one trial was a controlled clinical trial (Rosenberger et al., 2017) and the remaining 16 were RCTs (Bjerre et al., 2019a, b; Bourke et al., 2011, 2014; Cheville et al., 2019; Cormie et al., 2013; Dawson et al., 2018; Galvão et al., 2018; Litterini et al., 2013; Rief et al., 2014a, b, c, d, 2016; Scott et al., 2018; Solheim et al., 2017; Sprave et al., 2019; Uster et al., 2018; Uth et al., 2014, 2016a, b; Villumsen et al., 2019; Yee et al., 2019). Four (24%) trials included only participants with bone metastases (Cormie et al., 2013; Galvão et al., 2018; Rief et al., 2014a, b, c, d, 2016; Sprave et al., 2019), and the remaining 13 (76%) trials included participants with and without bone metastases. A total of 1489 participants were included in our review, of which 645 (43%) had bone metastases and 845 (57%) were assigned to an exercise intervention group. The mean (SD) participant age was 65 (5) years. Trials recruited participants with prostate cancer (n = 8, 47%) (Bjerre et al., 2019a, b; Bourke et al., 2011, 2014; Cormie et al., 2013; Dawson et al., 2018; Galvão et al., 2018; Uth et al., 2014, 2016a, b; Villumsen et al., 2019), breast cancer (n = 2, 12% (Scott et al., 2018, Yee et al., 2019)) or mixed tumor types (n = 7, 41%) (Cheville et al., 2019; Litterini et al., 2013; Rief et al., 2014a, b, c, d, 2016; Rosenberger et al., 2017; Solheim et al., 2017; Sprave et al., 2019; Uster et al., 2018).

Five (29%) trials had a low risk of bias (Bjerre et al., 2019a, b; Cheville et al., 2019; Dawson et al., 2018; Scott et al., 2018; Sprave et al., 2019), ten (59%) had some concerns (Bourke et al., 2011, 2014; Cormie et al., 2013; Galvão et al., 2018; Rosenberger et al., 2017; Solheim et al., 2017; Uster et al., 2018; Uth et al., 2014, 2016a, b; Villumsen et al., 2019; Yee et al., 2019), and two (13%) had a high risk of bias (Litterini et al., 2013; Rief et al., 2014a, b, c, d, 2016) (Fig. 1). Risk of bias concerns were predominantly due to a lack of published trial protocol or detailed trial registration (Bourke et al., 2011, 2014; Cormie et al., 2013; Litterini et al., 2013; Solheim et al., 2017; Yee et al., 2019), absence of appropriate analysis to measure between group effect (Galvão et al., 2018; Rief et al., 2014a, b, c, d, 2016; Uster et al., 2018; Uth et al., 2014, 2016a, b; Villumsen et al., 2019), unequal dropout between study arms that may have influenced results (Litterini et al., 2013; Rosenberger et al., 2017), and selection bias of reported results across multiple publications (Rief et al., 2014a, b, c, d, 2016).

3.2. Intervention Characteristics

The exercise intervention characteristics (i.e., frequency, intensity, time, type, duration) of each trial are described in Table 1 (additional information eSupplement eTable 2). Overall, 14 (82%) trials prescribed resistance exercise (resistance exercise only, n = 8; resistance and aerobic exercise, n = 6), two trials prescribed aerobic exercise alone (Litterini et al., 2013; Scott et al., 2018) and two trials evaluated a soccer intervention (Bjerre et al., 2019a, b; Uth et al., 2014, 2016). In studies including resistance exercise, 12 (86%) trials prescribed whole body resistance training (Bourke et al., 2011, 2014; Cheville et al., 2019; Cormie et al., 2013; Dawson et al., 2018; Galvão et al., 2018; Litterini et al., 2013; Rosenberger et al., 2017; Solheim et al., 2017; Uster et al., 2018; Villumsen et al., 2019; Yee et al., 2019) and two (14%) trials prescribed isometric spinal stabilization exercises with holds of 20-seconds or greater per exercise (Rief et al., 2014a, b, c, d, 2016; Sprave et al., 2019). Comparator groups included usual care (n = 12, 71%), attention control (n = 4, 24%) (Dawson et al., 2018; Rief et al., 2014a, b, c, d, 2016; Scott et al., 2018; Sprave et al., 2019), or an alternate exercise modality (e.g., resistance versus aerobic exercise) (n = 1, 6%) (Litterini et al., 2013). Fifteen (88%) trials used moderate-to-vigorous intensity aerobic and/or resistance exercise prescriptions.

Inclusion of at least one session of supervised exercise was a component of all but one (93%) trial (Solheim et al., 2017). Nine (53%) trials included only supervised exercise sessions (Bjerre et al., 2019a, b; Cormie et al., 2013; Dawson et al., 2018; Galvão et al., 2018; Litterini et al., 2013; Rosenberger et al., 2017; Scott et al., 2018; Uster et al., 2018; Uth et al., 2014, 2016a,b), five (29%) trials included a combination of supervised and unsupervised exercise (Bourke et al., 2011, 2014, Rief et al., 2014a, b, c, d, 2016; Sprave et al., 2019; Yee et al., 2019), one (6%) trial included a single exercise demonstration session followed by unsupervised exercise (Villumsen et al., 2019), one (6%) trial included unsupervised exercise only with distanced-based telephone check ins and optional in-person physical therapy sessions (Cheville et al., 2019) and one (6%) trial was entirely unsupervised (Solheim et al., 2017). Overall, unsupervised exercise was included with 892 (60% of total) participants. Exercise supervision was predominantly provided by qualified exercise professionals (n = 13, 76%) including

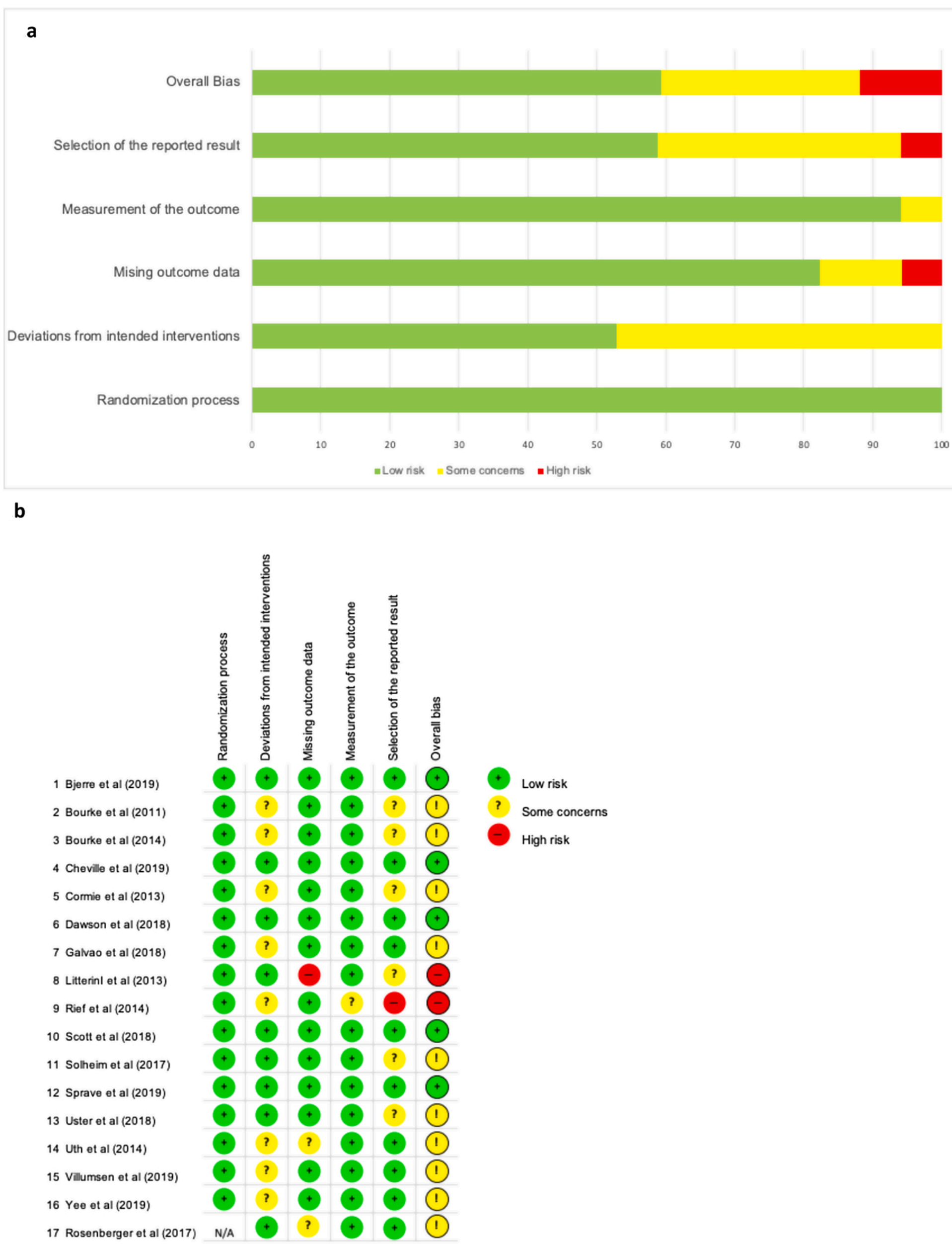

Fig. 1. Risk of Bias of included studies. 1a Risk of bias, all included trials, as percentage. 1b Risk of bias, individual trials.

Table 1
Overview of included trials.

Source	Cancer Type	Sample/ MBD (%)	Intervention	Significant findings of exercise intervention (between-group)
Bjerre et al., 2019a, b	Prostate	214/41 (19%)	Soccer vs UC	Improved mental health.
Bourke et al., 2011	Adv Prostate	50/13 (25%)	AET, RT & Diet vs UC	Improved exercise tolerance, physical function, strength, fatigue.
Bourke et al., 2014	Adv Prostate	100/20 (20%)	AET, RT & Diet vs UC	Improved QoL, exercise tolerance, fatigue.
Cheville et al., 2019	Mixed Adv	516/264 (51%)	(1a) AET & RT & PT vs (1b) +/- pain management vs control	(1a) improved physical function, QoL, discharge time, LOS, pain interference. (1b) improved discharge home, pain interference.
Cormie et al., 2013	Adv Prostate	20/20 (100%)	RT vs UC	Improved physical function, strength, body composition.
Dawson et al., 2018	Prostate	35/13 (13%)	RT vs control (stretch)	Improved QoL, strength, body composition.
Galvão et al., 2018	Adv Prostate	57/57 (100%)	AET, RT & Flex vs UC	Improved physical function, strength.
Litterini et al., 2013	Mixed Adv	66/16 (24%)	AET vs RT	No change.
Rief et al., 2014a, b, c, d, 2016	Mixed Adv	60/60 (!00%)	RT vs Control (breathing)	Improved physical function, body composition, pain score.
Rosenberger et al., 2017	Mixed Adv	25/6 (24%)	RT vs UC	Improved body composition, strength.
Scott et al., 2018	Adv Breast	65/17 (26%)	AET vs Control (stretch)	No change.
Solheim et al., 2017	Adv Lung & Panc.	46/8 (17%)	AET & RT vs UC	Improved body composition.
Sprave et al., 2019	Mixed Adv	60/60 (100%)	RT vs Control (muscle relax)	No change.
Uster et al., 2018	Mixed Adv	58/14 (24%)	AET, RT & Diet vs UC	No change.
Uth et al., 2014, 2016a, b	Adv Prostate	57/11 (19%)	Soccer vs UC	Improved body composition, strength.
Villumsen et al., 2019	Adv Prostate	46/16 (35%)	Exergaming vs UC	Improved physical function.
Yee et al., 2019	Adv Breast	14/9 (62%)	AET & RT vs UC	Improved QoL, fatigue, physical function.

Abbreviations: Adv = advanced; AET = aerobic exercise training; Flex = flexibility training; LOS = length of stay; Panc = Pancreatic; QoL = quality of life; RT = resistance training; UC = usual care.

physical therapists/physiotherapists (n = 6, 35%) (Cheville et al., 2019; Litterini et al., 2013; Rief et al., 2014a, b, c, d, 2016; Sprave et al., 2019; Uster et al., 2018; Villumsen et al., 2019), clinical exercise physiologists (n = 6, 35%) (Bourke et al., 2011, 2014; Cormie et al., 2013; Galvão et al., 2018; Scott et al., 2018; Sprave et al., 2019) or other university trained exercise professionals (e.g., kinesiologists or sports therapists) (n = 3, 18%) (Litterini et al., 2013; Yee et al., 2019; Rosenberger et al., 2017).

3.3. Safety

All but one trial reported on adverse events (AEs) (Bourke et al., 2011), with nine (53%) trials measuring AEs in both intervention and comparator groups and seven (41%) trials measuring AEs in the intervention group only (Table 2). Seven (41%) trials reported use of a comprehensive classification tool that specified AE grade and severity (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events). Overall, three trials (18%) reported serious adverse events (SAEs) associated with the trial and all included samples with and without bone metastases (Bjerre et al., 2019a, b; Solheim et al., 2017; Uth et al., 2014, 2016a, b). A total of 57 SAEs were reported in these three trials; 27 SAEs occurred in intervention group participants and 30 SAEs occurred in control group participants. Only four SAEs (0.5% of total exercise intervention participants) were attributed to an exercise intervention, all of which were attributed to soccer and were not related to bone metastases. One trial by Uth et al. reported three SAEs that included two fibula fractures and one partial achilles tendon rupture (Uth et al., 2014, 2016a, b). A second trial by Bjerre et al. reported 33 SAEs resulting in hospital admission, 11 in the intervention group and 22 in the usual care group, with one SAE attributed to the intervention, which was a soft-tissue injury that was not related to bone metastases (Bjerre et al., 2019a, b). Of note, in the four trials that exclusively included individuals with bone metastases, no SAEs occurred during the trials (Cormie et al., 2013; Galvão et al., 2018; Rief et al., 2014a, b, c, d, 2016; Sprave et al., 2019). Additionally, one trial reported specifically on the presence of pathological fractures and found no significant differences between the intervention and control groups at baseline (23% vs 30%, p = 0.56) or end of intervention (23% vs 30%, p = 0.59%) (Rief et al., 2014a, b, c, d, 2016).

Key to interpreting safety, criteria specific to inclusion and exclusion of participants with bone metastases is outlined in Table 3. Nine trials (53%) used exclusion criteria specific to bone metastases, namely excluding individuals presenting with unstable bone metastases (n = 4, 24%) (Bourke et al., 2011, 2014, Rief et al., 2014a, b, c, d, 2016; Rosenberger et al., 2017) or pain associated with the bone lesion (n = 7, 41%) (Bourke et al., 2011, 2014; Cormie et al., 2013; Galvão et al., 2018; Uster et al., 2018; Uth et al., 2014, 2016a, b; Yee et al., 2019). Four (24%) trials used inclusion criteria that required a physician clearance (Bjerre et al., 2019a, b; Cormie et al., 2013; Dawson et al., 2018; Litterini et al., 2013) and eight (47%) trials required a minimum performance status that included ambulation and basic self-care (i.e., Eastern Cooperative Oncology Group [ECOG] performance status 0 – 1/2; Karnofsky performance status [KPS] >70) (Rief et al., 2014a, b, c, d, 2016; Rosenberger et al., 2017; Scott et al., 2018; Solheim et al., 2017; Sprave et al., 2019; Uster et al., 2018; Villumsen et al., 2019; Yee et al., 2019). Three (18%) trials specifically included higher risk populations that presented with pain related to the lesion site (Rief et al., 2014a, b, c, d, 2016), functional impairments (Cheville et al., 2019) or unstable bone metastases (i.e., high fracture risk) (Sprave et al., 2019).

Exercise prescription modifications specific to bone metastases were used in seven (41%) trials (eSupplement eTable 3) (Cheville et al., 2019; Cormie et al., 2013; Dawson et al., 2018; Galvão et al., 2018; Litterini et al., 2013; Rief et al., 2014a, b, c, d, 2016; Sprave et al., 2019). Three (18%) trials in men with prostate cancer prescribed resistance exercises that minimized loading to the lesion area (e.g., avoided horizontal press exercises when lesion present in thoracic spine) (Dawson et al., 2018; Cormie et al., 2013; Galvão et al., 2018). Four (24%) trials in individuals with mixed tumor types used other exercise modification approaches (e.g., using resistance bands instead of machines) (Cheville et al., 2019; Litterini et al., 2013; Rief et al., 2014a, b, c, d, 2016; Sprave et al., 2019). The remaining ten trials (59%) did not report exercise modifications specific to bone-metastases and included soccer, resistance exercise and

Table 2
Safety considerations and outcomes of included studies

Source	AE Reporting	AE Criteria	Total SAEs Reported (I/C)	Total AEs Reported (I/C)
Bjerre et al., 2019a, b	I & C	GCP Guidelines	33 (11/12) 1 related to exercise[a]	Falls 26 (10/6) Fractures 3 (1/2) Injuries 60 (60/0)
Bourke et al., 2011	Not Reported	NA	NA	NA
Bourke et al., 2014	I & C	None	0	0
Cheville et al., 2019	I & C	None	0	0
Cormie et al., 2013	I & C	None. Incidence & severity.	0	Increased bone pain 1 (1/0) Adv disease 2 (1/1) Fall (home) 1 (1/0)
Dawson et al., 2018	I only	NCI CTCAE v4.3	0	0
Galvão et al., 2018	I only	None. Incidence & severity.	0	0
Litterini et al., 2013	I only	None	0	0
Rief et al., 2014a, b, c, d, 2016	I & C	GCP Guidelines	0	0
Rosenberger et al., 2017	I only	None	0	Weakness, pain or injury 11 (11/NR)
Scott et al., 2018	I & C	MedDRA	0	73% of AET group had AE (e.g., abnormal HR response, fatigue, back pain)
Solheim et al., 2017	I & C	NCI CTCAE v3.0	21 (13/8)None related to exercise	Grade 3 (e.g., pain, infection) 12 (7/5)
Sprave et al., 2019	I & C	NCI CTCAE v4.03	0	0
Uster et al., 2018	I only	None	0	0
Uth et al., 2014, 2016a, b	I only	None	3 (3/NR) 3 related to exercise[a] [Fractured fibula = 2, Partial Achilles rupture = 1]	Muscle strain 1 (1/NR)
Villumsen et al., 2019	I & C	None	0	Chest pain, non-heart related 1 (1/0)
Yee et al., 2019	I only	NCI CTCAE v4.0	0	0

[a] Not related to bone metastases; Abbreviations: AE = adverse event; C = Control group; GCP = Good Clinical Practice; I = intervention group; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NR = Not reported; SAE = serious adverse event.

Table 3
Participant inclusion and exclusion criteria of included trials

	Physician Clearance (n = 4)	Painful Metastases (n = 7)	Unstable Metastases (n = 4)	Function Impairment (n = 8)
Bjerre et al., 2019a, b	Inclusion	X	X	X
Bourke et al., 2011	X	Exclusion	Exclusion	X
Bourke et al., 2014	X	Exclusion	Exclusion	X
Cheville et al., 2019	X	X	X	Inclusion
Cormie et al., 2013	Inclusion	Exclusion	X	X
Dawson et al., 2018	Inclusion	X	X	X
Galvão et al., 2018	X	Exclusion	X	X
Litterini et al., 2013	Inclusion	X	X	X
Rief et al., 2014a, b, c, d, 2016	X	Inclusion	Exclusion	KPS <70
Rosenberger et al., 2017	X	X	Exclusion	ECOG >2
Scott et al., 2018	X	X	X	ECOG >1
Solheim et al., 2017	X	X	X	KPS <70
Sprave et al., 2019	X	X	Inclusion	KPS <70
Uster et al., 2018	X	Exclusion	X	ECOG >2
Uth et al., 2014, 2016a, b	X	Exclusion	X	X
Villumsen et al., 2019	X	X	X	ECOG ≥2
Yee et al., 2019	X	Exclusion	X	ECOG >2

Abbreviations: X = criteria not used; Inclusion = Required for participant to be included in trial; Exclusion = If present, criteria excluded participant from trial.

aerobic exercise interventions (Bjerre et al., 2019a, b; Bourke et al., 2011, 2014; Rosenberger et al., 2017; Scott et al., 2018; Solheim et al., 2017; Uster et al., 2018; Uth et al., 2014, 2016a, b; Villumsen et al., 2019; Yee et al., 2019).

3.4. Study Feasibility

Participant recruitment, attendance, study retention and adherence are reported in Fig. 2 (additional information eSupplement eTable 4). Overall, mean (SD) recruitment rate was 46(25)%, ranging from 12% to 93%. Trials exclusive to individuals with bone metastases reported mean recruitment rates of 64(12)% compared to mixed trials of 40(26)%. Mean attendance was 75(12)% across all trials, ranging from 59% to 100%, with supervised trials reporting attendance of 79(14)% and unsupervised trials 66(20)%. Trials exclusive to individuals with bone metastases reported mean attendance rates of 79(12)% compared to mixed trials 74(12)%. Mean retention was 83(10)% during the trial period, ranging from 53% to 100%. Trials exclusive to individuals with bone metastases reported mean retention rates of 74(14)% compared to mixed trials of 86(7)%. Adherence to the exercise intervention was only reported in eight trials, each measuring adherence differently, making it difficult to report the exercise intensity and duration completed (Bjerre et al., 2019a, b; Cormie et al., 2013; Dawson et al., 2018; Rosenberger et al., 2017; Scott et al., 2018; Solheim et al., 2017; Villumsen et al., 2019; Yee et al., 2019).

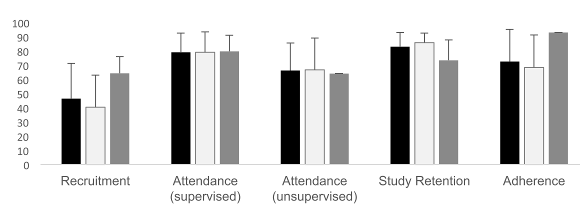

Fig. 2. Feasibility of all trials included in systematic review, mean (SD) %.

3.5. Efficacy

Across all 17 trials, no significant negative effects of the exercise intervention were reported in any efficacy outcome (Table 1, eSupplement eTable 2). A variety of patient reported outcomes and objective test measures were used. A summary of the between-group efficacy results of each trial is shown in eSupplement eFig. 2. Significant between group improvement in physical function, fatigue and quality of life that favour exercise was reported in seven (54%) trials (Bourke et al., 2011; Cheville et al., 2019; Cormie et al., 2013; Galvão et al., 2018; Rief et al., 2014a, b, c, d, 2016; Villumsen et al., 2019; Yee et al., 2019), three (23%) trials (Bourke et al., 2011, 2014; Yee et al., 2019) and four (31%) trials (Bourke et al., 2014; Cheville et al., 2019; Dawson et al., 2018; Yee et al., 2019), respectively. Significant between group improvements in body composition and objective measures of muscular strength that favour exercise was reported in six (43%) trials (Cormie et al., 2013; Dawson et al., 2018; Rief et al., 2014a, b, c, d, 2016; Rosenberger et al., 2017; Solheim et al., 2017; Uth et al., 2014, 2016a, b) and six (67%) trials (Bourke et al., 2011; Cormie et al., 2013; Dawson et al., 2018; Galvão et al., 2018; Rosenberger et al., 2017; Uth et al., 2014, 2016a, b), respectively. Finally, significant between group reductions in pain that favour exercise was reported in two (29%) trials (Cheville et al., 2019; Rief et al., 2014a, b, c, d, 2016).

In trials that exclusively included individuals with bone metastases (n = 4), results were mixed and a range of test measures were used (eSupplement eTable 2). Three (75%) trials (Cormie et al., 2013; Galvão et al., 2018; Rief et al., 2014a, b, c, d, 2016) reported significant between-group improvements in physical functioning that favour exercise and two (50%) trials (Cormie et al., 2013; Galvão et al., 2018) reported significant between-group improvements in muscle strength that favour exercise. All trials measured pain (n = 4), with one (25%) trial (Rief et al., 2014a, b, c, d, 2016) reporting a reduction in pain levels and three (75%) trials (Cormie et al., 2013; Galvão et al., 2018; Sprave et al., 2019) reporting no difference between groups. No significant between group exercise effect was reported for fatigue (n = 4) or quality of life (n = 3) (Cormie et al., 2013; Rief et al., 2014a, b, c, d 2016; Sprave et al., 2019).

4. Discussion

This systematic review supports that exercise is feasible in individuals with bone metastases and that participation in aerobic and resistance exercise does not appear to result in SAEs related to exercise. Soccer participation was associated with a small number of SAEs related to exercise (n = 4), however, none of these were related to the presence of bone metastases. Mixed efficacy results were found, with no negative effects of exercise reported. Participation in structured exercise showed an overall trend toward increasing physical function and muscular strength across all trials (54%, 67% respectively) and in trials exclusive to individuals with bone metastases (75%, 50% respectively).

Establishing the safety profile of exercise interventions for patients with bone metastases is a key consideration to enable medical professionals to advise on exercise suitability (Sheill et al., 2018a; Silver et al., 2015). The studies included in this systematic review reported no SAEs in interventions prescribing aerobic and/or resistance exercise that included at least one session of supervised exercise instruction. Participation in aerobic and resistance exercise did not appear to increase the rate of pathological fracture, pain or use of pain medication. The few SAEs reported were attributed to soccer participation, and these were all musculoskeletal injuries consistent with participation in a contact sport (i.e., fibula fracture) with none occurring at known lesion sites. Overall, our results suggest that in a controlled trial setting, the benefits of exercise may outweigh perceived risks. Future research should include the number, type and severity of each adverse event using pre-established criteria (e.g., Common Terminology Criteria for Adverse Events) and record AEs in both the intervention and control groups (Services UDoHaH, 2009).

Our findings support that the addition of unsupervised exercise for individuals with bone metastases may be safe, provided an element of supervised exercise instruction (i.e., individualized, in-person demonstration and practice) is initially included or regular check-in opportunities with suitably qualified exercise professionals are provided. This is somewhat contrary to the summary from Nadler et al. that suggested only exercise in a supervised setting is safe (Nadler et al., 2019). In our review, 47% of trials included an element of unsupervised exercise. Inclusion of unsupervised exercise may improve access for individuals who face barriers to supervised exercise sessions, such as difficulty travelling due to functional impairments or immunocompromise, or lack of access due to location or cost (Sheill et al., 2018b). For supervised exercise, supervision was predominately provided by university-trained exercise professionals including clinical exercise physiologists and physical therapists/physiotherapists; consistent with the recently published clinical guidance recommending that people with cancer with higher clinical needs should be referred to these highly qualified exercise professionals (Schmitz et al., 2019). These findings provide a foundation for future research and clinical exercise programming for individuals with bone metastases to explore different models of delivery combined with qualified oversight (Cormie et al., 2018; Schmitz et al., 2019; Body et al., 2016).

To safely translate these research findings into clinical practice, understanding appropriate pre-exercise screening and exercise modifications is required. All RCTs included in this review used screening criteria that required either: 1) physician clearance prior to exercise; or 2) a minimum level of functioning that included ambulation and basic self-care (e.g., ECOG 0-2 or KPS > 70); or 3) an absence of unstable bone metastases or pain related to lesion(s). Other screening approaches have been suggested in individuals with bone metastases to identify those at risk of a SAE (i.e., Mirels and Taneichi scales) (Maltser et al., 2017; Support, 2018; Nadler et al., 2019; Sheill et al., 2018c; Taneichi et al., 1997; Mirels, 2003). However, only two studies in our review implemented these tools, suggesting more research is required to confirm their utility for pre-exercise screening, especially for use in clinical practice (Rief et al., 2014a, b, c, d, 2016; Sprave et al., 2019).

While the optimal exercise prescription for individuals with bone metastases is currently undefined, our review found that exercise prescriptions predominantly fell within the levels recommended for individuals living with and beyond cancer by the American College of Sports Medicine (ACSM), including at least 90 minutes of moderate-to-vigorous intensity aerobic exercise and two days a week of resistance exercise (Campbell et al., 2019). The majority of trials (n = 14, 82%) included resistance training, which aligns with the clinical focus to preserve and increase physical function in individuals with bone metastases (Cheville et al., 2016; Padgett et al., 2018). Moderate-to-vigorous exercise intensity was prescribed in the majority of trials, highlighting the capacity of individuals with bone metastases to perform increased exercise intensities that have been previously shown to be efficacious for cancer survivors (Campbell et al., 2019; Hayes et al., 2019).

Based on our findings, evidence on exercise modifications for individuals with bone metastases currently appears mixed, with 10 (59%) trials included in our review reporting no exercise modifications. Of note, all studies that included higher risk individuals with functional impairments, unstable metastases or bone pain used exercise modifications and no SAEs were reported (Cheville et al., 2019; Rief et al., 2014a, b, c, d, 2016; Sprave et al., 2019). More research and enhanced reporting of exercise intervention adherence is required to better define exercise recommendations, modifications and optimal exercise dose in individuals presenting with bone metastases. Some of this work has commenced to progress the evidence base for exercise effectiveness in people with bone metastases or advanced cancers (of which many will have bone metastases), including for cancer-specific endpoints such as delays to symptomatic skeletal events and disease progression, and improvements to progression-free and overall survival (Brown et al., 2019; Hart et al., 2017, 2018; Newton et al., 2018). This work has been made possible, in part, because of established safety and feasibility data in the literature that we have systematically reported in this review. Given the ability to explore the minimum effective dose, dose-response relationships, and various physiological effects of exercise modalities, intensities and volumes; it is now worthwhile for future research to examine the use of wearable technology and telemedicine delivery of exercise medicine to promote pragmatic randomised controlled trials and implementation efforts beyond the exercise clinic, and into the community setting (including people in rural and remote areas who are often disadvantaged).

5. Strengths and Limitations

The main strengths of this review are the systematic approach and the focus on including of controlled trials that recruited participants with bone metastases. However, only 645 participants (43%) had bone metastases, as such, results should be interpreted with caution. A key limitation of this review is that the majority of trials did not collect or report detailed information specific to bone metastases, specifically type, location, lesion size, treatments received and use of pain medication, limiting the translation of these findings into clinical practice. Finally, efficacy of the interventions could not be quantitatively evaluated in this review, due to the variety of outcome measures used. Future controlled trials that specifically focus on individuals with bone metastases are needed and are advised to include standardized reporting of AEs, have sufficient statistical power to determine intervention efficacy on person-centred outcomes, and include robust descriptions of the exercise prescription and bone-related modifications.

6. Conclusions

In the existing literature examining exercise in people with bone metastases, exercise appears to be safe and feasible, when it includes an element of supervised exercise instruction delivered by qualified exercise professionals. More research is needed to understand the magnitude of effect that exercise can achieve in this population.

Author Contributions

Sarah Weller: Conceptualization, methodology, data curation, formal analysis, writing – original draft, reviewing and editing. Nicolas H Hart: Conceptualization, methodology, data curation, and writing – reviewing and editing. Kate A Bolam: Conceptualization, methodology, data curation, and writing – reviewing and editing. Sami Mansfield: Conceptualization, methodology, data curation, and writing – reviewing and editing. Daniel Santa Mina: Conceptualization, methodology, and writing – reviewing and editing. Kerri M Winters-Stone: Conceptualization, methodology, and writing – reviewing and editing. Anna M Campbell: Conceptualization, methodology, and writing – reviewing and editing. Friederike Rosenberger: Conceptualization, methodology, and writing – reviewing and editing. Joachim Wiskemann: Conceptualization, methodology, and writing – reviewing and editing. Morten Quist: Conceptualization, methodology, and writing – reviewing and editing. Prue Cormie: Conceptualization, methodology, and writing – reviewing and editing. Jennifer Goulart: Conceptualization, methodology, and writing – reviewing and editing. Kristin L Campbell: conceptualization, methodology, supervision, writing – reviewing and editing.

Declaration of Competing Interest

None.

Funding

No external funding has been received for the preparation of the systematic review. Production costs have been covered by Astellas Pharma Canada Inc.

Transparency document

The Transparency document associated with this article can be found in the online version.

Acknowledgements

We thank UBC librarian Charlotte Beck for assistance with the search strategy and the International Bone Metastases Exercise Working Group for their guidance on the development of the protocol document.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2021.103433.

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