**Exercise intervention in cancer patients undergoing neoadjuvant cancer treatment and surgery: A systematic review**

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**ABSTRACT**

**Background:** Neoadjuvant chemoradiotherapy decreases physical fitness which is associated with poor surgical outcome. Exercise training can stimulate skeletal muscle adaptations such as increased mitochondrial content and improved oxygen uptake capacity both contributors to physical fitness. This systematic review focuses on the effect of an exercise training programme in cancer patients undergoing the “multiple hit” of neoadjuvant cancer treatment and surgery.

**Methods:** A systematic database search of Embase, Ovid Medline without Revisions, SPORTDiscus, Web of Science, Cochrane Library and clinical trials.gov for any randomised controlled trials (RCT) or non-randomised controlled trial addressing the effect of an exercise training programme in those scheduled for neoadjuvant cancer treatment and surgery.

**Results:** The database search yielded 6,489 candidate abstracts of which 94 references included the required terms however, only 2 pilot studies were eligible for inclusion. Both studies illustrated that exercise training is safe and feasible in breast and locally advanced rectal cancer with acceptable adherence rates of 80-96%. Only one of the two included pilot studies reported a statistical significant increase in physical fitness. Furthermore, no studies reporting health related quality of life, fatigue, behaviour or surgical outcomes were found.

**Conclusion:** To our knowledge, this is the first systematic review including all cancer patients undergoing neoadjuvant cancer treatment and surgery. Because of the lack of adequately powered RCTs in this area, it remains unclear what is the optimal time to initiate an exercise programme and what is the kind of programme deemed effective in improving clinical outcome measures.

**Introduction**

Cancer is associated with cachexia which, in the pre-operative period, has been shown to influence perioperative outcome, increasing the risk of complications, mortality and length of stay in major gastrointestinal surgery [[1](#_ENREF_1)]. Chemotherapy has been related to skeletal muscle wasting, oxidative stress, mitochondrial death [[2](#_ENREF_2)] and *in vivo* mitochondrial function [[3](#_ENREF_3)]. Furthermore, cancer treatment has been linked to decreased physical fitness levels, which appears to be related to the type of treatment, being worse in those receiving surgery and radiotherapy in combination with chemotherapy than in those who receive radiotherapy or surgery alone [[4](#_ENREF_4)]. Unfortunately poor physical fitness reflects reduced physiological reserve, which is associated with a complicated post-operative period [[5](#_ENREF_5)]. Neoadjuvant chemoradiotherapy decreases physical fitness, as measured by cardiopulmonary exercise testing (CPET), and this decrease is associated with poor surgical outcome, i.e post-operative morbidity and mortality in both lower and upper gastrointestinal cancer patients [[6](#_ENREF_6), [7](#_ENREF_7)]. These data suggest that in some patients the harm of cancer treatment may outweigh the benefits of neoadjuvant cancer treatment.

Exercise training can stimulate skeletal muscle adaptations such as increased mitochondrial content and improved oxygen uptake capacity [[8](#_ENREF_8)], both contributors to physical fitness, which could possibly reduce the adverse effects of cancer treatment. Physical fitness is a modifiable prognosticator and it has been suggested that women with breast cancer who exercise at moderate intensity, 30 minutes or more per day on 5 days or more per week, have a lower risk of death [[9](#_ENREF_9)]. Jones and Aflano [[10](#_ENREF_10)] in 2013 reported a series of observational studies which suggest that higher levels of exercise may be associated with improved prognosis in those with solid tumours.

Furthermore, it has been shown in women who were physically active following diagnosis of non-metastatic colorectal cancer, had a significantly lower risk of colorectal cancer–specific death or death from any cause [[11](#_ENREF_11)].

To date, there has been little research conducted in exercise oncology on patients with newly diagnosed cancers. Most ongoing studies are being conducted either during or following adjuvant cancer treatment, mainly in women with breast cancer [[10](#_ENREF_10)]. Encouragingly, there have been a number of high quality systematic reviews published over previous years shifting the focus towards the pre-operative setting. Granger and colleagues in 2011[[12](#_ENREF_12)] conducted a systematic review investigating the effects of exercise interventions to improve exercise capacity and health-related quality of life (HRQoL) in non-small cell lung cancer (NSCLC). This review concluded that it was safe to exercise NSCLC patients during and following cancer treatment. Similarly, Crandall and colleagues in 2014[[13](#_ENREF_13)] undertook a systematic review specifically investigating exercise interventions in NSCLC patients but in those requiring surgery only. They reported that more trials are required in order to influence surgical outcome [[13](#_ENREF_13)]. Finally, Singh and colleagues in 2013 [[14](#_ENREF_14)] published a systematic review on pre-operative exercise interventions in surgical cancer patients which illustrated improved rate of urinary continence (in prostate cancer patients), cardiorespiratory fitness and length of hospital stay following an exercise intervention [[14](#_ENREF_14)]. In agreement with other reviews published [[10](#_ENREF_10), [12](#_ENREF_12), [13](#_ENREF_13), [15](#_ENREF_15)], this group highlighted there were a limited number of randomised controlled trials (RCT) undertaken in this area of research. To the best of our knowledge, there are currently no systematic reviews focussing on exercise interventions in cancer patients undergoing both neoadjuvant cancer treatment and surgery.

**Objectives**

The objective of this systematic review is to evaluate methods, safety and feasibility, outcome (in terms both of physical fitness and post-operative outcome) and health related quality of life (HRQoL), in studies that have utilised exercise interventions in cancer patients undergoing both neoadjuvant cancer treatment and surgery.

**Research questions**

i) Is exercise training in surgical cancer patients during neoadjuvant cancer treatment safe and feasible? ii) Does it improve a measure of physical fitness (including physical capacity and physical activity)? iii) Does it improve HRQoL? iv) Does it improve surgical outcome?

**Methods**

*Overview of methods and hypotheses*

All clinical trials that involved an exercise training programme in cancer patients undergoing both neoadjuvant cancer treatment and surgery were included in the systematic search. Abstracts were screened and reviewed against predefined inclusion and exclusion criteria by two independent assessors (LL and MW), and assessed using the Downs and Black quality assessment tool [[16](#_ENREF_16)]. Data was extracted by one investigator in accordance with predefined criteria.

The primary hypothesis was: exercise training in cancer patients undergoing neoadjuvant cancer treatment and surgery is safe and feasible.

The secondary hypotheses were: exercise training in this patient cohort improves some measure of physical fitness (including physical capacity and physical activity), HRQoL and post-operative outcome (clinical).

Other exploratory outcomes included defining the structure of the exercise training programme and adherence and behaviour towards exercise and other clinically relevant outcomes such as fatigue and biomarkers. Due to this relatively new area of research, any other exploratory measures were explored.

*Search strategy*

Searches were performed on Embase, Ovid Medline without Revisions, SPORTDiscus, Web of Science, Cochrane Library database and clinical trials.gov using search terms defined by the reviewers. A comprehensive, systematic search was performed on 23 May 2013 and an updated search on 1 October 2014 and 1 December 2014. Relevant keywords were categorised under five distinct headings: (i) cancer, (ii) cancer treatment, (iii) exercise, (iv) surgery and (v) outcome. (See appendix 1 for illustration of all search terms). First, each category was searched separately in the database. A combined search of all the categories was completed and duplicate results were removed. A manual title search of references from the previous review articles on exercise and cancer was also conducted. Data was extracted in accordance with predefined criteria.

*Inclusion and exclusion criteria*

Study design

Inclusion criteria were kept purposefully broad to ensure complete representation of this new topic: RCTs and non-RCTs investigating exercise training in cancer patients undergoing neoadjuvant cancer treatment and surgery. Published abstracts, case reports and theses were excluded.

Participants

Studies were included that recruited human adult (>18 years) cancer patients undergoing an exercise intervention during neoadjuvant cancer treatment awaiting surgery.

Studies were excluded that recruited: cancer survivors (defined as cancer patients who completed all forms of cancer treatment); cancer patient receiving adjuvant treatment, cancer patients receiving palliative treatment; patients with inoperable cancer; cancer patients undergoing an exercise programme following adjuvant treatment; cancer patients receiving androgen therapy.

Exercise intervention

Exercise interventions during cancer treatment and before surgery, done alone or in combination were included. These included 1) aerobic training (defined as exercise that involves large muscle groups performing continuous or intermittent activity over an extended period of time) [[17](#_ENREF_17)]; 2) prescribed resistance training (defined as exercise that involves performing sets of repeated movements against a resistance during which neuromuscular fatigue occurs within 6-12 repetitions [[18](#_ENREF_18)]); 3) pelvic floor muscle exercise training; 4) pectoral exercise training; and 5) stretching programme.

Data extraction and analysis

All studies that met the inclusion criteria were independently assessed for descriptive characteristics such as participant characteristics, study design, types of cancer, length of study (intervention and follow-up times) and primary outcomes by different types of cancers. Descriptive data was extracted about the individual exercise programmes, including the frequency intensity, duration, mode, supervision, location and adherence of the exercise sessions.

Assessment of methodological quality

Two reviewers (LL and MW) independently assessed the methodological quality of each study according to the Downs and Black quality appraisal checklist [[16](#_ENREF_16)]. This checklist consists of 27 questions to evaluate both randomised and non-randomised studies, evaluate study reports, internal validity and external validity. Each question was scored out of 1, except question 5 which was scored out of 2 and question 27 which was scored out of 5, giving a total score of 33. High scores reflect high-quality studies. All discrepancies were resolved by discussion between all authors.

**Results**

*Database search*

The database search yielded 6489 candidate abstracts. After review of the candidate abstracts by two independent reviewers (LL and MW), 94 references included the required terms; however, only 2 studies reported an exercise intervention in patients undergoing both neoadjuvant cancer treatment and surgery, and were therefore deemed eligible for inclusion [[19](#_ENREF_19)] [[20](#_ENREF_20)]. 92 studies were excluded as they did not meet all inclusion criteria.

A manual search through all the references from the two full text papers identified for inclusion was conducted which identified no further eligible articles. A further database search was done from references on all published exercise and cancer related systematic reviews, which identified no eligible articles for inclusion (as majority involved exercise interventions for cancer survivors). After full text screening and application of all inclusion criteria, 2 articles were included in this review. Meta-analyses were not performed due to the clinical and statistical heterogeneity of the included studies.

Figure 1. **Schematic of the** c**omprehensive systematic search conducted for this review**

*Study characteristics*

The characteristics of the studies are presented in Table 1. Of the 2 full text articles, 1 was reported as a pilot RCT [[19](#_ENREF_19)] and 1 as a non-randomized pilot [[20](#_ENREF_20)]. Of these, a breast cancer study [[19](#_ENREF_19)] included 10 patients and a rectal cancer study [[20](#_ENREF_20)] included 39 patients. The mean patient age ranged from 45 to 84 years.

*Study aims*

Both studies aimed to assess feasibility of an exercise intervention in the neoadjuvant setting. The breast cancer study [[19](#_ENREF_19)] aimed to assess feasibility of an exercise training programme during neoadjuvant cancer treatment whilst the rectal cancer study [[20](#_ENREF_20)] aimed to assess feasibility of an exercise training programme following completion of neoadjuvant chemoradiotherapy but prior to surgery.

*Quality assessment*

The quality of each study was evaluated by using a checklist designed to assess randomized and non-randomized trials [[16](#_ENREF_16)]. Quality assessments are reported in Supplementary Appendix 2. The median methodological quality score for the included studies was x out of x. The X scored highest for methodological quality, X out of x. The smaller studies scored lowest for methodological quality. The external validity and statistical power sections of the checklist scored poorly across the studies.

*Participants*

The only mixed gender study was the rectal cancer study [[20](#_ENREF_20)] whilst Roa and colleagues [[19](#_ENREF_19)] only included females in the breast cancer study.

*Type of cancer and cancer treatment*

Of the 2 studies included, 1 included breast cancer [[19](#_ENREF_19)] and 1 included rectal cancer patients [[20](#_ENREF_20)]. The breast cancer study included those with locally advanced breast cancer with no metastatic spread. All participants received standardised neoadjuvant chemotherapy at the discretion of the medical oncologist with the standard institutional regimen being dose dense adriamycin, cyclophosphamide and taxol. The rectal cancer study included those with locally advanced (circumferential resection margin threatened) resectable rectal cancer, undergoing 5 weeks of standardised neoadjuvant chemoradiotherapy on the basis of TNM (tumour, node, metastatic) classification; T2/N+with no distant metastasis. Standardised radiotherapy consisted of 45 Gy in 25 fractions on weekdays using a 3D conformal technique with CT guidance. A boost dose was given (5.4 Gy in three fractions) to the primary tumour only. Oral capecitabine (825 mg m -2) was given twice daily on radiotherapy days. No subjects received brachytherapy.

*Exercise intervention Characteristics and Outcomes*

Exercise intervention characteristics are summarised in Table 1

Exercise Intervention

The breast cancer studies mainly included aerobic and resistance exercise training programme in the form of a boot camp [[19](#_ENREF_19)]. Whilst the rectal cancer patients included an interval aerobic exercise programme [[20](#_ENREF_20)].

Exercise Intervention Adherence

Adherence rates were reasonably high amongst the two studies included in this review; >80% adherence in the boot camp programme [[19](#_ENREF_19)] and 96% adherence in the supervised exercise training programme [[20](#_ENREF_20)].

Exercise Intervention Frequency

The supervised exercise training programme for rectal cancer patients was undertaken 3 times per week for 6 weeks [[20](#_ENREF_20)]. Whilst the breast cancer study were unclear regarding exercise frequency; the boot camp breast cancer programme was 4-6 months in duration (1hour 3 times per week reported 48 sessions) [[19](#_ENREF_19)].

Exercise Intervention Intensity

The aerobic supervised exercise sessions were of moderate to high intensity: 80% work rate achieved at oxygen uptake at estimated lactate threshold (o2 at L) and 50% of the difference in work rate between o2 at L and oxygen uptake at peak exercise (o2peak) [[20](#_ENREF_20)]. The breast cancer boot camp programme was tailored to the participants’ individual tolerance [[19](#_ENREF_19)].

Exercise Intervention Time

The structured in-hospital aerobic exercise training programme progressed from 30 minutes in week 1 to 40 minutes per session thereafter [[20](#_ENREF_20)]. The boot camp programme entailed one hour of exercise per session [[19](#_ENREF_19)].

Exercise Intervention Type

The rectal cancer aerobic exercise training was undertaken on a cycle ergometer. Whilst the boot camp programme in the breast cancer study included intervals of activities such as jumping jacks, running in place, arm and leg work with exercise balls, bands, and weights up to 5 pounds.

Exercise Intervention Supervision

The rectal cancer study included supervised exercise training which was undertaken in-hospital by an exercise physiologist [[20](#_ENREF_20)]. The breast cancer study implemented the boot camp programme that was supervised in a community setting. However, participants in the breast cancer study were also given the option of receiving a home based programme where the personal trainer visited their house 3 times per week if they preferred [[19](#_ENREF_19)].

Inclusion of Control Group

The breast cancer study was a pilot RCT study which included a control group [[19](#_ENREF_19)]. The rectal cancer pilot study included a control group in their study, albeit of a non-randomised, parallel group design [[20](#_ENREF_20)].

*Exercise intervention Outcomes*

Safety and Tolerability

Both, Roa [[19](#_ENREF_19)] and West [[20](#_ENREF_20)] and colleagues assessed feasibility, tolerability, safety and benefits of an exercise programme in the neoadjuvant setting.

Physical Fitness Outcomes

A measure of physical fitness was used as a primary outcome in only the rectal cancer study [[20](#_ENREF_20)]. This study used CPET to measure the primary outcome; o2 at L and o2peak [[20](#_ENREF_20)]. This study reported a significant increase in o2 at L and o2peak following a 6-week in- aerobic interval exercise programme [[20](#_ENREF_20)].

Physical activity levels was a secondary outcome in the rectal cancer study as measured by SenseWear biaxial accelerometery [[20](#_ENREF_20)]. These data reported a significant decrease in physical activity following neoadjuvant chemoradiotherapy however there was a significant increase in physical activity levels reported in those who undertook the exercise programme [[20](#_ENREF_20)].

Health Related Quality of life (HRQoL) Outcome

No studies included in this review reported a measure of HRQoL.

Fatigue ± Other Symptoms

No studies included in this review reported a measure of fatigue or other symptoms.

Behaviour

No studies included in this review reported a measure of behaviour.

Biomarkers± other exploratory measures

Rao and colleagues [[19](#_ENREF_19)] investigated cell proliferation in breast cancer patients (ki-67) in the tumour, tumour size, axilary lymph node status, insulin growth factor 1 (IGF-1) levels, C-peptide levels and body mass index (BMI) as a secondary measure. Clinical and pathologic response to neoadjuvant chemotherapy at the breast and axillary sites were also recorded. The only statistical finding following the boot camp programme was in BMI, however, the boot camp programme did result in a decrease in insulin growth factor (IGF-1) levels, although insignificant.

Table 1. Summary of exercise interventions

| Author,  year, (Country) | Study design | n | Cancer type,  Cancer treatment | Exercise Program | Supervision,  Location | Frequency | Intensity | Duration | Adherence | Outcome measure |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Rao et al**[[19](#_ENREF_19)]**, 2012**  (USA) | Pilot RCT | 10 | Breast,  Neo-adjuvant chemotherapy | Boot camp programme | Supervised Home based | 3times/week X 4-6 months | NR | 60min | >80% | \*Feasibility,  Measure of tumour size/ levels |
| **West et al[**[**20**](#_ENREF_20)**], 2014**  (UK) | Pilot | 35 | Rectal cancer,  Neo-adjuvant CRT | Aerobic,  Interval | Supervised, In-hospital | 3times/week  x 6weeks | Prog:  Mod-high  (% of o2 at L & peak) | 40min | 96% | \*o2 at L  \*physical activity |

Abbreviations: \* - significant findings, RCT- randomised controlled trial, o2 at L- oxygen uptake at lactate threshold, Prog-progressive, Min- minute, CRT – chemoradiotherapy.

**Discussion**

*Main findings*

This is the first systematic review of reports of exercise training interventions in cancer patients undergoing neoadjuvant cancer treatment and surgery. Both studies illustrate that exercise training is safe and feasible in the neoadjuvant setting in breast and locally advanced rectal cancer, although both studies illustrated a small sample size. Overall adherence was acceptable with rates between of 80-96%. However, the question of which is the most effective exercise training programme aimed at improving physical fitness cannot be answered. Only one of the two included pilot studies reported a statistical significant increase in physical fitness [[20](#_ENREF_20), [21](#_ENREF_21)]. Furthermore, no studies reporting HRQoL, fatigue, behaviour or surgical outcomes were found.

*Feasibility*

MacVicar and colleagues [[22](#_ENREF_22)] were the first to conduct an exercise oncology trial (safety and feasibility) in the 1980s, at a time when general oncology advice to cancer patients was to rest and avoid exercise during cancer therapy. Following this revolutionary study, safety and feasibility has been well documented in the adjuvant setting. Shifting the focus towards the neoadjuvant setting, the papers reviewed here illustrate that work in this area is relatively new; the breast cancer study was published in 2012 and the rectal study in 2014. Although feasibility of initiating exercise training in cancer patients in the adjuvant setting is well documented, this review has illustrated that exercise training has been found to be safe in breast cancer patients [[19](#_ENREF_19)] and rectal cancer patients in the neoadjuvant setting [[20](#_ENREF_20)].

*Physical fitness*

Cancer patients experience cachexia, muscle loss and dysfunction. Furthermore cancer treatment has been associated to deleterious effects on whole body fitness, as assessed by CPET, which is related to poor surgical outcome [[7](#_ENREF_7), [23](#_ENREF_23)]. There is now evidence suggesting variables derived from CPET such as o2 at L, o2peak and ventilatory equivalent ratio for carbon dioxide (E/co2)are associated with post-operative outcome in several surgical patient groups [[5](#_ENREF_5), [24](#_ENREF_24), [25](#_ENREF_25)]. However, only one study reviewed here [[20](#_ENREF_20)] used clinically important outcome variables. This study illustrated clinically significant findings following a supervised in-hospital training programme with scaled exercise intensities tailored to individual CPET performance. Likewise, in the prehabilitation setting, two such exercise training programmes have reported significant effects on important clinical outcome measures [[26](#_ENREF_26), [27](#_ENREF_27)]. A higher level of physical fitness has been related to longer cancer-specific survival and lower cancer-related mortality [[28](#_ENREF_28)]. Exercise training has been suggestive to playing a role in ameliorating toxicity, completion rate and cancer treatment efficacy [[10](#_ENREF_10)]. However, studies reviewed here provide little data relevant to deciding on which training programme is most effective on such outcomes. Remaining physically active during and after cancer treatment is known to improve associated adverse effects, as well improve overall survival and reduce the probability of relapse [[29](#_ENREF_29)]. Unfortunately, physical activity tends to decrease at diagnosis in cancer patients [[30](#_ENREF_30)]. West and colleagues [[20](#_ENREF_20)] simultaneously assessed both physical fitness (using CPET) and physical activity (using SenseWear accelerometer) at diagnosis and post neoadjuvant chemoradiotherapy, demonstrating a significant decrease in both. Furthermore, participants were found to have achieved almost half of the recommended (10,000) number of steps a day. Yet, in comparison, a 50% increase in physical activity following diagnosis has been shown to decrease both risk of colorectal cancer-specific and all-cause mortality [[11](#_ENREF_11)]. The first RCT (The CHALLENGE Trial) investigating physical activity levels and survival is currently being conducted among colon cancer survivors following completion of adjuvant chemotherapy [[31](#_ENREF_31)].

*Biomarkers ± other exploratory measures*

High insulin levels have been associated to the risk of breast cancer recurrence or death [[32](#_ENREF_32)]. C-peptide levels greater than 2.5 ng/mL have been correlated with a two-fold increased risk of breast cancer death when compared to those women who’s C-peptides were lower [[33](#_ENREF_33)]. Literature suggests that women who participate in 2-3 hours of moderate intensity exercise per week, such as brisk walking, following diagnosis of breast cancer have a 40-67% reduced risk of death, linking a possible hormone mechanism to survival [[9](#_ENREF_9)]. Exercise training has been found to improve insulin-like growth factor levels in post-menopausal breast cancer survivors [[34](#_ENREF_34)]. However, the breast cancer study included in this review illustrated non-significant reduction in C-peptide levels following their exercise programme [[19](#_ENREF_19)]. However, Rao and colleagues [[19](#_ENREF_19)] argue that the lack of reduction may be associated to BMI and although there was a significant decrease in BMI following their programme it may not have been enough to influence C-peptide levels.

*Strengths ± weaknesses*

The main strength of this article is that it provides an up-to-date comprehensive review of all studies using an exercise programme in cancer patients undergoing neoadjuvant cancer treatment and surgery. The review was conducted in a rigorous manner using selected search terms over several databases. Furthermore, two independent assessors screened the candidate articles using the predefined search terms and evaluated the quality of each study using a checklist designed to assess randomised and non-randomised trials.

The main weakness of this article is the limited number of studies available. Furthermore, the breast cancer study offered participants the choice between a home based exercise programme where a personal trainer visited their home or joining a group session which was also open to the public which limits future application of such exercise interventions [[19](#_ENREF_19)] Although the breast cancer study illustrated positive results, the sample size was small and was not adequately powered which may contribute to the lack of statistical significance findings.

**Conclusion**

To our knowledge, this is the first systematic review including all cancer patients undergoing neoadjuvant cancer treatment and surgery. Because of the lack of adequately powered RCTs in this area, it remains unclear what is the optimal time to initiate an exercise programme and what is the kind of programme deemed effective in improving clinical outcome measures. Future studies will need to examine the mechanisms of cancer treatment and different exercise programmes as well as translating this to clinically important outcome measures such as health behaviour, disease-free survival and overall survival in different cancer cohorts. Encouragingly, there are ongoing studies investigating the effects of exercise on prevention or mitigation of adverse toxicities and their association to cancer therapy[[10](#_ENREF_10)].

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**Appendix 1**

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| --- |
| **Search terms** |
| 1. **CANCER** |
| 1. expNeoplasm |
| 1. Canc\*.tw. |
| 1. Neoplasm\*.tw. |
| 1. expTumor |
| 1. Tumo\*.tw. |
| 1. expCarcinoma |
| 1. Carcin\*.tw. |
| 1. expMalignant |
| 1. expOncology |
| 1. Oncol\*tw. |
| 1. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 |
| 1. **CANCER TREATMENT** |
| 1. expNeoadjuvant |
| 1. Neoadjuvant\*.tw. |
| 1. expChemo |
| 1. Chemo\*.tw. |
| 1. expRadiotherapy |
| 1. expCancer treatment |
| 1. 12 or 13 or 14 or 15 or 16 or 17 |
| 1. **EXERCISE** |
| 1. expExercise |
| 1. Exercise\*.tw. |
| 1. expFitness |
| 1. Fit\*.tw. |
| 1. expOxygen consumption |
| 1. expAerobic |
| 1. Aerobic\*.tw. |
| 1. Anaerobic |
| 1. Anaerobic\*.tw. |
| 1. 19 or 20 or 21 or 21 or 22 or 23 or 24 or 25 or 26 or 27 |
| **i) and ii) and iii)** |
| 1. **SURGERY** |
| 1. Surgery |
| 1. Surg\*.tw. |
| 1. Surgical (including Anatomy, drainage, mortality, patient, science, stress, wound, ward all terms) |
| 1. 30 or 31 or 32 |
| 1. **I) and ii) and iii) and iv)** |
| 1. **OUTCOME** |
| 1. Morb\*.tw. |
| 1. Mort\*.tw. |
| 1. Recurrence\*.tw. |
| 1. Outcom\*.tw. |
| 1. 34 or 35 or 36 or 37 |
| 1. **and ii) and iii) and iv) and v)** |

Figure 1.**Search terms used in this systematic review**

**Appendix 2**

Table 2: **Downs and Black Quality Assessment tool score**