STRUCTURED EXERCISE DURING NEO-ADJUVANT CHEMOTHERAPY IN PATIENTS WITH OPERABLE ADENOCARCINOMA OF THE OESOPHAGUS AND GASTRO-OESOPHAGEAL JUNCTION

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A thesis submitted in partial fulfilment of the requirements of Liverpool John Moore's University for the degree of Doctor of Philosophy

This research programme was carried out in collaboration with Guy's and St Thomas' NHS Foundation Trust Hospitals, London and the Centre for Health and Human Performance, London

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Abstract

Background: Neo-adjuvant chemotherapy (NAC) results in physical deconditioning prior to high-risk surgery in patients diagnosed with oesophageal adenocarcinoma but remains the gold standard of care for patients with operable disease. Overall, physical and mental decline has been reported in patients, with a delayed return to baseline health-related quality of life (HRQL) following treatment. Exercise has been shown to improve fitness in patients undergoing non-cancer elective surgery. Furthermore, improved cancer control and immune function has been reported in exercising mice under laboratory conditions. **Aim**: The aim of this thesis is to examine the feasibility of a structured exercise prehabilitation program commencing prior to chemotherapy and continuing during treatment and the impact on outcomes for cancer patients. **Methods**: Patients were invited to participate in a clinical trial of exercise prehabilitation concomitant with standard care versus standard care alone. Following informed and written consent, patients were enrolled into the Pre-EMPT study and clinical data collection commenced. Post-operative tumour histopathology assessment was carried out according to Royal College of Pathology guidelines. Cardiopulmonary exercise testing was performed during treatment. CT scans were assessed for body composition changes post-NAC. Immunity and Inflammatory bloods were assessed. HRQL was measured using validated patient reported outcomes. **Results:** A decline in patient fitness following NAC, measured by VO_{2peak}, was blunted by 7% in patients undergoing the structured exercise prehabilitation program (-19% Control vs -12% Intervention). Overall length of hospital stay was lower than the national average in both groups, as were post-operative complications. Improved cancer control was evident in the Intervention group, measured by pathological evidence of disease regression in both primary tumour and lymph nodes. There was reversal of sarcopenic obesity with improved visceral /subcutaneous fat ratios in patients undergoing exercise prehabilitation. In addition, immune function was significantly improved with greater regulation of inflammatory markers (*i.e.* Interleukin-6). Overall mental wellbeing, measured using the Shortened Warwick-Edinburgh Mental Well-Being Scale, was less perturbed in the Intervention group, also showing a recovery to baseline at 12 months after surgery. **Conclusions:** A structured exercise prehabilitation program during neo-adjuvant chemotherapy and prior to surgery is feasible and beneficial to patients with operable oesophageal adenocarcinoma. A structured exercise intervention reduces physical decline and improves cancer control in patients undergoing NAC.

Declaration

I confirm that the work presented in this thesis is my own work and that no portion of the work referred to has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

The work is described in the following sections:

In Part A, this thesis presents a brief overview of oesophageal cancer incidence, staging and treatment. More specific detail of the 'curatively intended' pathway is described along with a review of the current literature in Chapter 3 (as per pre-publication copy of published manuscript).

Part B starting with Chapter 4, gives details of the trial protocol followed by Chapter 5 which reviews patients' participation and withdrawals as well as those patients who declined participation. As a feasibility study, withdrawals/dropouts and patients declining participation are important considerations for future developments and exercise program implementations.

Chapters 6 to 10 cover the measured outcomes of the trial. In these outcomes chapters, specific methods and results relevant to each section will be included.

Part C includes an overall discussion and conclusion with recommendations for future work.

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Abbreviations

Abbreviation	Meaning
AC	Adenocarcinoma
AT	Anaerobic Threshold
CCG	Clinical Commissioning Groups
CHHP	Centre for Health and Human Performance
CPEX / CPET	Cardio-pulmonary Exercise Testing
CPR	Complete Pathological Response
CT	Computerised Tomography
CTIMP	Clinical trial of an investigative medical product
DICOM	Digital Imaging and Communications in Medicine
ECCG	Esophageal Complications Consensus Group
ECF	Epirubicin Cisplatin 5'Fluorouracil
ECX	Epirubicin Cisplatin Capecitabine
EORTC	European Organisation for Research and Treatment of Cancer
EOX	Epirubicin Oxaliplatin Capecitabine
ERAS	Enhanced Recovery After Surgery
EUS	Endoscopic Ultrasound
EUS	Endoscopic Ultrasound
FFM	Fat Free Mass
FFMi	Fat Free Mass index
FLOT	5'Fluorouracil Leucovorin Oxaliplatin Docetaxel
FM	Fat Mass
FMi	Fat Mass index
FMR	Fat to Muscle Ratio
FNA/B	Fine Needle Aspirate / Biopsy
GOJ	Gastro-oesophageal Junction
GP	General Practice/Practitioner
GSTC	Guys' and St Thomas' Charity
GSTT	Guy's and St Thomas' NHS Foundation Trust Hospitals

HRA	Health Regulatory Authority
HRQL	Health-Related Quality of Life
IL	Interleukin
INF-y	Interferon-gamma
IRAS	Integrated Research Application System
ITU	Intensive Care Unit
KCL	King's College London
LJMU	Liverpool John Moore's University
LN	Lymph node(s)
LNRS	Lymph Node Regression Score
MCP-1	Monocyte Chemoattractant Protein-1
MDM	Multi-Disciplinary Discussion
MDM/MDT	Multi-Disciplinary Meeting/Team
MRI	Magnetic Resonance Imaging
MTRG	Mandard Tumour Regression Grade
MTWH	Maidstone and Tunbridge Wells NHS Hospitals
NAC	Neo-adjuvant Chemotherapy
NHS	National Health Service
NOGCA	National Oesophago-gastric Cancer Audit
OBE	Order of the British Empire
OC	Oesophageal Cancer
OGD	Oesophago-gastric-duodenoscopy
OS	Overall survival
PET	Positron Emission Tomography
PhD	Doctor of Philosophy
PhD	Doctor of Philosophy
PI	Principle Investigator
Pre-EMPT	**Pre**habilitation in patients diagnosed with o**E**sophageal **M**alignancy, on a **P**eri-operative **T**reatment pathway
PROM	Patient Reported Outcomes Measure
QLQ	Quality of Life Questionnaire

R&D	Research and Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
SCC	Squamous Cell Carcinoma
SF or SA	Subcutaneous Fat or Subcutaneous Adipose tissue
SM	Skeletal Mass
STH	St Thomas' Hospital, London
SWEMWBS	Short Warwick-Edinburgh Mental Wellbeing Score
TME	Tumour Micro-Environment
TNFa	Tumour Necrosis Factor alpha
UGI	Upper Gastrointestinal
UK	United Kingdom
USA	United States of America
Use Sort	Make sure you check Table has Header Row.
VF or VA	Visceral Fat or Visceral Adipose tissue
VO2	Maximal Oxygen Consumption
WEMWBS	Warwick-Edinburgh Mental Wellbeing Score
WHO	World Health Organisation

Part A

Chapter 1 Introduction

1.1 Background

From October 2011, I had the privilege of managing the research studies within the Upper Gastrointestinal (UGI) cancer surgery unit at St Thomas' Hospital in London, United Kingdom (UK).

Amongst others, we were involved in studies evaluating Health Related Quality of Life after oesophago-gastric surgery; genetically based blood, tissue and clinical outcomes collaboration with Professor Rebecca Fitzgerald's group at Cambridge University; database studies assessing survival and recurrence in patients up to 10 years after surgery; novel measures of assessing comorbidities; internal audits of post-operative complications after surgery; and academic Bachelors, Masters and Doctoral thesis studies.

Data collection of patients undergoing treatment within the UGI cancer surgery group was routinely collected, under ethical approval, for the purposes of review and research and as an integral part of the group's efforts to improve the diagnosis, treatments and outcomes of patients after surgery.

The surgical group also contributed data to the mandatory National Oesophago-gastric Cancer Audit (NOGCA).

My career background in laboratory medicine, marketing management and product development in the pharmaceutical industry, and for the past 11 years in cancer research, equipped me well for the role of Clinical Research Manager within the Oesophago-gastric cancer surgery research group.

In the first half of 2014, I was in the St Thomas' theatre's coffee room going through some research study material when Consultant Surgeon, James Gossage, suggested that I should undertake further study towards a higher educational degree - 'as I was doing all the work but not being credited for it formally'. Initially, I dismissed his comment but as the next few months and years unfolded, and with the development of the Pre-EMPT study, I realised that if I could pull everything together it would be a great PhD thesis opportunity. The seed was planted.

1.2 Factors leading to the concept and development of the Pre-EMPT trial

- Between April 2015 and March 2016, approximately 3000 patients' surgical records of oesophageal and gastro-oesophageal resections were submitted to NOGCA. (*Why do patients with a curative treatment plan for oesophago-gastric cancer not go on to receive surgery?*, 2019).

  A topic of regular discussion and concern in this cohort of patients was, and continues to be, the high rate of post-operative complications after the high-risk surgery. Complications were measured using Clavien-Dindo scoring (Dindo, Demartines and Clavien, 2004; Clavien *et al.*, 2009) and the NOGCA's own scoring system. The Esophageal Complications Consensus Group (ECCG) was formed as an international group established to set a standardised format for recording of post-operative complications following oesophagectomy (Low *et al.*, 2015) . In the 2017, a NOGCA report (Maynard *et al.*, 2017) of the period April 2014 to March 2016, reported that 36.4% of patients were reported to have suffered complications after oesophagectomy (*National Oesophago-Gastric Cancer Audit 2017*, 2017). In-hospital mortality was 2.1% of patients operated with 90-day mortality rates remaining high at 3.3%.

  Although patients went on to recover from their surgery and post-op complications, there was concern that complications after surgery for cancer of the oesophagus led to increased rates of recurrence and therefore reduced survival (Lagarde *et al.*, 2008; Rutegård *et al.*, 2012).

- Health-Related Quality of Life (HRQL), at 3 years post-op, in these patients was worse than before surgery (Lagergren *et al.*, 2007) and more recently, Swedish studies showed that complications after surgery had a major influence on HRQL for up to 10 years post-surgery (Derogar *et al.*, 2012; Kauppila *et al.*, 2018)

- Following the results of the MAGIC clinical trial (Cunningham *et al.*, 2006a) which demonstrated that peri-operative chemotherapy (in the neo-adjuvant plus adjuvant settings) reduced tumour size, stage and improved rates of recurrence and survival in oesophageal cancer, the surgically-operable cohort of patients would undergo chemotherapy before surgery as standard-care. The downside of the introduction of neo-adjuvant chemotherapy as standard-care in the United Kingdom (UK), from a surgery and recovery-after-surgery perspective, was the impact of chemotherapy-related deconditioning on the fitness (Navidi *et al.*, 2018; Thomson *et al.*, 2018) of patients

scheduled for invasive intra-thoracic/intra-abdominal surgery and the impact on post-operative recovery, complications and HRQL.

- Enhanced Recovery After Surgery (ERAS) programs, aiming to minimise operative stress, improve post-operative recovery and shorter hospital stay, were later introduced in patients undergoing oesophagectomy, due to the complexity of surgery and high rates of post-op complications (Liu *et al.*, 2018). The main components of the ERAS programs were focussed on the immediate peri-operative period. The main benefits appeared limited to reduction of length of hospital stay rather than improvement in post-operative complications (Markar *et al.*, 2017).

As a group of clinicians and researchers, patient care and the improvement of diagnosis, treatment and outcomes was at the heart of our group's research focus. The most significant development in the previous few years had improved tumour and survival outcomes but had led to reduction in patient fitness before surgery. Post-op morbidity remained stable but high and health-related quality of life was reduced for up to 10 years after surgery. What was the future for our research?

In September 2014, Professor Greg Whyte was invited to address our oesophago-gastric cancer surgery research group. His presentation about fitness in relation to surgery and cancer stimulated discussion and consideration of developing pre-surgical physical/exercise optimisation of patients before major surgery. Some of the unanswered questions we had to consider were: Was exercise during neo-adjuvant chemotherapy feasible; was it safe; would it be beneficial physically and/or psychologically; might there be any 'unknown' outcomes?

Pre-operative optimisation before surgery had been discussed and introduced in various contexts (Azhar, 2015; Meka *et al.*, 2016) but not, to our knowledge, in patients undergoing neo-adjuvant chemotherapy followed by surgery, in any cancer.

In January 2015, we followed up Professor Whyte's presentation with a visit to the team at the Centre for Health and Human Performance (CHHP), of which Prof Whyte is Co-founder and Director of Human Performance Science. This was a pivotal point in the forward development of this trial and thesis: "Feasibility of a structured exercise program in patients undergoing a 'curative' pathway following a diagnosis of operable oesophageal adenocarcinoma". The trial name Pre-EMPT was adopted: '**Pre**habilitation in patients diagnosed with o**E**sophageal **M**alignancy, on a **P**eri-operative **T**reatment pathway'

We now had the essential ingredients: access to a suitable a patient group for the intervention; experts in clinical care in the relevant patient population, experts in physical performance and training, and in research practice; the necessary equipment and study locations.

What we lacked was a suitable control cohort (the annual patient numbers would be too small for a Randomised Control Trial (RCT) at St Thomas' Hospital alone); ethical approval, NHS approval, and of course, funding.

1.3 Regulations and collaborators

1.3.1 Developing a control cohort

In March 2015, we approached Dr Mike Browning, Consultant Anaesthetist and Cardio-pulmonary Exercise Testing (CPEX) Lead, at Maidstone and Tunbridge Wells NHS Hospitals (MTWH) to be Principle Investigator (PI) at MTWH.

There were two main reasons for approaching Dr Browning in Maidstone:

Firstly, he had a professional interest in pre-operative assessment using CPEX.

Secondly, the patients at MTWH were a good geographical Control cohort – since 2015 all patients with operable oesophago-gastric cancer at MTWH were referred to St Thomas' Hospital (STH) for cancer surgery; the patients received similar neo-adjuvant chemotherapy treatment at MTWH through online Multi-Disciplinary Discussion (MDM) with Guy's and St Thomas' NHS Foundation Trust (GSTT) Upper Gastro-intestinal Specialist MDM; Clinical Commissioning Groups (CCG) in Kent had requested a limit on patient travel to STH during the course of their treatment - largely for the purpose of minimising disruption to patients traveling long distances during their treatment. This made for a good, comparative, geographic control group for the study.

All patients were to receive the standard-care treatment pathway with clinical, nursing, dietetic, physiotherapy and pre-op assessment that was in practice locally whether participating in the trial or not.

1.3.2 Funding

In collaboration with Chief Investigator and Consultant Upper Gastro-intestinal Surgeon at St Thomas' Hospital, Mr Andrew Davies, I completed and submitted a funding application to the Guy's and St Thomas' Charity's Health Innovation Funding scheme in May 2015. Unfortunately, the application was rejected. Following a further meeting with the Charity and a revised funding

application, we were successful in obtaining enough funding to run a 3-year Pre-EMPT clinical trial.

CHHP generously offered to donate funding and staff to perform the CPEX testing and exercise training of patients in the Interventional cohort. Fitbit UK, donated Fitbit wearable trackers to monitor the patients in both Intervention and Control cohorts. Ultimately, data from the Fitbits would also provide information on heart rates and sleep patterns in patients undergoing neo-adjuvant chemotherapy - another first in this group of patients.

1.3.3 Research Ethics, Health Regulatory, NHS and R&D approvals

With project and staff funding secured, I embarked on the unenviable task of dealing with the UK's research ethics regulatory processes.

I wrote the trial Protocol with full set of trial documents followed by the Integrated Research Application System's (IRAS) online ethics application and documents. At the end of May 2016, the Health Regulatory Authority (HRA) added an additional level to the regulatory approvals process; however, this would assist by including the generic NHS approval prior to local site approval.

As this study was not a 'clinical trial of an investigative medical product' (CTIMP) we were able to submit the study ethics application through the 'Proportionate Review' process – a shorter, potentially quicker process.

In November 2016, we eventually received full Research Ethics Committee (REC), HRA, NHS and local GSTT Research and Development (R&D) approvals (*Prehabilitation of Patients With oEsophageal Malignancy Undergoing Peri-operative Treatment - Full Text View - ClinicalTrials.gov*). REC application number: 16/SC/0438

5 days later we consented our first patient into the Interventional arm of the Pre-EMPT trial.

It was a further few months until the trial was approved by the MTWH R&D department to start including patients in the Control cohort. The first control patient was consented in February 2017.

1.4 PhD thesis registration

Prof Greg Whyte OBE, Professor of Applied Sport and Exercise Science at Liverpool John Moore's University (LJMU) and Co-Investigator on Pre-EMPT, kindly agreed to be Director of Studies for my PhD.

Pre-EMPT Chief Investigator and Consultant Surgeon, Andrew Davies and Dr Lynne Boddy, Reader in Children's' Physical Activity, kindly agreed to be Co-Supervisors.

In October 2016, I enrolled as a PhD student at LJMU with the research proposal subsequently approved by the LJMU Research Degrees Committee.

Chapter 2 Cancer of the oesophagus and gastro-oesophageal junction cancer

2.1 Epidemiology

Oesophageal cancer (OC) is the 13th most common cause of cancer diagnosis, but the 7th most common cause of cancer death, in the United Kingdom (UK). In the UK, the one-year survival rate is around 42% falling sharply to 15% at 3 years after initial diagnosis (*Oesophageal cancer risk | Cancer Research UK*, no date). This sharp fall in survival is an indicator of the aggressive nature of the disease and the late presentation of patients for diagnosis and treatment.

The prevalence is higher in men than in women (*Oesophageal cancer risk | Cancer Research UK*, no date) with the age-adjusted incidence in the UK rising by 39.6% for men and 37.5% for women every 5 years (Pennathur *et al.*, 2013). The greatest incidence is in 70-74 year-old men (*Esophageal cancer in England by age and gender | 2016 statistic*).

Oesophageal cancer is divided largely into two main histological types: Squamous Cell Cancer (SCC) and Adenocarcinoma (AC). Over the past few decades, the incidence of AC has overtaken that of SCC in the UK, USA, Australia and some countries in Western Europe (Pennathur *et al.*, 2013). This histological change in AC is largely associated with an increase across all socio-economic groups but especially in those with greater affluence (Lepage *et al.*, 2008) and life-style factors including a diet low in fruit and vegetables, obesity, gastro-intestinal reflux disease, Barrett's oesophagus (abnormal oesophageal cell growth), and tobacco use (Pennathur *et al.*, 2013) – many, largely related to a sedentary lifestyle.

In this thesis, the focus is on patients diagnosed with the AC histological type.

2.1.1 Diagnosis

Patients present to their General Practitioner (GP) or to Accident and Emergency Departments with symptoms of pain or difficulty in swallowing (dysphagia), regurgitation after eating, vomiting, heartburn that does not go away, discomfort in the chest or back and / or weight loss (*Signs and symptoms of oesophageal cancer - Understanding your diagnosis - Macmillan Cancer Support*, no date).

The initial investigations include an endoscopic oesophago-gastric-duodenoscopy (OGD) for visual, clinical examination with biopsies of any abnormal-looking areas for histological confirmation of disease. A Computerised Tomography Scan (CT) is carried out to assess tumour location, size and possible spread of disease to the surrounding organs. Depending on the outcome of these initial investigations, further evaluation of disease-spread may be carried out

by the patient undergoing a Positron Emission Tomography scan (PET) and staging laparoscopy. If metastases are suspected, further investigations may include Magnetic Resonance Imagining (MRI) and/or Fine-Needle Aspirate/Biopsy (FNA/B) of suspected tissue for histological confirmation.

2.1.2 Staging

On completion of all investigations, an expert Multidisciplinary Team Meeting (MDT or MDM) is convened and full details of each patient is presented for staging of the disease. The staging-process assesses all the information available to decide on the location and TNM-stage of the disease (T.W. Rice *et al.*, 2016) :

T - stage provides information about the depth of tumour growing through the mucosal and deeper wall layers of the oesophagus or surrounding structures.

N - stage informs about any nodal spread of disease. This may include spread to local or distant lymph nodes.

M – stage is assessed by examining the whole body and potential spread of disease to any part of the body.

This TNM value of the disease has an important bearing on the treatment pathway selected for a given patient.

Location of the tumour is divided into upper-, mid-, lower- oesophagus or gastro-oesophageal junction. Location, in conjunction with the size, and containment or spread of disease, along with a patient's comorbidities and fitness for treatment are the main parameters evaluated to plan a suggested course of treatment. These factors will influence any discussion with the patient about suitable treatments.

2.1.3 Treatment

In the UK, the standard treatment for patients diagnosed with operable, or locally advanced AC, are placed on a so-called 'curatively-intended' treatment pathway. The pathway includes neo-adjuvant chemotherapy (or neo-adjuvant chemoradiotherapy in selected cases) followed by surgery. A further course of adjuvant treatment follows surgery in patients who are fit enough to resume oncological treatment after surgery and where the post-op histopathological assessment indicated the requirement for further oncological treatment.

Patients who are deemed to have inoperable or metastatic disease, or who are deemed physically unfit for radical treatment are placed on a palliative treatment pathway. This pathway

will offer chemotherapy to those patients well enough to tolerate the toxicity of treatment side-effects. Patients may be offered palliative radiotherapy for symptomatic control, artificial feeding or palliative stenting to support their nutrition and fluid requirements during treatment of 'Best Supportive Care'.

This thesis focuses on patients on a 'curatively-intended' treatment pathway.

2.2 The 'Curatively-intended' Treatment Pathway

2.2.1 Neo-adjuvant chemotherapy

Patients on a treatment pathway of 'curative intent' undergo neo-adjuvant chemotherapy (NAC) to downstage the tumour size, lymph node burden and reduce micro metastases ahead of surgery, leading to an improved 5-year survival (Andrew R Davies *et al.*, 2014).

Patients undergoing NAC have 3 x 21-day cycles of anthracycline and platinum/fluoropyrimidine-based triple therapy of Epirubicin (E), Cisplatin/Carboplatin (C) and 5-fluorouracil (5FU/F)/Capecitabine (X) (ECF/ECX) or those undergoing the more recently approved treatment regimen 'FLOT' which includes the addition of docetaxel combined with platinum/fluoropyrimidine therapy (Docetaxel, oxaliplatin, leucovorin and 5-fluorouracil), undergo 4 x 14-day cycles of treatment.

Patients on an ECX/ECF treatment protocol, often experience toxicities that include vomiting, nausea, thromboembolic events and anaemia while those on a FLOT regimen experience more diarrhoea, infections, neutropenia, and sensory neuropathy (Bose *et al.*, 2017).

NAC treatment and side-effects have a deconditioning effect on patient-fitness which is further compounded by major surgery.

2.2.2 Surgery and post-operative complications

Oesophagectomy for cancer of the lower oesophagus or gastro-oesophageal junction involves removing most, or a large section of the thoracic oesophagus and about 1/3 to 1/2 of the stomach.

The remaining stomach is refashioned into a pseudo-oesophagus/stomach with an intra-thoracic or cervical anastomosis to the remaining upper thoracic or cervical oesophagus.

This is high-risk, invasive surgery and has historically had high mortality rates although these are now improving with centralisation of specialist services in high-volume centres (Low, 2013). Post-operative complications, however, remain high and are associated with reduced survival (Rutegård *et al.*, 2012). Reduced fitness is also associated with increased post-operative

morbidity (Levett and Grocott, 2015a) in oesophageal cancer surgery that involves transthoracic or transhiatal, two-cavity surgery. Reduction in fitness, compounded by NAC and major surgery, significantly reduces the numbers of patients who commence or complete the standard treatment of post-operative chemotherapy to around 40%.

The combination of chemotherapy and surgery both represent significant physiological insults thought to have detrimental effects on physical activity and outcomes after surgery.

2.2.3 Enhanced Recovery after Surgery

Enhance Recovery after Surgery (ERAS) programs that focus on early post-operative mobilisation have helped to improve methods of pain-control and reduced-length of hospital stay. They have been introduced as standard-care in most UK oesophageal resection units. Analysis of ERAS-standardised protocols have proven to be safe, resulting in a reduced length of hospital stay (Gatenby *et al.*, 2015) and, in some cases, a reduction in non-surgical complications (Pisarska *et al.*, 2017).

To-date, however, the priority for improvement has been focused on the immediate peri-operative and in-hospital recovery period. Little attention has been given to physical preparation for high-risk oesophageal surgery complicated by neo-adjuvant oncological therapies.

2.2.4 Rehabilitation versus Prehabilitation

Preparing patients for surgery through a program of exercise before surgery has been shown to improve functional recovery in patients undergoing cardiovascular and orthopaedic surgery (Debes, Aissou and Beaussier, 2014). Rehabilitation after cancer treatment has been successful in improving physical and psychological impairments, and quality of life (Fialka-Moser *et al.*, 2003). Increasingly, advanced exercise programmes, sometimes termed 'prehabilitation', directed by experienced multidisciplinary teams are being used to mitigate the secondary effects of cancer treatment (Julie K Silver and Baima, 2013).

To date, no data has been published examining structured exercise prehabilitation programs for patients undergoing neo-adjuvant chemotherapy and surgery in oesophageal cancers but, it was hypothesised that a program of supervised physical activity during neo-adjuvant oncological treatment would be feasible, would reduce chemotherapy-related deconditioning and improve physical fitness before surgery.

This thesis aimed to investigate the feasibility, and potential benefits, for patients undertaking a prescribed physical activity program starting before commencing NAC, continuing throughout NAC, with further consolidation of physical optimisation during the period leading up to surgery.

Chapter 3 Review of Literature

The following chapter is based on an invited, published review article on prehabilitation in oesophageal cancer surgery (Zylstra *et al.*, 2018).

Prehabilitation

"By failing to prepare, you are preparing to fail."

Benjamin Franklin

Delivery of care for patients with oesophageal cancer is no longer the preserve of single modality surgical intervention but has become a multifactorial 'aggregation of marginal gains' in multidisciplinary practice. This review aims to explore the benefits of exercise prehabilitation in oesophageal cancer treatment.

Background

The physiological impact of having an oesophagectomy is often likened to that of running a marathon. Whilst nobody would consider starting a marathon without months of dedicated preparation, the majority of patients scheduled for surgery undergo little or no physical training in the lead up to their operation.

In recent years, Enhanced Recovery After Surgery Programs (ERAS/ERP) have resulted in improved short-term outcomes after surgery (Preston *et al.*, 2013) and have widely been integrated into surgical-oncology pathways as best practice. Yet, increasing the expectations on patients recovering from high-risk surgery without preparing them physically makes little sense. In some disciplines, where pre-operative exercise programs have been introduced to optimise physical function in patients before surgery, a positive benefit on post-operative functional capacity and return to activities of daily living has been seen in the short-term(Carli, Gillis and Scheede-Bergdahl, 2017). Physical or multimodal prehabilitation of patients before cardiovascular, abdominal and colorectal cancer surgery has resulted in improved pre-and post-operative functional capacity (Mayo *et al.*, 2011; Debes, Aissou and Beaussier, 2014; Minnella *et al.*, 2017; Steffens *et al.*, 2018). However, the focus in these programs has been in the peri-operative period. The opportunity for extended prehabilitation from the time of diagnosis, through neo-adjuvant oncological therapy, is the subject of a number of on-going clinical trials. (Table 1)

Current status in oesophago-gastric cancer

In patients diagnosed with locally advanced oesophago-gastric cancers, neo-adjuvant chemotherapy (NAC) or chemo-radiotherapy (NACRT) followed by surgery remains the treatment of choice (Low *et al.*, 2007; Chen *et al.*, 2017; Zhou *et al.*, 2020). Introduction of neo-adjuvant oncological therapies has resulted in improved overall and disease-free survival (Bosset *et al.*, 1997; Andrew R. Davies *et al.*, 2014). However, the effects of neo-adjuvant chemotherapy result in physiological deconditioning. In a study using cardiopulmonary exercise (CPEX) testing before and after NAC, Jack et al recorded a 15% decline in oxygen uptake at estimated lactate threshold in patients due to undergo oesophago-gastric surgery (Jack *et al.*, 2014; Thomson *et al.*, 2018).

Improvements in surgical techniques, including minimally invasive and robotic surgery, and centralisation of surgery to specialist centres have improved safety. As a result, the 30 day post-operative mortality has reduced from 10.3% to 1.9% in the UK national audit (Boddy, Williamson and Vipond, 2012; Maynard *et al.*, 2017). ERAS programs have resulted in reduced length of stay and readmissions to hospital after surgery(Preston *et al.*, 2013; Ashok *et al.*, 2020). However, whilst mortality rates have fallen, reported post-operative morbidity rates of 36 – 59% (Gockel, Exner and Junginger, 2005; Booka *et al.*, 2015; Low *et al.*, 2017) and resolution of quality of life remain a significant challenge - both of which may conceivably be improved by prehabilitation.

The demographic of patients being diagnosed with potentially 'curable' oesophageal cancer is also a changing landscape. With the ageing population, older patients on poly-pharmacy regimens are presenting with tumours that are technically surgically resectable but who are of borderline fitness for high-risk and physiologically demanding surgery. Profoundly unfit patients with comorbidities relating to sedentary lifestyles are also being seen with a cancer diagnosis at a young age.

The health benefits of exercise are well established (Warburton, Nicol and Bredin, 2006). These include lower mortality and morbidity rates (Paffenbarger *et al.*, 1993; Sandvik *et al.*, 1993), improved cardiovascular function, strength and muscle mass, postural stability and psychological function, improvements in depressive symptoms and sleep disorders(Butler *et al.*, 1998) and better overall quality of life (Penedo and Dahn, 2005). With the safety and benefits of exercise during cancer treatment being accepted as a principle(Galvão and Newton, 2005; Witlox *et al.*, 2018) and encouraged by cancer support organisations (*Benefits of being active - Information and support - Macmillan Cancer Support*, no date), the focus of attention in oesophageal cancer has turned to prehabilitation before surgery, specifically encompassing the neo-adjuvant treatment period.

Heldens et al. (Heldens *et al.*, 2016) reported on the feasibility of a structured exercise program during neo-adjuvant chemo-radiotherapy in patients diagnosed with rectal cancer. They concluded that an outpatient prehabilitation program was largely feasible and safe, and not only prevented the reduction in physical fitness decline associated with NACRT but improved functional exercise capacity by 9.0% and leg muscle strength by 39.2%.

Pre-operative programs, focusing mainly on respiratory function, have shown mixed results across a variety of surgical disciplines, including cancer (Banugo and Amoako, 2017). Dettling et al. reported on the benefits of Inspiratory Muscle Training (IMT) as significantly improving respiratory muscle function but with no benefit on post-operative pneumonia following oesophagectomy (D S Dettling *et al.*, 2013). However Boden et al. reported a 50% reduction in postoperative pulmonary complications after major upper abdominal surgery following a single preoperative physiotherapy session (Boden *et al.*, 2018). An increase in inspiratory muscle function but no increase in peripheral muscle strength or aerobic capacity using IMT, was reported by Valkenet at al. who suggested that the limited benefits were partly due to a short interval between screening and surgery (Valkenet *et al.*, 2016).

In a trial, which included pre-operative aerobic and resistance training versus rehabilitation in colorectal cancer patients, Gillis et al. reported similar hospital length of stay and post-operative outcomes (Gillis *et al.*, 2014). However, there was an improvement in 6-min walk test (6MWT) in the prehabilitation group at 8 weeks after surgery when compared to the rehabilitation group, suggesting a better maintained physical capacity and/or accelerated recovery post-surgery following prehabilitation.

Prehabilitation in surgery

Tew et al.(Tew *et al.*, 2018), in their 'Clinical guidelines and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery', graphically represent the physical trajectory of prehabilitation before surgery with the anticipated post-surgery improvement in functional capacity, versus that of the non-optimised surgical patient (Figure 1).

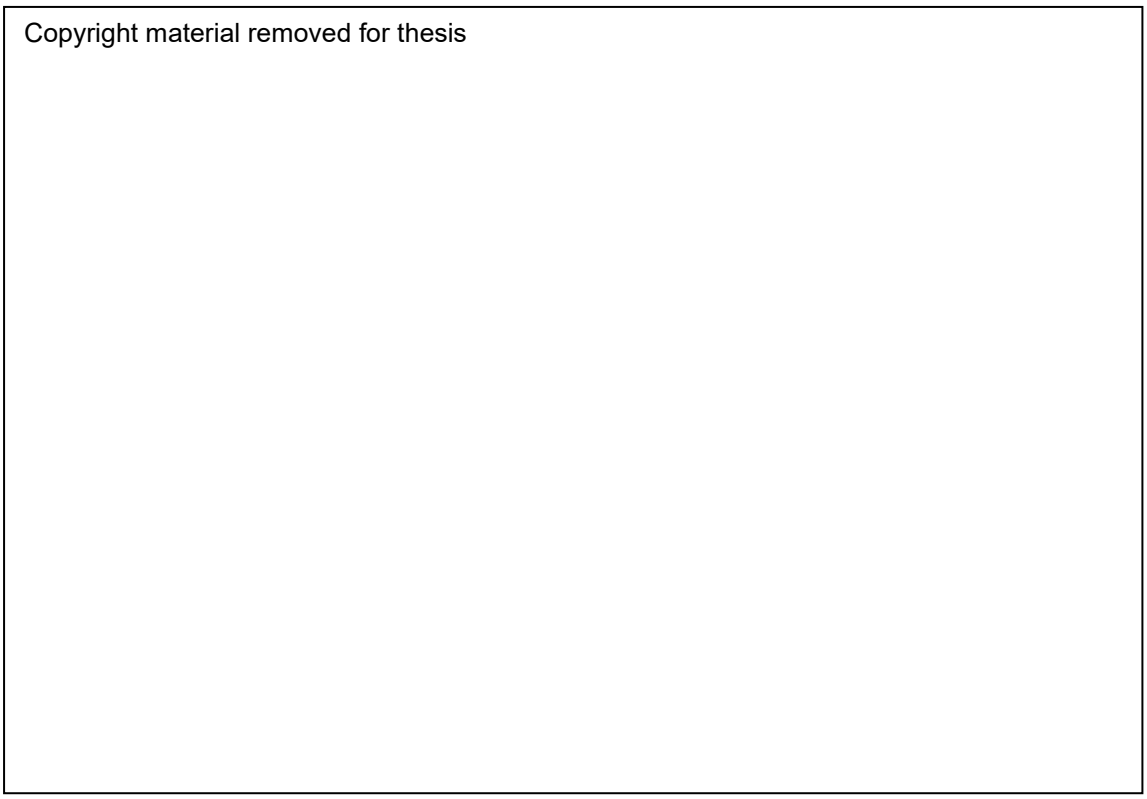


Figure 3-1 The prehabilitation concept. (Tew et al., 2018).

A summary of their key recommendations on peri-operative exercise include:

- Priority of patient selection, especially those identified with a higher risk of peri-operative complications
- Multimodal interventions including: smoking cessation; reduction in alcohol intake; and treatment of anaemia
- Presentation of the exercise program as pre-operative optimisation rather than as an optional extra
- Initial patient assessment, including comorbidity optimisation, risk evaluation and education on the benefits of exercise
- Objective functional evaluation and quality of life assessment
- Ongoing 'response to training' functional assessments
- Sufficient time for intervention, commencing as early in the surgical pathway as possible, ideally with a minimum of 4 weeks before surgery

- A combination of aerobic training, resistance training and inspiratory muscle training, tailored to each patient
- Supervised programs by trained individuals. Self-managed programs may be suitable in selected individuals.

In an elective surgical patient group, these are valuable and important recommendations. However, there are challenges in following these guidelines within a cancer treatment pathway. Patient selection after a diagnosis of cancer is based largely on tumour-stage and patient fitness. With 'time-to-treat' targets and established cancer treatment pathway guidelines, there is little time for optimization of modifiable comorbidities and lifestyle factors particularly if these interventions are constrained to the narrow window between diagnosis and start of NAC. Patient fitness, in the majority of these patients, is already compromised. Cramer et al. found that, on average, colorectal cancer patients had a baseline VO2 peak of 23% below that of general population, age-matched controls (Cramer *et al.*, 2014). To compound this, patients frequently develop induced complication toxicities from chemotherapeutic agents. Anthracyclines and anti-angiogenic targeted therapies, commonly used in the neo-adjuvant pathway, lead to increased exercise intolerance in cancer patients (Jones *et al.*, 2009; Bonsignore and Warburton, 2013). In the UK MRC OE05 chemotherapy trial, 12% of patients stopped chemotherapy early due to toxicities and 11 % of patients did not proceed to surgery. Of these, 15% developed significant comorbidities that precluded surgery. The mortality from combined Epirubicin, Cisplatin and Capecitabine (ECX) chemotherapy was 1.8%, equivalent to the post-operative mortality seen in the trial (Alderson *et al.*, 2017).

Therefore, a diagnosis of cancer, and especially oesophageal cancer, results in a unique group of patients requiring an individualised or tailored approach to prehabilitation. This mandates a fundamental understanding of the treatments they receive and an appreciation that the exercise intervention may differ at the various stages of the treatment pathway.

Prehabilitation in cancer

Silver and Baima describe *cancer prehabilitation as "a process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline function level, identifies*

impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments" (Julie K. Silver and Baima, 2013a).

Table 1 represents the current landscape of registered clinical trials of pre-operative exercise interventions in oesophageal cancer, focusing on those during NAC. They are limited to relatively small, prospective studies with numerous primary endpoints and large variations in how physical function is measured.

Each study has been evaluated according to Silver's definition of prehabilitation in cancer (Julie K. Silver and Baima, 2013a). The few studies that have reported results mainly include exercise interventions focusing on pre-operative respiratory muscle training with the aim of reducing post-operative pulmonary complications.

The awaited results will help to inform and shape the future of UGI cancer prehabilitation.

A number of important points are highlighted from the Silver's description that present challenges that need to be met in any attempt to successfully deliver prehabilitation in cancer patients:

1. **A process on the cancer continuum of care**

A continuum is *'A continuous sequence in which adjacent elements are not perceptibly different from each other, but the extremes are quite distinct.'* (Oxford Living Dictionaries, 2017)

In the context of the cancer patient, the investigative and treatment pathways may feel like a continuum. However, in reality, there are distinct needs during each element from diagnosis, through chemotherapy, surgery and into the recovery period.

The exercise advice given to a treatment-naïve patient will differ from that of a patient during active chemotherapy treatment especially in the first days following chemotherapy infusions. In the 'washout period' after NAC, as the effects of chemotherapy toxicities subside, activity may be designed to increase in intensity in preparation for surgery. Nutritional and psychological support will likewise adjust to each phase of treatment. In-hospital physiotherapy teams will oversee early post-operative recovery, but following discharge, any exercise program clearly needs to be sympathetic to the resultant physical deficiencies incurred by the surgery.

2. **Between the time of diagnosis and the beginning of acute treatment**

The timing of introducing prehabilitation programs poses a significant challenge with regards to imposed 'time-to-treat' treatment pathways. Once staging has been completed, patients may be required to attend the hospital multiple times for additional investigations including renal and cardiac function, and nutritional optimization prior to starting neo-adjuvant chemotherapy.

Patients also take time to process the diagnosis of cancer and the impact it will have on their lives and that of their families (Edwards and Clarke, 2004). Initiating exercise training during this period is challenging. Opportunities for exercise training need to be accessible and preferably provided on-site to avoid additional travel for patients (Ferreira *et al.*, 2018).

Prehabilitation during NAC aims to reduce physical deconditioning, increase pre-operative activity levels and as a result, optimise fitness and improved mental and emotional health ahead of demanding surgery. Much of the reported research in exercise training has focused on the 2 – 6 weeks before surgery. In Figure 2, Jack et al. present the CPEX results of VO2peak before and after NAC showing decline of physical function in patients during treatment (Jack *et al.*, 2014). This study highlights that exercise interventions, in patients undergoing neo-adjuvant treatments, need to be introduced from the time of diagnosis rather than waiting to begin prehabilitation in the pre-surgery period.

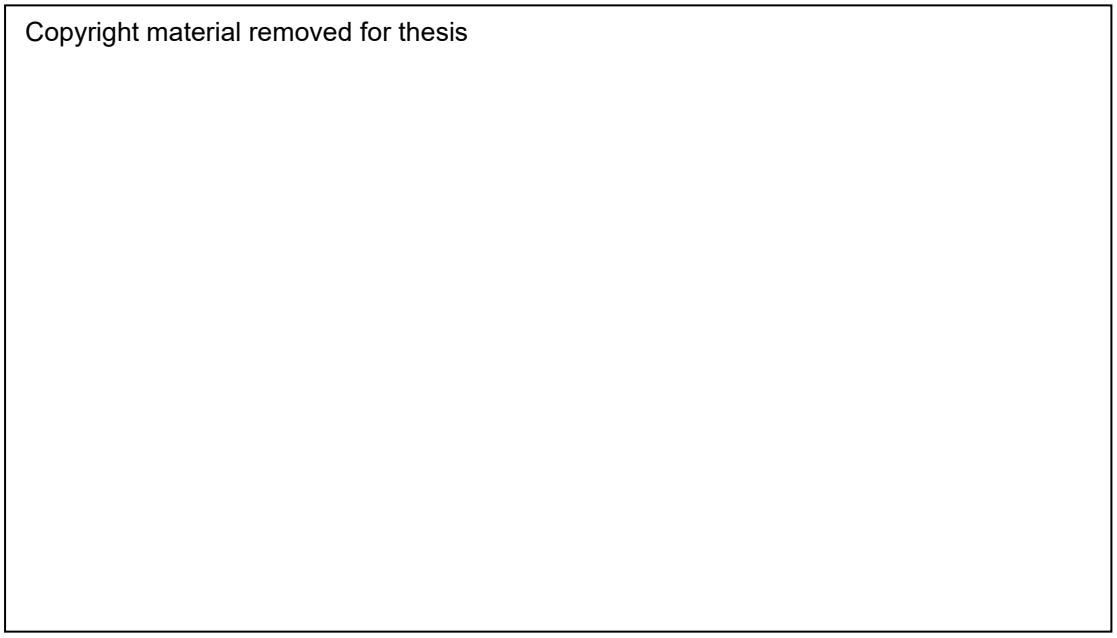


Figure 3-2 A ladder plot of oxygen uptake at estimated lactate threshold pre-and-post-neoadjuvant chemotherapy (NAC) (Jack et al., 2014)

3. Physical and psychological assessments that establish a baseline function level.

There is general consensus (Julie K. Silver and Baima, 2013b; Tew *et al.*, 2018) that patients undergoing prehabilitation in cancer should undergo baseline assessment of physical and psychological function. Cancer treatment is physically, emotionally and psychologically stressful (Hellstadius *et al.*, 2016, 2017) . Each patient will have unique comorbidities and physical

capabilities. As a result, physical training needs to be individualized to those specific needs, measured against a baseline assessment and with subsequent monitoring and guidance during training (Tew *et al.*, 2018) .

In clinical trials, baseline assessments vary and may include: 6-minute walk test, muscle function/strength tests (*i.e.* leg press and chest press), VO2max as measured by Cardiopulmonary Exercise Test (CPEX) or estimated from a sub-maximal test, grip strength, Forced Expiratory Volumes (FEV), in addition to measures of insulin resistance, haemoglobin, white cell and blood albumin levels.

Cardiopulmonary exercise testing (CPEX) is a holistic measure of cardiorespiratory capacity and oxygen delivery within an individual, including that of skeletal muscle function (Albouaini *et al.*, 2007). It is a useful tool in risk stratifying patients, may predict post-operative morbidity and can guide exercise prehabilitation programs (Levett and Grocott, 2015b). Early mobilization of patients is a key aspect of ERAS programs for good reason, given that the pulmonary and systemic circulation, and peripheral muscle function are all activated through ambulation of patients post-operatively.

Some of the 'softer' physical measures, for example, 6MWT, grip strength and Forced Expiration Volume (FEV) used in studies are restricted in how they measure overall physical function. However, these limitations need to be weighed against advantages such as ease of access, cost and time taken to perform the test.

Validated psychological and well-being measures are readily available for use in cancer patients (*EORTC | European Organisation for Research and Treatment of Cancer : EORTC*, no date; Zigmond and Snaith, 1983; Tennant *et al.*, 2007). Baseline measures will serve to inform the clinical team of a patient's current status, may highlight important areas where intervention may be required and also provide valuable context during the survivorship period.

4. Identifies impairments

Whilst surgery is still considered to be the cornerstone of curative treatment, discussion with the patient involves identifying limiting factors prior to treatment selection. Pre-existing comorbidities and specific cancer-related risk factors need to be considered in relation to the toxicities resulting from chemotherapy and chemo-radiation treatments. Renal, cardiac and pulmonary function, in addition to smoking status, synchronous cancers, morbid obesity and mental health are all considerable risk factors for patients. The need for single lung ventilation

during oesophagectomy needs to be considered at the outset in relation to patient fitness for surgery.

The Eastern Cooperative Oncology Group (ECOG) Performance Status (*ECOG Performance Status - ECOG-ACRIN*, no date) is a standard used by oncologists to establish how the patient's disease affects their daily living abilities and to determine appropriate treatment. Furthermore, personal goals and patient wishes should be considered. An understanding of the benefits of physical exercise will have a significant influence on the patient's compliance when enrolling in exercise programs. The concept of "teachable moments" where patients are receptive to, and may act upon, health advice is particularly relevant to prehabilitation. Nadler et al. discuss some of the barriers relating to exercise during cancer treatment including, poor knowledge, lack of time and safety concerns (Nadler *et al.*, 2017). Advice from oncology care providers may be important in addressing these concerns. In addition, tailored exercise programs, targeted to the needs and preferences of the patient, combined with the use of group activities including family and friends, and regular monitoring with feedback, are some of a number of ways to improve motivation and adherence.

A number of strategies are emerging to adequately assess elderly and more complex patients prior to surgery. These include dedicated, high-risk, anaesthetic clinics and specific services overseen by Geriatricians e.g. POPS - 'Proactive care of older persons undergoing surgery' services. These services assist in identifying modifiable impairments which, if not addressed, would pose increased risk of post-operative problems in older, or less fit, surgical patients (Harari *et al.*, 2007). Once identified, these impairments may be optimized through prehabilitation. Carli et al. described mitigation of the post-operative stresses of surgery using an integrated multi-disciplinary approach of prehabilitation in the pre-operative period, highlighting especially the benefits in the older patient (Carli and Ferreira, 2018). Of note, physical activity levels and physical capacity in the general population falls significantly with age. In the UK population, 43% of 55 to 64-year olds are inactive (less than 30 minutes of physical activity per week), rising to 68% inactive in the 75+ years age group. Accordingly, prehabilitation to improve physical capacity is of greater importance in older patients and likely to become increasingly important as activity levels in the general population continues to fall (*Sport England*, no date)

5. **Provide interventions to promote the physical and psychological health of the patient that reduce the incidence and severity of future impairments**

Macmillan Cancer Support (*How active should I be? - Information and support - Macmillan Cancer Support*, no date) encourage the World Health Organisation guideline of Activity in Healthy Adults (World Health Organization, 2015). The recommendation is for "150 minutes/week of moderate intensity or 75 minutes of high intensity activity. Adults (aged 19 – 65+) should also aim to undertake activity to improve muscle strength and balance training sessions twice per week". The advice for patients with cancer is to aim to achieve the WHO guidelines but to adjust activity according to their physical symptoms and treatment status (*How active should I be? - Information and support - Macmillan Cancer Support*, no date).

In a study of physical activity guideline compliance in U.S. adults, Tucker et al.(Tucker, Welk and Beyler, 2011) reported that fewer than 9.6% met the WHO guideline for physical activity when objectively monitored on accelerometer. In contrast, the self-reported level of compliance was 63%. In a Sport and Physical Activity: Special Eurobarometer Report (2013), 29% of EU adults claimed to undertake vigorous activity for 1-3 days per week. 25% of adults reported participating in moderate activity, 4-7 days per week ('Special Eurobarometer 412 SPORT AND PHYSICAL ACTIVITY REPORT Special Eurobarometer 412 / Wave EB80.2-TNS Opinion & Social', no date).

Physical training interventions in past studies described a range of exercises for pre-operative optimization. Some suggested exercise of selected muscle groups to reduce post-op complications e.g. Inspiratory Muscle Training, to selectively attempt to reduce post-operative pneumonia (Daniela S. Dettling *et al.*, 2013; Banugo and Amoako, 2017; Boden *et al.*, 2018). The majority of current trials include a combination of aerobic and resistance training programs. (Table1). A meta-analysis by Marzolini et al. reported improved body composition, strength and cardiovascular fitness, and 'probably quality of life as well', in combined aerobic and resistance training versus resistance training alone(Marzolini, Oh and Brooks, 2012). Furthermore, they concluded that in stroke patients, aerobic training may be reduced by up to 40%, but with similar improvements in mobility and VO2peak, if combined with resistance training (Marzolini *et al.*, 2018).

Psychological health of the patient is also important in cancer prehabilitation. The advantageous outcomes of exercise on psychological health during cancer rehabilitation have been reported by Smith et al. and Losito et al. (Losito, Murphy and Thomas, 2006; Smith, Broomhall and Crecelius, 2016) These include improved quality of life and cancer-related fatigue. 'Living with and beyond

cancer' and 'survivorship' are terms frequently being used in post-treatment cancer patient groups. Physical exercise before, during and after cancer treatment improves physical status and quality of life (Losito, Murphy and Thomas, 2006; Lynch, van Roekel and Vallance, 2016; Ubago-Guisado *et al.*, 2019).

Prehabilitation, cancer and immunity

The effect of exercise prehabilitation in cancer may also impact on tumour control through immune system regulation. In a review of patients who undertook monitored exercise following a diagnosis of cancer, there was a lower relative risk of cancer recurrence and cancer-related mortality compared to patients who did little or no exercise. Furthermore, the same patients experienced fewer or less severe treatment side effects (Cormie *et al.*, 2017). Patients who experience complications after surgery have higher rates of cancer recurrence independent of tumour stage (Shimada *et al.*, 2017). This implies an immunological component to cancer recurrence. Terra et al. (Terra *et al.*, 2012) described inherent activation of the immune response cascade through exercise, eliciting a pro-inflammatory response during moderate intensity exercise. However, during high intensity exercise an anti-inflammatory response was noted. Hojman (Hojman, 2017a) further described the effects of exercise on the control of immune cell function, modulation of inflammatory signalling and regulation of systemic inflammation linking these regulatory effects to lowered tumour incidence and disease progression. Pederson et al. linked exercise to reduced tumour growth and through increased infiltration of natural killer (NK) cells in exercised mice (Pedersen *et al.*, 2016a). The mechanism of increased mobilization of NK cells is speculated to be through increased release of Interleukine-6 (IL-6) myokines in response to muscle contraction (Idorn and thor Straten, 2017). Exercise-induced IL-6 is described as having a pro-inflammatory effect on bacterial infections and contrasting anti-inflammatory inhibiting effect on Tumour Necrosis Factor-alpha (Cullen *et al.*, 2016). Research programs in clinical practice aim to provide evidence that exercise reduces the risk of complications and may also have immunological benefits on tumour control and recurrent disease.

Summary and clinical implications

Mortality rates after oesophagectomy have fallen, however morbidity rates remain high. The introduction of ERAS programs provided a consolidated framework for improvements of care in the peri-operative period and has reduced length of hospital stay. The introduction of prehabilitation programs, in order to optimise patients physically and psychologically for surgery,

have proved to be beneficial in some tumour groups. The health benefits, safety and biological benefits on tumour control following exercise have also shown positive results. A number of questions remain in regards to prehabilitation in oesophageal cancer. These include the timing and accessibility of the intervention, how to improve compliance, the optimal makeup of training programmes, how to measure physical performance and, the cost-effective implementation of prehabilitation into standard practice.

With a coordinated, multidisciplinary approach to introducing a holistic prehabilitation program in cancer care, there is realistic potential to change the current status quo and improve surgical outcomes, physical health, psychological well-being and long-term survival in these patients.

Conclusion

'Living with and beyond cancer' begins at the time of cancer diagnosis - so too should prehabilitation. Dr Nick Cavill, a health promotion consultant said: "If exercise were a pill, it would be one of the most cost-effective drugs ever invented". Therefore, the challenge to those making clinical decisions in cancer care is to develop a greater understanding of exercise prehabilitation and its active promotion as an integral part of the treatment pathway. Much is said about empowering patients with long-term conditions and joint clinical decision-making with patients. ERAS provided an excellent matrix for a coordinated, multi-disciplinary approach to peri-operative improvements in patient care. Prehabilitation, or 'Pre-ERAS', is the opportunity to broaden the benefits of ERAS to include engagement of the patient in their care from the time of diagnosis.

Practice Points

- Exercise during cancer treatment is safe and advisable
- Prehabilitation in cancer should commence at diagnosis
- Benefits of prehabilitation extend beyond physical optimisation and include general health, well-being, psychological improvements and immune function support
- Prehabilitation should form the starting point of Enhanced Recovery After Surgery Programs

Future research agenda

- To define the timing and accessibility of the exercise prehabilitation intervention in order to optimise compliance
- To identify the optimal structure of the exercise program during the treatment pathway
- To achieve consensus on how best to measure baseline function and monitor physical performance changes during prehabilitation.

See following page for:

Table of Registered Clinical Prehabilitation Trials

Trial Registration	Author	Trial Design	Study Title	Participants	Intervention/Exercise Regimen	Outcomes	Target/ current status (intervention: control groups)	Adenocarcinoma/Squamous Cell Carcinoma	NAC/NACRT	Intervention during neo-adjuvant oncological treatment and surgery (continuum of care)	Intervention before start of acute oncological treatment	Baseline measures: 1. Physical, 2. Psychological	Cardiopulmonary exercise testing	Intervention to promote physical, psychological health and reduce future impairments
ClinicalTrials.gov Identifier: NCT03418298	Piraux; Gilles	Single group assignment	Prehabilitation in Patients With Esophageal or Gastric Cancers	Esophageal and Gastric cancer; Post NAC, >2 weeks pre-surgery	Preoperative internet-based program including aerobic and resistance training three sessions per week; IMT	Retention; Adherence; Patient satisfaction; adverse events	20/recruiting	Not specified	Not specified	Mixed	Mixed	Mixed		
ClinicalTrials.gov Identifier: NCT02962219	Lam; Hart	Randomised; Parallel assignment	Exercise Prior to Oesophagectomy (ExPO)	Oesophageal adenocarcinoma; 3-4 months before surgery; NAC + surgery	1) Behavioural change techniques (BCTs), 2) home inspiratory muscle training (IMT), 3) a home exercise programme (HEP) - which is also current standard care, 4) a 4 week hospital-supervised aerobic and muscle strengthening programme (Hos-PEP).	Feasibility data on whether PEP is acceptable, adhered to and safe, and whether it improves patient fitness above standard care.	32/recruiting	OAC	NAC	✓	✓	✓	✓	✓
ClinicalTrials.gov Identifier: NCT02780921	Lacarin; Le Roy	Randomised; Parallel assignment	Effect of Prehabilitation in Gastroesophageal Adenocarcinoma: Study Protocol of a Multicentric, Randomised Control Trial	Oesophageal and Gastric cancer; pre-chemo (NAC) +surgery	1 hour of supervised exercise for at least 3 days per week, for a total of 18 cycles, alternating between aerobic and resistance training	% Patients completing oncological treatment as determined by MDT	120/recruiting	OAC	NAC	✓	✓	✓	✓	✓
ClinicalTrials.gov Identifier: NCT02722785	Christensen	Non-randomised; Parallel assignment	PeRioperative Study of Exercise Training in Patients With Operable Cancer of the Gastroesophageal Junction (PRESET)	Operable gastro-oesophageal junction; pre-surgery but during NAC not specified	After a light warm-up, patients will perform 20-30 min of aerobic interval training of stationary bicycle. Resistance training comprises 4 exercises for the major muscle groups: chest press, leg press, lateral pull, and knee extension with 3-4 sets of 8 to 15 repetitions	Safety and Feasibility of pre-and-post-op exercise - Incidence of adverse events; Adherence to program	40/active, not recruiting	OAC	Not specified			✓		✓
ClinicalTrials.gov Identifier: NCT02680990	Hershey; Cooper	Randomised; Parallel assignment	Resilience and Exercise in Advanced Cancer Treatment (REACT)	Operable Oesophageal, Gastric and Pancreatic Cancer; during NAC	Sessions completed 3 times/week: 3 sets of 6 exercises: 1. chair stands, 2. chest press, 3. shoulder press, 4. arm curls, 5. pulls, and 6. calf raises. In addition, Band Together participants will be asked to work up to a walking goal of 10,000 additional steps per week	Feasibility: Adherence and Contamination	60/14 - closed	OAC	NAC/NACRT	✓	✓	✓		✓
ClinicalTrials.gov Identifier: NCT01952210	Xu; Chen	Randomised; Parallel assignment	Effectiveness of a Nutritional Consultation and Exercise Program in Esophageal Cancer Patient: Walk and eat	Neo-adjuvant chemoradiotherapy in oesophageal cancer (SCC)	Upper extremity muscle training and walking exercise at 45%-65% of maximal heart rate reserve, 3 times per week, 20-30 minutes per session.	6MWT; hand grip strength; lean muscle mass; body weight change; Nutritional status	56/50 - completed; published	OAC/SCC/NET	NAC/NACRT	✓	✓	✓		
ClinicalTrials.gov Identifier: NCT01666158	Carli	Randomised; Parallel assignment	Prehabilitation for Esophageal Resection Surgery	Oesophageal cancer surgery; 4 weeks before elective surgery	20 min of general exercise training, 3 days per week, alternating between aerobic and resistance training	Enhance Postoperative Functional Capacity Following Esophageal Resection; 6MWT	68/68	Not specified	Not specified			✓		✓
ClinicalTrials.gov Identifier: NCT02950324	Allen; Sultan	Randomised; Parallel assignment	Does Prehabilitation Improve Exercise Performance and Insulin Resistance After Surgery for Oesophago-gastric Cancer?	Oesophago-gastric cancer; 17 weeks before surgery	Multimodal programme that involves 15 weeks of exercise	Improved performance on CPEX; reduced insulin resistance; HRQL	50/recruiting	OAC	NAC	✓	✓	✓	✓	✓
ClinicalTrials.gov Identifier: NCT03626610	Zylstra; Davies	Non-randomised; Parallel assignment	Pre-EMPT: Prehabilitation in oEsophageal Malignancies on a Perioperative Treatment pathway including neo-adjuvant chemotherapy	Operable oesophago-gastric adenocarcinoma; during neo-adjuvant chemotherapy and pre-surgery	WHO guidelines for exercise in adults as minimum; 10,000 steps/day (measured using wearable device); Strength, core and relaxation exercise training commencing before NAC	Cardiopulmonary fitness; LOS & Post-op complications; Commencement of recommended adjuvant treatment; HRQL; DFS	66/recruiting	OAC	NAC	✓	✓	✓	✓	✓
ClinicalTrials.gov Identifier: NCT02478996	Pfirrmann; Gockel	Randomised; Parallel assignment	Internet-based Perioperative Exercise Program in Patients With Barrett's Carcinoma Scheduled for Esophagectomy (iPEP)	Barrett's carcinoma scheduled for surgery; 8-12 weeks before and after surgery	Internet-based perioperative exercise program (iPEP), including daily endurance, resistance and ventilation training	Peak oxygen uptake (VO2peak)	80/recruiting	OAC	Not specified			✓	✓	
ACTRN12613000664741	Boden et al. (2018)	Randomised; Parallel assignment	LIPPSMAck POP trial - Lung Infection Prevention Post Surgery (Major Abdominal) with Pre-Operative Physiotherapy education	Upper abdominal surgery; 2 weeks before surgery; NAC not specified	Interview and breathing exercise instructions	Pulmonary Complications	377/441; completed; published	Not specified - mixed tumour groups	Not specified					
Unknown	Dettling et al. (2012)	Non-randomised controlled trial	Feasibility and Effectiveness of Pre-operative Inspiratory Muscle Training in Patients Undergoing Oesophagectomy: A Pilot Study	Oesophageal cancer; NAC not standard care	Lung Function test	Post-operative pneumonia	90/48:42	Not specified	Not specified			✓		
ClinicalTrials.gov Identifier: NCT01893008	Valkenet et al. (2018)	Randomised; Parallel assignment	PREPARE: Pre-operative Inspiratory Muscle Training in patients undergoing oesophageal resection	Oesophageal resection - at least 2 weeks before surgery	Inspiratory Muscle Training using flow-resistance; 1 physiotherapy-lead training session	Decreased pulmonary complications after esophgeal resection	245/120:121; completed; published	Not specified	NACRT			✓		

Part B

Chapter 4 The Pre-EMPT trial

4.1 Protocol

The study protocol was designed to dovetail with the standard peri-operative pathway for patients with operable, oesophageal adenocarcinoma.

Current best practice treatment for patients diagnosed with operable oesophageal adenocarcinoma includes 8-9 weeks of pre-operative, or neo-adjuvant, chemotherapy followed by surgery. The currently recommended period between completing NAC and undergoing surgery is approximately 6 weeks after completing the last cycle of NAC. Depending on the post-operative histopathological tumour and lymph node result, patients may be advised by the MDM to undergo further post-operative, or adjuvant, chemotherapy or chemo-radiotherapy. Adjuvant treatment commences after the patient has been reviewed by the surgical team and have been assessed as fit to commence further oncological treatment. The oncology team subsequently review the patient for fitness to commence treatment before recommending adjuvant treatment starting.

The Pre-EMPT trial assessments, intervention and data collection took place at Baseline (after confirmed diagnosis with MDM treatment recommendation but prior to starting treatment), within a week after completing NAC (Post-NAC), within 1 week before surgery (Pre-surgery) and before commencing adjuvant oncological treatment – if recommended.

Figure 4-1 represents the time-line of patient pathway, associated trial activities and data collection points of patients, during the treatment pathway that consented to participate in the trial.

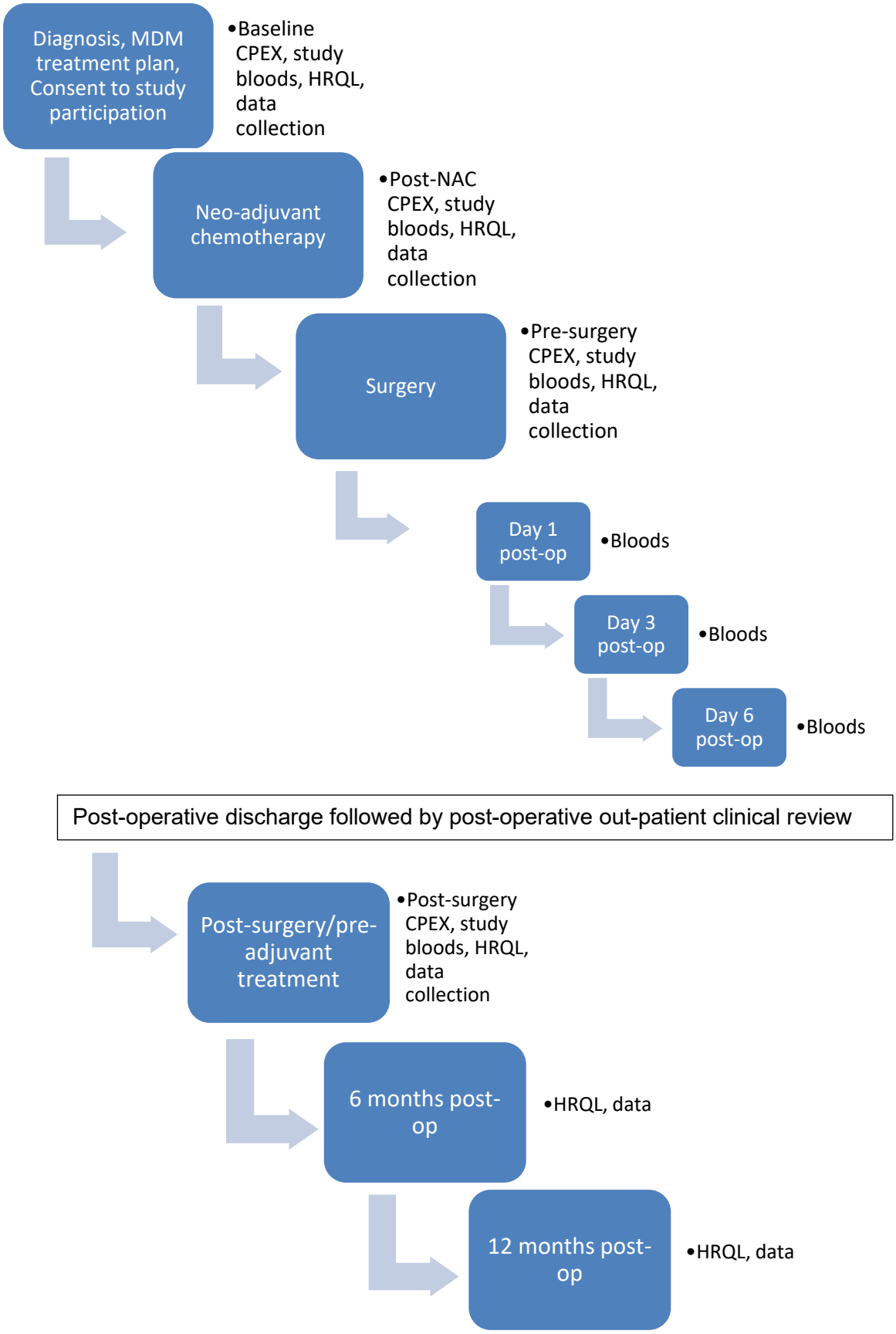


Figure 4-1 Flowchart of Pre-EMPT trial activity

4.2 Trial participation – identifying, approaching and consenting patients

Patients were identified in the UGI MDM and followed up in the joint surgical-oncology clinic following an initial discussion with a clinician (surgeon, oncologist, physiotherapist or specialist nurse). Standard guideline of Good Clinical Practice (*Good Clinical Practice - Health Research Authority*, no date) were followed at all times.

Patients had a face-to-face consultation with the research coordinator or research nurse during which an explanation of information was provided verbally. A Patient Information Leaflet was also given to the patients to take away to read. They were given 24 hours to consider participation in the trial before consenting and starting any trial-related activity.

In some cases, patients who had short breach dates (dates by which time they had to commence treatment according to NHS guidelines) were unable to participate in the trial due to baseline measures being required in a small 'window of opportunity'. In practice, such limitations would not necessarily exist, and more patients would be able to participate in an exercise prehabilitation program if it were offered at the treatment centre. This would be a significant benefit of the structured exercise program being available, supervised and supported onsite.

4.3 Exercise Intervention

It is readily accepted that exercise is beneficial to the general health of populations. The benefits are widely published in specific disease-types. Stress, both physical and psychological, have also shown to activate signalling pathways in cancer and is associated with the onset or exacerbation of diseases (Moreno-Smith, Lutgendorf and Sood, 2010).

While exercise has been shown to inhibit tumour growth (Pedersen *et al.*, 2016b) it was important that any exercise program did not cause patients, on neo-adjuvant chemotherapy and already immunocompromised, to become stressed physiologically or psychologically.

The World Health Organisation (WHO) Guidelines on Physical Activity and Adults (World Health Organization, 2015) and Macmillan guidelines for physical activity in patients with cancer (*Physical activity and cancer - A concise evidence review*, 2017) concur in their recommendations on physical activity for the adult population whether diagnosed with cancer or not. The WHO guidelines are as follows:

1. *"Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic*

physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.

2. *Aerobic activity should be performed in bouts of at least 10 minutes duration.*
3. *For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity.*
4. *Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week." (https://www.who.int/dietphysicalactivity/factsheet_adults/en)*

In a questionnaire-based Health Survey of Physical activity in adults in England in 2016, nearly two-thirds of all adults over the age of 16 reportedly met the WHO guidelines of aerobic activity (*Health Survey for England 2016 Physical activity in adults Health Survey for England 2016: Physical activity in adults*, 2017). In the USA, there was a big difference in self-reported versus accelerometer-measured compliance with activity guidelines – 62.0% versus 9.6% respectively.

The purpose of the Pre-EMPT program was not to train patients into becoming competitive athletes but to improve levels of physical activity according to recommended and approved practice. Taking all the above into consideration and working in consultation with the highly experienced clinical, physiotherapy and dietetic teams at GSTT, a structured exercise program was devised by Professor Whyte and the team at CHHP, based on the WHO and Macmillan guidelines for activity in adults and those with cancer.
The outline of the exercise program with instructions and diagrams is attached (see Appendix A).

4.4 Trial outcome measures

4.4.1 Clinical outcomes

Routine data collection of patient demographics, clinical history, tumour characteristics, treatment specific details and outcomes were part of routine data collection at St Thomas' Hospital. Additional specific data collected, and analysis is discussed in Chapter 6.

4.4.2 CPEX

CPEX and training took place at CHHP for the Intervention group while the Control group undertook their CPEX with Dr Browning at MTWH.

Other study-related activity was undertaken at the hospital at which the patient was receiving treatment. Further CPEX study methods will be described in Chapter 7.

4.4.3 Body composition - Computerised Tomography (CT) body tissue segmentation analysis

As this was a feasibility and explorative trial, we sought to use various measures to assess the outcomes of comparison between the two patient groups. As part of the standard treatment pathway CT scans were performed on the thorax and abdomen as part of routine diagnostic at baseline. Following NAC, patients underwent a second 'response to treatment' scan. Our group has previously published on assessment of sarcopenia and muscle deterioration after NAC using this method (Yip *et al.*, 2014a).

Body composition (fat and muscle segmentation) was assessed using axial images processed from the scans using 'FATS' software developed in at King's College London (KCL). See Chapter 8 for details and outcomes.

4.4.4 Immunity and Inflammatory blood markers

Exercise has been shown to produce pro-inflammatory and anti-inflammatory responses (Cullen *et al.*, 2016) and immune function regulation (Hojman, 2017b). The blood markers selected for this trial were based on markers from studies in elite athletes undergoing changes in their training programs.

We aimed to establish a baseline measure of immunity and inflammatory markers in patients diagnosed with oesophageal adenocarcinoma. In addition, we aimed to assess the changes in these markers between patients undertaking a structured exercise program and those who followed a standard treatment pathway. There were, at the time of study design, no published reports of these blood markers in oesophageal cancer.

Study-specific bloods samples were taken at 7 time points in the study:

Baseline; Post-NAC; Pre-surgery; Day 1 post-op; Day 3 post-op; Day 6 post-op; and Pre-adjuvant treatment. Chapter 9 details the method of blood marker analysis.

4.4.5 Health-Related Quality of Life

Health Related Quality of Life (HRQL) in patients undergoing oncological and surgical treatments for oesophageal cancer is historically poor with prolonged physical and psychological return to full function. The aim of this study was to assess the differences, if any, of structured exercise during treatment. Validated questionnaires were employed to assess patient-reported outcome measures (PROMS). Two questionnaires were used to assess physical symptoms of quality of life, and mental health and wellbeing.

The European Organisation for Research and Treatment of Cancer (EORTC) enable the use of validated general and disease-specific questionnaires to assess the quality of life of cancer patients. We used the general assessment EORTC QLQ-30 and disease specific EORTC QLQ-OES18 modules (*EORTC | European Organisation for Research and Treatment of Cancer : EORTC*, no date).

The Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWBS) uses 7 of the 14 statements from the longer Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS). The statements scored are worded from a positive perspective and are not cancer specific (Stewart-Brown *et al.*, 2009). Chapter 10 deals with Quality of Life in more detail.

Chapter 5 Trial Participation

5.1 Background

5.1.1 Identifying, approaching and enrolling patients

In both Interventional and Control groups, patients were identified through the UGI MDM. Following an initial clinical consultation in the surgical-oncology clinic, patients were approached for a trial discussion by the relevant research coordinator or research nurse.

In each of the groups there were eligible patients who were suitable for trial participation but were unable to start baseline trial activity due to imminent 'breach dates' to commence cancer treatment. (In the UK, NHS hospitals may be fined if a patient commences treatment more than 62 days after initial cancer diagnosis). These patients were excluded from the trial and analysis.

Patients in the Control cohort were asked to agree to undertake all the specific trial activity at each time point but were informed that there was no anticipated direct benefit to them. As part of the standard care for patients undergoing UGI cancer surgery at St Thomas', patients were informed of the Macmillan recommended activity guidelines and the Enhanced Recovery after Surgery (ERAS) protocol in which they would be included.

Patients in the Interventional cohort were invited to agree to undertake all the specific study activity with the addition of a structured exercise program delivered to them at the Centre for Health and Human Performance (CHHP) by a Specialist Exercise Physiologist. Patients were encouraged to attend training sessions at CHHP but also given advice on following the structured exercise program at home during their cancer treatment. In this group, training was also offered when attending for a CPEX.

According to ethical approvals, all patients were informed that trial participation was entirely voluntary and that they were at liberty to withdraw from the study at any point.

5.2 Aim

The aim of this study was to assess the feasibility of patients, recently diagnosed with operable oesophageal adenocarcinoma, undertaking a structured exercise program during neo-adjuvant chemotherapy and prior to surgery. The outcomes of measured physiological, physical and mental changes during the course of the study would assist in determining the feasibility of implementing such an exercise program in treatment pathways.

5.3 Results

At time of writing, participation numbers in the two groups provided a good comparative basis for this interim analysis. See Figures 5-1 and 5-2:

35 vs 34 patients had been approached in the Control and Intervention groups respectively.

Prior to Consent, 7 vs 3 patients were deemed ineligible following further investigations or became ineligible due to a change in treatment pathway. Eleven patients in each group declined participation. Some of the reasons for non-participation in both groups were:

- Patients feeling that they 'had enough going on already' and did not wish to add to their current burden
- Additional hospital visits relating to the pending treatment
- Additional visits for study activity
- Distance to travel for additional study visits

In the Intervention group, some further reasons for non-participation were:

- 'I'll do exercise on my own' / 'I do enough exercise already'
- I would do exercise if it were provided at the out-patient clinics

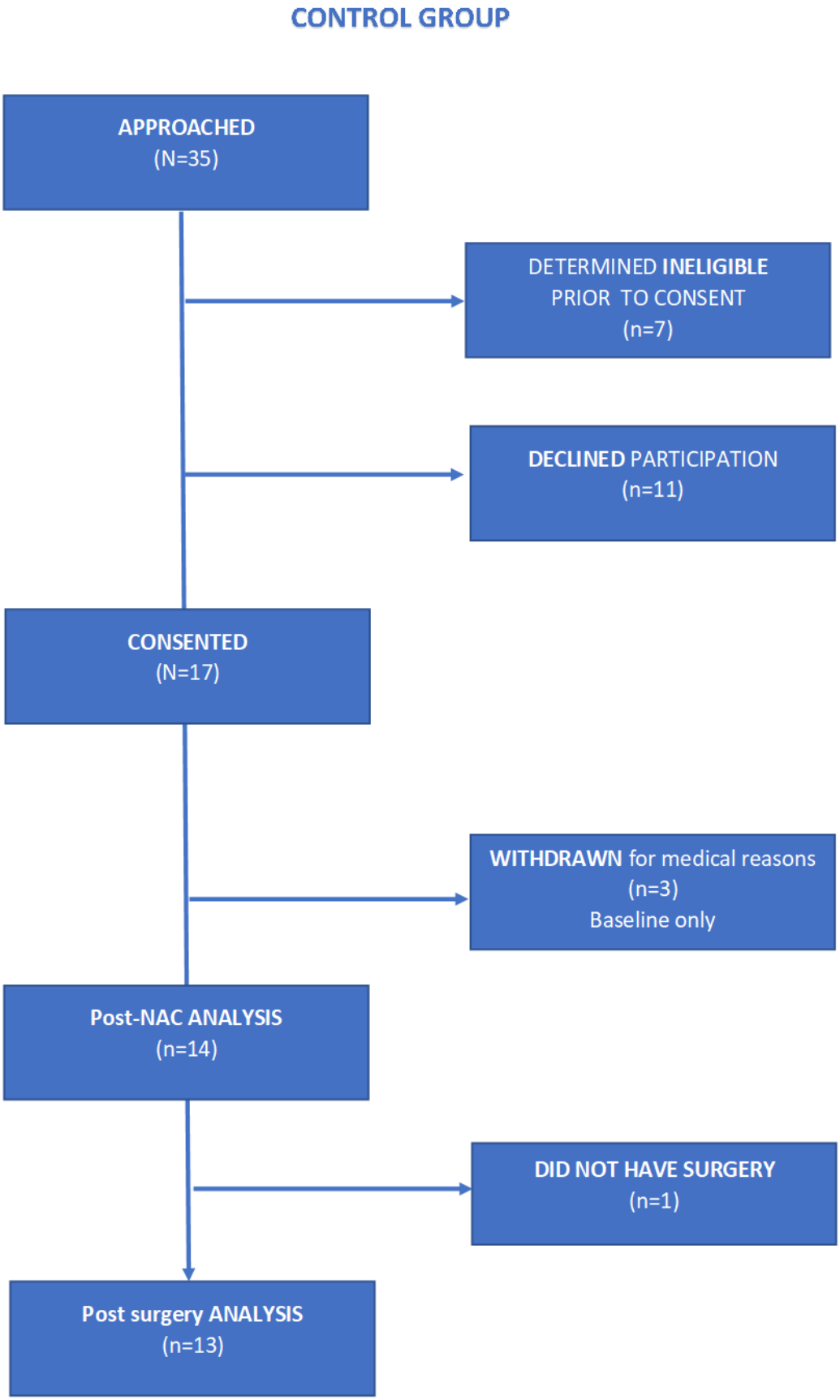


Figure 5-1 Flowchart of participation: Control group

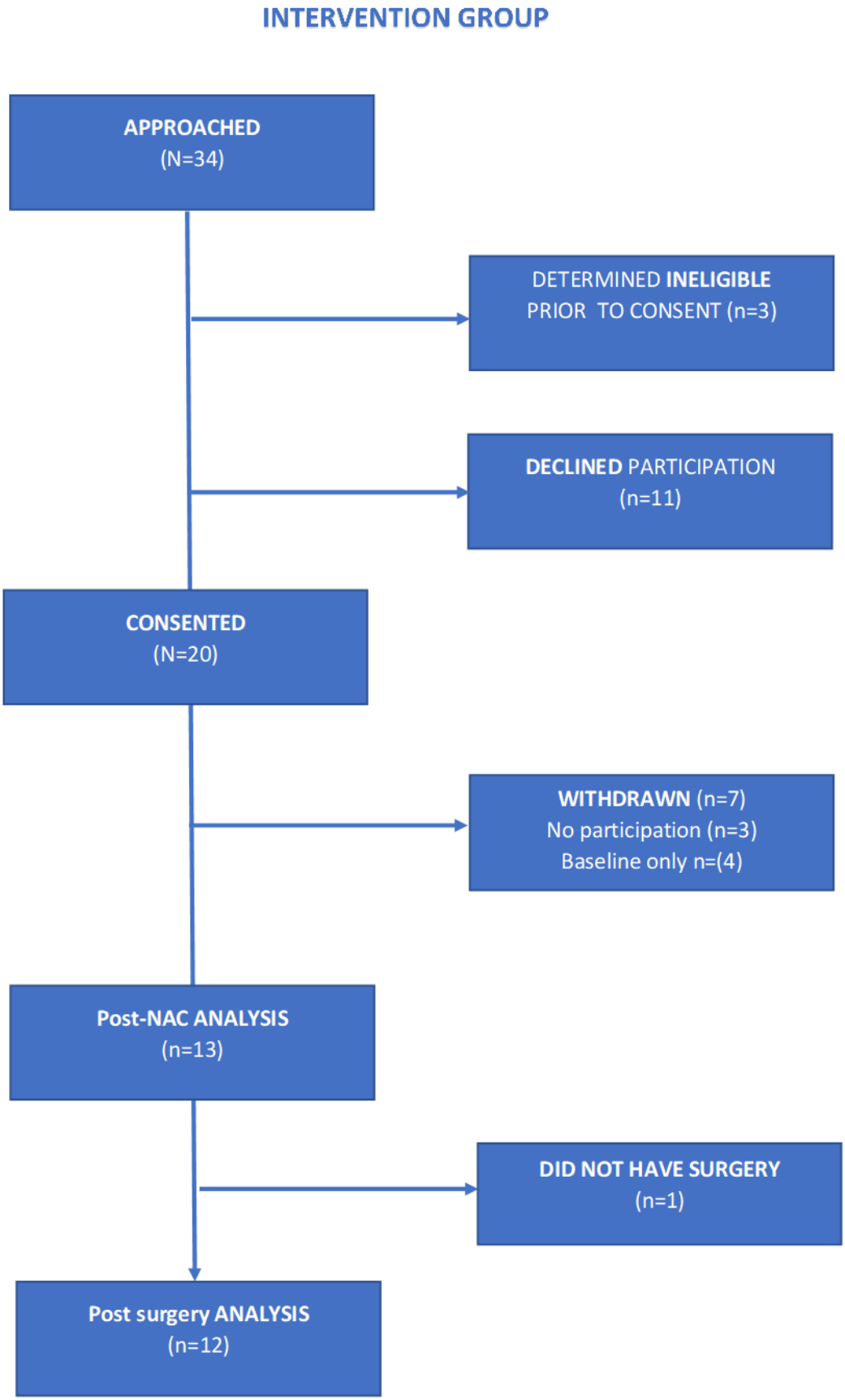


Figure 5-2 Flowchart of participation: Intervention group

17 Control vs 20 Intervention patients gave written informed consent to trial participation. 3 patients in each group withdrew or were withdrawn from the trial for medical reasons unrelated to their ability to participate in exercise. As a result, 14 and 13 patients were in the Intervention and Control group, respectively. One patient in each cohort did not proceed to surgery following NAC. The remaining patients all proceeded to surgery, leaving 13 vs 12 patients for analysis after surgery in the Control versus Intervention groups.

Written feedback received from the Intervention participants at the end of the trial was positive and encouraging of others to participate in a similar program. This is discussed further in Chapter 10.4.

Demographic and clinical analysis of trial recruits in the Control group indicated that non-participants were slightly older (67.0 vs. 63.6 years) and had fewer numbers of comorbidities than participants, especially hypertension (see Table 5-1). Body Mass Index (BMI) was similar, as was smoking status. The distance patients would have been required to travel for study participation was not recorded.

In the Intervention group, analysis of demographics and clinical characteristics in non-participants and patients who withdrew from active participation (did not undergo adequate study measures of at least 2 CPEX's before surgery), was also carried out (see *Table5-2).* Patients who declined participation or who withdrew from active participation had higher BMI's compared to study participants (Declined - 29.7 $kg.m^{-2}$ vs. Withdrew - 29.1 $kg.m^{-2}$ vs Participants - 24.7 $kg.m^{-2}$). Furthermore, participants who withdrew were younger than either those that declined participation or active study participants (Declined - 65.0 vs. Withdrew - 58.7 vs. Participants - 63.0 years respectively).

In the Control group, trial participants had a greater number of cumulative comorbidities compared to either those patients who declined participation or who withdrew from active participation in the Intervention group. Smoking status was similar between Interventional participants and those who withdrew.

Table 5-1 Demographic and clinical characteristics of Control group by participation status

Baseline characteristics	**Control group**				
	Number declined	**(%)**	**Number included**	**(%)**	**p- value**
Total	11		14		
Missing information	2		0		
Age-median years	67		63.6		0.46
BMI (kg.m^{-2}) (median)	28.8		28.6		0.95
Sex					
Male	8	(89)	13	(93)	0.74
Female	1	(11)	1	(7)	
Tumour location					
Lower oesophagus, Siewert type 1	6	(66)	8	(57)	0.63
Siewert type 2	1	(11)	6	(43)	
Siewert type 3	3	(33)	0	(0)	
Clinical stage – TNM 7&8					
cT1	0	(0)	0	(0)	0.3
2	0	(22)	1	(7)	
3	7	(78)	13	(93)	
4	0	(0)	0	(0)	
cN0	1	(11)	1	(7)	0.78
1	6	(67)	8	(57)	
2	2	(22)	5	(36)	
3	0	(0)	0	(0)	
cM0	9	(100)	14	(100)	
Comorbidities (NOGCA)					
None	2	(22)	1	(7)	0.11
1-Cardiovascular disease	5	(56)	10	(71)	0.44
2-COPD, Asthma	0	(0)	4	(28)	0.08
3-Chronic renal impairment	0	(0)	1	(7)	0.41
4-Liver failure/cirrhosis	0	(0)	0	(0)	
5-Diabetes	1	(11)	0	(0)	0.2
6-Mental illness (requiring medication)	0	(0)	0	(0)	
7-Cerebro/peripheral vascular disease	0	(0)	0	(0)	
8-Barrett's	0	(0)	1	(7)	0.41
9-Other significant disease	6	(67)	8	(57)	0.65
Smoking status					
Ex-smoker	3	(33)	7	(50)	0.53
Non-smoker/never	3	(33)	5	(36)	
Smoker	3	(33)	2	(14)	
NAC Type					

FLOT	n/a	4	(29)
Other	n/a	10	(71)

Table 5-2 Demographic and clinical characteristics of Intervention group - by participation status.

Baseline characteristics	**Intervention group**						**p-value**
	Number declined	**(%)**	**Number withdrew**	**(%)**	**Number included**	**(%)**	
Total	11		7		13		
Age-median years	65		58.7		63		0.43
BMI (kg.m^{-2}) (median)	29.7		29.1		24.7		0.08
Sex							
Male	9	(82)	6	(86)	12	(92)	0.38
Female	2	(18)	1	(14)	1	(8)	
Cancer site							
Lower oesophagus, Siewert type 1	6	(55)	3	(43)	5	(38)	0.77
Siewert type 2	4	(36)	4	(57)	8	(62)	
Siewert type 3	1	(10)	0	(0)	0	(0)	
Clinical stage							
cT1	0	(0)	0	(0)	0	(0)	0.33
2	0	(0)	0	(0)	2	(15)	
3	11	(100)	7	(100)	10	(77)	
4	0		0		1	(8)	
cN0	2	(18)	3	(43)	1	(8)	0.45
1	7	(64)	2	(29)	7	(54)	
2	2	(18)	2	(29)	4	(31)	
3	0	(0)	0	(0)	1	(8)	
cM0	11	(100)	7	(100)	13	(100)	-
Comorbidities (NOGCA)							
None	3	(30)	0	(0)	2	(15)	0.26*
1-Cardiovascular disease	6	(60)	4	(57)	7	(54)	
2-COPD, Asthma	0	(0)	2	(29)	2	(15)	
3-Chronic renal impairment	1	(10)	1	(14)	1	(8)	
4-Liver failure/cirrhosis	0	(0)	0	(0)	0	(0)	
5-Diabetes	0	(0)	1	(14)	3	(23)	
6-Mental illness (requiring medication)	0	(0)	1	(14)	1	(8)	
7-Cerebro/peripheral vascular disease	1	(10)	0	(0)	1	(8)	
8-Barrett's	0	(0)	0	(0)	0	(0)	
9-Other significant condition	3	(30)	4	(47)	7	(54)	
Smoking status							
Ex-smoker	5	(50)	1	(14)	5	(38)	0.15

Non-smoker/never	4	(40)	1	(14)	3	(15)
Smoker	1	(10)	5	(71)	5	(38)
NAC Type						
FLOT		n/a	3	(43)	4	(31)
Other		n/a	2	(29)	9	(69)
missing		n/a	2	(29)	0	(0)

*p-value from ANOVA (comparison of means) or chi2 (comparison of proportions)

Analysis of fitness levels of participants who withdrew from the study following consent demonstrated that participants in both Control and Intervention cohorts had better overall fitness (AT and VO_{2peak}) compared with patients who withdrew from participation. (See *Table 5-3)*

Table 5-3 Baseline fitness by participation status.

Baseline measures	**Control group**				**Intervention group**			
	Withdrew		**Participant**		**Withdrew**		**Participant**	
	n=3	(%)	n=14	(%)	n=7	(%)	n=13	(%)
Mean (SD)								
Median (IQR)								
Anaerobic	13.5	(1.0)	15.2	(3.6)	14.3	(2.8)	17.6	(3.3)
p=0.11	*12.9*	*(12.9-14.7)*	*14.2*	*(13.1 - 17.0)*	*14.7*	*(12.2 - 16.5)*	*17.9*	(16.9 - 20.9)
VO2peak	20.5	(2.8)	23.4	(4.1)	22.6	(1.5)	27.6	(5.6)
P=0.04	*20.4*	*(17.7-23.3)*	*22.5*	*(19.6 - 26.3)*	*22.4*	*(21.5 - 23.8)*	*27.6*	(26.5 - 31.1)
VeVCO2	30.7	(2.1)	29.8	(3.1)	31.6	(4.9)	31.1	(4.0)
p=0.75	*30*	*(29.0-33.0)*	*30*	*(28.0 - 31.0)*	*33*	*(28.4 - 34.8)*	*30.3*	(27.8 - 32.4)
BMI	30.6	(3.1)	28.6	(7.4)	30.1	(3.8)	25.5	(4.9)
p=0.27	*31.6*	*(27.1-33.0)*	*28.4*	*(23.1 - 30.7)*	*28.7*	*(27.1 - 34.7)*	*24.7*	(21.5 - 27.9)

*p-value from ANOVA

After adjusting for age and gender, established lifestyle factors of obesity and smoking, are reported to increase risk of developing oesophageal cancer (Veugelers *et al.*, 2006). The Pre-EMPT trial population was representative of these typical characteristics. Participants in the trial had overall more comorbidities, were older but fitter, and less obese, than those who declined or withdrew their participation.

5.4 Discussion

The analysis of patients who declined to participate in the trial, and those in the Intervention group who only undertook baseline assessments, provided useful insights into potential patient selection for introducing prehabilitation as part of routine care pathways. Patients who had higher BMI tended to withdraw from or decline to participate in the exercise intervention. In addition, participants who withdrew during the study tended to be to have lower fitness levels and were also younger. As with all specialist services, it is important to offer the same choice to all patients but also to assess which patients are likely to benefit by complying with protocols and by assessing which patients will need more encouragement and support to comply with the protocols.

Feedback from Intervention participants was positive and most recommended a structured exercise program to others in similar circumstances.

5.5 Conclusions

Exercise during neo-adjuvant chemotherapy was found to be feasible and viable in patients with operable oesophageal adenocarcinoma. Participation and compliance was more sustained in an older group of patients and those who had BMIs within the normal weight range. Patients in this study who had a higher BMI, and are more likely to be less active, seemed to be more resistant to participation in an exercise intervention. This group of patients may need more encouragement and support to undertake this type of program.

Chapter 6 Clinical Outcomes after Surgery

6.1 Background

As described previously, oesophagectomy is a high-risk, invasive surgery associated with high morbidity. Patient selection for cancer surgery is based largely on the disease location and tumour stage of invasion, with fitness of the patient taken into consideration.

In the UK, the surgical pathway follows defined protocols and the opportunity for patient selection according to comorbidities and fitness is very different on a cancer pathway compared to that of a benign pathway when expedition of surgery is not within a defined timeframe. The window of opportunity for pre-surgical patient optimisation is small and impacted by the reduction of fitness and development of new, chemotherapy-associated, comorbidities.

6.2 Aims

Amongst the broad clinical outcome measures routinely recorded at this institution, we aimed to assess the clinical and pathological outcomes of patients undertaking a structured exercise prehabilitation program versus patients in a 'standard care' control treatment pathway, to determine:

- The impact of exercise prehabilitation on post-operative complications
- The impact of prehabilitation on overall length of hospital stay post-operatively
- Onco-pathological outcomes of exercise during chemotherapy on histopathological examination outcomes
- Peri-operative oncological treatment completion rates between the intervention and control groups.

6.3 Methods

Following consent to trial participation, clinical data collection was carried out throughout the patient pathway, starting at MDM discussion and identification of potential participants. Clinical results were recorded for all patients who consented to participation under ethics approval for this trial. For eligible patients who did not consent to the trial, basic demographic data was recorded under ethical approval of the Guy's and St Thomas' Oesophago-gastric Database: REC. 17/NW/0377, for the purpose of assessing patient participation within the context of feasibility. Data was sourced from Electronic Patients Records (EPR), Cancer Information System (CIS/MOSAIQ), face-to-face patient discussion, in consultation with Consultant Clinicians and

feedback from questionnaires.

6.4 Results

6.4.1 Baseline patient and tumour characteristics

At baseline, the number of participants, ages and age-range, gender, tumour location and TNM-stage were comparable across the two groups. There were a greater number of non-smokers in the Control group (5 vs. 3), while 'current smoker' status was higher in the Intervention group (5 vs 2). (*See Table 6.1*)

There were a higher number of cardiovascular and pulmonary comorbidities in the Control versus Intervention groups (14 vs. 9) which, along with a higher BMI (28.3 vs 24.7 $kg.m^{-2}$) may have contributed to the lower recorded baseline fitness of AT and VO2peak in the Control group (see Chapter 7.4).

6.4.2 Oncological and surgical treatment

Oncological treatment within the two groups was very similar. At the start of the study, peri-operative treatment with epirubicin, cisplatin and 5 flurouracil (ECF) or epirubicin, oxaliplatin and capecitabine (ECX) were considered to be the first choice regimens (Cunningham *et al.*, 2006b). Both included 3 cycles of chemotherapy before and after surgery. Following publication of the FLOT trial (Al-Batran *et al.*, 2017), oncological practice changed simultaneously to 4 cycles of pre and post-operative FLOT. The study protocol accommodated this change. One patient in the exercise group underwent additional radiotherapy prior to surgery.

Oesophagectomy included transhiatal and transthoracic resections at the discretion of the individual surgeon, taking into account both patient and tumour characteristics. All patients in the Control group underwent trans-thoracic surgery compared to 75% of the patients in the Intervention group, 3 of whom underwent transhiatal oesophagectomy. Transhiatal oesophagectomy may be performed in patients with oncologically suitable tumours, with the perceived benefit of avoiding one-lung ventilation. Of patients who underwent transhiatal oesophagectomy, one patient developed a pneumothorax due to displacement of a chest drain. A new drain was inserted, and the patient was admitted to the Intensive Care Unit (ICU). Another patient suffered incarceration of an existing hernia requiring return to theatre and escalation of care.

Table 6-1 Clinical Outcomes: Control and Intervention cohorts

	Control Group		Intervention Group		p-value
Total patients	n=14		n=13		
Age – median (IQR)	67.2 (42.5-77.9)		63 (40.0-76.3)		0.73
Age range (years)	42.5-77.9		40.0-76.3		
Sex	Number	%	Number	%	
Male	13	(93)	12	(92)	0.96
Female	1	(7)	1	(8)	
BMI –baseline (kg.m^{-2}): Median (IQR)	28.3 (23.1-30.8)		24.7 (21.5-27.9)		
Smoking status					
Ex-smoker	7	(50)	5	(38)	0.35
Non-smoker (+never)	5	(36)	3	(24)	
Smoker	2	(14)	5	(38)	
Diagnostic tumour location: oesophagus/GOJ (Siewert 1,2,3)					
Lower 1/3; Siewert type 1	8	(57)	5	(38)	0.33
Siewert type 2	6	(43)	8	(62)	
Siewert type 3	0	(0)	0	(0)	
Clinical stage at diagnosis – TNM 7 & 8					
T-stage					
X	0	(0)	0	(0)	0.95
1	0	(0)	0	(0)	
2	1	(7)	2	(15)	
3	13	(93)	10	(77)	
4	0	(0)	1	(8)	
N-stage					
X	0	(0)	0	(0)	0.74
0	1	(7)	1	(8)	
1	8	(57)	7	(54)	
2	5	(36)	4	(31)	
3	0	(0)	1	(8)	
M-stage					
0	14	(100)	13	(100)	
1	0	(0)	0	(0)	
Comorbidities (NOGCA)					
none	1	(7)	2	(15)	
1 – Cardiovascular disease	10	(71)	7	(54)	
2 – COPD, Asthma	4	(29)	2	(15)	
3 – Chronic renal impairment	1	(7)	1	(8)	
4 – Liver failure/ cirrhosis	0	(0)	0	(0)	
5 - Diabetes	0	(0)	3	(23)	
6 – Mental illness (requiring medication)	0	(0)	1	(8)	
7 – Cerebro/peripheral vascular disease	0	(0)	1	(8)	
8 – Barrett's oesophagus	1	(7)	0	(0)	
9 – Other significant condition	8	(57)	7	(54)	

Six patients in each group, 46% Control and 50% Intervention, experienced no post-operative complications. Four patients in each group (36% and 33% respectively) required a pharmaceutical intervention only. The remaining 3 patients in the Control group, and 2 in the Intervention group, required surgical or radiological intervention. Whether the surgical intervention and ITU admission were related to a patient fitness, is debatable.

Post-op complications recorded using the NOGCA and ECCG sub-headings did not provide any specific insights due to large numbers of complication categories versus the small numbers of patients in this interim analysis.

Overall, the median hospital length of stay was shorter in the Control group, 9 days (range 7–44 days, IQR 8-12 days) versus 10.5 days (range 9-17 days, IQR 9-13 days). This is assumed to be due to the non-cancer related surgical 'return to theatre' and Intensive Care Unit admissions in the exercise Intervention group.

(*See Table 6.2*)

There were no in-hospital, 30-day or 90-day deaths post-surgery in either group.

Table 6-2 Oncological and Surgical outcomes

	Control		**Intervention**		**p-value**
Total patients	n=14	%	n=13	%	
NAC regimen					
ECX	8	(57)	7	(54)	0.99
FLOT	4	(29)	4	(31)	
Other	2	(14)	2	(15)	
NAC completed as scheduled					
Yes	12	(86)	9	(69)	0.45
Dose reduced	2	(14)	3	(23)	
Delayed	0	(0)	1	(8)	
Did not proceed to surgery	1	(7)	1	(8)	
Number proceeding to Surgery	**n=13**		**n=12**		
Operative approach					
Transthoracic oesophagectomy	13	(100)	9	(75)	0.06
Transhiatal oesophagectomy	0	(0)	3	(25)	
Operative access					
Open	1	(8)	3	(25)	0.24
Laparoscopically assisted abdomen, completed	12	(92)	9	(75)	
Lap to open	0	(0)	0	(0)	
Post-op complications:					
Clavien-Dindo					

none	6	(46)	6	(50)	0.29
1,2	4	(36)	4	(33)	
3a	3	(23)	0	(0)	
3b	0	(0)	1	(8)	
4	0	(0)	1	(8)	
NOGCA					
0 - none	6	(46)	6	(50)	
1 - Pneumonia	0	(0)	4	(33)	
2 - ARDS	0	(0)	1	(8)	
3 - PE	0	(0)	0	(0)	
4 – Pleural effusion	0	(0)	0	(0)	
5 – Anastomotic Leak	2	(15)	0	(0)	
6 – Chyle leak	0	(0)	0	(0)	
7 – Haemorrhage	0	(0)	0	(0)	
8 – Cardiac complication	1	(8)	1	(8)	
9 – Acute renal failure	0	(0)	0	(0)	
10 – Wound infection	0	(0)	0	(0)	
98 - Other	2	(23)	2	(17)	
ECCG					
P - Pulmonary	4	(31)	4	(33)	
C – Cardiac	3	(23)	1	(8)	
G – Gastrointestinal	2	(15)	0	(0)	
U – Urologic	1	8	0	(0)	
I – Infection	0	0	0	(0)	
N/P – Neurologic/ Psychiatric	2	15	1	(8)	
T - Thromboembolic	1	(8)	0	(0)	
W/D – Wound/Diaphragm	0	(0)	0	(0)	
O – Other	1	(8)	2	(17)	
E- Escalation of care	0	(0)	1	(8)	
ITU admission					
Yes	0	(0)	2	(17)	0.13
No	13	(100)	10	(83)	
Total days in OIR/HDU Median (IQR) days	2 (2-5)		3 (2-4)		
Overall length of Hospital stay (from date of surgery) Median (IQR)days	9 (8-12)		10.5 (9-13)		0.17
In-hospital mortality					
Yes	0	(0)	0	(0)	
No	13	(100)	12	(100)	
30-day mortality					
Yes	0	(0)	0	(0)	
No	13	(100)	12	(100)	
90-day mortality					
Yes	0	(0)	0	(0)	
No	13	(100)	12	(100)	

6.4.3 Histopathological Outcomes

Of particular note are differences between the Control and Intervention group histopathologically-assessed tumour responses to chemotherapy.

As standard at the centre, histopathology reports included the Mandard Tumour Regression Grade (MTRG) (Mandard *et al.*, 1994) which was developed as an objective measure for evaluation of tumour regression following chemoradiotherapy for oesophageal carcinoma. Histopathological assessment identifies microscopic regressive cellular and stromal changes in the resected tumour tissue. In the UK, it is the most widely used histopathological measure of cancer regression and response to chemotherapy in oesophageal adenocarcinoma and has been recommended for use in histopathological reporting of gastrointestinal cancers treated with neo-adjuvant therapies (Thies and Langer, 2013).

Mandard Tumour Regression Grades	
1	No residual cancer cells
2	Rare residual cancer cells
3	Fibrosis outgrowing residual cancer cells
4	Residual cancer cells outgrowing fibrosis
5	Absence of regressive changes

Figure 6-1 Mandard Tumour Regression Grade

In this cohort-controlled group of patients, histopathological examination of resected tumours in patients in the Intervention group, revealed that 45.4% had 'no or rare residual cancer cells' following chemotherapy, with a MTRG of 1 or 2 (n=5) compared to 0% (n=0) in the Control group. An MTRG score of 3, showing greater evidence of fibrosis to residual cancer cells, was observed in 27.3% (n=3) and 30.8% (n=4) in the prehabiliation versus Control cohorts. Likewise, poor or no regression measures of MTRG 4 and 5 were 27.3% (n=3) versus 69.2% (n=9) respectively. For the MTRG analysis, one patient was excluded as they had additional radiotherapy.

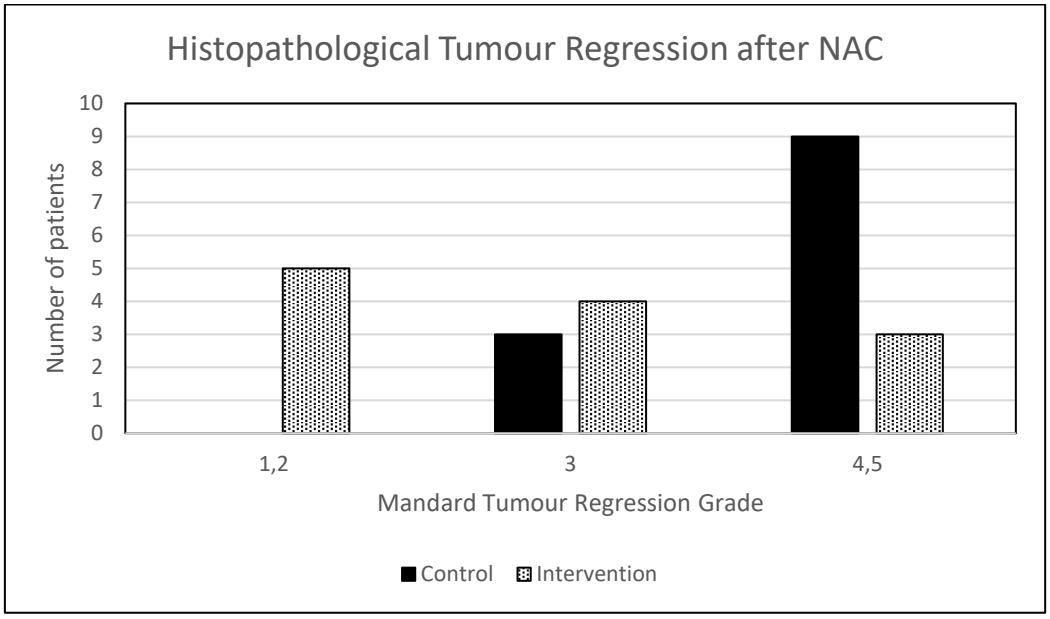


Figure 6-2 Graph showing histopathological Mandard Tumour Regression Grade

Tumour 'downstaging' following chemotherapy has been shown to be associated with improved survival in resectable oesophageal adenocarcinoma (Andrew R. Davies *et al.*, 2014). On comparing clinical and pathological T- stage (Baseline versus post-NAC) in the Control and Intervention groups, a greater number of patients' tumours were down-staged after NAC in the Intervention group, 7 vs. 4 patients (See *Figure 6-3*).

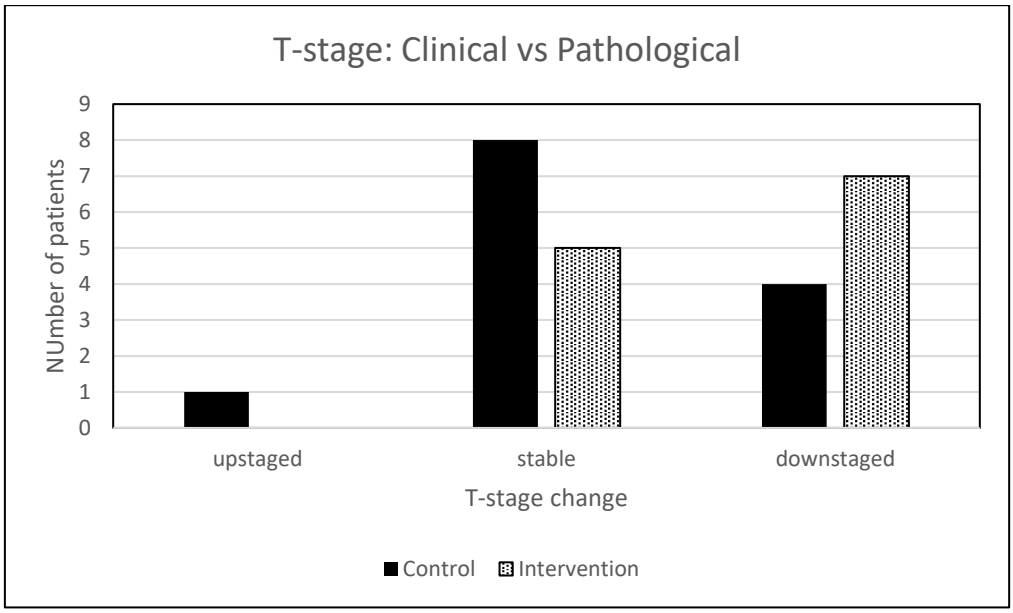


Figure 6-3 Histopathological Tumour downstaging

Histopathological tumour stage**,** measured according to the ypTNM post-neoadjuvant therapy staging (Thomas W. Rice *et al.*, 2016), showed better outcomes in the patients in the Intervention group. T-stage results, indicating depth of tumour invasion were improved: T0-2 – 50% (n=4) vs. 30.8% (n=1) Intervention vs. Control; T3 – 42% (n=5) vs 62% (n=8) respectively; and T4 – 1 patient in each group.

Similarly, there was greater downstaging of nodal disease in the Intervention group, 8 vs. 6 patients while pathological N-stage showed upstaging of nodal disease in 6 vs. 2 patients in the Control group with (See Figure 6-4).

Overall, histopathological nodal stage post-operatively was lower in the Intervention vs Control groups: N0-1 83.3% vs 53.8% ; N2-3 was reported as 16.7% vs 46.2% respectively.

Median numbers of lymph nodes resected at surgery and examined were comparative in the two groups.

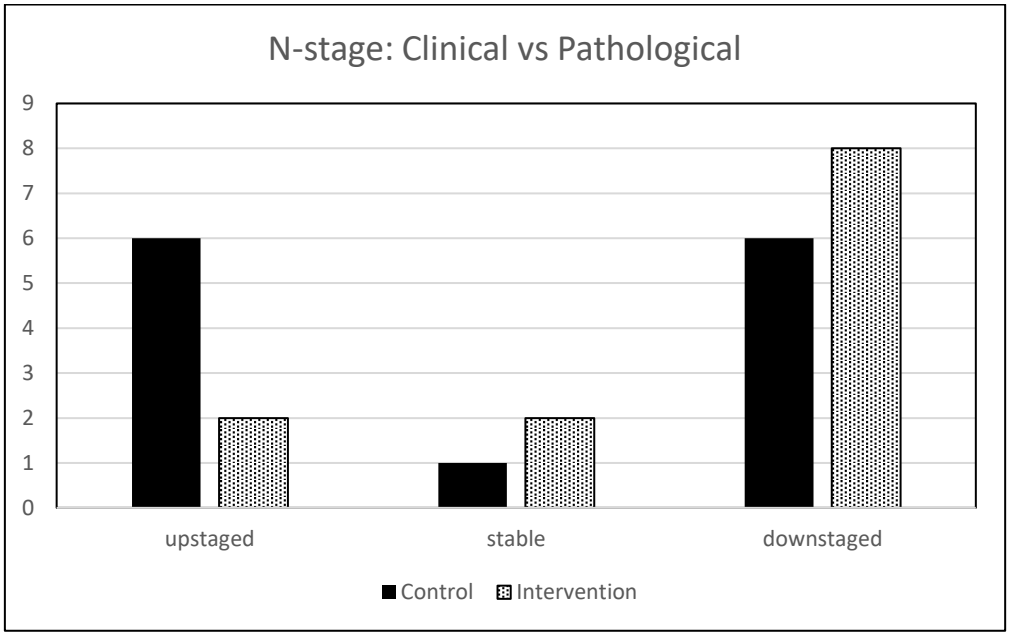


Figure 6-4 Histopathological Nodal downstaging

Additional prognostic cancer biological markers were recorded. Tumour differentiation was more favourable in the Intervention group with poor cellular differentiation being lower, 50% vs 69%; Moderate cellular differentiation was higher in the Intervention versus Controls groups, 42% vs 31%; 1 patient in the Intervention group resulted in complete cancer regression in the resected tumour.

Lymphovascular/perineural tumour invasion was more prevalent in the Control group: 42% vs. 62% (See Table 6-3).

Table 6-3. Histopathological results of resected tumours

	Control		Intervention		p-value
Number of surgical patients	**n=13**	%	**n=12**	%	
Post-op tumour location					
Lower 1/3; Siewert type 1	1	(7)	1	(6)	0.1
Siewert type 2	4	(28)	5	(29)	
Siewert type 3	9	(64)	11	(65)	
Resection margin status					
R0	10	(77)	8	(67)	0.57
R1	3	(23)	4	(33)	
Pathological stage – TNM 7&8					
T-stage					
0	0	(0)	1	(8)	0.31
1	1	(8)	3	(25)	
2	3	(23)	2	(17)	
3	8	(62)	5	(42)	
4	1	(8)	1	(8)	
N-stage					
0	5	(38)	7	(58)	0.34
1	2	(15)	3	(25)	
2	3	(23)	0	(0)	
3	3	(23)	2	(17)	
M-stage					
0	13	(100)	12	(100)	
1	0	(0)	0	(0)	
Post-op differentiation					
CPR	0	(0)	1	(8)	
Well	0	(0)	0	(0)	
Moderate	4	(31)	5	(42)	
Poor	9	(69)	6	(50)	
Lymphovascular/perineural invasion					
Yes	8	(62)	5	(42)	0.32
No	5	(38)	7	(58)	
Signet ring cells					
Yes	4	(31)	3	(25)	0.75
No	9	(69)	9	(75)	
Mandard Tumour Regression Grade					
1	0	(0)	1	(8)	0.03
2	0	(0)	4	(33)	
3	4	(31)	4	(33)	

4	8	(62)	1	(8)	
5	1	(8)	2	(17)	
Total number of lymph nodes examined (rounded up) Median (IQR)	35 (23-44)		29 (27-37)		

Table 6-4. Cancer recurrence and deaths

	Control		**Intervention**		**p-value**
Total patients	n=13	%	n=12	%	
In-hospital mortality					
Yes	0	(0)	0	(0)	
No	13	(100)	12	(100)	
30-day mortality					
Yes	0	(0)	0	(0)	
No	13	(100)	12	(100)	
90-day mortality					
Yes	0	(0)	0	(0)	
No	13	(100)	12	(100)	
12-month mortality					
Yes	1	(13)	0	(0)	0.30
No	7	(87)	8	(100)	
<12mth follow-up	5		4		
6mth recurrence-free %(CI) from surgery		(100)		(100)	
12mth recurrence-free % (CI) from surgery		73 (18-93)		(100)	0.13
Time to recurrence from surgery (mean-months)	8.3			n/a	
Time to recurrence from diagnosis (mean-months)	13.9			n/a	
12mth Overall Survival from surgery* % (CI)		(83)		(100)	
Time to death from surgery (months)	11.6			N/A	
Time to death from diagnosis (months)	17.6			N/A	
FU time surgery to date last seen Median (IQR)-months	9.6 (6.9-13.6)		15.4 (7.4-20.7)		
Total Follow-up time, diagnosis to date last seen Median (IQR)-months	14.2 (13.1-18.4)		21.3 (12.5-26)		
Commencement of adjuvant treatment					
Yes	13	(100)	10	(100)	
No	0	(0)	0	(0)	
Not applicable	1		3		

Time to adjuvant treatment Median (IQR)-days	64 (58-71)	64 (46-74)

6.4.3 Disease Recurrence and Deaths

At the time of data analysis, 12-month post-surgery follow-up data was available for 7 of 13 and 8 of 12 patients in the Control and Intervention groups respectively. During the 12-month follow-up period, 2 patients in the Control group had confirmed cancer recurrence compared to zero patients in the Intervention group.

There was 1 cancer-related death within 12 months of surgery in the Control group with none in the Intervention group.

Commencement of prescribed adjuvant treatment was similar in both groups of 64 days after surgery.

6.5 Discussion

Tumour response to chemotherapy, with tumour- and lymph-node downstaging are potentially the most important prognostic factors in oesophageal cancer. A high proportion of patients undergoing oesophagectomy have evidence of micro-metastases at the time of diagnosis and surgery. The introduction of NAC has been associated with improvements in survival, cancer recurrence and systemic control, however, a large number of patients do not respond to chemotherapy. These patients tend to have poorer outcomes. With current protocols of neoadjuvant treatment strategies and established methods of pathologically quantifying tumour regression, oesophageal cancer is an ideal tumour group on which to examine hypotheses of exercise-related oncological benefits. The results from this analysis, showing improvements in pathological regression in the primary tumour and lymph nodes and clinical down-staging following structured exercise programs are potentially clinically significant and hypothesis generating. The results also concur with an increasing body of evidence supporting exercise in animal cancer models.

6.6 Conclusions

This is the first study in patients diagnosed with oesophageal adenocarcinoma, and I believe in humans undergoing neo-adjuvant chemotherapy, to suggest that there may be the outcome of

improved cancer control both in the resected tumour, lymph nodes and in reduced disease progression after surgery. It is an unexpected and clinically important finding which may to be applicable to other cancers.

Further research in collaboration with other specialist centres will be essential in validating these notable and clinically relevant trial outcomes.

Chapter 7 Cardiopulmonary Exercise Testing (CPEX)

7.1 Introduction and rationale

In a clinical research context, CPEX testing is a well-recognised, quantitatively measurable, validated and objective method for assessing an individual's fitness or functional capacity. CPEX incorporates the functions of the cardiac, circulatory and respiratory systems with the altered muscular, metabolic and biochemical system responses when subjected to stress (Melzer, 2011). CPEX measures the physiological demands and effects of increased oxygen requirements associated with increased exercise intensity (Sue *et al.*, 1988), providing useful comparative information with the oxygen demands during surgery and the post-operative period (Older and Smith, 1988). This was of relevance in our cohort of study participants who were on a peri-operative treatment pathway, with NAC deconditioning prior to surgery.

Furthermore, CPEX is an objective measure to assess severity and impact of underlying impairments, such as comorbidities, rather than evaluating the cause thereof. It is, therefore, an appropriate measure for baseline fitness and subsequent deconditioning in patients undergoing treatment for cancer that may induce comorbidities as a result of drug therapy and associated toxicities.

7.2 Aim

To examine fitness changes in patients undertaking a structured exercise program during NAC and in preparation of surgery compared to those on a standard pathway.

7.3 Methods

CPEX testing was undertaken at two centres. Testing in the Control cohort was performed by a Consultant Anaesthetist and CPEX Lead at the Maidstone Hospital, the local hospital to the Control group of patients. The Intervention group underwent CPEX testing by a Specialist Exercise Physiologist at CHHP, who also provided the additional exercise training of the prehabilitation Intervention participants.

CPEX testing in the Interventional group was performed on an ergoline 900 model cycle ergometer. It is electromagnetically braked, and resistance is modulated automatically to a set work rate based on cadence. The protocol that was selected was a ramp protocol. The ramp speed in Watts.min^{-1} was selected based on predicted VO_2 and adjusted to the individual.

An Ergoline Ergoselect 200 cycle ergometer was used in the Control group according to the same protocol as the Intervention group.

Peak Oxygen Uptake (VO_{2peak}, $ml.kg^{-1}.min^{-1}$) and anaerobic threshold (AT, $ml.kg^{-1}.min^{-1}$) were recorded as the appropriate measures for fitness and fitness changes in this group of patients.

7.4 Results

Table 7-1 Anaerobic Threshold ($ml.kg^{-1}.min^{-1}$)

	Control group N=14			Intervention group N=13			
	Median	**(IQR)**	**% Change vs Baseline**	**Median**	**(IQR)**	**% Change vs Baseline**	**p-value**
Baseline	14.2	(13.1-17.6)		17.9	(16.9-20.3)		0.08
Post-NAC	11.5	(10.2-13.3)	-19%	14.4	(13.0-16.8)	-20%	0.02
Pre-Surgery	13.3	(11.5-15.2)	-6%	14.5	(13.4-17.2)	-19%	0.06
Post-surgery	12.1	(10.2-13.9)	-15%	13.9	(11.9-15.5)	-22%	0.17

There was a marked deterioration of AT in both Control and Intervention groups, of up to 20%, with better recovery towards baseline in the Control cohort and further decline in both groups after surgery.

Table 7-2 VO_{2peak} ($ml.kg^{-1}.min^{-1}$)

	Control group N=14			Intervention group N=13			
	Median	**(IQR)**	**% Change vs Baseline**	**Median**	**(IQR)**	**% Change vs Baseline**	**p-value**
Baseline	22.5	(19.6-26.3)		27.9	(26.5-31.1)		0.03
Post-NAC	18.3	(17.9-21.2)	-19%	24.5	(20.4-27.4)	-12%	0.01
Pre-Surgery	20.1	(19.1-24.6)	-11%	25.5	(22.5-29.5)	-9%	0.01
Post-surgery	18.1	(15.9-21.0)	-20%	20.6	(16.7-25.1)	-26%	0.24

Structured exercise prehabilitation resulted in better outcomes in oxygen consumption in the Interventional group with median VO_{2peak} demonstrating a blunted fitness deterioration of 7%

with an overall decline of 12%, compared to the Control Cohort's deterioration of 19% (see Figure 7-1).

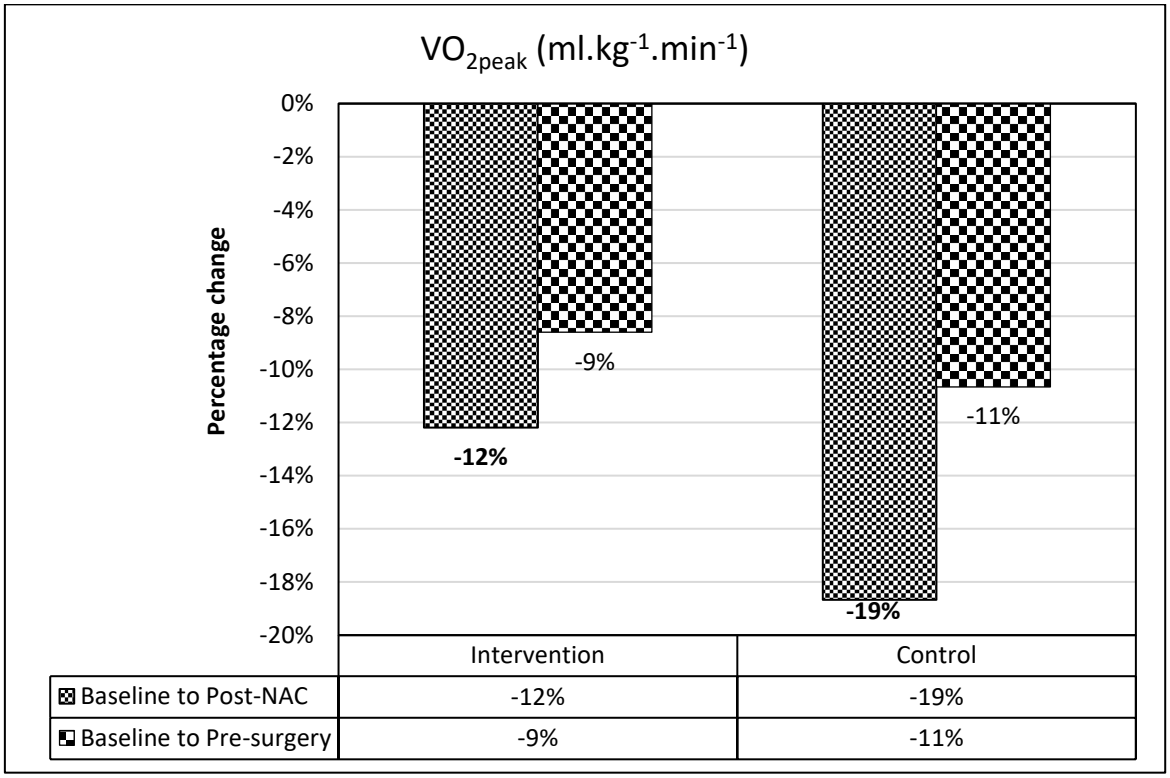


Figure 7-1 Graph representing VO_{2peak} changes

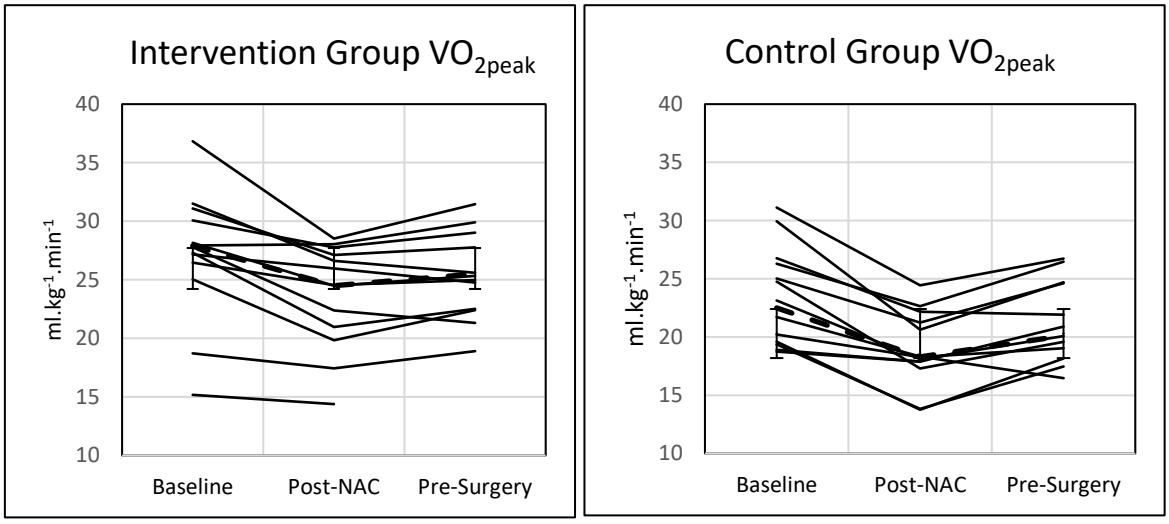


Figure 7-2 Ladder plot of individual VO_{2peak} changes: Intervention and Control groups. Baseline, Post-NAC, and Pre-surgery

(For earlier interim results also see Appendix B and Appendix C - Scientific Abstract & Poster: DOI: 10.1249/01.mss.0000561780.97589. June 2019 Medicine & Science in Sports & Exercise 51(Supplement):427 “Feasibility of exercise prehabilitation during neo-adjuvant chemotherapy in oesophago-gastric cancer surgery”.)

7.5 Discussion

Figure 7-2 graphically represents individual VO_{2peak} changes within each of the Intervention and Control groups. It is noted that the VO_{2peak} results were overall lower in the Control group. The underlying reason for the discrepancy between the groupings is likely to be as a result of the higher median BMI in participants the Control versus Intervention groups (28.3 $kg.m^{-2}$ vs. 24.7 $kg.m^{-2}$).

Reduced AT in both groups indicates reduced cardiorespiratory reserve through neo-adjuvant chemotherapy deconditioning. Navidi et al. suggested that a decline in AT was predictive of post-operative morbidity (Navidi *et al.*, 2018). According to NOGCA post-op complications classification, 4 cases of pneumonia were reported in the Intervention group which is in line with this prediction. Higher smoking status in the Intervention group may also underly the reduced cardiorespiratory reserve and subsequent respiratory complications in these patients despite the exercise prehabilitation. Patients who smoke are known to be at higher risk of pulmonary disease and post-op complications. The period of exercise prehabilitation, and with added cardiovascular toxicity from chemotherapy, may not be long enough on the current standard pathway to compensate for the negative effects of smoking. Smoking cessation should become compulsory to reduce pulmonary complications in patients that undergo this type of surgery.
(See Chapter 6 for surgical outcomes.)

This level of fitness deterioration observed in this study is concordant with other published data in similar cohorts of patients (Sinclair *et al.*, 2016). It is unlikely that any exercise program will negate or reverse the physical deterioration of patients undergoing chemotherapy. The reduction or blunting of deterioration, in participants in the Intervention group, as measured by VO_{2peak}, is an encouraging result in an intervention period of only 8 to 9 weeks during concurrent chemotherapy.

Patients in both Control and Intervention groups improved in fitness in the post-NAC period before surgery. However, with a further 5 to 6 weeks of prehabilitation prior to surgery, overall

fitness deterioration in the Intervention group continued to show less overall deterioration compared to the Control group (-9% vs. -11%).

7.6 Conclusions

A structured exercise prehabilitation program during neo-adjuvant chemotherapy reduces chemotherapy-associated deconditioning in VO_{2peak} compared to patients undergoing a standard treatment pathway. The reduced deterioration in oxygen uptake is provided by a supported, structured exercise prehabilitation program which should ideally be made available to all cancer patients who are willing to undertake such an exercise intervention.

Further collaborative research is indicated in larger patient cohorts and in patients on non-surgical and 'non-curative' cancer treatment pathways.

Chapter 8 Body Mass and Body Composition

8.1 Background

There is linear association between higher Body Mass Index (BMI) and incidence of upper gastrointestinal (oesophagus and stomach) cancers, independent of smoking status (Bhaskaran *et al.*, 2014; Coe, O'Reilly and Renehan, 2014). More specifically, the prevalence of oesophageal adenocarcinoma is associated with an increased BMI in men (Renehan *et al.*, 2008).

Obese patients are also at risk of increased rates of tumour growth and disease progression (Park *et al.*, 2014). Furthermore, there is evidence linking an increased visceral obesity with poorer clinical outcomes and changes in body composition in patients undergoing neo-adjuvant chemotherapy in oesophageal cancer (Yip *et al.*, 2014b, 2015), and a strong carcinogenic association of visceral adipose tissue enhancing tumorigenesis in epithelial tissue (Renehan, Zwahlen and Egger, 2015; Chakraborty *et al.*, 2017). Depletion of skeletal muscle mass is a poor prognostic factor in cancer (Martin *et al.*, 2013) while inactivity and ageing are known to be associated with loss of skeletal mass and function, with a loss of 1% to 5% per year in middle age (Wilkinson, Piasecki and Atherton, 2018).

In the recent Continuous Update Project (CUP) presented by the World Cancer Research Fund collaboration in 2018, 'convincing evidence of body fatness' was stated to increase the risk of all cancers including oesophageal adenocarcinoma, while 'physical activity and vegetables' was reported to 'suggest' a decreased risk (*"Diet, Nutrition, Physical Activity and Cancer: a Global Perspective". About the Third Expert Report*, no date; *Oesophageal cancer | World Cancer Research Fund International*, no date).

8.2 Aim

This study aimed to assess the impact of a structured exercise program versus standard care on body mass and body composition using the routine Computerised Tomography (CT) scans of patients before and after neo-adjuvant chemotherapy.

8.3 Methods

The use of CT scans for quantifying fat or adipose tissue (FAT), visceral fat and muscle tissue at the 3rd lumbar vertebral level (L3) has opened the opportunity for assessment of adiposity and sarcopenia in research and clinical settings (Mourtzakis *et al.*, 2008). The same group also linked

body composition, using CT scans, to sarcopenic obesity and clinical outcomes in oesophageal cancer treatment (Prado *et al.*, 2008)

In this study, patients in both Intervention and Control cohorts underwent routine pre- and post-neoadjuvant chemotherapy CT scans for disease staging purposes. The images were assessed, using FATS software developed at King's College London, within a standard Digital Imaging and Communications in Medicine (DICOM) process for tissue segmentation. Assessments were supervised by Professor Vicky Goh, Professor of Cancer Clinical Imaging, and performed by Radiology Clinical Research Fellow, Dr Louise Gervais-Andre.

Using Hounsfield unit thresholding, automated segmentation of subcutaneous and visceral fat and muscle parameters was evaluated in each participant. The equivalent of 10mm slices (z-axis image stacks) were sampled at L3 from the CT scans. Layers of the abdominal wall (skin, subcutaneous fat and skeletal muscle), intra-abdominal layers (visceral layers and viscera) and vertebral bone including spinal cord were delineated manually by a qualified radiologist. Automated segmentation of subcutaneous and visceral fat, and muscle parameters enabled tissue attenuation correlating with standardised values identifying skeletal muscle, visceral muscle, and fat (Mourtzakis *et al.*, 2008). (See Figure 8.1)

Segmented values of skeletal muscle, visceral and subcutaneous fat were obtained.

Using height and weight data at the relevant time points, the following standardised calculations were made (Mourtzakis *et al.*, 2008):

Total body FM (kg) = 0.042 × [total adipose tissue at L3 (cm^2)] + 11.2

Total body FFM (kg) = 0.3 × [skeletal muscle at L3 (cm^2)] + 6.06

FM and FFM were normalised for stature to derive FM index (FMi) and FFM index (FFMi)($kg.m^{-2}$) respectively:

FM index (kg/m^2) =Total body FM ÷ [height × height (m^2)]

FFM index (kg/m^2) =Total body FFM ÷ [height × height (m^2)]

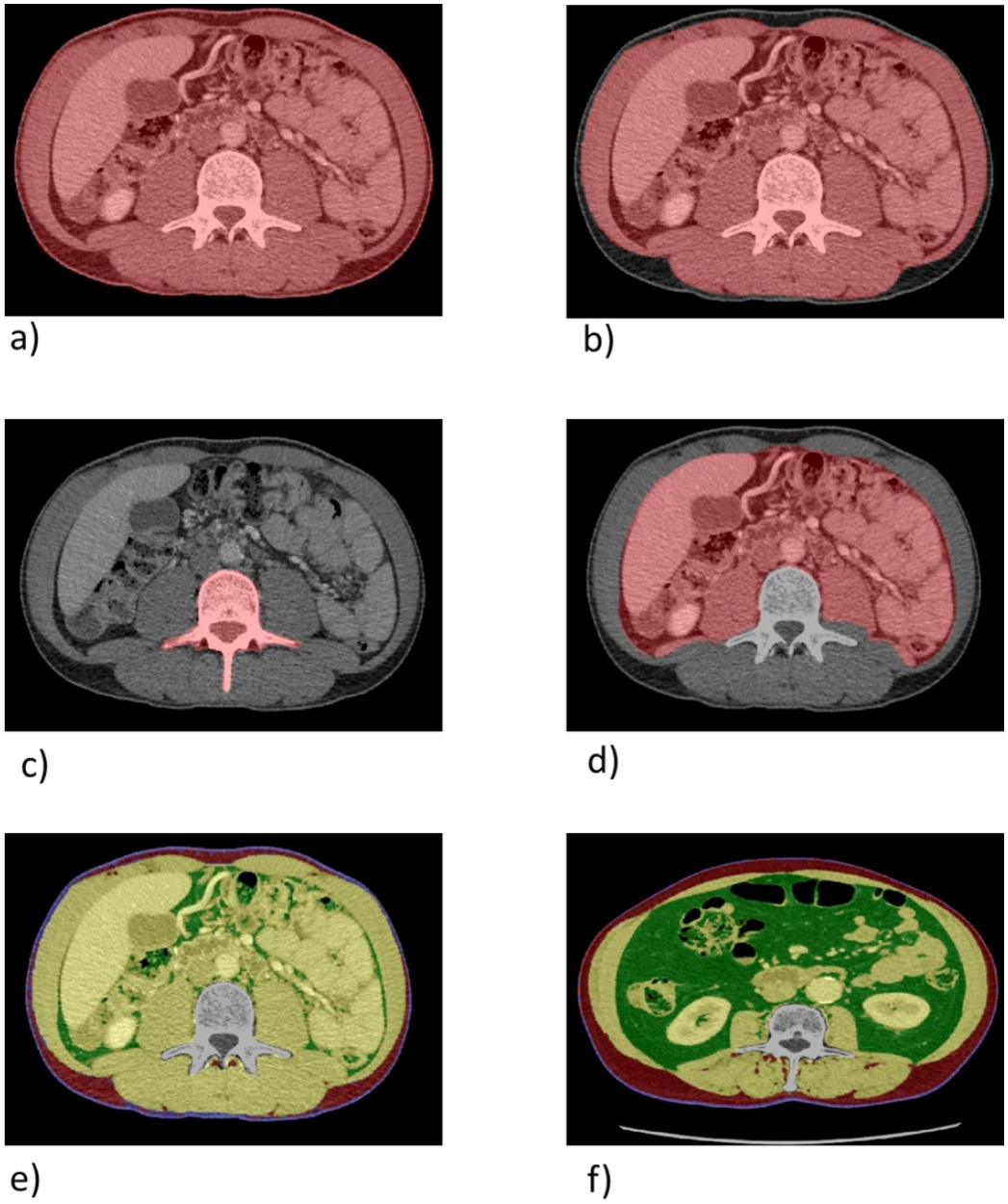


Figure 8-1 CT body composition segmentation at Lumbar 3 vertebrae: a) Subcutaneous boundary, b) Skeletal muscle boundary, c) Vertebral boundary, d) Visceral boundary, e) Fat segmentation 1, f) Fat segmentation 2

8.4 Results

An overall increase in FFMi and loss of FMi was observed in patients participating in the exercise prehabilitation program, with the opposite overall change in the Control group with this group also presenting with a weight increase. The increased weight in the Control group was mainly in the visceral fat, an increase of 4.5%, with a 2.5% increase in subcutaneous fat. The Interventional group had a greater median decrease of visceral fat compared to subcutaneous fat of 7.4% and

5.10%, with a median weight loss of 0.6% compared to baseline (see Table 8.1 and 8.2).

Table 8-1 Body composition parameters: Intervention versus Control groups

	Control		**Intervention**		
	n=14		n=13		
Parameters	Mean (SD)	Range	Mean (SD)	Range	**p- values***
	Median (IQR)		*Median (IQR)*		
FFM index (kg/m2)					
Baseline	15.4 (3.6)	10.3-22.4	17.4 (4.4)	9.2-24.1	0.23
	16.3 (11.8-18.5)		*17.8 (14.4-20.9)*		
Post NAC	15.4 (3.0)	9.4-18.8	17.7 (3.7)	12.5-23.3	**0.03**
	14.7 (12.3-17.3)		*18.7 (15.0-20.2)*		
Changes (%)	-3.0 (22.1)	-45.0-42.5	4.3 (16.9)	-18.5-41.3	0.36
	-1.9 (-19.0-9.9)		*2.3 (-7.2-10.1)*		
FM index (kg/m2)					
Baseline	8.5 (2.2)	4.1-11.8	8.9 (3.6)	4.9, 16.2	0.96
	8.1 (7.1-10.4)		*9.1 (6.4-9.6)*		
Post NAC	8.7 (1.9)	5.5-12.2	8.8 (3.1)	4.8, 15.0	0.70
	8.2 (7.4-10.5)		*8.2 (6.8-9.2)*		
Changes (%)	3.5 (10.7)	-6.9-34.7	0.7 (14.7)	-12.4-35.1	0.21
	0.7 (-3.7-5.8)		*-3.8 (-9.8-3.8)*		
FMR					
Baseline	1.31 (0.78)	0.14-3.12	1.31 (0.96)	0.17-3.34	0.85
	1.07 (0.90-1.58)		*1.08 (0.67-1.75)*		
Post NAC	1.45 (0.63)	0.41-2.78	1.25 (0.76)	0.15-2.47	0.41
	1.11 (0.88-2.16)		*0.91 (0.59-1.94)*		
Changes (%)	26.3 (61.3)	-31.6-200.0	8.4 (41.9)	-38.9-104.9	0.50
	12.4 (-11.9-36.6)		*-7.15 (-17.2-39.2)*		
Visceral fat (cm2)					
Baseline	202.9 (104.9)	25.5-376.0	186.0 (128.0)	27.0-468.3	0.70
	206 (141-274)		*204 (41-256)*		
Post NAC	211.0 (86.8)	42.4-351.2	173.2 (114.4)	25.0-433.7	0.21
	214 (163-249)		*154 (104-228)*		
Changes (%)	25.3 (66.5)	-15.1-247.0	10.9 (54.9)	-36.2-150.3	0.13
	4.5 (-5.1-28.7)		*-7.4 (-23.2-12.7)*		
Subcutaneous fat (cm2)					
Baseline	173 (91)	25-367	179 (126)	33-463	0.81
	165 (112-183)		*153 (109-214)*		
Post NAC	176 (79)	72-330	179 (106)	30-420	0.77
	158 (129-190)		*147 (111-227)*		
Changes (%)	15.2 (52.0)	-18.3-191.9	10.3 (37.9)	-30.8-101.5	0.47
	2.5 (-5.1-9.2)		*-5.1 (-9.4-9.3)*		
VA/SA ratio					
Baseline	1.30 (0.74)	0.16-3.29	1.08 (0.62)	0.24-2.47	0.31
	1.24 (0.84-1.50)		*0.83 (0.61-1.51)*		
Post NAC	1.31 (0.63)	0.30-2.84	1.04 (0.55)	0.25-1.97	0.36

	1.22 (0.99-1.41)		*0.83 (0.59-1.39)*		
Changes (%)	8.9 (26.2)	-18.0-87.0	-1.31 (20.6)	-31.7-36.6	0.47
	2.0 (-4.7-15.2)		*1.70 (-17.2-10.1)*		
Weight (kg)					
Baseline	91.1 (27.1)	61.7-170	76.0 (13.5)	56.8-99.6	0.05
	87.5 (68.7-94.5)		*80.1 (64.3-84.3)*		
Post NAC	92.1 (26.5)	63.8-169	75.6 (12.7)	56.0-96.9	0.05
	88.2 (74.0-95.6)		*76.4 (69.2-79.9)*		
Changes (%)	1.5 (3.7)	-6.7-8.4	-0.13 (4.9)	-8.6-8.1	0.36
	1.2 (-0.6-3.5)		*-0.6 (-2.7-4.6)*		

FFM-fat free mass, FM – fat mass, FMR – subcutaneous fat to muscle ration, VA/SA ratio – visceral to subcutaneous fat (adipose tissue) ratio, BMI- body mass index
*p-values derived from Wilcoxon-signed rank test

Table 8-2 Summary of body composition changes after NAC

Parameters	**Intervention**	**Controls**
FFM index (kg.m^{-2})	2.30%	-1.90%
FM index (kg.m^{-2})	-3.80%	0.70%
FMR	-7.15%	12.40%
Weight (kg)	-0.50%	1.20%
Visceral fat (cm^2)	-7.40%	4.50%
Subcutaneous fat (cm^2)	-5.10%	2.50%

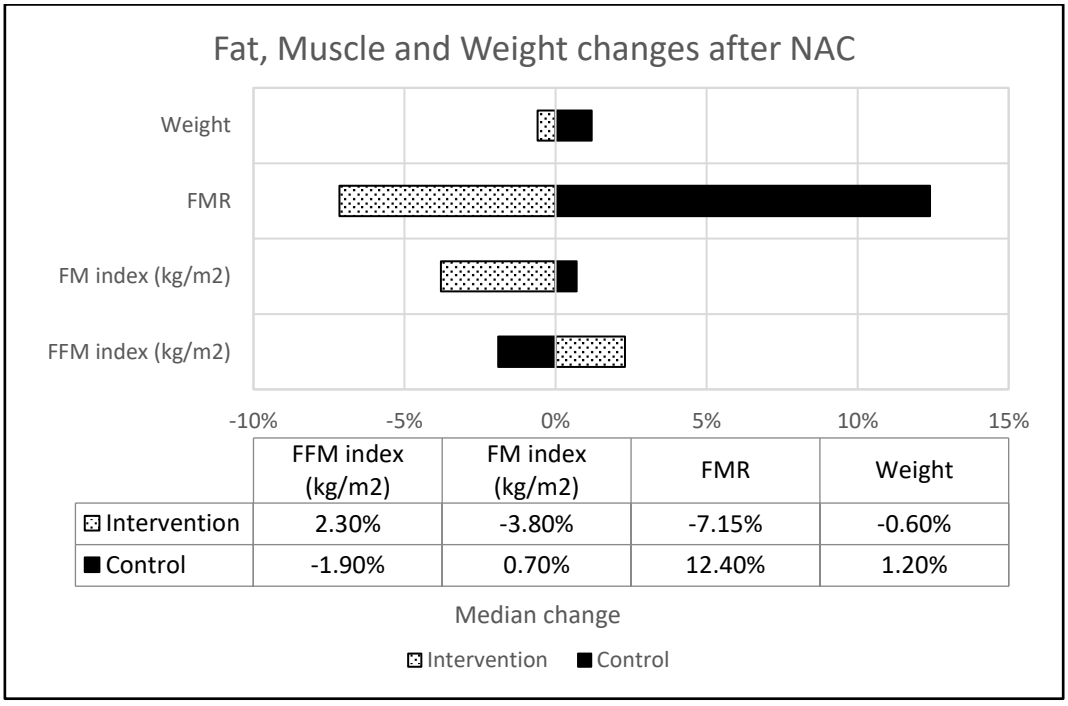


Figure 8-2 Bar chart showing body composition and weight changes post-NAC

8.5 Discussion

The observed increases in FFM and height adjusted FFMi combined with the decrease in FM and FMi in patients participating in the exercise intervention during NAC compared with the opposite increases in FM and FMi with synchronous decrease in FFM and FFMi, is another unexpected result from this trial.

Patients diagnosed with oesophageal cancer frequently present with nutritional deficiencies and weight loss due to disease-associated difficulties with swallowing. Oesophageal tumours may cause obstruction, regurgitation or pain during eating with subsequent diet restriction. Despite this, patients in the Intervention group remained weight stable with an increase in muscle development and reduction in fat. In contrast, patients in the Control group gained weight. The weight-gain occurred mainly as fat but particularly as visceral fat – known to be associated with tumour and disease progression.

The improvement in body composition in oesophageal cancer patients undergoing a structured exercise program during simultaneous chemotherapy treatment is a positive and clinically relevant outcome from this trial.

8.6 Conclusions

There were significant and striking differences between the Intervention and Control groups in relation to body composition changes in patients undergoing 8-9 weeks of neo-adjuvant chemotherapy. It was hypothesised that a reduction of sarcopenia would be achieved over this relatively short period of exercise intervention – and under difficult circumstances for the patients - whereas an overall reversal of sarcopenic obesity occurred in patients on the Interventional prehabilitation program. The opposite effect was noted in the Control cohort on a standard care pathway.

This contrast in body composition changes between the groups following neo-adjuvant chemotherapy and the potential deleterious role of increased fat on the tumour micro-environment is cause for clinical re-evaluation of the information on exercise and diet that is currently provided to patients.

Further collaborative research, in larger cohorts of patients is indicated to validate the results in this study.

Chapter 9 Immunity and Inflammatory Blood Markers

9.1 Background

The effect of exercise prehabilitation in cancer may impact tumour control through immune system regulation. In a review of patients who undertook monitored exercise following a diagnosis of cancer, there was a lower relative risk of cancer recurrence and cancer-related mortality compared to patients who did little or no exercise. Furthermore, the same patients experienced fewer or less severe treatment side effects (Cormie *et al.*, 2017). This finding supports the suggested immunological component to cancer growth and recurrence control. Terra et al. (2012) described inherent activation of the immune response cascade through exercise, eliciting a pro-inflammatory response during moderate intensity exercise. However, during high intensity exercise an anti-inflammatory response was noted. Hojman further described the effects of exercise on the control of immune cell function, modulation of inflammatory signalling and regulation of systemic inflammation linking these regulatory effects to lowered tumour incidence and disease progression (Hojman, 2017a). Pederson et al. (2016c) linked exercise to reduced tumour growth through increased infiltration of natural killer (NK) cells in exercised mice. The mechanism of increased mobilization of NK cells is speculated to be through increased release of Interleukin-6 (IL-6) myokines in response to muscle contraction (Idorn and thor Straten, 2017). Exercise-induced IL-6 is described as having a pro-inflammatory effect on bacterial infections and a contrasting anti-inflammatory inhibiting effect on Tumour Necrosis Factor-alpha (TNF-a) (Cullen *et al.*, 2016) .

The tumour micro-environment (TME) is therefore one in which a balance of tumour-promoting and tumour-suppressing signals is under constant surveillance and regulation by the immune system. In cancer, these signals are interrupted and imbalanced in favour of cell-growth. Exercise has been observed to have a tumour regulation effect (Pedersen *et al.*, 2016c). This effect is multifactorial. When the TME is under stress it is thought to release growth factors, with oxygen depletion a major stressor implicated in tumour regulation (Petrova *et al.*, 2018).

In addition, pro-inflammatory and inflammation-suppressing cytokines are released during exercise thereby assisting the immune system in regulation of the TME. Study of the TME is complex and pathological tissue samples are not always available. It has been shown, however, that the peripheral blood T-cell activity closely correlates with the activity within the TME providing a useful method of monitoring immune and inflammatory function during treatment (Iwahori *et al.*, 2019).

9.2 Aim

The aim of this study was to investigate the effect of exercise on immunity and inflammatory markers in patients on a combined chemotherapy-surgical pathway for oesophageal cancer using peripheral blood samples taken at the key study time points. This information would provide some insight into the TME in cancer patients undertaking exercise prehabilitation.

9.3 Methods

Blood samples were taken according to the study protocol.

Blood samples for Immunoglobulins (IG) and Lymphocyte subsets (LS) were analysed immediately while samples for Cytokine analysis were spun, stored and frozen for later batch testing and analysis.

9.3.1 Immunoglobulins

Immunoglobulins are measured using serum and plasma samples of patient's blood. A mechanised assay is used following addition of polyethylene glycol (PEG) to stimulate antigen-antibody reaction. Agglutination occurs resulting in increased turbidity. Turbidity is then measured, in nanometres (nm). A calibration curve is constructed and the absorbances determined calculate IgG, IgA and IgM concentrations.

9.3.2 Lymphocyte subsets

T-Lymphocyte subsets are analysed using Laser Flow Cytometry of a monoclonal antibody/blood sample reaction on a Beckman Coulter AQUIOS flow cytometer (BECKMAN COULTER Life Sciences, 5350 Lakeview Parkway S Drive, Indianapolis, IN 46268, USA) . Red cells are lysed through addition of a lysing solution. A stream of the remaining single cells of antibody-antigen reaction, are passed through a laser beam interrogation point. The emitted light passes through wavelength filters separating out the subset components. The results are produced as a series of histogram plots and analysed according to grouping. Manual 'gating' is carried out by an Immunologist for quality control.

9.3.3 Cytokines

Groups of cytokines - lymphokines, interferons, haemopoietic and non-haemopoietic growth factors were measured through quantitative detection of multiple analytes on a RANDOX Evidence Investigator (Randox Laboratories Ltd. 140 London Wall, London, EC2Y 5DN) using Competitive and Sandwich antibody, chemiluminescent, biochip immunoassays. Increased binding of horseradish-labelled antibody with the analytes, resulted from increased cytokine

levels in a specimen. A chemiluminescent response between the cytokine antigen and the HRP-labelled antibody was detected using digital imaging technology.

9.4 Results

The mean percentage changes, with standard deviation (SD), at each time point were analysed comparing baseline immunity and inflammatory blood results within Control and Interventional cohorts.

(see Appendix DE for full results: Table 9.2 - Immune markers, and Table 9.3 – Inflammatory markers; Figure 9-2 CD3+/CD4+ Histogram plot examples)

The post-NAC results summarised in Table 9.1, indicating those parameters which had greater than 25% difference in change between the Control and Intervention cohorts from Baseline to Post-NAC

Table 9-1 Percentage change in Immunity and Inflammatory Markers: Baseline to Post-NAC

	Control	Intervention		
Markers	**% Mean change**	**% Mean change**	**% Mean Difference**	**p-values**
Immunity				
CD3 (cells/uL)	4.53	34.26	29.73	**0.03**
CD4 (cells/uL)	9.36	42.08	32.72	0.1
CD8 (cells/uL)	0.98	29.41	28.43	**0.03**
Inflammatory				
IL-6 (ng/L)	126.41	27.93	-98.48	**0.04**
VEGF (ng/L)	51.79	10.51	-41.28	0.27
INF-γ (ng/L)	223.64	57.24	-166.4	0.36
TNFa (ng/L)	28.31	-1.77	-30.08	0.24
MCP-1 (ng/L)	169.69	52.11	-111.58	0.09
EGF (ng/L)	-8.23	20.06	28.29	0.61

There was a significantly different increase of % Mean change in T-Lymphocytes CD-3 and CD-8 in the Intervention group when compared to the Control group after NAC (34.26% and 29.08% vs. 4.53% and 0.98%, p=0.03 for both CD-3 and CD-8).

IL-6 resulted in a moderate increase in the Intervention group after NAC compared to a significantly greater increase of this inflammatory marker in the Control group (126.41% vs. 27.93%, p = 0.04).

TNFa was reduced by -1.77% in the Intervention group but increased by 28.31% in the Control group after NAC.

INF-y showed a 223.64% increase in the Control group compared to the moderate change of 57.24% in the Intervention group.

MCP-1 change was lower in the Intervention group while being markedly increased in the Control group (52.11% vs. 169.69%).

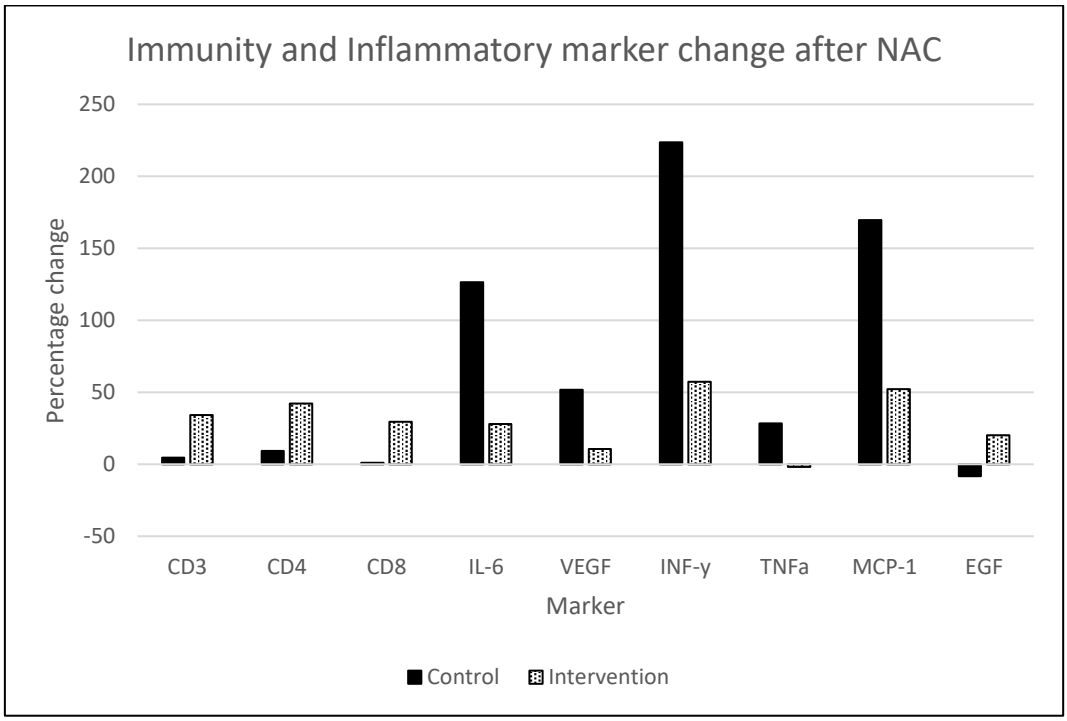


Figure 9-1 Percentage change in Immunity and Inflammatory markers after NAC

9.5 Discussion

The increase, and statistically significant ($p \leq 0.05$) difference, in T lymphocytes CD-3 (p = 0.03) and CD-8 (p = 0.03), in patients who exercised during neo-adjuvant chemotherapy suggests improved adaptive immune-system function and tumour-cell destruction capability, compared to patients in the Control cohort. Recent reports suggest that CD-3 and CD-8 as being predictive of improved response to NAC in breast cancer patients while other suggest their value in being prognostic of decreased cancer relapse (Brown *et al.*, 2014; Tsiatas *et al.*, 2018). This hypothesis appears to correlate with the reported improved Mandard Tumour Regression Grade scores discussed in Chapter 6.

IL-6 induced through exercise (muscle stimulation) has been reported to having a role in immune regulation (Hojman *et al.*, 2018) while IL-6 secretion related to visceral adiposity is reported to be directly associated with tumour cell growth and disease progression (Park *et al.*, 2014). Furthermore, IL-6 and TNFa are reported to strongly correlate with increased BMI (Park, Park and Yu, 2005). These hypotheses correlate with the moderate increases in IL-6 in the Intervention group – suggestive of resulting from muscle activation, while the greater change in IL-6 in the Control group, with synchronous increase in TNFa, suggesting activation through increased visceral fat stimulation in the Control group. This appears to be linked to the increase in visceral fat increase noted on CT scan in participants in the Control group. (Chapter 8)

Previously considered to have antitumor immunity properties, IFN-y has recently been found to have a converse, tumour-progressive function. The mechanism of this tumour progressive role is thought to be through immune-system evasion of cancer cells and is a topic of current exploration (Mojic, Takeda and Hayakawa, 2017; Zaidi, 2019). INF-y changes in the Control group were highly elevated compared to the Intervention group suggesting greater levels of immune-system evasion resulting in decreased tumour control.

MCP-1, believed to regulate the tumour cell and macrophage cycle promoting progression of tumours (Yoshimura, 2018) showed much greater changes in the Control group compared to the Intervention group. In vivo studies of mice with ovarian cancer, MCP-1 appeared to increase cell migration and invasion of tumour cells (Rattan *et al.*, 2019). In our study, 2 patients in the Control group were reported to have cancer recurrence within the follow-up period, with none in the Intervention cohort. Exercise would appear to moderate expression of MCP-1 and therefore have a controlling effect on tumour cell migration and disease relapse.

9.6 Conclusions

Statistically significant and correlating results in T Lymphocyte activation of CD-3, CD-8, and IL-6 were observed indicating that the exercise Intervention group appeared to experience improved cancer control at a molecular level. These results are particularly encouraging in patients who had recently finished immune-suppressive chemotherapy. In contrast, T- Lymphocyte results in the Control cohort showed suppressed immunity and high levels of inflammatory cytokines (IL-6, TNFa, INF-y and MCP-1) indicating unregulated or progressive inflammation in the TME.

Accordingly, data from the present study demonstrates a positive impact of structured exercise supporting the immune system despite chemotherapy suppression during NAC while moderating inflammatory responses.

Chapter 10 Health-Related Quality of Life

10.1 Background

An area of increased focus in patients with cancer is the impact of the diagnosis, treatment and survival, on their quality of life. The United Nations defines quality of life as the "notion of human welfare (well-being) measured by social indicators rather than by 'quantitative measures of income and production" (*UNdata | glossary*). In the context of cancer and health, quality of life extends beyond the 'impact of treatment and side-effects, but to the recognition of the patient as an individual, and as a whole person, body mind and spirit' (Calman, 1984). In practice, quality of life measures are those self-reported measures of changes in a person's circumstances reflecting the fulfilment of hopes and expectations, or lack thereof.

Validated Health-related quality of life (HRQL) questionnaires assess multiple facets of quality of life including: wellbeing; and physical, emotional, cognitive and social functioning; in addition to specific symptom scores. Studies have shown that HRQL is negatively impacted by oncological treatments (Noordman *et al.*, 2018) with a slow recovery after surgery (Djärv *et al.*, 2008; Safieddine *et al.*, 2009; Kidane *et al.*, 2018). Djarv et al.,(2008), (Noordman et al., 2018 and Kidane et al., 2018), reported that HRQL only returned to baseline 6 to 36 months after oesophagectomy. In oesophageal cancer, neo-adjuvant chemotherapy or chemoradiotherapy has been reported to result in an overall decline in HRQL (Blazeby *et al.*, 2005). Poor health and mental wellbeing are common hallmarks following a diagnosis of cancer and after undergoing cancer treatment, in the UK (Elliott *et al.*, 2011).

Of note, increased physical activity and exercise is associated with improved Health-related Quality of Life in the general population (Anokye *et al.*, 2012) and improved mental wellbeing, especially in later life (Windle *et al.*, 2010). Post-surgical studies in breast cancer patients have shown that engaging in physical activity helps to manage the decline in HRQL after surgery (Leach *et al.*, 2015).

10.2 Aim

This study aimed to examine self-reported Mental Wellbeing and HRQL in patients undertaking an exercise prehabilitation program during NAC versus patients on a standard care pathway.

10.3 Methods

The trial employed two validated questionnaires: A cancer-specific questionnaire, EORTC QLQ-C30 and the shortened Warwick-Edinburgh Mental Well-being scale (SWEMWBS) to evaluate **p**atient **r**eported **o**utcome**s** (PROMS).

The EORTC PROMS were developed and validated for cancer-specific measures and useful irrespective of the level of advancement of cancer (*EORTC | European Organisation for Research and Treatment of Cancer : EORTC*).

A collaboration between Warwick and Edinburgh Universities produced the Warwick-Edinburgh Mental Well-being scale (WEMWBS) for assessing mental wellbeing in the general population. In this study, the shortened version, SWEMWBS, was employed to reduce the burden of 'questionnaire-fatigue' on the patient.

Patients were asked to complete self-reported questionnaires at all major time points of the trial and at 6 and 12 months after surgery. EORTC QLQ-C30 (Quality of Life of Cancer Patients) and the SWEMWBS questionnaires were selected following registration with the relevant organisations. Published specified module guidelines were used for analysis.

Voluntary feedback comments from patients are also included in Appendix F.

10.4 Results

Mean scores with standard deviations were calculated from the completed questionnaires for patients at baseline and all subsequent time points. Questionnaires were composed of many questions, largely designed for research purposes of large cohorts, but also for use in clinical assessment. The numbers of patients in this analysis are insufficient to achieve any statistically significant results but were expected to produce a trend of any difference in effect between patients in the two patient groups.

Some groupings of mixed results were achieved; however, some groupings produced a more consistent trend. These can be seen graphically represented in Figures 10-1, 10-2 and 10-3 (Appendix E: Table 10-1)

10.4.1 Mental Wellbeing

Figure 10-1 demonstrates an overall benefit of exercise participation in the Intervention group with an improved WEMWBS and a reduced perturbation in mental wellbeing, with near return to baseline at 12 months after surgery. In comparison, participants in the Control group showed a large decline in Mental Wellbeing after NAC and at 6- and 12-months after surgery.

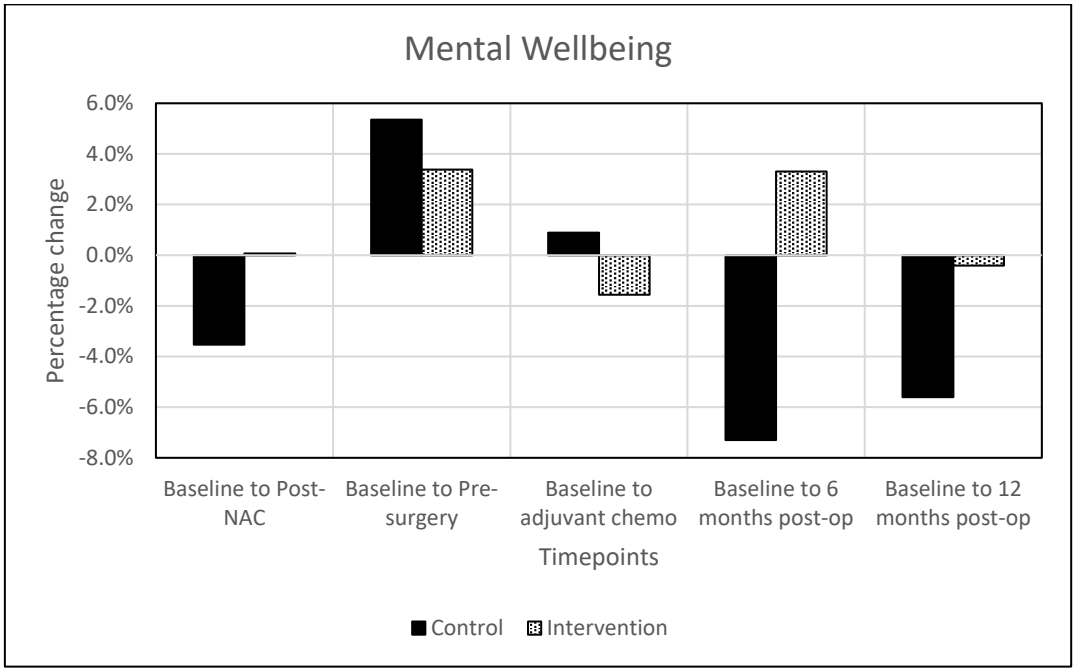
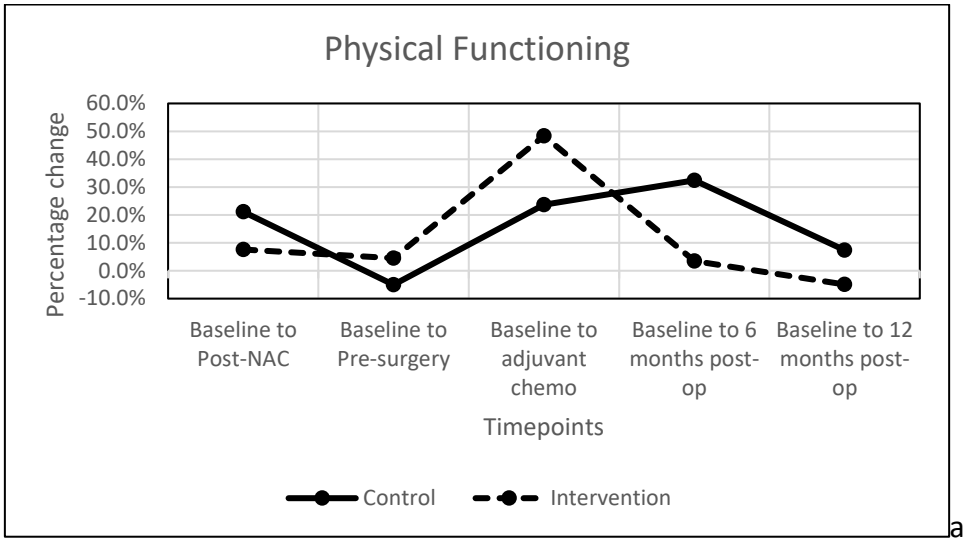


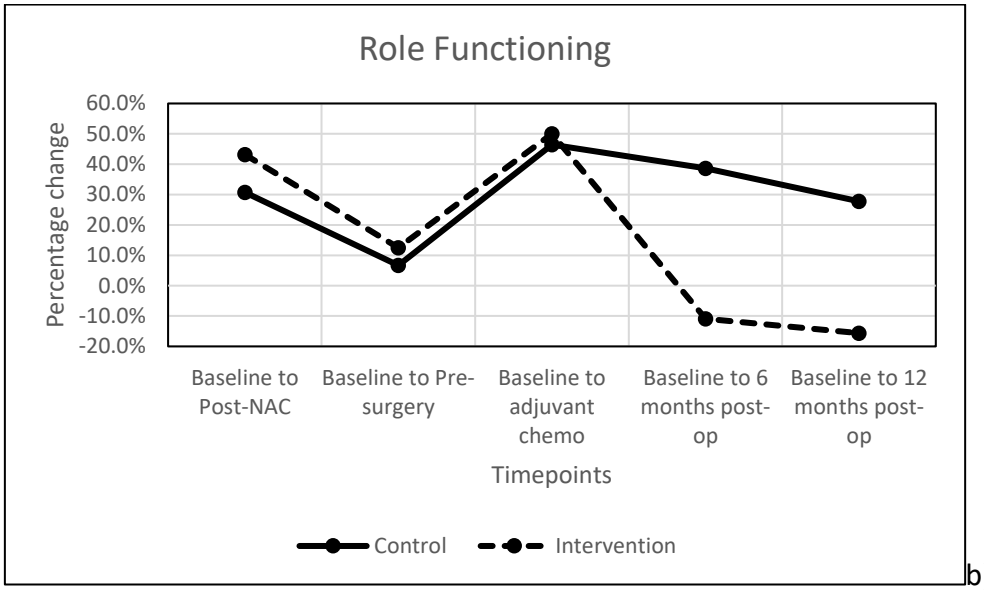
Figure 10-1 Mental Wellbeing scores (WEMWBS)

10.4.2 Health Related Quality of Life

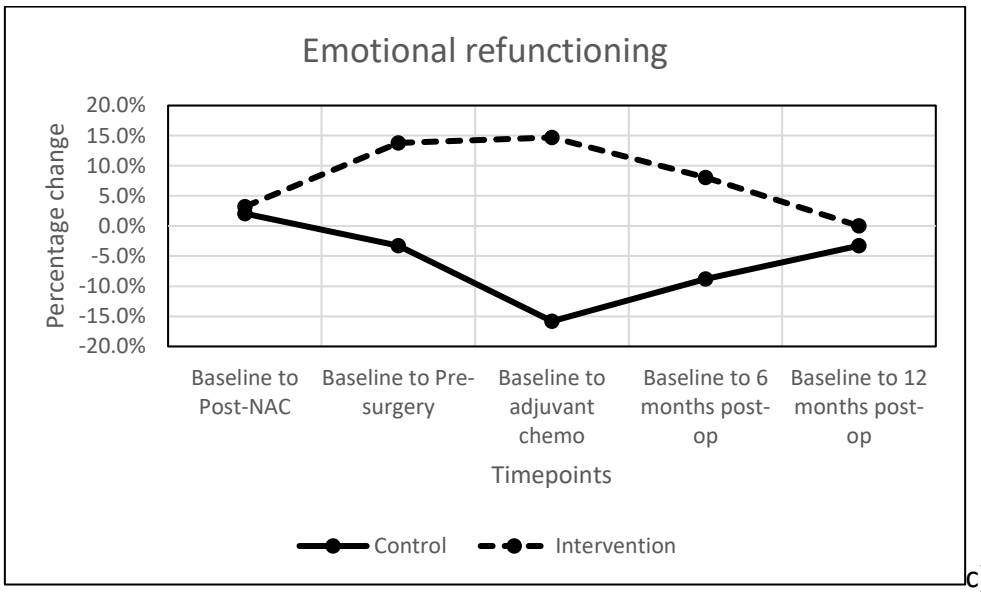
Figures 10-2 and 10-3 represent the EORTC QLQ C30 self-reported questionnaires evaluating HRQL using function- and symptom- related questions. In similarity to the SWEMWBS results, Emotional Functioning was markedly better in the Interventional group who undertook the exercise program. Similar results in both groups were noted in Social- and Role- Functioning except for an unexplained sharp decline in Role Function at 6 and 12 months in the Intervention group. Questions on Physical- and Cognitive-Function scores produced mixed results in both groups however a near return to baseline function was achieved at 12-months post-surgery.


Physical Functioning
Percentage change
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
-10.0%
Baseline to Post-NAC
Baseline to Pre-surgery
Baseline to adjuvant chemo
Baseline to 6 months post-op
Baseline to 12 months post-op
Timepoints
Control
Intervention

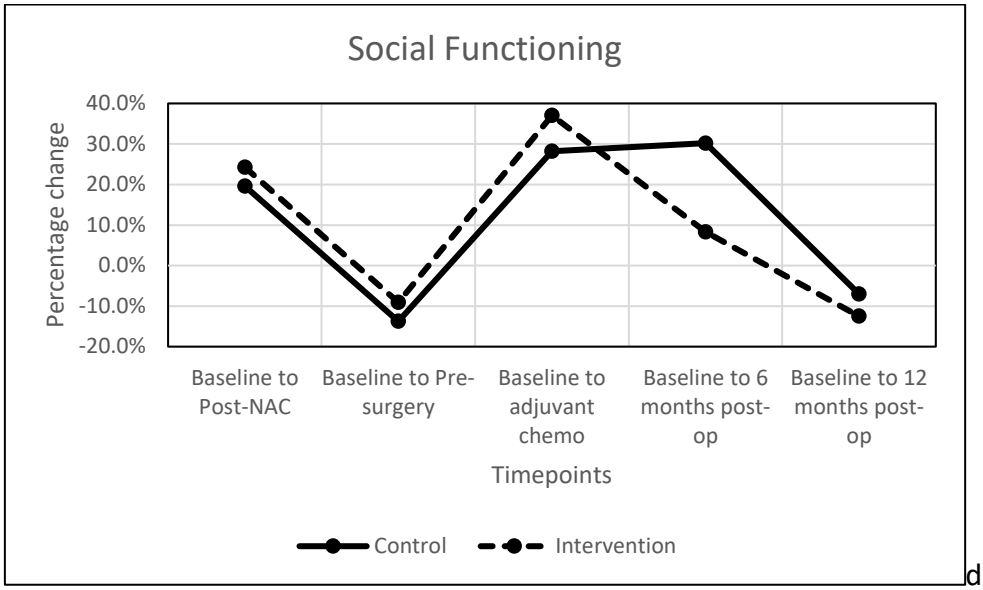
a)


Role Functioning
Percentage change
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
-10.0%
-20.0%
Baseline to Post-NAC
Baseline to Pre-surgery
Baseline to adjuvant chemo
Baseline to 6 months post-op
Baseline to 12 months post-op
Timepoints
Control
Intervention

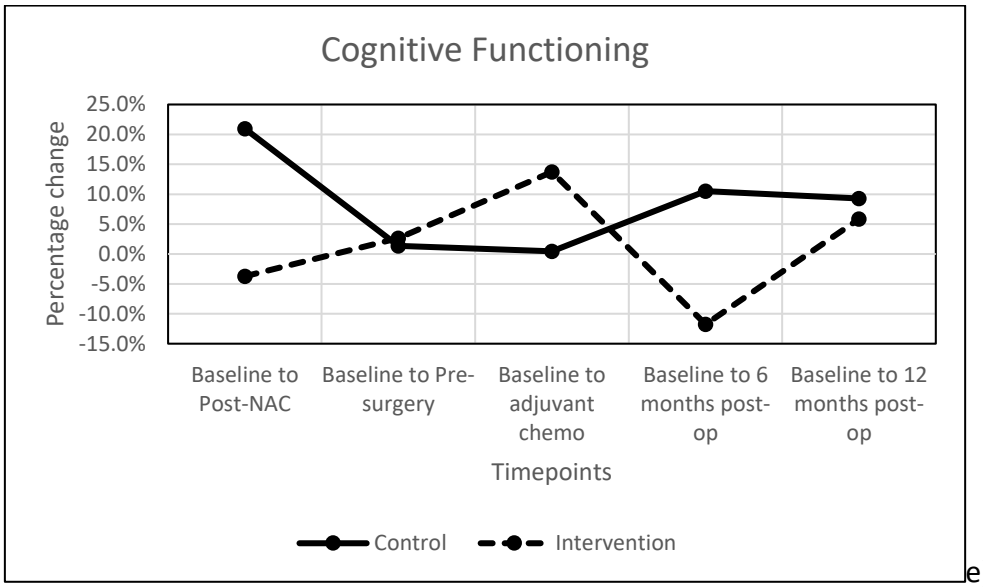
b)


Emotional refunctioning
Percentage change
20.0%
15.0%
10.0%
5.0%
0.0%
-5.0%
-10.0%
-15.0%
-20.0%
Baseline to Post-NAC
Baseline to Pre-surgery
Baseline to adjuvant chemo
Baseline to 6 months post-op
Baseline to 12 months post-op
Timepoints
Control
Intervention

c)



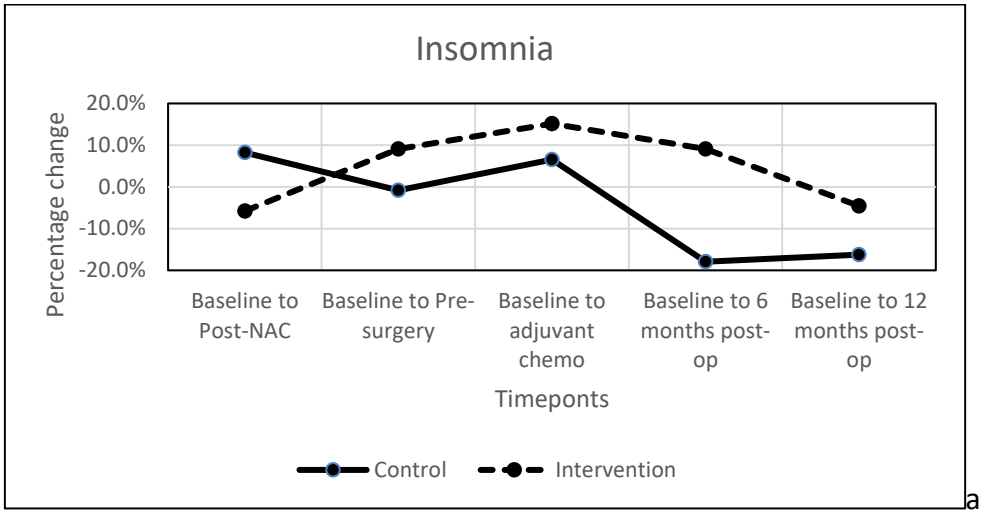
d)



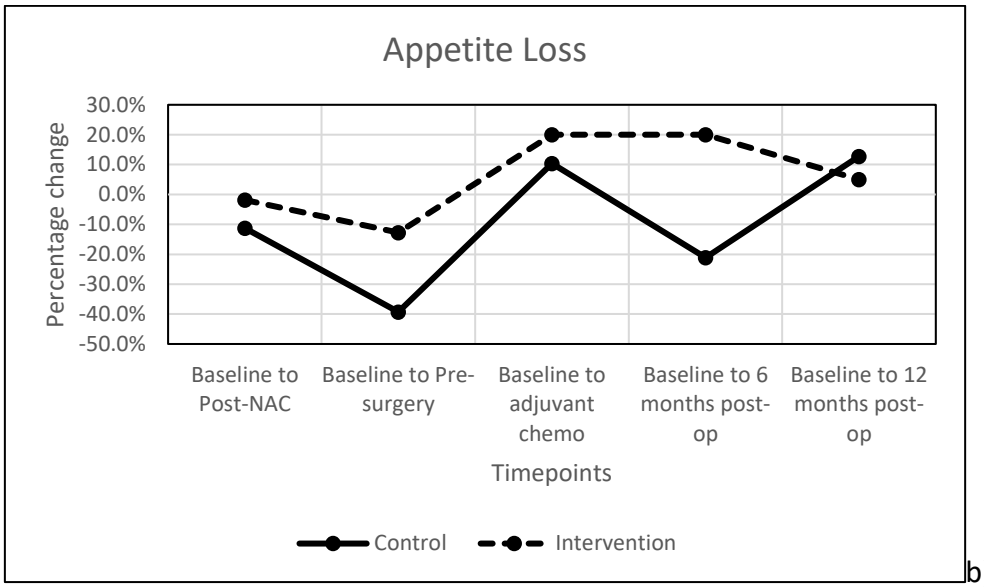
e)

Figure 10-2 EORTC QLQ C30 Grouped Functioning Scores –a,b,c,d,e

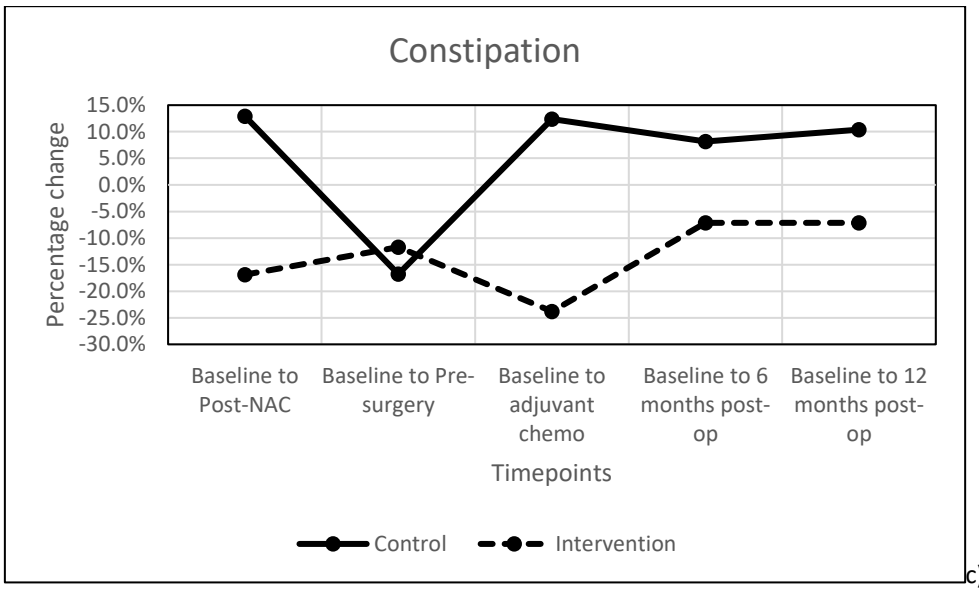
Results varied among the cancer-specific symptoms. There appeared to be greater fluctuations in insomnia in the Control group. Appetite variation was also greater in the Control group. Overall weight gain was noted in this group compared to the Intervention group while undertaking the structured exercise program. Constipation also fluctuated more in the Control versus Intervention group.



a)



b)



c)

Figure 10-3 EORTC QLQ C30 Selected Symptom Scores – a,b,c

10.5 Discussion

A cancer diagnosis has a powerful effect on an individual. Despite reduced self-reported outcome scores in the Intervention group they still produced good scores on Mental Wellbeing and Emotional Function compared to their study counterparts.

The confounding variables which may have impacted on the results in cancer-specific symptoms are numerous and more likely related to the disease status rather than to exercise-related physical activity, especially pain, nausea, and diarrhoea.

Constipation was markedly reduced in the exercise Intervention group but increased by more than 10% compared to baseline in the Control group. In a study of regular exercise on chronic constipation in middle-age adults, regular physical activity reportedly improved symptoms (De Schryver *et al.*, 2005). Appetite loss was lower in the Control group compared to an increased appetite loss in the Intervention group. This corresponds with the increase in overall weight and body fat in the Control group during neo-adjuvant chemotherapy (discussed in Chapter 8.4) but, does not seem to have had a negative Mental Wellbeing effect in the Intervention group who increased muscle mass without weight loss, despite reduced appetite.

From anecdotal evidence, it was noted that many of those who undertook the exercise intervention self-referred to physiotherapy and rehabilitation support services in the post-12-month follow-up period. This was encouraging as few had regularly participated in exercise or physical activity prior to their diagnosis of cancer. In contrast, the Control cohort, while scoring slightly better pre-surgery, scored lower after neo-adjuvant chemotherapy and were still struggling to return to baseline Mental Wellbeing at 12 months after surgery.

On completion of the trial at 12-months post-op, patients were invited to provide feedback and comments relating to their participation in the exercise prehabilitation. (See letters in Appendix E)

10.6 Conclusions

There was an overall improvement in Mental Wellbeing, and corresponding improvement in Emotional Refunctioning in HRQL after neo-adjuvant chemotherapy and at 6- and 12-months post-surgery in patients that participated in a structured exercise prehabilitation program. The chemotherapy and surgery treatment periods are arguably significantly 'negative' periods during the patient pathway. To achieve the difference in Mental Wellbeing at major time points in the

Interventional group supports the role of exercise intervention peri-treatment in oesophageal cancer patients.

Participation in the exercise program appeared to provide short-term benefits in the neo-adjuvant treatment period and longer-term benefits with many patients being self-motivated to enrol in physical activity and exercise programs in the post-treatment and 'Survivorship' period.

Clinical outcomes and disease-free survival analysis using correlation of HRQL in this study are recommended once both groups of patients have completed all aspects of the treatment pathway including 12 months of follow-up.

Results of the HRQL scores showed mixed and variable differences between the two study groups. The small numbers of patients and large number of variables being assessed were perhaps inappropriate for this interim analysis. The relevance of the questions in the self-reported outcome questionnaires may be more valuable in studies investigate the specific areas under scrutiny in the questionnaires.

Qualitative feedback from patients highlighted areas not specifically covered in the questionnaires but relevant to the patient outcomes, for example:

- Something to focus on other than the diagnosis and treatment
- A reason to 'get out of the house'
- 'Going motivated me to get out and about'
- 'I felt much better after each session'
- 'the simple fact of going gave me a purpose and the exercise boosted my morale which had been sapped by the chemo'
- 'The staff….watched me and made sure that I was comfortable and safe at all times'

These are important 'take home' messages for those directing treatment pathways in cancer care.

Part C

Chapter 11 General Discussion

The aim of the Pre-EMPT clinical trial was to assess the feasibility of a structured exercise prehabilitation program for patients on an operable, 'curatively-intended' peri-operative treatment pathway.

Inherent in some of the challenges to recruiting patients into the study, were the lifestyle factors associated with the increased risks of developing oesophageal adenocarcinoma, including: GORD (gastro-oesophageal reflux disease); obesity; low levels of physical activity and sedentary lifestyles; and smoking. These factors were also some of the challenges faced in retaining participants in the Intervention group of the study. In this group, there was a higher non-participant/self-withdrawal rate in the study than in the Control group who received standard care. Barriers to participation in physical activity and exercise programs is a burgeoning topic of interest, debate and research (Justine *et al.*, 2013). When considering the implementing of structured activity/exercise programs for patients as standard care, aspects of the availability and location of facilities, patient motivation, cost, instruction and activity monitoring are just some of the factors which require further investigation and refinement. In the present thesis, some of these aspects are mentioned in the patient feedback letters (Appendix F).

In this study, 13 of the original 20 patients that initially consented to participate in the exercise Intervention group completed the requirements of the trial (see Chapter 5). While, inevitable, during the period of the program there were days, if not weeks when patients did not feel physically capable or psychologically motivated enough to be active, the overall results indicate that a structured exercise prehabilitation program during neo-adjuvant chemotherapy and before surgery in trial patients is feasible and acceptable to the majority of patients to whom it was offered. Among those patients who withdrew from participation or who did not comply with the exercise intervention, it has been suggested that if the intervention were to be offered to patients as a part of the standard care pathway rather than as an optional extra, e.g. as part trial participation, more patients might have been inclined or persuaded to comply with a structured activity program as a requirement of treatment.

Larger collaborative trials, such as the Wesfit trial (The Wessex Fit-4- Cancer Surgery Trial) lead by Professor Sandy Jack of Southampton University Hospitals that started in March 2018 with the aim to recruit 1560 participants, are needed to confirm the results presented in this feasibility study (*The Wessex Fit-4-Cancer Surgery Trial - Full Text View - ClinicalTrials.gov)*

In the design of the Pre-EMPT trial, it was recognised that the reversal of chemotherapy deconditioning during NAC was an unrealistic goal, however, the exercise intervention as reported in this thesis did result in blunting of the chemotherapy-associated fitness decline over a period of only 8-9 weeks in those undertaking the intervention compared to those in the Control group. This is a positive outcome for patients who experience the omnipresent deleterious effects of chemotherapy including lethargy and physical decline as a result of treatment. Were a larger 'window of opportunity' available prior to commencement of chemotherapy, one might expect to achieve a greater degree of protection against treatment-induced reduction in patient fitness. The NHS target of 'time to treatment with associated penalties for breaching the 'treatment start date' after 62 days of diagnosis is a limiting factor in this regard.

Previous studies have all reported reduction in muscle mass concomitant to chemotherapy treatment. Chemotherapy treatment is also reported to be associated with reduction in VO_{2peak}. Furthermore, increased body mass is also linked to reduced VO_{2peak}.

In this study's Control group, there was a greater reduction in VO_{2peak} following NAC compared to the Intervention group. In the same group there was small median weight gain between Baseline to Post-NAC with marked deterioration in muscle mass and accompanying increase in fat mass observed on CT imaging. Together, these factors are likely to have contributed to the greater chemotherapy-associated decline in Post-NAC VO_{2peak} in the Control group. This data corroborates with previous studies.

However, the data from the Intervention group contrasts with previous findings. Amelioration of physical deterioration during NAC coincided with an increase in overall improvement in body composition *viz.* an increase in the Fat Free Mass (muscle mass) in the Intervention group. Patients in the Intervention group remained largely weight stable or showed minimal median decrease in body mass. The increased activity levels in the Intervention group appear to be concomitant with increased muscle mass. Increased muscle mass/ Fat Free Mass - through participation in a structured exercise program- with weight stability, in turn logically supports

blunted deterioration in VO_{2peak} indicating a causative role in the blunting of physical fitness deterioration during NAC. There appears therefore to be a positive correlation between the reduction in sarcopenia (relative and overall improvement in Fat Free Mass), with mitigating chemotherapy-associated deconditioning. This observation is supported by studies showing that greater total active muscle mass recruited during exercise results in elevated VO_{2peak}.

An additional positive impact of the intervention also lends itself to greater compliance with the exercise program. The improved body composition appeared commensurate with improved physical ability and wellbeing in the Intervention group. This in turn, appeared to support and enable the participants in the Intervention group to maintain, or increase, activity levels despite the deleterious effects of chemotherapy. This finding is opposite to that generally described amongst patients undergoing peri-oncology treatment.

Further to the above, the objectively assessed increase in Fat Free Mass and reduction in visceral fat, and improved visceral/subcutaneous fat ratio, in the intervention group further supports the suggestion that exercise improves body composition with subsequent improvement in the regulation of inflammatory and immune systems. The mechanisms for this control appear to be related to the influence of inflammatory cytokines, mainly Interleukin-6, TNFa and MCP-1, and the immune system through T lymphocyte activation, including Natural Killer (NK) cells. IL-6 activation from muscle contraction is reported to inhibit the pro-inflammatory activity of TNFa and mobilises the NK cells that may thereby assist in regulating inflammation and release of tumour growth factors in the TME. There is an additional increase in activation of the immune response through increased T lymphocyte activity despite immune-suppressive treatments. These observations are in contrast to the current body of knowledge and are therefore suggestive of the resultant physical benefits of the exercise intervention.

Conversely, a lack of exercise resulted in increased weight, increased visceral fat and reduced muscle mass in the Control group, leading to increased inflammation and suppression of T lymphocyte activity in the TME. Increased adipose tissue, and particularly visceral fat, exacerbated inflammation and the release of pro-inflammatory cytokines such as IL-6 and TNFa, while cell migration is dysregulated through increased levels of MCP-1. Together these inflammatory markers are related to reduced cancer control and increased risk of cancer relapse.

These findings correlate with current literature reporting cancer-associated sarcopenia and cancer treatment-related immune-suppression.

The improvements in body composition through exercise participation appear to support inflammatory and immune regulation resulting in improved cancer control by the body. This correlates with observations in animal models but there is as yet little evidence in human subjects.

Evaluating the clinical outcomes of the patients in the trial, the majority of patients in both groups, there were either no post-op complications or complications that were limited to pharmaceutical intervention only. Two patients in the Intervention cohort required surgical intervention and resultant escalation of care but the recorded complications were more likely to be surgically related that to have been affected by the fitness status of the 2 patients. Three patients in the Control group experienced post-surgery complications that required radiological/surgical intervention without anaesthetic. It is difficult to ascertain whether these complications may or may not have been associated with fitness or the numerous confounding variables to which a patient is exposed during the in-hospital surgical period. Overall, the complication rate in both groups was lower than the national average of 38% after oesophagectomy (National Oesophago-Gastric Cancer Audit, 2017). The reporting and grading of post-op complications is an area currently under scrutiny and international collaborative research. There is clearly a need for standardised, clinically useful, and practically measurable data collection and reporting, to be able to make meaningful conclusions in this area

Median hospital length of stay (LOS) following surgery was comparable in the Control and Intervention cohorts, respectively. Post-operative discharge from hospital after oesophagectomy is subject to approval by a number of different teams and processes including, but not limited to, dieticians; physiotherapists; Care of the Elderly teams; available care at home; patient confidence in being able to cope away from the care of hospital staff; procedural delays in post-radiology tests. Both groups, however, had a LOS below the national average. A satisfactory outcome, but difficult to relate directly to exercise/fitness differences between the two groups with the small numbers in this analysis.

All patients in the trial who were prescribed adjuvant chemotherapy or chemoradiotherapy started their post-operative treatment. Some patients experienced delays to commencing

treatment but the median time to starting treatment after surgery was similar in both groups. The range for starting adjuvant treatment was slightly lower in the Intervention group than in the Control group. This is a positive result in both groups. Larger numbers and specific data points would be required to suggest a link in an exercise intervention with uptake and completion of adjuvant treatment protocols.

Starting from diagnosis, there is national and international increased focus on mental health strategies and patients living 'with and beyond cancer'. More patients are surviving cancer treatments. Those same treatments result in significant changes to patients, their general health, financial circumstances, ability to work and function within families and social settings. In this study, limited results were achieved however the improved Mental Wellbeing achieved in the Intervention group would support an early introduction of exercise into the cancer treatment pathway.

The unexpected and most notable outcome of this thesis was the improved cancer control and pathological tumour response to chemotherapy in the Intervention group. To the author's knowledge, this is the first reported series of data demonstrating pathological evidence of tumour response to NAC in patients with operable oesophageal adenocarcinoma while undertaking a structured exercise program.

The results from the studies presented in this thesis demonstrate the pathological evidence of improved tumour and lymph node regression after NAC in patients undertaking a structured exercise program. Tumour and lymph node downstaging through the introduction of NAC strategies has resulted in the single largest improvement in survival and disease control in oesophageal adenocarcinoma in the past 20 years. With the evidence of enhanced response to chemotherapy resulting in cancer reduction/control in both tumour and lymph nodes through the introduction of exercise as a prehabilitation concept (*i.e.* from diagnosis through neo-adjuvant chemotherapy), it would seem that introducing structured exercise programs to patients on a peri-operative pathway may result in the next incremental shift towards improved cancer outcomes.

The combined interactions of a structured physical activity program supporting improved muscle mass that underpins blunting of chemotherapy-associated fitness deterioration, while synchronously reducing visceral fat and the associated pro-inflammatory responses but

supporting immune function in patients undergoing immune-suppressive chemotherapy has not, to the authors knowledge, been previously described.

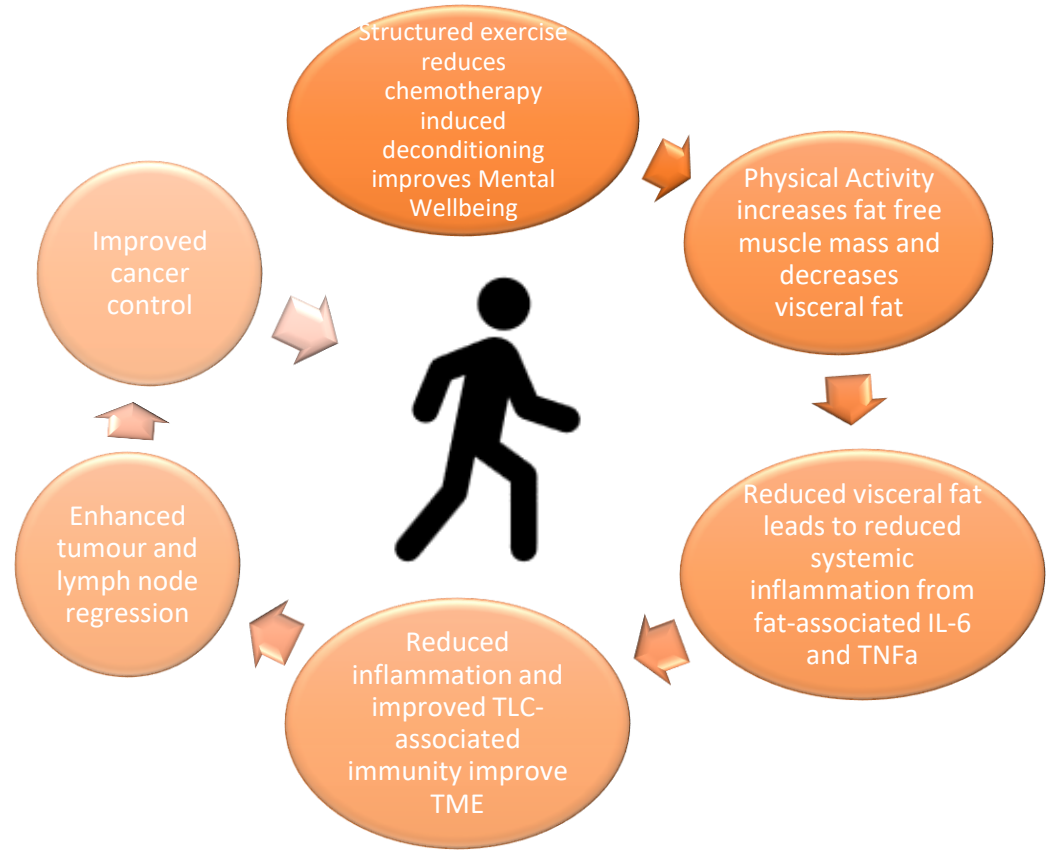


Figure 11--1 Intervention Cohort- Exercise in cancer

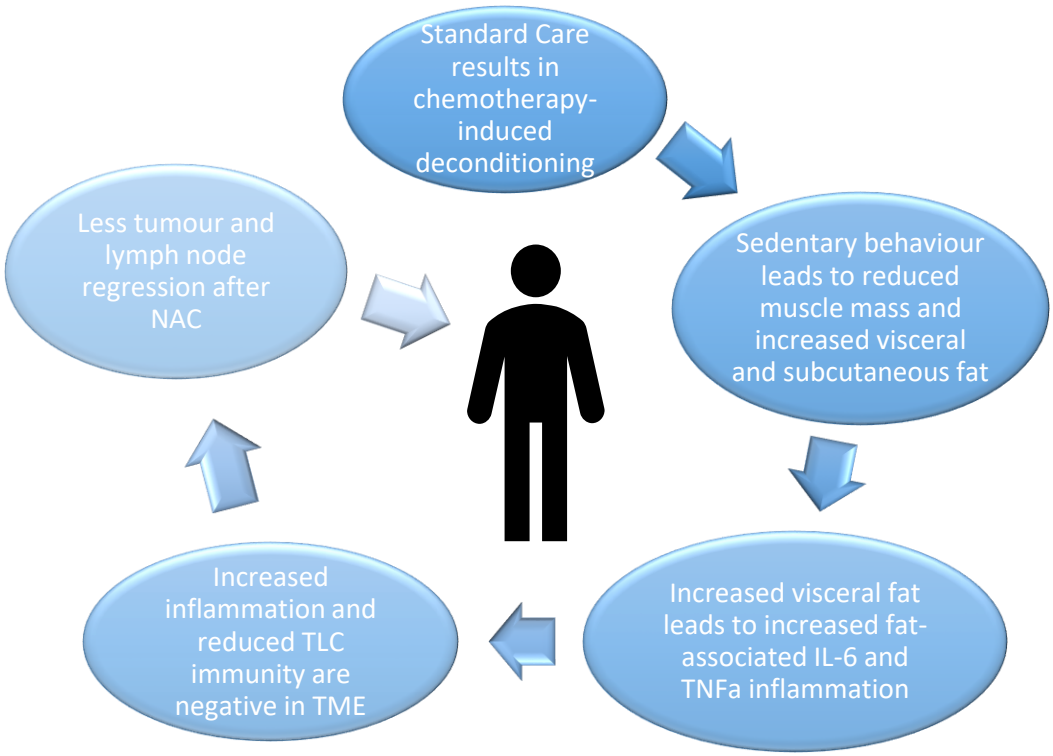


Figure 11-2 Control Cohort – Standard care pathway

In research and discovery, it has often been the unexpected which turns out to be the 'game-changer' – discovery of Corn flakes by the Kellogg's brothers, Greatbatch's pacemaker, Benoit's pre-mammalian therapsids and of course accidental discoveries that have altered the course of medicine such as Flemming, Jenner, Papanicolaou and Richet, to name but a few.

In this thesis, 'unexpected' result of improved pathological tumour response to chemotherapy may turn out to be the 'game-changer' in future treatment of oesophageal adenocarcinoma. Early indicators in a prehabilitation program during neo-adjuvant chemoradiotherapy in colorectal cancer treatment indicate that this may be applicable to multiple tumour groups (West *et al.*, 2019) .

Further clinically relevant differences that have been uncovered in patients undertaking exercise intervention in the present thesis, include:

- Improved tumour and lymph node regression after neo-adjuvant chemotherapy
- Improved body composition, especially a decrease in visceral fat and an increased muscle mass, with resultant metabolic improvements
- Statistically significantly increased TLC activation and enhanced immune function
- Improved inflammation regulation, associated with greater control of TME

The anticipated result of lessened levels of deconditioning during chemotherapy has been confirmed and potential mechanisms have been described.

The much sought after reduction in post-operative complications and reduced length of stay requires further trials, clear variable definitions, and greater numbers to confirm anticipated effects.

Limitations and future directions

While the overall results of this feasibility trial are promising, there are limitations in a trial of this nature especially within the time constraints of a PhD program.
Some of these limitations include: trial design, accessibility to funding streams , small numbers of participants, short period of follow-up and, lack of patient compliance and actigraphy data.

The trial was designed as a geographical cohort-controlled trial largely in adherence of funding limitations, imposed travel restrictions by local authorities and access to limited numbers of patients undergoing the relevant surgery at a single-centre. Furthermore, as a feasibility study, the trial was not powered to definitively answer questions other than feasibility of the intervention.

In future research, a trial of this nature would be improved by reducing potential bias through use of a Randomised Control Trial (RCT) design. To enable a RCT in this patient group, larger numbers of participants would also be required through a national, multi-centre trial, adequately powered to validate some of the points raised in this body of work. Adequate funding sources would be required to be accessible, to support research within exercise in cancer and exercise in health provision, generally. A national, multi-centre trial would support inclusion of greater numbers of participants to ensure robust datasets to provide generalisability of the outcomes presented.

Data from future studies would be improved by including a longer follow-up period of patients to provide a clearer, objective view of the longer term benefits of the intervention. The data collection activity in the first 4 major time-points of the trial would be useful in the later stages of the patient's treatment pathway. These would assist in informing clinical decisions based on physical, physiological and psychological aspect of patient's treatment and in longer term 'living with and beyond cancer'.

This thesis suggests that the mechanism of blunting the deleterious effects of chemotherapy are through improved body composition, especially improved muscle mass. The inclusion of objective actigraphy data from wearable Fitbit devices would have been of great benefit to the reliability and validation of the data presented. This would be an important consideration in the design and implementation of future trials of this kind.

The results of larger, randomised clinical trials have the potential to significantly alter the clinical treatment planning of patients diagnosed with oesophageal adenocarcinoma. If the benefits of a structured exercise intervention during cancer treatment as reported in this thesis can be validated by larger trials, there would potentially be a significant impact on the existing treatment options for newly diagnosed, and arguably all, oesophageal cancer patients. Inclusion of easily

accessible, structured exercise programs could be included into patients' hospital visits with little adjustment to treatment schedules but with potentially clinically significant results to cancer treatment. Physical therapy is available at most large cancer treatment centres that would enable patients to access specialist support.

However, if similar programs were to be introduced in the NHS, cost-analysis would be required to compare and offset the benefits of tumour regression and impact on long-term treatment strategies versus relatively inexpensive introductions of structured exercise prehabilitation programs. Appropriate out-patient and in-patient facilities, as well as suitably qualified staff with appropriate training, would also require investigation and cost analysis.

What has been shown is that exercise during pre-surgical cancer treatment is feasible, acceptable and has multi-faceted significant impacts on cancer treatment outcomes. Cancer patients who participate in structured exercise programs benefit physically, physiologically, psychologically, pathologically, and immunologically.

There is also the potential that patients previously considered to be non-operable at diagnosis, might be offered an exercise intervention with the aim of downstaging the cancer and improving operability – considered to be the gold standard treatment. This is an area of investigation which could make a substantial difference to the physical and psychological survival of the increasing numbers of patients diagnosed with advanced-stage disease, especially in the UK.

Finally, if the results presented here and in future validation studies were to be substantiated, then prevention of cancer through participation in structured exercise should be a further area of research. Studies of this nature would require national support for long term, population-based trials.

Chapter 12 Conclusion

The benefits of exercise in the general population are well recognised. The results of the Pre-EMPT clinical trial, presented in this thesis, provide evidence that a structured exercise program during neo-adjuvant chemotherapy is not only feasible but physically, psychologically, metabolically and physiologically beneficial in patients undergoing treatment for operable adenocarcinoma of the oesophagus and gastro-oesophageal junction.

This is the first reported evidence of improved tumour and lymph node response to neo-adjuvant chemotherapy through a structured exercise program in oesophageal adenocarcinoma. The results are from a small group of patients undergoing a non-randomised trial and should be viewed caution until further trials validate these unique findings. However, the impact for patients and clinicians is potentially significant and warrants further investigation.

The mechanisms of reduced inflammation, improved immune function and optimised body composition, through which the tumour and lymph node downstaging has been achieved, is hypothesis generating and worthy of further clinical trials, and in other cancer types.

The evidence presented in this analysis, provides a rationale to offer a structured exercise program as standard care to patients undergoing treatment for oesophageal cancer. There is also the possibility that exercise programs, with the associated control of the TME, may result in more cancers becoming down-staged and therefore operable, thereby providing more patients with enhanced cancer treatment.

It is proposed that structured exercise programs should be offered within the out-patient department for the convenience and improved access to patients undergoing oncological treatment. Appropriate instruction, support and encouragement will likely improve patient participation and compliance with prescribed exercise protocols.

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Appendix A. Exercise Prehabilitation Program

4 Week, 30 minutes Progressive Walking Programme

Week 1	**SESSION 1**	30 minutes moderate walk including; 10 x (30s hard walk with 1min 30s easy)
	SESSION 2	30 minutes moderate walk including; 2 x (5 x 1 minute hard walk with 1 minute easy) 5 minutes between sets
	SESSION 3	30 minutes moderate walk including; 2 x (10 x 30s hard walk with 1min 30s easy) 5 minutes between sets
	SESSION 4	30 minutes moderate walk
	SESSION 5	30 minutes moderate walk
Week 2	**SESSION 1**	30 minutes moderate walk including; 2 x (6 x 1 minute hard walk with 1 minute easy) 5 minutes between sets
	SESSION 2	30 minutes moderate walk including; 5 x (2 minutes hard walk with 1 minute easy) 5 minutes between sets
	SESSION 3	30 minutes moderate walk including; 10 x (1 minute hard walk with 1 minute easy) 5 minutes between sets
	SESSION 4	30 minutes moderate walk
	SESSION 5	30 minutes moderate walk
Week 3	**SESSION 1**	30 minutes moderate walk including; 2 x (10 x 30s hard walk with 1 minute 30s easy) 15 minutes between sets
	SESSION 2	30 minutes moderate walk including; 5 x (3 minutes hard walk with 2 minutes easy) 10 minutes between sets
	SESSION 3	30 minutes moderate walk including; 10 x (1 minute hard walk with 1 minute easy) 10 minutes between sets
	SESSION 4	30 minutes moderate walk

	SESSION 5	30 minutes moderate walk
Week 4	**SESSION 1**	30 minutes moderate walk including; 3 x (5 x 30s hard walk with 1 minute 30s easy) 5 minutes between sets
	SESSION 2	30 minutes moderate walk including; 10 x (2 minutes hard walk with 1 minute easy) 10 minutes between sets
	SESSION 3	30 minutes moderate walk including; 15 x (1 minute hard walk with 1 minute easy)
	SESSION 4	30 minutes moderate walk
	SESSION 5	30 minutes moderate walk

N.B. easy = able to hold full conversation; moderate = brisk walking, concentrating to maintain pace; hard = fast/power walking

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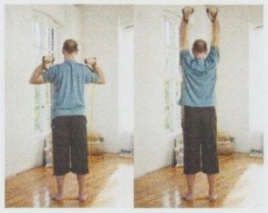
BAND STRENGTH EXERCISES

Below are some examples of strength exercises utilising a band to provide increased resistance that will help improve your strength, reduce the potential for fatigue and injury and enhance your performance. To further increase resistance you can change the strength (thickness) of the band, varying the resistance for each exercise. Band strength exercises should be performed slowly and under full control. Complete the exercise circuit (12 exercises) and repeat 3 times.



Shoulder Press

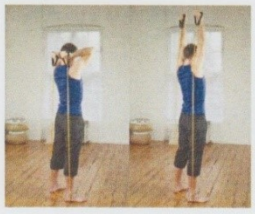
- Place the middle of the band under feet and hold a handle firmly in each hand Stand with feet shoulder width apart and arms bent with hands touching shoulders with elbows down
- Extend both arms upwards above your head until they are straight
- Return to start position
- Repeat 20 times

Leg Extension (Quadriceps)

- Place the band behind the front legs of the chair looping the band around the legs
- Sitting upright looking forward, hold the sides of the chair firmly
- Place a foot through each handle
- Extend both legs straight in front of you forming a straight line from your hip to knee to ankle
- Return to start position
- Repeat 20 times

Leg Curl (Hamstring)

- Place one foot through the handle and stand on the band adjusting the tension to create a hard resistance
- Stand upright with feet shoulder width apart looking forward
- Lift the lower leg behind you as high as possible aiming to touch the heel of the foot on your bum
- Return to start position
- Repeat 10 times
- Repeat above for other leg



Triceps Extension

- Place the middle of the band under feet and hold a handle firmly in each hand
- Stand upright with feet shoulder width apart looking forward
- Extend the arms above the head and keeping the elbows high bend the arms with the hands touching the shoulders
- Extend both arms above the head until they are straight
- Return to start position
- Repeat 20 times

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Biceps Curl

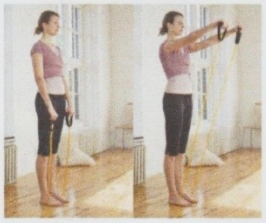
- Place the middle of the band under feet and hold a handle firmly in each hand
- Stand with feet shoulder width apart and hands on the front of your thighs with palms facing forwards
- Bend the arms to bring the hands to the chest keeping your elbows against your side
- Return to start position
- Repeat 20 times

Squat

- Place the middle of the band under your feet and hold a handle firmly in each hand
- Stand with feet wide apart with feet facing outwards
- Bend the arms with hands touching the shoulders palms facing forward and elbows touching your sides
- Keeping the back straight and looking forward bend the legs to 90°
- Return to start position
- Repeat 20 times

Posterior Deltoid

- Place the middle of the band under your feet and hold a handle firmly in each hand
- Stand with feet shoulder width apart bend forward from the hip keeping the back straight to an angle just less than 90°
- Extend the arms in front of you so that they are pointing at the ground in front of you
- Keeping the arms straight lift the arms directly upwards to the side of the body until they are level with your shoulders
- Return to start position
- Repeat 20 times



Anterior Deltoid

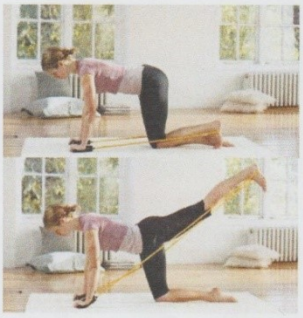
- Place the middle of the band under your feet and hold a handle firmly in each hand
- Stand with feet shoulder width apart and palms resting on the front of your thighs
- Keep the back straight and look forward
- Keeping the arms straight raise both arms directly in front of you until they are above your head
- Return to start position
- Repeat 20 times

Medial Deltoid

- Place the middle of the band under your feet and hold a handle firmly in each hand
- Stand with feet shoulder width apart and palms resting on the side of your thighs
- Keep the back straight and look forward
- Keeping the arms straight raise both arms directly to your side until they are above your head
- Return to start position
- Repeat 20 times

Bent-Over Rowing

- Place the middle of the band under your feet and hold a handle firmly in each hand
- Stand with feet shoulder width apart bend forward from the hip keeping the back straight to an angle just less than 90^{O}
- Extend the arms in front of you so that they are pointing at the ground in front of you
- Bending both arms bring your hands upwards until they touch your shoulders
- Return to start position
- Repeat 20 times



Leg Kick

- Holding the handles of the band firmly in each had place the middle of the band on the sole of the feet
- On all fours with weight evenly distributed looking forward
- Extend one leg straight behind you and lift the straight leg upwards as high as possible without turning out the hip
- Return to start position
- Repeat above for other leg
- Repeat 10 times

Sumo Squat

- Stand with the legs just more than shoulder width apart with feet turned out standing on the middle of the band
- Holding the handles, pull the bands over your shoulders
- Squat down keeping your back straight and looking forward
- Return to start position
- Repeat 20 times

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CORE STRENGTH & STABILITY

Below are some examples of exercises that will help improve your core strength and stability, reduce the potential for fatigue and injury and enhance your performance. Core strength and stability exercises should be performed slowly and under full control. Complete the exercise circuit (7 exercises) and repeat 3 times.

Round the clock

- Lying face down with arms out to the side and elbows bent at 90°
- Lift the right arm and hold for 5 seconds
- Return to the start position
- Repeat for right leg, left leg and left arm
- Repeat 10 times

*Think about length rather than height (stretch out the limbs)

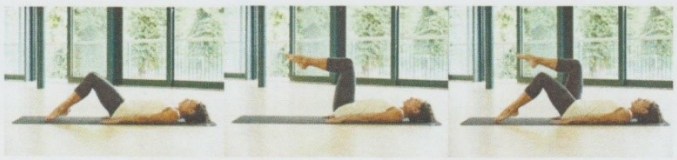
Plank

- Lie face down on the floor with your forearms on the ground with your palms facing down level with the top of your head
- Raise yourself onto you forearms and the balls of you feet making a straight line between your heel, hips and shoulders
- Hold for 20 seconds
- Relax and repeat 3 times

Toe Touch

- Lie on you back with your arms by your side
- Pull your knees up and hold them in the air making a 90° angle at your hips and knees
- Contract your core, lower one foot to the floor touching the toe lightly on the ground before returning to the start position
- Repeat above for other leg
- Repeat 10 times

MAKE IT HARDER: Engage your core (inner stomach muscles) and lower both feet to the floor, touching the toes lightly on the floor before returning to the start position. Repeat 20 times



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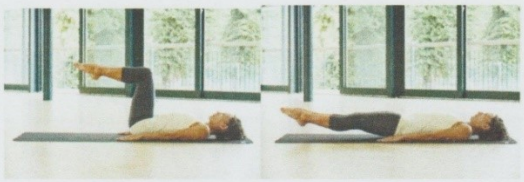
Leg Lower

- Lie on you back with your arms by your side and legs fully extended
- Lift both legs in the air making a 90^{0} angle at your hips
- Lower both legs until the heels gentle touch the ground
- Return to the start position
- Repeat 10 times

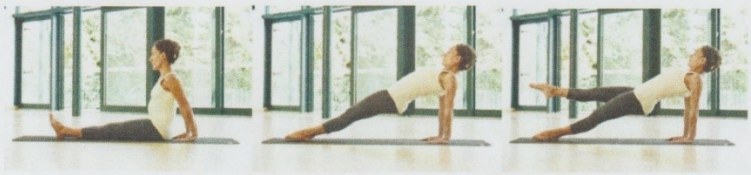


Cat

- On all fours with weight evenly distributed between hands and knees and the back long and straight
- Contract all of the muscles surrounding your abdomen and breath normally
- Without collapsing the arms extend your left leg directly backwards and your right arm directly forward
- Hold for 5 seconds
- Return to start position
- Repeat the above for the right leg and left arm
- Relax and repeat 5 times

Hip Extension

- Sit on the floor with your arms extended behind you and your upper body resting hands
- Lift your hips to the ceiling making a straight line from shoulders to hips to ankles
- In that position lift one leg to the same height as your hip and hold for 10 seconds
- Repeat fro your other leg
- Return to start position and repeat 3 times



Shoulder Bridge

- Lie on your back, hands by your side and knees bent with feet shoulder width apart
- Breathe in and roll your hips to the ceiling until your are resting on your shoulders with a straight line from shoulders to hips to knees
- In that position extend one leg and raise it with your knees at the same height, hold for 10 seconds
- Return to start position and repeat 5 times

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FLEXIBILITY

Below are some examples of flexibility exercises that are important for warm-up and cool-down from exercise to reduce the potential for injury and enhance your performance. Flexibility exercises should be performed slowly and under full control. **ALWAYS STRETCH BEFORE AND AFTER YOU EXERCISE.**

Back of shoulder

- Stand or sit upright with feet shoulder-width apart and looking in front of you.
- Bring one arm across your chest towards the opposite shoulder without rotating your upper body.
- Cup your elbow with your hand and pull the arm towards your chest until you feel a stretch in the back of your shoulder.
- Hold for 20–30 seconds.
- Repeat with the other arm.

Chest

- Stand or sit upright with feet shoulder-width apart and looking in front of you.
- Bend your arms to 90 degrees and raise them out to the sides until your elbows are at shoulder height.
- Pull your elbows backwards and push your chest out until you feel a stretch across your chest.
- Hold for 20–30 seconds.

Side neck

- Stand or sit with your body upright and stable.
- Lower your ear towards your shoulder on the same side.
- When you feel a stretch, hold for 20–30 seconds.
- Repeat with the other side.

Neck extension

- Stand or sit with your body upright and stable.
- Raise your chin as high as possible, keeping your mouth closed, without leaning back.
- Hold for 20–30 seconds.

Neck flexion

- Stand or sit with your body upright and stable.
- Lower your chin to your chest without leaning forwards.
- Hold for 20–30 seconds.

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Hamstring

- Begin seated with your body upright, one leg extended in front of you and the other leg bent with your foot in your groin.
- Bend forwards reaching for your toes until you feel a stretch along the back of your upper leg.
- Hold for 20–30 seconds.
- Repeat with the other leg.

Thigh

- Stand with your body upright and stable.
- Bend the knee of one leg and pull the heel to your bum (hold on to something for stability if required).
- Hold the ankle of the bent leg and pull the foot into your bum without leaning forwards (keep a straight line between shoulder, hip and knee).
- Hold for 20–30 seconds.
- Repeat with the other leg.

Calf

- Stand in the lunge position with your front foot about 30cm away from a wall or a chair.
- Lean on the wall or chair and bend your leading leg until you feel a stretch in the calf of your straight leg.
- Hold for 20–30 seconds.
- Repeat with the other calf.

Hip flexor stretch

- In the lunge position, drop your back knee to the floor, well behind your hip.
- With your back knee on the floor and hands on hips, extend forwards so that your front knee is at 90 degrees.
- Feel the stretch on the front of your hip joint and thigh.
- Hold for 20–30 seconds.
- Repeat with the other leg.

Bum and hip – knee to chest – hip rotated [c-head]

- Lie on your back on the floor with both legs bent.
- Place the ankle of one leg on the knee of the other.
- Place your hands behind the bent knee and pull it towards your chest.
- Hold for 20–30 seconds.
- Repeat with the other leg.

Seated outer thigh

- Sit on the floor with your legs out straight in front of you.
- Bend your left leg and place the foot over your right leg.
- Rotate your body and extend your right arm, placing it over the left leg.
- Gently ease your left knee to the right.
- Hold for 20–30 seconds.
- Repeat with the right leg.

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Appendix B. Scientific Abstract

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FEASIBILITY OF EXERCISE PREHABILITATION DURING NEO-ADJUVANT CHEMOTHERAPY IN OESOPHAGO-GASTRIC CANCER SURGERY

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PURPOSE: To determine the feasibility and potential benefits of patients, diagnosed with operable gastro-oesophageal cancer, undertaking a structured-exercise cancer prehabilitation program (prehab) during NAC versus patients on a standard care pathway.

METHODS: Patients were enrolled in a prospective, cohort-controlled trial.

Prehab was based on World Health Organisation (WHO) 'recommended levels of physical activity for adults over the age of 18'.

Cardiopulmonary exercise tests (CPEX) was performed at 4 time-points:

1. Baseline/pre-NAC
2. Post-NAC
3. Before surgery
4. After surgery

Participants wore wearable tracker devices. CPEX variables analysed included anaerobic threshold (AT) and peak oxygen uptake (VO2peak). Clinical and pathological data variables were recorded.

RESULTS:

At time of writing, 25 male and female patients, aged 25 – 78years, had participated in the study; 22 had undergone surgery.

Mean baseline AT in the prehab group was 17.57+-3.35SD (range10.77- 20.94; n=10) ml/kg/minute, compared to 15.19+-3.57SD (range 11.10 -22.90; n=12) ml/kg/minute in the control group.

Mean baseline V02peak achieved was 27.55+-5.63SD (range 15.18 – 36.83) ml/kg/minute and 23.39+-4.06SD (range 18.75- 29.94) ml/kg/minute, respectively.

Mean values of AT and VO2peak between the groups pre-surgery were of little scientific value. However, DVO2peak in individual patients showed a trend towards improvement in the prehab cohort.

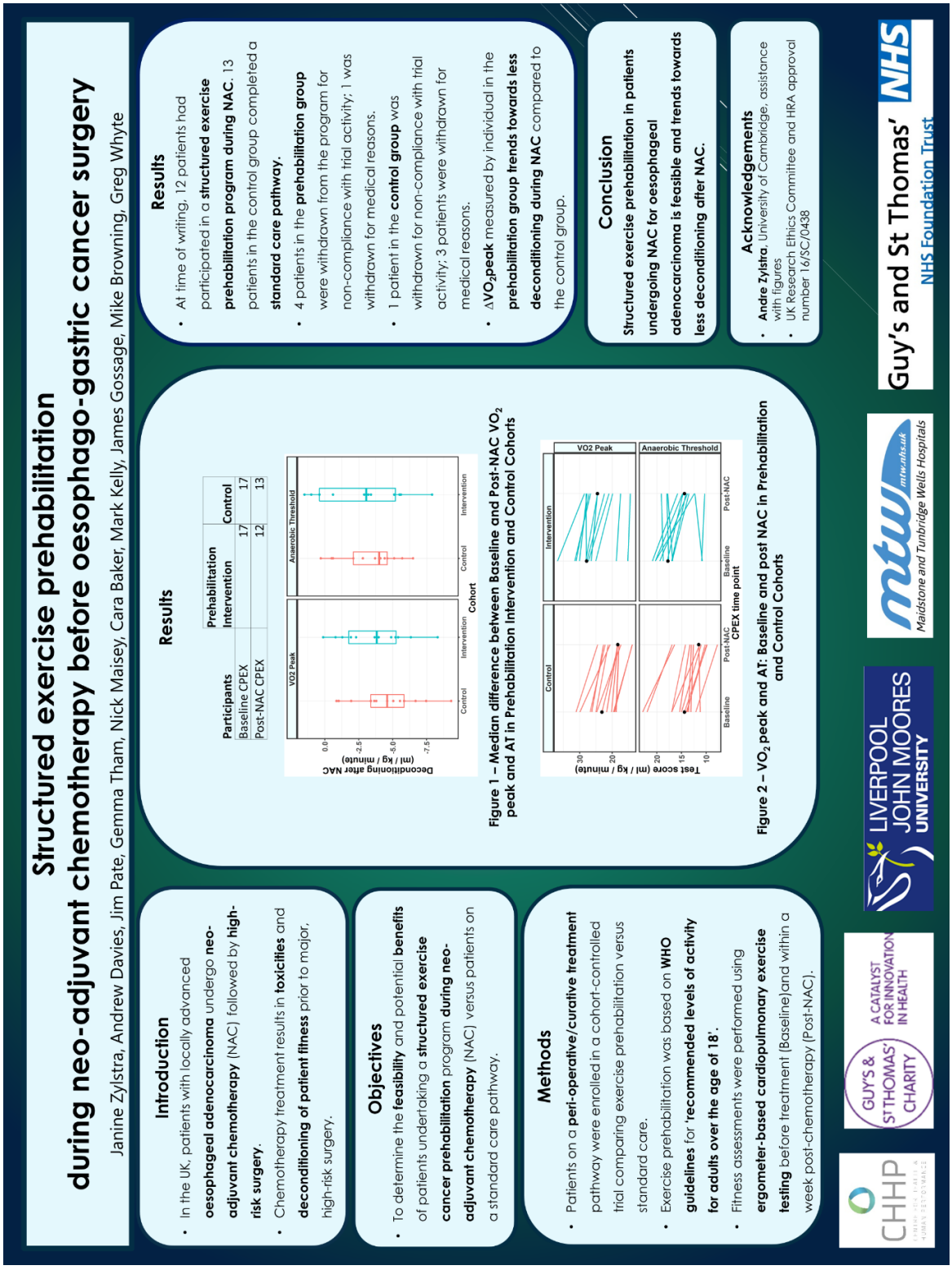
Post-surgery values decreased markedly in both groups:

Mean AT prehab decreased to 13.46+-2.29SD (range 10.54-15.91) ml/kg/minute versus 13.10+-2.60SD (range 10-18.4) ml/kg/minute in control group.

Mean VO2peak reduced to 20.33+-4.94 (range 14.01-26.81) ml/kg/minute compared to 19.56+-2.74SD (range18.00-24.76) ml/kg/minute respectively.

CONCLUSION: Cancer prehabilitation during NAC is feasible. Recovery of peak oxygen uptake shows an improvement trend in patients undergoing prehab during and after NAC. Post-surgery mean AT and VO2 values confirm physiological stress in patients undergoing high-risk, intra-thoracic and intra-abdominal oesophagectomy.

Appendix C. Scientific Poster American College of Sports Medicine, Florida, May 2019



Appendix D. Inflammatory and Immunity Marker – Full Results

Table 9-1 Immunity Markers - percentage change

Value change (%)	Control group			Intervention group			p-values
	N	Mean (SD)	Range	N	Mean (SD)	Range	
CD3 (cells/uL)							
Baseline to Post-NAC	12	4.53 (25.67)	(-23.00-63.41)	11	34.26 (36.58)	(-16.78-111.57)	0.03
Baseline to Pre-surgery	13	13.60 (44.09)	(-25.42-119.67)	13	-4.53 (35.46)	(-70.88-75.11)	0.26
Baseline to Pre-adjuvant	12	5.57 (42.66)	(-25.07-136.31)	11	-25.55 (26.08)	(-76.75-1.46)	0.05
CD4 (cells/uL)							
Baseline to Post-NAC	12	9.36 (37.90)	(-26.30-112.17)	11	42.08 (51.40)	(-22.45-179.45)	0.1
Baseline to Pre-surgery	13	20.22 (51.52)	(-20.81-164.09)	13	1.47 (46.75)	(-70.81-130.48)	0.34
Baseline to Pre-adjuvant	12	1.24 (46.24)	(-32.21-140.95)	11	-27.06 (30.09)	(-93.41-50.34)	0.13
CD8 (cells/uL)							
Baseline to Post-NAC	12	0.98 (19.69)	(-23.03-50.89)	9	29.41 (31.19)	(2.82-89.66)	0.03
Baseline to Pre-surgery	13	10.91 (40.09)	(-30.42-83.98)	10	-7.98 (29.82)	(-72.99-30.63)	0.23
Baseline to Pre-adjuvant	12	11.61 (40.62)	(-22.66-133.85)	10	-25.97 (30.43)	(-77.59-15.54)	0.03
IGG (g/L)							
Baseline to Post-NAC	14	-25.41 (14.06)	(-51.03- -3.78)	12	-27.74 (10.08)	(-41.17-8.91)	0.64
Baseline to Pre-surgery	13	-6.09 (11.42)	(-27.57-12.19)	13	13.20 (13.14)	(-32.01-9.20)	0.15
Baseline to Pre-adjuvant	12	15.38 (23.03)	(-14.06-62.52)	11	-0.09 (18.22)	(-25.05-22.94)	0.09
IGA (g/L)							
Baseline to Post-NAC	14	-12.70 (12.84)	(-37.74-4.28)	12	-22.80 (15.41)	(-45.03-8.41)	0.08
Baseline to Pre-surgery	13	-7.44 (26.02)	(-70-33.69)	13	-11.90 (16.43)	(-37.61-15.49)	0.61
Baseline to Pre-adjuvant	12	17.06 (15.75)	(-10.38-44.92)	11	11.96 (55.22)	(-30.99-167.27)	0.77
IGM (g/L)							
Baseline to Post-NAC	14	-33.48 (10.77)	(-51.16- -10.53)	12	-27.07 (8.08)	(-44.72- -11.11)	0.1
Baseline to Pre-surgery	13	-11.00 (18.57)	(-40.31-20)	13	12.21 (10.51)	(-27.33-4.35)	0.84

Baseline to Pre-adjuvant	12	18.45 (27.27)	(-38.10-68.57)	11	-7.48 (17.65)	(-40.49-20.59)	0.01

Table 9-2 Inflammatory Markers - percentage change

Value change (%)	**Control group**			**Intervention group**			**p-values**
	N	**Mean (SD)**	**Range**	**N**	**Mean (SD)**	**Range**	
IL-1a (ng/L)							
Baseline to Post-NAC	11	-3.18 (24.37)	(-45.83-43.75)	10	-17.17 (36.87)	(-65.65-9.13)	0.23
Baseline to Pre-surgery	12	-30.09 (34.52)	(-60.61-60.87)	12	-11.80 (37.74)	(-70.23-63.16)	0.23
Baseline to Pre-adjuvant	10	0.13 (33.80)	(-47.83-58.82)	9	-31.48 (35.01)	(-83.21-0.00)	0.06
IL-1b (ng/L)							
Baseline to Post-NAC	11	-9.78 (21.59)	(-61.02-17.32)	10	-9.46 (64.01)	(-75.51-126.09)	0.99
Baseline to Pre-surgery	12	-45.02 (36.24)	(-71.95-55.88)	12	2.81 (56.41)	(-72.13-94.06)	0.02
Baseline to Pre-adjuvant	10	-0.35 (24.13)	(-4.31-50.00)	9	14.01, (54.60)	(-70.49-84.62)	0.5
IL1RA (ng/L)							
Baseline to Post-NAC	11	7.65 (47.70)	(-57.35-97.80)	10	-9.96 (33.97)	(-58.80-44.25)	0.35
Baseline to Pre-surgery	12	10.22 (83.35)	(-68.39-246.39)	10	-27.06 (34.34)	(-70.69-44.21)	0.18
Baseline to Pre-adjuvant	10	14.04 (56.32)	(-51.84-137.93)	8	22.82 (120.60)	(-83.54-297.95)	0.85
IL-2 (ng/L)							
Baseline to Post-NAC	11	1.99 (29.19)	(-56.47-52.43)	10	1.93 (73.94)	(-70.69-195.10)	1
Baseline to Pre-surgery	12	-22.21 (46.30)	(-70-110.53)	12	-14.76 (32.12)	(-77.35-30)	0.65
Baseline to Pre-adjuvant	10	12.57 (32.68)	(-21.25-84.41)	9	23.53 (32.28)	(-80.42-0.00)	0.03
IL-4 (ng/L)							
Baseline to Post-NAC	11	-2.18 (5.79)	(-19.05-0.00)	10	1.95 (27.49)	(-57.19-52.58)	0.65
Baseline to Pre-surgery	12	-0.28 (22.32)	(-23.02-68.63)	12	-3.86 (20.96)	(-67.56-20.09)	0.69
Baseline to Pre-adjuvant	9	2.29 (6.86)	(0.00-20.59)	8	10.39 (26.13)	(-67.56-16.51)	0.18
IL-6 (ng/L)							

Baseline to Post-NAC	11	126.41 (107.59)	(-53.14-282.39)	10	27.93 (97.02)	(-55.94-275.00)	0.04
Baseline to Pre-surgery	12	36.63 (41.26)	(-50.17-119.77)	12	18638.20 (64491.17)	(-81.64-223425)	0.34
Baseline to Pre-adjuvant	10	111.09 (216.74)	(-71.62-650.00)	9	22.16 (102.24)	(-97.41-261.33)	0.27
IL-8 (ng/L)							
Baseline to Post-NAC	11	7.59 (56.13)	(-66.85-154.55)	10	1.04 (46.17)	(-72.78-82.47)	0.77
Baseline to Pre-surgery	12	62.11 (192.19)	(-58.22-657.35)	12	75.20 (217.21)	(-63.07-696.70)	0.88
Baseline to Pre-adjuvant	10	-32.43 (31.81)	(-68.73-32.50)	9	20.90 (89.14)	(-87.50-138.69)	0.12
IL-10 (ng/L)							
Baseline to Post-NAC	11	11.34 (30.58)	(-22.64-64.29)	10	-4.69 (37.40)	(-61.88-68.75)	0.29
Baseline to Pre-surgery	12	-37.05 (28.92)	(-72.57-39.53)	12	443.04 (1569.05)	(-83.43-5424.32)	0.3
Baseline to Pre-adjuvant	10	-28.07 (23.67)	(-69.03-2.44)	9	-23.19 (28.91)	(-69.06-35.42)	0.69
VEGF (ng/L)							
Baseline to Post-NAC	11	51.79 (99.54)	(-67.10-300.34)	10	10.51 (62.09)	(-60.27-149.58)	0.27
Baseline to Pre-surgery	12	44.42 (103.38)	(-56.26-313.70)	12	36.74 (101.27)	(-51.85-238.39)	0.86
Baseline to Pre-adjuvant	10	5.41 (50.07)	(-58.10-82.43)	9	15.60 (111.22)	(-72.82-269.41)	0.81
INF-y (ng/L)							
Baseline to Post-NAC	11	223.64 (562.36)	(-50-1900)	9	57.24 (140.13)	(-80.60-300)	0.36
Baseline to Pre-surgery	9	3336.19 (9961.65)	(-84.29-29900)	10	0.00 (59.56)	(-88.81-150)	0.34
Baseline to Pre-adjuvant	10	261.43 (461.15)	(-85.71-1300.00)	9	73.62 (267.82)	(-88.08-781.36)	0.3
TNFa (ng/L)							
Baseline to Post-NAC	11	28.31 (74.51)	(-30.99-233.33)	10	-1.77 (33.23)	(-53.03-45.45)	0.25
Baseline to Pre-surgery	12	27.76 (58.79)	(-34.62-125.64)	12	51.21 (159.12)	(-50.89-455.93)	0.64
Baseline to Pre-adjuvant	10	26.40 (38.20)	(-26.14-82.22)	9	1.10 (40.01)	(-46.23-75.76)	0.18
MCP-1 (ng/L)							
Baseline to Post-NAC	11	163.69 (193.53)	(-45.56-482.08)	10	52.11 (58.18)	(-34.01-174.16)	0.09
Baseline to Pre-surgery	12	58.59 (119.43)	(-33.18-405.88)	12	120.97 (336.28)	(-42.96-1174.49)	0.55

Baseline to Pre-adjuvant	10	32.28 (89.96)	(-48.38-259.66)	9	50.59 (146.26)	(-64.60-428.46)	0.74
EGF (ng/L)							
Baseline to Post-NAC	11	-8.23 (152.86)	(-95.21-440.00)	10	20.06 (80.48)	(-62.72-176.47)	0.61
Baseline to Pre-surgery	12	-53.47 (66.96)	(-98.65-140)	12	16.49 (125.27)	(-93.55-341.64)	0.11
Baseline to Pre-adjuvant	10	205.95 (437.67)	(-97.26-1285.71)	9	24.93 (157.86)	(-87.90-411.76)	0.26

Result	Value	Flag	Normal Range	Action Range
CD3+ (T Cells) Percent	57.77%			
CD3+ (T Cells) Count/uL	829			
CD3+/CD4+ (Helper T Cells) Percent	22.41%			
CD3+/CD4+ (Helper T Cells) Count/uL	321			
CD3+/CD8+ (Suppressor T Cells) Percent	33.63%			
CD3+/CD8+ (Suppressor T Cells) Count/uL	482			
CD4:CD8 Ratio	0.67			
*CD3+ Reliability Check	1.75%			
CD45+ Low SS Count/uL	1,435			
CD45+ Low SS Percent	38.16%			
CD45+ Count/uL	3,760			

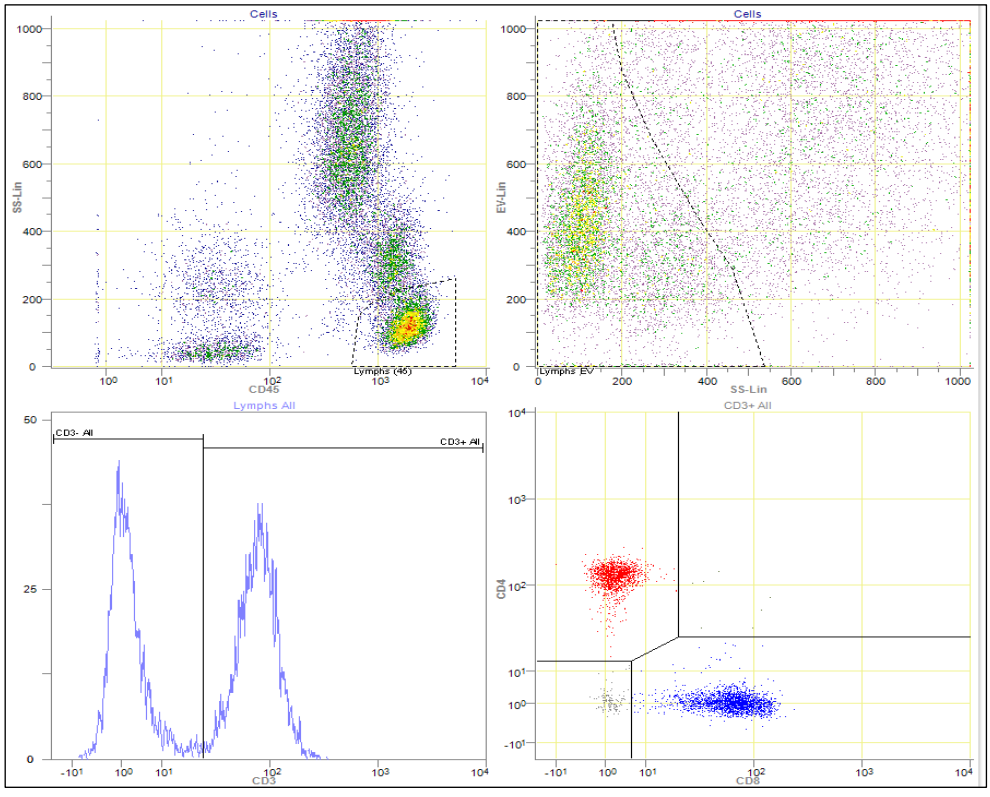


Figure 9-2 Exemplar plot of T-Lymphocyte subset results and histogram plot CD3, CD4 and CD8 gating

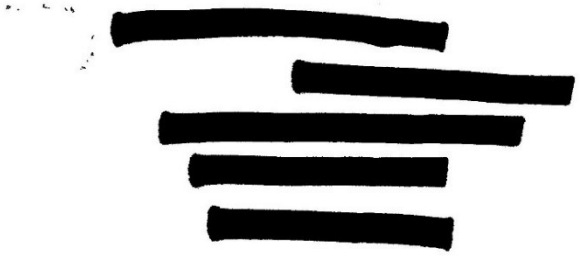
Appendix E. Table 10-1 Mental Wellbeing and HRQL scores

		Controls			Intervention			Intervention - Did not participate		
Measure	**Timepoint**	**N**	**Mean**	**(SD)**	**N**	**Mean**	**(SD)**	**N**	**Mean**	**(SD)**
Mental Wellbeing	Baseline	17	31.18	3.71	12	30.25	2.99	8	27.5	4.81
	Post-NAC	13	30.08	4.61	11	30.27	3.69			
	Pre-surgery	13	32.85	2.44	11	31.27	4.65			
	Before adjuvant chemo	11	31.46	4.37	9	29.78	4.68			
	6 months post-op	10	28.9	6.05	8	31.25	3.2			
	12 months post-op	7	29.43	3.31	8	30.13	3.14			
Physical functioning	Baseline	17	1.12	0.2	12	1.18	0.46	8	1.1	0.15
	Post-NAC	13	1.35	0.3	11	1.27	0.27			
	Pre-surgery	13	1.06	0.1	11	1.24	0.72			
	Before adjuvant chemo	11	1.38	0.28	9	1.76	0.86			
	6 months post-op	10	1.48	0.74	8	1.23	0.23			
	12 months post-op	7	1.2	0.23	8	1.13	0.18			
Role Functioning	Baseline	17	1.12	0.28	12	1.33	0.89	8	1.69	0.92
	Post-NAC	13	1.46	0.52	11	1.91	0.86			
	Pre-surgery	13	1.19	0.56	11	1.5	0.98			
	Before adjuvant chemo	11	1.64	0.6	9	2	0.97			
	6 months post-op	10	1.55	0.96	8	1.19	0.26			
	12 months post-op	7	1.43	0.79	8	1.13	0.23			
Emotional refunctioning	Baseline	17	1.45	0.38	12	1.55	0.51	8	1.6	0.59
	Post-NAC	13	1.48	0.45	11	1.6	0.4			
	Pre-surgery	13	1.4	0.45	11	1.76	0.81			
	Before adjuvant chemo	11	1.22	0.3	9	1.78	1.01			
	6 months post-op	10	1.32	0.43	8	1.68	0.48			
	12 months post-op	7	1.4	0.45	8	1.55	0.59			
Cognitive Functioning	Baseline	17	1.18	0.3	12	1.42	0.85	8	1.38	0.58
	Post-NAC	13	1.42	0.45	11	1.36	0.39			
	Pre-surgery	13	1.19	0.33	11	1.46	0.76			

	Before adjuvant chemo	11	1.18	0.34	9	1.61	1.02			
	6 months post-op	10	1.3	0.42	8	1.25	0.38			
	12 months post-op	7	1.29	0.39	8	1.5	0.54			
Social Functioning	Baseline	17	1.38	0.52	12	1.5	0.88	8	1.5	0.71
	Post-NAC	13	1.65	0.8	11	1.86	0.78			
	Pre-surgery	13	1.19	0.38	11	1.36	0.71			
	Before adjuvant chemo	11	1.77	0.52	9	2.06	1.07			
	6 months post-op	10	1.8	1.01	8	1.63	0.35			
	12 months post-op	7	1.29	0.49	8	1.31	0.46			
Fatigue	Baseline	17	1.63	0.44	12	1.47	0.83	8	1.63	0.72
	Post-NAC	13	2.21	0.65	11	2.06	0.71			
	Pre-surgery	13	1.44	0.46	11	2.03	0.97			
	Before adjuvant chemo	11	2.21	0.45	9	2.41	0.78			
	6 months post-op	10	2.07	0.66	8	1.88	0.53			
	12 months post-op	7	1.76	0.6	8	1.46	0.59			
Nausea	Baseline	17	1.24	0.4	12	1.33	0.62	8	1.19	0.26
	Post-NAC	13	1.46	0.52	11	1.46	0.65			
	Pre-surgery	13	1.04	0.14	11	1.64	1.1			
	Before adjuvant chemo	11	1.36	0.55	9	1.44	0.39			
	6 months post-op	10	1.25	0.43	8	1.44	0.62			
	12 months post-op	7	1.36	0.75	8	1.38	0.52			
Pain	Baseline	17	1.44	0.61	12	1.46	0.87	8	1.75	0.85
	Post-NAC	13	1.23	0.48	11	1.18	0.41			
	Pre-surgery	13	1.12	0.42	11	1.46	0.96			
	Before adjuvant chemo	11	1.64	0.64	9	2.11	0.99			
	6 months post-op	10	1.35	0.41	8	1.5	0.46			
	12 months post-op	7	1.43	0.45	8	1.38	0.52			
Dyspnoea	Baseline	17	1.47	0.62	12	1.25	0.87	8	1.5	0.54
	Post-NAC	13	1.69	0.63	11	1.64	0.81			
	Pre-surgery	13	1.39	0.51	11	1.36	0.92			
	Before adjuvant chemo	11	1.82	0.6	9	1.78	1.09			
	6 months post-op	10	1.4	0.52	8	1.25	0.46			
	12 months post-op	7	1.14	0.38	8	1.25	0.46			
Insomnia	Baseline	17	1.71	0.92	12	1.83	0.84	8	2	1.07

	Post-NAC	13	1.85	0.8	11	1.73	0.65			
	Pre-surgery	13	1.69	0.86	11	2	0.89			
	Before adjuvant chemo	11	1.82	0.98	9	2.11	1.17			
	6 months post-op	10	1.4	0.7	8	2	0.93			
	12 months post-op	7	1.43	0.54	8	1.75	1.17			
Appetite Loss	Baseline	17	1.65	0.86	12	1.67	0.99	8	1.38	0.52
	Post-NAC	13	1.46	0.66	11	1.64	0.67			
	Pre-surgery	13	1	0	11	1.46	0.93			
	Before adjuvant chemo	11	1.82	0.87	9	2	0.87			
	6 months post-op	10	1.3	0.68	8	2	0.93			
	12 months post-op	7	1.86	0.9	8	1.75	0.89			
Constipation	Baseline	17	1.29	0.47	12	1.75	0.87	8	1.75	1.04
	Post-NAC	13	1.46	0.66	11	1.46	0.69			
	Pre-surgery	13	1.08	0.28	11	1.55	0.93			
	Before adjuvant chemo	11	1.46	0.69	9	1.33	0.5			
	6 months post-op	10	1.4	0.7	8	1.63	0.74			
	12 months post-op	7	1.43	1.13	8	1.63	0.74			
Diarrhoea	Baseline	17	1.06	0.24	12	1.08	0.29	0	1	0
	Post-NAC	13	1.54	0.66	11	1.64	0.67			
	Pre-surgery	13	1.31	0.63	11	1.64	0.81			
	Before adjuvant chemo	11	1.55	0.52	9	1.78	0.67			
	6 months post-op	10	1.3	0.48	8	1.5	0.76			
	12 months post-op	7	1.29	0.76	8	1.63	0.74			
Financial difficulties	Baseline	17	1.24	0.56	12	1.67	1.07	8	1.13	0.99
	Post-NAC	13	1.31	0.63	11	1.64	0.81			
	Pre-surgery	13	1.39	0.51	11	1.46	0.93			
	Before adjuvant chemo	11	1.27	0.47	9	1.44	1.01			
	6 months post-op	10	1.6	0.97	8	1.5	0.93			
	12 months post-op	7	1.29	0.49	8	1.38	0.52			

Appendix F. PARTICIPANT LETTERS



Dear Jannie.

You asked me to jot down a few comments with regard to my taking part in the study prior to and during my chemo and surgery

I will attempt to be brief but this may be difficult as I have so many good things to say about my experience

1/ During chemo I was not able to attend every session at Harley St. due to tiredness but the sessions I did attend helped me through the chemo as the simple fact of going to Harley Street gave me purpose and the actual exercise boosted my flagging morale which had been sapped by the chemo

2/ I am totally convinced that the exercise I did greatly

[redacted]

contributed to my recovery after surgery as I felt fitter, stronger and more flexible than before I exercised.

3/ The staff at CHHP are of the highest calibre and I had every confidence in my trainer who adjusted the fitness programme to my needs on a minute by minute basis. That is, he constantly watched me and made sure that I was comfortable and safe at all times

4/ The level of excercise was that although tiring (No pain No gain) it was extremely beneficial to me as week by week, I felt fitter, stronger and better able to cope with the stresses of chemo

5/ Approximately six weeks after surgery, which as you know involved a 6 hour operation

and 10 days as an in patient, I was back at Harley Street continuing the fitness programme.

I think that for a 75 year old this is pretty remarkable and testament to the benefits of the programme and being/keeping fit.

b/ Finally I would urge any of your future patients to seriously consider taking part in the programme as it helped me enormously and I will be forever grateful to you and the team at CHHP.

Yours sincerely

[redacted]

ST. THOMAS' HOSPITAL & CHHP

During my cycles of Chemo and prior to my operation, I attended numerous excercise classes at CHHP, Harley Street.

Although, at first I was anxious about going I found them of great benefit. I felt much better after each session and the staff were excellent. Going motivated me to get out and about, and I'm certain that by building my body up, enabled me to get through both Chemo and Surgery.

I'm this would be of great benefit to other patients who have similar symtoms

Zylstra Janine

Subject: FW: Exercise study

From: [redacted]
Sent: 08 November 2017 21:35
To: Zylstra Janine <Janine.Zylstra@gstt.nhs.uk>
Subject: Exercise study

Hi Janine,

.....

I have written something below.....

Exercise study

I've found the exercise study helpful on keeping my mind focused on something other than my diagnosis and treatment.

Although it's been hard sometimes to muster the energy to go when I was on treatment and sore after my Operation I did find I felt much better after the sessions. In honesty, without the appointments I probably wouldn't of left the house!

The staff at CHHP were very understanding and recognised that my energy levels were sometimes very low and although they didn't make me over do it they encouraged me to push myself through it. Although I found this tough at the time, I believe that this was a huge aid in my recovery.

All in all I found the programme extremely helpful in motivating myself and would recommend it to everyone that finds themselves in a similar situation.

Regards

Pre-EMPT Study feedback

We would be very grateful if you would be happy to provide us with some feedback below with comments of your experiences of the Pre-EMPT study.

Things that went well:

The Free Fitness Bracelet was a great help, was not sure how the bicycle fitness test went for me in terms of fitness. Tests went Well. Excersise regime was good. Still try to do them.

Things that we could improve:

Sorry to say Harley st is not the easiest place to get to when your not 100%.

Any other comments:

Overall I enjoyed participating.