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UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

Clinical Experiment Sciences

The effect of neoadjuvant cancer treatment and exercise training on physical fitness and physical activity levels before elective rectal surgery

by

Lisa Anne Loughney

Thesis for the degree of Doctor of Philosophy

September 2017

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF MEDICINE

Clinical Experiment Sciences

Thesis for the degree of Doctor of Philosophy

THE EFFECT OF NEOADJUVANT CANCER TREATMENT AND EXERCISE TRAINING ON PHYSICAL FITNESS AND PHYSICAL ACTIVITY LEVELS BEFORE ELECTIVE RECTAL SURGERY

by Lisa Anne Loughney

This thesis addresses the effects of neoadjuvant cancer treatment (CRT) and a pre-operative exercise training programme on physical fitness and physical activity levels (PAL) in people with locally advanced rectal cancer prior to elective surgery.

An observational study was conducted to investigate the effects of neoadjuvant CRT on physical fitness cardiopulmonary exercise test (CPET) derived variable oxygen uptake ($\dot{V}o_2$) at lactate threshold ($\hat{\theta}_L$) and PAL (daily step-count), and other associated exploratory CPET and PAL variables in people with locally advanced rectal cancer scheduled for elective surgery. Following completion of neoadjuvant CRT (week-0) prior to surgery, a randomised controlled study (RCT) was conducted. Participants were randomised to an in-hospital pre-operative exercise training programme or to a usual care control group. The primary endpoint was $\dot{V}o_2$ at $\hat{\theta}_L$ at week-9 measured using CPET. The secondary endpoint was daily step-count at week-9 measured using physical activity monitors. Exploratory endpoints were associated CPET and PAL variables.

Thirty-one participants were recruited, of which, 24 completed the study (five dropped out and two were deemed palliative). Findings from the observational study showed no significant differences in $\dot{V}o_2$ at $\hat{\theta}_L$ or daily step-count following neoadjuvant

CRT (p>0.05). Findings from the RCT showed a significant difference in $\dot{V}O_2$ at $\hat{\theta}_L$ (ml.kg^{-1}.min^{-1}) at week-9 following participation in the exercise group programme (n=13) compared to the usual care control group (n=11): 16.7 (5.1) vs. 12.9 (1.6); p=0.021. There were no statistical significant differences between the groups in daily step-count at week-9 (p>0.05).

These findings suggest that pre-operative in-hospital exercise training can optimise physical fitness prior to major surgery. These results will aid the design of a large, multi-centre trial, to determine whether an increase in physical fitness improves post-operative outcome, length of stay and other important clinical outcomes.

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Chapter 6: Changes in physical fitness and physical activity levels following a preoperative exercise training programme: A randomised controlled trial

Academic Thesis: Declaration Of Authorship

I, LISA LOUGHNEY declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

The effect of neoadjuvant cancer treatment and exercise training on physical fitness and physical activity levels before elective rectal surgery

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Either none of this work has been published before submission, or parts of this work have been published as: [please list references below]:

Chapter 3 (Systematic review) is published as a protocol research paper and as two separate systematic reviews papers (in the neoadjuvant and adjuvant setting).

- Loughney LA, West MA, Kemp GJ, Grocott, Jack S. Exercise interventions for people undergoing multimodal cancer treatment that includes surgery. *Cochrane Database of Systematic Reviews* 2016, Issue 7, Art. No.: CD012280. DOI: 10.1002/14651858.CD012280.
- Loughney L, West MA, Kemp GJ, Grocott MP, Jack S. Exercise intervention in people with cancer undergoing neoadjuvant cancer treatment and surgery: A systematic review. *European Journal of Surgical Oncology* 2016, 42 (1):28–38.
- Loughney L, West MA, Kemp GJ, Grocott MP, Jack S. Exercise intervention in people with cancer undergoing adjuvant cancer treatment and surgery: A systematic review. *European Journal of Surgical Oncology* 2015, 41 (12):1590–602.

Signed:

Date: 26/09/2017

Declaration of contribution

This trial (apart of the EMPOWER trial, identifier; NCT01914068) is funded by the National Institute for Health Research (NIHR) for Patient Benefit Programme (PB-PG-0711-25093). I collected the pilot data which informed this grant application at University Hospital Aintree (UHA) in 2011 with chief investigator Dr Sandy Jack. I set up this trial in University Hospital Southampton (UHS) in 2013, which is the sponsor site. I gained ethical approval from the North West Centre for Research Ethics Committees (13/NW/0259) via the IRAS system and I was the main point of contact for this trial. This trial is supported by the Comprehensive Local Research Networks (CLRN's) in Hampshire and Isle of Wight. I was lead study coordinator and data manager of this multi-centre trial. Initially, this trial was intended to include only two sites (UHS and UHA). The recruitment rates for the EMPOWER trial were predicted based on pilot data, collected in UHA between June 2012 – August 2013, which forecasted a recruitment rate of 4 per month. However, due to a change in clinical pathway, recruitment rates were lower than forecasted (i.e. more patients were scheduled for surgical treatment only, as opposed to multimodal treatment). Therefore, additional sites were opened to increase recruitment.

This multi-centre trial included: UHS, opened to recruitment August 2013; UHA, opened to recruitment December 2013; Royal Hampshire County Hospital (RHCH), opened in January 2014 (this hospital site only invited eligible participants onto the study however recruitment and all study visits took place in UHS); South Tees Hospital (STH), opened to recruitment November 2014; and finally Royal Bournemouth Christchurch Hospital (RBCH), opened to recruitment March 2015. I led set-up and initiation of this trial at each site. This included communication with several multi-disciplinary teams, local principal investigators, research teams, research and development departments and ordering testing equipment to facilitate this research. I trained staff working on this trial (of whom, had no experience of working in this area with the exception of the UHA staff) in all aspects of the research and on test protocols such as: cardiopulmonary exercise testing (CPET); physical activity monitoring; and the exercise training protocol. I was responsible for organising and leading weekly team meetings (internally), monthly telephone conference meetings (including all sites) and trial steering group meetings where trial conduct was discussed in detail. As the exercise training programme was dependent

on each individual CPET, two experienced assessors (myself and Malcolm West) reported all tests during the study period for the exercise group to ensure agreement of results. I interpreted all physiological data for my thesis.

I devised the analysis plan and the SPSS database for the trial. I sought statistical advice from Dr. Borislav Dimitrov, Associate Professor of Medical Statistics in the Faculty of Medicine, University of Southampton (RIP) for my revisions. Following Dr. Dimitrov passing, I sought support from statistical consultant, Olivia Masson, Centre for Support and Training in Analysis and Research, University College Dublin. I set up the Trans European Network for patient randomisation in clinical trials randomisation service alongside clinical trials data officer (Mike Radford) provided by Southampton University. I coordinated the trial on a day to day basis in UHS and conducted all the tests and exercise training sessions with help from the critical care research nurses.

Declaration of contribution

I, Lisa Loughney, confirm that the work presented in this thesis is my own work and is part of the EMPOWER trial. However where information has been derived from other sources, I confirm that this has been indicated in the thesis (below).

Chapter 1 (nil)

Chapter 2 (nil)

Chapter 3

Assistance with screening eligible articles for inclusion in the systematic review by Malcolm West (MW). This chapter consists predominantly of a systematic review, written by myself representing the working group (Fit-4-Surgery), which is published as a study protocol in The Cochrane Database for Systematic Reviews and as two separate reviews in the European Journal of Surgical Oncology.

Chapter 4

Chapter 5 and 6

Data collection in UHA by Joanne Earley

Data collection in STH by Kerry Colling

Data collection in RBCH by Emma Willet

Help with data collection in UHS by my colleagues and critical care research nurses Clare Bolger and Karen Salmon

Chapter 7 and 8 (nil)

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Thanks to all the team, Anaesthesia, Critical Care and Perioperative Medicine Research Department in UHS, especially to the "dream team" who I have learned and grown with over the previous years. Special thank you to Malcolm West.

Thanks to my family for providing daily phone calls of encouragement and support. A special thank you to my wonderful parents. A special thank you also to my dear friends Dr Helena Gibbons, Dr Edwenia O'Malley and Ms. Susie O'Carroll for supporting me through the write up.

Finally, to all my patients who were my true inspiration, for their time and effort, I am truly grateful.

Glossary of abbreviations

Abbreviation	Definition
AAA	Abdominal aortic aneurysm
ACC/AHA	American College of Cardiology/American Heart Association
ACSM	American College of Sports Medicine
AE	Adverse event
APR	Abdomino-perineal resection
ASA	American Society of Anesthesiologist
ATP	Adenosine triphosphate
BMI	Body mass index
BORG	Borg rating of perceived exertion
BP	Blood pressure
CAFs	Cytokines and angiogenic factors
CEP	Circulating endothelial progenitor cells
CG	Control group
CLRN	Comprehensive local research networks
CO2	Carbon dioxide
CABG	Coronary artery bypass graft
COPD	Chronic obstructive pulmonary disorder
CPET	Cardiopulmonary exercise test
CRF	Cancer related fatigue
CRF	Case report form
CRT	Chemoradiotherapy
CT	Computerised tomogram
ECG	Electrocardiogram
EE	Energy expenditure
EG	Exercise group
EORTC QLQ-30	Cancer specific questionnaire
EQ-5D	Health outcome questionnaire
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-B	Functional Assessment of Cancer Therapy-Breast
FACT-G	Functional Assessment of Cancer Therapy-General
FEV1	Forced expiratory volume over 1 second
FS	Fatigue Scale
FU	Fluorouracil
FVC	Forced vital capacity
HR	Heart rate
HRQoL	Health related quality of life
IGF-1	Insulin Growth Factor-1
IQR	Inter quartile range
ISWT	Incremental shuttle walk test
LAR	Low anterior resection
LED	Light emitting display
LOS	Length of stay
LT	Lactate threshold

Glossary of abbreviations (Cont'd)

MCID	Minimum clinical important difference
MDT	Multidisciplinary team
MET	Metabolic equivalent threshold
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MWT	Minute walk test
N2	Nitrogen
NHS	National Health Service
NIHR	National Institute for Health Research
NSCLC	Non-small cell lung cancer
PA	Physical activity
PAL	Physical activity level
PCO_2	Partial pressure of arterial carbon dioxide
PO_2	Partial pressure of oxygen
POMS	Post-operative morbidity survey
POSSOM	Physiological and Operative Severity Score for the enumeration of Mortality and morbidity
RBCH	Royal Bournemouth Christchurch Hospital
RCT	Randomised control trial
RER	Respiratory exchange ratio
RHCH	Royal Hampshire County Hospital
RPE	Rate of perceived exertion
RPM	Revolutions per minute
SCT	Stair Climb Test
SF-36	Short form health survey questionnaire
SPO2	Peripheral capillary for oxygen saturation
SRETP	Structured responsive endurance training programme
STH	South Tees Hospital
TENALEA	Trans European Network for patient randomisation in clinical trials
TME	Total mesorectal excision
TNM	Tumour, Node, Metastasis
UHA	University Hospital Aintree
UHS	University Hospital Southampton
VE	Ventilation
$\dot{V}o_2$	Oxygen uptake
$\dot{V}o_2$ at $\hat{\theta}_L$	Oxygen consumption at lactate threshold
$\dot{V}o_2$ peak	Oxygen consumption at peak exercise
$\dot{V}_E/\dot{V}co_2$	Ventilatory equivalents for carbon dioxide
$\dot{V}co_2$	Carbon dioxide output

Chapter 1

Introduction

1.1. Introduction

This thesis addresses the effects of neoadjuvant chemoradiotherapy treatment (CRT) and pre-operative exercise training on physical fitness and physical activity levels (PAL) in people with locally advanced rectal cancer prior to elective surgery. This Chapter will begin with an introduction to the background of the thesis content.

Over 9,000 people were diagnosed with rectal cancer in 2014 in the United Kingdom[1]. Fifty-five percent of these patients underwent surgery and 40 % received neoadjuvant CRT prior to surgery[1]. Chemotherapy, combined with radiotherapy, improves local disease control and local recurrence for locally advanced rectal cancer[2-4]. However, chemotherapy and CRT are related to negative side effects such as skeletal muscle wasting, oxidative stress, mitochondrial death[5] and late toxic effects, which are linked to poor post-operative complications[6-7]. Cancer is associated with cachexia, sarcopenia and frailty, all of which are also linked to poor perioperative outcome[8-10]. The risk of major surgery has been recently highlighted by a large European study which reported that surgery is associated with significant morbidity and mortality[11]. Taken together, people with colorectal cancer are a high risk group for adverse outcome after surgery.

Cardiopulmonary Exercise Testing (CPET) has the ability to measure physical fitness to evaluate risk relating to surgery. More recently, CPET has been used in surgical-oncology to investigate the effect of neoadjuvant cancer treatment on physical fitness prior to surgery in two observational studies[11-12]. Findings from these studies showed that neoadjuvant chemotherapy and CRT significantly reduced physical fitness (reported using CPET-derived variable oxygen uptake at lactate threshold ($\dot{V}o_2$ at $\hat{\theta}_L$) in people with oesophageal[12] and locally advanced rectal cancer[13] prior to surgery. Changes in $\dot{V}o_2$ at $\hat{\theta}_L$ were shown to be clinically important: reduced 1-year survival in people with oesophageal cancer[12] and post-operative complications (day-5) in people with locally advanced rectal cancer[13].

Pre-operative exercise training has the ability to optimise physical fitness to enable an individual to maintain a normal level of function during and after surgery[14]. Research

on pre-operative exercise training in people with colorectal cancer is relatively new with only seven studies published since 2009 (studies are from three different centres in the United Kingdom, Canada, and Netherlands). A recent systematic review specifically examined the effects of pre-operative exercise training in colorectal cancer, of which, reported that the current evidence-base is limited due to a lack of adequately powered trials and clinically relevant outcome measures[15]. Therefore, our knowledge of what is the most optimal frequency, intensity, timing and type of exercise training programme and what its effect is on post-operative outcome remains unanswered.

The individual hypotheses, aims and objectives of this thesis are set out below.

1.2 Hypotheses, aims and objectives

1.2.1 Hypotheses

1.2.1.1 Primary hypothesis

A pre-operative exercise training programme (hospital-based) compared to a usual care control group (usual care and no formal exercise training) will result in a significant increase in physical fitness CPET-derived variable $\dot{V}O_2$ at $\hat{\theta}_L$ in people with locally advanced rectal cancer following neoadjuvant CRT and prior to surgery.

1.2.1.2 Secondary hypothesis

(a) Neoadjuvant CRT will result in a reduction in CPET-derived variable $\dot{V}O_2$ at $\hat{\theta}_L$ and PAL variable daily step-count in people with locally advanced rectal cancer.

(b) A pre-operative exercise training programme (hospital-based) compared to a usual care control group (usual care and no formal exercise training) will be associated with an increase in PAL variable daily step-count in people with locally advanced rectal cancer following neoadjuvant CRT and prior to surgery.

1.2.2. Aims

1. To conduct a **systematic review** including reports of any form of exercise training intervention for people with cancer undergoing multimodal treatment including surgery on physical fitness, safety and feasibility, health-related quality of life (HRQoL) and other important health outcomes.
2. To conduct an **observational study** to investigate the effect of neoadjuvant CRT on physical fitness and daily PAL in people with locally advanced rectal cancer prior to surgery.
3. To conduct a **randomised controlled trial** to investigate the effect of a pre-operative exercise training programme (supervised, hospital-based) compared to a usual care control group (usual care and no formal exercise training) on physical fitness and PAL in people with locally advanced rectal cancer following neoadjuvant CRT and prior to surgery (including the same group of participants from the observational study).

1.2.3 Objectives

1. To determine the effect of exercise interventions for people with cancer undergoing multimodal treatment including surgery on safety and feasibility, physical fitness, HRQoL and other important health outcomes.

2. To determine the effect of neoadjuvant CRT on physical fitness (using CPET) and PAL (using physical activity monitors) in people with locally advanced rectal cancer prior to surgery.

3. To determine the effect of a pre-operative exercise training programme on physical fitness and PAL compared to a usual care control group (usual care and no formal exercise training) in people with locally advanced rectal cancer following neoadjuvant CRT prior to surgery.

1.3 Study setting

Overall five NHS hospital sites participated in recruitment (August 2013 – October 2015): University Hospital Southampton (UHS); University Hospital Aintree (UHA); Royal Hampshire County Hospital (RHCH); South Tees Hospital (STH); and Royal Bournemouth Christchurch Hospital (RBCH). All assessments and exercise training sessions were performed in each of NHS hospitals delivering this study by supervised and trained staff personnel.

1.4. Organisation of the thesis

This thesis is presented as eight chapters. The chapter content is further outlined below:

- ***Chapter 1: The present chapter (Introduction)*** - this briefly outlines an introduction of the research area, hypothesis and aims of the research, study setting and organisation of the chapters presented.
- ***Chapter 2: Background*** – this chapter provides an overview of all aspects of the research to familiarise the reader including an overview of: (i) the rectal cancer treatment pathway; (ii) measures of pre-operative risk assessment; (iii) the use of CPET and physical activity monitors as objective measures of physical fitness and PAL; and (iv) the literature on pre-operative exercise training.
- ***Chapter 3: Systematic Review*** – this chapter is a systematic review synthesising all the literature on exercise training in people with cancer undergoing multimodal treatment including surgery.
- ***Chapter 4: Methods*** – this chapter provides an overview of the trial design and conduct, description of measurements and analysis of general experimental protocols, equipment and calibration as well as data acquisition and interpretation of methods. Specifically, CPET as an objective measure of physical fitness, physical activity monitors as an objective measure of PAL and the exercise training programme protocol are described.
- ***Chapter 5: The effects of neoadjuvant chemoradiotherapy on physical fitness and physical activity levels in people with locally advanced rectal cancer*** – this chapter describes an observational study investigating the

changes in physical fitness and PAL assessed using CPET and physical activity monitoring following neoadjuvant CRT in a cohort of people with locally advanced rectal cancer.

- ***Chapter 6: The effects of a pre-operative exercise training on physical fitness*** and ***physical activity in people with locally advanced rectal cancer prior to surgery*** - this chapter describes a randomised controlled study investigating the effects of a pre-operative exercise training programme compared to a usual care control group on physical fitness and PAL following neoadjuvant CRT and prior to surgery (including the same participants as Chapter 5).
- ***Chapter 7: Discussion*** – this chapter presents a brief summary of results from each study.
- ***Chapter 8: Future work*** – this chapter recommends future work that merits further investigation and specifies areas of research to be addressed.

Chapter 2

Background

2.1 Introduction

This chapter will briefly discuss rectal cancer, the treatment pathway including neoadjuvant chemoradiotherapy treatment (CRT) and surgery, and its associated risk. Pre-operative risk assessment and exercise tests will then be briefly discussed. Specific to this thesis, particular references will be placed on cardiopulmonary exercise test (CPET) and physical activity monitoring. Following this, an overview of the evidence-base on pre-operative exercise training will be described.

2.1. Rectal cancer

2.1.1. Rectal cancer incidence

Colorectal cancer was reported to be the third most common cancer in males and females in the United Kingdom in 2013[16-17]. Between 2013 and 2014, 9,048 people were diagnosed with rectal cancer. Of these, 55 % underwent surgery and approximately 40 % received neoadjuvant CRT prior to surgery[1]. Twenty-nine percent of whom were reported to be older than 75 years[1].

2.1.2. Rectal cancer treatment pathway

The standard treatment pathway for rectal cancer is pre-operative CRT followed by total mesorectal excision (TME)[9, 18]. This cancer (with no metastatic spread) is treated with curative intent and in some cases people may undergo additional adjuvant cancer treatment if indicated[18]. Pre-operative 5-fluorourcail (FU) based chemotherapy, combined with radiotherapy, improves survival for locally advanced rectal cancer[19-20]. With optimised local treatment, including neoadjuvant CRT and TME, local relapse rates have now been reduced to less than 10 %[18]. The time interval between completing neoadjuvant CRT and surgery is variable amongst different clinical practices: a recent review reported that prolonging the time interval beyond 6 weeks may achieve greater tumour regression and may allow for tissue swelling and inflammation to resolve prior to surgery[18]. This cancer treatment pathway carries a level of risk. Firstly, there is a risk of late toxic effect from neoadjuvant CRT: severe acute toxicity has been reported in up to 40 % of cases; long-term toxicity in 14-27 % of cases; and post-operative complications in 21-36 % cases, emphasising the need to identify people in whom the

benefit is balanced against long-term side effects[6]. Secondly, intensified neoadjuvant CRT prior to surgery can result in anastomotic leak rates of 27 % and perineal wound infection rates of 42 %[7], which in turn, are associated with a complicated post-operative period.

2.2 Perioperative risk assessment

2.2.1 Why is there a requirement for perioperative risk stratification?

The level of risk associated with surgery has been described in a recent European Surgical Outcome Study[11]. Of the 46, 539 people included in this audit, of which incorporated a number of different surgical groups, 1,855 (4 %) died before hospital discharge and 3,599 (8 %) were admitted to critical care after surgery. Worryingly, 1,358 (73 %) who died were not admitted to critical care at any stage after surgery and the mortality rate was 3.6 %, which was higher than expected for people undergoing such surgery[11]. The key factors associated with increased risk (morbidity) of surgery include: an older patient population; co-morbid disease; major and urgent surgical procedures; and acute physiological deterioration[21]. As mentioned, people with colorectal cancer undergoing multimodal treatment including neoadjuvant CRT and surgery have a high risk of adverse outcome post-operatively. Morbidity following major surgery is more common than mortality. Morbidity impairs the recovery process post-operatively and is associated with long term health implications[22].People with colorectal cancer treated with neoadjuvant CRT and surgery have a high risk of adverse outcomes, and therefore emphasise the importance of adequate pre-operative assessment to evaluate the risk relating to surgery.

2.2.2 Pre-operative assessment

The purpose of pre-operative risk assessment is to assess the medical status of the patient and recommend appropriate strategies to reduce the risk of adverse outcome. The pre-operative assessment aims to reduce surgical and anaesthetic perioperative morbidity or mortality, and to return individuals to desirable functioning as quickly as possible[23]. Current methods used to inform risk stratification pre-operatively include: American Society of Anesthesiologists (ASA) physical score; Duke's Activity Score; Physiological and Operative Score for Enumeration of Mortality and Morbidity

(POSSUM)[24-26]; plasma biomarkers[22]; and lung or cardiac function[27]. Additional exercise tests (measuring physical fitness) further inform the pre-operative risk assessment and some tests have the ability to predict myocardial ischemia, cardiac arrhythmias and estimate any perioperative cardiac risk[28]. Measuring physical fitness pre-operatively is clinically important: a lower physical fitness in rectal cancer prior to surgery is related post-operative complications[13]. The best documented exercise tests pre-operatively include: 6 minute walk test (6MWT)[29]; incremental shuttle walk test (ISWT)[30]; stair climb test (SCT), and cardiopulmonary exercise test (CPET)[31]. These tests will be discussed in greater detail below.

2.3 Physical fitness

Physical fitness is defined as a multidimensional concept including a set of attributes that people possess or achieve related to the ability to perform physical activity. Physical fitness is comprised of skill-related, health-related and physiologic components[32]. Physical fitness can be measured using field-based tests or laboratory-based tests and both of which will be discussed below.

2.3.1 Field (non-laboratory-based) tests

Pre-operative field-based tests provide a subjective measure of physical fitness. Such tests are practical, cheap and easy to administer. They are commonly used in clinic as they require little equipment and training. Several exercise tests exist but the most documented in the pre-operative setting include the 6MWT, ISWT and SCT, of which, will be briefly discussed below[33].

2.3.1.1 Six Minute Walk Test (6MWT)

The 6MWT is a self-paced test of walking capacity. The test protocol includes walking along a flat 20 metre surface as many times possible for 6 minutes. This test has been well documented in lung disease: a poor 6MWT is associated with increased mortality[34]. In colorectal cancer, the 6MWT has been used to measure changes in physical fitness in exercise trials[15] but its ability to predict post-operative outcome remains unknown.

2.3.1.2 Incremental Shuttle Walk Test (ISWT)

The ISWT is an incremental and progressive field-based test of walking ability, stressing the individual to a symptom limited maximal performance[35]. The test requires walking up and down a 10 metre course with walking speed dictated by a pre-recorded audio signal played on a recorder and increases throughout. Limitations include that the ISWT can be influenced by patient motivation and encouragement on the day of testing. A recent systematic review specifically addressed the use of field-based tests in the pre-operative setting to predict post-operative outcome in major abdominal surgery[33]. This review reported that the ISWT appears to be the most superior field-based test: lower distances on the ISWT were related to longer hospital length of stay and increased risk of overall complications. However this systematic review included a limited number of studies (n=5), therefore future work is required[33].

2.3.1.3 Stair Climb Test (SCT)

The SCT measures the ability to ascend or descend a flight of stairs. This test has been well documented in lung disease and the performance on a SCT has been shown to be associated with $\dot{V}O_2$ at peak: 56 % of people who climbed < 14m of steps had a $\dot{V}O_2$ at peak < 15 $ml.kg^{-1}.min^{-1}$ whereas 98 % of people who climbed > 22m of steps had a $\dot{V}O_2$ at peak > 15 $ml.kg^{-1}.min^{-1}$ [36]. However, the evidence-base on the use of the SCT in people with colorectal cancer is limited.

2.3.2 Laboratory-based tests

Pre-operative laboratory-based tests provide an objective measure of physical fitness. They require specialised and expensive equipment, and trained staff members. The most documented pre-operative laboratory-based test in surgery is CPET[31].

2.3.2.1 Cardiopulmonary exercise test (CPET)

CPET is usually conducted with the individual on an electromagnetically braked cycle ergometer breathing through a mouthpiece or facemask through which gas exchange is measured. CPET provides an objective measure of physical fitness compared to subjective non-laboratory-based tests, and uses simultaneous measurement of respiratory gas exchange and cardiovascular variables. The individual is continuously monitored using a continuous 12-lead electrocardiogram (ECG) and oxygen saturation

probe, with periodic measurement of blood pressure. CPET provides a global assessment of the integrative responses of the pulmonary, cardiovascular and haematological systems that are not adequately reflected through the measurement of individual organ system function[37-38].

During exercise, the increased demand for adenosine triphosphate (ATP) by exercising muscles requires increased tissue oxygen delivery mediated by increased cardiac output and ventilation[37-38]. Similarly, perioperatively, the increased ATP demand for metabolic work requires increased tissue oxygen delivery which must be matched by increased ventilation and cardiac output, if tissue perfusion and oxygenation are to be maintained.

Although requiring a moderate to high level of exertion, CPET is well tolerated and safe to conduct[39]. However, CPET requires specialised equipment, increased safety precautions and extra staff (and increased costs) which may limit wide clinical application.

2.4 Overview of the role of cardiopulmonary exercise testing in surgery

In Australia, Older and colleagues were the first to publish research that used CPET in general surgery during the early 1990's[40]. In a cohort study of 184 people undergoing major elective abdominal surgery, a lower $\dot{V}o_2$ at $\hat{\theta}_L$ was reported to be associated with increased post-operative mortality: hospital mortality was <1 % in people with $\dot{V}o_2$ at $\hat{\theta}_L \geq 11$ ml·kg^{-1}·min^{-1}, 18 % in people with $\dot{V}o_2$ at $\hat{\theta}_L \leq 11$ ml·kg^{-1}·min^{-1}, and 50 % in people with $\dot{V}o_2$ at $\hat{\theta}_L \leq 8$ ml·kg^{-1}·min^{-1}. Since this, over the past fifteen years, there has been growing interest in the use of CPET in the pre-operative setting in the United Kingdom[41-45]. A study investigating CPET in a group of people undergoing major intra-abdominal surgery showed a relationship between CPET-derived variables and morbidity: $\dot{V}o_2$ at $\hat{\theta}_L$ of 10.1 ml·kg^{-1}·min^{-1} was predictive of post-operative complications[46]. In a follow up study, a relationship between cardiorespiratory fitness and age was investigated in older people undergoing hepatobiliary surgery: $\dot{V}o_2$ at $\hat{\theta}_L$ was the most significant independent predictor for

post-operative mortality[47]. More recently, findings from one of the largest United Kingdom-based CPET studies[48] in colorectal cancer were consistent with the initial work undertaken by Older in the early 1990s[40], showing a similar optimal cut-off point for in-hospital morbidity identified with $\dot{V}o_2$ at $\hat{\theta}_L$ 11.1 ml·kg^{-1}·min^{-1}.

2.4.1 Why cardiopulmonary exercise testing was chosen as a measure of physical fitness for this thesis

The evidence-base on CPET is the strongest of all tests in the pre-operative setting. There is compelling evidence illustrating the strong relationship between reduced CPET-derived variable ($\dot{V}o_2$ at $\hat{\theta}_L$) and post-operative morbidity[49-67]. There is a growing evidence-base to support the use of CPET with more than 20 CPET studies in several surgical groups. These studies demonstrate an extremely consistent relationship between physical fitness, defined using CPET-derived variables, and post-operative morbidity (Table 2.1). In the majority of studies presented in Table 2.1, CPET-derived variables $\dot{V}o_2$ at $\hat{\theta}_L$ and at peak are associated with post-operative outcome although this association is statistically stronger for $\dot{V}o_2$ at $\hat{\theta}_L$ in most cases. Other CPET-derived variables such as abnormal ventilatory equivalents for carbon dioxide ($\dot{V}_E/\dot{V}co_2$) which reflect increased dead space are also associated with both mortality and morbidity in some case series but not in others. Therefore, CPET-derived variable $\dot{V}o_2$ at $\hat{\theta}_L$ was used to describe physical fitness (primary outcome measure) for the experimental work in this thesis.

Table 2.1 Overview of the literature using cardiopulmonary exercise testing derived variables in several patient groups as a prediction of post-operative outcome

Author, Year	Patient group	n	V o_2 at $\hat{\theta}_L$	V o_2 Peak	V_E/ V_{CO2}	Outcome
Older P, 1993 [40]	MIA	187	<11	NR	Y	CV Mortality
Nagamatsu Y, 1994 [54]	Upper GI	52	NR	Y	NR	CP comp
Nugent AM, 1998 [55]	AAA	30	NR	<20	NR	Mortality
Older P, 1999 [56]	MIA	548	<11	NR	NR	Mortality
Nagamatsu Y, 2001 [57]	Upper GI	91	Y	Y	NR	CP Comps
Epstein SK, 2004 [58]	Hepatic transplant	59	Y	Y	NR	Mortality
McCullough PA, 2006 [53]	Bariatric	109	Y	<15.6	NR	Composite
Carlisle and Swart, 2007 [50]	AAA	130	Y	Y	>42	Mortality
Forshaw MJ, 2008 [59]	Upper GI	78	Y	Y	NR	CP comp
Wilson RJ, 2010 [51]	MIA	847	<10.9	NR	>34	Mortality
Snowden CP, 2010 [47]	MIA (incl. HPB)	116	<10.1	Y	Y	POMS (Day 7)
Hightower CE, 2010 [24]	MIA	32	-	Y	Y	Morbidity
Hennis PJ, 2012 [45]	Bariatric	106	<11	Y	Y	Morbidity & POMS
Hartley RA, 2012 [42]	AAA	415	<10.2	<15	Y	Mortality 30 & 90 day
Prentis JM, 2012b [61]	AAA	185	<10	Y	NR	LOS & Morbidity

Table 2. 1 Overview of the literature using cardiopulmonary exercise testing derived variables in several patient groups as a prediction of post-operative outcome (Cont'd)

Author, Year	Patient group	n	V o_2 at $\hat{\theta}_L$	V o_2 Peak	V_E/V_{CO2}	Outcome
Junejo MA, 2012 [52]	Hepatic resection	131	Y	Y	>34.5	Mortality & morbidity
Chandrabalan VV, 2013 [62]	Pancreatic	100	<10	NS	NS	LOS, post-operative adverse events
Prentis JM, 2012 [43]	Liver transplant	165	<9	Y	Y	Mortality, critical care LOS
Ausania F, 2012 [63]	Pancreas	124	<10.1	Y	Y	Pancreatic leak, morbidity, LOS
Snowden CP, 2013 [47]	HPB	389	Y	Y	Y	Mortality & LOS
Goodyear SJ, 2013 [64]	AAA	230	<11	NR	NR	Mortality, LOS, Cost
West MA, 2014a [65]	Colonic Ca	136	<10.1	<16.7	Y	POMS (Day 5) & Morbidity
West MA, 2014b [13]	Rectal	105	<10.6	<18.6	NR	POMS (Day 5) & Morbidity
Dunne DF, 2014 [66]	Liver	197	NS	NS	NS	Comps, LOS
Brunelli A, 2014 [67]	NSCLC	157	NR	60%	NR	Survival
Grant SW, 2015 [68]	AAA	506	<10.2	<15	NR	Mortality
West MA, 2016 [48]	Colorectal	703	<11.1	18.2	>30.9	Morbidity

List of abbreviations: V o_2 at $\hat{\theta}_L$ – oxygen uptake at estimated lactate threshold (measured in $ml \cdot kg^{-1} \cdot min^{-1}$); VO_{2peak} – oxygen consumption at peak exercise (measured in $ml \cdot kg^{-1} \cdot min^{-1}$); V_E/V_{CO2} – ventilatory equivalents of carbon dioxide; MIA –Major intra-abdominal; NR – not reported; Y- yes; CV – cardiovascular; GI- gastro intestinal surgical patients; NSCLC – Non small cell lung cancer; CP- Cardiopulmonary; Comp – complications; AAA – abdominal aortic aneurysm; POMS- post operative mortality score; HPB- Hepatobiliary; LOS –length of stay; Comorb. – Comorbidity; NS – not significant.

2.5 Physical activity

Physical activity is defined as any bodily movement that is produced by the contraction of skeletal muscle which increases energy expenditure[32]. Daily PAL can be categorised into occupational, sports, household, or other activities. In 2010, the American College of Sports Medicine (ASCM) recommended physical activity guidelines for people with cancer. The recommendations followed the same guidelines for age appropriate healthy individuals developed in 2007which include undertaking 150 minutes per week of moderate intense aerobic exercise or 75 minutes per week of vigorous intense aerobic exercise, and strength training 2-3 times per week including 8-10 exercises of 10-15 sets. In addition, specifically for people with cancer, ACSM published guidelines advising to avoid inactivity, and to continue normal activities and exercise as much as possible during and after non-surgical treatments.

An increase in daily PAL following cancer diagnosis reduces the risk of cancer-specific death or death from any cause in non-metastatic colorectal cancer[69]. The most documented measure of daily PAL in cancer include subjective self-reported measures such as short form health survey-36 (SF-36)[70-73], Scottish physical activity questionnaire[71], and international physical activity questionnaire (IPAQ)[70]. However, more recently, the use of physical activity monitors in people with newly diagnosed cancer has received attention[74]. Physical activity questionnaires and monitors will be briefly discussed below.

2.5.1 Questionnaires

Questionnaires are a cheap and quick method to measure daily PAL. However, self-reported measures of PAL have been recently reported as being an unreliable measure of PAL in people with cancer[74]. This section will briefly discuss the most commonly used questionnaires to measure PAL in people with cancer.

2.5.1.1 Short Form Health Survey-36 (SF-36)

The SF-36 questionnaire is an established and widely-used measure of health related quality of life (HRQoL). It includes eight domains including physical functioning[70-72]. This domain reports limitations on ten mobility activities such as walking, carrying

groceries, bathing or dressing. The SF-36 has been shown to be a valid measure of mobility and disability in epidemiological studies involving an elderly population[75].

2.5.1.2 Scottish Physical Activity Questionnaire (SPAQ)

The SPAQ measures exercise behaviour change and 7-day recall of PAL. SPAQ is quick and easy to complete, and practical for large numbers. It has been shown to be reliable and valid with the stage of exercise behaviour change model. However, its main limitation is that it has a low reliability for measured occupational PAL (walking)[76].

2.5.1.3 International Physical Activity Questionnaire (IPAQ)

The IPAQ is a validated questionnaire developed to monitor self-reported PAL in healthy adults. However, its limitations include its length, low compliance and difficulties in completing the questionnaire. Therefore, a short form of the IPAQ (IPAQ-SF) which is a validated questionnaire is commonly preferred in oncology. The IPAQ-SF measures PAL in bouts of ≥ 10 min of leisure-time (domestic and gardening activities), work and transportation activities over the past seven days. However, it has been recently documented as being an unreliable measure of daily PAL in people with cancer (self-reported PAL were reported to be 336 % higher when compared to physical activity monitoring data)[74.]

2.5.2 Physical activity monitors

The existing evidence-base on physical activity monitors in clinical studies is mainly in chronic obstructive pulmonary disease (COPD), and has been validated as an objective measure of PAL in different stages of COPD[77]. However, there is limited literature on the use of physical activity monitors in people with newly diagnosed cancer. A strength to using physical activity monitors is that they provide direct objective measures of specific behaviours such as daily step-count[78], as well as time spent being active (intensity of activity), standing, sitting and lying down[79], of all of which provide researchers to new insights into the relation between physical activity and health. Furthermore, wearing these devices for up to seven days has been shown to be acceptable by participants. However, limitations include that physical activity monitors (for upper arm or wrist devices) can be limited for upright behaviours that

have a low ambulatory component. Furthermore, such devices do not report the type of activity undertaken[80].

2.5.2.1 Why physical activity monitoring was chosen as a measure physical activity levels for this thesis

A recent study reported that almost 90 % of people with cancer who participated in a lifestyle intervention (and chemotherapy), who self-reported PAL perceived themselves as meeting the recommended ACSM physical activity guidelines (150min/week of moderate activity). However, when this was compared against objective physical activity monitoring data, findings showed that less than 50 % were achieving these exercise recommendations[74]. The physical activity monitor, the SenseWear Amrband Pro, was chosen to measure PAL for this thesis as it has been reported as providing a reliable estimation of resting energy expenditure (EE). It provides useful information on daily EE when compared to indirect calorimetry[81] and reasonable agreement when compared with doubly labelled water (free living-adults)[82] in people with cancer. The most documented physical activity monitoring variable is daily step-count with emerging step-based recommendations documented worldwide in chronic illnesses[83]. Therefore, the SenseWear Armband Pro variable daily step count was used to describe PAL (secondary outcome) for the experimental work in this thesis.

2.6 Overview of the role of pre-operative exercise training

Over the past 15 years, evidence has emerged supporting the use of pre-operative exercise training in several surgical groups, some of which are summarised in Table 2.2. All exercise programmes differ in frequency, intensity, time, type and setting (hospital- and home-based). Additionally, studies vary in reporting outcome measures: feasibility; physical fitness; HRQoL; length of stay: and post-operative outcome. The exercise training programmes are reported using the FITT principle (American College of Sports Medicine), which include a set of guidelines to outline the delivery of an exercise training programme such as frequency, intensity, time and type of exercise training. Note: reference is made to terms such as functional capacity, exercise capacity and exercise tolerance, and are considered synonymous (all of which imply that a maximal test has been performed). These terms will be used

interchangeably throughout the thesis in accordance to how each research paper reported it. Note: reference is also made to feasible/feasibility which encompasses any sort of study that can help investigators prepare for full-scale research leading to intervention[84].

Overall, pre-operative exercise training prior to surgery appears to be safe and feasible and have a beneficial effect on physical fitness, PAL and HRQoL in all 19 studies reported in Table 2.2. To date, two systematic reviews have specifically investigated the effect of pre-operative exercise training on post-operative outcome. One review (n=17) which mainly included people who had hip or knee arthroplasty for osteoarthritis[85]. The other review (n=9), more specific to the research in this thesis, addressed intra-abdominal surgery and reported that pre-operative exercise training appears to be beneficial in decreasing the incidence of post-operative complications[86]. However, due to lack of adequately powered randomised controlled trials in major cancer surgery, there are no definite answers to the question of what is the optimal frequency, intensity, timing and type of training, and what are its' effects on post-operative outcome. Furthermore, whether training at home is as effective as supervised training still needs to be established.

2.6.1 Pre-operative exercise training in colorectal cancer

Research on pre-operative exercise training in colorectal cancer is relatively new since 2009 with seven studies. Of these studies, five are from the one research group in Canada.

Kim and colleagues[87] in Canada were the first to make an advance in the area of pre-operative training in people with colorectal cancer: the initial work was a feasibility pilot study in people with colorectal cancer awaiting surgery (n=14; exercise group (EG) and n=7; control group (CG). The exercise training incorporated a 4-week home-based exercise training programme on a portable cycle ergometer. Exercise intensities were prescribed using heart rate reserve and rating of perceived exertion. Findings from this study showed no change in $\dot{V}O_2$ at peak in the EG despite an acceptable adherence rate of 74 %, but that a 4-week home-based programme was feasible to implement. However the study had some limitations: pilot study with a small sample size; adherence data were self-reported; the exercise equipment was delivered to

homes and the research team provided regular home visits to provide encouragement, which limits its application in the future of home-based programmes.

Following this, in 2010, the same research group[88] compared the extent to which a pre-operative exercise training programme (n=58) (hospital-based) optimised recovery of functional walking capacity following surgery compared to a home-based walking programme (n=54). This study was the first RCT of its kind in colorectal cancer: people were randomised to a structured bike and strengthening programme (hospital-based exercise training programme) or to a walking and breathing programme (home-based exercise training programme). This study showed an unexpected benefit in the CG with an increase in walking distance and breathing exercises. However limitations included: the authors reported missing data and poor compliance to the programme which may have contributed to their findings; the CG became aware of their poor physical fitness which may have influenced their exercises further; and the CG received an intervention therefore findings should be interpreted with caution. Furthermore, both of the aforementioned studies measured physical fitness using VO^2 max tests and 6MWT, both of which were conducted on the same visit which may influence results (a suitable time between the tests allows for complete recovery to baseline).

In 2011, the authors[89] re-analysed these data. Their objectives were to estimate: (1) the extent to which physical fitness could be improved with either training programme and to identify variables associated with response, and (2) the impact of change in pre-operative physical fitness on post-operative recovery. Their findings showed that during the programme 33 % improved their physical fitness, 38 % stayed within 20 metres of their baseline measure and 29 % deteriorated. Furthermore, improved physical fitness was related to increased mental health, vitality, self-perceived health and peak exercise capacity. Additionally, people who improved physical fitness during the programme were more likely to have recovered to their baseline walking capacity post-operatively compared to those with no change or who deteriorated. Furthermore, people who deteriorated were at greater risk of complications requiring re-operation and/or intensive care management. Following these study findings, this research group had a more focused approach to the studies that followed.

In 2013, this research group[90] initiated a tri-modal prehabilitation intervention in people with colorectal cancer which incorporated exercise, nutritional counselling, protein supplementation and anxiety reduction (n=42; EG and n=45; CG (i.e. no formal intervention). This 4-week programme improved functional walking capacity and was associated with a faster post-operative recovery: 81 % of the EG recovered by 8 weeks compared to 40 % in CG. Interestingly, this was the first study to show that a tri-modal prehabilitation programme significantly improved 6MWT. Limitations included: participants chose their preferred type of exercise modality, therefore limiting comparison of individual fitness changes; and the assessment time points for both the EG and CG were not matched which limits comparison between groups.

In 2014, this research group[91] then compared the impact of a tri-modal programme initiated 4 weeks prior to surgery (prehabilitation group) to an identical tri-modal programme initiated post-operatively (rehabilitation group). Both groups received a home-based, moderate intensity, aerobic and resistance exercise training programme, as well as nutritional counselling with protein supplementation and relaxation exercises for 8 weeks following surgery. People in both groups were also managed by an enhanced recovery pathway. This study illustrated that the prehabilitation programme had a greater benefit on functional walking capacity prior to surgery compared to the rehabilitation programme. These findings highlight that pre-and post-operative exercise training has beneficial effects on physical fitness. However, there were no differences between the groups in post-operative outcome (complication rates or duration of hospital stay).

The advent of neoadjuvant cancer treatment has opened up a time window to implement exercise training in the time window between completing treatment and scheduled surgery date, without interfering with standard clinical pathway. This is a new area of research with few studies published. In 2014, in the United Kingdom, our research group (Fit-4-Surgery) reported that a 6-week pre-operative exercise training programme (hospital-based), initiated immediately after neoadjuvant CRT and prior to surgery, was safe and feasible, and furthermore had a clinically significant improvement on $\dot{V}O_2$ at $\hat{\theta}_L$ and at peak in people with locally advanced rectal cancer[92]. In addition to improvements in physical fitness, this 6-week pre-operative exercise training programme (hospital-based) (n=22) promoted positive changes in

patient's behaviours and helped them view their lives in a way that was fuller, richer, and more meaningful[93]. Limitations of this study include study design: a non-randomised parallel group interventional controlled pilot study whereby the CG (n=17) were people who were unable to commit to the exercise intervention (mainly due to living more than 15 miles from the hospital).

Following this, in 2016 in Canada[94], Moreilli and colleagues investigated the feasibility and safety of exercise training during and after neoadjuvant CRT in people with rectal cancer prior to surgery. This study demonstrated acceptable eligibility, recruitment, adherence and follow up assessment rates to the exercise training programme. This exercise programme was delivered in two phases: supervised exercise during neoadjuvant CRT and a choice of unsupervised or supervised/combination following neoadjuvant CRT. Additionally, this study explored motivational outcomes, perceived benefits and harms, and perceived barriers to exercise during and after CRT and findings showed that people with rectal cancer who were starting an exercise programme during CRT were motivated and anticipated that the programme would be beneficial and well-supported. There was also some indication that some people perceived that it may have worsened side effects of CRT whilst others perceived that exercise after CRT would help them prepare for surgery[95]. This study is the first to explore motivational outcomes in this setting and will inform future work.

Although pre-operative exercise training is still a new area of research in colorectal cancer, the early work is encouraging. Of the studies mentioned above, five conducted over the past three years[90-92, 94-95] have shown that pre-operative exercise training has beneficial effects on physical fitness prior to surgery, both in people scheduled for surgery alone or multimodal treatment including surgery. Future work should consider using similar outcome measures to allow for inter-study comparisons.

Table 2.2 Pre-operative exercise training and surgical outcome: an overview of the literature

Author, Year	Surgery (n=)	Study design	Exercise Programme	Location	Frequency	Intensity	Type	Time	Adherence	Primary Outcome
Asoh T, 1981[96]	GI (29)	Pilot	Cont. Aerobic	Hospital	2/day x 1-3 wk.	HR; <130 bpm	Cycle/ Treadmill	20min	NR	*PPC's
Debigaré R, 1999[97]	Lung (23)	Pilot	Cont. Aerobic & strength	Home	5/wk x 10-12 wk.	≥50% V_{O2} peak	Walking	15-45min	97%	*6MWD
Arthur HM, 2000[98]	CABG (246)	RCT	Interval Aerobic	Hospital	2/wk x 8wk	40-70% funct. capacity	Multimodal	90 min	(mean 14 classes)	*LOS
Hulzebos EHJ, 2006[99]	CABG (279)	RCT	IMT	Home + Hospital	Daily x 2wk.	Prog.IMP max	IMT loading device	20min	NR	*PPC's
Jones LW, 2007b[100]	Lung (25)	Pilot,	Aerobic	Hospital	5/wk x 4–8 wk.	Prog; 65% V_{O2}peak	Cycle	20-30min	72%	*V_{O2} peak
Bobbio A, 2008[101]	Lung (12)	Pilot, Observ.	Cont. aerobic, IMT,stretch	Home	5/wk x 4wk.	40 –65% HRR/RPE	Portable Cycle	90min	NR	*V_{O2}max
Kothmann E, 2009[102]	AAA (30)	Pilot, RCT	Cont. aerobic	Hospital	2/wk x 6 wk.	Mod.RPE/ BORG	Cycle	30min	NR	*V_{O2} at $\hat{\theta}_L$
Kim DJ, 2009[87]	CRC (21)	RCT, Pilot	Cont. aerobic	Home	5/wk x 4wk.	40– 65% HRR/RPE	Cycle	20-30min	74%	*measures of CV fitness
Carli F, 2010[88]	CRC (112)	RCT	Bike+strength/ walking + breathing prog	Home (1weekly visit)	Daily x 7-8 wk.	Prog;50% MHR	Cycle/ Walking	20-45 min	16%	6MWT
Dronkers JJ, 2010[103]	GI (42)	RCT	Cont.aerobic / strength/ breathing	Hospital + home	2/day x 2-4wk.	Prog.MHR /BORG,	Cycle/ Walking/ IMT device	60min	In-hospital - 97%, Home- NR	Feasibility/ *measure of functional capacity

Table 2.2. Pre-operative exercise training and surgical outcome: an overview of the literature (Cont'd)

Author, Year	Surgery (n=)	Study design	Exercise Programme	Location	Frequency	Intensity	Type	Time	Adherence	Primary Outcome
Timmerman H, 2011[104]	Abd./ Thor. (15)	Observ, Pilot	Cont.aerobic /strength	Hospital	2/wk x 5wk.	65-85% HRR/60-80%1-RM	Multi-modal	120min	84%	Feasibility *Cardio. Fitness *Muscle strength
Rao R, 2012[105]	Breast (10)	Pilot, RCT	Boot camp	Home	3/wk x 4-6months	NR	Multi-modal	60min	>80%	Feasibility
Tew GA, 2012[106]	AAA (28)	Pilot, RCT	Endurance	Exercise suite	3/wk x 12 wk.	Mod;RPE	Multi-modal	35-45min	94%	Feasibility
Coats V, 2013[107]	Lung (16)	Non-R, Interv.	Aerobic, strength	Home	3-5/wk x 4 wk.	60-80% workload	Walking/ Cycle	30-45min	81%	Feasibility
Li C, 2013[90]	CRC (46)	RCT	Trimodal	Home	3/wk x 6 wk.	50% MHR	Multi-modal	30-90min	45-70%	*6MWT
Barakat HM, 2014[108]	AAA (20)	RCT, Pilot	Aerobic	Hospital	3/wk x 6wk.	NR	Multi-modal	60min	70-100%	* V_{O2} at $\hat{\theta}_L$ * V_{O2}Peak
Mujovic N, 2014[109]	COPD with NSCLC	Prosp, Observ.	Pulmonary	Hospital	3daily x 5days/ wk x 2-4 wk.	Prog.	Multi-modal	45min	NR	*Lung function, *6MWD
West MA 2014[92]	Rectal (39)	Rand.	Interval Aerobic	Hospital	3/wk x 6wk.	Prog.(mod. – severe)	Cycle	40min	96%	* V_{O2} at $\hat{\theta}_L$
Gillis C, 2014[91]	CRC (77)	RCT	Trimodal	Home	3/wk x 4-wk.	RPE/HRR	Multi-modal	50min	NR	*Functional walking capacity
Morielli, 2016[94]	Rectal	Pilot	Aerobic	Hospital + home	3/wk x 6 wk.	40-60% VO2max	Multi-modal	40min	83%	Feasibility and safety

List of abbreviations: *($p<0.05$), NR- not reported, IG – intervention group, CG – control group, NR – not reported, Observ. – observational, Prosp. – prospective, Prog. – progressive, retrosp. – retrospective, wk – week; min – minutes; CV- cardiovascular, HR- heart rate, BPM-beats per minute, QoL- quality of life, IMT- inspiratory; muscle training, RCT- randomised control trial, Non-R-non randomised, Rand-randomised, LOS- length of stay, funct -functional, erg. – ergometer, mod. – moderate, cont. – continuous, CABG- coronary artery bypass surgery, GI – gastrointestinal; Abd - Abdominal surgery; Thor – thoracic surgery; IMPmax -maximal inspirometry mouth pressure, PPC-pulmonary postoperative complications, MHR – maximum heart rate, RPE – Rate of perceived exertion, 6MWT– 6 minute walk test, 1RM -1 repetition maximum, HHR-heart rate reserve, cardio. – cardiorespiratory, COPD- chronic obstructive pulmonary disease, NSCLC- non small cell lung cancer, V_{O2} at $\hat{\theta}_L$ oxygen uptake at lactate threshold, V_{O2}max – oxygen consumption at maximal exercise, V_{O2}peak – oxygen consumption at peak exercise; prog – programme.

2.7 Summary of Chapter 2

- Colorectal cancer was reported to be the third most common cancer in males and females in the United Kingdom in 2013.
- Neoadjuvant CRT prior to surgery can result in anastomotic leak rates of 27 % and perineal wound infection rates of 42 %, which in turn, are associated with a complicated post-operative period. Furthermore, neoadjuvant CRT significantly reduces physical fitness defined using CPET- derived variable $\dot{V}o_2$ at $\hat{\theta}_L$ in people with locally advanced rectal cancer

- CPET- derived variable $\dot{V}o_2$ at $\hat{\theta}_L$ is strongly associated with post-operative outcome. $\dot{V}o_2$ at $\hat{\theta}_L$ was used to report physical fitness (primary outcome measure) for the experimental work in this thesis.

- Physical activity monitors are a reliable measure of daily PAL when compared against self-reported questionnaires in people with cancer. Physical activity variable daily step-count was used to report PAL (secondary outcome measure) for the experimental work in this thesis.

- There is emerging evidence that pre-operative exercise training has beneficial effects on physical fitness although its effect on post-operative surgical outcome is not known due to a lack of randomised controlled trials.

Chapter 3

Exercise training for people undergoing multimodal cancer treatment including surgery: A systematic review

This systematic review is published as a protocol research paper and as two separate systematic reviews papers (in the neoadjuvant and adjuvant setting).

- Loughney LA, West MA, Kemp GJ, Grocott, Jack S. Exercise interventions for people undergoing multimodal cancer treatment that includes surgery. *Cochrane Database of Systematic Reviews* 2016, Issue 7, Art. No.: CD012280. DOI: 10.1002/14651858.CD012280.
- Loughney L, West MA, Kemp GJ, Grocott MP, Jack S. Exercise intervention in people with cancer undergoing neoadjuvant cancer treatment and surgery: A systematic review. *European Journal of Surgical Oncology* 2016, 42 (1):28-38.
- Loughney L, West MA, Kemp GJ, Grocott MP, Jack S. Exercise intervention in people with cancer undergoing adjuvant cancer treatment and surgery: A systematic review. *European Journal of Surgical Oncology* 2015, 41 (12):1590-602.

3.1 Background

3.1.1 Description of the condition

People with cancer are often faced with multimodal treatment including surgery and a medical cancer treatment such as neoadjuvant or adjuvant chemotherapy or combination chemoradiotherapy. Major surgery is associated with significant morbidity and mortality, as recently highlighted in the European Surgical Outcome Study[11]. Morbidity has a major impact on post-operative recovery and is associated with long-term health implications[1106-111]. Furthermore, prolonged post-operative morbidity is associated with an increased risk of death for up to three years after surgery[111].

Cancer and cancer treatment is associated with cachexia (loss of body weight, fat and muscle), sarcopenia (loss of muscle mass and strength) and frailty (a state of vulnerability to poor resolution of homeostasis). All of which have been linked to post-operative complications and mortality[5]. Cancer treatment has been linked to decreased physical fitness and is worse in people receiving surgery and radiotherapy in combination with chemotherapy than in those receiving radiotherapy or surgery alone[112]. This decrease in physical fitness may persist. In a series of studies, cardiorespiratory fitness was ~30 % below that of age-matched sedentary healthy women up to three years following completion of adjuvant cancer treatment[113]. Furthermore, a significant decrease in physical activity levels (PAL) has been associated with a higher level of fatigue during breast cancer treatment[70]. Taken together, these data highlight the high risk of adverse outcomes after major cancer surgery.

3.1.2 Description of the intervention

An exercise intervention may be defined 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[114]. The intervention may take place in any setting and be delivered to a group or an individual participant.

3.1.3 How the intervention might work

Remaining physically active during and after cancer treatment improves associated adverse effects and symptoms, overall survival, and reduces the rate of recurrence[115]. Increasing PAL by 50 % following colorectal cancer diagnosis decreases both the risk of colorectal cancer-specific and all-cause mortality[69]. Exercise training can stimulate skeletal muscle adaptations such as increased mitochondrial content and improved oxygen uptake capacity[117], both contributors to physical fitness, which possibly could reduce the adverse effects of cancer treatment. Furthermore, higher levels of exercise may be associated with improved prognosis in solid tumours[116] and in combination with chemotherapy, exercise training has been shown to slow tumour progression in solid tumours compared with chemotherapy alone[118]. Moderate intensity exercise in women with breast cancer (i.e. at least 30 minutes per day on at least 5 days per week) has been associated with a lower risk of death from the disease[119].

3.1.4 Why it is important to do this review

As interest in exercise-oncology has grown, a number of high-quality clinical trials and systematic reviews have been conducted, but so far trials have mainly focused on exercise training following adjuvant cancer treatment[115]. The literature on the effects of exercise training on improving physical fitness in people with cancer who undergo single modality treatment has been examined in two systematic reviews in people with non-small cell lung cancer (NSCLC)[120-121]. One systematic review reported beneficial effects on physical fitness, symptoms and health-related quality of life (HRQoL) in people treated by surgery or a form of cancer treatment[120] whilst the second reported beneficial effects on physical fitness and other important clinical measures in people treated by surgery[121]. One other systematic review (including a variety of different cancer types) reported that exercise training in people who were surgically treated improved urinary continence (prostate cancer), physical fitness, length of stay, and improved HRQoL in people who received cancer treatment[122]. A number of published reviews have pointed out the limited number of randomised controlled trials (RCT) undertaken in this area[114, 116, 120-124]. However, to the best of my 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 who undergo multimodal treatment including surgery.

3.2 Objectives and research questions

3.2.1. Objectives

To determine the effect of exercise interventions for people with cancer undergoing multimodal treatment including surgery on safety and feasibility, physical fitness and physical activity levels (PAL), HRQoL, and other important health outcomes.

3.2.2 Research questions

1. Is exercise training in people with cancer undergoing multimodal treatment including surgery safe and feasible?
2. Does exercise training in this context increase physical fitness and PAL?
3. Does exercise training improve HRQoL?
4. Does exercise training improve other clinically relevant outcomes such as fatigue and post-operative outcome?
5. What aspects of an exercise training programme have been reported as effective: what is the best time to initiate an exercise intervention and the optimal structure and composition of an exercise training programme?

3.3 Methods

3.3.1 Criteria for considering studies in this review

3.3.1.1 Types of studies

The inclusion criteria were kept deliberately broad to ensure complete representation of this relatively new topic: RCT and non-RCT (studies that did not include a control group such as pilot studies, case series and cohort studies) investigating exercise training in people with cancer undergoing both a form of medical cancer treatment and surgery. Published abstracts, case reports and theses were excluded.

3.3.1.2 Types of participants

Studies that recruited human participants with a confirmed cancer diagnosis who were scheduled to undergo a form of medical cancer treatment and cancer surgery were included. Furthermore, participants aged >18 years were included regardless of gender, tumour type and stage, and type of cancer treatment and participants of all exercise or activity level were included.

Studies that included people with cancer receiving palliative treatment; people with inoperable cancer; and people with cancer receiving androgen therapy were excluded.

3.3.1.3 Usual care

For the purpose of this review, control groups are referred to as usual care groups (i.e. standard care but no formal exercise training).

3.3.1.4 Types of outcome measures

3.3.1.4.1 Primary outcome

- (1.a) Safety and feasibility (number of adverse events (AE) and adherence to the intervention).
- (1.b) Physical fitness and PAL (a measure of physical fitness and PAL).

3.3.1.4.2 Secondary outcome

- (2.a) HRQoL.
- (2.b) Fatigue.
- (2.c) Post-operative outcome (post-operative morbidity and mortality).

The outcomes of interest assessing the elements and composition of an exercise intervention were:

- Optimal timing of initiation of an exercise training programme.
- Optimal structure and composition of an exercise training programme.

As this is a relatively new area of research, any other exploratory measures were considered.

3.3.2 Search methods for identification

3.3.2.1 Electronic searches

The following databases were used to obtain relevant studies (from 1980 to 2016) for this review:

- Embase
- Ovid Medline without Revisions
- SPORTDiscus
- Web of Science
- Cochrane Library database

A comprehensive systematic search was conducted on 23rd May 2013 and four further updated searches on 1st October 2014, 1st December 2014, 1st April 2015 and 1st September 2016. Relevant keywords were categorised under five distinct headings: (i) cancer; (ii) cancer treatment; (iii) exercise; (iv) surgery; and (v) outcome. (See Appendix 1 for diagrammatic presentation of all search terms and strategy). First, each category was searched separately in all the databases, then a combined search was conducted of all the categories, and finally removed duplicate results.

3.3.2.2 Searching other resources

An expanded search for articles to identify "grey literature" was performed which included:

- Hand searching of reference lists of all articles obtained for additional studies and other review articles on exercise and cancer;
- Clinicaltrials.gov;
- PubMed: citation search of key authors in the area of exercise and cancer;

- Attempts to communicate with study authors to obtain information not presented in the studies.

3.3.3 Data collection and analysis

3.3.3.1 Selection of studies

All records retrieved from the searches were imported into the reference management software package EndNote. Duplicates were removed and relevant articles were selected for screening. The remaining references were examined independently by myself (LL) and my research collaborator Malcolm West (MW) to ensure a high level of methodological quality for the purpose of publication. At this stage, studies that did not meet the inclusion criteria were excluded.

3.3.3.2 Data extraction

Two authors (myself and MW) retrieved all studies in which the abstract made reference to an exercise intervention in people with cancer undergoing both surgery and a form of cancer treatment. Full-text copies of relevant references were obtained and any disagreement was resolved through discussion. If required, disagreements were resolved by resource to Sandy Jack (SJ). All studies that met the inclusion criteria were extracted and independently assessed for descriptive characteristics such as study design and aims, participant characteristics including type of cancer and cancer treatment. Descriptive data were extracted about the intervention details: exercise prescription components (frequency, intensity, time, and type), setting (hospital, home, community) and adherence to the exercise sessions.

3.3.3.3 Methodological quality assessment

Two authors (LL and MW) independently scored the methodological quality of each study according to the Downs and Black quality appraisal checklist[125]. This checklist consists of 27 questions to evaluate study quality, external validity, internal validity bias, internal validity (selection bias) and power of both randomised and non-randomised studies. Each question was scored out of 1, except question 5 that was scored out of 2 and question 27 that 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 (LL, MW and SJ).

3.3.3.4 Data synthesis

A decision to conduct a meta-analysis was based on the following pre-defined criteria:

- To increase power: detecting a real effect as statistically significant if it exists;
- Many individual studies are too small to detect small effects, but when several are combined there is a higher chance of detecting an effect;
- To improve precision: the estimation of an intervention effect can be improved when it is based on more information;
- To answer questions not posed by the individual studies;
- To settle controversies arising from apparently conflicting studies or to generate new hypotheses;

A decision not to conduct a meta-analysis was based on the following pre-defined criteria:

- If studies were clinically diverse;
- If there were a mix of comparisons of different treatments with different comparators;
- If a consensus was hard to reach: decisions concerning which studies should and should not be combined are inevitably subjective, and require discussion and clinical judgement;
- If bias were present in each (or some) of the individual studies.

3.4 Results

3.4.1 Database search

The comprehensive database search strategy conducted for this systematic review is shown as a PRISMA Flow Diagram in Appendix 2. This included exercise interventions in people undergoing both cancer surgery and a form of cancer treatment, and yielded 6489 candidate abstracts. Review of the candidate abstracts by two independent reviewers (LL and MW) found that 94 references included the required terms, of which 72 were excluded as they did not meet all inclusion criteria. A manual search through all the references from included full text papers and recent updated searches using the same methodological approach resulted in an additional 17 full text papers for review, two of which were eligible for inclusion. After full text screening and application of all inclusion criteria, 24 articles were eligible for inclusion in this review. Meta-analyses were not performed on the basis of the predefined criteria.

3.4.2 Included studies

Of the 24 full text articles, 19 studies were reported as a RCT[, 22, 70, 71, 73, 112, 128-130, 132-135, 137-138, 141-143,150] and five studies did not include a control group[72, 92, 105, 126-127]. Only five studies included > 200 people [73, 134, 137-138, 150,] and four studies included 100-200 people [70, 130, 133, 142] the remaining studies included 7-67 people. Thirteen of the 24 studies were published within the last six years. The mean patient age ranged from 45 - 84 years. Note: four studies by Courneya and colleagues[136-138,145] result from one exercise training trial, the START trial, and two studies by Jones and Hornsby and colleagues[132, 142] are also from one exercise training trial.

3.4.3 Study aims

The study aims are presented in Table 3.1.

3.4.3.1 Breast cancer

In breast cancer studies, study aims varied widely. In the neoadjuvant setting, aims included assessing the effects of an exercise intervention on: feasibility; tolerability; safety; and physical fitness[132, 142]. In the adjuvant setting, aims included assessing the effects of an exercise intervention on feasibility; tolerability; safety; cancer related

fatigue (CRF); physical fitness and PAL[71, 105, 126, 124-127 137-139]; and other measures such as quality of life[112]; sleep; disturbance; mood disturbance; symptom distress[131]; sarcopenia and dyspnoea[134]. Other aims were to investigate the effect of an exercise programme on HRQoL, fatigue[70], muscular strength and fatigue[133,135] and factors/moderators predicting exercise training response[136-138].

3.4.3.2 Rectal cancer

In rectal cancer studies, aims included assessing feasibility of an exercise training programme during neoadjuvant CRT[94] and following completion of neoadjuvant CRT prior to surgery[92, 94].

3.4.3.3 NSCLC

In NSCLC studies, aims included assessing feasibility of an exercise training programme during adjuvant cancer treatment[127] and determining the effects of an exercise training programme on cancer related fatigue (CRF), other symptoms, functional status and HRQoL in a post-surgical intervention[72].

3.4.3.4 Mixed cancer group

One study which included people with 21 different cancers aimed to investigate the effects of an exercise intervention on fatigue and general well-being in the adjuvant setting[139].

3.4.4 Study characteristics

Table 3.2 summarises the characteristics of the included studies.

3.4.5 Participants

There were only five studies with mixed-genders[13, 72, 94, 127, 139]. All other studies involved only females with breast cancer, with one study only including postmenopausal females[144].

3.4.6 Type of cancer and cancer treatment

The included studies involved a variety of different cancer types in people undertaking an exercise intervention during both neoadjuvant and adjuvant cancer treatment. Of the 24 studies included, 19 were breast cancer[70-71, 105, 112, 126, 128-133, 134-138, 141-143], two were rectal cancer[92, 94], two were NSCLC[72, 127] and one included 21 different cancer types[139].

3.4.7 Risk of bias in included studies

The quality of each study, evaluated using a checklist designed to assess randomised and non-randomised trials is reported in Appendix 3. The median methodological quality score for the included studies was 23/33. The pilot study of rectal cancer in the neoadjuvant setting scored highest for methodological quality, 25/33[92]. The pilot study of breast cancer in the adjuvant setting scored the lowest for methodological quality, 17/33[126].

3.4.8 Effects of exercise intervention

The summary of findings table is presented in Table 3.1.

3.4.8.1 Primary outcomes

3.4.8.1.1 Safety and feasibility

3.4.8.1.1.1 Breast cancer

One study in the adjuvant setting[126] and one study in the neoadjuvant setting[132] assessed safety of exercise training in this context all of which reported that exercise in this context was safe.

Two studies assessed feasibility of an exercise programme in the adjuvant setting[126, 131] and one pilot study in the neoadjuvant setting[129] all of which reported exercise training in this context was feasible. Two studies in the adjuvant setting reported feasibility including recruitment and retention data[126, 131] combined with adherence[131]. Whereas the other study in the neoadjuvant setting reported feasibility using attendance (number of exercise sessions attended divided by number of planned sessions) and adherence (number of exercise sessions completed divided by number of planned sessions attended) data[129].

3.4.8.1.1.2 Rectal cancer

Two pilot studies in the neoadjuvant setting assessed safety and feasibility[92, 94]. One study reported that exercise training was safe and feasible during neoadjuvant CRT and following neoadjuvant CRT[94] whilst the other study reported it was safe and feasible following completion of neoadjuvant CRT prior to major surgery[92]. One study reported feasibility using eligibility rate, recruitment rate, follow-up rate and exercise

adherence[94] whereas the other study reported feasibility using adherence records to follow-up and exercise training[92].

3.4.8.1.1.3 Non-small cell lung cancer
One study assessed safety in the adjuvant setting and reported that exercise training in this context was safe and fesaible[127].

3.4.8.1.1.4 Mixed cancer group
The study including a mixed cancer group did not report safety and feasibility.

3.4.8.1.2 Physical Fitness and physical activity

3.4.8.1.2.1 Breast cancer
Six studies assessed the effects of an exercise intervention on physical fitness and physical activity: four in the adjuvant setting (all of which are from the same trial, START trial)[110, 128, 133, 141] and two in the neoadjuvant setting (both of these studies are from the same trial)[132, 142]. The two studies in the neoadjuvant setting reported significant improvements in $\dot{V}O_2$ at peak following a 12-week aerobic interval exercise training (both from the same exercise training trial), following prescribing exercise intensities tailored to individual cardiopulmonary exercise tests (CPET)[1328, 142]. In the adjuvant setting, one other study reported a significant increase in $\dot{V}O_2$ at peak as a secondary outcome[126], and one other study reported a significant improvement in $\dot{V}O_2$ at peak in the aerobic exercise training group but not in the resistance exercise training group or the usual care group[136]. One home-based exercise programme reported a significant improvement in physical fitness as measured by 12-minute walk test[131]. All other studies showed no statistical significant effects following participation in an exercise intervention[128, 135, 140 - 141]. One other study reported a statistically significant decrease in physical fitness in women during breast cancer treatment which was linked with high fatigue levels[70].

3.4.8.1.2.2 Rectal cancer
In the neoadjuvant setting, one study used physical fitness as a primary outcome measure[92] and PAL (step-count) as a secondary outcome whilst another study used a measure of physical fitness as a secondary outcome ($\dot{V}O_2$ max)[94]. The first study reported a significant increase in physical fitness and PAL following participation in a 6-week interval aerobic exercise programme compared to the usual care control group[92]. The other study reported a decline in physical fitness following moderate

aerobic exercise training during neoadjuvant CRT (6 weeks) and an increase in physical fitness following 6-8 weeks of exercise training programme following completing neoadjuvant CRT up to the point of surgery[94].

3.4.8.1.2.3 Non-small cell lung cancer

One study in the adjuvant setting used $\dot{V}O_2$ at peak as a measure of physical fitness as a primary outcome[127], while SF-36 (physical function) was used as a secondary outcome measure in another study[72]. The first study reported an increase in physical fitness following a 14-week continuous exercise training programme[127] and the other study reported a significant improvement in physical fitness following initiation of a 6-week home-based rehabilitation exercise programme 66-hours post-hospital discharge[72].

3.4.8.1.2.4 Mixed cancer group

One study in adjuvant setting used $\dot{V}O_2$ at peak to measure physical fitness and muscular strength as a secondary outcomes measure[73]. This study reported that following a 6-week multimodal exercise intervention (incorporating high and low intensities), physical fitness improved whilst muscular strength significantly improved.

3.4.8.2 Secondary outcomes

3.4.8.2.1 HRQoL

3.4.8.2.1.1 Breast cancer

HRQoL was used as a primary outcome in three of the included studies in the adjuvant setting[136-137,141]. HRQoL was used in almost all studies as a secondary outcome measure. Exercise training significantly improved different domains of HRQoL following circuit classes over a 12-week period[71] and a 16-week period[126], and aerobic/resistance exercise programme over a 17-week period[136]. The START trial reported significant improvements in some HRQoL domains were reported, but no significant improvements were shown in cancer-specific HRQoL (fatigue, depression or anxiety)[136]. Furthermore, no statistically significant differences in HRQoL were reported following the pectoral training programme, self-directed versus supervised walking intervention or progressive resistance training programme[130, 140-141].

3.4.8.2.1.2 Rectal cancer

No rectal cancer study reported HRQoL as an outcome measure.

3.4.8.2.1.3. Non-small cell lung cancer

HRQoL was used as a secondary outcome measure in one pilot study in the adjuvant setting[72]. This study reported a decrease in HRQoL between pre- and post-surgery and an increase following the 6-week exercise programme (the best results were obtained at week-3). However, five out of the seven participants in this trial initiated chemotherapy at week-5 which may account for the slight decrease reported between week 3 and 6[72].

3.4.8.2.1.4 Mixed cancer group

HRQoL was used as a secondary outcome in one study in the adjuvant setting[73]. This study reported that a multi-modal high intensity exercise programme improved some measures of HRQoL but not all following a 6-week multimodal exercise intervention (high and low intensities).

3.4.8.2.2 Fatigue

3.4.8.2.2.1 Breast cancer

Fatigue was used a primary outcome in six included studies in the adjuvant setting[70, 73, 130, 132, 134-135] and as a secondary outcome in three studies in the adjuvant setting[71, 128, 131]. In the adjuvant setting, two studies reported statistically significant improvements in fatigue levels six months after completing the exercise programme initiated during cancer treatment[129] and following a moderate intensity home-based walking intervention delivered during both radiotherapy and chemotherapy[70]. All other studies reported no statistically significant changes following exercise training[71, 73, 130-132, 134-135].

3.4.8.2.2.2 Rectal cancer

No included rectal cancer studies reported fatigue as an outcome measure.

3.4.8.2.2.3 Non-small cell lung cancer

Fatigue was used a primary outcome in one study in the adjuvant setting[72]. This study assessed CRF and symptom severity from pre-surgery, post-surgery and at week-6 of their exercise programme. Findings showed that on average participants experienced seven symptoms pre-surgery, ten symptoms post-surgery and six symptoms at week-6.

3.4.8.2.2.4 Mixed cancer group

Fatigue was used as a primary outcome in one study in the adjuvant setting[73]. Interestingly, this study reported that 65 % of study population had a fatigue level

greater than that of the general population at baseline and that 29 % reported severe fatigue[73]. Following a 6-week multimodal exercise training programme, there was a statistically significant improvement in fatigue levels compared to the usual care control group.

3.4.8.2.3 Post-operative outcome

No included studies reported post-operative outcome as an outcome measure.

3.4.8.3 Exploratory outcomes

As this is a new area of research, all other outcomes measures reported in the included studies are described below, of which, include breast cancer studies only.

3.4.8.3.1 Sleep disturbance

One study in the adjuvant setting assessed sleep disturbance (General Sleep Disturbance) and mood disturbance (Profile of Mood States-Brief Form) reporting improvements in mood and symptom distress in participants in the exercise group, however findings did not reach statistical significance[131].

3.4.8.3.2 Depression

One study in the adjuvant setting assessed depression (20-item Center for Epidemiological Studies Depression scale) and cognitive function (concentration, cognitive flexibility). There were no statistically significant differences in either measure, in either the control or exercise group. However, there was an increase in cognitive performance in the exercise group only (findings were not statistically significant)[130].

3.4.8.3.3 Exercise Behaviour

Two studies in the adjuvant setting investigated exercise behaviour[132,, 138]. One study investigated predictors of follow-up exercise behaviour 6 months following a RCT exercise trial. This RCT found a number of significant predictors among demographic, medical, fitness, psycho-social and motivational variables[138]. Moreover, 58 % of breast cancer survivors reported meeting at least one exercise guideline prescribed (≥ 75 minutes of vigorous or ≥ 150 minutes of moderate-to-vigorous exercise per week) and 21% of those reported meeting both following the START trial. At baseline, only 23 % were meeting either exercise guideline. The strongest predictor that indicated exercising at 6-month follow-up was pre-trial exercise levels. Other variables that predicted the likelihood of meeting exercise guidelines at follow-up included: younger

age; breast conserving surgery; strength improvements; lower post-intervention fatigue; a more positive attitude; and lower post-intervention body mass index (BMI). The other study measured exercise behaviour as an exploratory outcome (assessed using the Godin Leisure Time Exercise Questionnaire) but showed no statistical significant changes in exercise behaviour[132].

3.4.8.3.4 Biomarkers

One study in people with breast cancer (ki-67) in the neoadjuvant setting, measured cell proliferation in the tumour, tumour size, axillary lymph node status, insulin growth factor 1 (IGF-1) levels, C-peptide levels and BMI as secondary measures[105]. Clinical and pathologic response to neoadjuvant chemotherapy at the breast and axillary sites were also recorded. There was no statistically significant difference between groups in tumour size, age, BMI tumour grade, C-peptide levels or initial Ki-67. Following neoadjuvant chemotherapy, in people who participated in the boot camp, mean Ki-67 level was 7.2 % lower than in the usual care control group 29.2 %. Fasting C-peptide levels decreased in both groups, although this did not reach statistical significance. The only statistically significant difference following the boot camp programme was in BMI; 28 kg/m^2 in the exercise intervention group and 36 kg/m^2 in the usual care control group ($p=0.03$). The boot camp programme resulted in a decrease in insulin growth factor (IGF-1) levels, albeit findings were not statistically significant.

One other study in the neoadjuvant setting investigated serum cytokines and angiogenic factors (CAFs), endothelial function, tumour blood flow, intratumoral neoplaxtic phenotype and tumour gene expression in the neoadjuvant setting[142]. Following a 12-week exercise programme, there was a significant increase in circulating endothelial progenitor cells (CEP) surface markers in the exercise intervention group compared to the usual care control group. Additionally, there was a statistical significant difference in tumour gene expression analysis, which revealed 3 down-regulated (PAK4, FYB and TNFRSF10D) and 4 up-regulated (KREMEN1, LOC402057, SERPINA3, and NDUFS8) transcripts in the exercise intervention group compared to the usual care control group. The authors interpreted these as follows: PAK4, FYB, and TNFRSF10D transcripts function in NF-kB signalling, inflammation, and cell migration; KREMEN1, LOC402057, SERPINA3, and

NDUFS8 have critical roles in maintaining oxidative phosphorylation, ribosome biogenesis, and inhibiting pathway signalling supporting inflammation and Wnt/b-catenin activity. Subsequent pathway analysis revealed significant differential modulation of 57 pathways, including many that converge on NF-kB. Significant interaction effects were observed for 3/19 CAFs analysed. Additionally, there were significant changes in the proangiogenic factor placenta growth factor in the exercise intervention group compared to the usual care control group. Interleukin (IL)-1b, a cytokine produced by activated macrophages, decreased in both groups over the 12-week period, declined from week 0 to 6 in the exercise intervention group, reaching a plateau from weeks 9 to 12; an initial increase in the usual care control group in weeks 0 to 6 was followed by a steady decline in weeks 9 to 12. Furthermore, IL-2, a soluble cytokine and mediator of immunity, significantly decreased in the exercise intervention group compared to an increase in the usual-care control group.

3.4.8.3.5 Cardiac function

One study in the neoadjuvant setting investigated cardiac function in people with breast cancer who exercise-trained for the duration of chemotherapy[132]. This study used two-dimensional transthoracic echocardiographic images using standard views performed and averaged over three cardiac cycles according to American Society of Echocardiography guidelines. There were no echocardiographic abnormalities from baseline to week-12. Additionally, there were no statistical significant differences, within or between groups, in any cardiac parameters over the duration of neoadjuvant chemotherapy.

3.4.8.3.6 Sarcopenia and dynapenia

One study in the adjuvant setting investigated sarcopenia and dynapenia (as part of the START trial)[134]. This study reported that approximately 25 % of people with breast cancer presented with sarcopenia and 55 % with dynapenia prior to initiating adjuvant chemotherapy and that these were associated with poor HRQoL. Resistance exercise training in the exercise group significantly reversed sarcopenia and dynapenia. Notably, the reversal of sacropenia, but not dynapenia, was associated with clinically relevant improvements in HRQoL and fatigue.

Table 3.1 Study characteristics, outcome measures and key study findings

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Segal et al, 2001, (Canada) [142]	Breast, Adjuvant chemo/other adjuvant cancer treatment	RCT	123	Walking programme	Evaluate the effect of exercise on physical functioning and other dimensions of HRQoL (follow-up time point: 26 weeks)	1. Physical functioning (SF-36) 2. Changes in other scales of SF-36, FACT-General and FACT-Breast, aerobic capacity and body weight	1. * increase in physical functioning in EG. 2.no significant differences in HRQoL measures between groups.
Kolden et al, 2002, (USA) [126]	Breast, Adjuvant radiotherapy	Pilot study	40	Aerobic/ resistance/ stretching	Evaluate the feasibility, safety and tolerability, benefits of a comprehensive group exercise intervention (follow-up time point: 16 weeks)	1. Recruitment and retention, and safety and tolerability report 2. Aerobic capacity (a single-stage submaximal treadmill walking test) • Flexibility (Sit-And-Reach Test) • Strength (estimated 1-RM tests on bench press and leg press) • HRQoL- Mood/distress (Beck Depression Inventory, State-Trait Anxiety Inventory, Positive and Negative Affect Schedule, Hamilton Rating Scale for Depression) and(FACT-General).	1.safe, feasible and well tolerated. 2.* ↑physical fitness, flexibility, strength and in 7/11 HRQoL domains.
Campbell et al, 2005 (UK) [71]	Breast, Adjuvant radiotherapy & chemo	Pilot RCT	22	Aerobic training	Evaluate physical functioning, fatigue and QoL outcomes (follow-up time point: 12 weeks)	1. QoL (Cancer specific scales; FACT-G and FACT-B) 2. Global QoL (Satisfaction with Life Scale) • Fatigue (Revised Piper Fatigue Scale) • Physical (Scottish physical activity questionnaire (SPAQ) and 12MWD)	1.* ↑ in FACT-G in EG. 2. * improvements in 12MWD and SPAQ in EG.

Table 3.1 Study characteristics, outcome measures and key study findings (Cont'd)

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Mock et al, 2005 (USA) [70]	Breast Adjuvant radiotherapy	RCT	119	Walking programme	To determine the effects of a home-based walking exercise programme on levels of fatigue (follow-up time point: 6 weeks or 6 months dependent on patient pathway)	1. Fatigue (total score of Piper Fatigue Scale) 2. Physical functioning and activity levels (12-MWD, Medical Outcomes SF-36 and physical activity questionnaire)	1. *↑ in fatigue in EG. 2. no significant difference between groups.
Battaglini et al, 2006 (USA) [135]	Breast Adjuvant Chemo, radiation or both	RCT	20	CV/ resistance/ flexibility training	To identify the possible benefits that an individualised exercise programme composed primarily of resistance training would have on muscular strength and fatigue levels (follow-up time point: 21 weeks)	1. Fatigue (total score of Piper Fatigue Scale) 2. Fitness assessment (VO_2peak/max test using the Bruce treadmill protocol and maximum capacity for muscular strength)	1. *↑ in fatigue in EG. 2.* improvement in muscular strength in EG.

Table 3.1 Study characteristics, outcome measures and key study findings (Cont'd)

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Courneya et al, 2007, (Canada) [137]	Breast, Adjuvant chemo	RCT	242	Aerobic/ resistance training	Evaluated the effects of aerobic and resistance exercise on physical functioning, body composition, psychosocial functioning and QoL (follow-up time point: 17-weeks)	1. FACT-An scale 2.Psychosocial functioning (Rosenberg Self-esteem scale) • Aerobic fitness (maximal incremental exercise treadmill protocol); • Musclar strength (8-RM on bench press and leg extension); • Body composition (BMI and dual x-ray absorptiometry scan); • Chemotherapy completion rate (average relative dose-intensity for the originally planned regimen based on standard formulas); • Lymphedema (standard volumetric arm measurements based on water displacement)	1.no significant differences between groups. 2.*↑ chemotherapy completion rate in resistance intervention group, no significant differences between groups in other outcomes measures.
Lee et al, 2007 (Australia) [141]	Breast, Adjuvant radiotherapy	Single-blind RCT	61	Pectoral muscle stretching programme	To investigate whether a stretching programme reduced acute musculoskeletal impairments (follow-up time point: 6 weeks)	1.Passive range of movement for horizontal extension 2.Strength of shoulder muscles; arm swelling (circumferential measurements taken at 10 cm intervals from the ulnar styloid to the axilla of both limbs); • QoL (EORTC) Quality of Life Questionnaire Version 3 (QLQ-C30), and its Breast Module BR23)	1 and 2: no differences were detected between groups.

Table 3.1 Study characteristics, outcome measures and key study findings (Cont'd)

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Courneya et al, 2008, (Canada) [150]	Breast, Adjuvant chemo	RCT	242	Aerobic/ resistance training	Evaluate personal and clinical factors that may predict exercise training responses (follow-up time point: 17 weeks)	1. Qol (FACT-anaemia scale) 2. Aerobic fitness (maximal incremental exercise treadmill protocol) • Muscular strength (1-RM equation using 8-RM horizontal bench press) • Lean body mass (DEXA scan) • Percent body fat (Hologic QDR-4500 in Vancouver and the General Electric Lunar Expert in Ottawa and Edmonton) • Moderators were patient preference for group assignment, marital status, age, disease stage, chemotherapy regimen	1.*patient exercise programme preference moderated QoL response. 2. *marital status moderated QoL response, age moderated aerobic fitness response, chemo regimen moderated strength gain, and disease stage moderated lean body mass gain and fat loss.
Jones et al, 2008, (Canada) [127]	Lung, Adjuvant chemo & some received no chemo	Pros. single group	20	Aerobic training	To assess examining the effects of a supervised aerobic exercise training on aerobic fitness (follow-up time point: 14 weeks)	1. VO2peak (CPET) 2. Secondary cardiopulmonary endpoints; peak workload, ventilatory threshold, O_2 pulse and secondary QoL endpoints were overall fatigue and QoL subscale. endpoints; • QoL (FACT-L), Lung Cancer Subscale • Fatigue (Fatigue Scale of the FACT measurement system)	1.*↑ VO_2peak, Qol. 2.* ↑ peak workload. No differences between groups in any other outcome measure.

Table 3.1 Study characteristics, outcome measures and key study findings (Cont'd)

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	1. Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Adamsen et al, 2009, (Denmark) [73]	21 different cancers, 59 different chemo regimens	RCT	269	Resistance training, relaxation, body awareness and massage	Assess the effect of a multimodal group exercise intervention, as an adjunct to conventional care on fatigue, physical capacity, general wellbeing, physical activity and QoL (follow-up assessment time point: 6 weeks)	1.Fatigue (EORTC QLQ-C30) 2. QoL; Other scales on EORTC QLQ-C30, General well-being (Medical Outcomes Study Short Form • Leisure time IPAQ • Muscular strength (1-RM) • Aerobic capacity (VO_2max)	1.* ↑fatigue in EG. 2.* ↑ VO_2max, muscular strength in EG. No differences between groups in any other outcome measure.
Courneya et al, 2009, (Canada) [138]	Breast, Adjuvant chemo	Pros. RCT	242	Aerobic/ resistance training	Identify key predictors of aerobic and resistance exercise during the follow-up phase of the START Trial (follow-up time point: 6 months)	1. Predictors of follow-up exercise behaviour variables such as: • Demographics and behavioural; • Medical; • Post-intervention; • Change in physical fitness and body position; • Motivational variables.	1.* demographic, medical,behavioural, fitness, psychosocial & motivational variables predicted exercise behaviour at 6 months (higher pre-trial exercise, younger age, breast conserving surgery, strength improvements, lower post intervention BMI)

Table 3.1 Study characteristics, outcome measures and key study findings (Cont'd)

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Moros et al, 2010, (Spain) [112]	Breast, Adjuvant chemo	RCT	22	Aerobic / resistance training	Assess functional capacity, QoL and pyshcosocial status. Assess the influence of physical exercise programme throughout the course of chemotherapy (follow-up time point: 18-22 weeks)	1. Functional capacity (Karnofsky performance status) 2. Psychological wellbeing (General Health Questionnaire) • QoL (EORTC QLQ-C30)	1 and 2. no differences between groups in any other outcome measure.
Rao et al, 2012 (USA) [105]	Breast, Neoadjuvant chemo	Pilot RCT	10	Boot camp programme	Feasibility of an exercise intervention in the neoadjuvant setting.	1. Adherence to the exercise programme 2. Tumour characteristics including; Ki-67 in the tumour, size, axillary, lymph node status, insulin growth factor 1 (IGF-1) levels, C-peptide levels, BMI. • Clinical and pathologic response to neoadjuvant chemo at the breast and axillary site were recorded	1.feasible. 2.*↓BMI in EG. No differences between the groups in other outcome measures.
Jones 2013, (USA) [143]	Breast, NACT	Phase II RCT	20	12-week aerobic exercise intervention	To explore effects of aerobic training on host-related factors that could modulate chemotherapy response & whether modulation of host-related factors altered tumor tissue markers.	1. Physical fitness (CPET) and peripheral vascular endothelial function (brachial artery flow-mediated dilation) 2. Host-related circulating factors and other pro-inflammatory cytokines and angiogenic factors • Tumour phenotype, proliferation and PET, and physiology (microvessel density, hypoxia and tumour blood flow), tumour gene expression	1.*$\dot{V}o_2$ at peak, endothelial function in EG. 2.*tumour blood flow in EG.

Table 3.1 Study characteristics, outcome measures and key study findings (Cont'd)

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Milecki et al, 2013 (Poland) [128]	Breast, Adjuvant radiotherapy	RCT	46	Aerobic/ endurance, respiratory muscle training	Examine whether moderate-intensity endurance training would have a positive effect on aerobic capacity in comparison with those women who were not taking any physical activity during postoperative radiotherapy	1. Functional capacity (6MWD) 2. Breathlessness (Modified Borg scale)	1 and 2. no differences between groups in outcome measures.
West et al, 2014 (UK) [92]	Locally advanced rectal, Neoadjuvant CRT	Pilot	35	Aerobic training	Evaluate objectively measured physical fitness changes with neoadjuvant CRT and a pre-operative 6 week structured responsive exercise training programme	1. Physical fitness (CPET) 2. Physical activity (sensewear activity armbands) • $\dot{V}o_2$ at peak (CPET) • Safety and feasibility (number of adverse events and adherence records to CPET or exercise training)	1.*↑$\dot{V}o_2$ at $\hat{\theta}_L$ in EG. 2.* ↑physical activity and $\dot{V}o_2$ at peak. Safe and feasible.
Hoffman et al, 2014 (USA) [72]	NSCLC, Chemo (initiated week 5 in 5/7 people)	Pilot	7	Walking and balancing programme (Nintendo Wii Fit Plus)	Describe the effects of a home-based rehabilitation exercise intervention on CRF, other symptoms, functional status and QoL for post-surgical NSCLC starting within days after hospital discharge	1. CRF (Brief Fatigue Inventory) • Symptom severity and interference (M.D. Anderson Symptom Inventory Core and Lung Module) • Functional status (Medical Outcomes SF-36) 2. QoL (Ferrans and Powers Quality of Life Index, assessing satisfaction and important aspects of life to the person)	preliminary efficacy in improving CRF, other symptom severity, functional status and QoL.

Table 3.1 Study characteristics, outcome measures and key study findings (Cont'd)

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Schmidt et al, 2014 (Germany) [130]	Breast, Adjuvant chemo	Prop. RCT	101	Resistance exercise training	To investigate whether progressive resistance training in breast cancer during chemotherapy provides beneficial effects on fatigue and QoL beyond the potential effects of a supervised group-based training (follow-up time point: 12 weeks)	1. Fatigue (Fatigue Assessment Questionnaire • QoL (EORTC QLQ-C30) • Depression; 20-item Center for Epidemiological Studies Depression scale) • Cognitive function (concentration, cognitive flexibility)	1.*↑total and physical fatigue 2.no significant differences between groups.
Naraphong W, 2014 (Thailand) [131]	Breast, Adjuvant chemo	Pilot	23	Walking programme	To preliminarily examine the effects of an exercise programme on the symptoms of fatigue, sleep disturbance, mood disturbance, symptom distress and physical fitness for Thai women (follow-up time point: 10 weeks)	1. Feasibility (no. of enrolling and retaining participants in the study combined with patient adherence) 2.Physical fitness (12-MWD) • Fatigue (Revised Piper Fatigue Scale) • Sleep disturbance (General Sleep Disturbance) • Mood disturbance (Profile of Mood States-Brief Form) 2. Distress (Memorial Symptom Assessment Scale)	1.feasible. 2.*↑12-MWD, mood disturbance. No differences between groups in other secondary outcome measures.

Table 3.1 Study characteristics, outcome measures and key study findings (Cont'd)

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Hornsby et al, 2014 (USA) [132]	Breast, NACRT	Phase II RCT	20	12-week aerobic exercise intervention	Safety of supervised moderate-to-high intensity aerobic training	1.Safety: Treatment-related clinical AEs: nausea, myalgia, pain, alopecia, arthralgia, neutropenia and emergency room admittance); aerobic training-related AEs included resting and exercise heart rate, blood pressure, and arterial O2 saturation. Secondary outcome measures: Attendance (number of exercise sessions attended divided by number of planned sessions); Adherence (number of exercise sessions completed divided by number of planned sessions attended); Physical fitness (CPET); Cardiac function (two-dimensional transthoracic echocardiographic images); HRQoL (Functional Assessment of Cancer Therapy-Breast (FACTB), FACTGeneral (FACT-G)); Fatigue (Functional Assessment Chronic Illness Therapy (FACIT)); Clinical characteristics (medical chart review) and exercise behaviour (Godin Leisure Time Exercise Questionnaire)	*Safety, $\dot{V}_{O_2}$ at $\hat{\theta}_L$, HRQoL
Husebo et al, 2014 (Norway) [129]	Breast cancer, Adjuvant chemo	RCT	67	Walking programme and strength training	Investigate the effects of a scheduled home-based exercise intervention on CRF, physical fitness and activity level.	1. CRF (Schwartz Cancer Fatigue Scale-6) 2. Physical activity (IPAQ) • Physical fitness (6-MWD) • Exercise volume (exercise diaries) • Exercise adherence (extent to which the women in the intervention group performed the prescribed exercise regimen)	1 and 2. No significant differences between groups.
Adams et al, 2016 (Canada) [134]	Breast, Adjuvant chemo	Pros. RCT	242	Aerobic/ resistance training	To conduct an exploratory analysis of the START trial examining the effects of RET and AERT on sarcopenia, dynapenia and QoL.	3. Exploratory outcomes of the START trial:Patient reported outcomes: QoL, physical function and fatigue ((FACT-An scale) and objective health-related fitness outcomes: lean body mass and percent body fat (DXA scan), bone mineral content, muscular strength, Skeletal muscle mass, upper and extremity muscle dysfunction, QoL	*Skeletal muscle index, *upper extremity muscle dysfunction, *lower extremity dysfunction.

Table 3.1 Study characteristics, outcome measures and key study findings (Cont'd)

Author,year, (Country)	Cancer type, Cancer treatment	Study design	N	Exercise Programme	Study aim	Outcome measures: 1.Primary outcome measure; 2.Secondary outcome measure	Study findings
Morielli et al, 2016 (Canada) [94]	Rectal, Neoadjuvant CRT	Pilot	18	Aerobic training	Assess feasibility and safety of an aerobic exercise intervention during and after CRT	1.Feasibility: eligibility rate, recruitment rate, follow-up rate, exercise adherence rate Safety: monitoring and recording any serious adverse events 2.Adherence (Phase1) number of sessions attended out of 18; and (Phase 2) Godin & Shephard 1985) Health Related Fitness ($\dot{V}o_2$ at max) Patient reported outcomes: QoL (SF-36, fact-c), depression (Epidemiologic Studies Depression Scale); self-esteem (10-item Rosenberg Self-Esteem Scale)	1.eligibility(71%); recruitment (56%); follow-up health related fitness outcomes (83%); exercise adherence (83%) 2.adherence (Phase 1:74%) and (Phase 2:222 minutes), health-related fitness and patient-reported outcomes ↓ during NACRT and ↑ following NACRT.
Wiskemann et al, 2016 (Germany) [133]	Breast, Adjuvant radiotherapy	RCT	170	Resistance training	To assess the efficacy of a 12-week progressive resistance training during radiotherapy	1. Muscle strength (maximal isokinetic peak torque) 2. Maximal voluntary isometric contraction (shoulder external and internal rotation and for knee extension and flexion)	1.*↑muscle strength. 2.no differences between groups.

Note: (1) and (2) within key study findings refers to (1: primary outcome; 2: secondary outcome of studies). Abbreviations: * - significant findings ($p<0.05$); Chemo – chemotherapy; CRT – chemoradiotherapy; HRQoL – health related quality of life; QoL – quality of life; 1-RM – repetition maximum, SF-36 - Short Form (36) Health Survey; FACT – functional assessment of cancer therapy; FACT-An - functional assessment of cancer therapy-anaemic scale; RCT – randomised controlled trial; CV – cardiovascular; VO_2Peak and max– oxygen uptake at peak and max exercise; BMI – body mass index; CPET – Cardiopulmonary exercise test, 6 and 12 MWD- 6 and 12 minute walk distance test, EORTC – European Organisation for Research and Treatment of Cancer; IPAQ – international physical activity questionnaire; CRF – cancer related fatigue, NACT - Neoadjuvant chemotherapy; NACRT - Neoadjuvant chemoradiotherapy;, AE– adverse event, PET – positron emission tomography; NSCLC – non-small cell lung cancer; AE – adverse event; ↑ - increase; ↓ - decrease.

Table 3.2 Summary of exercise intervention characteristics

Author, year, (Country)	Study design	N	Gender	Cancer type, Cancer treatment	Exercise Programme	Supervision Setting	Frequency	Intensity	Duration	Adherence	Key study findings
Segal et al, 2001, (Canada) [142]	RCT	123	Female	Breast, Adjuvant chemo/ other adjuvant cancer treatment	Walking programme	Supervised & home based	Home; 5/wk x 26 weeks. In-hospital; 3/wk x 26weeks	50-60% VO_2Peak	NR	72%	* ↑ physical functioning in EG.
Kolden et al, 2002 (USA) [126]	Pilot study	40	Female	Breast, Adjuvant radiotherapy	Aerobic/ resistance training	Supervised	3/wk x 16 weeks	Prog: 40-70% VO_2Max	60min	78%	*↑physical fitness, flexibility, strength
Campbell et al, 2005 (UK) [71]	Pilot RCT	22	Female	Breast, Adjuvant radiotherapy & chemo	Aerobic training	Supervised	2/wk x 12 weeks	60-75% MHR	NR	70%	* ↑ in FACT-G in EG. * ↑ 12MWD & SPAQ in EG.
Mock et al, 2005 (USA) [70]	RCT	119	Female	Breast Adjuvant radiotherapy	Walking programme	Home-based Unsupervised	5-6/wk x 6-weeks during RET or 3-6months	50-70% MHR	15-30min	EG: 72% UG: 61%	*↑ in fatigue in EG.
Battaglini C, 2006 (USA) [135]	RCT	20	Female	Breast Adjuvant Chemo, radiation or both	CV/ resistance/ flexibility training	Supervised	2/wk x 16 weeks	40-60% max exercise capacity	60min	NR	*↑ fatigue in EG
Courneya et al, 2007, (Canada) [137]	RCT	242	Female	Breast, Adjuvant chemo	Aerobic/ resistance training	Supervised In-hospital	Duration of chemo	60-80% VO_2Peak/1 RM	15-45min	70%	*↑chemo completion rate in resistance group

Table 3.2 Summary of exercise intervention characteristics (Cont'd)

Author, year, (Country)	Study design	N	Gender	Cancer type, Cancer treatment	Exercise Programme	Supervision Setting	Frequency	Intensity	Duration	Adherence	Key study findings
Lee et al, 2007, (Australia) [141]	Single - blind RCT	61	Female	Breast, Adjuvant radiotherapy	Pectoral muscle stretching programme	Unsupervised Home based	2/day/wk x 6 weeks	NR	10min	90%	No difference between groups
Courneya et al, 2008, (Canada) [150]	RCT	242	Female	Breast, Adjuvant chemo	Aerobic/ resistance training	Supervised In-hospital	3/wk x 17 weeks	60-80% VO_2Peak/ 60-70% 1RM	15- 45 min	A; 72% R; 68.2%	*patient preference moderated QoL response
Jones et al, 2008, (Canada) [127]	Pros. single group	20	Mixed gender	Lung, Adjuvant chemo & some received no chemo	Aerobic training	Supervised: short term	3/wk x14 weeks	Prog: 60-70% WRpeak	15-45 min	85%	*↑VO_2Peak, QoL & peak workload
Adamsen et al, 2009, (Denmark) [73]	RCT	269	Mixed gender	21 different cancers, 59 different chemo regimens	Resistance training, relaxation, body awareness and massage	Supervised In-hospital	9hours/wk x 6weeks	Low & high intensity	90min	71%	↑fatigue, muscular strength &VO_2max in EG
Courneya et al 2009, (Canada) [138]	Pros. RCT	242	Female	Breast, Adjuvant chemo	Aerobic (A)/ resistance (R) training	Supervised In-hospital	3/wk x 17weeks	60-80% VO_2Peak/ 70% IRM	60min	A;72% R;68.2%	* range of variables predicted exercise behaviour at 6 months.

Table 3.2 Summary of exercise intervention characteristics (Cont'd)

Author, year, (Country)	Study design	N	Gender	Cancer type, Cancer treatment	Exercise Programme	Supervision Setting	Frequency	Intensity	Duration	Adherence	Key study findings
Moros et al, 2010, (Spain) [112]	RCT	22	Female	Breast, Adjuvant chemo	Aerobic/ muscle strength/ coordination training	Supervised In-hospital	3/wk x 18-22-weeks	60-70% HR	60min	91%	no differences between groups.
Rao et al, 2012 (USA) [105]	Pilot RCT	10	Female	Locally advanced breast, Neoadjuvant chemo	Boot camp programme	Supervised Home based	3/wk x 4-6 months	NR	60min	>80%	Feasible, *↓BMI in EG
Jones 2013 (USA) [143]	Phase II RCT	20	Female	Breast, NACT	Aerobic	Supervised, In-hospital	3/wk × 12 weeks	55-100% $\dot{V}o_2$ at peak	Prog: 15-30 min	66%	*$\dot{V}o_2$ at peak, endothelial function in EG. *tumour blood flow in EG.
Milecki et al, 2013 (Poland) [128]	RCT	46	Female	Breast, Adjuvant radiotherapy	Aerobic Endurance, Respiratory muscle training	Supervised, In-Hospital	5/wk x 6 weeks	65-70% MHR	40-45 min	NR	no differences between groups.

Table 3.2 Summary of exercise intervention characteristics (Cont'd)

Author, year, (Country)	Study design	N	Gender	Cancer type, Cancer treatment	Exercise Programme	Supervision Setting	Frequency	Intensity	Duration	Adherence	Key study findings
West et al, 2014 (UK) [92]	Pilot	35	Male & female	Locally advanced rectal, Neoadjuvant CRT	Aerobic interval exercise training	Supervised, In-hospital	3/wk x 6weeks	Prog: Mod-high (% of $\dot{V}o_2$ at $\hat{\theta}_L$ & peak)	40min	96%	*↑$\dot{V}o_2$ at $\hat{\theta}_L$ in EG, * ↑physical activity, $\dot{V}o_2$ at peak. Safe and feasible
Hoffman et al, 2014 (USA) [72]	Pilot	7	Mixed gender	NSCLC, Chemo (initiated week 5 in 5/7 people)	Walking and balancing program (Nintendo Wii Fit Plus)	Home based	5/wk x 6weeks	Prog: 5-30min	Light intensity	NR	preliminary efficacy in improving CRF, other symptom severity, functional status and QoL.
Schmidt et al, 2014 (Germany) [130]	Prop. RCT	101	Female	Breast, Adjuvant chemo	Resistance exercise training	Supervised, Training facility	2/wk x 12weeks	60-80% 1RM	60 min	71%	*↑total and physical fatigue.
Naraphong et al, 2014 (Thailand) [131]	Pilot	23	Female	Breast, Adjuvant chemo	Walking programme	Home based	3-5 days/wk x 12 weeks	Prog: 20-30min	Prog: light to moderate	NR	Feasible *↑12-MWD, mood disturbance.
Hornsby 2014 (USA) [132]	Pilot RCT	20	Female	Breast, NACT	Aerobic (interval)	Supervised, In-hospital	3/wk × 12 weeks	Prog: Mod-high (60-70% peak)	Prog: 15-30 min	66%	*↑$\dot{V}o_2$ at peak in EG.

Table 3.2 Summary of exercise intervention characteristics (Cont'd)

Author, year, (Country)	Study design	N	Gender	Cancer type, Cancer treatment	Exercise Programme	Supervision Setting	Frequency	Intensity	Duration	Adherence	Key study findings
Husebo et al, 2014 (Norway) [129]	RCT	67	Female	Breast cancer, Adjuvant chemo	Strength/ aerobic training	Home based	Daily x 17weeks	Self-reported	30 min	Walking group:17% Strength group:15%	no significant differences between groups.
Adams et al, 2016 [134]	Pros. RCT	242	Female	Breast, Adjuvant chemo	Aerobic (A)/ resistance (R) training	Supervised In-hospital	3/wk x 17weeks	60-80% VO_2Peak/ 60-70% IRM	60min	A;72% R;68.2%	*Skeletal muscle index, *upper & lower extremity muscle dysfunction,
Morielli et al, 2016 (Canada) [94]	Pilot	18	Male (66.7%) Female	Rectal, Neoadjuvant CRT Aerobic	Aerobic	Phase 1: Supervised Phase2: supervised/ unsupervised /combination	3wk x 6weeks	40-60% VO_2Peak	40min	Phase 1:85% Phase 2: 71%	follow up rates: health-related fitness outcome (83%).
Wiskemann et al, 2016 (Germany) [133]	RCT	170	Female	Breast, Adjuvant radiotherapy	Progressive resistance training vs. relaxation	Supervised, sports facility	2/wk x 12 weeks	60-80% 1-RM	60min	EG: 79% CG: 79%	*muscle strength.

Abbreviations: * - significant findings ($p<0.05$); RCT – randomised controlled trial; wk – week; Chemo – chemotherapy; Prog-progressive; NR – not reported; HRQoL – health related quality of life; QoL - quality of life; CV – cardiovascular; MHR- max heart rate; IG/EG – exercise/intervention group; CG - control group; NACT - Neo-adjuvant chemotherapy; NACRT - neoadjuvant chemoradiotherapy; CRT – chemoradiotherapy. Min- minute; VO_2Peak – oxygen uptake at peak exercise; VO_2max – oxygen uptake at max exercise, VO_2 at LT- oxygen uptake at lactate threshold; 1RM – 1 rep maximum; UC- Usual care' Min- minute, Prog – progressive increase; RET – resistance training, CP –cardiopulmonary endpoints; WRpeak – peak work rate, 6MWD-6 minute walk distance test, CRF – cancer related fatigue; ; ↑ - increase; ↓ - decrease

3.5 Discussion

3.5.1 Summary of main results

This is the first systematic review aiming to synthesise all available studies including exercise training interventions in people with cancer undergoing multimodal treatment including surgery. The majority of this work has been conducted in the adjuvant setting: nineteen studies in breast cancer (16 in the adjuvant setting, three in the neoadjuvant setting), two studies in NSCLC, one study with 21 different cancer groups, and two studies in locally advanced rectal cancer (in the neoadjuvant setting). Of the 24 included studies, 13 have been conducted in the past six years (five in the neoadjuvant setting and nine in the adjuvant setting). The reported evidence suggests that exercise training is safe and feasible in people with breast cancer undergoing neoadjuvant[132, 142] and adjuvant chemotherapy[126, 131] and in rectal cancer undergoing neoadjuvant chemoradiotherapy[92, 94]. Additionally, that an exercise intervention during neoadjuvant and adjuvant cancer treatment improves measures of physical fitness, HRQoL and fatigue but its effect on post-operative outcome remains unknown. Due to the broad range of studies included (varying in cancer type, treatment and surgery) and outcome measures reported, the question of what is the optimal timing of initiation and the most effective components of an exercise programme remains unanswered.

3.5.2 Quality of the included studies

The quality of the included studies were variable. Of the 24 full text articles, 19 studies were reported as a RCT [22, 70, 71, 73, 112, 128-130, 132-135, 137-138, 141-143,145, 150] (four studies by Courneya and colleagues[136-138, 145] resulted from one exercise training trial, the START trial), and two studies in the neoadjuvant setting also resulted from the one exercise training trial[132, 142]. It is difficult to compare included studies as they were heterogeneous for the type of cancer (breast, rectal, NSCLC, a mix of 21 different cancer types), and for cancer treatments. Furthermore, the exercise training varied in the initiation of the exercise training programme, type of programme (mainly aerobic and resistance exercise training), supervision and setting (supervised in-hospital and unsupervised at home), exercise frequency (2-26 weeks), exercise intensity (mainly moderate aerobic with high intensity), exercise time (15- 60 minutes) and type (mainly cycle ergometer) of exercise. Adherence ranged between 15– 96 % (home-based and hospital-based exercise training). Moreover, due to the use of a variety of outcome measures, and even

when similar outcome measures were reported, the exercise modalities used for testing were different (i.e. $\dot{V}O_2$ at peak measured on cycler ergometer or treadmill) which makes comparison of the effectiveness of exercise interventions difficult.

3.5.3 Strengths and limitations

The main strength of this review is that it provides an up-to-date comprehensive review of all studies using an exercise training programme in people with cancer undergoing multimodal treatment including surgery. The review was conducted in a rigorous manner using pre-selected search terms over several databases. Searches were updated several times. Furthermore, two independent assessors screened candidate articles using predefined search terms which minimised bias. The quality of each study was evaluated using a validated checklist designed to assess randomised and non-randomised trials[125].

Due to the inclusion of a variety of exercise interventions and outcome measures used across studies which limits inter-study comparisons. Due to the nature of the intervention, other limitations include the lack of blinding of participants and of professionals delivering the interventions. Of the 24 included studies, only five studies reported that the data assessors were blind to outcome measures therefore there was a high risk of performance bias. Due to the clinical and statistical heterogeneity of the included studies, a meta-analysis was precluded.

3.5.4 Findings of this review with other studies or reviews

3.5.4.1 Primary outcome

3.5.4.1.1 Safety and feasibility

MacVicar and colleagues were the first to conduct an exercise-oncology trial (safety and feasibility) in the 1980s, at a time when general oncology advice for people with cancer was to rest and avoid exercise during cancer treatment. Since then, the safety and feasibility of delivering such exercise interventions has been addressed in systematic reviews in NSCLC[120-121], and in another review including a variety of different cancer types[122] undergoing single modality treatment. Studies in this systematic review suggest that exercise training in this context is safe and feasible in people with breast cancer[71, 126, 133], NSCLC[127] and rectal cancer[92-94]. Only one study in the neoadjuvant setting reported three non-life-threatening/non-ECG-related adverse events (AE) during baseline exercise testing, although these did not preclude

study participation[132]. One other study reported a participant becoming unwell during the exercise programme, and they quickly recovered[137].

It has been proposed that feasibility studies should incorporate focusing on the following key areas: acceptability; demand; implementation; practicality; adaptation; integration; expansion; and limited efficacy testing. Yet studies included in this review reported feasibility by number of enrolling and retaining participants[94,126, 131] combined with adherence[92, 94, 131] and follow-up rates[92, 94]. Due to the lack of inclusion of all key areas, the feasibility of these studies remains questionable[139].

3.5.4.1.2 Physical fitness and PAL

The outcomes measures used in the included studies varied considerably: in the adjuvant setting measures such as karnofsy performance status[112]; 6MWD[128]; muscle strength[133]; and SF-36 physical functioning[142] were used, whilst in the neoadjuvant setting, CPET[143] was used as the primary outcome measure. The majority of other studies used physical fitness and PAL as secondary outcomes and similarly the outcome measurements varied: 12-MWD[59,71]; international physical activity questionnaire[71]; a single-stage submaximal treadmill walking test[126]; incremental treadmill test measuring $\dot{V}o_2peak$[135, 137, 150] (two from the same trial[136,150]); 6MWD[132]; muscular strength [112, 126, 135-138]; passive range of movement shoulder rotation[141]; cardiopulmonary fitness endpoints (peak workload, ventilatory threshold, oxygen pulse)[127]; and flexibility[126]. Four included studies used CPET-derived variables as outcome measures in the neoadjuvant setting: two studies in people with rectal cancer [92, 94] and two studies in people with breast cancer[132, 142]. Only one study reported improvements in $\dot{V}o_2$ at peak in the adjuvant setting (did not reach statistical significance)[127]. Consistency in using similar outcome measures across the literature is fundamental for comparison of effects across studies. Although studies in the neoadjuvant setting are new since 2012, four of the five included studies used CPET as an outcome measure of physical fitness which may direct future work in this area.

Considering the role of strength/muscular training, a recent meta-analysis concluded that resistance training was associated with clinically important improvements in muscular function and body composition in people with cancer undergoing cancer treatment and long term follow-up[146]. Most of the studies included in this review did incorporate a form of resistance exercise however only two studies showed significant findings[135-137]. Courneya and colleagues reported

that chemotherapy moderated the effects of exercise training on muscular strength in people receiving non-taxane based chemotherapy increasing muscular strength[136]. Moreover, this resistance exercise training programme improved cancer treatment completion rate.

3.5.4.2 Secondary outcome

3.5.4.2.1 HRQoL

Preparing for multimodal treatment including a form of cancer treatment and surgery can cause unanticipated fear, anxiety and psychological stresses. HRQoL is much studied in oncology[148]. The majority of studies included in this review support the conclusion of Granger and colleagues[120] that exercise training is associated with positive benefits on some domains of HRQoL. Exercise training significantly improved different domains of HRQoL following circuit classes[71, 126] and aerobic/resistance exercise programmes[136]. One other study[71] reported a change in FACT G score of ~15 units which represents change from requiring bed rest half the waking day compared to being fully ambulatory following a 12-week exercise intervention[149].

3.5.4.2.2 Fatigue

Fatigue is one of the most common symptoms of cancer and cancer treatment, manifested in the clinic as weakness and exercise intolerance, which can effect quality of life and physical activity[93]. In the adjuvant setting, one study reported that 65 % of study population had a fatigue level greater than that of the general population at baseline and that 29 % reported severe fatigue[73]. In the adjuvant setting in breast cancer, exercise training initiated during cancer treatment has beneficial effects: moderate intensity home-based walking intervention during both radiotherapy and chemotherapy maintains fatigue levels [70] and significant beneficial on fatigue levels at 6-months follow up[129].

3.5.4.3 Exploratory outcomes

One study highlighted the importance of fully considering demographic, medical, behavioural, fitness, psychosocial and motivational factors when designing behavioural support interventions to promote exercise during the important transition from breast cancer patient to survivor[138]. Insight into strategies that help people overcome barriers to exercise may help people to adopt and maintain PAL[123]. It has been suggested that people who are interested in participating in physical activity preferred to receive information from a cancer centre or face to face as opposed to leaflets[123]. Encouragingly, two studies reported increased PAL's post-

exercise training intervention[71, 134]. The first RCT (The CHALLENGE Trial) investigating PAL and survival is currently being conducted among colon cancer survivors following completion of adjuvant chemotherapy[150].

High insulin levels have been associated with the risk of breast cancer recurrence or death[151]. 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 with lower C-peptide levels[152]. It has been reported that women who participate in 2-3 hours moderate intensity exercise (e.g. brisk walking) per week following diagnosis of breast cancer have a 40-67 % reduced risk of death, suggesting a possible hormonal mechanism affecting survival[119]. Exercise training has been found to improve insulin-like growth factor levels in post-menopausal breast cancer survivors[153]. However, the study of people with breast cancer included in this review found a non-significant reduction in C-peptide levels following the exercise programme[104]. The authors argued that the lack of reduction may be associated with BMI and although there was a significant decrease in BMI following their programme, the small sample size (n=10) may not have been enough to influence C-peptide levels[104].

One study reported an exploratory study investigating modulation of circulating angiogenic factors and tumour biology in people with breast cancer receiving neoadjuvant chemotherapy [143]. The authors' tentative suggestion (given the small sample size) was that aerobic exercise training during neoadjuvant chemotherapy might have beneficial effects on symptom control endpoints, and on modulate host-related pathways potentially altering tumour phenotype and response to treatments. To my knowledge, this has not been investigated in any other exercise-oncology trial setting.

One other study reported an exploratory study investigating sarcopenia and dynapneia in people with breast cancer receiving adjuvant chemotherapy. This study reported for the first time that resistance exercise training improves sarcopenia and dynapenia in people with breast cancer during adjuvant chemotherapy[134].

3.6 Conclusion

This evidence synthesis indicates that exercise training in this context is safe and feasible in breast and rectal cancer. It appears that aerobic interval (moderate-severe intensity) exercise training between 6-12 weeks, undertaken in-hospital, is the most effective in significantly improving physical fitness CPET-derived variables in the neoadjuvant setting (breast and rectal cancer) and that a moderate continuous exercise training, undertaken in a supervised gym facility, is the most effective in improving $\dot{V}O_2$ max in the adjuvant setting (breast cancer). Furthermore, included studies illustrate that exercise interventions, delivered in the adjuvant or neoadjuvant setting, and indeed in any setting (in-hospital, home, community) has beneficial effects on different domains of HRQoL. Additionally, an exercise intervention, in the adjuvant setting, improves levels of fatigue (breast cancer) however no study in the neoadjuvant setting investigated this. Finally no included study reported the effects of exercise training on post-operative outcome. Due to the broad range of studies included (varying in cancer type, treatment and surgery) and variation in exercise programmes characteristics and outcome measure, the best time to initiate an exercise intervention, its optimal structure and composition of a programme remain unclear.

The exercise training protocol used for the experimental work in this thesis is the same as a previous similar pilot study (by the Fit-4-Surgery group) which is described as an included study in this systematic review[94].

Chapter 4

Methods

4.1 Introduction

This thesis is part of the EMPOWER trial. I was lead study coordinator and data manager of this multi-centre trial (February 2013 to December 2015) and remained a member of the trial management and steering committee until trial end date: December 2016. I led trial set-up and initiation in recruiting NHS sites and trained all the staff working on this trial. I coordinated the trial on a day-to-day basis in University Hospital Southamtpon (UHS) and conducted all the tests and exercise training sessions with help from my colleagues (critical care research nurses).

This Chapter describes the general experimental protocols and set up used in this thesis which include: cardiopulmonary exercise testing (CPET) (Chapter 5 and 6); physical activity monitoring (Chapter 5 and 6); and the pre-operative exercise training programme (Chapter 6). The study assessments and exercise intervention were integrated into the current colorectal cancer pathway ensuring that the standard NHS cancer pathway was not altered.

4.2 The EMPOWER trial

The EMPOWER trial is a parallel group randomised controlled trial investigating the effects neoadjuvant chemoradiotherapy (CRT) and a pre-operative exercise training programme on physical fitness and physical activity levels in people with locally advanced rectal cancer scheduled for elective surgery. The trial is funded by the National Institute for Health Research - Research for Patient Benefit Programme (PBPG-0711-25093), approved by North West Centre for Research Ethics Committees (13/NW/0259) and registered with clinicaltrials.gov (identifier: NCT01914068).

4.2.1 Recruiting hospitals

Overall five NHS hospitals recruited to this trial: UHS; University Hospital Aintree (UHA); Royal Hampshire County Hospital (RHCH); South Tees Hospital (STH); and Royal Bournemouth Christchurch Hospital (RBCH).

4.2.2 Participants

Eligibility criteria for inclusion included the following:

- Aged ≥ 18 years;

- Magnetic resonance-defined, locally advanced (circumferential resection margin threatened) resectable rectal cancer (≥ T2N +M0), undergoing standardised neoadjuvant CRT;
- No distant radiologically-defined metastasis.

Eligibility criteria for exclusion included the following:

- Inability to give informed consent;
- Non-resectable disease;
- Distant metastasis;
- Inability to perform cardiopulmonary exercise test (CPET) or bicycle exercise (based on lower limb dysfunction);
- Any contraindications on the American Thoracic Surgery CPET safety guidelines[150];
- Declined surgery or neoadjuvant chemoradiotherapy (CRT), or who received non-standard neoadjuvant CRT;
- Weight > 145kg (weight limit for exercise bike);
- Significant ischaemic changes of > 1.5mm symptomatic and > 2mm asysmptomatic observed on routine CPET.

4.2.3 Recruitment, randomisation and allocation concealment

All potentially eligible participants were identified at multidisciplinary meetings. If deemed eligible, participants were approached with a patient information sheet about the trial at the surgical/oncology outpatient appointment by a member of the research team (Appendix 4: patient information sheet for: (1) neoadjuvant CRT and surgery pathway; and (2) neoadjuvant CRT and chemotherapy, and surgery pathway). Note: in UHS and RBCH, only, in the first instance, prior to receiving neoadjuvant CRT, some participants (at risk of systemic spread) received four cycles of capecitabine and oxalilplatin chemotherapy. Eligible participants were given time (minimum 48 hours) to consider trial participation and given the opportunity to discuss the study and explain the study protocol along with the process of informed consent. Participants were contacted by telephone to provide additional information about the trial and if agreed to participate in the trial, the first research visit was organised. Written informed consent was obtained at the first visit and all baseline measurements were obtained (Appendix 5: informed consent form). The research team notified the general practitioners caring for the participant of trial participation (Appendix 6: general practitioner letter). Participant baseline characteristics were documented in the case report form (Appendix 7).

Each hospital site was assigned an identification number: UHS, UHA, STH and RBCH were 001, 002, 003 and 004, respectively. After signing the informed consent, each participant was assigned a study number appropriate to the hospital site, ie. 001_001 for the first participant recruited in UHS. On the last week of neoadjuvant CRT (week 0), participants were randomised (1:1) to either an exercise training programme or usual care control group using the Trans European Network for patient randomisation in clinical trials system (TENAELA System). An algorithm of the clinical pathway and the complete series of assessments for the duration of the trial is presented below (Figure 4.1)

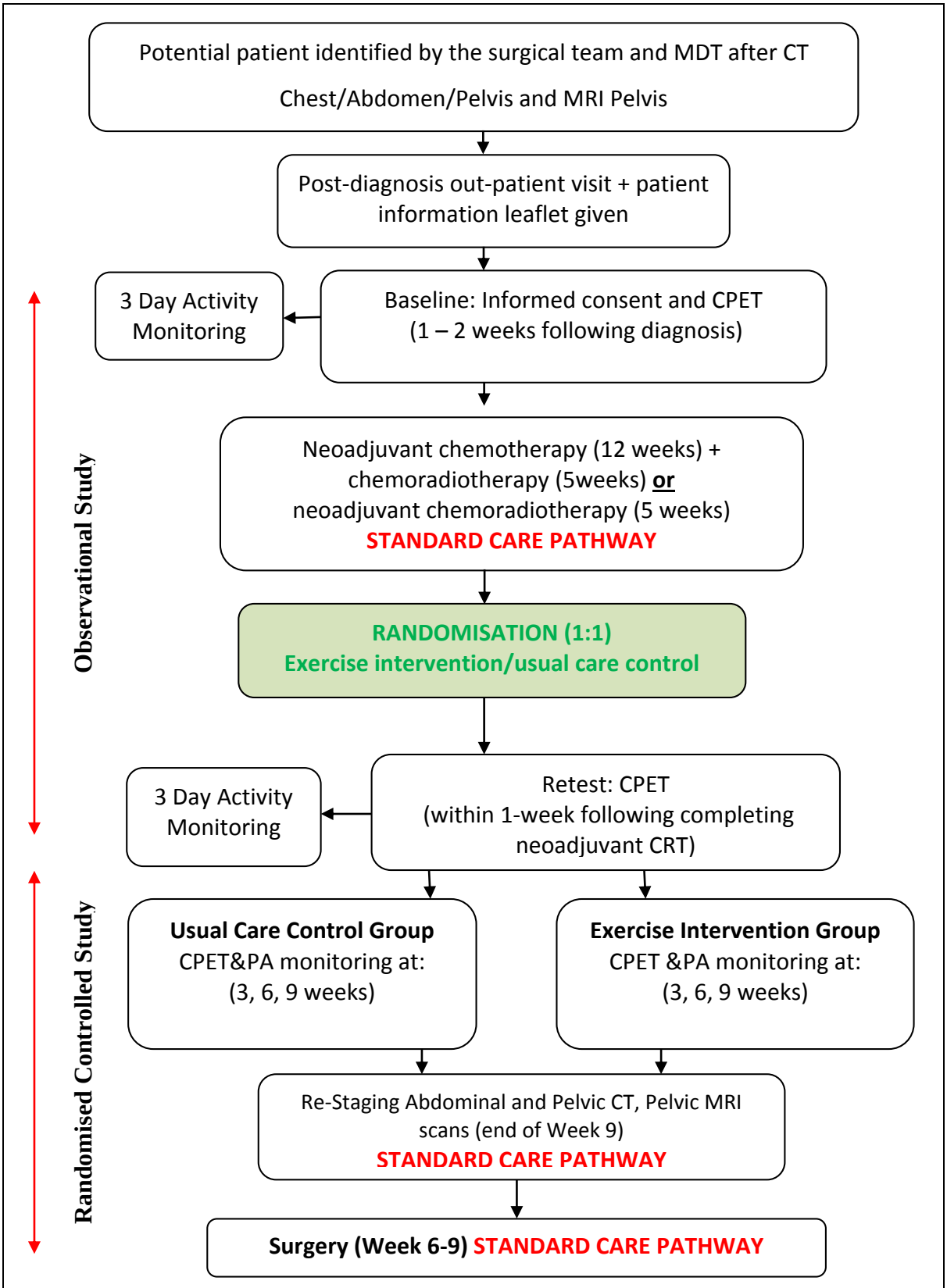


Figure 4.1 Clinical pathway from diagnosis to surgery and time points of assessments as part of the trial to include: (1) observational study (Chapter 5); and (2) randomised controlled study (Chapter 6).

Abbreviations- MDT – Multidisciplinary team; CPET – Cardiopulmonary exercise test; PA-physical activity; CT- Computerized Tomogram; MRI – Magnetic Resonance Imaging.

4.2.4 Interventions

4.2.4.1 Usual care control group

The usual care control group (no formal exercise training) received routine care throughout their cancer pathway from diagnosis to surgical resection. No specific advice about exercise training was offered.

4.2.4.2 Exercise intervention group

The supervised in-hospital exercise training programme was designed to improve physical fitness in the time interval following neoadjuvant CRT and prior to surgery. Exercise training commenced on the first week following completion of neoadjuvant CRT.

4.2.4.2.1 Procedures for all exercise training sessions

Prior to each session, participants were screened to ensure that it was safe to perform exercise. Exercise sessions could be terminated by the participant at any time or by the supervisor if required based on the ATS CPET safety guidelines[154]. The structured, responsive, exercise training programme is further described below (Table 4.1)

Table 4.1 Description of the exercise training programme

Structured	Supervised; 3 times a week in hospital for 6 - 9 weeks
Responsive	Informed by serial CPETs.
Exercise	Moderate - severe aerobic interval exercise
Training	Undertaking a course of exercise
Programme	A series of personalised goals.

4.2.4.2.2 Exercise training equipment

The exercise training programme was conducted on a computer controlled, electromagnetically-braked, cycle ergometer (Optibike Ergoselect 200; Ergoline, GnbH, Germany). Heart rate (HR) was continuously recorded (Polar FT7, Warwick, UK) (Figure 4.2). The training programme was preloaded on to a chip-and-pin card which executed the interval intensities automatically on to the screen displayed on the cycle ergometer.

Figure 4.2 Cycle ergometer used for the exercise training programme

4.2.4.2.3 Exercise training protocol

The FITT principle is one of the foundations of exercise which include a set of guidelines to outline the delivery of the exercise training programme such as; frequency, intensity, time and type of exercise training (American College of Sports Science, 2009).

4.2.4.2.3.1 Exercise training frequency

Participants were required to attend 3 in-hospital exercise training sessions per week for 6– 9 weeks (dependent on clinical pathway).

4.2.4.2.3.2 Exercise training Intensity

The exercise training was an aerobic interval exercise training programme incorporating moderate and severe intensities. Exercise training intensities were derived from each individual CPET at week-0 (immediately post neoadjuvant CRT). Moderate-intensity was at a power output equivalent to 80 % of oxygen uptake ($\dot{V}o_2$) at lactate threshold ($\hat{\theta}_L$). Severe-intensity was at a power output half-way between $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at peak (termed 50 %Δ).

Algebraically:

Moderate intensity exercise: (Work load at $\dot{V}o_2$ at $\hat{\theta}_L$ – ⅔ of work ramp) × 80 %

Severe intensity exercise: ((Work load at $\dot{V}o_2$ at Peak - Work load at $\dot{V}o_2$ at $\hat{\theta}_L$ - ⅔ of work ramp) × 50 %) + Work load at $\dot{V}o_2$ at $\hat{\theta}_L$.

Each exercise session included a 5-minute warm-up and cool-down using unloaded pedalling. Exercise training intensities were responsive to each CPET during the exercise programme derived and reported by two assessors. The absolute power output for subsequent training

sessions was adjusted according to the outcome of CPET.

4.2.4.2.3.3 Exercise training time

The first two exercise training sessions involved 30 minutes of exercise which increased to 40 minutes thereafter per session. In the first week of training, participants performed the interval exercise training protocol for 20 minutes with a 5-minute warm-up and cool down. The interval exercise training phase included 4 repeated bouts of moderate – severe intensity. Following week 1, the time of each exercise training session increased to 30 minutes with a 5-minute warm-up and cool down. The interval exercise training phase included 6 repeated bouts of moderate – severe intensity intervals.

4.2.4.2.3.4 Exercise training type

The exercise training programme was conducted on a computer-controlled electromagnetically-braked cycle ergometer (Optibike Ergoselect 200; Ergoline, GnbH, Germany). HR was continuously recorded (Polar FT7, Warwick, UK).

4.2.4.2.3.5 Exercise training adherence

Exercise adherence was reported by calculating number of sessions attended compared to number of planned sessions (i.e. scheduled: 3 sessions x 9 weeks).

4.3 Outcome measurements

Physical fitness and physical activity levels (PAL) were assessed simultaneously over a series of time points throughout the study period: baseline (pre-neoadjuvant CRT), following completion of the neoadjuvant CRT (week 0), week 3, 6 and 9 (surgery generally takes place between weeks 6-10, dependent on each hospital) (Figure 4.3). For the experimental work in this thesis, CPET-derived variable $\dot{V}o_2$ at $\hat{\theta}_L$ (primary outcome) and PAL variable daily step-count (secondary outcome), and other associated exploratory CPET and PAL variables were reported.

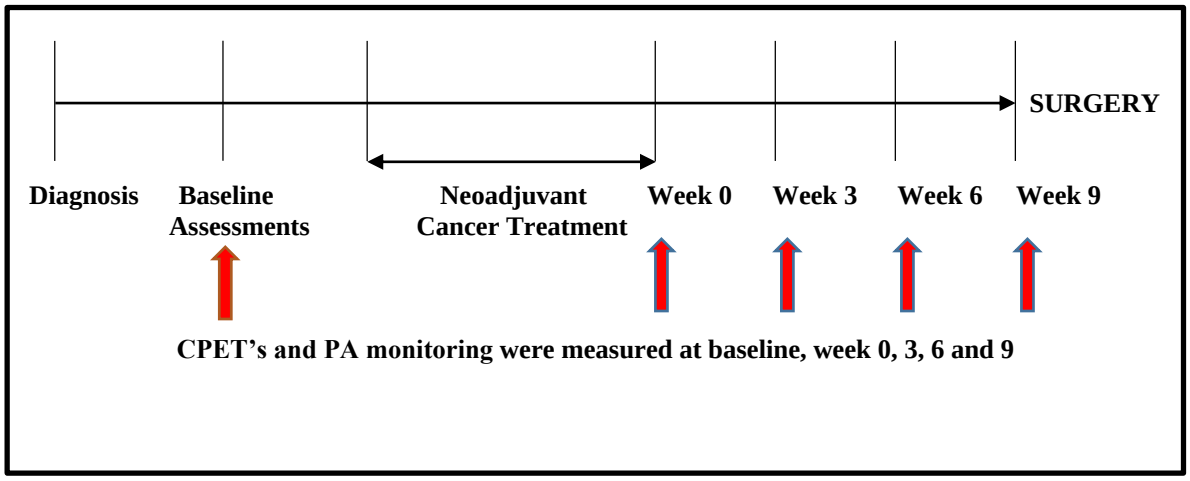


Figure 4.3 Trial schema of timing of study endpoints

Abbreviations: CPET – cardiopulmonary exercise testing; PA – physical activity monitoring.

4.3.1 Cardiopulmonary Exercise Test

4.3.1.1 Procedures for all cardiopulmonary exercise test protocols

All CPETs were performed in-hospital by trained and experienced staff in a variety of departments: Integrated Physiology Laboratory in the Welcome Trust Clinical Research Facility (UHS); CPET clinical service department (AUH); Anaesthetic department (STH); and Physiotherapy department (RBCH). Figure 4.4 is an image of CPET being performed in UHS. Every effort was made to coordinate the tests with other clinical appointments. Each individual CPET was conducted at a similar time of day. Participants were asked to refrain from caffeine ingestion and strenuous exercise prior to the test. All participants were assessed prior to CPET to ensure there were no contraindications to exercise testing. The contraindications to CPET

are based on American Thoracic Society and the American College of Chest Physicians Guidelines (Table 4.2).

Figure 4.4 CPET being performed in UHS (physiology lab)

Table 4.2 Contradindications to cardiopulmonary exercise test

Absolute Contraindications (Do not test)	**Relative Contraindications (Discuss with CPET doctor prior to starting test)**
Acute myocardial infarction	Left main coronary stenosis
Unstable angina	Moderate stenotic valvular heart disease
Uncontrolled arrhythmias causing symptoms or haemodynamic compromise	Severe untreated arterial hypertension at rest (systolic > 200mmHg, 120mm Hg diastolic)
Syncope	Tachyarrhythmia or bradyarrhythmia
Active endocarditis	Hypertrophic cardiomyopathy
Acute myocarditis or pericarditis	Significant pulmonary hypertension
Uncontrolled heart failure	Advanced or complicated pregnancy
Thrombosis of lower extremity	Electrolyte abnormalities
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary oedema	
Room air desaturation at rest <85% if no known lung pathologies	
Respiratory failure	
Acute non-cardiopulmonary disorder that may affect exercise performance	
Mental impairment leading to inability to co-operate	

(ATS/ACCP Statement on cardiopulmonary exercise testing)

4.3.1.1.1 Cardiopulmonary exercise test equipment

All CPETs were performed using an electromagnetically-braked cycle ergometer (Ergoline 2000), 12 lead ECG (Amadtec ECGPro), non-invasive blood pressure (BP), pulse oximetry and a metabolic cart (Geratherm Respiratory GmbH, Love Medical Ltd). The 12 lead ECG allows online monitoring of all leads for rate and rhythm and is used to monitor and record S-T changes and QRS complexes to assess whether ischaemia is occurring and to identify any significant arrhythmias. The metabolic cart has oxygen and carbon dioxide analysers with a response time of 90 m/s and a gas flow sensor to enable breath-by-breath measurements.

4.3.1.1.2 Cardiopulmonary exercise test calibration, validation, reliability, repeatability, and reproducibility

Equipment calibration and validation are important aspects of conducting CPETs. The manufacturer has the initial responsibility for demonstrating that the CPET system is accurate and precise (the same CPET kits, from the same manufacturer, were issued to each hospital site as part of the EMPOWER trial). However, the user is responsible for ensuring that the measurements are accurate. Therefore, a full calibration of the CPET kit was performed before each test. This consists of calibrating the flow sensor, the oxygen and carbon dioxide analysers. During the calibration of flow, adjustments for barometric pressure, humidity and temperature were made via the integral USB Ambstik. The flow sensor was calibrated using a 3 litre calibration syringe over a range of flow rates. Since the accuracy of the values obtained during testing is directly determined by the accuracy of the gases used to calibrate the gas analysers, calibration gases are gravimetrically weighed to ensure concentration accuracy. Calibration accuracy is accurate to two decimal places (± 0.01 %). The calibration uses a two-point calibration system; these two points correspond to the equivalent of normal gas concentrations at sea level (room air) and exhaled gas concentrations (calibration mixture: 5 % carbon dioxide (CO_2) and 15 % oxygen (O_2) in nitrogen (N_2) (purchased from BOC Special Gases). Gas calibration also includes a measure of the delay between the change in gas concentration at the distal end of the sample line and the time it takes for this change to be measured by the gas analysers to ensure that the data from the gas analysers is accurately aligned with measurements made by the flow sensor.

Validation refers to the extent to which the actual observed measurement may or may not directly measure the desired characteristic. Once calibration was completed, validation of the accuracy of the calibration using a flow validation procedure was performed. The device applies the correction factor calculated in the calibration manoeuvre and the syringe is used to

provide three inspiratory and three expiratory manoeuvres at three different flow rates. There should be little or no drift in the flow volume curve. The gas validation procedure was performed at the same time checking the calibrated system against the same gas.

Repeatability refers to the variation in repeat measurements made on the same subject under identical conditions[155]. To account for this, on a monthly basis, a healthy member of the research team, consuming a stable diet, performed a constant work rate test at workloads (eg. 50, 100, 150 W). Subsequent steady sate values for VE, $\dot{V}O_2$, and $\dot{V}CO_2$ were then compared with the database and values outside the 95% confidence interval for that individual suggested a system check.

Other important aspects of trial conduct include reproducibility and reliability. Although not controlled for within this study, CPET has been shown to be reproducible and reliable. Reproducibility refers to the variation in measurements made on a subject under changing conditions. Previous studies conducted reliability studies on CPET and reported it to be reproducible in people following myocardial infarction and with pulmonary arterial hypertension[156]. Reliability is the degree to which an assessment tool produces consistent results[157]. A previous study conducted a reliability study on CPET and reported it to have an acceptable reliability of $\dot{V}O_2$ at lactate threshold on a cycle ergometer. Furthermore, that there were no learning effect present with repeat testing[158].

4.3.1.1.3 Setting up the cardiopulmonary exercise test

Prior to each CPET, with more emphasis on the first CPET, the participants were coached on facemask placement and instructions for communicating during the test. All participants were encouraged to give their "best effort" however they were instructed to stop if they felt dizzy or faint. Prior to each CPET, all participants were asked to report any other symptoms. Prior to each CPET, ECG electrodes and leads were applied to the participant before getting on the stationary exercise bike. The incremental rise in work rate was pre-determined using the equation derived by Wasserman and colleagues[39] of which the same work rate protocol was used for each CPET. This is done in an objective manner with aiming for test duration of between 8 - 12 minutes. The ramp protocol equation is as follows[39];

$$\dot{V}O_2 \text{ unloaded } (ml.min^{-1}) = 150 + (6 \times \text{weight (kg)})$$

$\dot{V}$ o_2 at Peak ($ml.min^{-1}$) Men = [height (cm) – age (y)] × 20

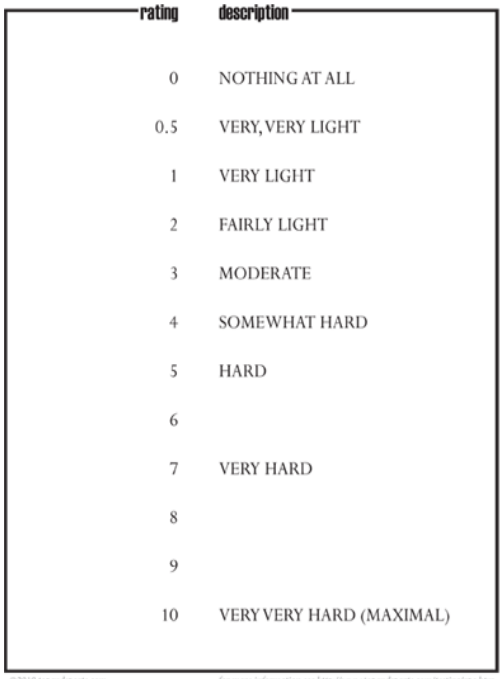
$\dot{V}$ o_2 at Peak ($ml.min^{-1}$) Women = [height (cm) – age (y)] × 14

Work Rate increment ($W.min^{-1}$) = Peak $\dot{V}$ o_2 - $\dot{V}$ o_2 Unloaded) / 100

Each participant was instructed how to rate the Borg Scale for rating of perceived exertion (Scale 0 to 10) which is a subjective rating of breathlessness and leg fatigue (assessed every 2 minutes during the test). Additionally, participants were informed that a BP reading would occur every 2 minutes during the test. The participants were asked to perform an incremental ramp test to the limit of tolerance and to maintain a cycling cadence at 55-65 revolutions per minute (RPM) throughout the test. Saddle height was also set to ensure that the participants extended leg was slightly bend. In people with hip/knee problems, the height was increased slightly to ensure a comfortable position. Saddle height was measured and recorded at the first CPET and remained constant for all other CPETs. Once the participant was comfortable on the bike, the mask was fitted.

4.3.1.1.3.1 BORG score

During each CPET, the modified BORG scale was used to assess breathlessness and leg fatigue (range from 0 – 10). A rate of O represents "nothing at all", 5 represents "somewhat" and 10 represents "maximal" (Figure 4.5). Prior to the discovery of the BORG scale, a scale called the rate of perceived exertion (RPE) scale was commonly used. However, this scale created discrepancies as RPE values were assumed to be related to HR: exercising within a HR range of 130 and 150 beat per minute was assumed to have a RPE of 13 and 15. In order to overcome these discrepancies, the BORG scale was developed[159]. In the first instance, Borg developed a 21 grade scale similar to the RPE scale which was then followed by the modified Borg scale which is now used commonly in clinical practice[160]. The BORG scale has been shown to be a valid measure of exercise intensity but its validity may not be as high for other variables measured in exercise tests such as: HR; blood lactate concentration; percent maximal oxygen uptake; oxygen uptake; ventilation; and respiration rate[161]. The modified BORG was developed to increase linearly with work load and is a part of the American Thoracic Society exercise guidelines. The BORG was used during CPET's to allow the researcher to communicate with participants. This was to establish how participants perceived exercise intensity but was not used to inform the exercise training programme. BORG scores were recorded in participant case report form (Appendix 7).



rating	description
0	NOTHING AT ALL
0.5	VERY, VERY LIGHT
1	VERY LIGHT
2	FAIRLY LIGHT
3	MODERATE
4	SOMEWHAT HARD
5	HARD
6	
7	VERY HARD
8	
9	
10	VERY VERY HARD (MAXIMAL)

Figure 4.5 The BORG scale

4.3.1.1.4 Cardiopulmonary exercise test protocol

Resting HR was recorded for 5-minutes prior to getting the participant on the bike. Resting measures were recorded for 3-minutes on the bike to ensure that the participant was comfortable with the facemask and baseline measurements of ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}_{O2}$), carbon dioxide output ($\dot{V}_{CO2}$) HR, BP and the partial pressure for end-tidal O_2 and CO_2 are stable.

Following the rest period, there was a 3-minute warm up phase which consisted of freewheel cycling. Following the warm up phase, the incremental ramp was initiated (based on the pre-determined workload detailed above). CPET variables were monitored continuously for the duration of the test however particular attention was placed on monitoring the 12 lead ECG reading and the peripheral capillary oxygen saturation (SpO_2). Non-invasive BP and the BORG score were measured approximately every - minutes during the test. The reason for stopping the test was recorded. Participants were encouraged to exercise until exhaustion; if the participant failed to maintain greater than 40 RPM for more than 1 minute the operator terminated the test. Additionally, CPETs were terminated based on "stopping criteria" illustrated in Table 4.3 if required.

Table 4.3 Criteria for stopping a cardiopulmonary exercise test

• Angina • > 2mm ST depression if symptomatic or 4mm if asymptomatic or > 1mm ST elevation • Significant arrhythmias • Fall in systolic BP > 20mmHg from the highest value during the test • Hypertension > 250mm Hg systolic; > 120 mm Hg diastolic • Severe desaturation: SpO_2 < 80% accompanied by limiting hypoxemia • Sudden pallor • Loss of coordination • Mental confusion • Signs of respiratory failure

Once the incremental ramp test ended, recovery data was collected for a period of 5 minutes. This included 2 minutes of unloaded pedalling followed by 3 minutes of complete rest whilst sitting on the exercise bike. ECG readings were continuously monitored for this period ensuring any arrythmia or ST changes (if any) reverted to pre-test levels, or until HR is within 10 bpm of the pre-test rate. BP and BORG score were measured at 2 and at 5 minutes (or until BP returned back to normal resting values)

4.3.1.1.5 Cardiopulmonary exercise testing interpretation

During the study period, CPETs were assessed by myself and research collaborator Malcolm West (MW) for the exercise group, only, to inform the exercise training programmes. The inter-observer variability for experienced clinicians is very acceptable[162]. The final physiological data were assessed by myself. CPET interpretation was done using a systematic approach. The output from an incremental CPET is by convention represented graphically in a 9-panel plot (Figure 4.6)[163,164]. Firstly, test quality was evaluated, checking for appropriate calibration (respiratory exchange rate (RER) > 0.7 at rest) and identifying pre-test hyperventilation (RER > 1 at rest) which can interfere with interpretation of the anaerobic threshold causing a pseudothreshold[165]. Estimation of lactate threshold was derived using the modified V-Slope method[38, 166]. The modified V-Slope method identifies the estimated lactate threshold as the tangential breakpoint in the $\dot{V}CO_2$- $\dot{V}O_2$ (oxygen uptake – carbon dioxide) relationship from the line of unity ('line of one') during the incremental stage of the exercise test with confirmatory data from end tidals, ventilatory equivalents and RER. The V-slope methods depend solely on the physicochemical reaction of hydrogen ions with bicarbonate and so the breakpoint is independent of chemoreceptor sensitivity and the ventilatory response to

exercise[38]. The primary outcome of interest was $\dot{V}o_2$ at $\hat{\theta}_L$ and $\dot{V}o_2$ at peak. These variables are metabolic rates expressed in mls $\dot{V}o_2$ per minute absolute, indexed to bodyweight or as percentages of predicted values. $\dot{V}o_2$ at peak is defined as the highest oxygen uptake recorded during an incremental exercise test at the point of volitional fatigue or symptom limitation. As such $\dot{V}o_2$ at peak includes a volitional element (the patient may not produce a maximal effort). The $\dot{V}o_2$ at $\hat{\theta}_L$ characterises the upper limit of exercise intensity that can be accomplished almost wholly aerobically[163].

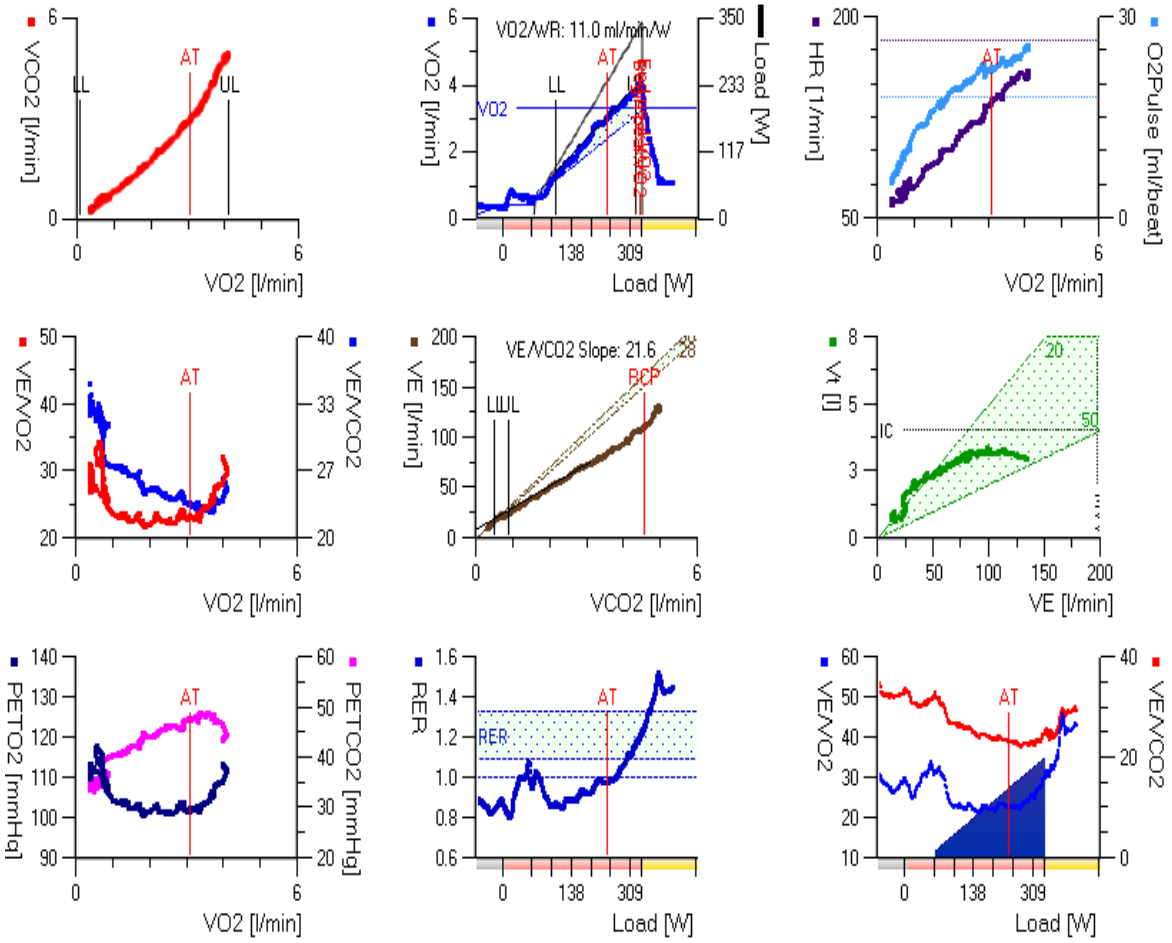


Figure 4.6 Graphical illustration of the 9-panel plot

Panel 1, illustrates the V-Slope method of the estimated lactate threshold determination – at the lactate threshold the gradient of the $\dot{V}O_2$–$\dot{V}CO_2$ relationship increases above 1. The $\dot{V}o_2$ at $\hat{\theta}_L$ is confirmed by evaluation of the ventilatory response to the excess CO_2 in panel 4 – ventilatory equivalents to oxygen ($\dot{V}E/\dot{V}CO_2$), panel 7- end tidal oxygen and panel 9 –ventilatory equivalents against workload. The breakpoint marked by the red vertical line is the estimated lactate threshold.

4.3.2 Physical activity monitoring

Physical activity monitors were issued to all participants to assess daily PAL at several time points over the study period: baseline (pre-neoadjuvant CRT); post-neoadjuvant CRT (week 0); and at week 3, 6, and 9.

4.3.2.1 Physical activity monitoring software and equipment

Daily PAL was measured using a multi-sensory accelerometer (SenseWear Pro® armband (Model MF-SW, display model DD100; BodyMedia, Inc., Pittsburgh, PADL, USA) using the SenseWear software package. The armband estimates energy expenditure (EE) using measurements from a biaxial accelerometer and sensors that quantify galvanic skin response, heat flux and skin temperature The device records and reports daily movement: total and active EE; PA duration; number of steps; lying down time; average metabolic equivalent threshold (MET) score; sleep duration and efficiency (number of minutes of sleep divided by number of minutes in bed). PAL is commonly quantified by using metabolic equivalent threshold (MET) score (ratio of the metabolic rate associated with physical activity divided by the resting metabolic rate) which is scored as follows: 1.1 – 2.9 (light intensity aerobic activity); 3.0 – 5.9 (moderate intensity aerobic activity); and ≥ 6.0 (vigorous intensity aerobic activity)[167].

The Sensewear Pro can distinguish between lying down and sleep time by using algorithms that detect the characteristics combination of orientation, motion, temperature and skin conductivity with each state. The SenseWear system components include the armband and the optional display device. The armband estimates EE using measurements from a biaxial accelerometer and sensors that quantify galvanic skin response, heat flux and skin temperature. The biaxial accelerometer records the number of steps per day and the duration of PA. See Figure 4.7 below for an image of the monitor and example of report the software generates.

Figure 4.7 Physical activity monitor and sample report

4.3.2.2 Setting up the physical activity monitor

Physical activity armbands were set up for each participant via a USB cable connecting the armband to a computer. Armband configuration for each participant included entering appropriate details such as: participant information number; date of birth; height; weight; smoking status; and the arm the armband would be worn on. Once all data were entered and the battery light emitting display (LED) was blinking green to indicate full charge, the armband was detached from the USB cable ready for data collection.

4.3.2.3 Physical activity monitoring protocol

Participants were instructed to wear the physical activity armbands on their upper right arm continuously during three consecutive week days and nights, except when bathing.

4.3.2.4 Physical activity monitoring report

The BodyMedia's SenseWear Professional Software retrieved and saved physiological data collected by the SenseWear armband over the period of three days the participant had worn for. The software organised, graphed and exported all the data onto the computer for data entry. Data was averaged over the 72h period.

4.4 Quality control

4.4.1 Standard operating procedures (SOP)

SOP's are an essential element for the control of clinical research. I (LL) was responsible for writing a set of step-by-step instructions to guide research teams in all sites on processes and procedures to ensure consistency and quality across all sites.

4.4.2 Staff training and communication

I (LL) provided protocol and staff training at each site. The protocols were clearly defined to allow for a standardisation across all sites. All research teams contacted LL on a weekly basis to ensure standardised protocols were being delivered. On a monthly basis, screening and recruitment logs were sent to LL and team research meetings were conducted via telephone conference call.

4.5 Blinding

Due to nature of the trial, it was not possible to blind the participants or the personnel delivering the intervention. Research teams in each NHS site documented trial participation in medical notes following recruitment and enclosed a copy of patient information sheet to the medical notes. Allocated intervention arms were not documented in a bid to blind the multi-disciplinary team (MDT). However, participants were attending outpatient clinics during the trial therefore allocated intervention arms may have been discussed. Furthermore, the data assessor for outcome measures was not blinded but efforts were made to code each individual test in order to reduce researcher bias. The MDT which incorporates clinicians and nurses caring for the participants were not provided with any information regarding outcome measures (e.g. CPET variables) to ensure a low risk of confounding by indication[168].

4.6 Data analysis

4.6.1 Sample size

A sample of 28 participants was estimated to detect a difference between groups of 2.0 $ml \cdot kg^{-1} \cdot min^{-1}$ in $\dot{V}o_2$ at $\hat{\theta}_L$ using a two-sample t-test at the 5 % significance level with 80 % power. This is based on a standardised deviation of the change in $\dot{V}o_2$ at $\hat{\theta}_L$ values of 1.8 $ml.kg^{-1}.min^{-}$

[1] and is inflated to allow for 20% dropout[102]. A minimum clinically important difference (MCID) was accepted as a change of 2.0 $ml \cdot kg^{-1}.min^{-1}$ in $\dot{V}O_2$ at $\hat{\theta}_L$[102].

4.6.2 Description of patient characteristics

Descriptive analyses were carried out to summarise participants' characteristics including baseline and changes in physical fitness and PAL. Continuous variables were reported as mean (range), mean (SD) or median and inter-quartile range (IQR), depending on distribution, and categorical variables as frequency (%).

4.6.3 Data interpretation

The Shapiro-Wilk test for normality of distributions was applied. The effect of neoadjuvant CRT on physical fitness and PAL were assessed using a two- sample t-test when relevant distributional assumptions were met and the Mann–Whitney U-test otherwise. The effect of the exercise intervention on physical fitness and PAL were assessed by within each group, using a two- sample t-test when relevant distributional assumptions were met and the Mann–Whitney U-test otherwise. The differences between the groups in physical and PAL at week-9 were assessed using a paired t-test when relevant distributional assumptions were met and a Wilcoxin test otherwise. Due to the evaluation of multiple endpoints, the gatekeeper approach was employed to control the false positive rate[169]. The gatekeeper approach takes advantage of the hierarchically-ordered multiple analyses and the analyses are examined sequentially. First the primary outcome will be tested and evaluated at the 5% significance level. If the primary outcome is not statistically significant, the other outcomes should not be tested for significance; however, if the primary outcome is statistically significant, the secondary outcome can then be tested again at a 5% significance level. The same procedure is employed for all variables until an insignificant result is found, and the following variables are then not tested. In the case of missing data, case complete approach was employed. Statistical significance was accepted at $p<0.05$. All analyses were performed with the statistical software IBM SPSS Statistics Ver.22 (IBM Corporation, Armonk, NY, USA).

Chapter 5

The effects of neoadjuvant chemoradiotherapy on physical fitness and physical activity levels in people with locally advanced colorectal cancer prior to surgery: An observational study

5.1 Introduction

This chapter describes an observational study which investigates the effects of neoadjuvant chemoradiotherpy (CRT) on physical fitness and physical activity levels (PAL) in people with newly diagnosed locally advanced rectal cancer scheduled for surgery.

5.2 Background

The perioperative cardiopulmonary exercise testing (CPET) literature strongly demonstrates a consistent relationship between physical fitness, defined using CPET-derived variables, and post-operative outcome (Chapter 2, Table 2.1)[30, 41]. In the surgical-setting, CPET-derived variable oxygen uptake ($\dot{V}O_2$) at lactate threshold at ($\hat{\theta}_L$), has been used in several patient groups to risk stratify people for surgery[58, 170-172]. More recently, in the surgical-oncology setting, CPET has been used to demonstrate that cancer treatments significantly reduce $\dot{V}O_2$ at $\hat{\theta}_L$ values and that this reduction is associated with adverse post-operative outcome: reduced 1-year survival and post-operative complications in people undergoing neoadjuvant chemotherapy[12] and CRT[13] prior to upper gastrointestinal and rectal cancer surgery.

Physical fitness is closely connected to PAL, although relationships of cause and effect are complex. The evidence base on PAL in newly diagnosed cancer is more limited than that relating to physical fitness. Yet, PAL in people with cancer receiving adjuvant cancer treatment (following surgery), has been documented, mainly in breast, using subjective measures such as questionnaires (Chapter 2, Section 2.2.5.1). To date, little is known about PAL in people with newly diagnosed cancer scheduled for multimodal treatment including surgery.

5.3 Study objective

To quantify changes in physical fitness (measured using CPET) and daily PAL (measured using physical activity monitors) following neoadjuvant CRT in people with locally advanced rectal cancer scheduled for surgery.

5.4 Hypotheses

5.4.1 Primary hypothesis

Neoadjuvant CRT will significantly reduce physical fitness ($\dot{V}o_2$ at $\hat{\theta}_L$) in people with locally advanced rectal cancer prior to surgery.

5.4.2 Secondary hypothesis

Neoadjuvant CRT will significantly reduce daily PAL (step-count) in people with locally advanced rectal cancer prior to surgery.

5.4.3 Exploratory hypothesis

Neoadjuvant CRT will result in a significant decrease in other exploratory CPET and PAL variables: 1) CPET variables: $\dot{V}o_2$ at peak; oxygen (O_2) pulse at $\hat{\theta}_L$ and at peak; ventilatory equivalents carbon dioxide ($\dot{V}_E/\dot{V}co_2$) at $\hat{\theta}_L$ and at peak exercise; ventilatory equivalents oxygen ($\dot{V}_E/\dot{V}o_2$) at $\hat{\theta}_L$ and at peak exercise; work rate at $\hat{\theta}_L$ and at peak exercise; forced expiratory volume over 1-sec (FEV1); forced vital capacity (FVC) and 2) PAL variables: sleep duration and efficiency; lying down time; total and active energy expenditure (EE); metabolic equivalent threshold (MET) score; PAL; duration on body.

5.5 Participants and methods

5.5.1 Study design

This multi-centre, prospective, observational study is a part of the EMPOWER trial. The study is funded by the National Institute for Health Research for Patient Benefit Programme (PB-PG-0711-25093), approved by North West Centre for Research Ethics Committees (13/NW/0259) and registered with clinicaltrials.gov (NCT01914068).

5.5.2 Hospital sites

As described in Chapter 4, Section 4.2.1

5.5.3 Participants

Participants with locally advanced rectal cancer were recruited between August 2013 and October 2015, listed to undergo neoadjuvant cancer treatment (both chemo- +/ chemoradio-therapy) and elective rectal cancer resection. Predefined inclusion and exclusion criteria are described in Chapter 4, Section 4.2.2. Recruitment process is described in Chapter 4, Section 4.2.2. Written informed consent was obtained from all participants (Appendix 5).

5.5.4 Cancer treatment

All participants underwent five weeks of neoadjuvant CRT. Preoperative radiotherapy consisted of 45 Gy in 25 fractions on weekdays using a three-dimensional conformal technique with CT guidance. Participants were treated prone (on a belly-board) to spare small bowel, with a comfortably full bladder. The clinical target volume included the primary tumour, the mesorectum and mesorectal lymph nodes, including the perirectal, pre-sacral and internal iliac nodes. The upper radiation extent was 3 cm above the tumour but no further than the sacral promontory. The perineum was included if an abdomino-perineal resection (APR) was planned, while for low anterior resection (LAR) the lower radiation border was 3 cm below the tumour. A boost dose was given (5.4 Gy in 3 fractions) to the primary tumour only. 825 $mg.m^{-2}$ oral capecitabine was given twice daily on radiotherapy days (section 2.4.5). In University Hospital Southampton (UHS) and Royal Bournemouth Christchurch Hospital (RBCH), only, in the first instance (prior to receiving neoadjuvant CRT), some participants (at risk of systemic spread) received four cycles of capecitabine and oxalilplatin chemotherapy. No participant received brachytherapy.

5.5.5 Procedures and Measurements

5.5.5.1 Procedures

All participants underwent two CPETs to assess physical fitness: (1) before starting neoadjuvant CRT (1-2 weeks following cancer diagnosis dependent on individual pathway) and; (2) immediately after neoadjuvant CRT (within 1 week). Additionally, all participants underwent a continuous 72 h period of physical activity monitoring using Sensewear biaxial accelerometer at the same time points (pre- and post- neoadjuvant CRT): physical activity monitors were issued at each CPET. The clinical pathway and complete series of assessments is described in Figure 5.1.

5.5.5.2 Measurements

5.5.5.2.1 CPET

Both CPETs followed standard protocol described in Chapter 4, Section 4.3.1. Recorded baseline characteristics included: age; gender; height; weight; cancer staging and treatment; smoking status; and any co-morbid disease. Resting heart rate (HR) was measured for 5 minutes while seated prior to each CPET. Resting flow-volume loops were used to derive forced expiratory volume over 1 second (FEV1) and forced vital capacity (FVC). The physiological data was assessed by myself (LL) using the modified V-Slope method to identify the estimated lactate threshold as the tangential breakpoint in the $\dot{V}CO_2$- $\dot{V}O_2$ (oxygen uptake – carbon dioxide) relationship from the line of unity ('line of one') with confirmatory data from end tidals, ventilatory equivalents and respiratory exchange ratio (RER) (CPET interpretation is further described in Chapter 4, Section 4.3.1.1.4). The multidisciplinary team (MDT) which incorporates clinicians and nurses caring for the participants were not provided with any information regarding outcome measures.

5.5.5.2.2 Physical activity monitoring

Physical activity monitoring followed standard protocol described in Chapter 4, Section 4.3.2.

5.5.5.3 Statistical analysis

Continuous variables are reported as mean (range), mean (SD) or median and inter-quartile range (IQR), depending on distribution, and categorical variables as frequency (%). The Shapiro-Wilk test for normality of distributions was applied. Descriptive statistics and univariate statistical comparisons of patient characteristics between the groups were undertaken: for continuous variables, a paired sample t-test when relevant distributional assumptions were met and the Wilcoxon Signed-Rank test otherwise. Due to the evaluation of multiple endpoints, the gatekeeper approach was employed to control the false positive rate. In the case of missing data, case complete approach was employed. Statistical significance was accepted at $p<0.05$. All analyses were performed with the statistical software IBM SPSS Statistics Ver.22 (IBM Corporation, Armonk, NY, USA).

5.5 Results

The study flow is presented in Figure 5.1. During the study period, 224 people were identified for screening following weekly MDT meetings: 64/224 (28.5 %) met inclusion criteria and 31/64 (48 %) agreed to participate. A total of 31 participants were recruited, of whom 24 completed the study. The study process is presented in Figure 5.2. Baseline characteristics of the 31 recruited participants are summarised in Table 5.1. The mean age was 61 (17) years and 26 were male (84 %). Eight (26 %) participants received cancer treatment 1 (four cycles of capecitabine and oxaliplatin chemotherapy + neoadjuvant CRT for five weeks) whilst 23 (74 %) participants received cancer treatment 2 (neoadjuvant CRT for five weeks). Five participants dropped out (three from cancer treatment 1 and two from cancer treatment 2) and two participants were deemed palliative during neoadjuvant CRT (one from cancer treatment 1 and one from cancer treatment 2). Two participants from cancer treatment 1 stopped chemotherapy following cycle two (due to developing sub-acute bowel obstruction) and cycle three (due to rising carcinoembryonic antigen and pelvic pain). Both participants required dose reduction in capecitabine by 20 %. Cancer treatment 1 was prescribed in UHS only (mid-point of the trial).

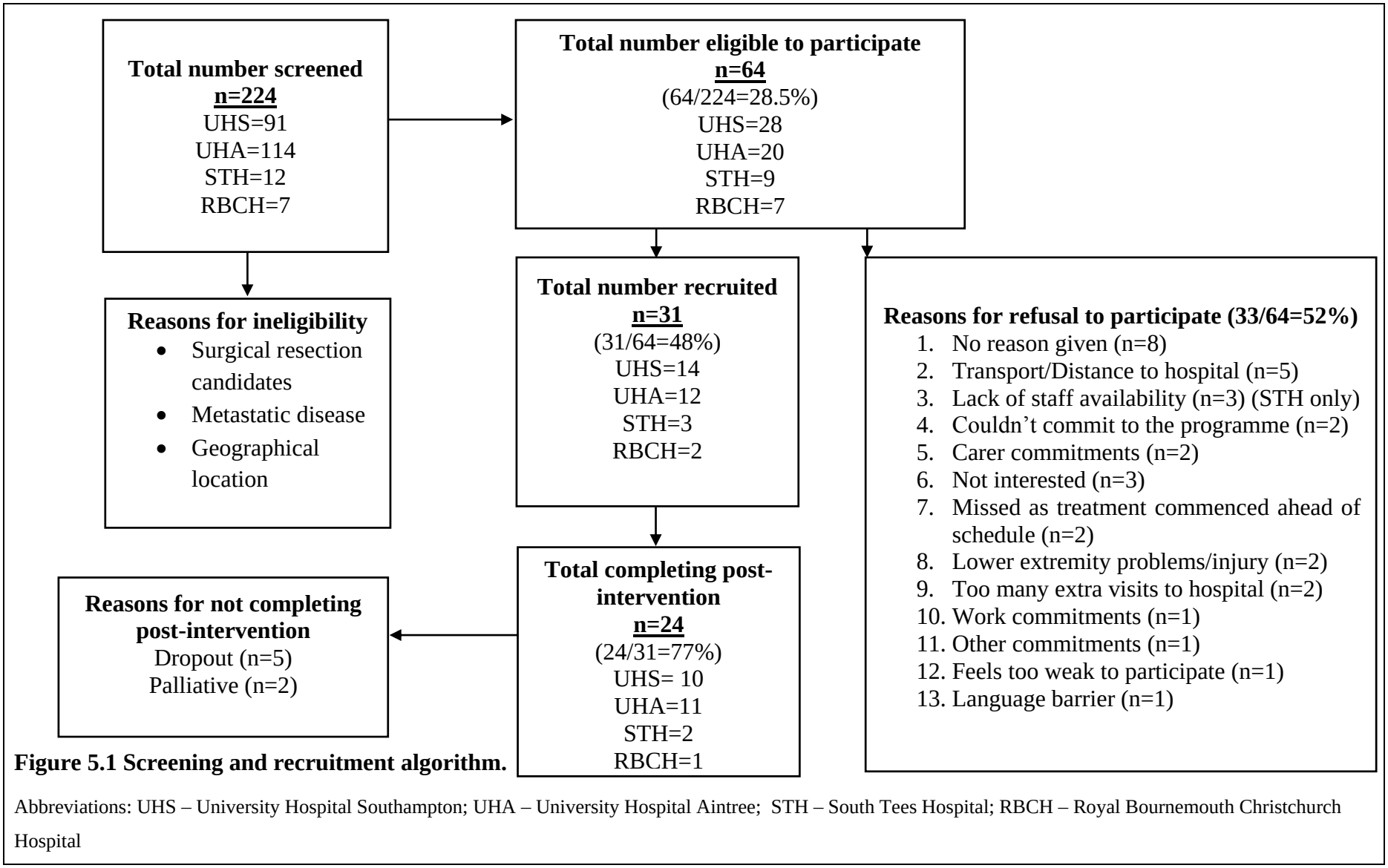


Figure 5.1 Screening and recruitment algorithm.

Abbreviations: UHS – University Hospital Southampton; UHA – University Hospital Aintree; STH – South Tees Hospital; RBCH – Royal Bournemouth Christchurch Hospital

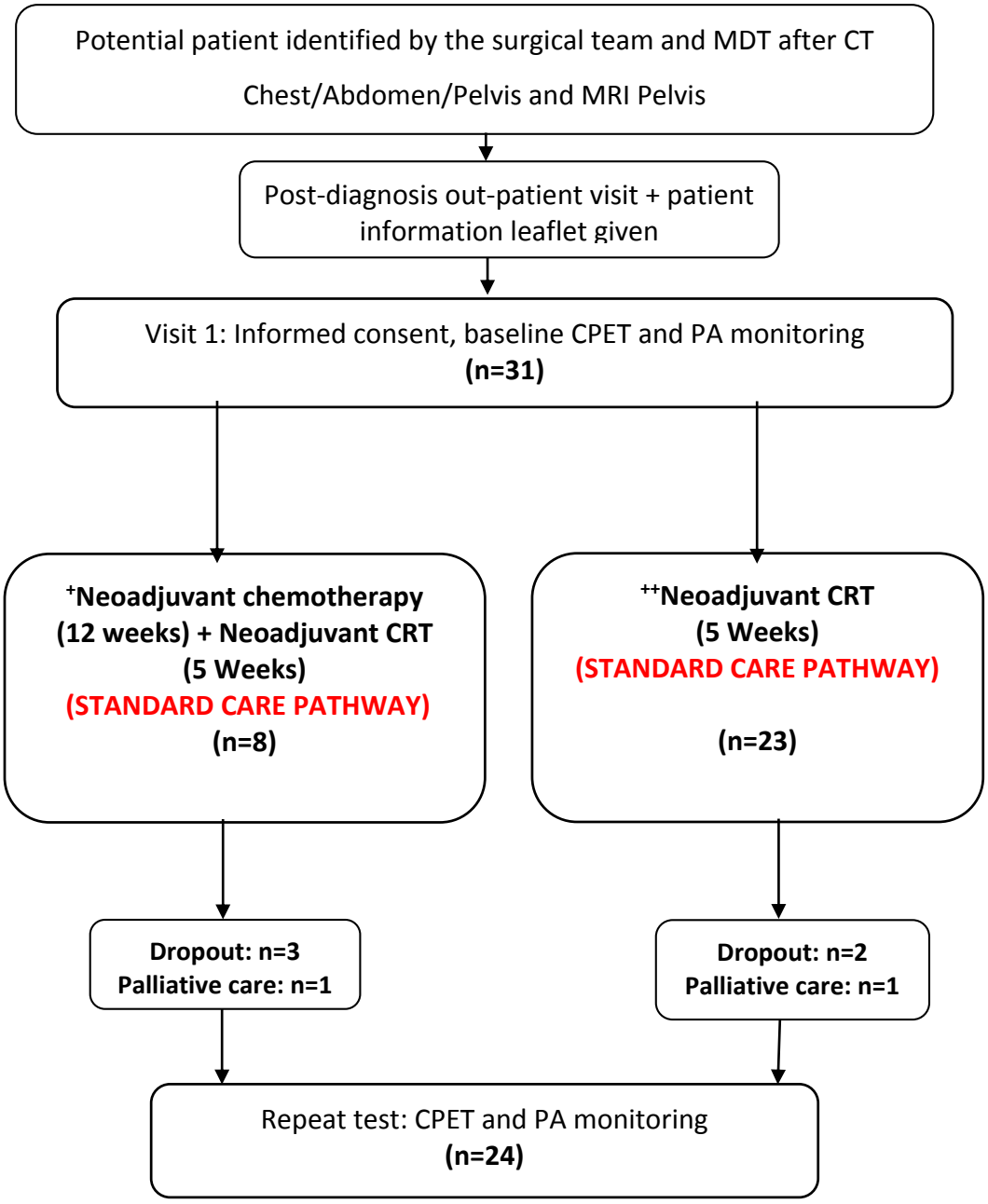


Figure 5.2 Participant pathway as part of the study.

List of abbreviations: MDT – multidisciplinary team; CT – computed tomography; MRI – magnetic resonance imaging; CPET – cardiopulmonary exercise test; PA – physical activity; CRT – chemoradiotherapy.
Note: + Cancer treatment 1 (Neoadjuvant chemotherapy and CRT group); ++ Neoadjuvant CRT group (cancer treatment 2)

Table 5.1 Baseline participant characteristics

	n=31	**Completers (n=24)**	**Non-completers (n=7)**
	Mean (SD)		
Age (years)	61 (17)	62 (13)	57 (17)
Height (cm)	172 (7)	174 (7)	171 (7)
Weight (kg)	76 (14)	79 (14)	73 (13)
BMI (kg/m^2)	26 (4)	26 (4)	25 (3)
	Number (%)		
Gender M:F (ratio)	26 (84): 5 (16)	20 (83): 4 (18)	6 (86): 1 (14)
Current smoker	4 (13)	3 (13)	1 (14)
Past medical history	7 (23)	6 (27)	1 (14)
Diabetes	2 (6)	1 (5)	1 (14)
Hypertension	2 (6)	2 (9)	0 (0)
AAA	1 (3)	1 (3)	0 (0)
Medication	7 (23)	6 (27)	1 (14)
Clinical TNM classification	**Number**		
cT2	6	**6**	
cT3	20	**17**	**3**
cT4	5	**1**	**4**
cN0	6	**4**	**2**
cN1	15	**14**	**1**
cN2	5	**2**	**3**
cM0	11	**7**	**2**
cM1	1	**1**	
Unknown	4	**4**	
Cancer treatment			
Neoadjuvant Chemotherapy	8	5	3
Neoadjuvant CRT^{++}	23	19	4

Values are presented as mean (SD); frequencies with percentages in parentheses. Smoking status assessed as currently smoking: yes (1) vs no (0); past medical history is based on medical history reported in clinical notes; medication assessed as currently on medication: yes (1) vs no (0).
Abbreviations: CRT – chemoradiotherapy.
Note: + Cancer treatment 1 (Neoadjuvant chemotherapy and CRT group); ++ Cancer treatment 2 (Neoadjuvant CRT group).

5.5.1 Outcome measures

5.5.1.1 Primary outcome

5.5.1.1.1 Oxygen uptake at lactate threshold

There was no statistically significant differences in physical fitness CPET-derived variable $\dot{V}o_2$ at $\hat{\theta}_L$ following neoadjuvant cancer treatment ($p>0.05$) (Table 5.2). Sub-group analysis were not conducted as only four of the eight participants scheduled for cancer treatment 1 completed the study.

Table 5.2 Oxygen uptake at lactate threshold pre- and post- neoadjuvant cancer treatment: completers (n=24)

Primary outcome	Pre neoadjuvant CRT	Post neoadjuvant CRT	Mean Difference (95% CI)	P - value
$\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$)	12 (3.1)	12 (3)	-0.01(-1.5,1.4)	0.991

Data are presented in mean (SD). * P<0.05 was taken as statistically significant following paired sample t-test. Abbreviations: $\dot{V}o_2$ at $\hat{\theta}_L$ - Oxygen uptake at estimated lactate threshold.

5.5.1.2 Secondary outcome

5.5.1.2.1 Daily step-count

Daily PAL variable step-count following neoadjuvant CRT is presented in Table 5.3.

Table 5.3 Daily step-count pre- and post- neoadjuvant cancer treatment: completers (n=24)

Secondary outcome	Pre neoadjuvant CRT	Post neoadjuvant CRT	Mean Difference (95% CI)	P - value
Daily step-count (steps/day)	6433 (4160)	6487 (4785)	82 (-286,2450)	0.943[#]

Data are presented in mean (SD). * P<0.05 was taken as statistically significant following paired sample t-test. [#]P-value can't be meaningfully interpreted based on the gatekeeper approach.

Baseline values for primary and secondary outcome measures in both completers and non-completers are presented are Table 5.4.

Table 5.4 Descriptive baseline (pre neoadjuvant cancer treatment) values for primary and secondary outcome for completers (n=24) and non-completers (n=7)

Baseline values	Completers (n=24)	Non-completers (n=7)
Primary outcome		
$\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$)	12 (3.1)	8.6 (2.5)
Secondary outcome		
Daily step count	6133 (4160)	3651 (3476)

Descriptive data are presented in mean (SD). Abbreviations: $\dot{V}o_2$ at $\hat{\theta}_L$ - Oxygen uptake at estimated lactate threshold.

5.5.1.3 Exploratory outcomes

5.5.1.3.1 CPET exploratory variables

There was a difference in exploratory CPET variable heart rate (HR) ($beats.min^{-1}$) at peak exercise between pre- and post- neoadjuvant CRT: 142 (16) vs. 135 (17). Another exploratory CPET variable workload (Wattage) at $\hat{\theta}_L$ and peak exercise showed a difference between pre- and post- neoadjuvant CRT: 75 (35) vs. 69 (32) and 164 (60) vs. 154 (52). Baseline values for exploratory CPET variable are presented in Table 5.5. Exploratory CPET variables pre- and post- neoadjuvant CRT are presented in Table 5.6.

5.5.1.3.2 PAL exploratory variables

Baseline values for exploratory PAL variable are presented Table 5.7. Exploratory PAL monitoring variables pre- and post- neoadjuvant CRT are presented in Table 5.8.

Table 5.5 Descriptive baseline (pre neoadjuvant cancer treatment) exploratory cardiopulmonary exercise testing variables for completers (n=24) and non-completers (n=7)

Exploratory CPET Variables	Completers (n=24)	Non-completers (n=7)
$\dot{V}$ o_2 Peak ($ml.kg^{-1}.min^{-1}$)	22 (8.1)	17.6 (7)
O_2 pulse at $\hat{\theta}_L$ ($ml.beat^{-1}$)	10 (3.7)	6.2 (2.9)
O_2 pulse Peak ($ml.beat^{-1}$)	13.1(4.8)	9 (4.2)
$\dot{V}_E/\dot{V}$ o_2 at $\hat{\theta}_L$	25.7(3.5)	25.2 (4.1)
$\dot{V}_E/\dot{V}$ o_2 Peak	37.2(6.7)	37.7 (9.6)
$\dot{V}_E/\dot{V}$ co_2 at $\hat{\theta}_L$	31.6 (6)	31.2 (4.9)
$\dot{V}_E/\dot{V}$ co_2 Peak	32.3(6.3)	33.3 (7.5)
Baseline HR ($beats.min^{-1}$)	85 (28)	89 (17)
HR at $\hat{\theta}_L$ ($beats.min^{-1}$)	100 (9)	105 (16)
HR Peak* ($beats.min^{-1}$)	142 (16)	144 (24)
Work load at $\hat{\theta}_L$* (Wattage)	75 (35)	43 (32)
Work load at Peak* (Wattage)	164 (60)	128 (80)
FEV1 (Litres)	3.3 (0.9)	3 (0.7)
FVC (Litres)	4.3 (1)	4.1 (0.8)

Descriptive data are presented in mean (SD).

List of abbreviations: $\dot{V}$ o_2 at $\hat{\theta}_L$, Oxygen uptake at estimated lactate threshold; $\dot{V}$ o_2 at Peak, Oxygen uptake at peak exercise; O_2 pulse at $\hat{\theta}_L$, Oxygen pulse at estimated lactate threshold; O_2 pulse at Peak, Oxygen pulse at peak exercise; $\dot{V}_E/\dot{V}$ co_2 at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at estimated lactate threshold; $\dot{V}_E/\dot{V}$ co_2 at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at peak exercise; Work load at $\hat{\theta}_L$ and Peak, work load at estimated lactate threshold and peak exercise; FEV1; Forced expired volume in the first second; FVC; Forced vital capacity.

Table 5.6 Exploratory cardiopulmonary exercise testing variables pre- and post- neoadjuvant cancer treatment: completers (n=24)

Exploratory CPET Variables	Pre neoadjuvant CRT	Post neoadjuvant CRT	Mean Difference (95% CI)	P - value
$\dot{V}$ o_2 Peak ($ml.kg^{-1}.min^{-1}$)	22 (8.1)	22 (6)	-0.01 (-2.9,2.8)	0.993#
O_2 pulse at $\hat{\theta}_L$ ($ml.beat^{-1}$)	10 (3.7)	9.1 (3.1)	0.7 (-0.7, 2.2)	0.295#
O_2 pulse Peak ($ml.beat^{-1}$)	13.1(4.8)	12 (3.8)	0.8 (-1.1, 2.7)	0.381#
$\dot{V}_E/\dot{V}\,o_2$ at $\hat{\theta}_L$	25.7(3.5)	25.2 (6.3)	0.6 (-2.6, 3.8)	0.700#
$\dot{V}_E/\dot{V}\,o_2$ Peak	37.2(6.7)	39.6 (6.9)	-2.3 (-5.4, 0.6)	0.116#
$\dot{V}_E/\dot{V}\,co_2$ at $\hat{\theta}_L$	31.6 (6)	31 (4.4)	-1.3 (-3.5,0.9)	0.222#
$\dot{V}_E/\dot{V}\,co_2$ Peak	32.3(6.3)	33.2 (5.7)	-1.7 (-4,0.7)	0.161#
Baseline HR ($beats.min^{-1}$)	85 (28)	78 (11)	7 (-5,19)	0.270#
HR at $\hat{\theta}_L$ ($beats.min^{-1}$)	100 (9)	99 (14)	2 (-2,6)	0.285#
HR Peak* ($beats.min^{-1}$)	142 (16)	135 (17)	8 (0.5,15)	0.039#
Work load at $\hat{\theta}_L$* (Wattage)	75 (35)	69 (32)	12 (1,23)	0.035#
Work load at Peak* (Wattage)	164 (60)	154 (52)	11 (1,21)	0.030#
FEV1 (Litres)	3.3 (0.9)	3.2 (0.8)	0.1 (-0.1,0.2)	0.438#
FVC (Litres)	4.3 (1)	4.3 (1)	-0.01 (-0.2,0.2)	0.910#

Data are presented in mean (SD). * P<0.05 was taken as statistically significant following paired sample t-test. #P-value can't be meaningfully interpreted based on the gatekeeper approach.

List of abbreviations: $\dot{V}$ o_2 at $\hat{\theta}_L$, Oxygen uptake at estimated lactate threshold; $\dot{V}$ o_2 at Peak, Oxygen uptake at peak exercise; O_2 pulse at $\hat{\theta}_L$, Oxygen pulse at estimated lactate threshold; O_2 pulse at Peak, Oxygen pulse at peak exercise; $\dot{V}_E/\dot{V}\,co_2$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at estimated lactate threshold; $\dot{V}_E/\dot{V}\,co_2$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at peak exercise; Work load at $\hat{\theta}_L$ and Peak, work load at estimated lactate threshold and peak exercise; FEV1; Forced expired volume in the first second; FVC; Forced vital capacity.

Table 5.7 Baseline (pre neoadjuvant cancer treatment) exploratory physical activity variables for completers (n=24) and non-completers (n=7)

Baseline PAL Exploratory Variables	Completers (n=24)	Non-completers (n=7)
Physical activity duration (min.day^{-1})	74 (62)	45 (54)
Active energy expenditure (kcals.day^{-1})	392 (326)	226 (263)
Total energy expenditure (kcals.day^{-1})	2241 (609)	1808 (839)
MET	1.4 (0.3)	1.0 (0.6)
Lying down (min.day^{-1})	538 (178)	612 (216)
Sleep duration (min.day^{-1})	415 (123)	473 (140)
Sleep efficiency (%)	71 (19)	66 (22)
Duration of monitor on body (min.day^{-1})	1344 (133)	1208 (401)
PAL	1.5 (0.2)	1 (0.2)

Data are presented in mean (SD). List of abbreviations: MET -Metabolic equivalent threshold score; PAL – Physical activity levels. Note: All data is averaged over the 72 h period of PA monitoring.

Table 5.8 Exploratory physical activity variables pre- and post- neoadjuvant cancer treatment (completers: n=24)

PAL Exploratory Variables	Pre neoadjuvant CRT	Post neoadjuvant CRT	Mean Difference (95% CI)	P-value
Physical activity duration (min.day^{-1})	74 (62)	81 (69)	-3 (-39,33)	0.865[#]
Active energy expenditure (kcals.day^{-1})	392 (326)	430 (388)	-66 (-253,121)	0.473[#]
Total energy expenditure (kcals.day^{-1})	2241 (609)	2279 (630)	-37 (-322,247)	0.788[#]
MET	1.4 (0.3)	1.3 (0.2)	0.1 (-0.1,0.1)	0.531[#]
Lying down (min.day^{-1})	538 (178)	504 (126)	35 (-58,128)	0.440[#]
Sleep duration (min.day^{-1})	415 (123)	390 (110)	29 (-46,104)	0.436[#]
Sleep efficiency (%)	71 (19)	72 (16)	-0.5 (-8,7)	0.900[#]
Duration of monitor on body (min.day^{-1})	1344 (133)	1333 (127)	12 (-69,92)	0.767[#]
PAL	1.5 (0.2)	1.5 (0.3)	0 (-0.1,0.1)	0.797[#]

Data are presented in mean (SD). * P<0.05 was taken as statistically significant following paired sample t-test. [#]P-value can't be meaningfully interpreted based on the gatekeeper approach. List of abbreviations: MET -Metabolic equivalent threshold score; PAL – Physical activity levels. Note: All data is averaged over the 72 h period of PA monitoring.

5.6 Discussion

5.6.1 Summary of findings

This observational study demonstrated that neoadjuvant CRT has no statistically significant difference on $\dot{V}o_2$ at $\hat{\theta}_L$ or on daily step-count. Following neoadjuvant CRT, there was a notable difference in exploratory CPET exploratory variables HR at peak exercise, and in workload at $\hat{\theta}_L$ and at peak exercise, however further work is required to determine statistical significance.

5.6.2 Results in the context of the current literature

The use of CPET in colorectal surgery is relatively new. In 2016, a large study in the United Kingdom reported that CPET was a reliable measure to assess risk before colorectal elective surgery[48]. This study included over 700 people with colorectal cancer who underwent a CPET before major elective surgery and reported that a $\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$) value of 11.1 was associated with increased risk of post-operative complications at day-5 following surgery. However, this study excluded people scheduled for neoadjuvant CRT and surgery which limits comparison against this observational study. Prior to this, in 2014, for the first time, CPET was used to measure changes in physical fitness following neoadjuvant CRT[13] prior to rectal cancer surgery and showed a significant reduction in $\dot{V}o_2$ at $\hat{\theta}_L$ following neoadjuvant CRT: $\dot{V}o_2$ at $\hat{\theta}_L$ value of 10.7 $ml.kg^{-1}.min^{-1}$ following neoadjuvant CRT was related to post-operative complications at day-5. To my knowledge, my study is the first to report the effects of neoadjuvant CRT on physical fitness since 2014. In contrast, this study reported no statistically significant differences in $\dot{V}o_2$ at $\hat{\theta}_L$ following neoadjuvant CRT. My observational study has similar characteristics to the study reported in 2014[13]: sample size (24 vs. 25) and baseline $\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$) values 12.2 vs. 12.1. However, both studies differ in study design (multi-centre vs. single site) and mean (SD) age 61 (17) vs. 67 (9). Furthermore, 23 % of participants in my study had co-morbid disease compared to almost 50 % in the comparable study, which may also be a contributing factor for the differences in findings. However, my study would have benefited from using baseline co-morbidities score such as the Charlson Index score as it captures 19 categories of comorbidity.

The use of physical activity monitors in colorectal cancer is less documented than CPET. To my knowledge, only one study has investigated this in people with colorectal rectal. Authors reported a significant decrease in daily step-count from 5352 (3913) to 3725 (2217) following neoadjuvant CRT which is almost comparable to daily-step count in people living with chronic obstructive pulmonary disease (COPD)[164]. At baseline, participants in my study had a daily step-count of 5276 (5754) which is similar to that reported in the comparable study 5352 (3912). However, neoadjuvant CRT had a greater impact on daily-step count in the other study compared to my study: a reduction of 3725 steps compared to no change in my study. The data reported for number of physically active minutes reported in this study suggest that participants maintained their normal PAL throughout neoadjuvant CRT. Furthermore that participants were achieving the recommended physical activity guidelines for people with cancer (150 minutes per week). The MET value reported at both time points (pre- and post- neoadjuvant CRT) of 1.5 suggests that participants in this study were undertaking PAL at light intensity. Therefore, they were not meeting the ACSM recommended intensity of PAL (moderate intensity).

5.6.3 Clinical significance

- The physical fitness levels reported suggest that participants in my study are at a reduced physical fitness level of 30 % when compared against aged-matched counterparts.
- The daily step-count reported in this study suggest that participants were undertaking 30-50% less than that recommended: 7,000 – 10,000 steps/day[83].
- The metabolic equivalent threshold (MET) score reported both pre- and post-neoadjuvant CRT suggest that the intensity of PAL was light (ACSM recommend PAL at a moderate intensity). This may be clinically important: a MET score of 27 MET-hours per week in men with colorectal cancer is associated with a 50 % reduced risk of colorectal cancer-specific mortality and overall mortality compared against engaging in <3 MET-hours/week (regardless of age, stage, body mass index, year of diagnosis, tumour site or pre-diagnosis PAL). The MET score reported in the observational study equates to 10.5 MET-hours per week which is almost 60 % less than that reported for disease free survival benefits mentioned above.

- Although numbers were not matched, the non-completers appeared to have a lower physical fitness and PAL value compared to completers. This may be clinically important for future intervention trials.

5.6.4 Strengths and weaknesses

Strengths of this study include: the multi-centre study approach and a homogeneous cancer (MR-defined rectal cancer staging) ensuring a low risk of selection bias. Additionally, the CPET protocol remained constant at each hospital, using the same software which allowed for accurate interpretation at final data analysis, and the multi-disciplinary team caring for the participants were not provided with any information regarding predictive measures (e.g. CPET variables) ensuring a low risk of confounding by indication[168]. Furthermore, PAL were measured in an objective manner, assessed using validated Sensewear activity monitors.

Weaknesses include the observational nature of the study. Furthermore, although thirty-one participants were recruited to account for the increased dropout, the dropout rate was higher than predicted (>20%) therefore there is a high risk of attrition bias. The assessor was not blinded to outcome measures therefore there is a high risk of detection bias. Potential weaknesses lie in the heterogeneity of the neoadjuvant CRT regimen (due to a change in clinical cancer treatment pathway during the study period in UHS). The sample population largely consisted of males (85 %) which may be a potential bias as the bowel cancer incidence rates presented by Cancer Research UK statistics report a male to female ratio incidence rate of 12:10.

5.7 Conclusion

This observational study demonstrates that neoadjuvant CRT has no statistically significant effect on CPET-derived variable $\dot{V}O_2$ at $\hat{\theta}_L$ or PAL variable daily step-count. The number of physically active minutes and MET score reported suggest that participants were meeting the ASCM physical activity recommendations in terms of number of minutes of physical activity however not at the recommended level of intensity: they were undertaking PAL at a light intensity compared to the ACSM recommendation of moderate intensity.

Chapter 6

Changes in physical fitness and physical activity levels following a pre-operative exercise training programme in people with locally advanced rectal cancer: A randomised controlled trial

6.1 Introduction

This chapter describes a randomised controlled trial (RCT) which investigates whether a pre-operative in-hospital exercise training programme, initiated following neoadjuvant CRT and prior to surgery, can improve physical fitness and PAL compared to a usual care control group prior to elective surgery.

6. 2 Background

The systematic review in Chapter 3 highlighted the infancy of the area of exercise-oncology. Specifically, in the neoadjuvant setting, only five exercise-oncology studies (pilot) have been conducted[92, 94, 105, 132, 142]. Yet, the early data suggests that exercise training is safe and feasible, and improves measures of physical fitness. Of the five pilot studies, four studies have shown statistically significant improvements in physical fitness following hospital-based, aerobic interval exercise training (using intensities tailored to CPET), over 6[92], 12[94, 43] and 12-14 weeks[94]. In the adjuvant setting, the majority of studies reported in Chapter 3 used continuous exercise training programmes, and interestingly none of these studies reported statistically significant improvements in physical fitness. In the cardiac rehabilitation setting, aerobic interval exercise programmes have been tested against the standard continuous exercise training programme which similarly shows clinically and significant improvements in physical fitness[167]. To my knowledge, this is the first RCT to investigate the effects of a pre-operative aerobic interval exercise training compared to a usual care control group on physical fitness and PAL following neoadjuvant CRT and prior to surgery in people with locally advanced rectal cancer.

6.3 Study objective

To evaluate changes in physical fitness (measured using CPET) and daily PAL (measured using physical activity monitors) following participation in an exercise training programme compared to a usual care control group (usual care and no formal exercise training) in people with locally advanced rectal cancer prior to surgery.

6.4 Hypotheses

6.4.1 Primary hypothesis

Participation in a pre-operative in-hospital exercise training programme will result in a clinically (2.0 $ml.kg^{-1}.min^{-1}$) and statistically significant increase in oxygen uptake ($\dot{V}O_2$) at lactate threshold ($\hat{\theta}_L$) compared to a usual care control group in people with locally advanced rectal cancer.

6.4.2 Secondary hypothesis

Participation in a pre-operative in-hospital exercise training programme will result in a significant increase in daily step-count compared to a usual care control group in people with locally advanced rectal cancer.

6.4.3 Exploratory hypothesis

Participation in a pre-operative training programme will result in changes in other exploratory variables: 1) CPET variables: $\dot{V}O_2$ at Peak; ventilatory equivalents carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) at $\hat{\theta}_L$ and at peak exercise; ventilatory equivalents oxygen ($\dot{V}_E/\dot{V}O_2$) at $\hat{\theta}_L$ and at peak exercise; work rate at $\hat{\theta}_L$ and at peak exercise; forced expiratory volume over 1-sec (FEV1); forced vital volume (FVC); and 2) PAL variables: sleep duration and efficiency; lying down time; total and active energy expenditure (EE); metabolic threshold score (MET); physical activity level; duration on body.

6.4 Participants and methods

6.4.1 Study design

This study is a part of the EMPOWER trial, as described in Chapter 4, Section 4.2.

6.4.2 Participants and hospital sites

As described in Chapter 4, Section 4.2.

6.4.4 Procedures and Measurements

6.4.4.1 Procedures

All participants underwent a series of CPETs and physical activity monitoring to assess changes in physical fitness and PAL variables throughout the study period at week 0 (post-neoadjuvant CRT) and week 3, 6 and 9. Participants were randomised (1:1) to either an exercise intervention group (structured in-hospital exercise training programme) or usual care control group (no formal exercise training) on the last week of neoadjuvant CRT. Randomisation as conducted using blocked randomisation stratified for each site using an online service TENALEA system. Participants were issued with a schedule of proposed dates for research visits on the day randomisation was concealed: a structured exercise training schedule was given to the exercise intervention group.

6.4.4.2 Measurements

The participant pathway for this study is illustrated below (Figure 6.1).

6.4.4.2.1 CPET

Each CPET followed standard protocol described in Chapter 4, Section 4.3.

6.4.4.2.2 Physical activity monitoring

Physical activity monitoring followed standard protocol described in Chapter 4, Section 4.3.2.

6.4.3.2 Interventions

6.4.3.2.1 Usual care control group

The usual care control group (no formal exercise training) received routine care throughout their cancer pathway from diagnosis to surgical resection. No specific advice about exercise training was offered.

6.4.3.2.2 Exercise intervention group

Participants who were randomised to the exercise intervention group undertook a pre-operative supervised exercise training programme (hospital-based). The exercise training programme started on the first week following completion of neoadjuvant CRT. The exercise intervention group exercise trained three times per week under supervision by experienced staff at each site for 6 - 9 weeks (dependent on time

interval to surgery). The training involved aerobic interval exercise at moderate to severe intensities tailored to each individual CPET (Chapter 4, Section 4.2.4.2). The training programme was preloaded on to a chip-and-pin card which executed the interval intensities automatically on to the screen displayed on the cycle ergometer (Figure 6.2). The exercise training was conducted on a computer controlled, electromagnetically-braked, cycle ergometer (Optibike Ergoselect 200; Ergoline, GmbH, Germany). HR was continuously recorded (Polar FT7, Warwick, UK). Exercise training tolerance and attendance per session were also recorded in the case report form (CRF). The exercise training protocol is described in more detail in Chapter 4, Section 4.2.4.2.

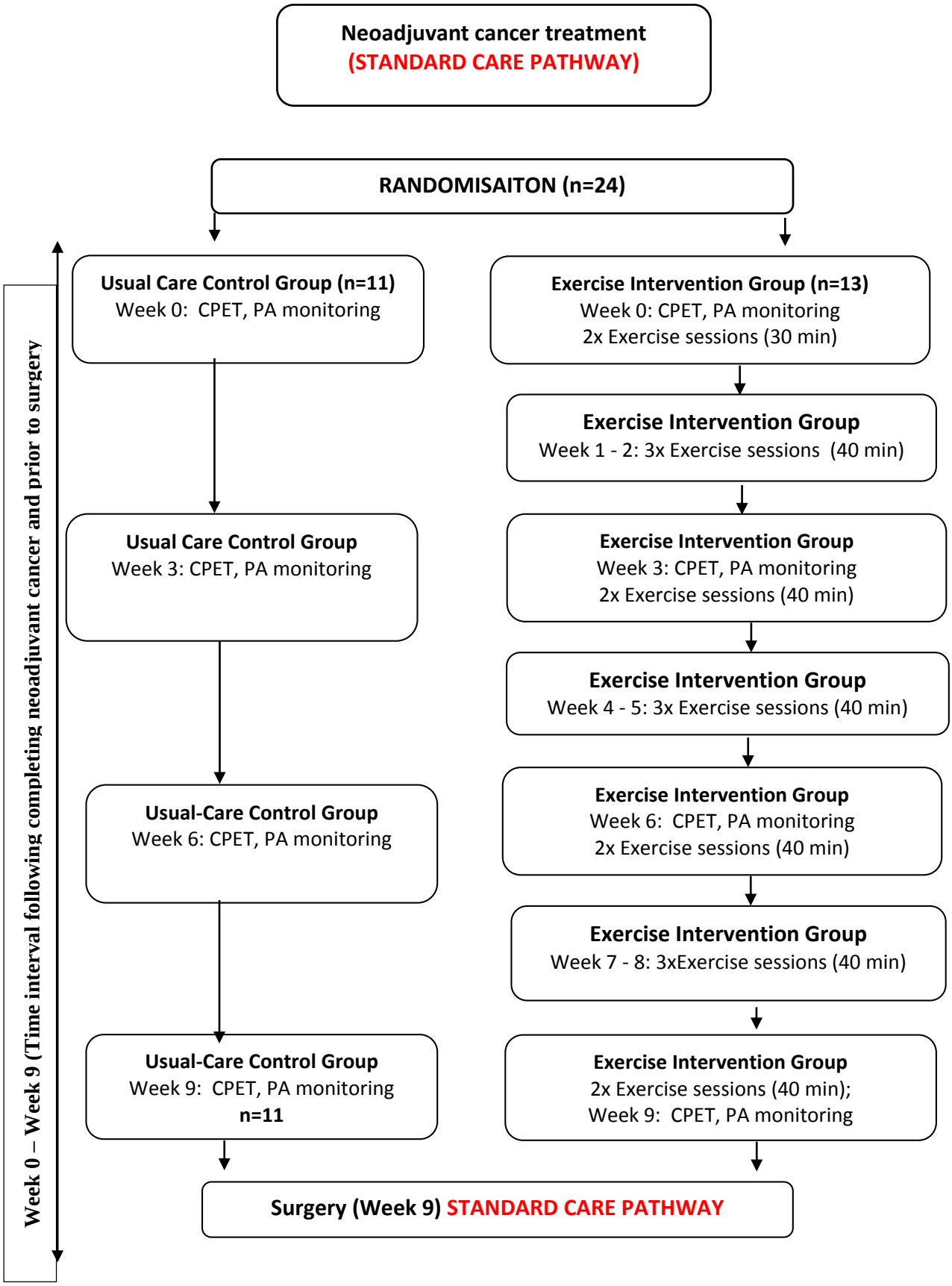


Figure 6.1 Patient pathway as part of the trial

Abbreviations: CPET – cardiopulmonary exercise test; PA monitoring – physical activity monitoring.

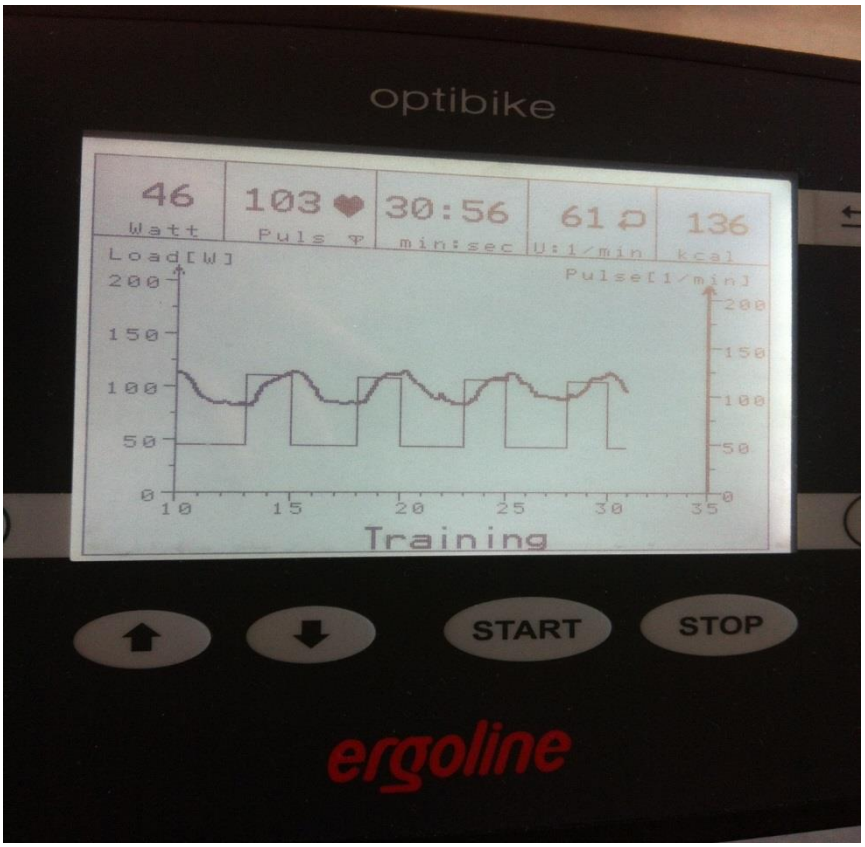


Figure 6.2 Display on exercise ergometer during exercise
Note: Blocked lines represent changes in work load: moderate (3 minutes) and severe (2 minutes) exercise intensities interspersed throughout the exercise session. Waved line represents heart rate traces throughout the exercise session.

6.4.4 Data analysis

6.4.4.1 Sample size calculation

A sample size of 28 participants who were scheduled for neoadjuvant CRT and surgery was estimated. The sample size was estimated to detect a difference between groups of 2.0 $ml \cdot kg^{-1} \cdot min^{-1}$ in $\dot{V}o_2$ at $\hat{\theta}_L$ using a two-sample t-test at the 5 % significance level with 80 % power. This is based on a standardised deviation of the change in $\dot{V}o_2$ at $\hat{\theta}_L$ values of 1.8 ml kg^{-1} min^{-1} and is inflated to allow for 20 % dropout[102]. No a priori formal power calculation was undertaken for change in daily step-count.

6.4.4.2 Statistical analyses

Continuous variables are reported as mean (SD) or median and inter-quartile range (IQR), depending on distribution, and categorical variables as frequency (%). The Shapiro-Wilk test for normality of distributions was applied. Descriptive statistics and univariate statistical comparisons of participant characteristics between the groups were undertaken: for continuous variables, a two- sample t-test when relevant

distributional assumptions were met and the Mann–Whitney U-test otherwise. The effect of the exercise intervention on physical fitness and PAL were assessed by within each group, using a two- sample t-test when relevant distributional assumptions were met and the Mann–Whitney U-test otherwise. The differences between the groups in physical and PAL at week-9 were assessed using a paired t-test when relevant distributional assumptions were met and a Wilcoxin test otherwise. Due to the evaluation of multiple endpoints, the gatekeeper approach was employed to control the false positive rate[169]. Statistical significance was accepted at $p<0.05$. All analyses were performed with the statistical software IBM SPSS Statistics Ver.22 (IBM Corporation, Armonk, NY, USA.

6.5 Results

The study flow is summarised in Chapter 5, Section 5.1 and Figure 5.1. Twenty-four participants were allocated to study arm on the last week of neoadjuvant CRT: 13 were allocated to the exercise group and 11 to the usual care control group. Baseline characteristics for both groups are shown below (Table 6.1). Of the 24 participants that completed the study, there was 100 % compliance to CPET and PAL follow-up. Note: the exercise training group took the PA monitors off the duration of each in-hospital exercise session (120 min/week x 9 weeks). Overall, there was 96 % adherence to the exercise training programme. There was one attributable adverse event to exercise training where a participant became light-headed following the exercise session (the participant was advised to attend local practitioner to review prescribed medication list and immediately resumed exercise training).

Table 6.1 Participant characteristics

	Exercise (n=13)	Control (n=11)	P value
Gender	12 (M): 1 (F)	8 (M): 3 (F)	
Height (cm)[a]	172 (7)	173 (7)	0.930
Weight (kg)[a]	78 (16)	78 (12)	0.362
BMI ($kg.m^{-2}$)[a]	26.5 (4.3)	26.1 (3.2)	0.318
Age (yr)[b]	68 (21)	55 (13)	0.324
Cancer treatment[+]			0.817
Chemotherapy + CRT[+]	3 (23)	3 (27)	
CRT[++]	10 (77)	8 (73)	
Past medical history[+*]	3 (23)	1 (9)	0.388
Diabetes	2 (15)	0 (0)	
Hypertension	2 (15)	1 (9)	
AAA	1 (8)	0 (0)	
Asthma	1 (8)	0 (0)	
Epilepsy	0 (0)	1 (9)	
Medication[+]			0.418
Yes	4 (31)	2 (18)	
No	9 (69)	9 (82)	
Smoking status[+]			0.736
Current smoker	3 (23)	1 (9)	
Ex-smoker	6 (46)	7 (64)	
Non smoker	4 (31)	3 (27)	

*P<0.05 was taken as statistically significant following independent t-test or Mann-Whitney tests dependent on distribution. [a]Values are presented as median (IQR).[b] Values are presented as Mean (SD). [+]Frequencies with percentages in parentheses, smoking status assessed as currently smoking: yes (1) vs no (0). Abbreviations: CRT – chemoradiotherapy. Note: + Cancer treatment 1 (Neoadjuvant chemotherapy and CRT group); ++ Cancer treatment 2 (Neoadjuvant CRT group). The past medical history is based on information listed on clinical notes and reported as frequencies with percentages in parentheses.

6.5.1 Outcome measures

6.5.1.1 Primary outcome

6.5.1.1.1 Oxygen uptake at lactate threshold

There were statistically significant differences in $\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$) between the groups at week-9: increased in the exercise group mean difference: -4.4 (-6.7,-2) compared to a reduction in the usual care control group 0.1 (-1.3, 1.5); p=0.021. Values for $\dot{V}o_2$ at $\hat{\theta}_L$ at week- 0 and week-9 between the groups are presented in Table 6.2. A point-by-point graph illustrating individual changes in $\dot{V}o_2$ at $\hat{\theta}_L$ for the exercise group is presented in Figure 6.3 and usual care control group in Figure 6.4. A box plot illustration of $\dot{V}o_2$ at $\hat{\theta}_L$ at week-0 and week-9 in the exercise group (n=13) is illustrated in Figure 6.5. Values for $\dot{V}o_2$ at $\hat{\theta}_L$ data measured at each time point (week 0, 3, 6 and 9) for both groups are presented in Figure 6.6 (Graphical illustration).

6.5.1.2 Secondary outcome

6.5.1.2.1 Daily step-count

There were no statistical significant differences in daily step-count between the groups at week-9. Values for daily step-count at week-0 and week-9 between the groups are presented in Table 6.3. Daily step-count measured at each time point (week 0, 3, 6 and 9) for both groups are presented in Figure 6.7.

Table 6.2 Oxygen lactate threshold at Week-0 and Week-9

Primary Outcome	Exercise (n=13)				Usual care control (n=11)				P‡
	Week 0	Week 9	Mean difference 95% CI	P┼	Week 0	Week 9	Mean difference 95% CI	P┼	
$\dot{V}o_2$ at $\hat{\theta}_L$ (ml.kg^{-1}.min^{-1})	12.3 (3.5)	16.7 (5.1)	-4.4 (-6.7,-2)	*0.002	13 (2.5)	12.9(1.6)	0.1 (-1.3,1.5)	0.890	*0.021

Values presented as mean (SD). * P<0.05 was taken as statistically significant. P┼ Paired t-test p-value for change within group from baseline to week 9; P‡ Independent t-test p-value for difference between groups at week-9.

Table 6.3 Daily step-count at Week-0 and Week-9

Secondary outcome	Exercise (n=13)			Usual care control (n=11)			P‡
	Week 0	Week 9	P┼	Week 0	Week 9	P┼	
Daily step-count (steps/day)	6204 (6308)	4246 (5578)	0.657	5640 (7962)	6424 (5408)	0.959	0.114

Values presented as median (IQR). * P<0.05 was taken as statistically significant. P┼ Wilcoxon test p-value for change within groups from baseline to Week-9; P‡ Mann-Whitney test p-value for differences between groups at week-9.

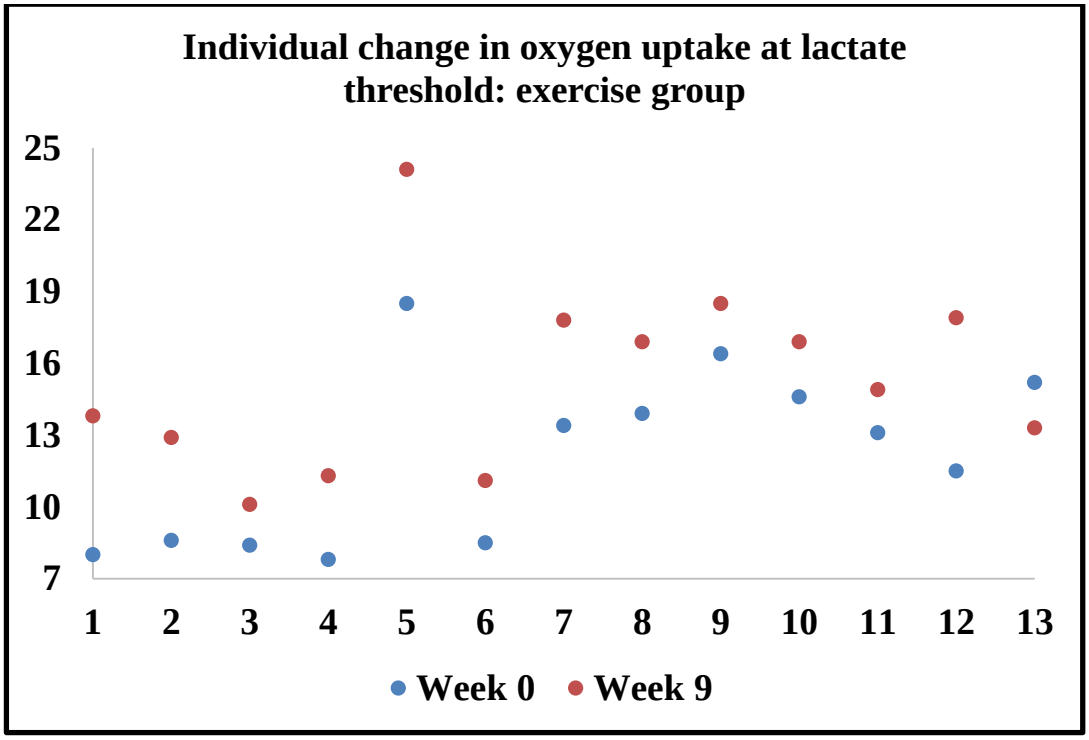


Figure 6.3 Point-by-point graph showing individual change in oxygen uptake at lactate threshold in the exercise group (n=13) between week 0 – 9.

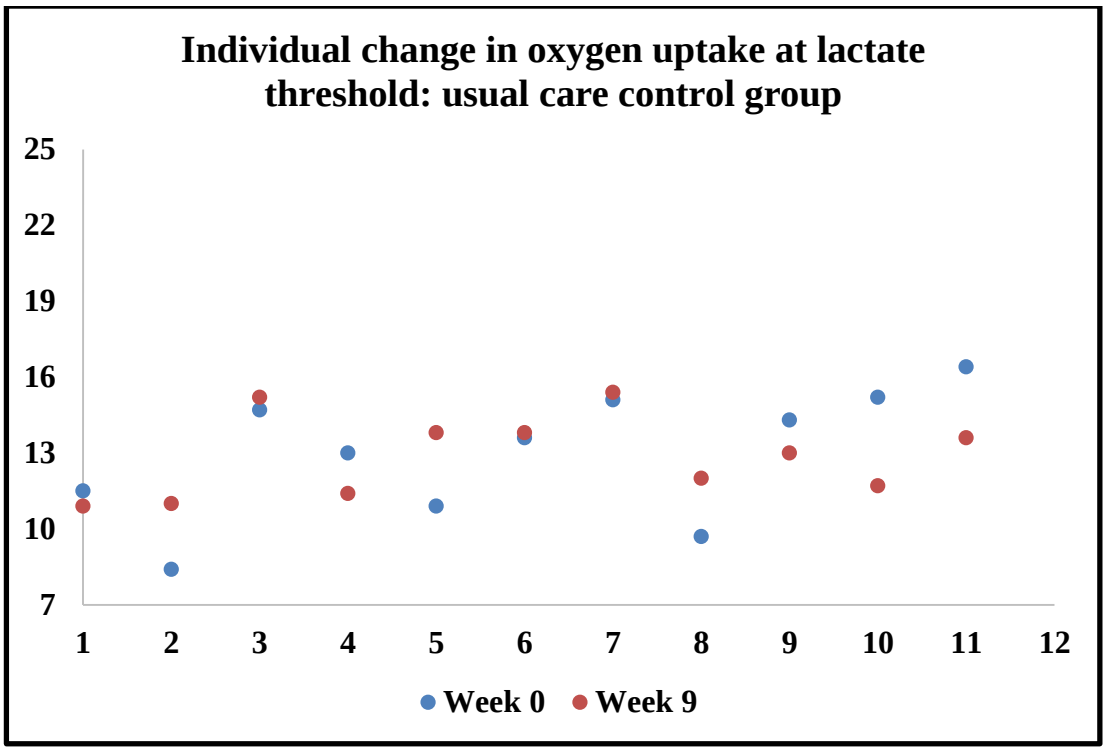


Figure 6.4 Point-by-point graph showing individual change in oxygen uptake at lactate threshold in the usual care control group (n=11) between week 0 – 9.

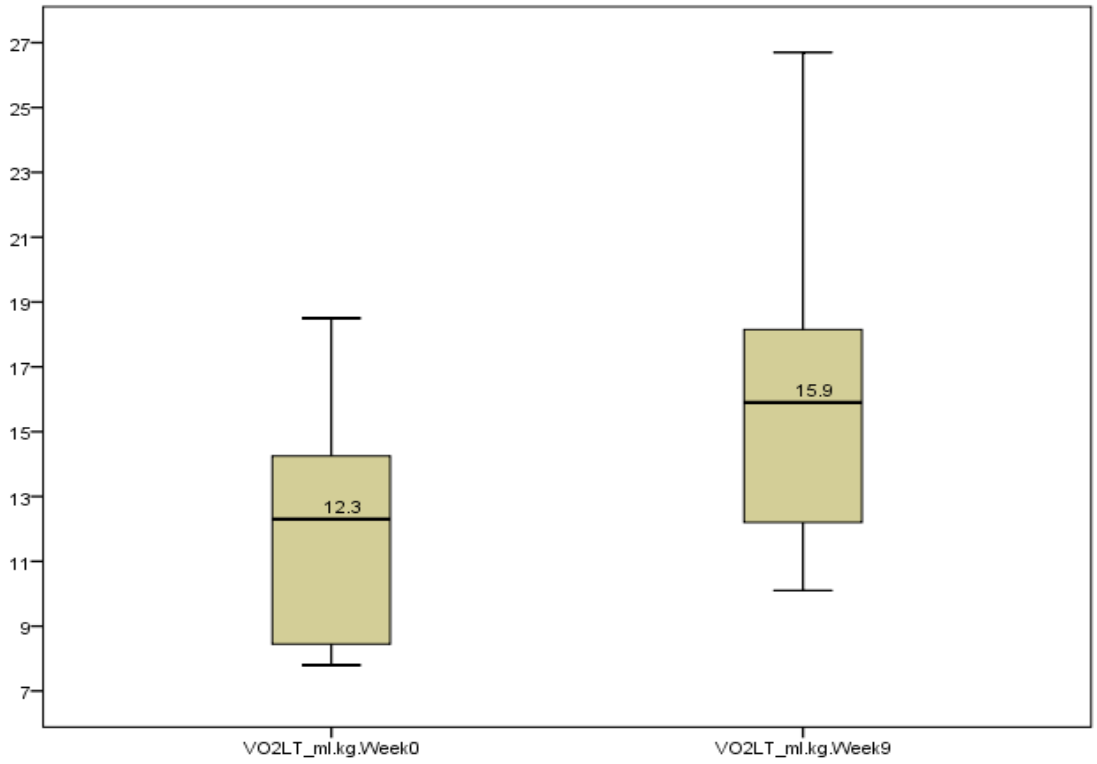


Figure 6.5 Box plot illustration of oxygen uptake at lactate threshold at week 0 and week-9 in the exercise group (n=13). Values are reported as Median (IQR). $\dot{V}o_2$ **at** $\hat{\theta}_L$ **reported is measured in ml.kg^{-1}.min^{-1}.**

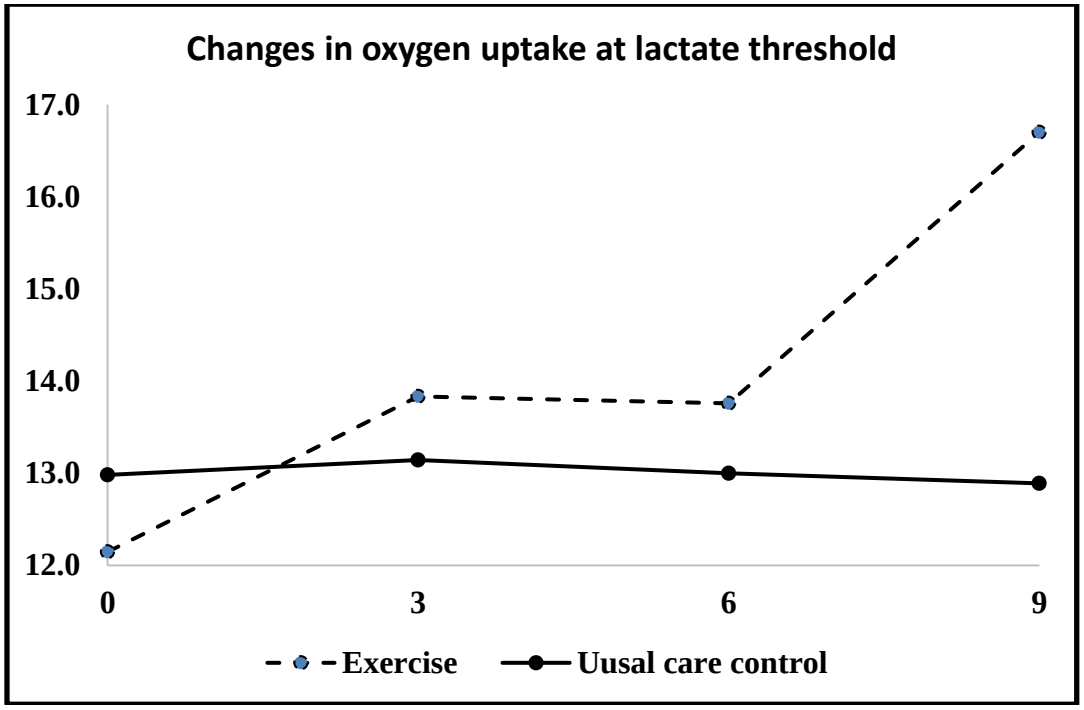


Figure 6.6 Graphical Illustration: changes in oxygen uptake at lactate threshold at week 0, 3, 6 and 9 between both groups

Y-axis represents values for $\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$). X-axis represents these values at time points: week 0, 3, 6 and 9. Note: the exercise group (dashed line) and the usual care control group (solid line).

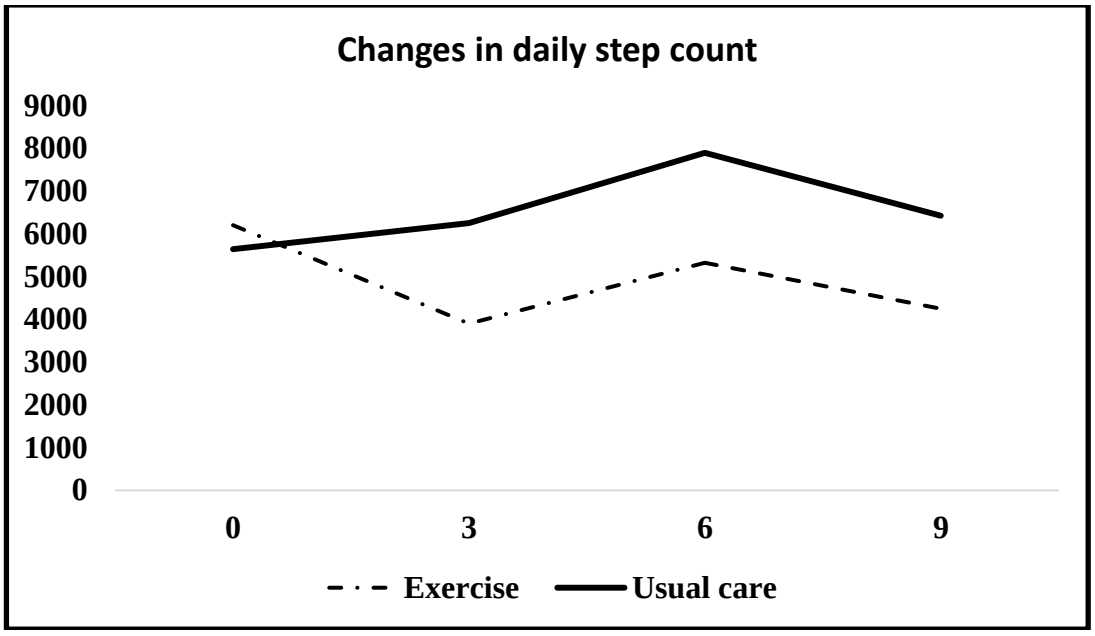


Figure 6.7 Graphical Illustration: changes in daily step-count at week 0, 3, 6 and 9 between both groups

Y-axis represents number of daily steps. X-axis represents these values at time points: week 0, 3, 6 and 9. Note: the exercise group (dashed line) and the usual care control group (solid line).

6.5.1.3 Exploratory outcomes

6.5.1.3.1 CPET variables

Exploratory CPET variable $\dot{V}o_2$ Peak ($ml.kg^{-1}.min^{-1}$) increased in both groups at week 9: -4.8 (-7, -2.6) in the exercise group and -7.6 (-14,1.2) in the usual care control group. Exploratory CPET variables for both groups measured at week-0 and week-9 are illustrated in Table 6.4. Exploratory CPET variables measured at each time point (week 0, 3, 6 and 9) for both groups are presented in Appendix 7 (Supplementary Table).

6.5.1.3.2 Physical activity variables

Exploratory PAL variables for both groups measured at week-0 and week-9 are illustrated in Table 6.5. Exploratory PAL variables measured at each time point (week 0, 3, 6 and 9) are presented in Appendix 9 (Supplementary Table).

Table 6.4 CPET exploratory outcomes between the groups from week 0-9

	Exercise (n=13)				Usual care control (n=11)				$P^{\ddagger}$
CPET Exploratory Variable	**Week 0**	**Week 9**	**Mean difference**	$P^{\dagger}$	**Week 0**	**Week 9**	**Mean difference**	$P^{\dagger}$	
$\dot{V}$ o_2 Peak ($ml.kg^{-1}.min^{-1}$)	23.1 (7.7)	28.2 (9.1)	-4.8 (-7, -2.6)	*****0.001	17 (9.7)	24.3 (2.9)	-7.6 (-14,-1.2)	*****0.025	*****0.006[#]
$\dot{V}_E/\dot{V}\ o_2$ at $\hat{\theta}_L$	25.8 (2.8)	27.2 (3.6)	-1.3 (-3.7,1)	0.226	26.7 (3)	26.7 (2.7)	0.04 (-1.6,1.7)	0.952	0.196[#]
$\dot{V}_E/\dot{V}\ o_2$ at Peak	39 (5.7)	39.8 (3.8)	-0.8 (-3.4,1.8)	0.497	42.2(8.9)	38.4 (4.6)	3.7 (-1.8,9.2)	0.157	0.920[#]
$\dot{V}_E/\dot{V}\ CO_2$ at $\hat{\theta}_L$	30.6 (4.4)	28 (9.1)	2.7 (-2.4,7.7)	0.265	31 (5)	27.1 (10)	4 (-3.4,11.3)	0.250	0.862[#]
$\dot{V}_E/\dot{V}\ CO_2$ at Peak	30.1 (4.4)	32.2 (9.8)	-1.5 (-7.5,4.4)	0.564	31.8(4.4)	27.1 (10)	1.9 (-5.3,9.1)	0.553	0.987[#]
Baseline HR $beats.min^{-1}$)	75 (9)	73 (13)	1 (-4,6)	0.601	84 (12)	76 (12)	8.6 (-1.9,19)	0.097	0.641[#]
HR at $\hat{\theta}_L$ ($beats.min^{-1}$)	96 (13)	102 (9)	-5 (-11,1)	0.079	113 (22)	96 (17)	16 (-8,41)	0.163	0.220[#]
HR at Peak ($beats.min^{-1}$)	133 (16)	138 (17)	-5 (-10,1)	0.070	135 (32)	144 (20)	-9 (-22,5)	0.179	0.206[#]
O2 Pulse at $\hat{\theta}_L$ ($ml.beat^{-1}$)	9.7 (3.7)	12.7 (4.9)	-3.1 (-4.5,-1.9)	*****0.000	8.6 (1.6)	10.6 (1.9)	-2 (-3.7,-0.4)	*****0.021	0.182[#]
O2 Pulse Peak($ml.beat^{-1}$)	12.8 (4.5)	15.4 (5.4)	-2.7 (-3.9,-1.4)	*****0.001	10.5(1.9)	13.3 (2.5)	-2.8 (-4.4,-1.3)	*****0.003	0.249[#]
Work load at $\hat{\theta}_L$ (W)	66 (39)	102 (50)	-35 (-54, -16)	*****0.002	70 (23)	81 (16)	-11 (-27,5)	0.150	0.203[#]
Work load at Peak (W)	154 (59)	178 (76)	-25 (-40,-10)	*****0.004	139 (44)	167 (35)	-29 (-56,-3)	0.035	0.638[#]

Values presented as mean (SD). * P<0.05 was taken as statistically significant. $P^{\dagger}$ Paired t-test p-value for change within group from baseline to week 9; $P^{\ddagger}$ Independent t-test p-value for difference between groups at week-9. [#]P-value can't be meaningfully interpreted based on the gatekeeper approach.

List of abbreviations: $\dot{V}\ o_2$ at $\hat{\theta}_L$, Oxygen uptake at estimated lactate threshold; $\dot{V}\ o_2$ at Peak, Oxygen uptake at peak exercise; O_2 pulse at $\hat{\theta}_L$, Oxygen pulse at estimated lactate threshold; O_2 pulse at Peak, Oxygen pulse at peak exercise; $\dot{V}_E/\dot{V}\ co_2$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at estimated lactate threshold; $\dot{V}_E/\dot{V}\ co_2$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at peak exercise; Work rate at $\hat{\theta}_L$, Work rate at estimated lactate threshold; Work rate at Peak, Work rate at peak exercise.

Table 6.5 Changes in physical activity variables between the groups from week 0 - 9

	Exercise (n=13)			Usual care control (n=11)			P‡
PAL Exploratory Variable	**Week 0**	**Week 9**	**P†**	**Week 0**	**Week 9**	**P†**	
Physical activity duration (min.day^{-1})	70 (86)	78 (60)	0.530	52 (90)	78 (65)	0.799	0.620[#]
Active energy expenditure (kcals.day^{-1})	394 (327)	370 (753)	0.182	240 (668)	359 (332)	0.646	0.468[#]
Total energy expenditure (kcals.day^{-1})	2152 (951)	2369 (464)	0.494	2385 (531)	3654 (3383)	0.799	0.756[#]
PAL	1.5 (0.3)	1.4 (0.3)	0.475	1.4 (0.3)	1.5 (0.1)	0.765	0.597[#]
MET	1.3 (0.2)	1.3 (0.3)	0.722	1.3 (0.2)	1.4 (0.2)	0.385	0.247[#]
Lying down (min.day^{-1})	476 (71)	493 (161)	0.657	493 (123)	518 (184)	0.721	0.429[#]
Sleep duration (min.day^{-1})	342 (77)	400 (112)	0.091	383 (98)	361 (172)	0.508	0.644[#]
Sleep efficiency	70 (20)	80 (14)	0.657	75 (20)	72 (21)	0.575	0.710[#]
Duration on body (min.day^{-1})	1403 (40)	1397 (85)	0.533	1392 (100)	1402 (177)	0.959	0.947[#]

Values presented as median (IQR). * P<0.05 was taken as statistically significant. P† Wilcoxon test p-value for change within groups from baseline to Week-9; P‡ Mann-Whitney test p-value for differences between groups at week-9. [#]P-value can't be meaningfully interpreted based on the gatekeeper approach.
List of abbreviations: MET, metabolic threshold; PAL – physical activity levels.

6.6 Discussion

6.6.1 Summary of findings

This is the first RCT to investigate the effects of a pre-operative exercise training programme (hospital-based) following neoadjuvant CRT prior to surgery in people with locally advanced rectal cancer. This RCT demonstrates that the pre-operative exercise training programme resulted in a clinical and statistically significant improvement on physical fitness as measured using CPET-derived variable $\dot{V}O_2$ at $\hat{\theta}_L$ compared to the usual care control group. Participation in the exercise programme showed no statistically significant effect on physical activity levels as measured using physical activity monitoring variable daily step-count compared to the usual care control group. There was a notable difference between the groups in exploratory CPET variable $\dot{V}O_2$ peak however further work is required to determine the statistical difference. Overall there was a 96 % adherence rate to the exercise programme.

6.6.2 Results in the context of the current literature

To date, seven studies have reported the effects of pre-operative exercise training in colorectal cancer since 2009[87-92, 94]. Of these, two pilot studies have shown significant increases in physical fitness in people with colorectal cancer undergoing multimodal treatment[92,94]. Three other similar exercise-oncology studies (pilot) have been conducted in breast cancer: two of which incorporated hospital-based aerobic interval exercise training programmes[92,132,142] and one community-based programme, in the form of a boot camp[105]. Preliminary data by my working group (Fit-4-Surgery) had confirmed the feasibility of the exercise training programme (over 6 weeks) in people with locally advanced rectal cancer in a non-randomised contemporary controlled pilot study which produced encouraging pilot data[94]. My study shows that pre-operative exercise training increases important physical fitness variables and builds on the current evidence-base in colorectal cancer.

To date, only one pilot study in colorectal cancer in the neoadjuvant setting has investigated PAL[92] in people with colorectal cancer which reported a statistically significant increase in daily step-count in the exercise group and a reduction in the

usual care control group. This RCT showed that there were no statistically significant differences in daily step-count between the exercise group and the usual care control group contrary to findings from the aforementioned study[92]. Participation in an exercise training programme during cancer treatment in the adjuvant setting (following surgery) has been linked to an overall improvement in PAL outside the programme[71, 73, 129]. This RCT showed the opposite: although findings were not statistically significant, the usual care control group had a tendency towards an increased daily step-count, PA duration and active EE between week-0 and week-9 whilst the exercise group had a tendency towards a reduction in daily step-count and active EE. Interestingly, similarly to findings in Chapter 5, the MET score reported at week-9 suggests that participants in this study continued undertaking PAL at a light intensity in the time window between completing neoadjuvant CRT prior to surgery.

6.6.3 Clinical implications

- Participation in the exercise training programme resulted in a clinical and significant improvement in physical fitness. An increase in $\dot{V}o_2$ at $\hat{\theta}_L$ of 2.0 $ml \cdot kg^{-1} \cdot min^{-1}$ is generally accepted as clinically significant[102].
- Improvements in physical fitness were achieved at week-3 and week-6 of the exercise programme. This may be important for the application of such an exercise training programme for other surgical groups who have a shorter time window between diagnosis and surgery.
- The exercise training programme had a more than double clinically-significant effect on $\dot{V}o_2$ at $\hat{\theta}_L$ suggesting participants in this study were responders to this particular aerobic interval exercise training programme delivered on a cycle ergometer. The exercise training programme resulted in a wide inter-individual response to changes in $\dot{V}o_2$ at $\hat{\theta}_L$. However, little is known about threshold values between responders and non-responders to exercise training. Moreover, there is no consensus whether to define a responder by the presence of clinically relevant changes or of measurable change[172]. This may be clinically important for choosing specific exercise training programmes for patients.
- The low MET score (1.3-1.5) reported for both groups at week-9 demonstrates that participants were undertaking daily PAL at a light intensity throughout the

cancer care journey and suggests that PAL at a light intensity does not influence positive effects on physical fitness levels.

6.6.4 Strengths and weaknesses

Strengths of this study include: cancer group were homogeneous (MR-defined rectal cancer staging) ensuring a low risk of selection bias; multi-centre randomised controlled study design; and randomisation (1:1) was conducted using TENALEA system ensuring a low risk of selection bias. The CPET protocol remained constant for each CPET at each hospital using the same software which allowed for accurate interpretation at final data analysis and clearly defined exercise intervention and exercise training intensities were derived and reported by two assessors (myself and MW). Physical activity was averaged over a 72-h period, measured in an objective manner using validated SenseWear activity monitors. Furthermore, participants in the exercise group did not wear the physical activity monitors during exercise sessions allowing for accurate comparisons between the groups. Additionally, the MDT caring for the participants were not provided with any information regarding predictive measures (e.g. CPET variables) ensuring a low risk of confounding by indication[168]. Other strengths include the high adherence rates to exercise training. Additionally, the high compliance rate to follow-up assessments ensuring a low risk of attrition bias and all outcome measures were reported ensuring a low risk of reporting bias.

Weaknesses of the study include a high risk of attrition bias. Although efforts were made to over-recruit to account for the greater than estimated dropout rate (> 20%) (31 participants were recruited, 28 was the estimated power sample calculation), only 24 participants completed the study. The nature of the underpowered study increases the false negative rate. Weaknesses include a high risk of performance and detection bias: both participants and personnel delivering the intervention were not blinded, and additionally the assessor was not blinded to outcome measures (efforts were made to code each individual test in an attempt to reduce bias). Furthermore, participants had regular contact with the MDT at outpatient visits therefore it is unlikely that the MDT were blinded from intervention allocation. The sample population largely consisted of males: 92 % in the exercise group and 73 % in the usual care control group which

may be a potential bias (male to female ratio incidence rate of rectal cancer in the United Kingdom is 12:10).

6.7 Conclusion

Pre-operative aerobic interval exercise training (hospital-based) incorporating moderate-severe intensities resulted in a clinical and significant increase in $\dot{V}O_2$ at $\hat{\theta}_L$ at week-9 compared to a usual care control group (no formal exercise training). However, there were no statistically significant differences between the groups in daily step-count. The MET score reported suggests that both groups undertook PAL at a light intensity throughout the study period.

Chapter 7

Discussion

7.1 Introduction

This thesis has described in detail changes in physical fitness and physical activity levels (PAL) following neoadjuvant CRT and a pre-operative exercise training programme in people with locally advanced rectal cancer prior to surgery. First, all the existing literature on exercise training interventions in people with cancer undergoing multimodal treatment including surgery were explored. An observational study was conducted to investigate the effect of neoadjuvant CRT on oxygen uptake at lactate threshold ($\dot{V}o_2$ at $\hat{\theta}_L$) and daily step-count, and on other exploratory cardiopulmonary exercise test (CPET) and physical activity levels (PAL) variables. Following this, a randomised controlled trial (RCT) was conducted to investigate the effect of a pre-operative exercise training programme compared to a usual care control group (usual care and no formal exercise training) on $\dot{V}o_2$ at $\hat{\theta}_L$ and daily step-count, and other exploratory CPET and PAL variables. It was hypothesised that neoadjuvant CRT would significantly reduce $\dot{V}o_2$ at $\hat{\theta}_L$ and daily step-count, and that a pre-operative an in-hospital exercise training programme compared with a usual care control group would result in a significant increase in both variables. The experimental work was based around well-validated objective measures such as CPET (physical fitness) and physical activity monitors. CPET was also used to inform the exercise training programme.

7.2 Principal findings

In Chapter 3, a systematic review was conducted to synthesise the literature on exercise training interventions in people with cancer undergoing multimodal treatment including surgery. This review further supports findings from similar systematic reviews[120-122], all of which agree that exercise training has beneficial effects on physical fitness, domains of health-related quality of life (HRQoL) and other clinical measures. Furthermore, all are in agreement that there are few randomised controlled trials (RCT) in this area, limiting our understanding of the most effective exercise training programme[113,120-121 ,123-124]. Due to the heterogeneity of studies included in the systematic review, varying in cancer type, treatment and surgery, exercise characteristics and outcome measure, inter-study comparison was difficult. This

highlights a more focused approach in future studies to include similar outcome measures. Furthermore, blinding of outcome assessors is important to accurately interpret the effect of exercise training on such outcomes. This systematic review also identified that there is a requirement for adequately powered randomised controlled trials (RCTs) to investigate the effects of exercise training on post-operative outcome in this context. The included studies demonstrate that the countries currently leading this area of research are Canada and United States with seven studies, followed by Germany and the United Kingdom with two, whilst other countries such as Norway, Thailand, Australia, Poland, Spain and Denmark have one study. Perhaps the next step is to join forces and establish an international collaboration with neighbouring countries to advance this area and answer this research question. In Chapter 5, the observational study reported that neoadjuvant CRT had no statistically significant effect on physical fitness (CPET-derived variable $\dot{V}O_2$ at $\hat{\theta}_L$) and PAL (daily step-count) contrary to findings from a similar study in people with rectal cancer[13]. Interestingly, this study did show however that when comparing values for $\dot{V}O_2$ at $\hat{\theta}_L$ reported in the observational study against aged-matched healthy colorectal cancer counterparts in the United Kingdom, participants in my study had a reduced physical fitness level of 32 %[173]. Furthermore, despite maintaining a constant PAL throughout neoadjuvant cancer treatment, the metabolic equivalent threshold (MET) score reported suggest that the intensity of PAL was light (ACSM recommend PAL at a moderate intensity). This may be clinically important: a MET score of 27 MET-hours per week in men with colorectal cancer is associated with a 50 % reduced risk of colorectal cancer-specific mortality and overall mortality compared against engaging in <3 MET-hours/week (regardless of age, stage, body mass index, year of diagnosis, tumour site or pre-diagnosis PAL). The MET score reported in the observational study equates to 10.5 MET-hours per week which is almost 60 % less than that reported for disease free survival benefits mentioned above. Additionally, the daily step-count reported in the observational study suggest that participants were undertaking 30-50% less than that recommended: 7,000 – 10,000 steps/day[83]. As there was a change in clinical practice mid-point of the trial (i.e. in UHS participants were treated with two types of neoadjuvant cancer treatment regimens) comparison between such regimens and its effect on physical fitness and PAL in an adequately powered trial is required.

In Chapter 6, a RCT was reported which investigated the effects of a pre-operative exercise training programme compared to usual care control group on physical fitness and PAL prior to surgery. To my knowledge, this RCT is the first exercise clinical trial in this context to report such increases in $\dot{V}O_2$ at $\hat{\theta}_L$ following exercise training (a synthesis of relative literature is presented in Chapter 2, Section 2.6.1 and Chapter 3, Table 3.1 and Table 3.2). Findings reported are in line with studies presented in Chapter 3 and further demonstrate that in-hospital aerobic interval exercise training programmes (cycle ergometer), significantly improves $\dot{V}O_2$ at $\hat{\theta}_L$ in the pre-operative setting[92,132, 142] . The values for $\dot{V}O_2$ at $\hat{\theta}_L$ at week-9 demonstrate an increase of 32 % in the exercise group but the usual care control group remained at a reduced level of 28 % when compared against healthy aged-matched colorectal counterparts in the United Kingdom[173]. Interestingly, the usual care control group showed a tendency towards improved step-count, PA duration and active EE compared to a tendency towards reduction in the exercise group. This may suggest that the usual care control group became more active throughout the duration of the study period whilst the exercise training programme may have replaced normal PAL in the exercise group. Increasing PAL in usual care control groups has been previously documented in almost 30 % of interventional studies[172]. The most common factors attributed to improvements in PAL include: number on interim assessments; mode of measurement administrations; exclusion of participants meeting physical activity guidelines at baseline; pre-existing health status; and mean baseline body mass index[172]. Possible factors which may have influenced findings in this RCT include: duration of the trial (ranged between 3.5 – 6.5 months); number of assessments (5 time points); and measurement (CPET/physical activity monitor). Other studies in exercise-oncology trials have reported that factors such as young age and positive attitudes positively influence exercise behaviour[138]. Additionally others such as: demographics; medical; behavioural; fitness; psychosocial; and motivational variables have been associated with positive exercise behaviour in people with breast cancer in the adjuvant setting[138]. To date, only one study in colorectal cancer in the neoadjuvant setting have explored factors towards exercise behaviour such as motivation, perceived benefits, harms and barriers to exercise in this context[95]. This study illustrated that people with colorectal cancer who exercised during neoadjuvant CRT reported it to be more enjoyable and less difficult than anticipated.

Thirty-one participants were recruited to this study which was a recruitment uptake rate of 50 % when compared against the number of eligible participants. Although there is limited literature published in this area to make comparisons against, two previous studies in people with rectal[92] and breast cancer[105], both similar to my study (recruited participants at diagnosis who were scheduled for multimodal treatment) reported uptake rates of 50 % and 73 %, respectively. This poses the question of whether people who participate in such studies are more motivated. Although the data were not matched, the non-completers compared to the completers (Chapter 5) appeared to have a lower physical fitness and PAL. Additional data collection including motivational levels and perceived attitudes to exercise in both groups would have contributed to this study. Furthermore, it would have been useful if previous exercise patterns of recruited participants were known. Recruitment may have influenced changes in PAL and furthermore study participation may have been a stimulus for exercise behaviour change, specifically in the usual care control group. However, these data were not available for analysis. Although not related to my thesis, the EMPOWER trial is exploring people attitudes to exercise through semi-structured interviews at week 0 and week 9, which will give us further insight. These data will be reported in late 2017.

Although the exercise training programme had a positive effect on physical fitness its application may not be generalizable: this study was conducted in a hospital setting and required skilled staff to conduct CPET's, of which, were conducted every 3 weeks. Furthermore, the exercise training programme was pre-recorded onto a chip and pin card which requires a specialised cycle ergometer to deliver the exercise programme. The uptake rate for this study was 50 % and the sample population largely consisted of males which further questions its generalizability.

7.3 Clinical implications

1) Health care

People with colorectal cancer remain a high risk group with adverse outcomes after major cancer surgery. This emphasises the importance of adequate pre-operative

assessment to evaluate the risk relating to surgery and optimise patients pre-operatively. CPET remains gold standard as an objective measure of physical fitness pre-operatively. However, due to cost and expertise required to implement CPET in clinic, physical activity monitors in this setting are worthy of attention. Physical activity monitors may play a role at the initial out-patient appointment to allow the oncological/surgical consultant to: measure baseline PAL; track changes in PAL throughout the cancer care journey; and inform patient selection for a formal CPET in addition to current pre-operative assessment scores.

Improvements in physical fitness were achieved at week-3 and week-6 of the exercise programme. This may be important for the application of such an exercise training programme for other surgical groups who have a shorter time window between diagnosis and surgery. Improved physical fitness levels may be related to a reduction in morbidity rates. Further development of formal exercise training programmes that may be generalisable across different cancer groups is required. Furthermore, the cost of delivering such programmes should be weighed up against the cost of hospital length of stay.

2) Patients

Physical fitness levels following a 9-week exercise training programme resulted in a 32 % increase in physical fitness levels which puts the exercise training group at a physical fitness level comparable to aged-matched counterparts compared to a 28 % reduced level in the usual care control group.

Alteration in clinical care pathways by the introduction of exercise testing combined with a formal exercise training programme/physical activity advice depending on patients prior to major surgery may allow for effective patient risk assessment and risk mitigation prior to surgery, thereby improving precision of risk estimation and guiding choice of care pathway.

The high adherence rates suggest patients are willing to participate in such interventions. Fitter patients may lead to a healthier society and improved health outcomes. Modifying health behaviours in people with newly diagnosed cancer may restore physical fitness levels.

7.4 Conclusion

Of the 31 participants recruited, 24 completed the observational study (five dropped out and two were deemed palliative). Following this, the same 24 participants completed the RCT, of which there was 100 % compliance to CPET and PAL follow-up, and 96 % adherence to exercise training. Findings from the observational study showed no statistically significant differences in physical fitness and PAL variables following neoadjuvant CRT. Findings from the RCT showed that a pre-operative in-hospital aerobic interval exercise training incorporating moderate-severe intensities resulted in a clinical and statistically significant increase in $\dot{V}O_2$ at $\hat{\theta}_L$ at week-9 compared to a usual care control group (no formal exercise training) but no statistically significant differences between the groups at week-9 were reported for daily step-count.

Chapter 8

Future work

8.1 Future work

It has been recently reported by a panel of expert consultant colorectal surgeons that pre-operative exercise training should be part of a pre-operative care package[174]. This is encouraging however much work is required in order to design the most effective programme. This thesis adds to the existing evidence-base in the area of exercise-oncology but has identified a number of areas that require further investigations.

My thesis reported that an in-hospital exercise training programme was reported to have a clinical and statistically significant increase on physical fitness. Future work is required to address the following questions.

Exercise training intervention questions include:

1) 'Dose-response': what is the optimal frequency, intensity, time and type of an exercise training programme?
2) The exercise training programme for my study was pre-recorded onto a chip and pin card which requires a specialised cycle ergometer. Future work should address how to prescribe exercise intensities using a less specialised and low cost method. Exercise studies reported in Chapter 2 and 3 mainly used the BORG score to inform exercise training prescription, of which none reported improvements in physical fitness. There is a requirement for other low cost methods to be developed and validated. Perhaps using a combination of BORG and heart for example may be more effective.
3) Does combining aerobic and resistance exercise programmes improve the response? Does combining such programmes elicit greater benefits?
4) Is a home-based/community-based exercise training intervention as effective as supervised training in-hospital? Although home programmes may be cheaper and more convenient for the patient, to date the evidence suggests that they may not be as effective. Furthermore, can technology be used to provide an element of supervision within a home-based exercise training programme?
5) Can CPET be validated against a simpler and less expensive field based test? Can the exercise training programme be validated against a simpler and less expensive measure such as heart rate to prescribe the exercise training? This would perhaps allow access to this exercise programme without the additional cost and expertise

required for conducting CPETs. Can we establish an exercise programme that requires low technology in a community-based setting?

6) Can responders and non-responders to exercise training programmes be identified and can this be used to tailor exercise prescription to the individual?
7) Does phasing out exercise training programmes from predominantly supervised to non-supervised work in terms of effectiveness on clinical outcomes and adherence?

<u>PAL questions include:</u>

1) Does participation in an exercise programme replace normal PAL patterns?
2) Does participating in an exercise programme throughout the cancer care journey have a long lasting effect on tumour recurrence?
3) Does participation in an exercise interventional study change behaviour to exercise and daily PAL?
4) Is there a role for triaging people with cancer to selected exercise training programmes: supervised (for less motivated/less active people); unsupervised (for motivated/previously active patient); and home-based/exercise advice (for active patient).
5) What MET score is required to influence changes in physical fitness?

<u>Other questions include:</u>

1) Does exercise training effect cancer treatment efficacy?
2) Is there a relationship between responders to exercise training and cancer treatment efficacy?
3) Does exercise training have an effect on clinically important outcome measures such as health behaviour, disease-free survival and overall survival in different cancer cohorts?

Although a supervised an in-hospital exercise training programme was shown to improve important physical fitness CPET-derived variables, further work is required to investigate the health economics of delivering exercise programmes in different settings. These costs need to be measured up against post-operative complications (short-term costs as it prolongs length of stay in hospital). Additionally, future work is required to include patient activation which is a uni-dimensional scale covering 4 stages of activation: believing the patient role is important, having the confidence and knowledge necessary to take action, taking action to maintain and improve health;

staying the course even under stress[175]. Finally future work in the pre-operative setting is required to design effective prehabilitation programmes to include pre-operative exercise training programmes, nutrition, smoking and alcohol cessation, and psychological support[174].

8.2 Ongoing work

Encouragingly, the EMPOWER trial has informed other exercise-oncology trials. I am member of the trial design and steering management team as part of the Fit-4-Surgery group at UHS where we are currently investigating the effects of exercise training in people with advanced lung cancer (The EMBRACE trial) and upper gastrointestinal cancer (The ENCOURAGE trial). The EMBRACE trial is investigating the effects of exercise training before and during carboplatin based chemotherapy. This exercise training programme incorporates three exercise training components: component one includes in-hospital exercise training for week-0 to week-3 (using the aerobic interval exercise training programme as described in this study); component two includes phasing in-hospital exercise training to home between week-4 to week-6; and component three includes only home-based exercise from week-7 to week-12 (using a personal home-based programme). Although data have not yet been published, the EMBRACE trial currently shows a 15-20 % increase in physical fitness after 3 weeks of exercise training (two exercise sessions for 40 minutes per week). The ENCOURAGE trial is a pilot study investigating the effects of exercise training on physical fitness and cellular energetics before and during neoadjuvant chemotherapy or chemoradiotherapy in people with resectable oesophagogastric cancer. Together, the EMPOWER, EMBRACE and ENCOURAGE RCTs will investigate the effects of exercise training in both curative (upper and lower gastrointestinal) and palliative (NSCLC) cancer cohorts. Data from these trials may inform more generalisable exercise training programmes for other oncological cohorts.

8.3 My current programme of work

Following completing my thesis in 2016, I relocated to MedEx, Dublin City University, Ireland. MedEx is a community-based medically supervised exercise

programme for people with chronic illnesses. My main aim was to address one of my proposed future work investigations outlined above: Is a community-based exercise training intervention as effective as a hospital-based exercise training programme? I therefore developed The Power Through Surgery Programme (start date: May 2016) in collaboration with the Mater Misericordiae University Hospital, for people with colorectal, prostate and lung cancer as part of a feasibility study. This exercise training programme is unique to Ireland as: (1) it is community-based; (2) it is medically supervised; (3) targets physical fitness at four important time points: pre-cancer treatment, during cancer treatment, time interval between cancer treatment and surgery and following surgery when deemed clinically fit; and (4) it combines pre- and post-operative patients within the programme. The exercise training includes a combination of aerobic (interval and high intensity) and resistance exercise. The preliminary findings are encouraging: 20 % increase in physical fitness (CPET-derived variables) and strength following a 3-4 week programme (the most common time interval between referral and surgery date).

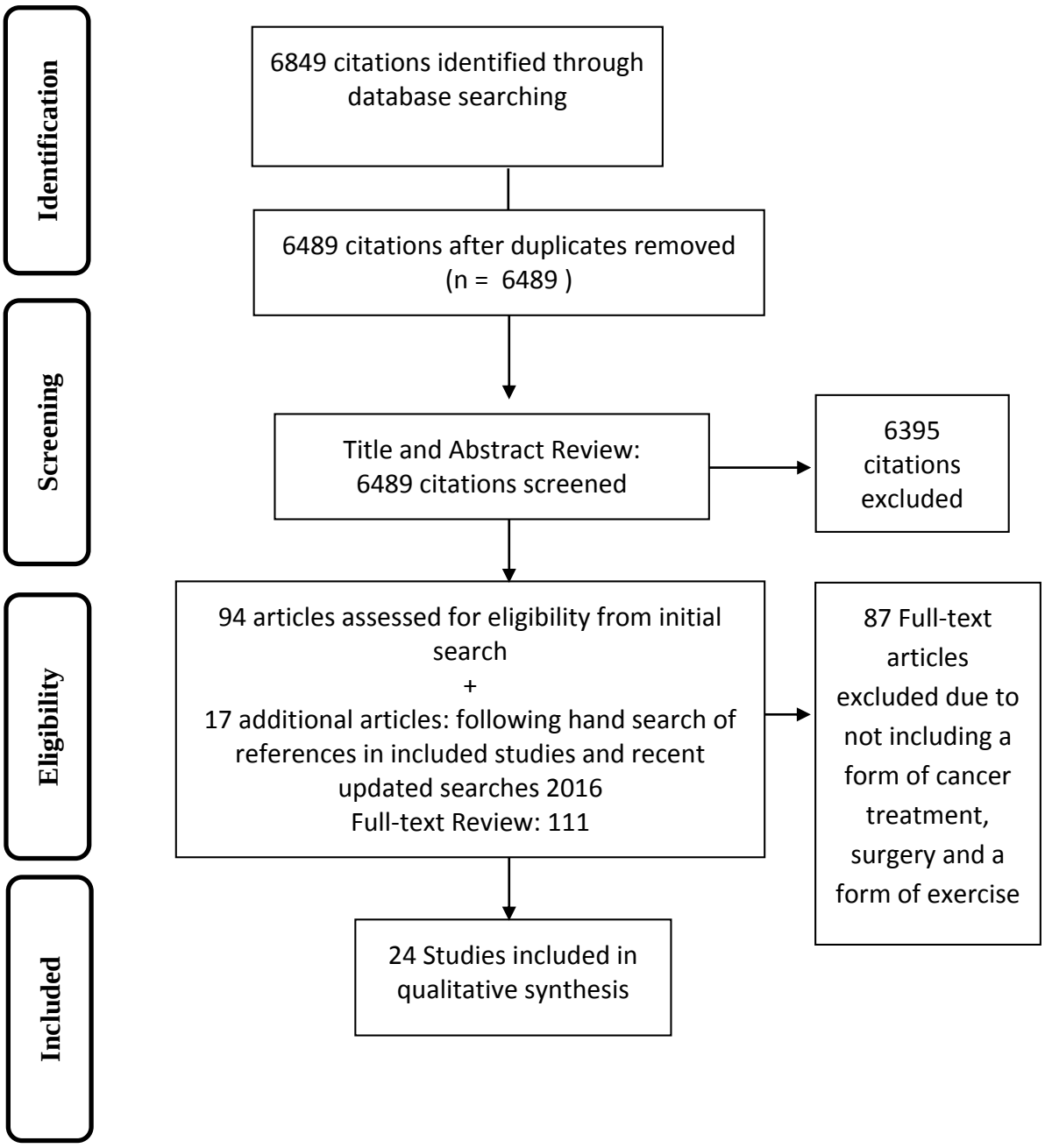
As part of my research programme of work, I am currently conducting The PERIOProgramme research study which is investigating the feasibility of a community-based pre-operative exercise training on physical fitness as well as post-operative outcome, nutritional status, PAL, molecular and cellular adaptations, HRQoL, blood pressure, and body composition in newly diagnosed colorectal and prostate cancer. Additionally, MedEx (Dublin) in collaboration with Fit-4-Surgery group (Southampton) submitted (*July 2016*) a study proposal to the Health Research Board Ireland to fund an international multi-centre trial (S*hort-listed: October 2016, not awarded for funding March 2017*) whose aim is to evaluate the feasibility of pre-operative community-based exercise compared with usual care in people with colorectal cancer. This proposed programme aims to advance the findings reported in this thesis and provide further insight into translating exercise interventions into the community setting.

Appendices

Appendix 1 Supplementary Table: search terms used for the systematic review

Search terms
i) CANCER
1. expNeoplasm
2. Canc*.tw.
3. Neoplasm*.tw.
4. expTumor
5. Tumo*.tw.
6. expCarcinoma
7. Carcin*.tw.
8. expMalignant
9. expOncology
10. Oncol*tw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
ii) CANCER TREATMENT
12. expNeoadjuvant
13. Neoadjuvant*.tw.
14. expChemo
15. Chemo*.tw.
16. expRadiotherapy
17. expCancer treatment
18. 12 or 13 or 14 or 15 or 16 or 17
iii) EXERCISE
19. expExercise
20. Exercise*.tw.
21. expFitness
22. Fit*.tw.
23. expOxygen consumption
24. expAerobic
25. Aerobic*.tw.
26. Anaerobic
27. Anaerobic*.tw.
28. 19 or 20 or 21 or 21 or 22 or 23 or 24 or 25 or 26 or 27
i) and ii) and iii)
iv) SURGERY
29. Surgery
30. Surg*.tw.
31. Surgical (including Anatomy, drainage, mortality, patient, science, stress, wound, ward all terms)
32. 30 or 31 or 32
33. **I) and ii) and iii) and iv)**
v) OUTCOME
34. Morb*.tw.
35. Mort*.tw.
36. Recurrence*.tw.
37. Outcom*.tw.
38. 34 or 35 or 36 or 37
i) and ii) and iii) and iv) and v)

Appendix 2 Supplementary Figure: search results conducted for systematic review (Chapter 3)



Appendix 3 Supplementary Table: methodological quality assessment

	Lee et 2007	Courneya 2009	Campbell 2005	Kolden 2002	Courneya 2007	Adamsen 2009	Mock 2005	Courneyae 2008	Moros 2010	Jones 2008	Segal 2001	Battaglini 2005	Milecki 2013	Hoffman 2014	Husebo 2014	Naraphong 2014	Schmidt 2014	Rao 2012	West 2014	Hornsby 2014	Jones 2013	Adams 2016	Morielli 2016	Wiskemann 2016
Reporting	9	8	10	9	10	10	10	10	10	10	10	10	8	10	10	8	10	10	10	10	10	8	10	9
Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the main outcomes to be measured clearly described in the introduction or methods section?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the characteristics of the patients included in the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the interventions of interest clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Are the main findings of the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Does the study provide estimates of the random variability in the data for the main outcomes?	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Have all important adverse events that may be a consequence of the intervention been reported?	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	0	1	0
Have the characteristics of patients lost to follow-up been described	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
Have actual probability values been reported for the main outcomes except where the probability value is less than	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1
External validity	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

	Lee et 2007	Courneya 2009	Campbell 2005	Kolden 2002	Courneya 2007	Adamsen 2009	Mock 2005	Courneyae 2008	Moros 2010	Jones 2008	Segal 2001	Battaglini 2005	Milecki 2013	Hoffman 2014	Husebo 2014	Naraphong 2014	Schmidt 2014	Rao 2012	West 2014	Hornsby 2014	Jones 2013	Adams 2016	Morielli 2016	Wiskemann 2016
Internal validity bias	5	4	4	4	4	5	4	4	4	4	4	4	5	5	5	5	5	4	6	5	6	5	4	4
Was an attempt made to blind study subjects to the intervention they have received?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Was an attempt made to blind those measuring the main outcomes of the intervention?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	1	0	0
If any of the results of the study were based on data dredging, was this made clear?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-	1	0	0	0	0	1	0	0	0	0	0	0	1	1	1	1	1	0	1	0	1	0	0	0
Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1
Was compliance with the intervention/s reliable?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Internal validity - confounding (selection bias)	5	5	4	1	5	5	5	5	5	2	5	5	4	4	5	5	5	4	5	5	5	5	1	5
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Were the study subjects randomised to intervention groups?	1	1	1	0	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	0	1
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1
Were losses of patients to follow-up taken into account?	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1
Power	1	0	0	0	1	1	1	1	0	0	1	1	1	1	1	0	1	0	1	1	1	1	1	1
Did the study have sufficient power to detect a clinically important effect where the probability value for a	1	0	0	0	1	1	1	1	0	0	1	1	1	1	1	0	1	0	1	1	1	1	1	1
Total	**23**	**20**	**21**	**17**	**23**	**24**	**23**	**23**	**22**	**19**	**23**	**23**	**21**	**23**	**24**	**21**	**24**	**21**	**25**	**24**	**24**	**22**	**19**	**22**

Note: All studies were scored individually. Numerical 1 represents yes and 2 represents no.

Appendix 4 Patient information sheets

1. <u>Patient Information Sheet</u> (chemotherapy and chemoradiotherapy pathway)

University Hospital Southampton
Tremona Road
Southamtpon
SO16 6HU

Study Number:

Patient Information Number:

Does a 9 week exercise intervention improve pre-operative physical fitness following neoadjuvant chemoradiotherapy in colorectal cancer patients?

<u>Patient Information Sheet</u>

We would like to invite you to take part in our research study, but firstly we would like you to understand why this research is being done. This form should take about 20 minutes to read. Please contact us if there is anything that is unclear or if you have any questions.

Research Purpose
The main aim of the study is to find out if tailored exercise training after chemoradiotherapy can improve fitness. Others aims are to find out if the exercise programme can improve quality of life, physical activity levels, if we can improve outcome after major colorectal surgery and also aim to identify an optimal time for fitness to recover following chemoradiotherapy prior to major surgery.

It is usual, before having surgery, to have a six-week course of chemoradiotherapy to try to reduce the tumour size and to make it easier for the surgeon to remove it during the operation. Although chemoradiotherapy may have beneficial effects on the tumour, we now know that it can lower fitness. Therefore, we would like to investigate the effects of exercise training after the 6-week period where chemoradiotherapy treatment is given. We believe that the exercise training will improve fitness and quality of life. We also believe that improvements in physical fitness will improve recovery following surgery. Although we believe that exercise training is beneficial, we need to prove that this is the case. To do this, we need to compare exercise training after chemoradiotherapy with the current standard hospital treatment. In this study we will randomly select whether each patient will receive in-hospital, supervised exercise training or out of hospital best exercise advice. Patients who volunteer for this study are 1:1 chances of being in the exercise intervention group or the control group.

Why have you received this invitation?
You have been told by your doctor that unfortunately you have a form of cancer in your large bowel. To treat this it is advised that you undergo a course of chemoradiotherapy to try to reduce the size of the cancer, followed by an operation to remove the cancer. This is routine care for this condition.

Chemoradiotherapy can make you feel tired and lower your level of physical fitness. Fitter people tend to recover quicker following large operations compared to less fit people. This is why we would like to investigate your fitness and try to improve it after you have had chemoradiotherapy.

Will my treatment be any different if I take part?
If you agree to take part in this study your cancer treatment will not be any different. If you are assigned to the exercise treatment group you will be asked to undergo a supervised exercise regime (3 sessions per week for 9 weeks). If you are assigned to the control group you will be given best exercise advice to be carried out in your own home for the 9 week period. This study will not cause any delays in your cancer treatment.

Do I have to take part?
No. It is up to you to decide whether or not you should take part. If you decide to give us permission, we will give you this information sheet to keep and ask you to sign our consent form at a later date. If you do take part you can withdraw from the research project at any time and without having to give any reason. If you decide to withdraw or not take part, this will not affect the quality of care you receive whilst in hospital.

What will happen to me if I take part?
Recruited patients will be divided into a control and exercise intervention group. You will have 1:1 chances of being placed in the exercise intervention group. If you are assigned to the exercise intervention group, we will provide facilities for you to have regular supervised, tailor-made exercise. This exercise regime will take place in a supervised, safe, hospital environment in our new exercise laboratory in the University Hospital Southampton. Here our staff will help you perform a total of 27 exercise sessions (3 sessions per week for 9 weeks). These sessions will be tailored to your previous fitness levels by using results derived from your post-chemoradiotherapy CPET tests. Every exercise training session will involve 30-40 minutes of exercise on our exercise bike. Every effort will be made to arrange for the exercise training sessions to fit in with other hospital appointments. If you are randomly assigned to the control group, you will receive best exercise advice, which you will undertake in your own home for the 9 week period.

As part of the research project we would also like you to complete two short quality of life questionnaires which will be undertaken when you enter the study, in between your chemotherapy and chemoradiotheapy, post your chemoradiotherapy(week 0), week 3, 6 and week 9(before surgery) and 4-6 weeks after surgery. These questionnaires are easy to fill in and will only take 20 minutes of your time. During the 9 week period after your chemoradiotherapy, we would also like to invite you to have 2 quality of life face-to-face interviews. These will take place on the same hospital sessions at week 0 and 9 and will last for less than an hour. We will also perform 1 CPET(maximal exercise test) and oxygen kinetics test (sub-maximal exercise test) before you start chemoradiotherapy, 1 CPET in between your chemotherapy and chemoradiotherapy, 4 CPET tests during the 9 week period after chemoradiotherapy and before surgery, and an oxygen kinetics test (sub-maximal exercise) at week 0 and 9. After 9 weeks exercise or best advice programme is complete, you will undergo your routine tumour examination (at 9 weeks after chemoradiotherapy) by CT and MRI scans.

We are also interested in how much physical activity you typically do, and whether this changes with your treatment. Therefore on 6 occasions (prior to, during, immediately after and 3, 6 and 9 weeks after chemoradiotherapy) we will ask you to wear an "accelerometer", which is a small watch like device worn on the upper arm (fits underneath clothing). This will be worn on each occasion for a 3-day period (day and night). This unit will measure your typical physical activity levels and is unobtrusive. This will be fitted during the first CPET test and will be shuttled back and forth to you on all 6 occasions, to cause you the least amount of inconvenience.

What are the risks or side effects of taking part?
The exercise sessions are performed at a lesser exertion when compared to CPET and should not present any additional risk. There exists the possibility that your muscles may feel achy or sore following exercise training sessions but any soreness or aches should subside within a day or two. There is also a very small risk (1:10,000) associated with CPET of heart attacks or irregular heartbeat, but this is very rare.

What if something goes wrong?
We have no reason to believe that you will come to any harm as a result of this research. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

What will happen if I don't want to carry on with the study?
You can withdraw from the research project at any time and without having to give any reason.

What will we do with the information?
Your personal information (name, address, diagnosis, date of birth etc.) associated with your test results will not be available to anyone outside your medical team. We expect that the data will be published in a medical journal to help doctors make decisions about patients in the future. All information will be anonymised; that is, all figures and numbers will not be traceable to you and personal details (name etc.) will be removed. Your medical records may be accessed for research purposes by members of staff not directly part of the clinical care team.

Involvement of the General Practitioner/Family doctor (GP)
With your permission we will inform your GP if you decide to take part in this trial.

Contact information
If you would like further information you should contact one of the research team on Tel: or email address below.

Lead Researcher – Ms Lisa Loughney (Lisa.Loughney@uhs.nhs.uk)
Lead Clinical Physiologist - Dr S. Jack
Consultant Surgeon - Mr Alex Mirnezami

2. <u>Patient Information Sheet</u> (neoadjuvant chemoradiotherapy pathway)

University Hospital Southampton
Tremona Road
Southamtpon
SO16 6HU

Study Number:

Patient Information Number:

Does a 9 week exercise intervention improve pre-operative physical fitness following neoadjuvant chemoradiotherapy in colorectal cancer patients?

<u>Patient Information Sheet</u>

We would like to invite you to take part in our research study, but firstly we would like you to understand why this research is being done. This form should take about 20 minutes to read. Please contact us if there is anything that is unclear or if you have any questions.

Research Purpose
The main aim of the study is to find out if tailored exercise training after chemoradiotherapy can improve fitness. Others aims are to find out if the exercise programme can improve quality of life, physical activity levels, if we can improve outcome after major colorectal surgery and also aim to identify an optimal time for fitness to recover following chemoradiotherapy prior to major surgery.

It is usual, before having surgery, to have a six-week course of chemoradiotherapy to try to reduce the tumour size and to make it easier for the surgeon to remove it during the operation. Although chemoradiotherapy may have beneficial effects on the tumour, we now know that it can lower fitness. Therefore, we would like to investigate the effects of exercise training after the 6-week period where chemoradiotherapy treatment is given. We believe that the exercise training will improve fitness and quality of life. We also believe that improvements in physical fitness will improve recovery following surgery. Although we believe that exercise training is beneficial, we need to prove that this is the case. To do this, we need to compare exercise training after chemoradiotherapy with the current standard hospital treatment. In this study we will randomly select whether each patient will receive in-hospital, supervised exercise training or out of hospital best exercise advice. Patients who volunteer for this study are 1:1 chances of being in the exercise intervention group or the control group.

Why have you received this invitation?
You have been told by your doctor that unfortunately you have a form of cancer in your large bowel. To treat this it is advised that you undergo a course of chemoradiotherapy to try to reduce the size of the cancer, followed by an operation to remove the cancer. This is routine care for this condition.

Chemoradiotherapy can make you feel tired and lower your level of physical fitness. Fitter people tend to recover quicker following large operations compared to less fit people. This is why we would like to investigate your fitness and try to improve it after you have had chemoradiotherapy.

Will my treatment be any different if I take part?
If you agree to take part in this study your cancer treatment will not be any different. If you are assigned to the exercise treatment group you will be asked to undergo a supervised exercise regime (3 sessions per week for 9 weeks). If you are assigned to the control group you will be given best exercise advice to be carried out in your own home for the 9 week period. This study will not cause any delays in your cancer treatment.

Do I have to take part?
No. It is up to you to decide whether or not you should take part. If you decide to give us permission, we will give you this information sheet to keep and ask you to sign our consent form at a later date. If you do take part you can withdraw from the research project at any time and without having to give any reason. If you decide to withdraw or not take part, this will not affect the quality of care you receive whilst in hospital.

What will happen to me if I take part?
Recruited patients will be divided into a control and exercise intervention group. You will have 1:1 chances of being placed in the exercise intervention group. If you are assigned to the exercise intervention group, we will provide facilities for you to have regular supervised, tailor-made exercise. This exercise regime will take place in a supervised, safe, hospital environment in our new exercise laboratory in the University Hospital Southampton. Here our staff will help you perform a total of 27 exercise sessions (3 sessions per week for 9 weeks). These sessions will be tailored to your previous fitness levels by using results derived from your post-chemoradiotherapy CPET tests. Every exercise training session will involve 30-40 minutes of exercise on our exercise bike. Every effort will be made to arrange for the exercise training sessions to fit in with other hospital appointments. If you are randomly assigned to the control group, you will receive best exercise advice, which you will undertake in your own home for the 9 week period.

As part of the research project we would also like you to complete two short quality of life questionnaires which will be undertaken when you enter the study, during your chemoradiotherapy (week 0), week 3, 6 and week 9(before surgery) and 4-6 weeks after surgery. These questionnaires are easy to fill in and will only take 20 minutes of your time. During the 9 week period after your chemoradiotherapy we would also like to invite you to have 2 quality of life face-to-face interviews. These will take place on the same hospital sessions at week 0 and 9 and will last for less than an hour. We will also perform 1 CPET(maximal exercise test) and oxygen kinetics test (sub-maximal exercise test) before you start chemoradiotherapy, 4 CPET tests during the 9 week period after chemoradiotherapy and before surgery, and an oxygen kinetics test (sub-maximal exercise) at week 0 and 9. After 9 weeks exercise or best advice programme is complete, you will undergo your routine tumour examination (at 9 weeks after chemoradiotherapy) by CT and MRI scans.

We are also interested in how much physical activity you typically do, and whether this changes with your treatment. Therefore on 6 occasions (prior to, during, immediately after and 3, 6 and 9 weeks after chemoradiotherapy) we will ask you to wear an "accelerometer", which is a small watch like device worn on the upper arm (fits underneath clothing). This will be worn on each occasion for a 3-day period (day and night). This unit will measure your typical physical activity levels and is unobtrusive. This will be fitted during the first CPET test and will be shuttled back and forth to you on all 6 occasions, to cause you the least amount of inconvenience.

What are the risks or side effects of taking part?
The exercise sessions are performed at a lesser exertion when compared to CPET and should not present any additional risk. There exists the possibility that your muscles may feel achy or sore following exercise training sessions but any soreness or aches should subside within a day or two. There is also a very small risk (1:10,000) associated with CPET of heart attacks or irregular heartbeat, but this is very rare.

What if something goes wrong?
We have no reason to believe that you will come to any harm as a result of this research. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

What will happen if I don't want to carry on with the study?
You can withdraw from the research project at any time and without having to give any reason.

What will we do with the information?
Your personal information (name, address, diagnosis, date of birth etc.) associated with your test results will not be available to anyone outside your medical team. We expect that the data will be published in a medical journal to help doctors make decisions about patients in the future. All information will be anonymised; that is, all figures and numbers will not be traceable to you and personal details (name etc.) will be removed. Your medical records may be accessed for research purposes by members of staff not directly part of the clinical care team.

Involvement of the General Practitioner/Family doctor (GP)
With your permission we will inform your GP if you decide to take part in this trial.

Contact information
If you would like further information you should contact one of the research team on Tel: or email address below.

Lead Researcher – Ms Lisa Loughney (lisa.loughney@uhs.nhs.uk)
Lead Clinical Physiologist - Dr S. Jack
Consultant Surgeon - Mr Alex Mirnezami.

Appendix 5 Patient informed consent form

Name of Researcher: _____

1. I confirm that I have read and understand the information sheet dated _____ (version _____) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Southampton University Hospitals research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that my participation in the health related quality of life interviews is voluntary and that these session will be audio taped. These tapes will then be transcribed by persons blinded to your details and any personal information. ☐

5. I understand that I will be undertaking a series of blood tests, and these will be stored in a safe and responsible manner. These blood tests will be genetically analysed. ☐

6. I agree to my GP being informed of my participation in the study. ☐

7. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature

_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix 6 General practitioner letter

Dear Dr. _____

The above patient has kindly consented to enter a randomised control trial in patients undergoing neoadjuvant chemoradiotherapy (NACRT) prior to elective rectal cancer resection at Aintree University Teaching Hospitals NHS Foundation Trust.

Exercise capacity, specifically the lactate threshold (LT) measured by a cardiopulmonary exercise test (CPET), is a good predictor of postoperative outcome. Our pilot studies in upper gastrointestinal cancer and rectal cancer cohort of patients have shown that neoadjuvant chemotherapy significantly lowers exercise capacity and therefore this may increase the risk of poor postoperative outcome. We have pre-pilot data showing that we can improve physical fitness by exercise training our rectal cancer patients following chemoradiotherapy. This study aims to investigate the effects of a 9 week exercise training program following chemoradiotherapy and we think we can improve physical fitness, health related quality of life, physical activity and that increased physical fitness may improve postoperative outcome.

Patients will be randomised into an intervention group or a control group. All patients will be asked to perform 4 additional CPET exercise tests, an addition MRI scan and an exercise regime (compared to standard treatment). Patients will also have additions tests like oxygen kinetics tests, pulmonary function tests and a quality of life questionnaire (EQ-5d and EORTC) to fill in pre, mid and post chemoradiotherapy and on four other occasions during the fourteen week period before surgery. Patients will undergo activity monitoring for 3 day periods pre-chemoradiotherapy, mid chemoradiotherapy, post chemoradiotherapy and 3 occasions during the exercise regime and the week before surgery.

The patients allocated to the intervention group will adhere to a 9 week individualised exercise training program after their 6 week period of chemoradiotherapy treatment. All patients will be followed up during the postoperative period and objective outcome measures will be taken. The Post-Operative Morbidity Score (POMS) and resource use (e.g. hospital bed utilisation) will be noted.

This study does not change any part of the patient's clinical care. Please contact a member of the study group listed below if you have any questions or concerns. We will let you know the outcome of your patient during the study period. A protocol sheet is available on request.

Many thanks for your co-operation and kind regards,

Appendix 7 Case report form

CASE REPORT FORM

EMPOWER:
Does a 9 Week Exercise Intervention Improve Pre-Operative Physical Fitness Following Neoadjuvant Chemoradiotherapy in Rectal Cancer Patients?

REC: 13/NW/0259

CLINICAL TRIAL SITE: **…….**

PRINCIPAL INVESTIGATOR: **…….**

BASELINE VISIT

INCLUSION CRITERIA		
1. Male or female patients, aged over 18 years old	Yes	No
2. Histologically or cytologically confirmed diagnosis of colorectal cancer	Yes	No
3. Listed to undergo long course neoadjuvant chemoradiotherapy and elective rectal cancer resection	Yes	No
4. Willing to consent to a blood/urine/saliva sample taken before and after every CPET session	Yes	No
*If any inclusion criteria are circled no then the patient is not eligible for the study.		
EXCLUSION CRITERIA		
1. Unable to consent	Yes	No
2. Under 18 years	Yes	No
3. Restrictive lower limb disease (therefore, unable to cycle)	Yes	No
4. Severe claustrophobia (therefore, unable to tolerate mask)	Yes	No
5. Significant cardiac ischaemia of > 1.5mm symptomatic and > 2mm asymptomatic observed on the baseline ECG	Yes	No
6. Weight > 160kg	Yes	No
7. Contraindications to Cardiopulmonary Exercise Test (see next page)	Yes	No
* If *any* exclusion criteria are circled yes then the patient is not eligible for the study		

Signature: ..... Date: | | | | | | | | | |

d d m m m y y y y

ABSOLUTE CONTRAINDICATIONS TO CPET (Do not test)		
Acute MI	Yes	No
Unstable angina	Yes	No
Uncontrolled arrhythmias causing symptoms or haemodynamic compromise	Yes	No
Syncope	Yes	No
Acute endocarditis	Yes	No
Acute myocarditis	Yes	No
Acute pericarditis	Yes	No
Symptomatic severe aortic stenosis	Yes	No
Uncontrolled heart failure	Yes	No
Acute pulmonary embolism or infarction (if asymptomatic for 3 weeks then discuss with PI/CI)	Yes	No
Thrombosis of lower extremities (if asymptomatic for 3 weeks then discuss with PI/CI)	Yes	No
Suspected dissecting aneurysm	Yes	No
Uncontrolled asthma	Yes	No
Pulmonary oedema	Yes	No
Room air desaturation at rest < 85% if no known lung pathologies	Yes	No
Respiratory failure	Yes	No
Acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise	Yes	No
Mental impairment leading to inability to co-operate	Yes	No

Participant should not be tested if the answer to any question is YES

RELATIVE CONTRAINDICATIONS **(Discuss with CI)**		
Left main coronary stenosis or its equivalent	Yes	No
Moderate stenotic valvular heart disease	Yes	No
Severe untreated arterial hypertension at rest (>200 mm Hg systolic, > 120 mm Hg diastolic)	Yes	No
Tachyarrhythmias or bradyarrhythmias	Yes	No
High degree atrioventricular block	Yes	No
Hypertrophic cardiomyopathy	Yes	No
Significant pulmonary hypertension	Yes	No
Advanced or complicated pregnancy	Yes	No
Electrolyte abnormalities	Yes	No
Orthopaedic impairment that compromises exercise performance	Yes	No

Participant should not be tested if the answer to any question is YES

PREVIOUS MEDICAL HISTORY

Is there any relevant medical history in the following systems?

Code	System	*Yes	No	Code	System	*Yes	No
1	Cardiovascular			9	Neoplasia		
2	Respiratory			10	Neurological		
3	Hepato-biliary			11	Psychological		
4	Gastro-intestinal			12	Immunological		
5	Genito-urinary			13	Dermatological		
6	Endocrine			14	Allergies		
7	Haematological			15	Eyes, ear, nose, throat		
8	Musculo-skeletal			00	Other		

		Currently Active?	
Code	**Details (including dates)**	**Yes**	**No**

CONCOMITANT MEDICATIONS

Medication	Total Daily Dose	Units	Reason	Start Date *(MM/DD/YYYY)*	Stop Date *(MM/DD/YYYY)*	Continu-ing
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
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				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐

BASELINE TEST DATA COLLECTION

Baseline Patient Data				
Date:				
Hospital ID:				
Age (yrs):				
Date of Birth:				
Gender:			Female	Male
Height (m):				
Weight (Kg):				
Body Mass Index (BMI = Wt (kg)/H² (M):				
Weight Loss in past six months:			< 5%	>5%
Calculated ideal weight:				
Postcode:				
Tumour				
TNM (Pre-NAC):				
Tumour Type:				
Proposed cancer treatment:				
Smoking				
Does the patient currently smoke or use tobacco products?			Yes	No
If yes, how many cigarettes per day?				
If no, what is their smoking history:			Never	Previous
Drinking				
Which accurately describes alcohol intake?	Never	Minimal	Moderate	Heavy
Assessments				

Questionnaires	Yes	No
Urine	Yes	No
Saliva	Yes	No
Pre test blood samples	Yes	No
CPET	Yes	No
Post test blood sample	Yes	No
Activity Monitor	Yes	No
Physical examination (by medical staff as part of standard pre chemo assessment)	Yes	No

BASELINE CPET TEST

Mask size:

Seat height:

Work Rate Protocol:

	EXERCISE TIME	BORG SCORE	BP
REST	Start		
	After 2 minutes		
UNLOADED	After 2 minutes		
RAMP	After 2 minutes		
	After 4 minutes		
	After 6 minutes		
	After 8 minutes		
	After 10 minutes		
	After 12 minutes		
RECOVERY	After 2 minutes		
	After 5 minutes		

Recover until:

- Any dysrythmias or ST changes have reverted to pre test status
- Heart rate is within 10 bpm of pre test rate
- BP returned to pre test level

COMMENTS:

CPET WEEK 3

Mask size:

Seat height:

Work Rate Protocol:

	EXERCISE TIME	BORG SCORE	BP
REST	Start		
	After 2 minutes		
UNLOADED	After 2 minutes		
RAMP	After 2 minutes		
	After 4 minutes		
	After 6 minutes		
	After 8 minutes		
	After 10 minutes		
	After 12 minutes		
RECOVERY	After 2 minutes		
	After 5 minutes		

Recover until:

- Any dysrythmias or ST changes have reverted to pre test status
- Heart rate is within 10 bpm of pre test rate
- BP returned to pre test level

COMMENTS:

CPET WEEK 6

Mask size:

Seat height:

Work Rate Protocol:

	EXERCISE TIME	**BORG SCORE**	**BP**
REST	Start		
	After 2 minutes		
UNLOADED	After 2 minutes		
RAMP	After 2 minutes		
	After 4 minutes		
	After 6 minutes		
	After 8 minutes		
	After 10 minutes		
	After 12 minutes		
RECOVERY	After 2 minutes		
	After 5 minutes		

Recover until:

- Any dysrythmias or ST changes have reverted to pre test status
- Heart rate is within 10 bpm of pre test rate
- BP returned to pre test level

COMMENTS:

CPET WEEK 9

Mask size:

Seat height:

Work Rate Protocol:

	EXERCISE TIME	BORG SCORE	BP
REST	Start		
	After 2 minutes		
UNLOADED	After 2 minutes		
RAMP	After 2 minutes		
	After 4 minutes		
	After 6 minutes		
	After 8 minutes		
	After 10 minutes		
	After 12 minutes		
RECOVERY	After 2 minutes		
	After 5 minutes		

Recover until:

- Any dysrythmias or ST changes have reverted to pre test status
- Heart rate is within 10 bpm of pre test rate
- BP returned to pre test level

COMMENTS:

Appendix 8 Supplementary Table: Changes in cardiopulmonary exercise testing variables between the groups over the study period

CPET Variable		Week 0	Week 3	Week 6	Week 9
$\dot{V}o_2$ at $\hat{\theta}_L$ ($ml.kg^{-1}.min^{-1}$)	Exercise	12.2 (3.7)	13.8(4.2)	14 (6.1)	16.6 (5.4)
	Usual care	13.3 (2.6)	13.1(2.2)	13.0(2.2)	12.9 (1.4)
$\dot{V}o_2$ Peak ($ml.kg^{-1}.min^{-1}$)	Exercise	22.1(7.3)	24.5(7.6)	22.6(10.8)	27.5 (9.2)
	Usual care	14.4(8.6)	21.9(1.6)	11.6 (3.6)	23.8 (3)
$\dot{V}_E/\dot{V}o_2$ at $\hat{\theta}_L$	Exercise	25.7(2.9)	28.8 (3)	28.2 (5.2)	26.9 (3.6)
	Usual care	27.3(2.8)	28.5(5.6)	28.5 (3.5)	26.7 (2.5)
$\dot{V}_E/\dot{V}o_2$ at Peak	Exercise	38.3(5.5)	39.4 (6)	38.2 (5.8)	39.4 (3.8)
	Usual care	42.4(9.4)	41.6(6.1)	40.8 (4.1)	39.4 (4.1)
$\dot{V}_E/\dot{V}co_2$ at $\hat{\theta}_L$	Exercise	30.6(4.7)	31.1(3.1)	30.7 (3.4)	28 (9.6)
	Usual care	31.7(4.8)	30.6(3.5)	40 (1.8)	27.3(10.7)
$\dot{V}_E/\dot{V}co_2$ at Peak	Exercise	30.6(4.7)	33.1(4.3)	38.4(16.7)	31.9(10.3)
	Usual care	32.4(4.4)	34.1(4.5)	33.3 (2.7)	29.8(11.2)
Baseline HR ($beats.min^{-1}$)	Exercise	76 (8)	82 (14)	80 (13)	75 (13)
	Usual care	87 (14)	80 (19)	77 (12)	76 (12)
HR at $\hat{\theta}_L$ ($beats.min^{-1}$)	Exercise	98 (13)	104 (14)	106 (12)	103 (9)
	Usual care	125 (44)	109 (19)	101 (15)	101 (14)
HR at Peak ($beats.min^{-1}$)	Exercise	132 (16)	139 (21)	127 (39)	137 (17)
	Usual care	126 (34)	150 (20)	142 (23)	145 (22)

Appendix 8 Supplementary Table: Changes in cardiopulmonary exercise testing variables between the groups over the study period (Cont'd)

CPET Variable		Week 0	Week 3	Week 6	Week 9
O2 Pulse at LT (ml.beat^{-1})	Exercise	9.7 (3.9)	10.6(4.2)	11.3 (3.2)	12.9 (5.1)
	Usual care	9 (2)	9.4 (2.1)	10 (1.3)	10.6 (2)
O2 Pulse at Peak(ml.beat^{-1})	Exercise	13.2(4.6)	13.9(4.6)	16.1 (6.8)	15.5 (5.7)
	Usual care	10.4(2.2)	11.6(2.5)	12.4 (1.6)	12.8 (2.4)
Work load at $\hat{\theta}_L$ (W)	Exercise	68 (42)	81 (44)	94 (56)	104 (52)
	Usual care	73 (31)	80 (23)	73 (14)	77 (13)
Work load at Peak (W)	Exercise	152 (62)	163 (73)	160 (78)	177 (80)
	Usual care	123 (31)	153 (34)	157 (41)	165 (38)
FEV1 (L)	Exercise	2.9(0.8)	3.0 (0.9)	3.0 (0.5)	3.1 (0.7)
	Usual care	3.7 (0.8)	3.4 (1.1)	3.3 (0.8)	3.7 (1.0)
FVC (L)	Exercise	4.0 (0.7)	4.2 (1.2)	4.5 (0.6)	4.5 (0.9)
	Usual care	4.6 (0.9)	4.6 (1.1)	4.5 (1)	4.9 (1.1)

Values presented as mean (SD). List of abbreviations: $\dot{V}_{O_2}$ at $\hat{\theta}_L$, Oxygen uptake at estimated lactate threshold; $\dot{V}_{O_2}$ at Peak, Oxygen uptake at peak exercise; O_2 pulse at $\hat{\theta}_L$, Oxygen pulse at estimated lactate threshold; O_2 pulse at Peak, Oxygen pulse at peak exercise; $\dot{V}_E/\dot{V}_{CO_2}$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at estimated lactate threshold; $\dot{V}_E/\dot{V}_{CO_2}$ at $\hat{\theta}_L$, Ventilatory equivalents for carbon dioxide at peak exercise; Work rate at $\hat{\theta}_L$, Work rate at estimated lactate threshold; Work rate at Peak, Work rate at peak exercise; FEV1, forced expiratory volume over 1-sec; FVC, forced vital capacity.

Appendix 9 Supplementary Table: Changes in physical activity variables between groups over the study period

Physical Activity Variables		Week 0	Week 3	Week 6	Week 9
Step-count (steps/day)	Exercise	6204(6308)	3900(6792)	5322(6858)	4246(5578)
	Usual Care	5640 (7962)	6251 (6648)	7895 (8212)	6424 (5408)
PA duration (min.day)	Exercise	72 (96)	42 (102)	129 (179)	79 (127)
	Usual Care	52 (90)	76 (140)	115 (90)	78 (65)
MET	Exercise	1.3 (0.3)	1.3 (0.3)	1.6 (0.5)	1.3 (0.3)
	Usual Care	1.3 (0.2)	1.4 (0.3)	1.4 (0.3)	1.4 (0.2)
Active EE (kcals.day^{-1})	Exercise	370 (753)	290 (667)	634 (1044)	394 (327)
	Usual Care	240 (468)	414 (1298)	766 (759)	359 (332)
Total EE (kcals.day^{-1})	Exercise	2234 (810)	1977 (1006)	2278 (858)	2632 (981)
	Usual Care	2359 (612)	2250 (1480)	2586(1165)	2198 (914)
Lying down (min.day)	Exercise	476 (71)	453 (229)	490 (189)	493 (161)
	Usual Care	493 (123)	486 (155)	527 (205)	518 (184)
Sleep duration (min.day^{-1})	Exercise	342 (77)	328 (103)	380 (125)	400 (112)
	Usual Care	383 (98)	403 (109)	404 (178)	361 (172)
Sleep efficiency (%)	Exercise	70 (20)	72 (19)	74 (20)	80 (14)
	Usual Care	75 (20)	75 (41)	81 (27)	72 (21)
Duration on body (min.day^{-1})	Exercise	1403 (40)	1380 (575)	1410 (118)	1397 (85)
	Usual Care	1392 (100)	1388 (49)	1403 (90)	1402 (177)
PAL	Exercise	1.5 (0.3)	1.5 (0.4)	1.7 (0.4)	1.4 (0.3)
	Usual Care	1.4 (0.3)	1.5 (0.4)	1.6 (0.4)	1.5 (0.1)

Values presented as median (IQR). Abbreviations: PA – physical activity; MET, metabolic threshold, EE – energy expenditure; PAL – physical activity levels.

Appendix 10 Publications and chapters associated with my work

Publications

1) Otto JM, Plumb JOM, Wakeham D, Clissold E, **Loughney L**, Schmidt W, et al. Total haemoglobin mass, but not haemoglobin concentration, is associated with preoperative cardiopulmonary exercise testing-derived oxygen-consumption variables. British Journal of Anaesthesia 2017; 118 (5):747-754
2) **Loughney L**, West MA, Dimitrov BD, Kemp GJ, Grocott MPW, Jack S. Physical activity levels in locally advanced rectal cancer patients following neoadjuvant chemoradiotherapy and an exercise training programme before surgery: a pilot study. *Perioperative Medicine* 2017; 6:3
3) **Loughney LA**, West MA, Kemp GJ, Grocott MPW, Jack S. Exercise interventions for people undergoing multimodal cancer treatment that includes surgery. *Cochrane Database of Systematic Reviews* 2016; DOI: 10.1002/14651858.CD012280.
4) **Lisa Loughney**, Michael PW Grocott. Exercise and nutrition prehabilitation for evaluation of risk and therapeutic potential in cancer patients: a review. *International Anesthesiology Clinics* 2016; 54 (4): e47-e61.
5) West MA, Dimitrov BD, Kemp GJ, **Loughney L**, Grocott MPW, Jack S , Brown G. Timing of surgery following neoadjuvant chemoradiotherapy in locally advanced rectal cancer - A comparison of magnetic resonance imaging at two time points and histopathological responses. *European Journal of Surgical Oncology* 2016; 42:1350-8
6) MA West, **L Loughney**, G Ambler, B Dimitrov, J Kelly, M Mythen, R Sturgess, P Calverley, MPW Grocott, S Jack. The Effect of Neoadjuvant Chemotherapy and Chemoradiotherapy on Exercise Capacity and Outcome Following Upper Gastrointestinal Cancer Surgery: An Observational Cohort Study. *British BMC Cancer.* 2016; 2(1):710.
7) **Loughney L**, West MA, Kemp GJ, Grocott MPW, Jack S. The effects of neoadjuvant chemoradiotherapy and a prehabilitation programme on physical fitness and quality of life in those with locally advanced rectal cancer (The EMPOWER Trial): study protocol for a randomised controlled trial. *Trials.* 2016; 17:24

8) **Loughney L**, West MA, Kemp GJ, Grocott MPW, Jack S. Exercise intervention in cancer patients undergoing neoadjuvant cancer treatment and surgery: A systematic review. *European Journal of Surgical Oncology.* 2016; 42(1):28-38.
9) **Loughney L**, MA West, GJ Kemp, MPW Grocott, S Jack. Exercise intervention in cancer patients undergoing adjuvant cancer treatment and surgery: A systematic review. *European Journal of Surgical Oncology.* 2015*;* 41 (12) 1590-602
10) West MA, Parry M, Asher R, Key A, Walker P, **Loughney L**, Pintus S, Duffy N, Jack S, Torella F. The effect of beta-blockade on objectively measured physical fitness in patients with abdominal aortic aneurysms - A blinded interventional study. *British Journal of Anaesthesia.* 2015; 114 (6): 878-85
11) West MA, **Loughney L**, Lythgoe D, Barben CP, Adams VL, Bimson WE, Grocott MPW, Jack S, Kemp GJ. The Effect of Neoadjuvant Chemoradiotherapy on Whole-Body Physical Fitness and Skeletal Muscle Mitochondrial Oxidative Phosphorylation In Vivo in Locally Advanced Rectal Cancer Patients - An Observational Pilot Study. *PLOS ONE*. 2014; 9 (12)
12) West MA, **Loughney L**, Lythgoe D, Barben CP, Sripidam R, Kemp GJ, Grocott MPW, Jack S. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. 2014. *British Journal of Anaestheia.* 2014; 114 (2): 244-51.
13) West MA, **Loughney L**, Barben CP, Sripadam R, Kemp GJ, Grocott MP, Jack S. The effects of neoadjuvant chemoradiotherapy on physical fitness and morbidity in rectal cancer surgery patients. 2014. *European Journal of Surgical Oncology.* 2014; 40 (11): 1421-8.
14) **Loughney L**, Pintus S, West M, Lythgoe D, Jack S, Torella F. Comparison of oxygen uptake during arm or leg cardiopulmonary exercise testing in vascular surgery patients and control subjects. *British Journal of Anaesthesia* 2014. 112 (1): 57-65.

Book chapters

1) Preoperative cardiopulmonary exercise testing and prehabilitation. **L. Loughney**, S.Jack, D. Levett. *Clinical Exercise Science*. Chapter 10. London: Routledge. 2016

2) Cardiopulmonary Exercise Testing. MA. West, **L. Loughney**, MPW. Grocott, S. Jack. *Anaesthesia and perioperative care of the high risk patient*. September 2014.

Media exposure associated with this topic of research from my working group (Fit-4-Surgery)

1) BBC South News (10 November 2015):

Website:https://www.BBCSouthToday/videos/934971129926811/?pnref=story

Southampton University Hospital, News and publication (22 October 2014):

Website:http://www.uhs.nhs.uk/AboutTheTrust/Newsandpublications/Latestnews/2014/Doctors-boost-fitness-of-cancer-patients-using-novel-prehab-programme.aspx

University of Southampton, News release (24 October 2014):

Website:http://www.southampton.ac.uk/mediacentre/news/2014/oct/14_196.shtml#.VFNwzfmsV1Z

2) Cancer Research UK, (24 January 2014):

Website: http://thecancermarathon.org/

3) BBC News, Health Check, BBC World Service (2 March 2013 last updated 02:01):

Website: http://www.bbc.co.uk/news/health-21627235

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