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[Intervention Protocol]

Exercise interventions for people undergoing multimodal cancer treatment that includes surgery

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the effect of exercise interventions for people undergoing multimodal treatment including surgery on physical fitness, safety and feasibility, health-related quality of life and other important health outcomes.

BACKGROUND

Description of the condition

People with cancer are often faced with multimodality treatment that includes surgery in combination with other treatments, such as chemotherapy, radiotherapy and immunotherapy. These treatments are of two kinds: adjuvant treatment is given after surgery to treat residual disease, in order to minimise the likelihood of tumour recurrence or spread (Papadimitriou 2015), whereas the aim of neoadjuvant treatment is to reduce tumour bulk prior to surgery, in order to improve the likelihood of a complete surgical resection of the cancer (Chau 2006). Major surgery is associated with significant morbidity and mortality, as recently highlighted in the European Surgical Outcome Study (Pearse 2012), and morbidity has a major impact on postoperative recovery, quality of life, and survival (Khuri 2005; Moonesinghe 2014).

Cancer is frequently associated with cachexia (body weakness and wasting), which can worsen perioperative outcomes (Brown 1991). This condition can be exacerbated by chemotherapy, which is associated with muscle wasting and dysfunction. Furthermore, cancer treatment has been linked to decreased physical fitness, apparently related to the type of treatment, being worse in those receiving surgery and radiotherapy in combination with chemotherapy than in those receiving radiotherapy or surgery alone (Moros 2010). Moreover, this decrease in physical fitness may persist. In a series of studies, cardiorespiratory fitness was around 30% below that of age-matched sedentary healthy women up to three years fol-

lowing completion of adjuvant treatment for breast cancer (Jones 2007). A significant decrease in physical activity has been associated with a higher level of fatigue during breast cancer treatment (Mock 2005). Poor physical fitness reflects reduced physiological reserve, which predisposes people undergoing surgery to postoperative complications (West 2011; Hennis 2012; Moran 2016).

Description of the intervention

For the purposes of this review, we define an exercise intervention as a prescribed period of aerobic physical activity, involving large muscle groups, with a minimum of three planned exercise sessions, each session lasting at least 10 minutes (O'Doherty 2013). The intervention may take place in any setting and be delivered to a group or to an individual participant; however, it must be supervised or delivered by a trainer or healthcare professional.

How the intervention might work

Higher physical fitness has been associated with improved prognosis in solid tumours (Jones 2013), longer cancer-specific survival, and lower cancer-related mortality (Brunelli 2014). Remaining physically active during and after cancer treatment could therefore be an important way of reducing associated adverse effects, improving overall survival, and reducing the rate of tumour recurrence (Thomas 2014). It has been shown that women with non-metastatic colorectal cancer who were physically active following diagnosis had a significantly lower risk of death than those who were not physically active (Meyerhardt 2006). Similarly, women with breast cancer who exercised at moderate intensity (i.e. at least 30 minutes per day on at least five days per week) were shown to have a reduced risk of death (Holmes 2005). Exercise training stimulates skeletal muscle adaptations such as increased mitochondrial content and improved oxygen uptake capacity (Holloszy 1984), both contributors to physical fitness. In combination with chemotherapy, exercise training has been shown to slow tumour progression in solid tumours compared with chemotherapy alone (Betof 2015). Exercise training may also reduce chronic inflammation, which has been associated with worse outcomes in people living with cancer (Proctor 2011).

Why it is important to do this review

Studies in people undergoing multimodal cancer treatment, in the form of neoadjuvant chemotherapy and chemoradiotherapy and surgery, for upper and lower gastrointestinal cancer, suggest that the reduced physical fitness associated with these treatment modalities may be linked to higher in-hospital morbidity and mortality at one year post-treatment (Jack 2014; West 2014). The literature covering the effects of an exercise intervention to improve physical fitness in people with cancer undergoing single modality treatment has been synthesised in a number of systematic reviews. Two systematic reviews in people with non-small cell lung cancer (NSCLC) reported beneficial effects on physical fitness and other important clinical measures following participation in an exercise intervention in people who were treated surgically (Crandall 2014), and beneficial effects on physical fitness, symptoms and health-related quality of life (HRQoL) in people who were treated by surgery or a form of cancer treatment (Granger 2011). Two other systematic reviews in people with cancer (different cancer types) found evidence that exercise training in people who were surgically treated improved urinary continence (prostate cancer), cardiorespiratory fitness, and length of stay (Singh 2013) and improved HRQoL in people who received cancer treatment (Mishra 2012). However, to the best of our knowledge, there are no systematic reviews specifically addressing the effects of an exercise intervention on physical fitness and other important clinical outcomes in people with cancer undergoing multimodality treatment that includes surgery.

OBJECTIVES

To determine the effect of exercise interventions for people undergoing multimodal treatment including surgery on physical fitness, safety and feasibility, health-related quality of life and other important health outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider only randomised controlled trials (RCTs) for inclusion.

Types of participants

We will include studies that evaluate the effect of an exercise intervention in adults (18 years and over) with a confirmed cancer diagnosis requiring multimodal cancer treatment that includes surgery, of any age, regardless of gender, tumour type, tumour stage and type of cancer treatment, and of any exercise/activity level.

Types of interventions

Any exercise intervention that involves a prescribed period of aerobic physical activity, involving large muscle groups, with a minimum of three planned exercise sessions, each session lasting at

least 10 minutes, delivered by trained personnel or a healthcare professional. The intervention may take place in any setting and be delivered to a group or to an individual participant. We will include studies of exercise counselling interventions or prescribed exercise only, such as prescribed daily walking. We expect that interventions will vary to some extent with regard to the timing of initiation, duration and content.

Types of outcome measures

Primary outcomes

- Physical fitness (a measure of physical fitness and physical activity)
- Safety and feasibility ((number of adverse events and adherence to the intervention (attrition rate and reasons for withdrawal))

Secondary outcomes

- Health-related quality of life (HRQoL)
- Fatigue
- Postoperative outcome (morbidity, disease-free survival at 12 months, overall survival at five years)

Search methods for identification of studies

Electronic searches

We will search the following electronic databases up to the latest issue to obtain relevant studies for this review: Cochrane Central Register of Controlled Trials (CENTRAL, latest issue); MEDLINE; EMBASE: SPORTDiscus. We present the MEDLINE (via Ovid) search strategy in Appendix 1. For databases other than MEDLINE, we will adapt the search strategy accordingly. We will apply no language or date restrictions in the searches.

Searching other resources

We will also perform an expanded search for articles to identify 'grey literature'. This will include:

- Handsearching of reference lists of all articles, texts and other review articles on exercise and cancer;
- PubMed: 'Related articles' feature;
- Web of Science: citation search of key authors;
- Clinical trials registers search: Clincaltrials.gov and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/) for ongoing trials and trial protocols;
- Unpublished literature through searches of conference proceedings;
- Attempts to contact study authors for missing data and information related to study methods.

Data collection and analysis

Selection of studies

We will import all records retrieved from the searches into the reference management software package EndNote. We will then remove duplicates and select relevant articles for screening. Two review authors (LL and MAW) will examine the remaining references independently. We will exclude those studies which clearly do not meet the inclusion criteria. We will obtain full-text copies of potentially relevant references. We will resolve any disagreement between the two review authors (LL and MAW) through discussion or, if required, we will resolve disagreements by recourse to a third review author (SJ). We will link together multiple records on the same study and document the selection process in the Covidence web-based software platform. We will exclude case reports and theses.

Data extraction and management

Two review authors (LL and MAW) will independently extract study characteristics and outcome data, in accordance with predefined criteria, to a data collection form (Excel). We will retrieve full texts of all studies in which the abstract refers to an exercise intervention in people with cancer, and studies for which there is no abstract but the title suggests relevance. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. One review author (LL) will transfer data into the Review Manager 2014 (RevMan) file and will double-check that the data are entered correctly by comparing the data entered into RevMan with the study reports. A second review author (MAW) will spot-check study characteristics for accuracy against the trial report. For included studies, we will extract the following data:

1. Study details
   - Author, country and year of publication
   - Study aim
   - Sample size
   - Study design, methodology
   - Duration of follow-up
   - Study funding source
   - Declarations of conflict of interest

2. Participant characteristics
   - Cancer type
   - Cancer treatment
   - Age
   - Gender

- Ethnicity

3. Intervention details
- Exercise prescription components (frequency, intensity, time, type)
- Setting (in-hospital, community-based, home-based)
- Randomisation details
- Specified follow-up time points
- Safety and feasibility (number of adverse events and adherence to the intervention (attrition rate and reasons for withdrawal)
- Categorisation of the intervention (e.g. supervised, independent, educational)

4. Comparison details
- Description of usual-care control groups
- Additional information if appropriate

5. Outcomes: Primary and secondary outcomes; method of outcome measurement and time point of outcome measurement.

Assessment of risk of bias in included studies

Two review authors (LL and MAW) will independently assess and score the methodological quality of each study in accordance with the Cochrane tool for assessing risk of bias (Higgins 2011). This tool has the following seven domains:
• Random sequence generation
• Allocation concealment
• Blinding of participants and personnel
• Blinding of outcome assessment
• Incomplete outcome data
• Selective reporting
• Other potential sources of bias
Two review authors (LL and MAW) will apply the 'Risk of bias' tool independently, and will resolve differences by discussion with a third review author (SJ). We will summarise results in both a 'Risk of bias' graph and a 'Risk of bias' summary figure. We will score each item according to the criteria set out by Higgins 2011, and will provide a quote from the study report and/or a statement of justification for the judgement for each item in the 'Risk of bias' table. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome.

Measures of treatment effect

For continuous outcomes (e.g. physical fitness/activity and HRQoL), we will extract the point estimate for the measure of central tendency for the final value of the outcome of interest and the number of participants assessed at stated follow-up in each treatment arm, to estimate the standardised mean difference (SMD) between treatment arms and its 95% confidence interval (CI). For dichotomous outcomes, we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at follow-up, to estimate a risk ratio (RR) with 95% CI. For time-to-event outcomes, we will extract the log hazard ratio (HR) and its standard error, assuming that the hazard ratio is constant over time. If we are unable to obtain the standard error, we will attempt to obtain the CI or P value to calculate it. In cases where we cannot obtain sufficient data for hazard radios, we will dichotomise the data.

Dealing with missing data

We will attempt to contact study authors to obtain missing data (participant, outcome, or summary data). We will report the level of loss to follow-up and assess this as a source of potential bias. We will document reasons for missing data. We will analyse participants in their assigned groups using intention-to-treat analysis where appropriate. When intention-to-treat has not been used, we will note this in the 'Risk of bias' assessment under 'Incomplete outcome data', and will use available-case analysis if feasible and appropriate.

Assessment of heterogeneity

Where we consider studies to be similar enough (based on consideration of participants, cancer treatment, exercise training characteristics or outcome measures), we will use clinical expertise to decide whether it is appropriate to combine trials in a meta-analysis. We will assess the degree of heterogeneity by visual inspection of forest plots, by estimation of the percentage of heterogeneity (I^2 measurement) between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Chi^2) (Deeks 2001) and, if possible, by subgroup analyses. We will regard heterogeneity as substantial if I^2 is greater than 30% and either Tau^2 is greater than zero, or there is a low P value (< 0.10) in the Chi^2 test for heterogeneity.
Where we have concerns regarding clinical, methodological or statistical heterogeneity across included studies, we will not report pooled results from meta-analysis. We will use a narrative approach to data synthesis and report possible clinical or methodological reasons for this.

Assessment of reporting biases

We will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects such as publication bias if we include more than 10 studies in an analysis.

Data synthesis

We will carry out statistical analysis using a random-effects model with inverse variance weighting for all meta-analyses

(DerSimonian 1986). We will consider the random-effects summary as the average range of possible treatment effects and will discuss the clinical implications of treatment effects differing between studies. We will present results as the average treatment effect with its 95% CI, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses where there are sufficient data according to:

- Cancer type (solid and haematological tumours);
- Cancer treatment (neoadjuvant, adjuvant chemotherapy, adjuvant radiotherapy, immunotherapy);
- Exercise intervention characteristics (frequency, intensity, timing, type);
- Participant characteristics (gender and age).

Sensitivity analysis

We will conduct a sensitivity analysis to assess the effects of including trials with a high risk of bias.

Summary of findings table

Two review authors (LL and MAW) will independently rate the certainty of the evidence for each outcome. (GRADE Working Group 2004).

We will create a Summary of findings table in GRADEpro GDT using the GRADE approach (GRADE Working Group 2004). For assessments of the overall certainty of evidence for each outcome that includes pooled data from RCTs only, we will downgrade the evidence from 'high certainty' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. We will include the following outcomes in the Summary of findings table:

- Physical fitness (including physical capacity and physical activity)
- Safety and feasibility
- HRQoL
- Fatigue
- Post-operative outcome (morbidity, overall survival at 5 years, disease free survival at 12 months)

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1. exp Neoplasms/
2. (neoplas* or carcinoma* or adenocarcinoma* or malignan* or cancer* or tumor* or tumour*).ti.
3. 1 or 2
4. exp Surgical Procedures, Operative/
5. surgery.fs.
6. (surgery or surgical).ti.
7. 4 or 5 or 6
8. exp Combined Modality Therapy/
9. (combined modality or multimodal* or multi modal*).ti.
10. drug therapy.fs.
11. exp Antineoplastic Agents/
12. Antineoplastic Combined Chemotherapy Protocols/
13. chemotherap*.ti.
14. exp RAdiotherapy/
15. radiotherapy.fs.
16. (radiotherap* or irradiat* or radiat*).ti.
17. exp Immunotherapy/
18. immunotherap*.ti.
19. ((adjuvant or neoadjuvant or neo-adjuvant) adj3 therap*).ti.
20. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp Exercise/
22. exp Exercise Therapy/
23. exp Exercise Movement Techniques/
24. Physical Fitness/
25. exp Physical Endurance/
26. exp Muscle Strength/
27. Muscle Fatigue/
28. (exercis* or movement* or stretch* or aerobic* or anaerobic*).ti.
29. ((resistance adj3 train*) or stamina or (physical adj3 fit*) or ((musc* or neuromisc*) adj3 fatigue)).ti.
30. (walk* or swim* or cycl* or run* or yoga or tai chi or pilates).ti.
31. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32. 3 and 7 and 20 and 31
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. randomized.ab.
36. placebo.ab.
37. clinical trials as topic.sh.
38. randomly.ab.
39. trial.ti.
40. 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 32 and 40
Key:
mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

WHAT'S NEW

Date	Event	Description
21 September 2016	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Study conception and design: Loughney, West, Kemp, Grocott and Jack

Acquisition of data: Loughney and West

Analysis and interpretation of data: Loughney and West

Drafting of manuscript: Loughney

Critical revision: Loughney, West, Kemp, Grocott, Jack

DECLARATIONS OF INTEREST

Lisa A Loughney: None known

Malcolm A West: None known

Graham Kemp: None known

Michael PW Grocott: None known

Sandy Jack: None known

Michael Grocott: received honoraria for speaking, for travel expenses, or both from Edwards Lifescience, Fresenius-Kabi, BOC Medical (Linde Group), Ely-Lilly Critical Care, and Cortex GmBH. He has also received research grants from the National Institute of Health Research, Association of Anaesthetists of Great Britain and Ireland, Sir Halley Stuart Trust, and Francis and Augustus Newman Foundation. He leads the Xtreme-Everest hypoxia research consortium, who have received unrestricted research grant funding from BOC Medical (alinde Group) Ely-Lilly Critical Care, Smiths Medical, Deltex Medical, London Clinic, and Rolex. None of these activities are related to the work under consideration in this review.

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Not applicable

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Not applicable