Review Article

The Effect of Exercise on Quality of Life, Fatigue, Physical Function, and Safety in Advanced Solid Tumor Cancers: A Meta-analysis of Randomized Control Trials

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Abstract

Background. People with metastatic cancers experience poor quality of life (QoL), fatigue, and decreased physical function. Exercise improves these symptoms in the curative setting, but the efficacy and safety of exercise in the metastatic setting is uncertain.

Methods. Prospective, randomized trials of moderate/high-intensity aerobic exercise or resistance training vs. control in patients with advanced/metastatic solid cancers were identified from prior reviews and updated using a search of PubMed. The mean and SD for validated outcome measures (QoL, physical function, and fatigue) were extracted for intervention and control groups at baseline and postintervention. The Mann-Whitney test was used to evaluate the effect of exercise on the pooled change between baseline and postintervention. Safety was evaluated qualitatively.

Results. Sixteen trials were analyzed. Among patients with scores at the mean or 2SD above, exercise was not associated with significant or clinical difference in QoL or fatigue. In patients with baseline scores 2SD below mean, exercise was associated with nonsignificant difference meeting minimal clinical important difference in QoL (−2.8 vs. 4.6, $P = 0.28$). For function, patients at the mean had nonstatistically significant, but clinically meaningful difference in the six-minute walk test (6-MWT) (14.7 vs. 29.0 m, $P = 0.44$). In patients 2 SD below the mean, there was a clinically meaningful difference in two patient-reported functional subscales (0.1 vs. 5.3, $P = 0.076$ and 0.44 vs. 8.5, $P = 0.465$) and a clinically meaningful improvement in the 6-MWT (−7.5 vs. 27.0 m, $P = 0.34$), although none of these associations met statistical significance. There were no differences in falls, fractures, or pain.

Discussion. Exercise is associated with clinically meaningful improvements in QoL, function, and 6-MWT in some patients with metastatic cancer. Despite poor reporting of safety, there was no signal of increased harm from exercise in this setting. J Pain Symptom Manage 2019;58:899−908. © *2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words
Metastatic cancer, advanced cancer, exercise, physical activity, cancer-related fatigue, physical function, quality of life, safety

Introduction

With improvements in treatment, people with incurable, locally advanced or metastatic cancer (referred to as metastatic cancer henceforth) are living longer.[1,2] Typically, this population is treated with sequential lines of palliative, anticancer therapy to improve overall survival and/or quality of life (QoL). These patients commonly experience disease and

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Accepted for publication: July 5, 2019.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2019.07.005

therapy-related side effects, including pain, gastrointestinal symptoms, neuropathy, insomnia, anxiety, and depression.[3–5] The most prevalent and distressing symptoms reported by patients in this setting are cancer-related fatigue (henceforth referred to as fatigue) and decreased physical function (henceforth referred to as function).[4,6–8]

Fatigue is the subjective experience of tiredness or lack of energy that varies in magnitude, frequency, and duration and is not relieved by sleep or rest.[8,9] It is reported by a majority of patients with incurable cancers and is associated often with poor QoL.[4,7] In contrast to intermittent dosing of cytotoxic chemotherapy, the increasing use of prolonged courses of targeted agents also increases fatigue.[10–12] The most clinically relevant definition for physical function describes a person's ability to perform basic and instrumental activities of daily living independently,[13,14] which can be estimated using validated measures.[14] Functional decline is common across all cancer types in the incurable setting.[6,15,16] Maintenance of function is important to patients as it is associated with independence and its decline can limit the oncologists' ability to deliver anticancer therapy safely.

Exercise has been shown to improve QoL, fatigue, and function in cancer survivors.[17–20] The recommendation to engage in exercise is supported strongly by various international guidelines[21–23]; however, these guidelines often do not apply to patients with metastatic cancer given the lack of inclusion of this population in the trials upon which guidelines are based. Recent reviews have shown that exercise interventions are safe and feasible in the advanced setting and in those with metastatic bone disease.[24–26] Despite this, clinicians are not recommending exercise to patients with metastatic cancer routinely and clinicians report concern regarding safety of exercise in the metastatic setting.[27–31]

A recent Cochrane review found that exercise improved the six-minute walk distance and QoL in patients with advanced or metastatic lung cancer[32]; otherwise, there are no quantitative reports on the potential benefits or harms of exercise on QoL, fatigue, or function, in the metastatic setting. This information can support clinicians in having evidence-based discussions with patients regarding the efficacy and safety of this intervention.

Here, we report on a meta-analysis of the benefits and harms of exercise in the advanced typically incurable/metastatic cancer setting. Our primary hypothesis was that exercise is beneficial in terms of improving, maintaining, and/or slowing decline in QoL, fatigue, and function relative to a usual care group and that harms would consist mostly of musculoskeletal pain and nontraumatic falls with few fractures. As a secondary aim, we assessed benefits and risks in those with the most fatigue and lowest function at baseline, anticipating that this group would benefit most.

Methods

Data Sources

We included prospective randomized controlled trials of moderate to vigorous aerobic and/or resistance exercise vs. control in patients with metastatic solid cancers. We included only English language, full-text studies. Eligible studies included those in which at least half of study participants had metastatic disease or advanced, typically incurable, disease. Exercise was defined using the American College of Sports Medicine as "physical activity causing an increase in energy expenditure and involving a planned or structured movement of the body performed in a systematic manner and designed to maintain or enhance health-related outcomes." Interventions could include mental health components, so long as exercise at moderate to vigorous intensity was included. Consequently, interventions composed exclusively of Tai Chi, Qi Gong, breathing exercises, or yoga were excluded. There were no limits placed on the time (length) or type of exercise. Control was defined as any intervention which did not meet the definition of exercise. Trials required a validated outcome measure of QoL, fatigue, or function (see below for list). Reporting of safety outcomes was not required for inclusion.

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Fig. 1 and Appendix Table 1), we reviewed and collected all papers that met the previously mentioned inclusion criteria. Studies were identified initially based on three reviews that were completed recently.[24–26] A search of MEDLINE (host: PubMed) was then performed using a modified search strategy[33] to update the search and identify additional studies up to October 2018. Citation lists were then reviewed to improve the sensitivity of the search strategy. The Peddle-McIntyre meta-analysis was searched for eligible studies upon its publication in early 2019.[32] Disagreements were resolved by discussion and consensus.

Data Extraction

The full text and any available supplementary appendices were downloaded and reviewed by one author (M. B. N.). The following data were extracted: name of first author, year, type of cancer (including stage and/or percentage with bone metastases), type, length, and amount of supervision of the exercise intervention, and exclusion criteria of that study. First, any reported outcome measure of QoL, fatigue, or PF

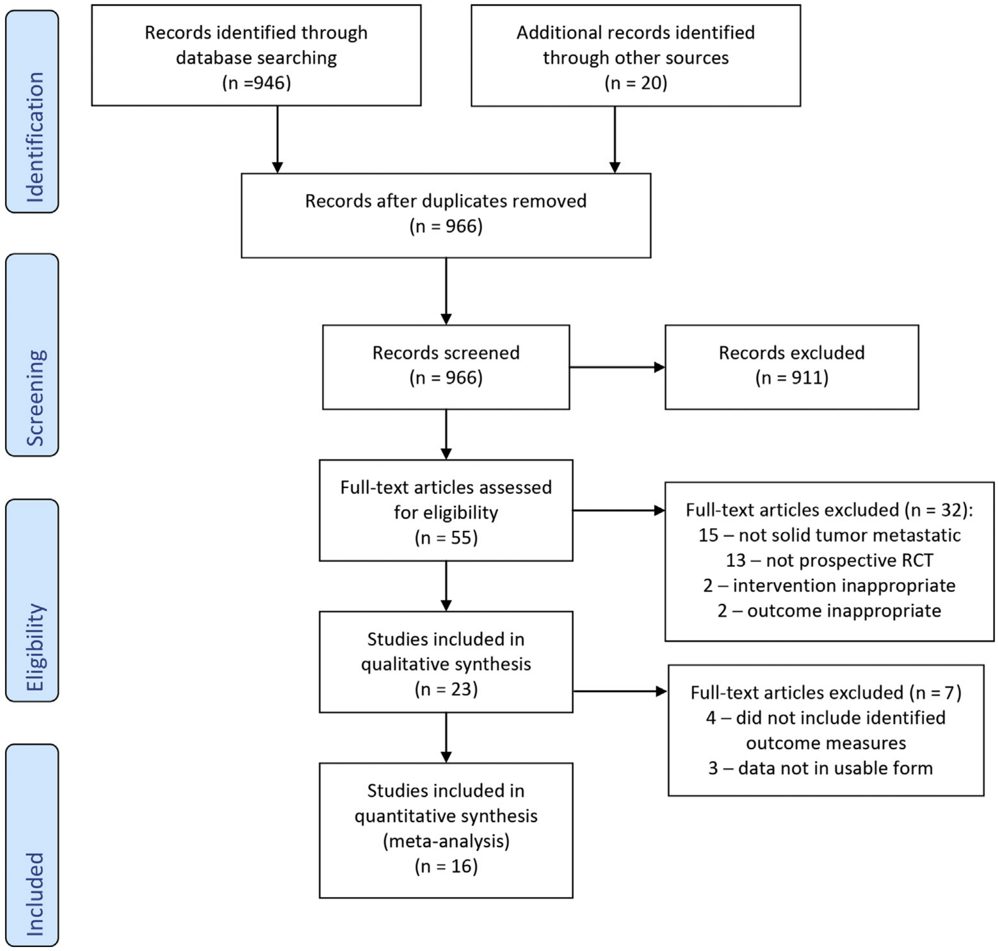

Fig. 1. PRISMA diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

was extracted, listed, and authors were contacted if data were missing. If a specific outcome measure was not present in at least three studies, it was excluded from further analysis. If a trial met all inclusion criteria but did not include any outcome which could be pooled, the trial was subsequently excluded. A list of trials excluded at this step is included in Appendix Table 2. The included outcome measures were as follows: European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire (C30) total score, functional subscale, and fatigue subscale[34]; Medical Outcomes Survey 36-item Short Form (SF-36) total score, physical component summary (PCS), and mental component summary (MCS)[35]; Functional Assessment of Cancer Therapy−Fatigue (FACT-F),[36] FACT-General (FACT-G),[37] sit-to-stand (STS),[38] and six-minute walk test (6-MWT).[39]

Subsequently, a standardized data extraction form was used to extract study characteristics and the mean score and SD for each outcome measure for intervention and control groups at baseline and at the first reported postintervention period. If a study was presented twice, we extracted the outcome with the largest sample size. Data abstraction was not blinded. We did not extract data on longer term follow-up after completion of the intervention. We calculated the mean values and those 2 standard deviations above and below the mean ("mean ± 2 SD") for each outcome value (based on classical statistical assumptions that this covers 95% of a normal population distribution). We capped −2SD at the lowest score possible for the scale in question (typically at 0) and capped +2SD at the highest score possible for the scale (typically at 100). The STS and 6-MWT were not capped. We then calculated the change from baseline to postintervention for participants at the mean. This was then repeated for 2SD above and below the mean. Quality assessment was performed based on the Cochrane risk of bias tool version 2.[40]

The reporting of safety data was too heterogeneous to extract quantitative information; therefore, it was synthesized qualitatively. Each study was reviewed independently by two authors (M. B. N. and A. D.) and assigned to the following categories: no data reported, data reported in the experimental group only, data reported for experimental and control groups, but unclear if measured in a standardized approach, or data reported for experimental and control groups in a standardized manner. Disagreements were resolved by consensus. Prespecified events (musculoskeletal pain, falls, and fractures) were extracted if reported. The duplicate abstraction of the qualitative data was blinded to authors and institutions of the studies.

Statistical Analysis

Data were reported descriptively as mean, median, and respective ranges. The effects of exercise were assessed for patient at mean, 2SD below the mean (−2SD), and 2SD above the mean (+2SD) for each outcome measure with available data. The effect of exercise was evaluated as the pooled change between baseline and postintervention comparing exercise and control groups. Analysis was performed using the Mann-Whitney test using SPSS version 25.0 (IBM Corp, Armonk, NY). Statistical significance was defined as $P < 0.05$. No correction was applied to address multiple significance testing. In view of the low number of studies and expected low power, we reported quantitative differences based on magnitude of change. If this was greater than the threshold for minimal clinically important difference for the specific outcome measure (see Appendix Table 3 for definitions for this for each outcome), this was reported as clinically meaningful irrespective of whether it met statistical significance. Sensitivity analyses could not be performed owing to small number of studies.

Results

Nineteen unique studies were identified from the four recently published reviews. The extended PubMed search yielded 946 citations of which an additional three studies were identified. An additional study identified during review of citation lists was noted to meet inclusion criteria by the reviewers. Among the total of 23 studies meeting eligibility criteria, seven trials were excluded because they did not report an outcome measure of interest that could be pooled. Consequently, analyses were based on data from 16 trials comprising 1318 patients. One trial had two intervention arms both compared to a control arm, both of which were used in the analysis of the 6-MWT.

Overall, 10 trials included only one type of cancer, whereas the remaining six trials included mixed tumor sites. In terms of exercise type, six trials tested aerobic exercise, one resistance exercise, one American football training, and the remaining eight trials were mixed aerobic/resistance. Trials varied from 2 to 16 weeks. See Table 1 for an overview of included trials. Specific details about each trial, including which outcomes were included in the analysis, are included in Appendix Table 4. Based on the revised Cochrane risk-of-bias tool, most trials had one to three domains that were low or some concerns of bias. Every trial had at least one domain judged to be at high risk of bias; therefore, all trials had overall high risk of bias.

Quality of Life

Quality of life was evaluated by the C30 total score, FACT-G, SF-36 total score, and the SF-36 MCS (Appendix Table 5). Among patients with scores at the mean and 2SD above, there was no improvement in QoL on any subscale. In those with baseline scores 2SD below mean, exercise showed nonsignificant difference on the SF-36 total (0.4 vs. 4.9, $P = 0.28$) and clinically meaningful, but nonsignificant improvement on the SF-36 MCS (−2.8 vs. 4.6, $P = 0.28$).[41]

Fatigue

Fatigue was measured by the C30 fatigue subscale and FACT-F. There was a numerical difference in the FACT-F score (3.8 vs. 5.7, $P = 0.47$) in those with baseline scores 2SD below the mean. There were no clinically meaningful or statistically significant differences in fatigue in any group of patients (Appendix Table 6).

Physical Function

Physical Function was measured by the C30 PF subscale, SF-36 PCS, and two functional tests (6-MWT and STS) (Fig. 2; Appendix Table 7). Among patients with scores at the mean or 2SD above, there was no improvement in patient-reported function; however, patients at the mean showed nonsignificant, but clinically meaningful improvement in the 6-MWT (14.7 vs. 29.0 m, $P = 0.44$) and a nonclinically meaningful but statistically significant difference in STS scores (0.4 vs. 2.1, $P = 0.047$). In patients 2 SD below the mean, there was clinically meaningful improvement in both patient-reported functional subscales (SF-36 PCS 0.1 vs. 5.3, $P = 0.076$ and C30 PF 0.44 vs. 8.5, $P = 0.465$)[41,42] and a clinically meaningful difference in the 6-MWT (−7.5 vs. 27.0 m, $P = 0.34$),[43] although none of these associations met statistical significance. The greatest effect size for STS scores was also seen in patients 2 SD below the mean (−0.4 vs. 1.5, $P = 0.3$).

Safety

Safety was not measured or reported in a standardized manner. Therefore, data were reported qualitatively.

Table 1
Overview of Included Trials

Characteristic	Number *n* (%) of 16 Trials
Tumor type	
Mixed tumor sites	6 (37.5)
Prostate	4 (25)
Lung	4 (25)
Breast	2 (12.5)
Sample size; median (range)	58.5 (20–269)
Advanced/metastatic disease	
All patients (90% or greater)	7 (43.75)
Not reported/unclear	6 (37.5)
Most patients (50%–90%)	3 (18.75)
Bone metastases	
Not reported/not collected	9 (56.25)
All patients (90% or greater)	3 (18.75)
Some (any reported)	3 (18.75)
Excluded	1 (6.25)
Exercise type	
Mixed aerobic/resistance	8 (50)
Aerobic alone	6 (37.5)
Resistance alone	1 (6.25)
American football training	1 (6.25)
Exercise supervision	
Fully supervised	8 (50)
Partially supervised	7 (43.75)
Unsupervised	1 (6.25)
Exercise duration	
Between 2–8 weeks (up to 2 months)	8 (50)
Between 8–16 weeks (3–4 months)	8 (50)

Three trials (19%) did not report any data on adverse events. In eight trials (50%), it was either unclear or definitively stated that adverse events were not collected in the control arm. Therefore, only five trials (31%) described and reported adverse events related to exercise using standardized methods in both groups. Most studies reported no adverse events or minor musculoskeletal pain related to exercise, with the exception of the American Football training intervention that reported 2 fibular fractures and a partial Achilles tendon rupture.[44]

Discussion

In this article, we quantify the benefits of exercise in the metastatic setting. Patients with mean baseline scores had no improvements in reported QoL, fatigue, or PF, although they did have clinically meaningful, but nonsignificant improvement in 6-MWT and a nonclinical but statistically significant change in STS. Patients with baseline scores 2 SD below the mean had clinically meaningful differences in QoL and function (patient-reported and 6-MWT) compared to usual care as well as the largest relative change in STS.

Our results demonstrate that patients who were more deconditioned and reported worse QoL at baseline were most able to benefit from exercise. This is similar to results reported in a meta-analysis by Buffart, where exercise had the greatest effect on PF and fatigue for patients with worse symptoms at baseline.[45] This nonlinear trend of benefit shares similarities to adults without cancer, where it has been demonstrated that the greatest relative benefits of physical activity in terms of positive health outcomes are seen in those who move from no (or limited) activity to small volumes of physical activity.[46] This has important implications for future clinical trial design and patient referral pathways. Although it is recognized that exercise should be encouraged for all cancer survivors (and that exercise can benefit patients in the metastatic setting as well), future studies should seek to identify patients with higher levels of fatigue and reduced function who may experience increased benefits from supervised exercise programs. Although our findings add evidence that patients with more symptoms and worse physical function can participate in and benefit from supervised exercise programs, the exercise prescription (frequency, intensity, time, and type) has yet to be defined or optimized for adherence in this group of patients. It is therefore still premature to apply exercise-oncology guidelines for patients in the curative setting to those living with advanced cancer.

Patients with baseline scores at the mean and −2SD had clinically meaningful improvement in functional reported outcomes and 6-MWT, suggesting exercise can improve function in patients with metastatic disease. However, this is based on measures that only approximate outcomes important to patients and clinicians. Patients may be more interested to know if exercise interventions can maintain independence of ADLs or delay time to requiring long-term care or hospice. Oncologists and patients may be interested in knowing if maintenance of function can lead to longer independence, time at home, or more lines of therapy in this setting. Future studies should examine whether exercise or rehabilitation interventions can improve these end points.

This meta-analysis showed some improvements in QoL and PF, but no differences in fatigue relative to the control groups. This is similar to findings from Peddle-Mcintyre et al. showing improvements in 6-MWT and global QoL, but no changes in fatigue[32] in adults with advanced lung cancer and to conclusions from Dittus et al. which found no consistent improvement in fatigue across advanced cancer populations. This is in contrast to the curative setting, where exercise has more definitively improved fatigue.[20] There are several possible explanations for this. First, in the metastatic setting, participants have an ongoing burden of disease and receive several ongoing lines of therapy, making fatigue difficult to improve. It is possible that in this setting, prolongation of time to worsening of fatigue may be a more realistic outcome.

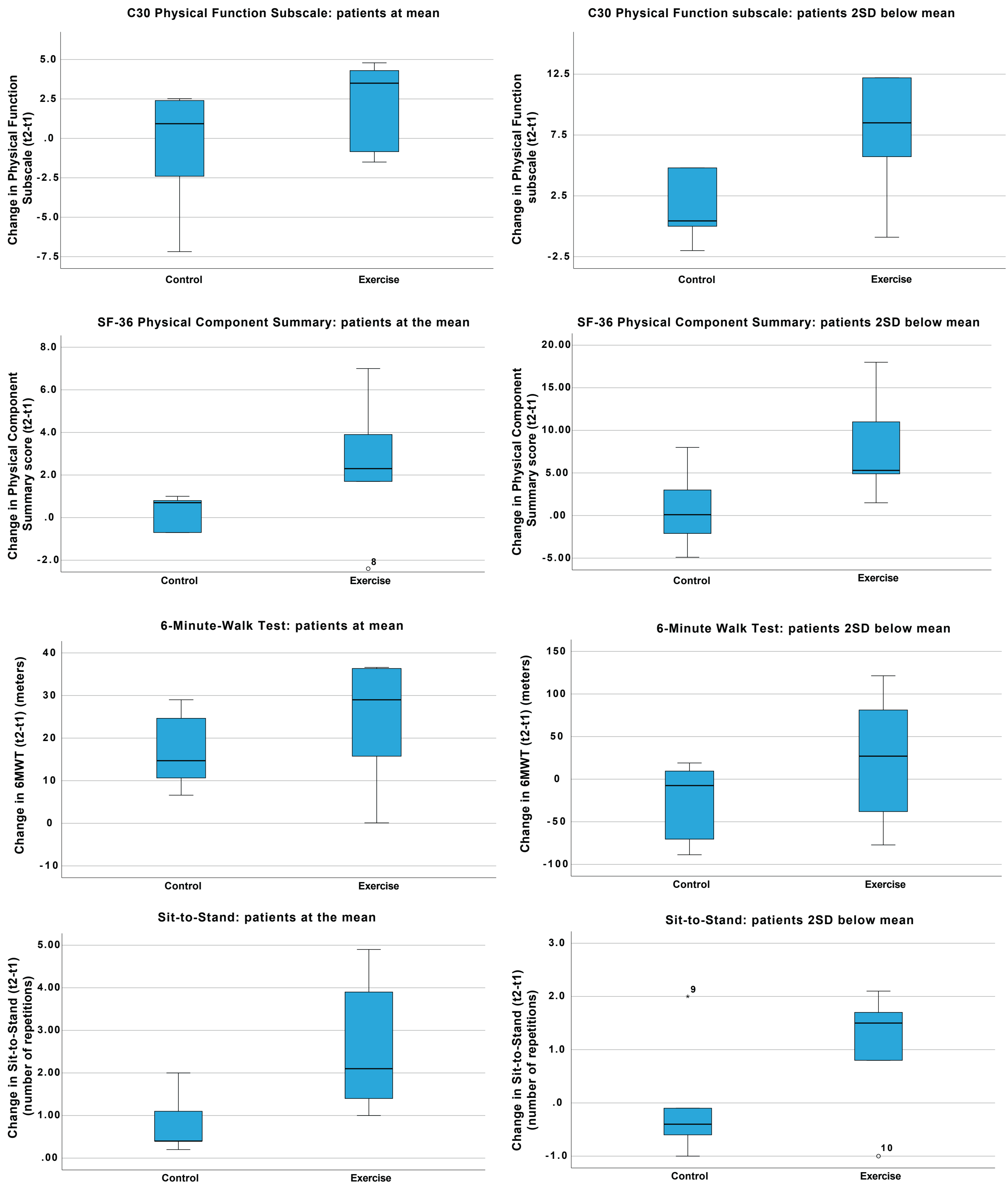

Fig. 2. Physical Function scores for patients at the mean and 2SD below mean.

Second, it may be that the type, duration, or frequency of exercise (including the number of visits required) were not optimized for a population of patients with metastatic cancer. Replacing a proportion of in-person visits with online exercise modules may decrease the travel burden on patients which may alleviate the fatigue severity. Finally, it is possible that more follow-up time is required before detecting a difference in fatigue, a time point not captured in our study. Headley and colleagues found that effect of exercise on fatigue only begin to be observed after 60 days,[47] and Rief and colleagues found no difference in fatigue at three months but a statistical difference at six months.[48] This suggests that these types of interventions may be most useful to prevent worsening of fatigue, rather than to improve it. It may also be important to consider early recruitment onto a clinical trial from time of diagnosis of metastatic disease (or an expected survival of greater than six months) if the outcome of interest is fatigue.

Despite being unable to quantify the safety of exercise, it appeared safe based on qualitative results. Although only a small proportion of studies reported safety in a standardized fashion, a larger proportion described it either only in the intervention group or only during exercise training. There were very few adverse events reported across the included trials, suggesting no data signal of harm from exercise. Most adverse events were minor and related to musculoskeletal complaints, with the only major adverse events reported in the American Football intervention. Safety of exercise in the metastatic setting is corroborated by Heywood and colleagues, who reported exercise-related adverse events occurring in fewer than 1% of participants and no adverse effects being serious enough to necessitate discontinuation of the exercise intervention.[24] Although this low adverse event probability appears promising, its accuracy is difficult to confirm and inconclusive given the very few studies that have reported safety outcomes in a standardized manner in both the experimental and control groups. Higher quality and more standardized reporting on adverse events could provide more certainty regarding exercise safety in the metastatic setting.

Furthermore, it is difficult to draw firm conclusions regarding safety of exercise in patients with bone metastases. The numbers of patients with bone metastases included in eligible studies of this analysis was small, and many authors did not collect or report this information. In a recent narrative review focusing on metastatic bone disease, no exercise-related adverse events were reported.[26] However, all interventions including patients with bone metastases required assessment and a custom exercise prescription designed to reduce the risk of pathologic fracture. Similarly, in the study by Rief and colleagues, bone lesions were reviewed by a radiologist and an orthopedic surgeon to ensure safety before enrollment in a spinal isometric exercise program.[49] Taken together, it is likely that exercise can be safe for patients with bone metastases when the appropriate assessment, customized exercise programming, and supervision are in place. However, there remains little information to guide the oncology practitioner on how to counsel a patient with metastatic bone disease who does not have access to these resources. The Mirels system to assess risk of pathologic fracture includes four variables to predict long bone fracture and to help clinicians to make recommendations for or against prophylactic fixation.[50] Sheill and colleagues suggest that this tool could be used to identify those suitable for exercise programs.[26] However, there are practical difficulties implementing such a tool within a conventional oncology practice. Without specific radiographic expertise and the inability to apply Mirels scoring criteria to axial lesions makes exercise clearance challenging. Future studies could aid physicians and qualified exercise professionals working with patients with metastatic disease by defining clearly metastasis-related inclusion and exclusion criteria and number of patients with bone metastases enrolled in the trial.

Our study had several limitations. First, the systematic review was based on prior reviews on this topic and supplemented by a search of only a single database. This may reduce sensitivity of the search strategy. Second, 30% of trials that met inclusion criteria were not included in the meta-analysis as they did not measure the outcomes of interest in a manner that could be pooled. It is possible that the inclusion of other studies or the excluded studies with different outcome measures could have influenced the results. Third, we combined trials that were quite heterogeneous, from type of malignancy, to proportion with metastatic disease and/or bone metastases, and types of exercise interventions. Many included studies did not report specific staging of patients, thus making it difficult to determine exactly how many were metastatic. Future trials in the metastatic setting should be careful to include only those with clearly defined metastatic disease, locally advanced incurable disease, and/or cancers with a very low cure rate and future systematic reviews and meta-analyses should exclude trials with any early-stage patients. Fourth, we were unable to perform a sensitivity analysis given the low number of studies in each outcome category. Fifth, we compared theoretical groups of patients at 2 SD above and below the mean. This method which relies on summary outcome measures would not have been able to examine the effect of exercise in individual patients. Sixth, studies of exercise are inherently prone to participant bias and may not reflect the effects expected if the same intervention would be applied to less selected patients. Finally, not all outcome measures had clinically meaningful differences determined or published in patients with cancer, so we instead compared to other chronic diseases. Although some of our findings showed clinically meaningful differences, they did not reach statistical significance, possibly because of low power. Larger studies are required to validate these findings. However, despite these limitations, our results share consistencies with recent reviews in the curative setting by Buffart and the advanced lung cancer setting by Peddle-McIntyre providing some support that the associations reported may be real.[32,45]

Conclusion

In summary, among patients with metastatic solid cancers, exercise interventions are associated with clinically meaningful improvements in QoL, function, and 6-MWT. The effects are seen in patients with baseline score at the mean and lower. There was no signal of harm from exercise in a supervised setting for patients with metastatic disease including those with bone metastases, although more data are required to be certain of this and to guide oncology practitioners regarding which patients can be given the recommendation to exercise on their own versus those for whom supervision is warranted to ensure safety during exercise.

Disclosures and Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. There have been no relevant financial activities outside the submitted work and no relationships that could influence the submitted work. None of the authors have any conflicts of interest to disclose.

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Appendix

Appendix Table 1
PRISMA Reporting Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	16-17
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12 Supplementary Tables 5,6,7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Libe rati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 . For more information, visit: **www.prisma-statement.org**.

Appendix Table 2
Outcome Measures Which Could Not Be Pooled

Outcome Measure	Number of Studies Which Include Outcome Measure	Citation
FACT-P	1	Bourke 2014[51]
Multidimensional Fatigue Inventory	1	Schuler 2017[52]
Brief Fatigue Inventory	1	Pyszora 2017[53]
Self-Reported Physical Activity (Godin)	3	Bourke 2011[54], Cormie 2013[55] (required data not available), Ligibel 2016[56]
LASA	1	Cheville 2010[57]

The following manuscripts met inclusion criteria and authors published on outcomes that were included in our analysis, but the manuscripts or outcomes were not included because of data not being available in a manner which could be pooled (after attempted contacts); Cheville 2013: FACT-F and FACT-G; Headley 2004: FACT-F; Dhillon 2017: STS.

Appendix Table 3
Minimal Clinically Important Difference (MCID) for Various Measures

Outcome Measure	MCID Categories (by Change Score)	Supporting Citations
European Organisation for Research and Treatment of Cancer—Quality of Life Questionnaire (C30):	5—10, “a little change”; 10—20, moderate change; >20, very much change	Osoba 1998[41], Cocks 2012[58]
Medical Outcomes Survey 36-item Short Form (SF-36) total score, physical component summary (PCS), mental component summary (MCS)	General Health, 5 points; PCS, 5 points; MCS, 5 points	Wyrwich 2005[42] (see full table of MCID in citation)
Functional Assessment of Cancer Therapy (FACT) - Fatigue scale (FACT-F) - General scale (FACT-G)	FACT-F, 3 points; FACT-G, 4 points	Cella 2002[59]
Sit-to-stand (STS)	Two repetitions	Zanini 2018[60] in respiratory conditions
Six-minute walk test (6-MWT)	Between 14.0 and 30.5 m across patient groups with cardiac or respiratory conditions (including lung cancer)	Bohannon 2017[43]

Appendix Table 4
Overview of Trials

Author, Year	Population, *n*	Metastatic Disease, *n* (%)	Bone Metastases, *n* (%)	Major Exclusion Criteria	Intervention Type and Duration (Aerobic/ Resistance) (Supervised/ Unsupervised)	Outcome Measure (Included in Meta-analysis)	Safety Outcomes
Adamsen 2009[61]	Mixed, advanced, receiving chemotherapy ($n = 269$)	Approximately 50% had "evidence of disease"	Excluded	Brain and bone metastases	Aerobic/resistance Supervised 6 weeks	C30 - total - fatigue - PF subscale - fatigue subscale SF-36 - total - MCS - PCS	AE not reported in Results section In discussion: one patient with seizure during exercise testing
Bourke 2011[54] and Bourke 2014[51]	Prostate cancer locally advanced and metastatic ($n = 100$)	Unclear	Unclear	Unstable cardiac conditions Painful or unstable bony metastases Already undertaking PA	Aerobic/resistance Partly supervised 12 weeks	FACT-F (2014 paper, $n = 100$) FACT-G STS (2011 paper, $n = 50$)	Unclear if reporting standardized between groups Knee pain prevented outcomes testing in two participants
Cormie 2013[55]	Prostate cancer with bone metastases ($n = 20$)	20 (100%)	20 (100%)	Bone pain limiting ADLs MSK, cardiac, or neurologic disorders that could inhibit from participating	Aerobic (home, unsupervised) Resistance (supervised) Three months	SF-36 - total - MCS - PCS	Reporting standardized One participant in exercise group fell at home and fractured a rib
Dhillon 2017[62]	Lung cancer, Stage III/IV ($n = 112$)	106 (95%)	Not reported	ECOG > 2 Life expectancy less than six months Not medically fit by PAR-Q and treating physician	Aerobic Partially supervised Two months	C30 - total - PF subscale - fatigue subscale FACT-F 6-MWT	Unclear if reporting standardized between groups Four participants had MSK back or muscle soreness and four participants had "other minor AE"
Galvao 2018[63]	Prostate cancer with bone metastases ($n = 57$)	57 (100%)	57 (100%)	Bone pain limiting ADLs MSK, cardiac, or neurologic disorders that could inhibit from participating	Aerobic/resistance Supervised Three months	SF-36 - PCS	Reporting standardized No AE
Henke 2014[64]	Lung cancer, unresectable Stage III and Stage IV receiving inpatient chemotherapy ($n = 46$)	Not reported	Data not collected	Symptomatic cardiac conditions Epilepsy KPS < 50	Aerobic/resistance Supervised Three cycles of chemotherapy	C30 - total - PF subscale - fatigue subscale 6-MWT	AE not reported in Results section Report no AE in discussion

(*Continued*)

Appendix Table 4
Continued

Author, Year	Population, *n*	Metastatic Disease, *n* (%)	Bone Metastases, *n* (%)	Major Exclusion Criteria	Intervention Type and Duration (Aerobic/ Resistance) (Supervised/ Unsupervised)	Outcome Measure (Included in Meta-analysis)	Safety Outcomes
Hwang 2012[65]	Lung Cancer, NSCLC – Stages III/IV receiving EGFR TKI ($n = 22$)	20 (90%)	2 (9%) Both in control group	Severe cardiac or MSK conditions Unstable condition from metastasis Diabetes	Aerobic Supervised Two months	C30 - total - PF subscale - fatigue subscale	AE only measured in intervention group States no AE related to exercise but that patients had low adherence due to fatigue, body discomfort, falls, or hospitalization
Jastrzębski 2015[66]	Lung cancer, unresectable Stage III and IV receiving inpatient chemotherapy ($n = 20$)	Not reported	Not reported		Aerobic Supervised Two months	SF-36 - total - MCS - PCS 6-MWT	AE not reported
Ligibel 2016[56]	Breast—locally advanced incurable and metastatic ($n = 101$)	Not reported	Data not collected	Uncontrolled cardiac disease Untreated brain metastases	Aerobic Mostly unsupervised 16 weeks	C30 - total - PF subscale - fatigue subscale FACT-F	Reporting standardized No AE
Oldervoll 2011[67]	Mixed ($n = 231$)	218 (94%)	Not reported	Life expectancy less than three months Inadequate pain relief Unimpaired cognitive function KPS < 60	Aerobic/resistance Supervised Two months	STS	Unclear if reporting standardized between groups No AE reported during or immediately after sessions
Rief 2014[48,49]	Mixed with spinal bone metastases; stability ($n = 60$)	60 (100%)	60 (100%)	Dementia/epilepsy Unstable bony lesions (assessed by radiology & orthopedic surgery) KPS < 70	Resistance Mixed supervised/ unsupervised Two weeks	STS	Unclear if reporting standardized No pathological fractures or progression of neurological deficits in both groups

Schuler 2017[52]	"Advanced cancer, life expectancy more than six months, undergoing active treatment or postcompletion of treatment" ($n = 70$)	Treated with palliative intent $n = 45$ (64%) Not balanced between groups	Not reported	Severe infection, cardiac, respiratory, neurologic, or MSK condition (others in text)	Aerobic/resistance Partially supervised 12 weeks Two intervention arms each compared to same control arm	6-MWT	Reporting standardized No AE at home or during physiotherapy sessions
Scott 2018[68]	Breast − metastatic ($n = 65$)	65 (100%)	Not reported	ECOG > 2, not approved for cardiopulmonary exercise test by primary oncologist or electrocardiogram not cleared by cardiologist, greater than 150 minutes of MVPA	Aerobic Supervised 12 weeks	FACT-G SF-36 - PCS FACT-F 6-MWT STS	AE only measured in intervention arm Safety evaluated very clearly by the type and prevalence of serious and nonserious AE
Solheim 2017[69]	Lung cancer, Stages 3 and 4 and inoperable pancreatic cancer ($n = 46$)	NSCLC 21 (46%) Pancreatic 9 (20%)	8 (17%) Balanced between groups	KPS < 70 (more related to NSAID use)	Aerobic/resistance Partially supervised Six weeks	6-MWT	Reporting standardized Eight serious AE in control arm and 13 in treatment arm; report none related to intervention
Tsianakas 2017[70]	Mixed ($n = 42$)	Not reported (inclusion criteria table defines advanced/ incurable)	Not reported	Bone metastases which the responsible health care professional considers a contraindication to participating in walking intervention	Aerobic (walking) 12 weeks	FACT-G	Unclear if reporting standardized States no adverse outcomes or events were reported
Uth 2016[44]	Prostate on ADT at least six months ($n = 57$)	Unclear ≥ T3n 40 (70%)	11 (19%) Seven in intervention, four in control	Cardiac or pulmonary disease, osteoporosis ($T_{score} < -2.5$), bone pain limiting ADLs, on chemotherapy, on anticoagulant	Football training Supervised 12 weeks	STS	AE only measured in intervention arm Two fibula fractures (nontraumatic, not reported if pathologic), one partial Achilles tendon rupture, and two muscle/ tendon injuries

C30 = European Organisation for Research and Treatment of Cancer−Quality of Life Questionnaire; PF =physical function; SF-36 = Medical Outcomes Survey 36-item Short Form; PCS = physical component summary; MCS = mental component summary; FACT-F = Functional Assessment of Cancer Therapy−Fatigue; FACT-G = Functional Assessment of Cancer Therapy−General; STS = sit-to-stand; 6-MWT =six-minute walk test; AE = adverse event; PA = physical activity; ADLs = activities of daily living; MSK = musculoskeletal; PAR-Q = Physical Activity Readiness Questionnaire; KPS = Karnofsky Performance Status; NSCLC = non−small cell lung cancer; EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

Appendix Table 5
Quality of Life Outcomes

Outcome Measure (*n*)	Minimal Clinically Important Difference	Delta Mean −2SD (Median, IQR)		Delta Mean (Median, IQR)		Delta Mean +2SD (Median, IQR)	
		Control	Intervention	Control	Intervention	Control	Intervention
EORTC-QLQC30[5]	5 points	3.1 (−10.6 to 16.8)	5.0 (−3.87 to 13.87)	3.1 (−10.6 to 16.8)	5.1 (1.03 to 9.17)	0 (−7.75 to 7.75)	0 (−1.63 to 1.63)
MOS-SF-36 Total[3]	5 points	0.4	4.9	0.7	0.7	1.2	−1.0
MOS-SF-36 MCS[3]	5 points	−2.8	4.6	0.4	2.3	0.4	3.4
FACT-G[3]	4 points	0.4	−2.0	−2.0	0	−3.0	0

Appendix Table 6
Fatigue Outcomes

Outcome Measure (*n*)	Minimal Clinically Important Difference	Delta Mean −2SD (Median, IQR)		Delta Mean (Median, IQR)		Delta Mean +2SD (Median, IQR)	
		Control	Intervention	Control	Intervention	Control	Intervention
EORTC Fatigue Subscale[5,a]	5 points	0 (0–0)	0 (0–0)	−2.0 (−13.3 to 9.3)	−3.8 (−11.69 to 4.09)	−4.4 (−25.32 to 16.52)	−5.6 (−13.79 to 2.59)
FACT-F[4,b]	3 points	3.8 (−0.1 to 7.7)	5.7 (−5.1 to 16.5)	1.0 (−1.0 to 3.0)	2.4 (−2.2 to 7.0)	0.4 (−5.8 to 5.0)	−0.2 (−2.7 to 2.4)

[a]On EORTC Fatigue subscale, higher scores represent more fatigue. Therefore, more negative differences (delta) represent more improvement in fatigue.
[b]On FACT-F, higher scores represent less fatigue.

Appendix Table 7
Physical Function Outcomes

Outcome Measure (*n*)	Minimal Clinically Important Difference	Delta Mean −2SD (Median, IQR)		Delta Mean (Median, IQR)		Delta Mean +2SD (Median, IQR)	
		Control	Intervention	Control	Intervention	Control	Intervention
C-30 PF Subscale[5]	5 points	0.44 (−13.62 to 14.5)	8.5 (−9.49 to 26.49)	0.93 (−6.32 to 8.18)	3.5 (−2.22 to 9.22)	0	0
SF-36 PCS[5]	5 points	0.1 (−8.9 to 9.1)	5.3 (−6.0 to 16.6)	0.7 (−2.1 to 3.5)	2.3 (−3.5 to 8.1)	−1.3 (−5.3 to 2.7)	0 (−15.4 to 15.4)
6-MWT (six studies, seven comparisons)	Between 14.0 and 30.5 meters	−7.5 (−105.5 to 140.1)	27 (−142.7 to 196.7)	14.7 (−7.7 to 37.1)	29.0 (5.2 to 52.8)	48.1 (−49.9 to 146.1)	22.6 (−67.0 to 112.2)
STS[5]	Two repetitions	−0.4 (−2.2 to 1.4)	1.5 (−0.5 to 3.5)	0.4 (−0.85 to 1.7)	2.1 (−1.1 to 5.3)	1.8 (0.9 to 2.7)	3.0 (−1.8 to 7.8)