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PII: S0003-9993(18)30281-8

DOI: 10.1016/j.apmr.2018.04.008

Reference: YAPMR 57223

To appear in: *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION*

Received Date: 30 November 2017

Revised Date: 13 March 2018

Accepted Date: 7 April 2018

Please cite this article as: Heywood R, McCarthy AL, Skinner TL, Efficacy of exercise interventions in patients with advanced cancer: A systematic review, *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION* (2018), doi: 10.1016/j.apmr.2018.04.008.

Efficacy of exercise interventions in patients with advanced cancer: A systematic review

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Acknowledgements:

No sources of funding were used to assist in the conduct of this review or preparation of this article. No conflicts of interest relevant to the content of this review exists.

ABSTRACT

Objective: To critically analyse the literature surrounding the efficacy of exercise interventions in patients with advanced cancer.

Data Sources: A literature search was undertaken of health and medical electronic databases (PubMED, Medline, CINAHL, Embase, PEDRO, Web of Science and Scopus) until 1st March 2017.

Study Selection: Studies were included if they were published in the English language and met the following criteria: structured exercise as the primary intervention, ≥80% study participants diagnosed with advanced cancer that is unlikely to be cured; reported outcomes concerning physical function, quality of life, fatigue, body composition, psychosocial function, sleep quality pain and/or survival.

Data Extraction: Following title and abstract screening, 68 articles were eligible for full-text review, with a total of 25 studies (n=1188; 16 controlled trials, 9 non-controlled trials) included in the quantitative synthesis. Two reviewers assessed methodological quality using the Cochrane Risk of Bias Tool for controlled trials and a modified Newcastle-Ottawa Scale for non-controlled trials.

Data Synthesis: Aerobic exercise was utilised in six studies, resistance training in three studies and combination training (aerobic and resistance) in 15 studies. Significant between- and within-group improvements were reported with exercise in ≥50% of studies assessing physical function (83%), quality of life (55%), fatigue (50%), body composition (56%), psychosocial function (56%), and sleep quality (100%). Improvement within or between groups in pain following exercise was only observed in two studies (25%), while survival was unaffected in any study.

Conclusions: Most studies reported significant between- and/or within-group improvements in physical function, quality of life, fatigue, body composition, psychosocial function and sleep quality in patients with advanced cancer, although the effects on pain and survival rates are

unclear. Exercise appears to be an effective adjunct therapy in the advanced cancer context, although targeted studies are required to determine the optimal exercise dose to enhance outcomes for specific cancer diagnoses.

Key Words:

Neoplasms, physical medicine and rehabilitation, exercise, exercise therapy, treatment outcome.

Supportive cancer practice guidelines have advocated that attention to physical, psychological, social, and spiritual well-being is of equal importance across all stages of the cancer continuum. [1] However, it could be argued that patients with advanced cancer have the greatest need for interventions targeting quality of life, and their physical and psychosocial function, due to the greater symptom prevalence and emotional distress associated with non-curable disease. Furthermore, improving and maintaining function, quality of life and independence have been identified as key goals of patients with advanced illness. [2] Appropriately prescribed clinical exercise interventions are recognised as an effective adjunct treatment in cancer care, with a recent review highlighting the safety and feasibility of exercise prescription in advanced cancer patients. [3] However, the most recent evidence surrounding the efficacy of exercise in advanced cancer populations has yet to be systematically reviewed.

Five previous systematic reviews have examined the effects of physical activities (as opposed to exercise) on cancer patients with advanced disease. [4, 5, 6, 7, 8] Since this review's analysis was undertaken and shortly prior to submission, a similar review of exercise in advanced cancer patients appeared on line, indicating the importance of elucidating this area of oncology care given the increasing amount of research published in recent years.[4] Albrecht and Taylor [7] examined physical activity across the broad end-of-life spectrum (i.e., palliation and survival), while Lowe and colleagues [7] exclusively investigated the effects of physical activity in palliative care populations. Like these reviews, the most recently published review by Dittus and colleagues [4] included studies delivering unstructured physical activity and multidisciplinary interventions (e.g., physiotherapy, education, psychological and nutrition counselling), thereby limiting the ability to translate research findings into the clinical practice of exercise delivery and prescription. This is of particular importance considering the requirement for targeted evidence to inform the design of safe and effective clinical exercise interventions for these patients. Only two systematic reviews [5, 6] have examined the effects of structured exercise interventions on

cancer patients with advanced disease. In 2009, Beaton and colleagues [5] investigated the effects of structured exercise interventions in metastatic cancer, while Ribeiro and colleagues [6] specifically examined the effectiveness of exercise in advanced solid tumours. Both reviews excluded studies of lymphoma, melanoma, and myeloma patients from their analyses, which limits the applicability of the results to the entire advanced cancer patient population. Moreover, the majority of research in this area has been published recently, [4] while four of five past reviews have been limited to studies published prior to 2011, which may result in outdated recommendations regarding the delivery of clinical exercise in these patients. The limited number of high quality studies analysed in past reviews does not provide a robust evidence base to develop clinical practice guidelines in advanced cancer patient care.

Thus, there is a clear need for the synthesis of more recent and robust evidence to address gaps in the exercise oncology literature and inform evidence-based clinical practice in advanced cancer care. The aim of this paper was to systematically review the efficacy of exercise interventions in advanced cancer patients, inclusive of both blood and solid tumour diagnoses.

2 METHODS:

2.1 Data Sources and Search Strategy

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. [9] From the earliest time point to March 2017, the following databases were systematically examined: PubMED, Medline, CINAHL, Embase, PEDRO, Web of Science and Scopus. Searches were limited to full-text articles published in the English language in peer-reviewed journals.

A search of PubMed Central was undertaken, followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe articles. A three-step search strategy was used for this review including the following free-text and MeSH terms: neoplasms (MeSH Terms), OR cancer (MeSH Terms), OR “malignan*” AND “incurable”, OR “advanced", OR “metastat*” AND humans (MeSH Terms) AND exercise (MeSH Terms), OR "physical activity", OR "weight training" AND treatment outcome (MeSH Terms) AND humans (MeSH Terms) AND randomised controlled trials (Publication Type) OR experimental studies(MeSH Terms). The search strategy for PubMed Central is shown in Appendix 1.

The search terms were modified according to the specific vocabulary map of each database. The reference lists of retrieved articles were examined to locate additional studies that potentially met the inclusion criteria.

Articles were included if they satisfied the following criteria:

a) Analysed outcome measures relevant to physical function, quality of life, fatigue, body composition, psychosocial function, sleep quality, pain, or survival.
b) Involved >1 session of structured exercise (specified frequency, intensity, time or type) where direct effects of exercise could be isolated from other interventions effects.
c) Included ≥80% participants classified as having “advanced cancer”.

For our analysis, we coded groups as “control” if they were identified as controls by the original authors. Alternatively, if a group received “conventional,” or “usual care” intervention without being specifically named as control, it was assumed that this was a control condition. We excluded case studies, observational studies, conference abstracts and animal studies.

Disagreements were resolved by discussion and consensus was achieved in consultation with a third review author (AM) as arbiter.

2.2 Study Selection Process and Data Extraction

The titles and abstracts of all articles were screened by one author (RH). Two authors (RH and TS) independently screened full text articles of the relevant abstracts for eligibility. Data were extracted by one reviewer (RH), and checked by another (TS), using a standard data extraction form developed by the review authors. The extraction form included the following information:

1. General: publication status (published/unpublished), title, authors, source, contact address, country, language of publication, year of publication, duplicate publications, sponsoring.
2. Methods: randomisation procedure, allocation, blinding (participants, people administering treatment, outcome assessors), duration of study, design, analysis method (e.g. intention-to-treat).
3. Participants: number, age, diagnostic criteria, history (including treatment), baseline characteristics, setting.
4. Interventions: intervention (frequency, intensity, time, type), comparison group.
5. Outcomes: physical function, quality of life, fatigue, body composition, psychosocial function, sleep quality, pain, survival, any other outcomes assessed, other events, length of follow-up.
6. Results: results for each outcome and time of assessment specified above, including a measure of variation.

2.3 Risk of Bias and Methodological Quality assessment

The quality of the included articles was assessed by two authors (RH and TS) independently using the Cochrane Risk of Bias tool for randomised trials, [10] and a modified version of the Newcastle-Ottawa scale described by Wells et al. [11] for non-controlled trials. The modified Newcastle-Ottawa scale assessed each study on a scale from 0-3 (0=high risk of bias; 1=mostly

high risk of bias; 2=mostly low risk of bias; 3=low risk of bias) (Appendix 2). Disagreements were resolved by discussion and consensus or by consulting a third review author (AM) as arbiter.

2.4 Data Synthesis and Analysis

Results were analysed and reported using a combination of quantitative, descriptive and narrative data synthesis. The efficacy of the intervention for each of the analysed domains was determined by the presence of ≥1 outcome measure.

3 RESULTS:

3.1 Search and Selection of Studies

The initial search of the specified electronic databases yielded a total of 1872 studies, of which 1664 were deemed relevant after duplicate removal. Additional searching of reference lists returned seven further potentially-relevant articles. Following title and abstract screening, 68 articles were eligible for full-text review. The full texts of 68 articles were examined, of which 40 were excluded. A total of 25 trials reported across 28 articles were included in the quantitative synthesis (Appendix 3).

3.2 Study Design and Quality Assessment

Of the 25 included studies, 16 were randomized, controlled trials (National Health and Medical Research Council (NHMRC) evidence Level II), with the remaining nine pretest-posttest experimental studies (NHMRC evidence Level IV). The Level II and IV studies comprised eight

(50%) and two (22%) pilot studies, respectively. Courneya et al. [16, 17] reported results for a single RCT across two papers analysing different outcomes, while Rief et al. [27-29] reported results for a single RCT across three papers analysing different outcomes. Methodological quality ratings of Level II and IV studies are presented in Tables 1 and 2, respectively. Ten of 19 Level II papers (53%) were deemed to be at a low risk of bias, [13-17, 20, 23, 26, 27, 30] with only three (15%) rated as high risk. [18, 21, 27] Three of nine Level IV studies (33%) scored greater than 15 points (from a possible 21), indicating a low risk of bias [31, 32, 37] while the remaining six (67%) scored between 12-15 points indicating a moderate risk of bias (Figures 1 and 2). [33-39]

Table 1 Cochrane Risk of Bias Summary

Table 2 Modified Newcastle-Ottawa Scale Summary

Figure 1 Controlled Trials Risk of Bias Summary

Figure 2 Controlled Trials Risk of Bias Graph

3.3 Participants

The 28 included studies involved 1188 participants. The age of participants across studies ranged from 18 [17]-88 [37] years (mean (standard deviation)). Reports of disease stage were varied, with only three (12%) Level II [22, 23, 30] and one Level IV study [39] describing their sample as patients with "advanced cancer". Five studies defined the patient sample as advanced by cancer stage (III-IV), with ≥80% diagnosed with at IIIb or above, [13, 18, 19, 20, 21, 30] Three studies [26, 35, 39] described their samples as "palliative care" patients, with Oldervoll et al. [26] further providing a life expectancy of ≤2 years as additional criteria. Populations were otherwise classified as advanced cancer patients due to the severity of their described pathologies and/or the aggressiveness of treatment received.

The majority of studies (n=7) were undertaken in patients with lung cancer, [19, 21, 34, 36-38] followed by blood (including multiple myeloma, leukaemia, relapsed germ cell tumour, Hodgkin's and non-Hodgkin's lymphoma), [12, 14, 16, 17, 25] breast, [18, 23, 32] prostate, [15, 33] and gastrointestinal [22] cancer. The remaining ten studies included mixed cancer populations.

3.4 Control or Comparison Groups

The majority of Level II studies compared the intervention group to a control group receiving standard care (n=17). Standard care within one study [19] involved conventional physiotherapy, included breathing exercises. Of the remaining studies, two compared resistance training with aerobic exercise, [22, 24] while another compared Walking Qi-gong with standard exercise training. [30] A detailed analysis of the frequency, intensity, time and type of exercise interventions utilised in advanced cancer patients has previously been described. [4]

3.5 Efficacy Outcome Measures

3.5.1 Physical Function

Physical function was assessed in 23 studies [12-16, 19-28, 30, 31, 33-39] and was the primary outcome in eight studies. [13, 16, 20, 21, 23, 25, 31, 37] Of the 23 studies, 20 (87%) reported significant ($p<0.05$) improvements in ≥1 measure of physical function in response to the exercise intervention. [13, 15, 16, 19-22, 24-27, 30, 31, 33-39]

Results from 10 questionnaires relevant to physical function were reported across eight studies, [13, 15, 16, 19, 21-23, 33] with participants in four [13, 16, 19, 21] of seven [13, 15, 16, 19, 21-23] Level II studies reporting significantly ($p<0.05$) better physical function following exercise compared with controls (Table 3). The remaining Level IV study reported significant within-group improvements in physical function ($p=0.001$) in response to exercise. [33]

Exercise capacity was the most commonly-reported measure of physical function, with 12 studies assessing exercise capacity outcomes [15, 19, 21, 22, 30, 33-39] and two reporting exercise capacity as a primary outcome measure. [21, 36] Significant ($p<0.05$) improvements in exercise

capacity were reported in response to exercise in 10 of 12 (83%) studies. [14, 15, 19, 30, 33-37, 39] Three Level II studies [19, 21, 30] assessed six minute walk test (6MWT) distance, although only two [19, 30] observed a significant ($p<0.05$) improvement in the exercise group relative to the control (Table 3). The crossover study by Vanderbyl et al. [30] observed a significant order effect for both intervention groups, which led to reduced effect on all outcomes in the second interval of the trial, although standard exercise training was still improved significantly in comparison to the Walking Qi-Gong group (Table 3). Four [35-37, 39] of six [34-39] Level IV studies that included the 6MWT reported significant ($p<0.05$) improvements in response to exercise (Table 3 & 4). Kuehr et al. [34] reported significant improvements in 6MWT distance from baseline directly after the exercise intervention ($p<0.01$), with no difference from baseline observed at 2-month follow-up ($p=0.46$). Balke treadmill protocol results were reported in one study, [14] with greater increases seen in the exercise group compared to the control, although statistical significance was not reported. No significant between-group differences ($p>0.05$) in 12-minute walk test [12] or Bruce Treadmill test [23] distances were observed.

Cormie et al. [15] reported a significantly faster 400-meter walk time following exercise compared to usual care ($p=0.01$). Cormie et al. [33] also observed significant improvements at 3 months follow-up in 400-meter walk time ($p=0.007$), 6-meter fast walking speed, ($p=0.002$), and Godin Leisure Time Physical Activity Questionnaire ($p=0.001$). At 6-month follow-up, usual walking speed ($p=0.046$) was the only variable to remain significantly improved compared to baseline, with 6 m fast walking speed, 400-meter walk time, timed up-and-go, Sensory Organisation Test, Godin Leisure Time Physical Activity Questionnaire scores and Activity-specific Balance Confidence scores returning to baseline ($p>0.05$; Table 4). Jensen et al. [22] reported exercise capacity, as assessed by the Physical Work Capacity-130 test, was not significantly different between groups following the intervention (although the actual p value was not reported).

Litterini et al. [24] observed a significantly greater improvement (p=0.045) in Short Physical Performance Battery scores in response to aerobic training exercise relative to resistance training. Oldervoll and associates [26] reported significant between-group changes favouring improvements in the exercise group in shuttle walk time (p=0.008), although maximal stepping distance (p=0.22) and timed sit-to-stand (p=0.34) performance were not significantly different between groups. Vanderbyl et al. [30] also assessed sit to stand performance, although no significant (p>0.05) between-groups differences were observed.

Aerobic capacity was reported in five studies [16, 25, 31, 36, 37] with four reporting this as a primary outcome measure. [20, 25, 31, 36] All studies reported significant improvements in aerobic capacity in response to exercise (Tables 3 & 4). Four studies [16, 31, 36, 37] utilised maximal oxygen uptake ($\dot{V}O_2max$) or peak oxygen uptake ($\dot{V}O_2peak$) as measures of aerobic capacity, while the remaining study reported $\dot{V}O_2$ at 2 mmol/L lactate during a cycle ergometer exercise test. [25] One Level II study [16] observed significantly greater improvements in $\dot{V}O_2peak$ (+0.40 vs +0.03 L/min, p<0.001), peak power (+31 vs +2 W, p<0.001), and ventilatory threshold (+0.32 vs -0.03 L/min, p<0.001) in the exercise group relative to the control, while three Level IV studies [31, 36, 37] reported significant improvements (p<0.05) in aerobic capacity in response to exercise compared to baseline (Tables 3 & 4).

Muscular strength was assessed in 13 studies, [15, 19, 20, 22, 25, 26, 31, 33, 34, 36-39] with two studies reporting strength as the primary outcome of interest. [31, 37] Significant improvements in ≥1 measure of muscle strength were reported in 11 of 12 studies (85%) in response to the exercise intervention. [15, 19, 22, 25, 26, 31, 33, 36-39] The only Level II study assessing strength using a 1RM test observed significantly (p=0.02) greater improvements in the exercise group relative to the control, [15] while five [31, 36-39] of the six Level IV studies assessing 1RM found significant (p<0.05) improvements in response to exercise compared with baseline (Table 4). Cormie et al. [33] found significant changes (p=0.005) at the 3 month follow-up in 1RM, although this was not

maintained at the 6 month follow-up (p=0.291). Both Level II studies estimating 1RM [22, 25] found significantly (p<0.05) greater improvements in the exercise group relative to the control (Table 3). Jensen et al. [22] reported improvements in estimated 1RM of the legs, back, elbow flexors, and knee flexors (p<0.05), but not in the elbow extensors (p=0.072) or knee extensors (p=0.841) in response to resistance training. Kuehr et al. [34] reported significant improvements in knee extension (p<0.01) and knee flexion (p<0.01) from baseline, however elbow flexion and elbow extension were only significantly improved directly after the exercise intervention (p<0.05), with no difference from baseline observed at follow-up (p=0.68 and p=0.49, respectively). Three studies assessed isometric grip strength, [26, 34, 39] with one Level II study [26] reporting a significantly (p=0.01) greater increase in grip strength in the exercise group compared to the control and one Level IV study [39] observing a significant (p<0.01) improvement from baseline in response to exercise. Henke and colleagues [19] observed significantly (p<0.05) greater increases in maximal number of tricep extension, bicep curl and abdominal exercise repetitions to fatigue in the exercise group compared with the control. One Level II study assessed peak isometric joint torque and observed no significant (p>0.05) differences between the exercise and control groups following the intervention. [20]

Lung capacity was reported in three studies, [21, 36, 37] although none assessed this as a primary outcome measure. Only one [21] study reported significantly greater within-group improvements (p=0.02) in forced expiratory volume over 1 second (FEV1) and Medical Research Council dyspnoea scale (p=0.047) relative to the control, with no significant (p>0.05) differences observed in forced vital capacity (FVC) or the Baseline Dyspnoea Index (Table 3).

3.5.2 Quality of Life

Quality of life (QOL) was assessed in 20 studies, [12, 13, 15, 16, 19-23, 25, 28, 30-39] with six (30%) reporting QOL as the primary outcome of interest. [16, 21, 26, 28, 30, 35] Of all studies, 11 (55%) [12, 16,

[19, 20, 22, 25, 28, 31, 32, 38, 39] reported significant improvement in ≥1 measure of QOL in response to the exercise intervention (Tables 3 & 4).

Seven Level II studies [12, 16, 19, 20, 22, 25, 28] reported significant between-group differences following the intervention, with the exercise group reporting higher QOL as measured by Symptom Distress Modified Outcome scale, [12] Functional Assessment of Cancer Therapy (FACT)-Anemia, [16] European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ)-Core questionnaire (C30) [19, 20, 22, 25] and psychosocial domain of EORTC QLQ-Bone Metastases [28] (Table 3). No significant between-group changes were seen in any other Level II studies reporting EORTC QLQ-C30 ($p=0.17$), [23] Short Form-36 ($p=0.4$) [15] and FACT-General ($p=0.74$; $p=0.98$). [13, 30] Jastrzębski et al. found no significant ($p>0.05$) within-group changes or between-group differences in Short Form-36 Mental or Physical Capacity subscale (Table 3). [21] Of the three Level IV studies [31, 35, 39] reporting EORTC QLQ-C30 scores, two [31, 39] showed significantly ($p<0.05$) improved scores following the intervention (Table 4). Oldervoll et al. [35] did not detect a significant change in EORTC QLQ-C30, although a trend favouring improvement in QOL was observed ($p=0.06$). Rief et al. [28] utilised the EORTC QLQ-Bone Metastases (BM22) module, observing significant between-group differences favouring exercise in the psychosocial domain of the questionnaire ($p=0.01$).

One Level IV study [31] observed a significant ($p<0.05$) within-group change in Short Form-36 scores ($p<0.001$) compared to baseline, while the other [33] observed no significant ($p>0.05$) change following the intervention. Van den Dungen and colleagues [39] reported significant ($p=0.04$) within-group improvements in Edmonton Symptom Assessment System scores. Carson et al. [32] utilised a 10-point Likert scale to assess patients' daily experiences of invigoration, relaxation, distress, and acceptance; multilevel modelling revealed significant improvements in all outcome measures in the following the intervention (Table 4).

Whilst no Level II studies utilised the FACT-Lung questionnaire, of the four Level IV studies, [34, 36-38] that described FACT-Lung outcomes, two (50%) reported significant ($p<0.05$) within-group improvements with exercise. [34, 38] Temel et al. [38] reported a significant ($p<0.05$) improvement in the lung cancer subscale of the FACT-Lung, but not in any other subscale, in response to exercise. Kuehr et al. [34] reported a significant within-group improvement in FACT-Lung score following the intervention ($p=0.03$), however Patient Health Questionnaire-9 scores were unchanged from baseline ($p=0.39$).

3.5.3 Fatigue

Fatigue was measured in 16 studies [12-16, 18, 23-26, 28, 33-36, 39] with five (31%) Level II studies reporting fatigue as their primary outcome of interest. [12, 14, 18, 19, 23] Of the 16 studies, eight (50%) reported significant improvement in ≥1 measure of fatigue in response to the exercise intervention. [13, 16, 18, 23, 25, 28, 39] Six Level II studies reported significant between-group differences in fatigue following the intervention, with the exercise group reporting lower Levels of fatigue as measured by the FACT-Fatigue scale ($p=0.03$), [13] FACT-Anemia Fatigue subscale ($p=0.01$), [16] Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F; $p=0.025$), [18, 23] Visual Analogue Scale (VAS; $p=0.05$), [24] Modified Fatigue Impact Scale scores ($p=0.02$) [25] and 'physical fatigue' ($p=0.01$) domain of the EORTC QLQ-Fatigue 13 [28] compared to usual care. However, Rief et al. [28] did not find significant between-group differences in the 'cognitive fatigue' ($p=0.43$) or 'emotional fatigue' ($p=0.16$) domains of the EORTC QLQ-Fatigue 13. [28] Coleman et al. [14] also reported Profile of Mood States (POMS)-Fatigue Inertia scores resulted in a 'desired change' in the exercise group compared with usual care, however no significance Level was described (Table 3). Van den Dungen et al. [39] reported significant within-group improvements in fatigue as measured by the Checklist Individual Strength ($p=0.01$) and Research and Development (RAND)-36 ($p=0.02$) questionnaires following exercise compared to baseline. Ligibel et al. [23] reported no change in FACIT-F scores in either group, while Headley et

al. [18] reported both groups' scores declined over the course of the intervention, though the exercise group scores declined significantly less than the control (p=0.03). No significant between- or within-group changes were observed in the remaining studies assessing Multidimensional Fatigue Symptom Inventory-Short Form, [18, 33] or patient experiences of daily fatigue assessed with 10-point Likert scale. [32]

3.5.4 Psychosocial Function

Psychosocial function was assessed in nine studies [14-16, 25, 28, 30, 33, 37, 38] although none reported psychosocial function as the primary outcome. Five studies (56%) reported significant ($p<0.05$) improvements in response to exercise in ≥1 measured outcome. [16, 25, 28, 33, 37] Courneya et al. [16] observed significantly (p=0.031) less depressive symptoms, as assessed with the Centre for Epidemiological Studies Depression Scale-Short Form following the intervention compared to the control group, although anxiety measured using the Spielberger State Anxiety Inventory-Short Form scores were not significantly different between groups (p=0.642). Oechsle et al. [25] found significant differences between groups in the psychosocial (p=0.03) and cognitive (p=0.02) function domains of the Modified Fatigue Impact Scale, with results favouring the exercise group (Table 3). Rief et al. [28] reported significantly higher scores on the Questionnaire on Stress in Cancer Patients-R10 following exercise in comparison to standard care (p=0.02). Hospital Anxiety and Depression Scale scores were reported in one Level II [30] and two Level IV studies, [37, 38] although only Quist et al. [37] reported significant differences, with improvements observed in response to exercise (p=0.007). No significant ($p>0.05$) changes following exercise were observed in POMS, [14] SF-36 or Brief Symptom Inventory scores. [15, 33]

3.5.5 Body Composition

Body composition was assessed in nine studies, [14-16, 22, 33, 35-37, 39] although none assessed this as a primary outcome measure. Five (56%) reported significant improvements in ≥1 measure of body composition in response to the exercise intervention. [14-16, 33, 39] Exercise significantly improved

lean body mass in all four studies measuring this outcome with air displacement plethysmography [14] or dual energy X-ray absorptiometry (DXA). [15, 16, 33] Fat mass, [33] body mass [16, 22] and body mass index (BMI) [35-37] were not significantly different ($p>0.05$) between- or within-groups in any study assessing these outcomes (Tables 3 & 4). Significant improvements between- ($p=0.05$) and within-groups ($p=0.02$) were reported in body fat percentage calculated by DXA [20] and skinfold thickness measurement, [39] respectively. Cormie et al. [33] found significant reductions in whole body fat mass ($p=0.016$) measured by DXA, however this was not evident at 6-month follow-up ($p=0.208$).

3.5.6 Sleep Quality

Sleep quality was assessed in four studies, [13, 14, 17, 22] with one [13] examining sleep as the primary outcome measure. All studies (100%) reported significant ($p<0.05$) between-group improvements in response to exercise relative to the control groups (Table 3), while Jensen et al. [22] reported significantly improved sleep duration in response to both aerobic and resistance training groups ($p=0.028$).

3.5.7 Pain

Pain was assessed in seven studies [13, 15, 24, 27, 28, 30, 32, 33] with only one study (14%) reporting pain as a primary outcome of interest. [32] One Level II and one Level IV study (29%) showed significant ($p<0.05$) between- and within-group improvements, respectively, following exercise in ≥1 measured pain outcome. [27, 32] Carson et al. [32] reported patients' daily experiences of pain, as assessed with a 10-point Likert scale, were significantly improved from baseline ($\beta=0.15$, $t=2.71$, $p<0.01$) following the intervention. One Level II study identified significantly lower VAS pain scores ($p=0.003$) in the intervention group compared with the control, [27] however no significant within- or between-group changes in the remaining studies assessing VAS, [24, 33] numerical rating scale, [13] FACT-Bone Pain questionnaire [15, 28, 33] or 10-point Likert scale [30] were observed (Tables 3 & 4).

3.5.8 Survival

Survival was assessed in one study (across two papers) [27, 29] and was the primary outcome measure of one paper. [29] Mortality, [29] overall survival (time from initial diagnosis to death), progression free survival, and bone survival (time from initial spinal bone metastatic diagnosis until death) [27] were assessed. No significant ($p>0.05$) differences in any measure of survival were observed between the exercise group and standard care in either study (Table 3).

4 Discussion

This systematic review summarises the available evidence regarding exercise as supportive care in advanced cancer patients. Based on the evidence presented, the incorporation of exercise into the care of advanced cancer patients may significantly improve physical function, body composition, fatigue, QOL and psychosocial function. Evidence is less clear surrounding the role of exercise in pain management and survival.

The vast majority (87%) of studies assessing physical function reported significant improvements in response to exercise. Decline in physical function has been reported as one of the most debilitating symptoms associated with advanced cancer. [40] Thus, interventions targeting improvements in this domain are of utmost importance in optimising advanced cancer patient care and reducing the burden of disease associated with diminished physical function.

All studies found improvement in aerobic capacity as measured by V̇O2max or V̇O2peak, with an average improvement of 0.25 L/min across the four studies assessing this outcome. A meta-analysis of early stage cancer patients' exercise response established the improvement in V̇O2peak was a weighted mean difference of 2.9 ml/kg/min. [41] Based on available participant body mass data reported by Courneya et al., [16] average improvements in relative V̇O2 equate to approximately 3.1 ml/kg/min (based on average body mass of 81.8kg). These normative reference values suggest that cardiorespiratory adaptations in response to exercise training may

be similar in advanced stage cancer patients to that of early stage cancer patients, although exercise intervention heterogeneity and poor reporting of participant body mass data across studies makes this conclusion difficult to confirm. Further investigation into this area is of considerable clinical importance considering cancer specific survival is established to improve by 5% for each 3.5 ml/kg/min increase in $\dot{V}O2$. [42]

Six of the nine studies [19, 30, 35-37, 39] assessing 6MWT distance observed significant improvements in response to the exercise intervention. Two [21, 38] of the remaining three studies had small sample sizes that limit the ability to detect statistically meaningful changes, while the third study [34] reported a significant improvement favouring exercise at the first post-intervention assessment time point, but not at follow-up. Distance achieved in the 6MWT has been established as an important prognostic indicator of morbidity and mortality in cancer and other advanced disease populations. [43, 44] The average improvement in 6MWT distance in response to exercise was 39.2 m (Tables 3 & 4); this is comparable with the minimal clinically meaningful changes of 32.0 m and 34.4 m that have been established for perceived improvement by patients with chronic heart failure [44] and following cerebrovascular infarct [45], respectively. Thus, the benefits of exercise interventions on exercise capacity and patient perceived functional improvements in advanced cancer populations are both statistically and clinically meaningful.

Fatigue, QOL and psychosocial function have been identified as areas of particular clinical significance for optimising cancer outcomes with exercise. [1, 46] In advanced cancer patients specifically, improvements in QOL and psychosocial function may be of the greatest importance, considering the emotional challenges associated with an incurable disease. [47] The variability in outcome measures used across studies limits the conclusions that can be made regarding why some studies observed improvements in these outcomes, whereas others did not. It is also plausible that participants' interpretation of fatigue was confounded by the usual physiological response to increases in physical exercise; which may include shortness of breath/dyspnoea,

441 muscle soreness and transient reductions in physical working capacity. [48] Despite this, ≥50% of
442 studies assessing fatigue, QOL and psychosocial function reported significant improvements in
443 these outcomes in response to exercise. Additionally, sleep quality was improved in all studies
444 assessing this outcome; however, further studies should be conducted to confirm these findings
445 considering only three studies specifically investigated this outcome. Despite limited research
446 surrounding sleep quality modification in advanced cancer patients, clinical practice guidelines
447 for cancer-related fatigue management advocate the use of sleep enhancement therapies
448 (including exercise) and should thus be investigated further in this population. [49] These findings
449 lend support to the argument that exercise interventions can improve outcomes in patients with
450 advanced cancer through the management of frequently encountered debilitating symptoms
451 associated with the latter stages of disease.
452 Changes in body composition were not the primary outcome of any study exploring the effects
453 of exercise in patients in advanced cancer, despite the strong association between body
454 composition changes and survival in advanced cancer populations. [49] DXA-assessed fat mass
455 was not improved in any study, suggesting that exercise did not have had a direct effect on body
456 fat in advanced cancer patients. In contrast, all four studies assessing lean body mass with DXA
457 [15, 16, 33] or air displacement plethysmography [14] observed significant improvements in response to
458 exercise, likely due to the resistance training component of each trial. This could explain the
459 presence of significant body fat percentage changes [16, 39] favouring exercise in the absence of
460 concurrent reductions in body fat mass, given the greater lean body mass/fat mass ratio. It should
461 be noted that no studies observed significant changes in body mass or BMI, although this could
462 be attributed to the poor sensitivity of these measures in evaluating body composition changes. [51]
463 The improvements in lean body mass observed following exercise intervention are of clinical
464 importance considering the marked skeletal muscle atrophy typical of cancer-induced cachexia,
465 which affects up to 80% of advanced cancer patients. [52] These improvements could be of the

greatest benefit in advanced cancer patients considering the close association between cancer-induced cachexia and disease progression. [53] These findings suggest that exercise can improve lean mass in advanced cancer patients, although it is unclear whether exercise can elicit changes in body mass or fat mass.

Pain was only improved in response to exercise in 25% [27, 32] of studies. However, the effect of exercise on pain management was the primary outcome in only one study, [32] suggesting many studies were not designed with the specific aim of pain management. Interestingly, the improvements in pain observed by Rief et al. [27, 28] occurred in patients with spinal bone metastases who performed exercises that specifically targeted the site of metastasis with spinal muscle exercises. This contrasts with guidelines recommending those with bone metastases perform modified exercise programs designed carefully to avoid exercising the site of metastasis due to safety concerns. [1, 54] These reductions in pain observed in response to isometric exercise in the studies by Rief et al. [27, 28] are comparable to those observed in healthy individuals, [55] suggesting increases in pain thresholds can be safely elicited in response to appropriately prescribed exercise. The improvements in pain reported by Carson et al. [32] might also be explained by the nature of the 'Yoga of Awareness' intervention, which targeted improvements in pain and emotional distress. Based on these results, it appears that certain types of exercise could be more effective than others in managing pain associated with advanced cancer, although further research is warranted to confirm these findings.

Survival was only assed in two studies, [27, 29] with neither study demonstrating changes in survival between exercise and control interventions. Despite the lack of evidence suggesting exercise interventions reduce mortality, the data imply that improved physical function, body composition, QOL, psychosocial function and fatigue can be achieved. This highlights that the quality of life of advanced cancer patients lives can be improved through reduced morbidity and greater symptom tolerance. In comparison, a recent review by Cormie and colleagues [56] reported

that cancer patients performing more exercise have a lower relative risk of cancer mortality; however, the studies reporting survival in this review analysed small samples of patients with already-compromised life expectancy and inconsistent sites of primary tumour origin. It was also noted by Cormie et al. [56] that the majority of reported studies controlled for cancer stage, thereby limiting the ability to determine the effects of exercise on survival outcomes between disease stages. Thus, there is clear indication for further research investigating the association between exercise and survival with longer follow-up periods, particularly within the advanced cancer patient population.

Study Limitations

This systematic review had several limitations worthy of comment, particularly with respect to the heterogeneity of the exercise interventions and outcome assessment methods. Studies investigating psychosocial function, body composition, pain, sleep quality and survival as primary outcomes of interest were lacking. Specifically, inconsistent outcome measures reported across studies limit the ability to draw conclusions based on the pooled results of numerous studies and thus, meta-analysis of the data was not feasible. Further, some authors described results for participants drawn from single trials in numerous studies without clear definition of which participants' outcomes were reported more than once. [16, 17, 27-29] Few studies compared responses to interventions with different exercise parameters, which limits the ability to determine the optimal dose of exercise to enhance outcomes for patients with advanced cancer. Furthermore, accurate comparison of different exercise interventions' effects on specific efficacy domains was confounded due to the range of assessment tools utilised across studies. Thus, it is recommended that future research utilise consistent outcome measure assessment reporting using standardised protocols and aim to compare different frequencies, intensities, durations and types of exercise to ensure clinicians and future researchers are able to accurately assess the efficacy of specific exercise interventions on outcomes of clinical relevance. The majority of included

studies were Level II studies, however, 36% of studies were constrained by lack of a control/comparison group. It is therefore suggested future studies utilise a control/comparison to better determine the efficacy of exercise interventions relative to standard advanced cancer care and different intervention parameters. A recent review highlighted the safety and feasibility of high intensity interval training and high load resistance training,[4] which are methods capable of eliciting substantial improvements in aerobic capacity, muscle strength, body composition and QOL in cancer patients across the disease continuum.[57-59] Current findings suggest these outcomes are highly responsive to exercise in advanced cancer patients, and thus, further research should specifically explore the clinical utility of these training methods.

Conclusions

This systematic review offers a comprehensive evaluation of the existing literature surrounding exercise interventions in advanced cancer patients. Based on the available evidence, exercise appears to be an effective intervention that should be recommended in advanced cancer care to improve physical function, QOL, fatigue, body composition, psychosocial function, and sleep quality, although its effects on pain and survival are still unclear. Targeted research is also required to enhance understanding of the most effective dose of exercise required to elicit the most favourable responses. Thus, clinicians are encouraged to consider referring their patients with advanced cancer to appropriately-qualified exercise professionals capable of delivering individually-tailored exercise programs to improve physical function, QOL, fatigue, body composition, psychosocial function, and sleep disturbances commonly seen throughout the advanced stages of cancer.

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Appendix 1

PubMed Central Search Algorithm (PICO)
• *Population*: ((((((neoplasms(MeSH Terms)) OR ("cancer" OR "Malignan*"))) AND ((((recurrence(MeSH Terms) OR "recurrence" OR "advanced" OR "metastat*" OR "incurable"))) AND
• *Intervention*: (exercise(MeSH Terms) OR "exercise" OR "physical activity" OR "weight training" OR "resistance training" OR "strength training" OR "muscle strengthening" OR "run*" OR "cycl*" OR "yoga" OR "tai chi" OR "walk*")))) AND
• *Outcome*: (treatment outcome(MeSH Terms) OR "treatment outcome" OR fatigue(MeSH Terms) OR "fatigue" OR quality of life(MeSH terms) OR "physical wellbeing" OR "functional wellbeing" OR musculoskeletal and neural physiological phenomena(MeSH Terms) OR physical examination(MeSH Terms) OR "physical function" OR "aerobic capacity" OR "activities of daily living" OR body composition(MeSH Terms) OR anthropometry(MeSH Terms) OR "body fat" OR "lean body mass" OR "fat mass" OR "muscle mass" OR "bone density" OR pain(MeSH Terms) OR "pain" OR survival(MeSH Terms) OR “survival” OR psychological phenomena and processes(MeSH Terms) OR "psychological function" OR "psychosocial function" OR "mental health" OR "cognition"AND "humans"(MeSH Terms).

Appendix 2

Adapted version of a modified Newcastle-Ottawa Scale for non-controlled studies

Modified Newcastle-Ottawa Scale (NOS) Legend

0 = Definitely no (high risk of bias)
1 = Mostly no
2 = Mostly yes
3 = Definitely yes (low risk of bias)

Domain of evaluation: Methods for selecting study participants (*i.e. Selection bias)*
Is the source population (cases, controls, cohorts) appropriate and representative of the population of interest?

(high risk of bias)	**0**	**1**	**2**	**3**	(low risk of bias)

Example of low risk of bias: A consecutive sample or random selection from a population that is representative of the condition under study.
Example of moderate risk of bias: A consecutive sample or random selection from a population that is not highly representative of the condition under study.
Example of high risk of bias: The source population cannot be defined or enumerated (i.e. volunteering or self-recruitment).

Domain of evaluation: Methods to control confounding (*i.e. Performance bias)*
Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?

(high risk of bias)	**0**	**1**	**2**	**3**	(low risk of bias)

Example of low risk of bias: Sample size was adequate and there was sufficient power to detect a difference in the outcome.
Example of high risk of bias: Sample size was small and there was not enough power to test outcome of interest.

Did the study identify and adjust for any variables or confounders that may influence the outcome?

(high risk of bias)	**0**	**1**	**2**	**3**	(low risk of bias)

Example of low risk of bias: The study identified and adjusted for all possible confounders that may influence estimates of association between exposure and outcome (*i.e. Was the patient being treated for a medical condition such as chronic pain and was being prescribed opioids while on methadone treatment?*)
Example of moderate risk of bias: The study identified and reported possible variables that may influence the outcome but did not explore the interaction.
Example of high risk of bias: The study either did not report any variables of influence or acknowledge variables of influence when it was clear they were present.

Domain of evaluation: Statistical methods (*i.e. Detection bias)*
Did the study use appropriate statistical analysis methods relative to the outcome of interest?

(high risk of bias)	**0**	**1**	**2**	**3**	(low risk of bias)

Example of low risk of bias: The study reported use of appropriate statistical analysis as required (*i.e. adjusting for an unbalanced distribution of a specific covariate among sexes, or correcting for multiple testing error*)
Example of moderate risk of bias: The study either used correct statistical methods but did not report them well, or used the incorrect methods but reported them in detail.
Example of high risk of bias: The study did not use appropriate statistical analysis as required (*i.e. did not adjust for an unbalanced distribution of a specific covariate among sexes, or correct for multiple testing error when necessary*) or did not report them adequately.

Is there little missing data and did the study handle it accordingly?

(high risk of bias)	**0**	**1**	**2**	**3**	(low risk of bias)

Example of low risk of bias: The study acknowledged missing data to be less than 10% and specified the method of handling it.
Example of moderate risk of bias: The study either had greater than 15% but they specified the method they used to handle it.
Example of high risk of bias: The study had greater than 15% missing data and did not handle it at all.

Domain of evaluation: Methods for measuring outcome variables (*i.e. Information bias)*
Is the methodology of the outcome measurement explicitly stated and is it appropriate?

(high risk of bias)	**0**	**1**	**2**	**3**	(low risk of bias)

Example of low risk of bias: The study provides a detailed description of the outcome measure(s) which are appropriate for the outcome of interest.
Example of moderate risk of bias: The study provides a somewhat complete description of outcome measurements and they are justified.
Example of high risk of bias: The study provides limited information on the methods of measuring the outcome and the measure is not appropriate considering the outcome.

Is there an objective assessment of the outcome of interest?

(high risk of bias)	**0**	**1**	**2**	**3**	(low risk of bias)

Example of low risk of bias: The study used objective methods to discern the outcome status of participants (*i.e. laboratory measurements, medical records*).
Example of moderate risk of bias: The study relied on subjective data as the primary method to discern outcome status of participants (*i.e. self-report*).
Example of high risk of bias: The study had limited reporting about assessment of outcomes.

Appendix 3

PRISMA Flow Diagram

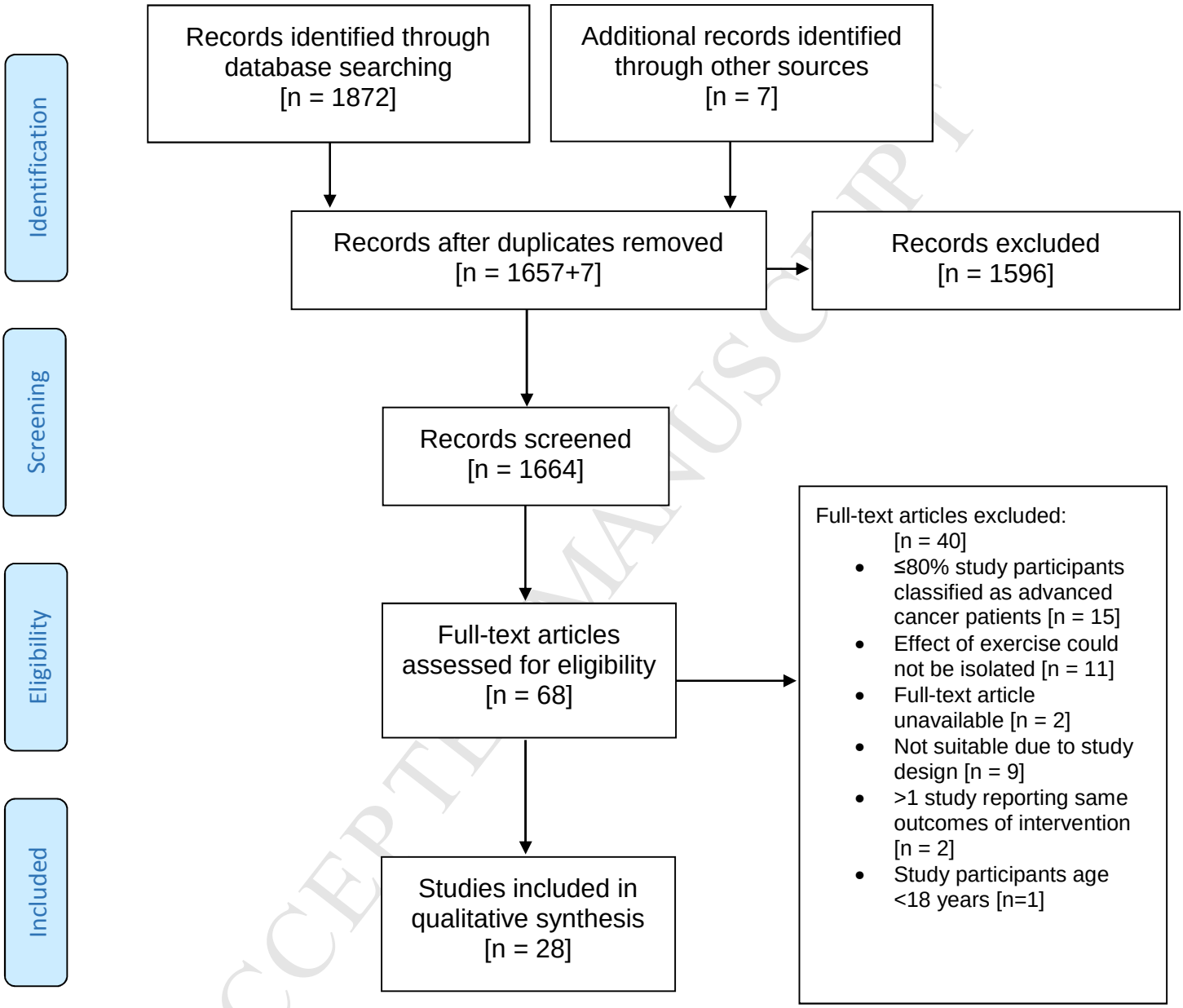


Table 1 Cochrane Risk of Bias Summary

Y = low risk of bias; U = Unclear risk of bias; N = High risk of bias

	Cochrane Quality Appraisal Tool																		
STUDY	**Chang et al 2008 [12]**	**Cheville et al 2013 [13]**	**Coleman et al B 2003 [14]**	**Cormie et al 2013 [15]**	**Courneya et al 2009 [16]**	**Courneya et al 2012 [17]**	**Headley et al 2004 [18]**	**Henke et al 2014 [19]**	**Hwang et al 2012 [20]**	**Jastrzębski et al 2015 [21]**	**Jensen et al 2014 [22]**	**Ligibel et al 2016 [23]**	**Litterini et al 2013 [24]**	**Oechsie et al 2014 [25]**	**Oldervoll et al 2011 [26]**	**Rief et al 2014 A [27]**	**Rief et al 2014 B [28]**	**Rief et al 2016 [29]**	**Vanderbyl et al 2017 [30]**
Sequence Generation	**U**	**Y**	**U**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**U**	**N**	**U**	**Y**	**U**	**Y**	**Y**	**Y**	**Y**	**Y**
Allocation Concealment	**U**	**Y**	**Y**	**Y**	**Y**	**Y**	**U**	**U**	**N**	**U**	**U**	**U**	**U**	**U**	**U**	**U**	**U**	**Y**	**Y**
Blinding (personnel)	**U**	**N**	**U**	**U**	**U**	**U**	**U**	**U**	**Y**	**U**	**U**	**U**	**N**	**U**	**Y**	**U**	**U**	**N**	**Y**
Incomplete outcome data	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**U**	**Y**	**Y**	**N**
Free of selective outcome reporting	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**U**	**N**	**Y**	**Y**
Free of other sources of bias?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**N**	**N**	**Y**	**Y**	**N**
Total Y (Risk)	**3 (Mod)**	**5 (Low)**	**4 (Mod)**	**5 (Low)**	**5 (Low)**	**5 (Low)**	**2 (High)**	**3 (Mod)**	**5 (Low)**	**1 (High)**	**3 (Mod)**	**3 (Mod)**	**4 (Mod)**	**3 (Mod)**	**4 (Mod)**	**1 (High)**	**3 (Mod)**	**5 (Low)**	**4 (Mod)**

Table 2 Modified Newcastle-Ottawa Scale Summary

Modified Newcastle-Ottawa Quality Appraisal Tool

STUDY	Adamsen et al 2006 [31]	Carson et al 2007 [32]	Cormie et al 2014 [33]	Kuehr et al 2014 [34]	Oldervoll et al 2006 [35]	Quist et al 2015 [36]	Quist et al 2012 [37]	Temel et al 2009 [38]	van den Dungen et al 2014 [39]
1) Domain of evaluation: Methods for selecting study participants (i.e. Selection bias)									
Is the source population (cases, controls, cohorts) appropriate and representative of the population of interest?	**2**	**2**	**2**	**2**	**3**	**2**	**2**	**2**	**3**
2) Domain of evaluation: Methods to control confounding (i.e. Performance bias)									
Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?	**2**	**1**	**1**	**2**	**2**	**3**	**1**	**1**	**1**
Did the study identify and adjust for any variables or confounders that may influence the outcome?	**2**	**2**	**2**	**1**	**1**	**3**	**1**	**1**	**0**
3)Domain of evaluation: Statistical methods (i.e. Detection bias)									
Did the study use appropriate statistical analysis methods relative to the outcome of interest?	**2**	**3**	**3**	**2**	**2**	**3**	**2**	**2**	**2**
Is there little missing data and did the study handle it accordingly?	**3**	**3**	**2**	**1**	**0**	**2**	**1**	**1**	**3**
4) Domain of evaluation: Methods for measuring outcome variables (i.e. Information bias)									
Is the methodology of the outcome measurement explicitly stated and is it appropriate?	**3**	**3**	**2**	**3**	**3**	**3**	**3**	**2**	**3**
Is there an objective assessment of the outcome of interest?	**3**	**2**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Total(Risk)	**17 (Low)**	**16 (Low)**	**15 (Mod)**	**14 (Mod)**	**14 (Mod)**	**19 (Low)**	**13 (Mod)**	**12 (Mod)**	**15 (Mod)**

0 = Definitely no (high risk of bias) 1 = Mostly no 2 = Mostly yes 3 = Definitely yes (low risk of bias)

Table 3 Study Characteristics of Controlled/Comparative Trials

Author	Study Type (NHMRC Level)	Diagnosis	Age (years)	Treatment (n)	Intervention	Control/ Comparison	Exercise parameters	Outcomes (Intervention vs Control/Comparison)		Comments
								Δ Intervention > Δ Control/Comparison ($p<0.05^{*}$)	Δ Intervention ≤ Δ Control/Comparison ($p\geq0.05^{*}$)	
Chang et al 2008 [12]	Randomised control trial (Level II)	Acute myelogenous leukaemia (n=24 allocated; n=22 analysed)	49.4±15.3 (intervention) 53.3±13.6 (control)	Cytarabine 7 days + Idarubicin 3 days (n=14) High dose Cytarabine (n=8)	3 week supervised walking program (n=11)	Standard care (n=11)	5x/week Walking @ HR 30 bpm above resting HR x 12 min	QOL: Symptom Distress Scale-Modified Form (p=0.045)	Fatigue: BFI worst (p=0.08), average (p=0.08), interference with ADL (p=0.19). QOL: Depression and anxiety: POMS (p=0.31). Physical function: 12 min walking distance (p=0.35)	
Cheville et al 2013 [13]	Randomised control trial (Level II)	Stage IV lung cancer (n=34) stage IV colorectal cancer (n=32)	63.8±12.5 (intervention) 65.5±8.9 (control)	Radiation (n=5) Chemotherapy: Biologics (n=7) Single agent (n=3) Combination (n=3) Platinum based (n=2), Bevacizumab based (n=16) Other (n=6)	8 week unsupervised home exercise program; aerobic + resistance training (n=26)	Standard care (n=30)	4x/week Incremental walking equal to 3.5 MET hours/week; 5 Theraband exercises x 10 reps	Fatigue: FACT-F (Δ=4.46±8.65 vs -0.79±9.11points, p=0.03) Physical function: AM-PAC Mobility (Δ=4.88±4.66 vs 0.23±5.22 points, p=0.002), Sleep: NRS (Δ=1.46±1.88 vs -0.10±1.71 points, p=0.002)	QOL: FACT-G (Δ=1.07±11.60 vs 0.12±10.22 points; p=0.54), Physical function: AM-PAC Activity (Δ=1.56±5.53 vs 0.94±5.91 points, p=0.74) Pain: NRS (Δ=-0.62±2.69 vs -0.50±2.01 points, p=0.87)	
Coleman et al 2003 [14]	Pilot randomised control trial (Level II)	Multiple myeloma with bone metastasis (n=24)	55 (42-74)	DCEP + CAD, high-dose Melphalan with peripheral blood stem cell transplantation (n=24, 50% randomised to receive Thalidomide)	6 month unsupervised home exercise program; aerobic + resistance training (n=14)	Standard care (n=10)	Self-managed frequency + volume Walking @ RPE 12-15; Theraband or bodyweight exercises @ RPE 9-10 1-2 sets x 8 reps	Aerobic capacity: Balke protocol (Δ=-0.61 vs -3.3 min, p value NR) Muscle strength: 1RM (Δ=+2.4 vs -12.6%, p value NR) Fatigue: POMS fatigue-inertia (Δ=-1.2 vs +0.3, p value NR) Psychosocial function: POMS (Δ=-5.7 vs -8.4, p value NR) Sleep: Ambulatory monitoring (Day Δ=+113 vs +137 min, night Δ=+58 vs -15 min, p value NR) Body composition: Lean body mass (Δ=+0.40 vs -0.44 kg/month, p<0.01)		50% of patient randomised to receive thalidomide therapy (results reported for non-thalidomide group)

Cormie et al 2013 [15]	Pilot randomised control trial (double-blinded) (Level II)	Prostate cancer with bone metastasis (n=20; Gleason 8.2)	73.1±7.5 (intervention) 71.2±6.9 (control)	Previous ADT (n=20) Previous radiotherapy (n=11) Previous surgery (n=4)	3 month unsupervised aerobic home exercise program + supervised resistance training (n=10)	Standard care (n=10)	2x/week Resistance training, 2-4 sets 8-12 reps x 60 min Walking and/or stationary cycling, moderate intensity x 150 min/week	Muscle strength: 1RM (+1.4 vs -2.7 kg, p=0.02), Physical function: 400-m walk (Δ=-6.2 vs +6.8 sec, p=0.01), 6-m walk usual pace (Δ=-0.25 vs +0.31 sec, p<0.001), timed up and go (Δ=-0.44 vs -0.27 sec, p=0.15) Body composition: DXA lean mass (Δ=+0.6 vs -0.7 kg, p=0.03)	Fatigue: MFSI-SF Δ=+3.6 vs -2.2 points, p=0.52) QOL: SF-36 (physical Δ=+0.7 vs +0.7 points, p=0.96, mental Δ=-1.5 vs +0.4 points, p=0.4) Body composition: DXA fat mass (+0.01 vs +0.03 kg, p=0.642) Physical function: 6-m walk fast paced (Δ=-0.05 vs +0.16 sec, p=0.07), Godin Leisure score (Δ=+7.7 vs +2.1 points, p=0.35) Balance: SOT (Δ=-0.90 vs +0.03 points, p=0.36), ABC score (Δ=+1.6 vs -2.9 points, p=0.75) Psychosocial function: BSI-18 depression (Δ=+1.8 vs +2.3 points, p=0.11, anxiety Δ=+1.6 vs +1.2 points, p=0.47) Pain: FACT BP (Δ=-3.1 vs + 2.2 points, p=0.26, VAS (Δ=+0.6 vs +0.3 cm, p=0.60)	
Courneya et al 2009 [16]	Randomised control trial (Level II)	Aggressive non-Hodgkin's lymphoma (n=48); Indolent non-Hodgkin's lymphoma (n=52); Hodgkin's lymphoma (n=22)	53.2 (range 18-80)	Chemotherapy (n=54) Radiotherapy (n=28)	3 month supervised aerobic exercise program (n=60; 24 aggressive non-Hodgkin's lymphoma)	Standard care (n=62; 24 aggressive)	3x/week Aerobic exercise cycle ergometer @ 60% - 75% $\dot{V}O_{2peak}$ by week 4, 15-20 min x 4 weeks increased by 5 min weekly to 45 min in week 9	QOL: FACT-An total (Δ= +10.6 vs +1.1 points, p=0.039) Fatigue: FACT-An fatigue (Δ= +4.5 vs =0.1 points, p=0.012) Psychosocial function: CESD SF (Δ=-2.2 vs +0.2 points, p=0.031) Physical function: FACT-An TOI-An (Δ=+9.4 vs +0.4 points, p=0.017) Aerobic capacity: $\dot{V}O_{2peak}$ (Δ=+0.40 vs +0.03 L/min, p<0.001), peak power (Δ=+31 vs +2 W, p<0.001), VT (Δ=+0.32 vs -0.03 L/min, p<0.001) Body Composition: DXA lean mass (Δ=+0.9 vs +0.1 kg, p=0.01), body fat % (Δ=-0.2 vs +0.6%, p=0.050)	Psychosocial function: SSAI SF (Δ=-1.6 vs -0.6 points, p=0.642) Body composition: bodyweight (Δ=+1.2 vs -0.5 kg, p=0.381), DXA fat mass (Δ=+0.3 vs +0.6 kg, p=0.386)	Adjusted group difference in change was adjusted for baseline value of the outcome, major cancer type, disease stage, current treatment status, age, sex, and baseline exercise
Courneya et al 2012 [17]	Randomised control trial (Level II)	Aggressive non-Hodgkin's lymphoma (n=49) Indolent non-Hodgkin's lymphoma (n=47); Hodgkin's	<50 (n=38) ≥50 (n=79)	Chemotherapy (n=53)	3 month supervised aerobic exercise program (n=60; 24 aggressive non-Hodgkin's lymphoma)	Standard care (n=62; 25 aggressive non-Hodgkin's lymphoma)	3x/week Aerobic exercise cycle ergometry @ 60-75% $\dot{V}O_{2peak}$ by week 4, 15-20 min x 4 weeks increased by 5 min weekly to 45 min in	Sleep: Pittsburgh Global Sleep Quality Index (Δ=-1.0 vs -0.35 points, p=0.17)	Exercise improved global sleep quality in patients with indolent NHL by 2.35 points (p<0.01); no effect in patients with aggressive NHL (p=0.27) or HL (p=0.93)	

		lymphoma (n=21)					week 9			
Headley et al 2004 [18]	Pilot randomised control trial (Level II)	Stage IV breast cancer (n=32)	52.25±11.43 (intervention) 50.0±7.10 (control)	Scheduled to initiate chemotherapy (n=32)	3-month unsupervised seated exercise program with instructional video (n=16)	Standard care (n=16)	3x/week Seated exercise using Armchair Fitness, gentle exercise video, x 30 min (n=16)	Fatigue: FACIT-F (entire sample 120.61±22.87 - 118.04±23.53 - 114.83±26.89 - 99.66±29.59 points, p<0.001‡) (intervention group declined at slower rate than control, p=0.025‡)		
Henke et al 2014 [19]	Randomised control trial (Level II)	Stage IIIA-IV lung cancer (n=29)	>18	Platinum-based chemotherapy (n=29)	Supervised aerobic + resistance training + breathing exercises for 3 cycles of chemotherapy (n=18)	Conventional physiotherapy + 5x/week breathing exercises (n=11)	5x/week, breathing exercises, walking/stair climbing @ 55-70% $HR_{reserve}$ Resistance training 3x/week, 4 Theraband exercises of progressive difficulty, 3 sets to fatigue @ 50% capacity	Physical function: Barthel index (Δ=-0.55 vs -10.41 points, p=0.003), 6MWT (Δ=+18.71 vs -47.5 m, p <0.05) Muscle strength: max. reps to fatigue (tricep extension Δ=+1.65 vs -5.17 reps, bicep curl Δ=+2.06 vs -2.42 reps, abdominal exercise Δ=+1.47 vs -1.83 reps, p<0.05)	QOL: EORTC-QLQ C30 global (Δ=+ 5.73 vs -6.41 points, p>0.05)	
Hwang et al 2012 [20]	Randomised control trial (Level II)	Non-small cell lung cancer stage IIIA (n=2), stage IIIB (n=2), stage IV (n=20)	61.0±6.3 (intervention) 58.5±8 (control)	Iressa (n=8), Afatinib (n=5), Tarceva (n=11); Previous chemotherapy (n=15) Radiotherapy (n=13)	2 month supervised aerobic exercise program (n=13)	Standard care (n=16)	3x/week, high intensity aerobic @ 60-80% $\dot{V}O_{2peak}$, 2-5 min intervals x 30-40 min, treadmill or cycle ergometry	QOL: EORTC-QLQ C30 global (Δ= +5.1 vs +3.1 points, p<0.005) Muscle strength: peak torque (Δ= +5.5 vs +5.4 Nm, p<0.005) Aerobic capacity: $\dot{V}O_{2peak}$ (Δ= +1.7 vs -0.4 ml/kg/min, p<0.005), exercise test workload achieved (Δ= +12 vs -5 W, p<0.005)		
Jastrzębski et al 2015 [21]	Randomised control trial (Level II)	Stage III + IV Small cell lung cancer (n=2) non-small cell lung cancer (n=18)	59.0±7.0	Platidiam – Vepeside (Cisplatin + Etoposide) (n=20)	2 month supervised aerobic exercise program; 2 week cycles interspersed with consecutive chemotherapy rounds (n=12)	Standard care (n=8)	Group A (n=8): 5x/week, target 70% of APMHR (termination criteria 88% SaO_2), and dyspnoea (termination criteria MRC scale <3) x 45 min, Nordic Walking Group B (n=4): Individually determined cycle ergometry prescription	Dyspnoea: MRC (Δ=-0.7, p=0.047† vs +0.4 points, p=0.31†) Lung capacity: FEV_1 (Δ=+11.5%, p=0.02† vs +2.8% predicted, p=0.84†)	QOL: SF-36 MCS (Δ=+2.3, p=1.0† vs -1.2 points, p=0.64†), PCS (Δ=-0.4 points, p=0.84† vs -1.6 points, p=0.38†) Physical function: 6MWT (Δ=+36.6 m, p=0.25† vs +6.6 m, p=0.82†), Baseline Dyspnoea Index (Δ=+0.4, p=0.84‡ vs 0 points, p=0.84†), Lung capacity: FVC (Δ=+6.6% vs +2% predicted, p=0.84†)	Of the 12 patients in rehabilitation, 7 were evaluated after 8 weeks of rehabilitation, one after 12 weeks, one after 10 weeks, one after 6 weeks, and two after 4 weeks.

Jensen et al 2014 [22]	Pilot randomised comparative trial (Level II)	Advanced gastrointestinal cancer (n=21)	55.0±13.1	5-fluorouracil +Oxaliplatin (n=6) 5-fluorouracil+ other (n=6) Capecitabin+ other (n=7) Cisplatin + Gemcitabine (n=2)	3 month supervised resistance training (RT) program (n=10)	3 month supervised aerobic exercise training (AET) 2x/week @ 60–80% APHRM x 10-30 min, cycle ergometer; (n=11)	Resistance training 2x/week 2–3 sets x 15–25 reps @ 60–80% 1RM, x 45 min Flexibility x 5 min	QOL: EORTC-QLQC30 global (Δ=+14.5, p=0.09† (RT) vs +13.3 points, p=0.045†(AET)), Muscle strength: increased in RT leg muscles (p=0.001), biceps (p=0.017), back (0.048), and knee flexors (p=0.002), but not triceps (p=0.072) or knee extensors (p=0.841) Sleep: daily duration (6.4±1.8-7.5±1.1 hours, p=0.028)	Physical function: Freiburger Questionnaire of PA (Δ=+1.9, p<0.05† (RT) vs +3.76 points, p<0.05†(AET)) Body composition: No Δ in body weight observed in either group (median 72.9±17.3 vs. 73.2±18.0 kg) or BMI (median 24.5±5.1 vs. 24.6±5.2 kg/m^2, p>0.05) Aerobic capacity: PWC130 (Δ=+0.1 w/kg, p value NR(AET))	Improvements in muscle strength were seen in the resistance group, however, PWC130 revealed no change in aerobic capacity in the aerobic group.
Ligibel et al 2016 [23]	Randomised control trial (Level II)	Metastatic breast cancer (n=76)	age 49. 3±9.6 (intervention) 50.7±9.4 (control)	Endocrine therapy (n=52) Chemotherapy (n=38) Biologics (n=36) None (n=3)	16-week unsupervised, moderate-intensity aerobic exercise program (n=33)	Standard care (n=43)	Supervised weekly x 4 weeks, monthly + telephone call weekly x 12 weeks 150 min/week moderate intensity exercise		QOL: EORTC QLQ-C30 Global (Δ=+4.79±2.40 vs +0.93±2.10 points, p=0.17) Fatigue: FACIT-F (Δ=+2.7±8.4 vs +2.7±9.3 points, p=0.63) Physical Function (mean±SE): 7 Day PA recall (Δ=+62.4±102.8 vs +46.0 ±154.3 min, p=0.17) Aerobic Capacity: Bruce Ramp Treadmill (Δ=0.61±0.2 vs 0.37±0.2 min, p=0.35)	The effect of the intervention on Bruce Ramp Treadmill test times differed according to breast cancer therapy (p=0.003). Women in the exercise arm who were treated with endocrine therapy had improvements in treadmill times compared with women in the control group (increase of 1.04 min vs 0.05 min)
Litterini et al 2013 [24]	Randomised comparative trial (Level II)	Advanced cancer with visceral, skeletal, central nervous system or multiple metastases breast (n=8); colorectal (n=3); lung (n=6) prostate (n=2);	62.4±13.5	Chemotherapy (n=24) Radiation (n=6) Chemotherapy + radiation (n=19) Other (n=6) None (n=11)	10 week supervised resistance training (RT)/ program (n=10 intention to treat, n=34)	10 week supervised aerobic exercise training (AET) program @RPE12-14x30-60 min (n=29 intention to treat, n=32)	Resistance training 2x/week 1 set 8-15 reps x 14 machine exercise circuit (intensity & duration increased as tolerated) x 30-60 min	Physical function: SPPB total score (Δ=+0.43 (RT)vs +1.07 points (AET), p=0.045) Fatigue: VAS (total sample Δ=-24%, p=0.05)	Fatigue: VAS (Δ=-13.3 (RT) vs -4.93 mm (AET), p=0.37) Pain: VAS (Δ=-1.83 (RT) vs -1.59 mm (AET), p=0.50)	

		gynaecologic (n=4); Hodgkin's lymphoma (n=1); other (n=17)								
Oechsle et al 2014 [25]	Pilot randomised control trial (Level II)	Leukemia (n=18), non-Hodgkin's lymphoma (n=9), multiple myeloma (n=9), relapsed germ cell tumour (n=12)	Median 52	Myeloablative chemotherapy + haematopoietic stem-cell transplantation (n=58 allocated; 48 analysed)	Median duration of training period 21 days (range, 16–33), median 15±6 days training, supervised aerobic + resistance training program (n=26)	Conventional physiotherapy (n=26)	5x/week Aerobic training 10-20 min, cycle ergometer Resistance training 3 exercises, 2 sets x 16-25 reps @ 40-60% 1RM x 20 min	Fatigue: Modified Fatigue Impact Scale impairment in cognition (IG>CG, p=0.02, psychosocial function (IG>CG, p=0.03) QOL: EORTC QLQ C30 global (endpoint=92 vs 88 points, p=0.04) Aerobic Capacity: $\dot{V}O_2$ at 2 mmol Lactate (Δ=+0.7 vs -19 L/min, p=0.03). *Intervention group only:* Muscle strength: Estimated 1RM bridging (48.5±24.7 - 57.6±33.7 kg, p value NR), sit-ups (35.8±15.2 - 31.8±34.4 kg, p value NR), Theraband Exercise (41.5±24.1 - 56.3±43.6 kg, p=0.04[†])		
Oldervoll et al 2011 [26]	Randomised control trial (Level II)	Cancer patients with life expectancy ≤2 years (n=163 allocated; 231 baseline) gastrointestinal (n=73) breast (n=51) lung (n=38) urological (n=30) gynecological (n=12) hematological (n=7) other (n=20)	Mean 62.1±11.2	Chemotherapy (n=126) Radiotherapy (n=13) Hormonal therapy (n=44) Targeted therapy (n=9)	2 month supervised aerobic + circuit resistance training program (n=121)	Standard care (n=110)	2x/week Aerobic warm-up seated/standing exercise/cycle ergometer x 10-15 min Resistance training circuit 6 exercises x 2 min each with 1 min rest x 30 min Flexibility + relaxation x 5 min	Physical function: shuttle walk distance (Δ=+41 vs -31 m, p=0.008) Muscle Strength: Isometric grip dynamometer (Δ=+1.1 vs -1.3 kg, p=0.01)	Fatigue: Fatigue Questionnaire, Physical (Δ=-1.0 vs -0.5 points, p=0.62) Mental (Δ=-0.3 vs -0.2 points, p=0.53) Total (Δ=-1.3 vs -0.8 points, p=0.53) Physical function: maximal stepping distance (Δ=+3.1 vs -2.0 cm, p=0.22), sit-to-stand (Δ=+0.8 vs +0.3 repetitions, p=0.34)	ANCOVA using multiple imputation

Rief et al 2014A [27]	Randomised control trial (Level II)	Cancer patients with spinal bone metastasis lung, (n=20), breast, (n=11), prostate, (n=14), melanoma, (n=2), renal (n=3), other (n=10)	61.3±10.1 (intervention) 64.1±10.9 (control)	Radiotherapy + bisphosphonates (n=60) Hormone therapy (n=26) Immunotherapy (n=12) Chemotherapy (n=45)	2 week supervised resistance training program + unsupervised resistance training, median follow-up 3.3 months (n=25)	Respiratory therapy x 15 min (n=23)	Supervised: 5x/week Isometric spinal resistance training x 30 min each treatment day Unsupervised: 3x/week Isometric spinal resistance training x 30 min	Physical function: 30 sec sit-to-stand (Δ=+3.9 vs +0.7 repetitions, p<0.001) Pain: VAS (Δ=-2.9 vs -1.3 cm, p=0.003)	Overall survival: Median (88.6 vs 72 months, p=0.63) 6 month (90.0 vs 96.6%, p value NR) 12 month (83.1 vs 78.6%, p value NR) Bone Survival: Median (23.3 vs 11.2 months, p=0.56)	
Rief et al 2014B [28]	Randomised control trial (Level II)	Cancer patients with spinal bone metastasis lung, (n=20), breast, (n=11), prostate, (n=14), melanoma, (n=2), renal (n=3), other (n=10)	61.3±10.1 (intervention) 64.1±10.9 (control)	Radiotherapy + bisphosphonates (n=60) Hormone therapy (n=26) Immunotherapy (n=12) Chemotherapy (n=45)	2 weeks supervised resistance training program + unsupervised resistance training; median follow-up 6.3 months (n=18)	Respiratory therapy x 15 min (n=23)	Supervised: 5x/week Isometric spinal resistance training x 30 min each treatment day Unsupervised: 3x/week Isometric spinal resistance training x 30 min	QOL: EORTC QLQ-BM22 Psychosocial (Δ=-28.21 vs -6.66 points, p=0.01) Fatigue: EORTC-FA13 Physical (Δ=-21.57 vs +6.85 points, p=0.01) Psychosocial function: QSC-R10 (Δ=-9.26 vs +0.82 points, p=0.02)	QOL: EORTC QLQ-BM22 Pain characteristics (Δ=-22.84 vs -9.75 points, p=0.76), EORTC QLQ BM22 functional interference (Δ=-25.28 vs -6.90 points, p=0.08) Fatigue: EORTC-FA13 Emotional (Δ=-19.36 vs +1.61 points, p=0.16) cognitive (Δ=-1.97 vs +1.52 points, p=0.43)	Intervention: n=5/30 (16.7%) died within first 12 weeks, 7 (23.3%) within 6 months Control: n=8/30 (26.7%) died within 3 months, 4 (13.3%) within 6 months.
Rief et al 2016 [29]	Randomised control trial (Level II)	Cancer patients with distal metastasis lung cancer (n=20) breast cancer (n=11) prostate cancer (n=14) melanoma (n=2) renal cancer (n=3) other (n=10)	61.3±10.1 (intervention) 64.1±10.9 (control)	Hormone therapy (n=26) Immunotherapy (n=12) Chemotherapy (n=45)	2 weeks supervised resistance training program + unsupervised resistance training; median follow-up 10.3 months (n=18)	Respiratory therapy x 15 min (n=23)	Supervised: 5x/week Isometric spinal resistance training x 30 min each treatment day Unsupervised: 3x/week Isometric spinal resistance training x 30 min		Progression free survival: (24.3 vs 20.5 months, p[§]=0.30) Overall survival: 12 months (80 vs 70%; 24 months 63 vs 57%, p[§]=0.69) Bone survival: 12 months 58 vs 51%; 24 months 42 vs 30%, p[§]=0.30)	
Vanderbyl et al 2017 [30]	Randomised comparative trial (crossover) (Level II)	Stage III/IV Gastrointestinal (n=12) lung (n=12)	66.1±11.7 (intervention) 63.7±7.7 (control)	Chemotherapy (n=18)	5 weeks supervised + unsupervised Walking Qi-gong (n=11)	Supervised aerobic + resistance training @60-70% APHRM / 2-4 METS (n=13)	Supervised: 1x/week Walking Qi-gong x 45 mins Unsupervised: Walking Qi-gong x 60 mins daily	Physical function: 6MWT (1st interval Δ=−4.04±5.7 vs 73.3±60 m, p<0.01; 2nd interval Δ=−36.4±54.4 vs 29.2±81.4 m, p<0.02, p=0.01[‖¶])	QOL: FACT-G (1st interval Δ=+3.6±6.6 vs 3.5±14.1%, p=0.98; 2nd interval Δ=−0.6±8.9 vs +1.2±7.8 m, p=0.70, p=0.01[‖]) Physical function: Sit-to-stand (1st interval Δ= -0.3±0.4 vs +0.9±3.7 reps, p=0.25; 2nd interval Δ=0.3±0.5 vs +0.1±0.8 reps, p=0.16, p=0.17[‖]) Speed walk (1st interval Δ=-0.2±0.5 vs -0.7±1.7 sec, p=0.38; 2nd interval	Significant order effect in both groups (2x2 ANOVA)

				Δ=−0.1±0.9 vs +0.4±1.8 sec, p=0.90, p=0.37‖) Reach forward (1st interval Δ=+0.8±4.5 vs -0.4±3.1 cm, p=0.46; 2nd interval Δ=−0.5±4.6 vs +0.4±3.8 cm, p=0.69, p=0.24‖) Reach up (1st interval Δ=-0.4±1.2 vs +0.2±0.7 sec, p=0.14; 2nd interval Δ=−0.4±0.9vs +0.1±1.2 sec, p=0.20, p=0.32‖) Psychosocial function: HADS-Anxiety (1st interval Δ=-0.6±2.1 vs -0.4±3.3 points, p=0.82; 2nd interval Δ=-0.3±1.9 vs -0.3±2.2 points, p=1.00, p‖=0.13), Depression (1st interval Δ=-0.7±2.6 vs -1.6±3.4 points, p=0.48; 2nd interval Δ=+0.5±3.3 vs -1.1±2.0 points, p=0.18, p=0.09‖) Pain: Likert (1st interval Δ=0.0±0.9 vs -1.1±1.9 points, p=0.07; 2nd interval Δ=0.5±52.2 vs 0.1±2.7 points p=0.67, p=0.03‖)

6MWT, six minute walk test; ABC, Activity-specific Balance Confidence scale; ADL, activities of daily living; AMPAC, Activity Measure for Post-Acute Care; APHRM, age predicted heart rate max; BFI, brief fatigue inventory; BMI, body mass index; CAD, Cyclophosphamide, Adriamycin, Dexamethasone; CESD-SF, Centre for Epidemiological Studies Depression Scale-Short Form; DXA, Dual Energy X-Ray Absorptiometry; DCEP, Dexamethasone, Cyclophosphamide, Etoposide, Cisplatin; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-BM, bone metastases; FACT, Functional Assessment of Cancer Therapy -G, general, -F, fatigue, -L, lung, -BP, bone pain; FACIT, Functional Assessment of Chronic Illness Therapy-F, fatigue; FEV_1, forced expiratory volume in one second; HR, heart rate; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; RM, repetition maximum; RPE, rating of perceived exertion; MCS, mental cumulative scale; MET, metabolic equivalent task; MFSI-SF, Multidimensional Fatigue Symptom Inventory Short Form; NR, not reported; NRS, numerical rating scale; PA, physical activity; PCS, physical cumulative scale; POMS, profile of mood states; PWC130, Physical Working Capacity; QOL, Quality of Life; QSC-R10, Questionnaire on Stress in Cancer Patients; SE, Standard Error; SF, Short Form; SOT, Sensory organisation test; SPPB, short physical performance battery; SSAI-SF, Spielberger State Anxiety Inventory- Short Form; VAS, Visual Analogue Scale; $\dot{V}O_{2max}$, maximal volume of total oxygen consumption; $\dot{V}O_{2peak}$, peak volume of total oxygen consumption.

Data reported as mean±standard deviation unless otherwise denoted

***Between-group difference at endpoint**
†Within-group difference at endpoint
‡Mixed-model multilevel analysis
§Kaplan-Meier survival method
‖Order effect 2x2 ANOVA
¶Favouring Control/Comparison group

Table 4 Study Characteristics of Non-controlled Trials

Author	Study Type (NHMRC Grade)	Diagnoses	Age (years)	Treatment	Intervention	Exercise parameters	Outcomes		Comments
							Significant change from baseline ($p < 0.05$*)	No significant change from baseline ($p \geq 0.05$*)	
Adamsen et al 2006 [31]	Pretest-posttest experimental (Level IV)	Patients receiving chemotherapy for advanced disease breast (n=4), ovarian (n=7), colon (n=2), testis (n=3), cervical (n=1), small cell lung cancer (n=2), oesophageal (n=2), unknown primary tumour (n=2), Ewing sarcoma (n=1), gastrointestinal (n=1), myxoidt sarcoma (n=1), oral (n=1), rhinopharynx (n=1), Hodgkin's lymphoma (n=6), non-Hodgkin's lymphoma (n=3), myelomatosis, (n=2), myelofibrosis (n=1)	Median 40 (18–63)	*Taxanes* *Anthracyclines* (Epirubicin, Doxorubicin), *Anti-metabolites* (5-FU, Capecitabine, Gemcitabine, Methotrexate, Hydrea, Ara-C) *Alkylating agents* (Cisplatin, Carboplatin, Ifosfamide, Leukeran) *Combination* ABVD, CHOEtoP, VAD, PEB) *Other* (Etoposide, Leucovorin Topotecan, Vincristine, m-AMSA)	6 weeks supervised multimodal exercise program 1.5 h exercise 3x/week 0.5 h relaxation 4x/week 1.5 h body awareness 1x/week 0.5 h massage 2x/week	Aerobic training, 33 MET hours/week, cycling intervals @ 60-100% HR_{max} x10min; Resistance training, 2-3x/week, 3 sets x 5-8 reps @ 85-95% 1RM x10 min, leg press, chest press, lat pull down; relaxation + body awareness exercises; mas sage	QOL: EORTC-QLQ C30 global (60.37±18.77 - 67.18±21.85 points, p=0.017), SF-36 PCS (41.96±7.41 – 45.44±8.25 points, p<0.001) MCS (47.96±9.81 – 51.3±8.9 points, p<0.001), Muscle strength: (1RM chest press (42.99±19.26 – 56.95±21.3 kg, p<0.001) leg press (103.17±28.76 – 145.95±35.62 kg, p<0.001) lat pull down (45.85±18.29 – 58.76±18.89 kg, p<0.001) Aerobic capacity: $\dot{V}O_2$max (2.21±0.59 – 2.51±0.65 L/min, p<0.001)		The different components of the programme constituted a total package, which implied that the patients could not select one activity (exercise, massage, etc.) in preference of another.
Carson et al 2007 [32]	Pretest-posttest experimental (Level IV)	Stage IV metastatic breast cancer (n=13)	59 (44-75)	Receiving Chemotherapy (n=7)	8 week supervised Yoga program + encouragement to practice Yoga independently x10 min/day	1x/week Yoga x120 min	QOL: 10 point Likert scale Daily pain (β=0.15, *t*=2.71, p<0.01†) Daily invigoration (β=0.16, *t*=2.99, p<0.01†) Daily acceptance (β=0.11, *t*=2.54, p=0.02†)	QOL: 10 point Likert scale Daily fatigue (β=0.11, *t*=1.81, p=0.07†) Daily distress (β=0.04, *t*=0.60, p=0.55†) Daily relaxation (β=0.11, *t*=1.83, p=0.07†)	
Cormie et al 2014 [33]	Pretest-posttest experimental (longitudinal follow-up) (Level IV)	Prostate cancer with bone metastasis, Gleason score 8.0±0.9 (n=20, 14 completed follow-up)	70±9.8	Previous ADT (n=20) Previous Radiotherapy (n=11) Previous Surgery (n=4)	6 month follow-up of 3 month unsupervised aerobic home exercise program; supervised resistance training program	2x/week, Resistance training, 2-4 sets 8-12 reps x 60 min Walking and/or stationary cycling, moderate intensity x 150 min/week	Physical function: 6-m walk speed usual pace (4.59±0.45 – 4.32±0.37 – 4.40±0.51 sec, p<0.001, p=0.046) Body composition: DEXA whole body lean mass (52.9±9.9 – 54.4±9.4 – 53.6±9.7 kg, p=0.039, p=0.039)	QOL: SF-36 PCS (44.1±10.1– 46.1±9.0– 46.0±8.3 points, p=0.095, p=0.166) MCS (43.0±11.5 – 43.3±9.1 – 45.7±6.6 points, p=0.836, p=0.276) Fatigue: MFSI-SF (9.5±20.1 – 5.4±14.2 - 6.0±15.0 points, p=0.09, p=0.213) Physical function: 400-m walk (262.6±43.6 – 255.4±43.4 – 264.±53.5 sec, p=0.007, p=0.481) 6-m walk speed fast	N=14 (20 analysed; intention to treat approach)

								pace (3.29±0.46– 3.12±0.44– 3.25±0.67 sec, p=0.002, p=0.651) TUG (7.18±1.33 – 6.92±1.27 – 7.21±1.91 sec, p=0.147, p=0.915), SOT (75.5±8.0 – 76.3±7.9 – 75.9±9.2 points, p=0.437, p=0.434), ABC score (79.6±23.7 – 83.3±19.7 – 79.7±20.0 points, p=0.095, p=0.939) Godin PA score (18.6±14.7 – 30.5±22.1 – 21.6±14.8 points, p=0.001, p=0.277), Muscle strength: 1RM (70.8±18.8 – 73.5±18.9 – 68.6±18.5 kg, p=0.005, p=0.291) Psychological function: BSI-18 global severity (8.3±9.5 – 8.1±9.8 – 5.8±5.9 points, p=0.849, p=0.143) Body composition: DEXA whole body fat mass (22.0±4.7 – 22.9±4.5 – 22.2±4.5 kg, p=0.016, p=0.208), Pain: FACT BP (50.9±8.9 – 51.5±7.6 – 50.6±6.9 points, p=0.614, p=0.834), VAS (1 ±1.9 – 1.5±2.1 – 0.6±0.6 cm, p=0.06, p=0.45)
Kuehr et al 2014 [34]	Pretest-posttest experimental (longitudinal follow-up) (Level IV)	Advanced non-small cell lung cancer stage IIA (n=2), stage IIIA (n=3), stage IIIB (n=8), stage IV (n=27) (n=31 completed post-intervention assessment, n=22 completed follow-up)	Median 63 (22-75)	Chemotherapy (n=33) Radiotherapy + Chemotherapy (n=7)	2 month supervised (1 month) aerobic + resistance training program; unsupervised aerobic + resistance training (1 month) program 2 month post intervention follow-up	*Inpatient*: Aerobic exercise 5x/week (3 x supervised) @ RPE 12-14, treadmill/cycle ergometry; Resistance training 5x/week Thera band/Dumbbell exercises @ RPE 12-16 *Outpatient*: 3x/week home exercise program	QOL: FACT-L (100.7±14.9 – 103±15.6 – 100.4±16.7 points, p=0.39, p=0.03), Muscle strength: Isometric knee extension (201±86 – 279±71 – 327±116 N, p<0.01, p<0.01), knee flexion (140±41 – 177±61 – 192±57 N, p<0.01, p<0.01),	QOL: PHQ9 (5.4±3.8 – 6.0±4.6 – 4.7±3.6 points, p=0.09, p=0.39) Fatigue: MFI physical (10.7±3.9 – 10.4±3.6 – 11.8±4.9 points, p=0.75, p=0.10) mental (8.9±3.3 – 8.9±3.4 – 9.0±3.6 points, p=0.61, p=0.68) Physical function: 6MWT (493±100 – 525±95 – 543±120 m, p<0.01, p=0.46) Muscle strength: Isometric elbow flexion (144±52 – 152±55 – 158±69 N, p=0.02, p=0.68), elbow extension (124±44 – 136±49 – 129±41 N, p<0.01, p=0.49)
Oldervoll et al 2006 [35]	Phase II pilot pretest-posttest experimental (Level IV)	Palliative gastrointestinal (n=16). breast (n=5), genitourinary (includes prostate, ovary, and kidney, n=5),	65±122	Chemotherapy (n=9) Hormone Therapy (n=12)	6 week supervised aerobic + resistance training program	2x/week (3–8 patients per group) personalised circuit training, 6 stations x 2 min each station focused on muscle strength, standing	Physical function: 6MWT (481±144 - 510±156 m, p=0.007), timed sit to stand (5.1±2.3 – 4.1±1.4 sec, p=0.001), functional reach (30.4±6.9 – 32.8±8.3 cm, p=0.07)	QOL: EORTC-QLQ global (62±21 - 60±20 points, p=0.26) Fatigue: FQ (17.5±4.7 – 15.5±5.8 points, p=0.06) Body composition: BMI (25.2±3.4 – 25.0±3.1 kg/m^2, p=0.08), Weight (74±11.5 –

		lung cancer (n=1), other (sarcoma, haematological cancer, and lymphoma, n=7)				balance, and aerobic endurance, x50 min		73.6±12.4 kg, p=0.10)
Quist et al 2012 [36]	Pretest-posttest experimental (Level IV)	Stage IIIB-IV non-small cell lung cancer (n=25), small cell lung cancer with extensive disease (n=4) (n=23 completed intervention)	63 (43-80)	1st line Carboplatin + Vinorelbine (n=16) 2nd and 3rd line Erlotinib (n=2) 2nd line Pemetrexed (n=1) 1st line Cisplatin + Etoposide + Thoracic Radiotherapy (n=2) 1st line Carboplatin + Etoposide (n=2)	6 week supervised aerobic + resistance training; unsupervised aerobic training program	2x/week x 1.5 h Resistance training 3 sets 5 reps @70-90% 1RM, 6 TechnoGym exercises Aerobic training bicycle ergometer intervals @85-95% HR_{max} x 10-15 min Flexibility x 10-15 min Home exercise program 3x/week walking (20 mins week 1–2, 30 mins week 3–4, 40 mins week 5–6)	Aerobic capacity: $\dot{V}O_{2peak}$ (1.48±0.41 – 1.57±0.41 L/min, p=0.014) Physical function: 6MWT (524.7±88.5 – 564.0±88.6 m, p=0.006) Muscle strength: 1RM leg press (70.4±26.9 – 86.9±28.8 kg, p<0.001), chest press (30.8±13.2 – 40.3±16.3 kg, p<0.001) lat pull down (35.8±13.8 – 39.2±17.6 kg, p=0.049), abdominal crunch (24.9±10.7 – 29.5±11.3 kg, p<0.001), lower back (35.3±14.1 – 43.1±16.2 kg, p<0.001), leg extension (38.6±15.5 – 45.1±18.9 kg, p<0.001)	QOL: FACT-L total (91.7±16.7 – 94.3±14.2 points, p=0.452), Fatigue: FACT-L fatigue (73.4±14.2 – 74.2±12.4 points, p=0.780) Lung capacity: FEV_1 (1.76±0.7 – 1.96±0.63 l/min, p=0.061), Body composition BMI (25.1±5 - 25.3±4.8 kg/m^2, p=0.076)
Quist et al 2015 [37]	Pretest-posttest experimental (Level IV)	Stage IIIB-IV non-small cell; lung cancer (n=94) small cell lung cancer with extensive disease (n=20) (n=71 completed intervention)	66 (31-88) 71 completers: age 63 (45-80)	Carboplatin/ Cisplatin + Vinorelbine±Bevacizumab (n=73) Carboplatin/ Cisplatin + Docetaxel/Paclitaxel (n=4) Cisplatin + Pemetrexed + Bevacizumab (n=7) Pemetrexed (n=10) Carboplatin/ Cisplatin + Etoposide (n=19) Carboplatin/ Cisplatin + Topotecan (n=1)	6 week supervised aerobic + resistance training; unsupervised aerobic training program	2x/week x1.5 h Resistance training 3 sets, 5 reps @ 70-90% 1RM, 6 TechnoGym exercises Aerobic training bicycle ergometer intervals @85-95% HR_{max} x10-15 min Flexibility x10-15 min Home exercise program 3x/week walking (20 min week 1–2, 30 min week 3–4, 40 min week 5–6)	Aerobic capacity: $\dot{V}O_{2peak}$ (1.3±0.4 – 1.4±0.5 L/min, p<0.001), 6MWT (527.4±121.5 - 561±124.7 m, p<0.001) Muscle strength: 1RM leg press (71.5±30.2 – 86.1±32.8 kg, p<0.001), chest press (29.±13.4 – 34.5±15.8 kg, p<0.001), lat pull down (34.6±13.3 – 36.5±15.0 kg, p=0.006), abdominal crunch (35.5±13.5 – 42.2±15.7 kg, p<0.001), lower back (37.5±14.7 – 43.3±16.7 kg, p<0.001), leg extension 24.9±9.9 – 28.3±11.5 kg, p<0.001), Psychological function: HADS anxiety (7.2±4.4 – 6.3±4.2 points, p=0.007) depression 5.3±3.8 – 4.7±3.5 points, p=0.076)	QOL: FACT-L total (94.4±18.9 – 96.0±18.4 points, p=0.282) Lung capacity: FEV_1 (1.9±0.7 – 1.9±0.7, p=0.508) Body composition: BMI (24.7±3.8– 24.8±3.8 kg/m^2), p=0.258
Temel et al 2009 [38]	Pretest-posttest experimental (Level IV)	Advanced non-small cell lung cancer stage IIIB with effusions (n=4) stage IV (n=21)	Median 68 (48-81)	Chemotherapy (n=18) Radiation (n=5) Chemotherapy + Radiation (n=2)	2 month supervised resistance + aerobic training program	2x/week Resistance training 3 sets 10 reps @ 60-80%1RM, 6 exercises x30-40 min Aerobic training @ 70-85% HR_{max} x30 min (15 min bike, 15 min treadmill)	Muscle strength: Elbow extension (5.64±2.77 – 6.82±3.76 kg, p<0.05),	QOL: FACT-L (103.44±14.19 – 104.66±14.51, p>0.05) Physical function: 6MWT (n=11, 410.55±83.28 - 435.73±72.66 m, p>0.05) Muscle strength: shoulder flexion (5.50±1.96 – 6.09±2.66 kg, p>0.05) elbow flexion (11.23±5.59 – 12.36±6.71 kg,

								p>0.05) hip extension (8.15±4.90 – 9.05±6.88 kg, p>0.05), hip abduction (8.20±1.81 – 9.75±5.64 kg, p>0.05), knee extension (23.11± 11.56 – 27.83± 19.43 kg, p>0.05) Psychological function: HADS anxiety (2.91±3.02 – 2.36±2.20 points, p>0.05) depression 3.73±4.29 – 4.45±3.98 points, p>0.05)
Van den Dungen et al 2014 [39]	Pretest-posttest experimental (Level IV)	Advanced cancer patients receiving palliative care breast (n=7) gastrointestinal (n=8) other (n=11)	54.5±8.9	Surgery (n=1), Chemotherapy (n=10), Hormone Therapy (n=6), Other Treatment (n=3), No Treatment (n=6)	6 week supervised group aerobic + resistance training program	2x/week Aerobic exercise, Cycle ergometer intervals, 3 mins @50-70% HR_{peak} alternating with 4 mins @80-90% HR_{peak} x30 min Resistance exercise, 3 sets 12 reps @60-80% of 1RM, Leg Press, Lunge, Vertical Row, Lat Pull Down, Abdominal Crunch, Pull Over, Bench Press	Physical function: 6MWT (435.0±135.2 – 464.1±132.5 – 480.0±137.0 m, p<0.01, p<0.01), Fatigue: RAND 36 (59.3±22.6 – 66.±19.2 – 67.2±22.9 points, p=0.86, p=0.02), CIS (30.4±13.7 – 26.5±13.5 – 26.0±14.1 points, p=0.61, p=0.01) QOL: EORTC-QLQ C30 (63.5±23.3 – 68.3±22.0 – 69.9±20.5 points, p=0.38, p=0.02), ESAS (28.4±15.2 – 24.8±14.8 – 25.2±14.3 points, p=0.73, p=0.04), Muscle strength: 1RM leg press (100±37.4 – 116.3±45.9 – 145.1±65.6 kg, p<0.01, p<0.01), bench press (21.7±11.1 – 25.7.3±13.1 – 30.2±17.7 kg, p<0.01, p<0.01), lat pull down (37.1±19.6 – 42.5±24.4 – 47.2±27.8 kg, p<0.01, p<0.01), abdominal crunch (14.9±19.8 – 20.0±22.6 – 25.0±25.9 kg, p<0.01, p<0.01) isometric grip dynamometer (36.1±12.6 – 37.9±13.2 – 39.7±13.2 kg, p=0.07, p<0.01) Body composition: Skinfolds fat % (38.2±5.8 – 37.2±5.8%, p=0.02)

1RM, one repetition maximum; 5-FU, 5-fluorouracil; PEB, cisplatin+etoposide+bleomycin; 6MWT, six-minute walk test; ABC, activity specific balance confidence; ABVD, doxorubicin+bleomycin+vinblastine+dacarbazine; ADT, androgen deprivation therapy; Ara-C, cytosinarabinosid; BSI, brief symptom inventory; CHOEtoP, cyclophosphamide+doxorubicin+vincristine+etoposide+prednisone; CIS, Checklist Individual Strength; DEXA, dual X-ray absorptiometry; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ESAS, Edmonton symptom assessment system; FACT, Functional Assessment of Cancer Therapy -F, fatigue, -L, lung, -BP, bone pain; FEV1, forced expiratory volume; FQ, fatigue questionnaire HADS, hospital anxiety and depression scale; HR, heart rate; Hy, hydrea; L, leukeran; m-AMSA, amsakrine; MCS, mental composite score; MET, metabolic equivalent task; MFI, Multidimensional Fatigue Inventory; MFSI-SF, Multidimensional Fatigue Symptom Inventory Short Form; NR, not reported; PCS, physical composite score; PHQ, Patient health questionnaire; QOL, quality of life; RPE, rating of perceived exertion; SF, short form; SOT, sensory organisation test; TUG, timed up and go; VAD, vincristine+doxorubicin+dexamethasone; VAS, visual analogue scale

Data reported as ±standard deviation unless otherwise denoted

[*]***P value represents within-group difference***

[†]***Multilevel Random Effects Estimate***

Figure 1 Risk of Bias Summary (Controlled Trials)

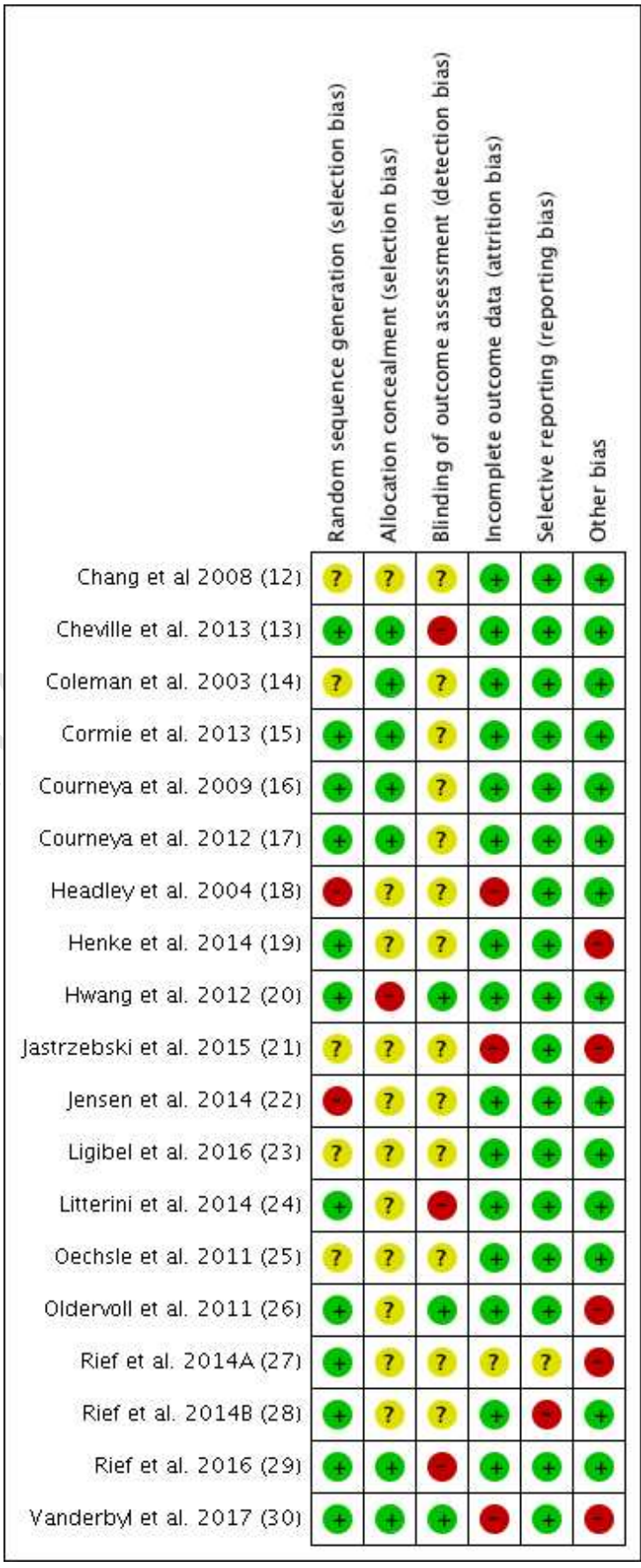
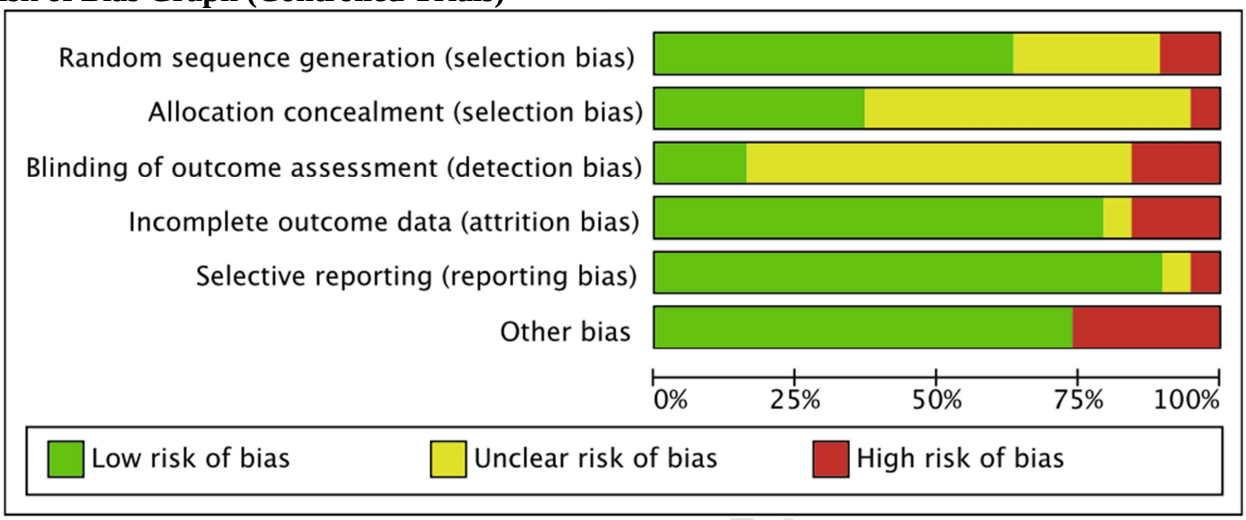


Figure 2 Risk of Bias Graph (Controlled Trials)



HIGHLIGHTS

- Strong evidence exists in support of exercise in oncology settings, however research in the field of exercise medicine for advanced cancer patients has expanded rapidly in recent years. This review provides a comprehensive analysis of the current literature surrounding individual symptom responses to targeted exercise in advanced cancer patients.

- Exercise interventions for patients with advanced cancer appear to be effective in improving physical function, QOL, fatigue, body composition, psychosocial function, and sleep quality deteriorations.

- The optimal dose of exercise regarding the most effective frequency, intensity, time and type to achieve clinically favourable outcomes is not entirely clear, however the literature is limited in both quantity and quality of studies specifically investigating this topic.

- Clinicians are strongly encouraged to consider referring their patients with advanced cancer to appropriately-qualified exercise professionals capable of delivering individually-tailored exercise programs if seeking interventions to improve symptoms commonly seen throughout the advanced stages of cancer.