IMPERIAL

The physiological and cellular effects of pre-operative exercise in patients with oesophago-gastric cancer: what role can prehabilitation play in improving peri-operative outcomes?

Miss Laura Halliday MBChB BSc (Hons) MSc MRCS(Ed)

Department of Surgery and Cancer, Imperial College London

2024

A thesis submitted to Imperial College London for the degree of Doctor of Philosophy

Supervised by:

Mr Krishna Moorthy MD FRCS

Mr Christopher Peters MBChB PhD FRCS

ABSTRACT

Prehabilitation aims to utilise the time before surgery to improve a patient's physiological status through exercise, nutritional support and psychological interventions. This thesis aims to determine the effects of prehabilitation on post-operative outcomes in patients with oesophago-gastric cancer and establish the mechanism by which this occurs.

Through comparison of patients who have completed prehabilitation with propensity score matched controls, prehabilitation was found to be associated with a significantly lower incidence of post-operative pneumonia and shorter length of stay following oesophageal cancer surgery. During prehabilitation, cardiorespiratory fitness was preserved during neoadjuvant chemotherapy (NAC) and then increased immediately prior to surgery. Completing increasing amounts of physical activity was associated with a lower risk of post-operative pneumonia.

Using this local cohort data, changes in body composition during prehabilitation were studied through analysis of CT images. This identified less decline in skeletal muscle during NAC in prehabilitation patients compared to controls. Completing higher volumes of exercise was associated with greater loss of visceral adipose tissue (VAT), and loss of VAT is associated with a lower risk of post-operative complications.

Through a systematic review I found evidence that exercise can reduce inflammation in cancer patients undergoing oncological treatment. Therefore, I also explored the effect of prehabilitation on systemic inflammation and inflammation within VAT. Using sandwich enzyme linked immunosorbent assays, a significant reduction in plasma TNFα during NAC was seen with prehabilitation, with correlation between the exercise volume and change in TNFα. Finally, using quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemistry on VAT samples, differences in the VAT inflammation were identified between pre-NAC patients, post-NAC prehabilitation patients and post-NAC controls.

In conclusion, this thesis has identified significantly improved post-operative outcomes with prehabilitation in oesophageal cancer patients, with positive impacts upon cardiorespiratory fitness, body composition and inflammation.

DECLARATION

I hereby declare that I am the sole author of this thesis, and all work was carried out by myself. Elements of Chapters 2, 3 and 4 have already been published in peer-reviewed journals with myself as first author.

The work of other authors is appropriately referenced, and all contributors and collaborators have been clearly declared in the acknowledgements.

The copyright of this thesis rests with the author. Unless otherwise indicated, its contents are licensed under a Creative Commons Attribution Non-Commercial 4.0 International Licence (CC BY- NC). Under this licence, you may copy and redistribute the material in any medium or format. You may also create and distribute modified versions of the work. This is on the condition that: you credit the author and do not use it, or any derivative works, for a commercial purpose. When reusing or sharing this work, ensure you make the licence terms clear to others by naming the licence and linking to the licence text. Where a work has been adapted, you should indicate that the work has been changed and describe those changes. Please seek permission from the copyright holder for uses of this work that are not included in this licence or permitted under UK Copyright Law.

Laura Halliday

January 2024

PEER REVIEWED PUBLICATIONS & PRESENTATIONS ARISING FROM THIS WORK

Publications

Halliday LJ, Boshier PR, Doganay E, Wynter-Blyth V, Buckley JP, Moorthy K. The effects of prehabilitation on body composition in patients undergoing multimodal therapy for oesophageal cancer. Diseases of the Esophagus 2023 DOI:10.1093/doac046

Halliday LJ, Doganay E, Wynter-Blyth V, Hanna G, Moorthy K. The Impact of Prehabilitation on Post-operative Outcomes in Oesophageal Cancer Surgery: a Propensity Score Matched Comparison. Journal of Gastrointestinal Surgery 2020 DOI:10.1007/s11605-020-04881-3

Halliday LJ, Doganay E, Wynter-Blyth V, Osborn H, Buckley J, Moorthy K. Adherence to pre-operative exercise and the response to prehabilitation in oesophageal cancer patients. Journal of Gastrointestinal Surgery 2020 DOI:10.1007/s11605-020-04561-2

Oral presentations

Halliday L, Doganay E, Osborn H, Halley M, Wynter-Blyth V, Moorthy K. Pre-operative functional and psychological impact of prehabilitation in patients with oesophago-gastric cancer. Presented at: International Surgical Congress of ASGBI; 2019 May 7-9; Telford, UK

Halliday L, Doganay E, Buckley J, Osborn H, Hanna GB, Wynter-Blyth V, Moorthy K. Adherence to exercise during prehabilitation: the relationship with changes in fitness and post-operative pneumonia. Presented at: 7th ERAS World Congress, 2019 May 1-3; Liverpool, UK

Prizes

Oral presentation runner up, 7th ERAS World Congress 2019

ACKNOWLEDGEMENTS

The completion of the thesis would not have been possible without the help and guidance of many people.

Firstly, I would like to thank my supervisors, Mr Krishna Moorthy and Mr Christopher Peters, both of whom have guided the development of this thesis and my career to date. They have been extremely supportive, and their enthusiasm for academic surgery is a continual source of motivation.

I am grateful to the many members of the PREPARE for Surgery team, both past and present, and I particularly would like to thank Mrs Venetia Wynter-Blythe and Ms Claudia Rueb for their long-standing support.

I would also like the thank the following people for their assistance with this research: Mr Piers Boshier for teaching me the principles of body composition analysis and for providing a useful sounding board throughout my research; Prof George Hanna, Miss Bhamini Vadhwana and Mr Bibek Das for assisting with sample collection; Prof Robert Goldin, Dr Jacques Behoaras, Dr Antoni Olona and Dr Charlotte Hateley for patiently teaching me how to perform the laboratory techniques used in Chapters 6 and 7; Mr Emre Doganay for assisting with the paper selection in Chapter 5; and Prof John Buckley for his guidance with exercise testing.

Most importantly, I wish to thank the patients who participated in the studies contained within this thesis. None of this work would be possible without their help, and the desire they show to improve outcomes for future patients is the inspiration for my research.

Finally, I wish to dedicate this work to Jonathan and to my parents. I am incredibly grateful for their constant support, patience and encouragement.

Laura Halliday

January 2024

TABLE OF CONTENTS

Abstract 2

Declaration 4

Peer reviewed publications and presentations arising from this work 5

Acknowledgements 6

Table of contents 7

List of tables 13

List of figures 15

Abbreviations 17

Chapter 1 – Introduction

1.1 What is prehabilitation? 19

1.2 Literature review 21

1.2.1 Pre-operative outcomes 21

1.2.2 Post-operative outcomes 24

1.2.3 Studies in oesophageal cancer 25

1.2.4 Studies of prehabilitation during neoadjuvant chemotherapy or radiotherapy 26

1.2.5 Limitations of the evidence base 26

1.2.6 Summary 27

1.3 How does prehabilitation affect the body and why is this important? 28

1.4 Thesis hypothesis and rationale 29

1.4.1 Cardiorespiratory fitness and post-operative outcomes 30

1.4.2 Body composition and post-operative outcomes 32

1.4.3 Inflammation and its relationship to body composition and cardiorespiratory fitness 33

1.4.4 Inflammation and post-operative outcomes 35

1.4.5 Exercise and inflammation 37

1.4.6 Hypothesis 39

1.5 Thesis aims and objectives 40

Chapter 2 – The impact of prehabilitation on post-operative outcomes in oesophageal cancer surgery

2.1 Objective & hypothesis 41

2.2 Introduction 41

2.3 Methods 42

2.3.1 The PREPARE for Surgery programme 42

2.3.2 Measurement of adherence 47

2.3.3 Study population 48

2.3.4 Study outcomes 49

2.3.5 Statistical analysis 50

2.4 Results 51

2.4.1 Post-operative outcomes 53

2.4.2 Compliance with enhanced recovery protocols 54

2.5 Discussion 56

2.5.1 Study limitations 61

2.5.2 Future studies 62

2.6 Conclusions 63

Chapter 3 – Cardiorespiratory fitness and adherence to pre-operative exercise

3.1 Objectives & hypothesis 64

3.2 Introduction 65

3.3 Methods 67

3.3.1 Study population 67

3.3.2 Measurement of cardiorespiratory fitness 67

3.3.3 Measurement of adherence 69

3.3.4 Definition of pneumonia 70

3.3.5 Statistical analysis 70

3.4 Results 71

3.4.1 Changes in fitness during prehabilitation 72

3.4.2 Factors predictive of improvement in cardiorespiratory fitness 75
3.4.3 Factors predictive of post-operative pneumonia 75
3.4.4 Relationships between baseline fitness and adherence, fitness and pneumonia 78
3.5 Discussion 80
3.5.1 Study limitations 83
3.5.2 Future studies 84
3.6 Conclusions 85

Chapter 4 – Prehabilitation and changes in body composition during neoadjuvant therapy for oesophageal cancer

4.1 Objectives & hypothesis 87
4.2 Introduction 88
4.3 Methods 89
4.3.1 Study population 89
4.3.2 Assessment of body composition 89
4.3.3 Outcome measurements 91
4.3.4 Statistical analysis 92
4.4 Results 92
4.4.1 Changes in body composition during neoadjuvant therapy 94
4.4.2 Hand grip strength 98
4.4.3 Changes in body composition and adherence to pre-operative exercise in prehabilitation patients 98
4.4.4 Changes in body composition and post-operative outcomes 100
4.5 Discussion 102
4.5.1 Study limitations 105
4.5.2 Future studies 106
4.6 Conclusions 107

Chapter 5 – Exercise and inflammation in patients undergoing oncological treatment: A systematic review

5.1 Objective & hypothesis 108
5.2 Introduction 108

5.3 Methods 110
5.3.1 Search strategy 110
5.3.2 Study selection 110
5.3.3. Data extraction and analysis 111
5.3.4 Assessment of bias and therapeutic validity 111
5.4 Results 112
5.4.1 Selection of studies 112
5.4.2 Exercise interventions 116
5.4.3 Assessment of bias 120
5.4.4 Therapeutic validity of exercise interventions 123
5.4.5 Effects of exercise on inflammation 123
5.5 Discussion 133
5.6 Conclusions 138

Chapter 6 – Prehabilitation and systemic inflammation in patients with oesophago-gastric cancer

6.1 Objectives & hypothesis 139
6.2 Introduction 139
6.3 Methods 140
6.3.1 Study population 140
6.3.2 Prehabilitation programme 2020-2021 141
6.3.3 Measurement of inflammation 144
6.3.4. Statistical analysis 146
6.4 Results 147
6.4.1 Changes in inflammatory markers 149
6.4.2 Change in inflammation and physical activity levels 150
6.5 Discussion 152
6.5.1 Study limitations 156
6.5.2 Future studies 158
6.6 Conclusions 159

Chapter 7 – Prehabilitation and inflammation within visceral adipose tissue in patients with oesophago-gastric cancer

7.1 Objective & hypothesis 160

7.2 Introduction 160

7.3 Methods 163

7.3.1 Study population 163

7.3.2 Study outcomes 164

7.3.3 Measurement of inflammation 164

7.3.4 Statistical analysis 167

7.4 Results 167

7.4.1 Differences in inflammatory markers 170

7.4.2 Exercise and inflammatory markers 173

7.4.3 Body composition and inflammatory markers 173

7.4.4. Macrophage infiltration within VAT 174

7.5 Discussion 178

7.5.1 Study limitations 181

7.5.2 Future studies 182

7.6 Conclusions 182

Chapter 8 – Final conclusions and future directions

8.1 Key findings 183

8.2 Future research 186

8.2.1 Clinical studies 186

8.2.2. Laboratory studies 191

8.3 Summary 192

References 194

Appendices

Appendix I: Example of personalised exercise prescription and diary card used to record adherence 215

Appendix II: Esophagectomy Complication Consensus Group (ECCG) guidelines 216

Appendix III: Chester Step Test protocol 217

Appendix IV: Systematic review search strategy 221

Appendix V: Godin-Shephard Leisure Time physical activity questionnaire 222

Appendix VI: qRT PCR forward and reverse primers 223

LIST OF TABLES

Table 1.1: Summary of systematic review comparing outcomes in prehabilitation patients and controls 23
Table 2.1: Demographic factors before and after propensity score matching 52
Table 2.2: Comparison of study outcomes in unmatched and propensity score matched analysis 55
Table 2.3: Factors associated with the development of post-operative pneumonia 56
Table 3.1: Chapter 3 study participant characteristics 72
Table 3.2: Factors associated with improvement in pVO_2max between P2 and P3 75
Table 3.3: Characteristics of patients who did and did not develop post-operative pneumonia 76
Table 3.4: Factors associated with the development of post-operative pneumonia 77
Table 4.1: Chapter 4 study participant characteristics 95
Table 4.2: Change in body composition parameters during neoadjuvant therapy 96
Table 4.3: Baseline comparison of propensity score matched groups 97
Table 4.4: Propensity score matched comparison of change in body composition parameters during neoadjuvant therapy 98
Table 4.5: Changes in body composition parameters stratified by adherence to personalised exercise prescriptions 99
Table 4.6: Factors associated with loss of skeletal mass and loss of visceral adipose tissue during prehabilitation 100
Table 4.7: Variation in body composition, stratified by post-operative complications 101
Table 4.8: Factors associated with post-operative complications 101
Table 5.1: Characteristics of included studies 114
Table 5.2: Inclusion and exclusion criteria 117
Table 5.3: PEDro scale assessment of bias 121
Table 5.4: CONTENT scale assessment of therapeutic validity 122
Table 5.5: Effect of exercise on plasma IL-6 levels 125
Table 5.6: Effect of exercise on plasma TNFα levels 126
Table 5.7: Effects of exercise on immune cell parameters, plasma adipokines, IGF-1 and CRP 130
Table 6.1: Chapter 6 study participant characteristics 148
Table 6.2: Changes in inflammatory markers 149

Table 7.1: Chapter 7 study participant characteristics 169

Table 7.2: Comparison of inflammatory markers 170

Table 7.3: Chapter 7 immunohistochemistry study participant characteristics 175

Table 7.4: Comparison of CD68+ cell count and adipocyte size 176

LIST OF FIGURES

Figure 1.1: Model of changes in functional capacity during the peri-operative period 20

Figure 1.2: Model of the potential mechanisms by which exercise may reduce post-operative complications 39

Figure 2.1: Components of the PREPARE for Surgery programme 43

Figure 2.2: Borg scale rating of perceived exertion 46

Figure 2.3: Enhanced recovery protocol following oesophagectomy 50

Figure 2.4: Chapter 2 study participant flow chart 51

Figure 3.1: Weekly adherence calculation 70

Figure 3.2: pVO_2max during prehabilitation 73

Figure 3.3: O_2 pulse during prehabilitation 74

Figure 3.4: Incidence of post-operative pneumonia 78

Figure 3.5: Baseline fitness in patients who had (a) ≥75% adherence and (b) those with ≥10% increase pVO_2max during chemotherapy. 79

Figure 4.1: Assessment of body composition using a contrast enhanced CT image at L3 level 90

Figure 4.2: Chapter 4 study participant flow chart 93

Figure 5.1: PRISMA flow chart 113

Figure 5.2: Cochrane risk of bias assessment 120

Figure 6.1: Types of prehabilitation used during study period 143

Figure 6.2: Timing of plasma sample collection 145

Figure 6.3: Chapter 6 study participant flow chart 147

Figure 6.4: Correlation between changes in TNFα and physical activity levels, measured by (a) Leisure Score Index and (b) Godin Score Scale 151

Figure 7.1: Macrophage polarisation 162

Figure 7.2: Timing of VAT sample collection 163

Figure 7.3: CD68+ macrophage staining in VAT samples 166

Figure 7.4: Calculation of adipocyte size using Image J Adiposoft 166

Figure 7.5: Chapter 7 study participant flow chart 168

Figure 7.6: Comparison of expression of Il-1β mRNA 171

Figure 7.7: Comparison of expression of CCL3 mRNA 172

Figure 7.8: Comparison of expression of CD163 mRNA 172

Figure 7.9: IL-10 expression and Godin Score Scale 173

Figure 7.10: Comparison of CD68+ cell count 176

Figure 7.11: CD68+ cell count and Godin Scale Score 177

Figure 8.1: Thesis hypothesis and key findings 184

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists physical status classification
AT	Anaerobic threshold
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CCI	Charlson comorbidity index
CCL	Chemokine C-C motif ligand
CI	Confidence interval
CRP	C-reactive protein
CST	Chester step test
CT	Computerised tomography
CNS	Clinical nurse specialist
CONTENT	Consensus on therapeutic exercise training
DEXA	Dual energy x-ray absorptiometry
DICOM	Digital Imaging and Communications in Medicine
DNA	Deoxyribonucleic acid
ECCG	Esophagectomy Complication Consensus Group
ELISA	Enzyme linked immunosorbent assays
ERP	Enhanced recovery programme
ESPEN	European Society for Parental and Enteral Nutrition
FEV_1	Forced expiratory volume over one minute
GI	Gastro-intestinal tract
GOJ	Gastro-oesophageal junction
GLUT4	Glucose transporter type 4
HIIT	High intensity interval training
HRR	Heart rate reserve
HU	Hounsfield Unit

IGF	Insulin-like growth factor
IL	Interleukin
IQR	Inter-quartile range
MET	Metabolic equivalent
NAC	Neoadjuvant chemotherapy
NG	Nasogastric
OG	Oesophago-gastric
PA	Physical activity
PACS	Picture archiving and communication system
PBS	Phosphate-buffered saline
PI3K	Phosphoinositide 3-kinase
PRISMA	Preferred reporting items for systematic review and meta-analysis
pVO_2max	Predicted maximum volume of oxygen uptake
qRT-PCR	Quantitative real-time polymerase chain reaction
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RPE	Rating of perceived exertion
SAT	Subcutaneous adipose tissue
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SM	Skeletal muscle
SMI	Skeletal muscle index
TAT	Total adipose tissue
TNF	Tumour necrosis factor
VAT	Visceral adipose tissue
VO_2	Volume of oxygen uptake
VO_2max	Maximum volume of oxygen uptake
WHO	World Health Organisation
6MWT	Six-minute walk test

CHAPTER 1

-

INTRODUCTION

Surgery for oesophageal cancer is a monumental undertaking for a patient. Prolonged surgery, often preceded by neoadjuvant chemotherapy or chemoradiotherapy, takes a significant physiological strain on the body. Through activation of inflammatory, endocrine and immunological responses, the 'surgical stress response' creates increased metabolic demand and a pro-catabolic state (1,2).

Prior to surgery, there are multiple physiological stresses and demands placed upon the body of a patient with oesophageal cancer. Firstly, the presence of cancer induces a catabolic state (3,4). Oesophageal cancer patients are often frail with multiple co-morbidities (5-8). For most patients this poor physiological state is compounded by neoadjuvant chemotherapy or chemoradiotherapy, which is associated with a significant impairment in functional capacity (9,10). The physical deconditioning caused by these factors represents a clear mismatch with the metabolic demand being place on the body during an oesophagectomy. Consequently, surgery for oesophageal cancer is has a high morbidity and is associated with a prolonged post-operative recovery (11-13).

1.1 What is prehabilitation?

When a person decides to undertake a physical sporting challenge, such as a cycle or running race, they train for the event to allow their body to adapt and be able to meet the physical demand that the event will place on it. Patients too must prepare their bodies to ensure that they are ready to meet the physiological challenge of major surgery.

With the advent of Enhanced Recovery After Surgery (ERAS) protocols in the 2000s, a greater emphasis was placed upon interventions to reduce perioperative stress during and after surgery (14). However, the pre-operative interventions within many ERAS protocols were largely limited to avoiding prolonged fasting, bowel preparation or over-sedation, and trying to optimise known medical co-morbidities (14-16). Prehabilitation takes this concept further, using the time between diagnosis and surgery to optimise a patient's functional capacity to prepare them for the physiological challenge of a major operation. This increase in functional capacity then acts as a 'buffer' for the post-operative period, ensuring the fall in fitness seen after major surgery does not result in as poor a state of physical health as otherwise would have occurred (**Figure 1.1**). This in turn is thought to reduce the risk of developing post-operative complications and improve the patient's ability to deal with a complication should one arise (17).

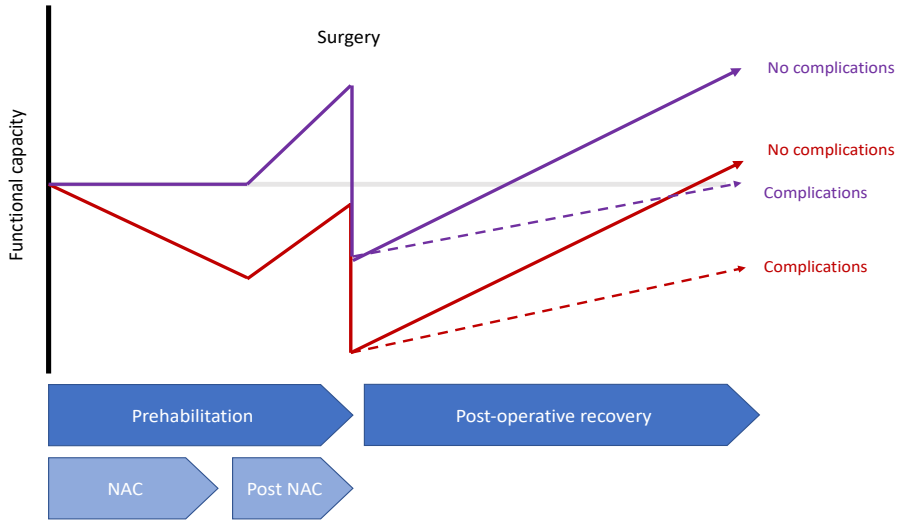


Figure 1.1 Model of changes in functional capacity during the peri-operative period with prehabilitation (purple line) and usual care (red line). Adapted from Carli et al., 2017 (17)
NAC = neoadjuvant chemotherapy

There is a large amount of heterogeneity in the design of prehabilitation programmes and whilst pre-operative exercise is widely regarded as the central component of prehabilitation, many programmes also address other domains, such as nutrition and psychological support

(18,19). Even within the topic of exercise interventions, there are substantial differences in the programmes that are used, with different types of exercise, intensity of exercise, frequency of sessions and programme duration (18,20,21).

There is no gold-standard model for delivering prehabilitation (22). Both clinic-based and home-based programmes have been studied (18). However, it is increasingly recognised a shift towards home-based interventions is needed for prehabilitation to be sustainable and scalable (23). Furthermore, there is a growing consensus favouring multimodal interventions (24), with programmes often including a combination of exercise, nutrition, psychological wellbeing, optimisation of medical co-morbidities and smoking/alcohol cessation. As well as making the most of the limited time before surgery, this may have synergistic effects; for example, a healthy diet alongside exercise may lead to greater gains of muscle or loss of fat, whilst improved psychological wellbeing and optimisation of medical co-morbidities may increase participation with exercise programmes. Guidelines published by Macmillan Cancer Support in 2020 endorse the principle of multimodal interventions and also recommend that programmes should be personalised and adherence to the programme should be monitored (25).

1.2 Literature review

Over the last decade, there has been a rapidly growing number of publications addressing pre-operative exercise. More recently, the evidence base is strengthened by randomised controlled trials and meta-analyses.

1.2.1 Pre-operative outcomes

Three systematic reviews have examined the impact of pre-operative exercise on pre-operative fitness. The first systematic review looked at aerobic exercise in patients undergoing resection for gastrointestinal cancer (18) and the second at programmes

combining both aerobic and resistance exercises in patients who were undergoing resection of any solid tumour (26). Both reviews showed that patients who undergo prehabilitation have an increase in fitness and functional capacity from baseline to the time of surgery, with three out of four and three out of five studies in the respective reviews showing improved fitness by the time of surgery in patients who received prehabilitation. However, when the changes in fitness in prehabilitation patients were compared that seen in control groups, there is less evidence of significant benefit (**Table 1.1**).

The third systematic review included studies with any exercise or any nutritional intervention in patients undergoing resection of any gastrointestinal cancer (27). It identified 11 studies in total, although only five of which had an exercise component to the intervention. Four of these studies measured changes in pre-operative functional walking capacity, assessed using the six-minute walk test (6MWT), and all four reported improvement in the prehabilitation group by the time of surgery. The review does not state how many of these studies found a significant difference in the change in 6MWT compared the control groups. However, they undertook a meta-analysis, which found a significantly greater improvement in 6MWT in the prehabilitation patients compared to controls (mean difference 32.5m, 95% confidence interval 10.8 to 54.3, p=0.003).

Since these systematic reviews were published, four other randomised controlled trials (RCTs) have looked at the effect of prehabilitation on pre-operative fitness. One study examined the effects of high intensity interval training on patients undergoing surgery for a urological cancer and found a significantly higher increase in VO_2 at anaerobic threshold in prehabilitation patients compared to controls (28). Three other studies did not show a significant difference in the change in fitness between prehabilitation patients and controls (29-31). Of note, one of these studies only recruited patients aged over 65 years old or those who were clinically frail (31). Another of the three studies was a feasibility study and therefore was not adequately powered to detect a clinically significant difference (30). However, this study noted a non-significant trend for increased functional walking capacity from baseline to the time of surgery in the prehabilitation group, in comparison to a fall in the control arm.

Study name	Intervention	Population	Outcome	Number of studies reporting outcome	Number of studies showing significant difference between groups
Santa Mina et al., 2014 (32)	Any exercise	Patients undergoing any operation	Post-operative complications	5	2
Moran et al., 2016 (33)	Any exercise	Patients undergoing any intra-abdominal operation	Post-operative complications	9	3
Vermillion *et al.*, 2018 (18)	Aerobic exercise	Patients undergoing resection of gastrointestinal cancer	Change in pre-operative functional walking capacity (6MWT)	2	1
			Change in post-operative functional walking capacity (6MWT)	2	1
Piraux *et al., 2018* (26)	Combined aerobic and resistance exercise	Patients undergoing resection of any solid tumour	Change in pre-operative functional walking capacity (6MWT)	5	2
			Post-operative complications	2	0
			Post-operative respiratory complications	6	2
Hughes *et al*., 2019 (20)	Any exercise	Patients undergoing any intra-abdominal operation	Post-operative complications	9	2
			Post-operative respiratory complications	9	2
Thomas *et al*., 2019 (34)	Any exercise	Patients undergoing resection of any intra-abdominal cancer	Post-operative complications	7	1
			Length of stay	7	0
			Length of ICU stay	2	0
			30-day readmission	2	0
Lau & Chamberlain, 2019 (27)	Any exercise	Patients undergoing resection of gastrointestinal cancer	Change in pre-operative functional walking capacity (6MWT)	4	N/A [1]
			Change in post-operative functional walking capacity (6MWT)	3	N/A [1]

Table 1.1 Summary of systematic reviews comparing outcomes in prehabilitation patients and controls. *6MWT = 6-minute walk test.*

[1] The number of studies showing difference between prehabilitation and controls was not reported (results reported as a meta-analysis only).

1.2.2 Post-operative outcomes

Five systematic reviews have looked at the impact of prehabilitation on post-operative complications following abdominal surgery (**Table 1.1**). All five reviews looked at overall complication rate and, in each review, less than half of the included studies showed a statistically significant difference in complications between prehabilitation patients and controls.

Two of the reviews conducted a meta-analysis for post-operative complications and both of these included studies with any type of pre-operative exercise prior to any intra-abdominal surgery. Both analyses found a significant reduction in the risk of post-operative complications after prehabilitation in comparison to controls: OR=0.59, 95% confidence interval 0.38 to 0.91 (p=0.03) (33); and OR 0.63, 95% confidence interval 0.46 to 0.87 (p=0.005) (20). The latter review also found a significant reduction in pulmonary complications (OR 0.4, 95% confidence interval 0.23 to 0.68, p=0.0007).

Two systematic reviews looked at the impact of prehabilitation on post-operative fitness (**table 1.1**), both of which included studies of patients undergoing resection of a gastrointestinal cancer. All of these studies reported change in 6MWT from baseline to four to eight weeks after surgery. The first review, undertaken in 2018, looked at aerobic exercise interventions (18). It identified two studies, one of which showed a significant difference in the change in 6MWT between prehabilitation patients and controls.

The second review was undertaken in 2019 and included any exercise interventions (27). This identified a third another study, in addition to the two included in the previous review. They conducted a meta-analysis and found a significantly greater improvement in 6MWT in the prehabilitation patients compared to controls (mean difference 48.2m, 95% confidence interval 1.5 to 94.9, p=0.043).

Three other studies published since these reviews have looked at post-operative outcomes, two of which found a difference in post-operative fitness in the intervention group compared with controls. One of these studies included patients with prostate cancer (35) and the other

included those with bladder cancer (29). Neither found a significant difference in post-operative complications. The third study, which examined patients with colorectal cancer who were over 65 years old or frail, did not find a significant difference in post-operative fitness, complications or length of stay between prehabilitation patients and controls (31).

1.2.3 Studies in oesophageal cancer

Three studies of pre-operative exercise in oesophageal cancer patients have been published. The first was an RCT, in which 51 patients were randomised to either prehabilitation or usual care (36). 77% of patients in the RCT received neoadjuvant chemotherapy; however, the timing of the intervention in relation to the neoadjuvant therapy is not clarified within the protocol. The second study was a cohort study with patients who underwent prehabilitation whilst receiving neoadjuvant chemotherapy (37). This was a pilot study, with 11 patients in each study arm. The most recent study was an RCT with 54 patients randomised to prehabilitation or usual care (38).

None of the studies found any significant difference in post-operative complications in comparison to matched controls. Two of the three studies also looked at changes in fitness. The second study found significantly larger increases in fitness in the prehabilitation group from baseline to both before and after surgery in comparison to changes in the controls (pre-operative change in 6MWT = 36.9 vs -22.8, $p<0.001$; post-operative change in 6MWT = 15.4 vs -81.8, $p<0.001$) (36). The most recent RCT reported significantly less decline in peak VO_2 in prehabilitation patients compared with the controls (-0.4 ml/kg/min vs -2.5 ml.kg/min, $p=0.022$) (38).

1.2.4 Studies of prehabilitation during neoadjuvant chemotherapy or radiotherapy

In addition to the three studies of oesophageal cancer patients described above, three other studies have examined prehabilitation during and/or after neoadjuvant therapy. One of these was an RCT of patients undergoing prehabilitation during and after neoadjuvant chemoradiotherapy for rectal cancer (30). This found an increase in 6MWT from baseline to the time of surgery in the prehabilitation patients, in contrast to a fall in 6MWT in the controls. However, the between group difference in change in 6MWT was not significant.

The second study compared changes in VO_2 at anaerobic threshold in rectal cancer patients who received prehabilitation after neoadjuvant chemoradiotherapy to historical controls. They found a significant difference in the change in VO_2 at anaerobic threshold from the end of neoadjuvant therapy to the time of surgery, with an increase in the prehabilitation patients and a fall in controls (9). The final study found a significant increase in pre-operative 6MWT in pancreatic cancer patients who underwent prehabilitation during neoadjuvant chemotherapy (39). However, there was no control group for comparison in this study.

1.2.5 Limitations of the evidence base

There are significant limitations to the existing evidence base. The vast majority of the studies are based on small sample sizes, and many do not provide evidence of sample size calculations to determine whether the trial has adequate power to detect a clinically significant effect. This increases the chance of a type II error.

There is substantial heterogeneity between the studies. This exists in multiple areas: type of surgery, underlying pathology, type of exercise, duration of exercise programme, intensity of exercise, and the provision of other pre-operative interventions alongside exercise. The comparison of studies with conflicting results is difficult because there are often multiple differences in both the study population and the nature of the intervention.

When fitness is considered as an outcome, there is also a large degree of heterogeneity in the method used for assessment. Therefore, despite fitness being a very commonly reported outcome measure, the ability to perform a large meta-analysis into the effect on fitness is limited. The differences in the study populations may also explain some of the opposing findings for post-operative fitness and complications. The physiological impact of different surgical procedures varies considerably. Therefore, it is not surprising that studies or reviews that include a broad range of procedures within the study population have conflicting results for post-operative outcomes. However, the small size of many studies makes it difficult to examine procedures individually.

1.2.6 Summary

The evidence base for pre-operative exercise continues to grow, and although the findings are mixed, the literature demonstrates some evidence that pre-operative exercise can improve fitness from baseline to the time of surgery. However, this is not seen in all studies. Only one meta-analysis has been performed, and although it showed significant benefit, it only included four studies.

The strongest evidence of a link between pre-operative exercise and reduced post-operative complications is in studies of patients undergoing intra-abdominal surgery (20,33). However, to date, only three studies have examined prehabilitation in oesophageal cancer patients and none demonstrated a significant difference in post-operative complications in comparison to controls.

1.3 How does prehabilitation affect the body and why is this important?

The growing number of studies on prehabilitation reflects the increasing desire to explore pre-operative interventions that may improve outcomes for patients. Despite this burgeoning interest in prehabilitation, we fundamentally do not understand how prehabilitation works and do not know what the optimum structure and design of the programmes should be.

The abilities and needs of patient populations will vary, and thus the type and intensity of the interventions will not be the same in every prehabilitation programme. Even within a discrete patient group, such as those undergoing a particular type of surgery or those with the same underlying pathology, the abilities and needs of the individual patient will vary considerably. However, the large amount of heterogeneity between the prehabilitation protocols, even between comparatively similar study populations, is reflective of the absence of consensus on how to deliver prehabilitation to particular patient groups. Furthermore, because the heterogeneity exists in so many areas of the intervention, and the sample sizes for individual procedure types or patient groups are relatively small, it is difficult to compare studies to determine the optimum way to deliver prehabilitation.

If we can achieve a better understanding of the effects that pre-operative exercise has on the patient's physiology and of how pre-operative exercise influences post-operative outcomes, we will be better placed to understand what the key components of pre-operative exercise should be. This can then be used as a structure upon which to develop prehabilitation programmes.

In not fully understanding how pre-operative exercise effects patients, we also do not know how to monitor progress during the programmes. Therefore, it is not possible to identify 'response' until after patients have reached the time of their surgery, or worse, until we see their response to the physiological challenge of their resection. A more proactive approach in monitoring response during the programme could allow real-time modifications to be made where needed to try to gain the maximum benefit from exercise in the pre-operative period.

The challenge lies in knowing what to monitor and what changes to make, and to do this we need to understand how exercise is exerting an effect on post-operative outcomes.

It is intuitive that exercise is a good thing for people to do. However, prehabilitation and pre-operative exercise programmes go beyond providing general advice on physical activity and the benefits of regular exercise. In delivering structured exercise as a clinical intervention, health professionals need to fully understand the effects of the intervention and the rationale behind it. Prehabilitation programmes have significant logistical challenges for healthcare providers and patients alike, alongside financial implications for healthcare services. In patients undergoing surgery for cancer, the time available for prehabilitation is limited. All of these factors highlight the importance of ensuring that the time spent delivering and participating in pre-operative exercise is used efficiently to maximise the benefits that can be accrued. To do this, we first need to address a key question: *what are we trying to achieve with pre-operative exercise?*

1.4 Thesis hypothesis and rationale

It has not been proven to date that pre-operative exercise can reduce complications in oesophageal cancer patients. Although three studies published with patients undergoing surgery for oesophageal cancer have not shown a statistically significant difference in complications, none was powered to detect a difference in this outcome (36-38). One of the studies was a pilot cohort study to assess the feasibility of delivering prehabilitation (37), and the primary outcome in the other studies were functional capacity/walking distance (36) and anaerobic threshold (38). However, two meta-analyses have demonstrated that pre-operative exercise can reduce post-operative complications by 40% in patients undergoing intra-abdominal surgery (20,33). Given the prolonged intra-abdominal phase of an oesophagectomy, this finding warrants further investigation into the effects of prehabilitation on post-operative outcomes after oesophagectomy.

Outside of the field of structured exercise interventions, other studies have also demonstrated that the level of physical activity undertaken by patients in the pre-operative period is associated with post-operative outcomes, including the risk of complications. Two studies have been undertaken with oesophagectomy patients. Low levels of pre-operative physical activity were independently associated with the risk of complications (40). In keeping with this finding, the other study reported that patients who developed post-operative pulmonary complications had more pre-operative sedentary time and spent less time undertaking moderate intensity physical activity in comparison to patients who did not develop pulmonary complications (41).

Similar associations are seen in other patient groups. Self-reported pre-operative physical activity levels were independently associated with early post-operative mortality, length of stay and discharge destination in a study of colorectal cancer patients (42). Furthermore, breast cancer patients who reported high levels of pre-operative physical activity were more likely to report feeling fully recovered by three weeks after surgery, in comparison to sedentary patients (43).

Building upon this supposition, the possible mechanisms underlying the relationship between higher levels of exercise and improved post-operative outcomes should be considered. These include improving cardiorespiratory fitness, improved muscle mass, reduced visceral adiposity and reduced levels of inflammation. As detailed below, there is evidence that each of these factors are associated with both pre-operative exercise and with the occurrence of post-operative complications.

1.4.1 Cardiorespiratory fitness and post-operative outcomes

Various measures are used to assess cardiorespiratory fitness pre-operatively and many studies have explored the relationship between these parameters and post-operative outcomes. Maximum uptake of oxygen (VO_2max) is calculated from cardiopulmonary exercise testing and represents the maximum rate of oxygen consumption in millilitres of oxygen per

kilogram of body mass per minute. Submaximal exercise tests, such as the incremental shuttle walk test or Chester Step test, can also be used and provide a validated predicted maximum uptake of oxygen (pVO_2max) (44-46).

The anaerobic threshold (AT) is another widely used measurement of fitness derived from cardiopulmonary exercise testing, which represents the level of oxygen uptake at which the body switches to aerobic metabolism and thus lactate levels begin to rise (47). This switch occurs when oxygen supply is insufficient for the demand being placed upon the body. The fitter the patient is, the more oxygen they will be able to supply and therefore their corresponding anaerobic threshold will be higher.

A review of 120 patients undergoing an oesophagectomy found a significant difference in both pre-operative VO_2max and AT between patients who subsequently developed complications and those who did not (48). VO_2max was also an independent risk factor for developing severe complications (48).

Similar associations are found across a broad spectrum of patient populations. A large multi-centre study of 1200 patients undergoing non-cardiac surgery found that pre-operative pVO2max was a risk factor for the development of respiratory complications, with a 44% decrease in the risk of respiratory complications for every 5ml/kg/min increase in pVO_2max (49). In keeping with this finding, studies of patients undergoing bariatric surgery and surgery for colorectal cancer have demonstrated that a lower pVO_2max is associated with a higher incidence of post-operative complication (50,51). Colorectal cancer patients who developed complications also had a lower AT (50).

In patients undergoing hepatobiliary surgery, those aged over 75 years old with an AT > 10 had a comparable overall length of stay and length stay in an intensive care unit (ICU) in comparison to patients aged less than 75 years; those with an AT <10 had significantly longer admissions than younger patients (52). Different AT thresholds have been investigated to see whether they can predict outcomes. A systematic review suggested a cut off of AT 10.9 for predicting mortality and 10.1 for predicting morbidity after intra-abdominal surgery (33). However, another systematic review found that whilst AT thresholds had a good negative

predictive value for overall mortality (96-100%) in patients undergoing non-cardiopulmonary surgery, the positive predictive value was poor (3-42%) (53). This finding suggests that whilst pVO2 AT could be used to confirm that a patient has a low risk of peri-operative death and therefore is fit for surgery, it is less well suited to predicting which patients will die and therefore should not solely be used to decide that a patient is not fit for surgery.

Measures of lung function have been studied with regard to their relationship to post-operative outcomes. A study of 61 participants undergoing an oesophagectomy reported that pre-operative FEV_1 (forced expiratory volume over one minute) was associated with the risk of respiratory complications following an oesophagectomy (54). However, when FEV_1 was examined within a large multicentre study of non-cardiac surgery, they did not find a relationship between FEV_1 and complications (49). This study included a wide range of procedures with the study population (34% upper abdominal and/or thoracic, 31% urology or gynaecology, 23% orthopaedic, 12% other), and this heterogeneity may explain the contrasting results in comparison to the oesophagectomy only study.

1.4.2 Body composition and post-operative outcomes

Cancer cachexia is the result of an imbalance between basal metabolic demands and energy intake. A systemic inflammatory response is triggered in response to the developing cancer, resulting in a raised metabolic rate and endocrine changes creating a catabolic state (3,4). This imbalance results in the loss of muscle mass and function, leading to the development of sarcopenia. Oesophageal cancer patients often have a decreased nutritional intake due to mechanical obstruction within the oesophagus causing difficulty eating, which in turn can leads to malnutrition and muscle mass loss. Furthermore, many oesophageal cancer patients receive neoadjuvant chemotherapy, which is associated with loss of muscle mass and an increased risk of sarcopenia (55,56).

In oesophageal cancer patients, sarcopenia is a risk for overall complications (56) and for respiratory complications in particular (56-58). It is also associated with poorer overall survival in this population (57,59). In other patient populations there is also a relationship

between body composition and post-operative outcomes. Total psoas area is associated with post-operative morbidity and 90-day mortality following an emergency laparotomy (60). In colorectal cancer patients, both visceral obesity and sarcopenia have been identified as independent risk factors for post-operative complications (61), whilst the ratio of visceral fat area to total abdominal muscle area was found to be an independent risk factor for complications in a study of patients undergoing surgery for gastric cancer (62).

1.4.3 Inflammation and its relationship to body composition and cardiorespiratory fitness

As previously discussed, the systemic inflammatory response is a key factor in the development of sarcopenia (3,4). The inflammation results in a raised metabolic rate and triggers endocrine changes creating anorexia and muscle breakdown, resulting in cachexia and sarcopenia. Serum markers of systemic inflammation, such as C-reactive protein (CRP), are associated with the amount of weight loss in patients with oesophago-gastric cancer (63).

There is also growing body of evidence showing a strong link between obesity, visceral adiposity and systemic inflammation. Adipocytes have important endocrine and metabolic actions through the secretion of inflammatory cytokines, such as IL6, IL8, TNFα, CCL2, leptin and adiponectin (64,65). Visceral adipose tissue has more secretory activity than subcutaneous adipose tissue (65). Obesity is associated with high levels of leptin, which is a pro-inflammatory adipokine, and low levels of adiponectin, which has anti-inflammatory properties (64,65). It is also associated with more macrophage infiltration within the adipose tissue, which is mediated by chemokines such as CCL2 (66) .

The secretion of pro-inflammatory mediators from adipose tissue has multiple systemic effects. In the obese state, high levels of pro-inflammatory cytokines and leptin are secreted by adipose tissue, and this chronic inflammatory state is an important driver of the development of insulin resistance (64,67). These cytokines act directly upon liver and muscle cells, and through reducing PI3K signalling pathways, they impair the downstream response to insulin receptor signalling (68,69). This results in reduced trafficking of the GLUT4

transporter and therefore reduced glucose uptake by muscles and liver cells causing hyperglycaemia (64,69). The pro-inflammatory cytokines also lead to the accumulation of macrophages within the adipose tissue. The macrophages then release further cytokines, including IL-1β and TNFα, which potentiate this response and further inhibit the action of insulin on liver and muscle cells (67,69).

Patients who are diabetic experience higher levels of protein breakdown and in patients undergoing surgery, those with diabetes have a larger post-operative loss in whole-body protein (67). As previously discussed, inflammation is a potent stimulator of muscle mass loss and cachexia, and therefore chronic inflammation from obese adipose tissue may be part of the mechanism underlying the relationship between diabetes and muscle breakdown.

High levels of insulin and IGF1 are associated with an increased risk of developing many different cancer types, including breast, colon, pancreatic and endometrial cancer (70,71). Serum levels of IL6 and TNFα have been found to be higher in breast cancer patients compared to controls, and measurements of these two cytokines correlated with stage and lymph node metastases (72). Serum IL6 and TNFα have also been shown to be higher in patients with metastatic prostate cancer, in comparison to controls (73).

Whilst these findings may reflect a systemic pro-inflammatory response to the presence of a cancer or direct inflammatory effects of the cancer itself, ex-vivo studies have demonstrated that inflammatory mediators, such as IL6, can stimulate proliferation, migration, invasion, apoptosis angiogenesis and differentiation of many different types of cancer cells (74). Activation of the IGF1 receptor on cancer cell stimulates invasion and metastasis (75). Insulin itself can also stimulate cancer cell proliferation and inhibit cancer cell apoptosis (71). Furthermore, murine studies have shown that low levels of IGF1 can inhibit colon cancer growth and can stimulate apoptosis in prostate cancer cell line (70). Adiponectin is an anti-inflammatory cytokine produced by adipose tissue. It increases insulin sensitivity and secretion of adiponectin is reduced in obesity (64,75). (Adiponectin has been shown to directly affect cancer cell behaviour, through inhibits cell growth in breast, endometrial, prostate and colon cancer cell lines, increasing the rate of cancer cell apoptosis and inhibiting angiogenesis (64,75).

In cell culture studies, adipose tissue from centrally obese patients induces significantly more proliferation in cancer cells lines compared to adipose tissue from non-obese populations (65). Furthermore, greater cancer cell proliferation seen with visceral adipose tissue culture medium compared to subcutaneous adipose tissue media (65). This therefore suggests that mediators within the visceral adipose tissue are having direct effects on cancer cell behaviour.

In addition to these links between inflammation and body composition, inflammation has also been associated with cardiorespiratory fitness. Studies of colorectal cancer patients have demonstrated that a higher neutrophil:lymphocyte ratio and a higher modified Glasgow Prognostic Score (derived from CRP and albumin) are both associated with lower pre-operative cardiorespiratory fitness (76,77). Further studies in a healthy population have shown that CRP is negatively associated with VO_2max and positively associated with body mass index (BMI) (78).

The nature of the link between inflammation and fitness has not been fully explored. However, it is possible that some of this association may be linked to differences in adiposity. Two further studies of healthy participants noted that inflammatory markers, such as CRP, and pro-inflammatory cytokines, such as IL6 and IL18, were inversely associated with cardiorespiratory fitness (79,80). However, after adjusting for visceral fat area, waist circumference, truncal fat percentage and other markers of metabolic syndrome, these relationships were either attenuated or lost significance altogether.

1.4.4 Inflammation and post-operative outcomes

Several studies have identified albumin and CRP, either independently or combined within the modified Glasgow Prognostic Score, as independent risk factors for post-operative infectious and/or pulmonary complications in patients undergoing surgery for colorectal cancer, hepatocellular cancer or undergoing cardiac surgery (81-84). The pre-operative neutrophil count and neutrophil:lymphocyte ratio have also been shown to be predictive of overall post-operative infections and major post-operative infections (Clavien Dindo

classification III or higher) following resection of liver metastases (85). The presence of pre-operative sepsis is a known risk factor for post-operative pulmonary complications, including infection and reintubation, in patients undergoing major surgery (86). Direct effects of inflammatory cytokines, endothelial adhesion factors and humoral immune cells may contribute to post-operative pulmonary dysfunction (87), which in turn may explain the higher risk of pulmonary complications in patients with high levels of pre-operative inflammation.

Inflammation is a key mediator of the 'surgical stress response'. When the body undergoes a major operation, the physical trauma of the operation stimulates the activation of inflammatory, immunological and endocrine mediators. This is a natural response to the trauma, and initially is advantageous; these responses increase the body's metabolism and create a pro-catabolic state to mobilise resources to heal the 'damage' that is being done. However, this response also has a negative impact on renal, neurological, haematological and immunological function (1,2,88). Following the initial pro-inflammatory response to surgery, the latter stages of the surgical stress response have immunosuppressive effects on monocytes, NK cells, T cells and lymphocytes (2,88).

The magnitude of the stress response is typically proportionate to the extent of the physical surgical trauma. Minimally invasive operations are associated with lower serum concentrations of IL6, CRP and ACTH, lower levels of insulin resistance, improved glucose tolerance and improved nitrogen balance (indicating less protein breakdown) (67,87,89).

Despite the physiological need for a stress response to surgery, if it becomes excessive or unregulated, the response can lead to systemic inflammatory response syndrome (SIRS) and multiorgan failure (90). In patients undergoing an oesophagectomy, having an elevated serum lactate at 48 hours after surgery is associated with a higher risk of post-operative complications in comparison to patients with a normal lactate level (91). It has also been found that pancreatic cancer patients who experience persistent hypotension requiring vasopressor support have higher levels of inflammation in the first 24 hours after surgery in comparison to those who do not require blood pressure support (92), demonstrating the link between perioperative inflammation and organ dysfunction.

There is evidence that high levels of inflammation in the early post-operative period is particularly associated with the risk of developing infectious complications. The presence of a persistent SIRS response on day two after oncological resection is predictive of the risk of developing severe post-operative sepsis (93), and in a study of patients undergoing colorectal cancer resection, serum TNFα levels on post-operative days one to three were significantly higher in patients who subsequently developed infectious complications (94).

In addition to the severity of the surgery, several other risk factors for an excessive surgical response have been identified. Aging is associated with a higher baseline cortisol, impaired negative feedback on the hypothalamic-pituitary-adrenal axis and higher post-operative cortisol levels, indicating an amplified surgical stress response (89,95,96). A larger inflammatory response has also been found in patients who are female (89), have a high BMI (96) or have a history of excessive alcohol intake (87).

A study of patients undergoing intra-abdominal surgery found that patients who received prehabilitation had non-significant trend for lower intra-operative vasopressor requirements in comparison to patients who did not receive prehabilitation (97). This may indicate a reduced peri-operative stress response as a result of prehabilitation; however, given the lack of statistical significance, more research is needed to further investigate this trend.

1.4.5 Exercise and inflammation

The impact of exercise on systemic inflammation has been an area of significant research over the last decade, studying the effects of exercise in both diseased and healthy populations. There is a large body of evidence on the effects of exercise on inflammation in breast cancer survivors. A meta-analysis has shown that exercise can decrease IL6, IL8 and TNFα, and increase the anti-inflammatory cytokine IL2, in breast cancer survivors (98).

A more recent meta-analysis of exercise interventions in patients who are undergoing or have recently undergone treatment for cancer also found that exercise can decrease pro-

inflammatory markers (99). Subgroup analyses within this study found most evidence of benefit within breast and prostate cancer patients (although these were the most numerous patient populations within the meta-analysis) and that the effects on inflammation were greatest for interventions that combined both aerobic and resistance training. Furthermore, they identified that CRP and TNFα were the markers that were most sensitive to change.

To date, one study has examined exercise interventions in patients who had previously undergone treatment for oesophageal cancer and were at least twelve months after the completion of treatment (100). They found a significant reduction in IL8 from baseline to the end of the exercise intervention, with a non-significant trend for a decrease in IL1β, IL6 and TNFα However, this study did not include a control group as a comparison so the conclusions are limited.

As previously discussed, chronic inflammation is associated with impaired insulin sensitivity, and several studies have examined the effect of exercise on insulin sensitivity, leptin, adiponectin. In comparison to controls, breast cancer survivors who underwent an exercise programme had a greater decrease in insulin and leptin, a greater increase in adiponectin and a greater decrease in the incidence of sarcopenic obesity (101). Some studies have found that a decrease in insulin, leptin and IGFBP1 in response to exercise is dependent on weight loss due to exercise (102,103). A large cross-sectional study of healthy participants also found that differences in CRP, IL6, TNFα and adiponectin with different levels of physical activity were attenuated by adjusting for BMI, waist circumference or fat mass (104).

However, other studies have found that exercise induced changes in insulin sensitivity occur independently to changes in weight or body composition (71). Acute bouts of exercise have also been shown to improve insulin sensitivity for up to 12 hours after exercise (105), suggesting direct effects of exercise on insulin activity. Furthermore, changes in adiponectin in healthy but previously inactivity adults who underwent an exercise intervention were seen without changes in weight or body fat percentage (106). A meta-analysis of studies involving breast cancer survivors concluded that whilst there was a reduction in fasting insulin levels irrespective of weight loss in patients participating in exercise programmes in comparison to,

a greater reduction was seen amongst patients who also lost weight (107). It is therefore possible that whilst exercise may have direct effects on insulin sensitivity and inflammation, a significant proportion of its actions are derived from changes in weight and adiposity.

Finally, exercise interventions have been shown to have effects of immune cell populations. A further study of breast cancer patients found that exercise decreased the number of pro-inflammatory M1 macrophages and increases the M2 macrophage subtype (108). M2 macrophages have a regulatory role and produce the anti-inflammatory cytokine IL-10. This is in keeping with other studies showing that exercise stimulates an increase in IL-10 expression (109). Several studies have also found an increase in NK cell activity in response to exercise (109-111).

1.4.6 Hypothesis

This thesis will examine the hypothesis that pre-operative exercise reduces post-operative complications in patients undergoing surgery for oesophago-gastric cancer and the mechanisms by which it has this effect are multifactorial, with synergistic actions on cardiorespiratory fitness, body composition and systemic inflammation (**Figure 1.2**).

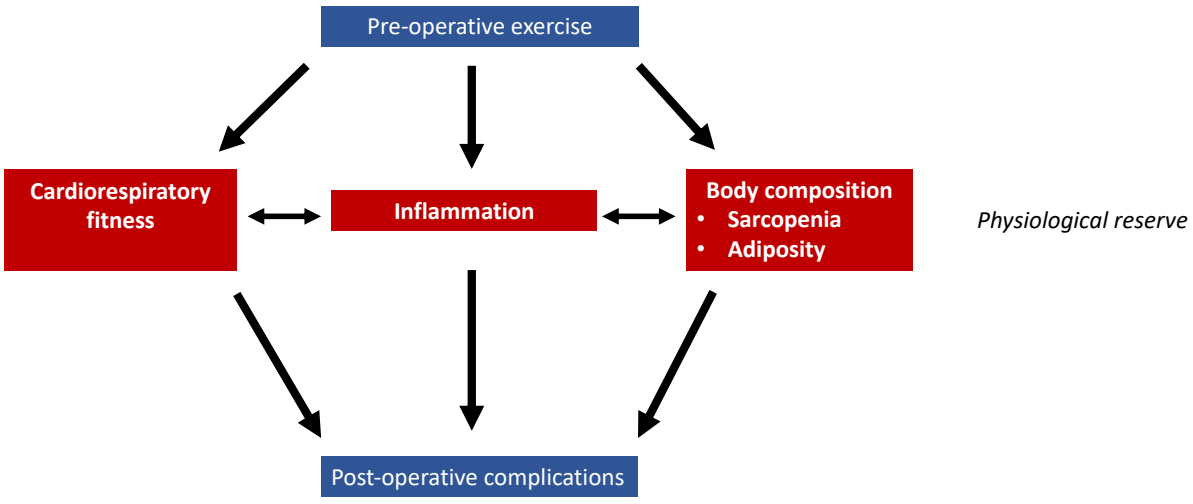


Figure 1.2 Model of the potential mechanisms by which exercise may reduce post-operative complications

1.5 Thesis aim and objectives

The aim of this thesis is to understand the mechanisms by which pre-operative exercise affects post-operative outcomes.

Objectives:

I. To establish the effect of a home based prehabilitation programme on post-operative outcomes following surgery for oesophageal cancer (**Chapter 2**)
II. To characterise the changes that occur in cardiorespiratory fitness during prehabilitation in oesophageal cancer patients (**Chapter 3**)
III. To examine the relationship between adherence to pre-operative exercise, changes in cardiorespiratory fitness and the occurrence of post-operative pneumonia (**Chapter 3**)
IV. To examine whether prehabilitation impacts upon changes in body composition during neoadjuvant therapy for oesophageal cancer (**Chapter 4**)
V. To establish how changes in body composition during prehabilitation are related to the amount of exercise completed and subsequent post-operative outcomes (**Chapter 4**)
VI. To review the published literature on the effects of exercise on systemic inflammation in patients undergoing chemotherapy or radiotherapy (**Chapter 5**)
VII. To characterise changes in systemic inflammation between diagnosis and surgery in patients with oesophago-gastric cancer (**Chapter 6**)
VIII. To examine whether prehabilitation impacts upon pre-operative changes in systemic inflammation (**Chapter 6**)
IX. To examine whether prehabilitation impacts upon levels of inflammation within visceral adipose tissue in patients with oesophago-gastric cancer (**Chapter 7**)

CHAPTER 2

-

THE IMPACT OF PREHABILITATION ON POST-OPERATIVE OUTCOMES IN OESOPHAGEAL CANCER SURGERY

Work within this Chapter has already been published within a peer-reviewed journal:

Halliday LJ, Doganay E, Wynter-Blyth V, Hanna G, Moorthy K. The Impact of Prehabilitation on Post-operative Outcomes in Oesophageal Cancer Surgery: a Propensity Score Matched Comparison. *Journal of Gastrointestinal Surgery* 2020. Available from: DOI:10.1007/s11605-020-04881-3

2.1 Objective and hypothesis

Objective: To establish the effect of a home based prehabilitation programme on post-operative outcomes following surgery for oesophageal cancer

Hypothesis: Participation in prehabilitation is associated with a reduction in post-operative complications

2.2 Introduction

Prehabilitation has been shown to reduce post-operative complications in patients undergoing intra-abdominal surgery (20,33). However, the evidence for prehabilitation in oesophageal cancer patients is scarce (112). Surgery for oesophageal cancer has a high morbidity and is associated with a prolonged recovery (11-13) so there is significant potential to improve outcomes in this high-risk population. To date, three studies have examined

prehabilitation in this population and none have shown significant changes in post-operative complications (36-38).

PREPARE (*P*hysical activity, *R*espiratory exercises, *E*at well, *P*sychological well-being, *A*sk about medications, *R*emove bad habits, *E*nhanced recovery) for Surgery is a personalised, home-based, multimodal prehabilitation programme for patients undergoing treatment for oesophageal and gastro-oesophageal junctional cancer at Imperial College Healthcare NHS Trust. The PREPARE for Surgery programme was introduced in January 2016 and is offered to all patients undergoing surgical resection with curative intent.

This study will use a propensity score matched comparison to compare post-operative outcomes in patients who have undertaken the PREPARE for Surgery programme to those in control patients who did not receive any prehabilitation.

2.3 Methods

2.3.1 The PREPARE for Surgery programme

Patients attended the multi-professional prehabilitation clinic within one week of the completion of staging investigations, before or just at the commencement of neoadjuvant chemotherapy. The patients were reviewed by a cancer clinical nurse specialist (CNS), exercise specialist and dietitian during a single visit to the hospital to develop and agree a personalised prehabilitation plan (**Figure 2.1**).

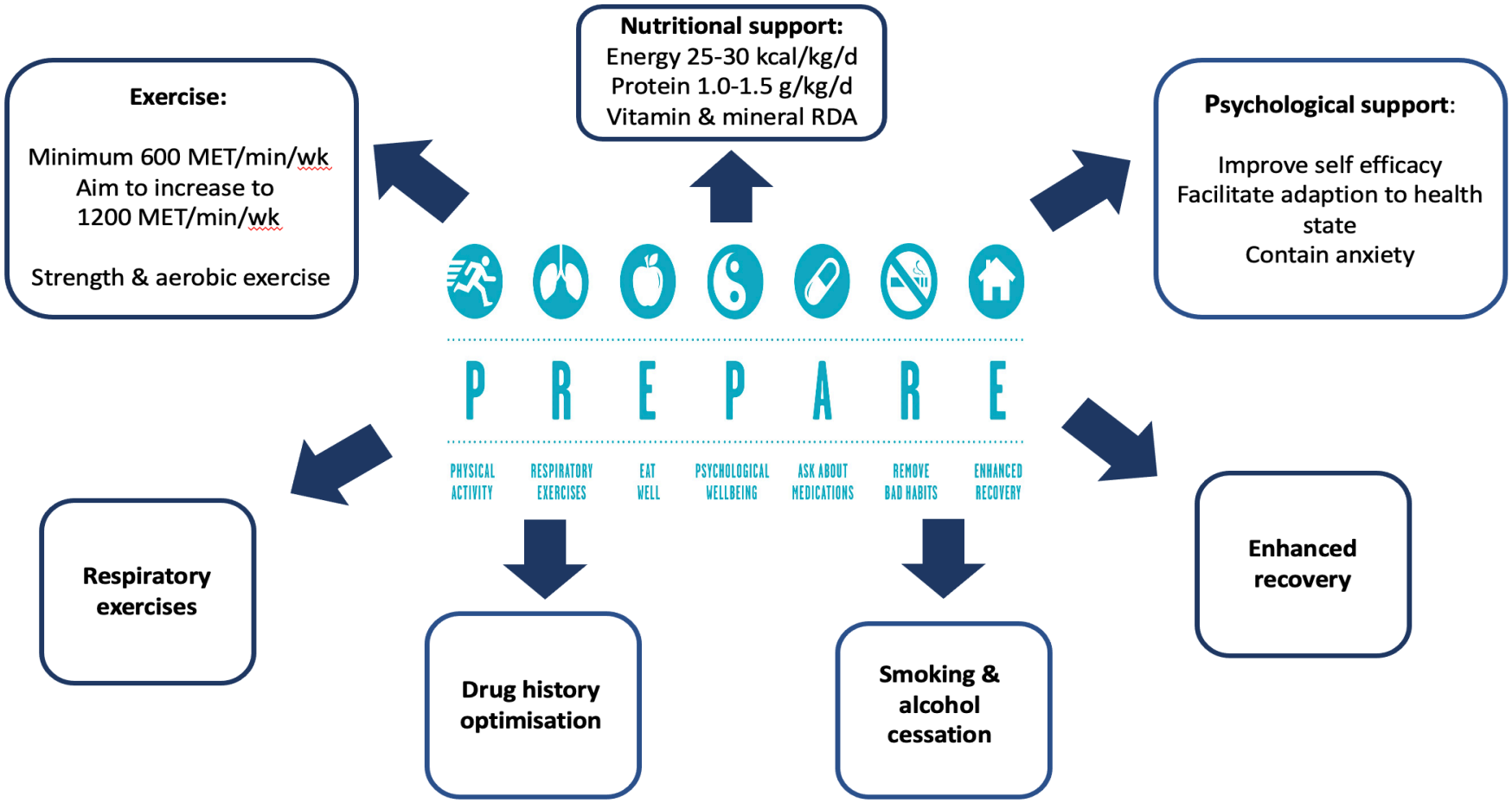


Figure 2.1 Components of the PREPARE for Surgery prehabilitation programme.
MET= metabolic equivalent; RDA= recommended daily amount.

The programme started as soon as staging investigations were completed and a decision to proceed with curative resection was made and continued throughout chemotherapy until the time of surgery. For patients who received neoadjuvant therapy, the programme lasted approximately 16 weeks, and for those who did not require neoadjuvant therapy, it lasted four to six weeks. The exact duration of the programme was determined by the time between the start of their curative pathway and the time of surgery; this was a clinical decision, unaffected by the prehabilitation programme, and the programme was provided to the patients for the whole duration of their pre-operative period.

The PREPARE for Surgery programme was developed as a quality improvement at Imperial College Healthcare NHS Trust for patients with oesophageal or gastric cancer. In 2014, a pre-operative assessment with a care of the elderly physician was established for all patients aged 70 or older. This was initially undertaken to help to identify whether older patients were fit for neoadjuvant chemotherapy and/or a major surgical resection. However, it became apparent that factors were being identified that could be optimised in the pre-operative period, such as poor cardiovascular fitness, smoking, obesity or malnutrition and poor management of medical conditions such as cardiac disease or diabetes.

A quality improvement project was established and registered with the hospital trust to look at ways to identify and address these factors. A working group was established with surgeons, anaesthetists, care of the elderly physicians, clinical nurse specialists, and as the programme evolved, physiotherapists, exercise therapists, dietitians, psychologists and ward nurses. Different interventions were introduced over time, and as the programme evolved, the interventions themselves and the way they were delivered changed in response to feedback and other findings from the quality improvement project. Assistance in quality improvement methodology was provided by NIHR CLAHRC (National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care) North West London. Patient participation events were held throughout the project to ensure that patients were not only giving feedback on the programme but were an integral part in the quality improvement process. Patients and their families were encouraged to suggest ideas for changes and interventions and helped to design the project evaluation tools.

By January 2016, the full prehabilitation programme had been established. A key principle of the programme was its universality; everyone can gain something in the pre-operative period. The programme included exercise and nutrition interventions, psychological support, optimisation of medical co-morbidities and interventions aim at using the diagnosis as a 'teachable moment' to address smoking, alcohol and other lifestyle factors. Finally the programme was fully integrated with the enhanced recovery programme. Patients were taught about the enhanced recovery programme during prehabilitation. Members of the healthcare team who delivered the enhanced recovery programme and cared for the patients following surgery were invited to attend the weekly prehabilitation team meetings where patient's progress with prehabilitation was discussed. This enabled the enhanced recovery team to become familiar with the patients before their surgery, identifying their individual needs and concerns for recovery.

2.3.1.1 Exercise programme

A personalised, home-based exercise programme was prescribed by an exercise therapist. In keeping with WHO guidelines, patients were prescribed a minimum of 600 MET minutes week^{-1}, which equates to 150 minutes of moderate intensity activity, with the aim of increasing this to 1200 MET minutes week^{-1} (300 minutes of moderate intensity activity) (113). Patients were prescribed a mixture of aerobic and strength exercises, each with a defined frequency, intensity, and duration American College of Sports Medicine (114). The exercises were personalised according to the results of submaximal exercise testing, activities of daily living, previous exercise behaviour, patient preference, medical co-morbidities and social circumstances. An example of a personalised exercise prescription is shown in **Appendix I**.

Patients received training on how to undertake the exercises and how to self-regulate the intensity using the Borg scale rating of perceived exertion (RPE) (**Figure 2.2**) (115-117), with a target range of 13 to 15 depending on the patient's medical history and type of exercise. A weekly telephone touch-point was held with an exercise therapist. Providing the goals were achieved, the exercise programme was progressed by frequency, duration and then intensity.

For those who were unable to meet their goals, the programme was adapted to their clinical condition and re-evaluated at the next touch-point.

Rating of perceived exertion	Description
6	No exertion, resting
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy exertion)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Figure 2.2 Borg scale rating of perceived exertion
Adapted from Borg, 1982 (118)

2.3.1.2 Nutritional support

A specialist dietitian undertook an assessment of nutritional status including identification and stratification of nutritional risk. A plan was agreed based on symptoms, dietary eating habits and nutritional deficiencies. ESPEN guidelines for clinical nutrition in cancer patients were used to determine estimated dietary requirements: energy intake of 25-30 kcal/kg/day, protein intake of 1.0-1.5g/kg/day, and vitamin and mineral intake at the recommended daily allowances (119) .The individualised programmes and targets were highly personalised because the needs of patients was very variable. For example, some patients were obese and therefore needed a nutrition programme to aid weight loss. Others were malnourished and cachexia and therefore needed an anabolic nutrition programme to aid muscle gain and replenishment of vitamin and minerals.

Weekly or fortnightly phone calls from the dietitian were used to monitor adherence to the programme. Interventions, such as oral supplementation or enteral feeding via a jejunostomy, were established when risk was identified.

2.3.1.3 Psychological support

The overall aim of the psychological support component of the programme was to contain anxiety, facilitate adaptation to their current psychological health and disease state and improve self-efficacy. Psychometric screening was completed immediately prior to the first CNS consultation to assess anxiety, depression, social support, self-efficacy and relevant background information (such as past trauma, major life events, mental health history). The aims the consultation were threefold: i) to explore and address any anxieties or concerns the patient may have regarding their diagnosis, symptoms and/or treatment plan; ii) to outline the rationale for prehabilitation and identify any potential barriers or facilitators to adherence; iii) to facilitate positive behaviour change.

Motivational interviewing techniques were used to engage patients, establish their motivation for change and increase their sense of confidence and control (120). This was accompanied by a timeline of agreed goals with personalised written and visual information. When clinically indicated, patients were referred to a specialist clinical psychologist for support.

2.3.2 Measurement of adherence

There is no standardised method for measuring adherence in exercise studies (121). In prehabilitation studies, it is typically assessed by attendance at exercise sessions (18,34). However, this measurement does not account for the intensity of the exercise that is completed and duration of each session. A measurement of adherence that include duration, intensity and frequency of exercise provides a more accurate representation of the adherence

to the overall prescribed exercise volume (121). Therefore, a method for measuring adherence based upon the overall amount of exercise was created.

Firstly, the volume of exercise undertaken each week by a patient was calculated. Patients self-reported the frequency, duration and intensity with which they completed each exercise every week using exercise diaries (**Appendix I**). Patients recorded the intensity of exercising using RPE scores, which equate to the percentage of METSmax at which they were exercised (117). Metabolic equivalents, or METS, are a ratio of the body's working metabolic rate relative to its resting metabolic rate. One MET represents the oxygen consumption of an adult at rest (~3.5 ml kg^{-1} min^{-1}). The number of METS a patient can achieve on exercise indicates how much a patient can increase their oxygen consumption, and thus indicate their level of cardiopulmonary fitness. METSmax represents the maximal METS that a patient can achieve.

Each patient's METSmax was calculated using submaximal exercising testing (further details are given in **Chapter 3.3.2**). Therefore, using the METSmax and the percentage METSmax achieved in each exercise episode, the estimated achieved intensity in METS was calculated for each exercise episode. The weekly exercise duration, intensity and frequency for each activity were multiplied to quantify the volume of physical activity (PA) in MET minutes $week^{-1}$. The scores for each activity were added together to give a weekly total volume of PA completed.

Weekly adherence was then calculated as a percentage of actual/prescribed MET minutes $week^{-1}$.

2.3.3 Study population

All patients who completed the PREPARE for Surgery programme between January 2016 and March 2019 were included in this study. All patients referred to the oesophago-gastric multi-disciplinary team, aged ≥ 18 years and with a diagnosis of potentially resectable oesophageal cancer were invited to participate in the PREPARE for Surgery programme. Exclusion criteria

included inability to give informed consent, non-resectable disease and patients who declined surgery.

A control group of patients who underwent resection at the same centre but had not undertaken prehabilitation was identified. This group comprised of patients who received treatment in 2015 (before the introduction of the programme), alongside patients from 2016 to 2018 who underwent resection at the same centre as the prehabilitation cohort but either started their treatment at a different centre so did not participate in the prehabilitation programme or were not included in the programme for administrative reasons. Ethical approval for analysis of patient data was granted by the UK Health Research Authority (268837) and the study protocol registered with Imperial College London (19SM5445).

2.3.4 Study outcomes

The primary study outcome was 60-day post-operative complications. Other outcomes included 60-day pulmonary complications, severe complications (Clavien Dindo grade 3 and higher), length of stay and 30-day readmission rate. The 60-day end-point for complications was chosen to ensure that any complications that resulted in readmission within 30 days of discharge would be included in the overall complication figure. Complications were defined according to the Esophagectomy Complication Consensus Group (ECCG) guidelines (**Appendix II**) (122) .

The unit has an Enhanced Recovery Programme (ERP) since 2014 and the same protocol was used for both cases and controls (**Figure 2.3**). Compliance with each element of the ERP was measured to assess whether there were any differences in post-operative care and early recovery between the two groups.

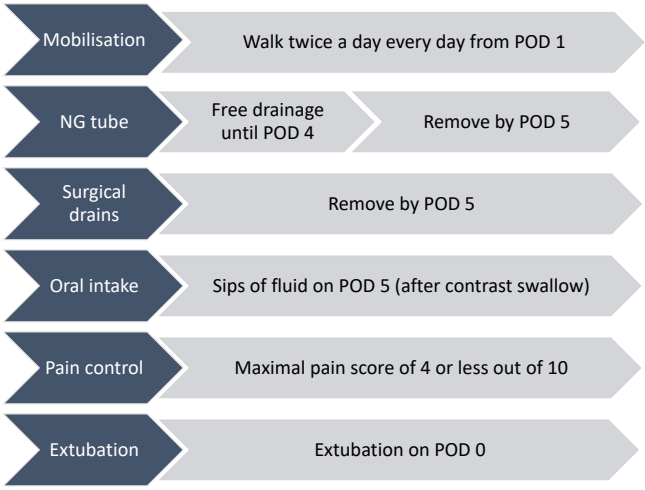


Figure 2.3 Enhanced recovery protocol following oesophagectomy
NG = nasogastric; POD = post-operative day

2.3.5 Statistical analysis

To reduce the effects of potential confounding factors on the comparison between the two groups, a propensity score matched analysis was performed (123,124). A propensity score was created using a multivariate logistical regression model, with the following potential confounding factors as covariates: age, ASA grade, pre-operative cancer staging, use of neoadjuvant chemotherapy and Charlson Comorbidity Index (CCI). Using the propensity score, patients in the prehabilitation group were matched 1:1 to those in the control group.

Outcomes were compared between cases and controls using chi-squared tests for categorical outcomes. For continuous outcomes, either Mann Whitney or unpaired T tests were used, depending on distribution. Multivariate analysis of factors associated with complications was performed using binary logistic regression. Two-tailed tests were used throughout with a significance level of $p<0.05$. Statistical analysis was performed using SPSS version 25 (IBM, New York, USA).

2.4 Results

72 patients who completed the programme between January 2016 and March 2019 and underwent surgery were included in this study (**Figure 2.4**). 39 control patients who underwent surgery but did not complete prehabilitation were identified (**Figure 2.4**). Prior to propensity score matching, there were no statistically significant differences in age, ASA grade, clinical stage, CCI, the use of chemotherapy, operative approach, pre-operative weight or pre-operative body mass index between the two groups (**Table 2.1**). After propensity score matching, 38 matched pairs were generated.

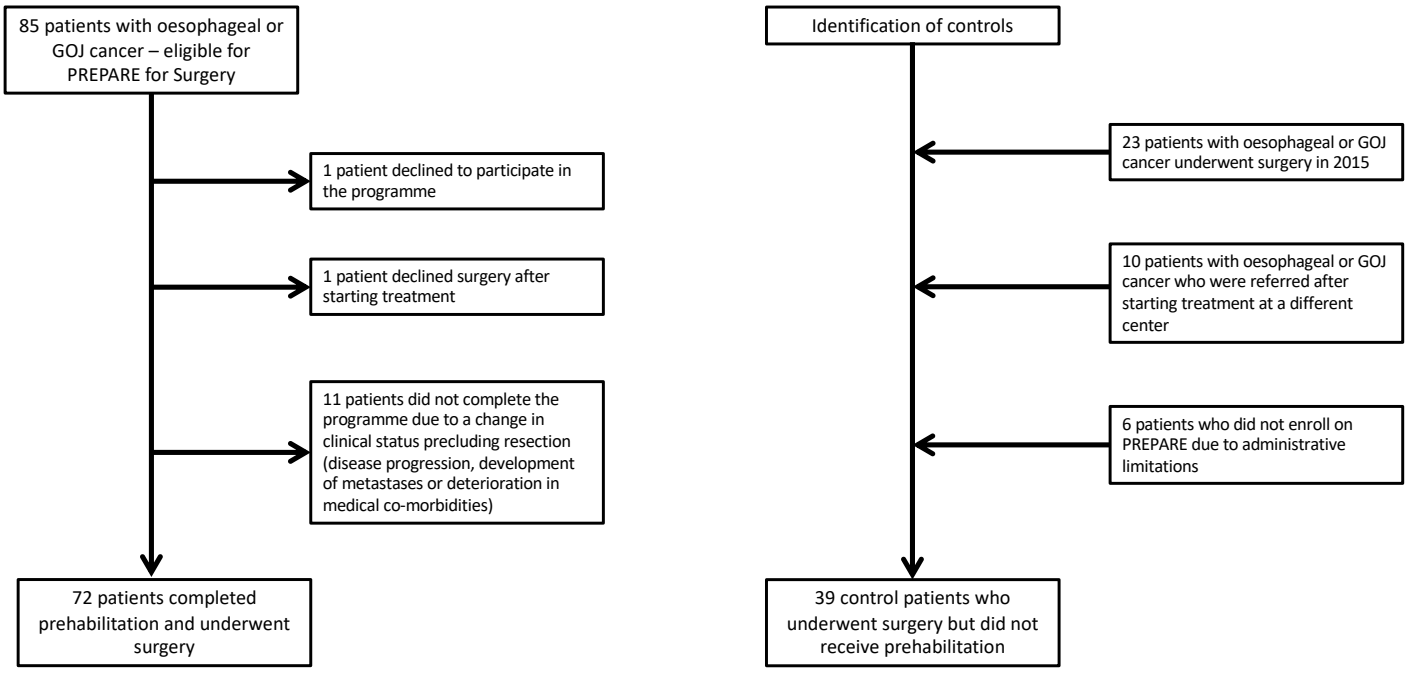


Figure 2.4 Study participant flow chart

	Unmatched groups			Matched groups		
	Prehabilitation	**Controls**	**p value**	**Prehabilitation**	**Controls**	**p value**
N	72	39		38	38	
Age, years [1]	68 (61-73)	67 (62-74)	0.973	69 (60-73)	68 (61-74)	0.979
ASA n (%)			0.557			0.574
1	0	0		0	0	
2	59 (82%)	30 (77%)		31 (82%)	29 (76%)	
3	12 (17%)	9 (23%)		7 (18%)	9 (24%)	
4	1 (1%)	0		0	0	
Stage n (%)			0.736			0.842
1	7 (10%)	4 (10%)		2 (5%)	4 (10%)	
2	8 (11%)	4 (10%)		5 (13%)	4 (10%)	
3	44 (61%)	21 (54%)		21 (55%)	21 (55%)	
4	13 (18%)	10 (26%)		10 (27%)	9 (27%)	
CCI [1]	5 (4-5)	5 (4-5)	0.872	5 (2-8)	5 (4-5)	0.944
NAC n (%)	63 (88%)	21 (87%)	0.961	33 (87%)	33 (87%)	>0.999
Pre-operative weight, kg	80.7 (18.6)	77.7 (13.9)	0.340	81.9 (18.9)	77.0 (12.6)	0.217
Pre-operative BMI, kg/m²	27.4 (5.8)	26.1 (3.7)	0.154	27.5 (5.6)	25.9 (3.7)	0.172
Comorbidities						
Cardiac	18 (25%)	5 (13%)	0.131	10 (26%)	5 (13%)	0.150
Respiratory	19 (26%)	2 (5%)	0.006	11 (29%)	2 (5%)	0.006
Neurological	5 (7%)	1 (3%)	0.330	1 (3%)	1 (3%)	>0.999
Endocrine	11 (15%)	6 (15%)	0.988	4 (11%)	6 (16%)	0.497
Psychiatric	8 (11%)	5 (13%)	0.789	2 (5%)	5 (13%)	0.234
Procedure			0.152			0.280
3-stage	12 (17%)	11 (28%)		7 (18%)	11 (29%)	
2-stage	60 (83%)	28 (72%)		31 (82%)	27 (71%)	
Operative approach – abdominal stage [2]			0.450			0.692
Laparotomy	66 (92%)	34 (87%)		34 (89%)	35 (92%)	
Laparoscopy	6 (8%)	5 (13%)		4 (11%)	3 (8%)	

Table 2.1 Demographic factors before and after application of propensity score matching
Continuous data presented as mean ± SD unless otherwise stated. *CCI = Charlson Comorbidity Index; NAC = neoadjuvant chemotherapy; ASA = American Society of Anesthesiologist physical status classification; BMI = body mass index.* [1] *Non-parametric data, displayed as median (interquartile range);* [2] *In all cases the thoracic component was performed as an open procedure*

There was a higher incidence of respiratory comorbidities in the prehabilitation group in comparison to the controls, but there was no difference in the incidence of cardiac, endocrine, neurological or psychological comorbidities (**Table 2.1**).

In the prehabilitation group, no patients asked to withdraw from the programme once they had enrolled. The mean amount of physical activity completed each week was 848 MET minutes week^{-1} (SD 659) during neoadjuvant chemotherapy, and 1198 MET minutes week^{-1} (SD 1225) after chemotherapy was completed. The mean adherence to the personalised exercise prescriptions was 55% (SD 29.8) during chemotherapy and 66% (SD 35.9) after it was completed.

25 patients (35%) in the prehabilitation group received oral nutritional supplementation and 6 patients (8%) had supplemental feeding via a jejunostomy or nasogastric tube before surgery. In the control group, 10 patients (26%) had oral nutritional supplementation and 2 patients (5%) had supplemental feeding via a jejunostomy or nasogastric tube. There was no significant difference between the two groups in the use of these supplemental feeding interventions (p=0.326 and p=0.533 respectively).

5 patients (7%) in the PREPARE group were referred to a specialist clinical psychologist for management of depression or anxiety. No patients within the control group were referred to clinical psychology.

2.4.1 Post-operative outcomes

The overall incidence of complications was lower in the prehabilitation group compared to controls, but this difference was not statistically significant (**Table 2.2**; unmatched analysis 68% vs 79%, p=0.089; matched analysis 63% vs 82%, p=0.073).

In both the unmatched and the matched analyses, there was a significant reduction in the incidence of 60-day pulmonary complications and post-operative pneumonia in the prehabilitation patients in comparison to controls (**Table 2.2**; unmatched analysis overall

pulmonary complications 36% vs 67% p=0.002 and post-operative pneumonia 33% vs 64% p=0.002; matched analysis overall pulmonary complications 32% vs 68% p=0.001 and post-operative pneumonia 26% vs 66% p=0.001).

There was a shorter length of stay in the prehabilitation group in comparison to controls (10 days vs 13 days in both the unmatched and matched analyses, p=0.019 and p=0.018 respectively). In the unmatched comparison, the rate of severe complications (Clavien Dindo grade 3 or higher) was lower in the prehabilitation group, but this difference lost significance in the matched comparison (**Table 2.2**; unmatched analysis 24% vs 46%, p=0.015; matched analysis 32% vs 47%, p=0.159).

On multivariate regression analysis of the whole cohort, participation in prehabilitation was associated with a 77% lower risk of developing of post-operative pneumonia (**Table 2.3**; OR 0.23 95% CI 0.09 to 0.55 p=0.001). There was no significant effect of age, the use of neo-adjuvant treatment, pre-operative stage, CCI or ASA grade.

There was a non-significant trend for a higher 30-day readmission rate in the prehabilitation patients (**Table 2.2**). In the overall prehabilitation cohort, 13 patients were readmitted within 30 days (18%). The reasons for readmission included: pneumonia (n=2); recurrent pleural effusions (n=2); pneumothorax (n=1); wound infection (n=2); inadequate pain control (n=2); cardiac arrythmia (n=1); diarrhoea (n=1); intra-abdominal collection (n=1); and a new diagnosis of metastatic disease (n=1). The median length of stay for the readmissions was 6 days (IQR 3 to 13 days).

2.4.2 Compliance with enhanced recovery protocols

There was a higher rate of compliance with the post-operative target for removal of nasogastric (NG) tubes in the prehabilitation patients (**Table 2.2**). In the unmatched analysis, there was also a significantly higher compliance with the removal of surgical drains in the prehabilitation patients, but this lost significance once propensity score matching was

performed. Compliance with all other ERP elements was comparable between the two groups.

	Unmatched groups			**Matched groups**		
	PREPARE	**Controls**	**p value**	**PREPARE**	**Controls**	**p value**
Any complication n (%)	46 (68%)	31 (79%)	0.089	24 (63%)	31 (82%)	0.073
Pulmonary complication n (%)	26 (36%)	26 (67%)	0.002	12 (32%)	26 (68%)	0.001
Post-operative pneumonia n (%)	24 (33%)	25 (64%)	0.002	10 (26%)	25 (66%)	0.001
Severe complications n (%) [1]	17 (24%)	18 (46%)	0.015	12 (32%)	18 (47%)	0.159
Length of stay, days [2]	10 (8-17)	13 (11-20)	0.019	10 (8-17)	13 (11-20)	0.018
30-day readmission n (%)	13 (18%)	3 (8%)	0.138	9 (24%)	3 (8%)	0.059
Enhanced recovery protocol compliance n (%)						
Mobilisation	24 (33%)	14 (36%)	0.679	11 (29%)	13 (34%)	0.449
NGT removal	40 (56%)	13 (33%)	0.053	23 (61%)	13 (34%)	0.046
Drain removal	34 (47%)	11 (28%)	0.048	16 (42%)	11 (29%)	0.179
Oral intake	28 (39%)	12 (31%)	0.442	15 (39%)	12 (32%)	0.583
Fluid balance	3 (4%)	4 (10%)	0.203	1 (3%)	4 (11%)	0.144
Pain control	41 (57%)	23 (59%)	0.656	21 (55%)	23 (61%)	0.362
Day 0 extubation	51 (71%)	28 (72%)	0.905	27 (71%)	27 (71%)	>0.999

Table 2.2 Comparison of study outcomes in unmatched and propensity score matched analysis.
NGT = nasogastric tube. [1] Severe complications were defined as Clavien Dindo grade 3 or higher; [2] Non-parametric data, displayed as median (interquartile range)

Variable	Odds ratio (95% CI)	SE	p value
Age	1.04 (0.97 to 1.12)	0.04	0.280
ASA grade	1.19 (0.39 to 3.66)	0.57	0.761
Clinical stage (II) [1]	3.39 (0.37 to 31.28)	1.13	0.281
Clinical stage (III) [1]	0.72 (0.12 to 4.00)	0.88	0.707
Clinical stage (IV) [1]	1.94 (0.60 to 6.31)	0.60	0.271
CCI	0.92 (0.49 to 1.73)	0.32	0.806
NAC	1.34 (0.22 to 8.02)	0.91	0.751
Prehabilitation	0.23 (0.09 to 0.55)	0.46	0.001

Table 2.3 Factors associated with development of post-operative pneumonia
CCI = Charlson Comorbidity Index; NAC = neoadjuvant chemotherapy; ASA = American Society of Anesthesiologist physical status classification. [1] Compared against clinical stage I

2.5 Discussion

This study has found a significantly lower incidence of post-operative pneumonia and a shorter length of stay in patients who had undergone the PREPARE for Surgery programme in comparison to controls. A trend for a lower overall incidence of complications in the prehabilitation cohort was also seen, although this did not reach statistical significance.

To date, this is the first study to show improved post-operative outcomes in oesophageal cancer patients who have undergone prehabilitation. Three previously published randomised controlled trials have examined the impact of prehabilitation on post-operative outcomes, and none found a significant difference between prehabilitation patients and control (36-38).

There are several reasons that may explain why these studies did not find the differences in complications that have been observed in this study. Firstly, the incidence of post-operative pneumonia was particularly high in this patient population. Reported rates of complications after an oesophagectomy often exceed 60% (11,125) and respiratory complications are particularly commonplace, with previous studies reporting post-operative pneumonia rates of between 16% and 50% (8,126-128). Within this study, all patients underwent an open thoracotomy and approximately 90% of patients underwent an open laparotomy for the

abdominal stage (**Table 2.1**). This approach is used with the aim of maximising oncological outcomes but is known to be associated with a greater incidence of post-operative pneumonia (129). The high incidence of post-operative pneumonia was a driving factor behind the adoption of prehabilitation.

A non-significant trend for a lower rate of pulmonary complications was noted in one study: 59% in prehabilitation patients had pulmonary complications compared with 78% of controls (p=0.079) (38). 11% of patients in this study had gastric cancer and underwent a total gastrectomy, which does not require a thoracotomy. It is possible that the different nature of the operation and the different risk of complications in surgery for oesophageal and gastric cancer may have attenuated the effect of prehabilitation on complications in their analysis.

The sample size in the three previously published studies was smaller than that in the study presented here, and thus the failure to detect a significant difference in post-operative complications in those papers may reflect a type 2 error. The finding of an association between prehabilitation and a reduction in post-operative complications is not without precedent. Two meta-analyses into prehabilitation in patients undergoing intra-abdominal operations have reported 37% and 41% reduction in the risk of post-operative complications (20,33). The impact of prehabilitation on respiratory complications is particularly notable, with a 60% lower risk in comparison to controls (20). In this study, prehabilitation was associated with a 77% reduction in the risk of developing pneumonia following oesophagectomy.

Differences in the prehabilitation programme itself and the way it is delivered may also account for the different magnitude of impact on complications. Whilst there is a growing consensus that prehabilitation programmes should be multimodal (24,25), within the published literature there is a large amount of heterogeneity in the time, type, frequency and intensity of exercise programmes, the way the programmes are delivered, and the number of different domains that are included alongside exercise (18,21,130).

This study found a shorter length of stay in patients who received prehabilitation. Clinicians decide when to discharge patients and therefore they directly influence this outcome.

Although this is a retrospective study and data was not being collected at the time of the clinical decision making, the clinicians making decisions regarding discharge where not blinded to whether prehabilitation had been undertaken. If they believe that prehabilitation patients have a better recovery and therefore can be discharged sooner, this may lead to bias for this outcome. However, the finding of a significantly lower rate of post-operative complications is in keeping with a decreased length of stay. The lower length of stay may be reflective of fewer early complications and a better post-operative recovery.

Exercise during chemotherapy is challenging (131). Adherence to the personalised exercise prescriptions was lower whilst patients were undergoing neoadjuvant chemotherapy in comparison to once it was completed (55% and 66% respectively). The exercises were personalised and adapted over the course of each patient's programme dependent on their progress and clinical condition. This dynamic approach was adopted with the aim of maximising participation. Whilst the adherence percentages show that most patients did not fully complete their exercises as prescribed, it is notable that no patients asked to withdraw from the programme and the average amount of physical activity completed in MET minutes $week^{-1}$ exceeded the WHO recommendations both during and after chemotherapy (113).

PREPARE for Surgery is a multimodal prehabilitation programme, and thus included nutritional and psychological interventions in addition to exercise. There was no significant difference in the use of supplemental feeding interventions between the two groups. However, the regular touch-point reviews with a dietitian may have led to other unmeasured improvements in nutritional intake, such as improved oral calorie and micronutrient intake within the patients' diet, or improved compliance with oral supplementation.

Within the programme, psychological support was provided by the CNS and from clinical psychologists when clinically indicated. Addressing nutrition, psychological wellbeing and behaviour change alongside a personalised exercise programme may maximise the benefits that can be accrued from exercise in the limited time available before surgery. These interventions could have a synergistic effect; for example, optimising nutrition and psychological wellbeing may improve both participation and output from exercise programmes.

There a non-significant trend for a higher pre-operative weight in the prehabilitation cohort in comparison to controls. As this measurement is taken at the end of prehabilitation in the prehabilitation group, it is possible that this may reflect less pre-operative weight loss due to prehabilitation. Further research is needed to test this hypothesis and the effects of prehabilitation on body composition will be explored in **Chapter 4**.

Compliance with six out of the seven ERP elements in the matched analysis were comparable between the two groups, suggesting that there were not substantial differences in post-operative care to account for the lower rate of pneumonia and shorter hospital stay. However, in the prehabilitation group there was a higher rate of compliance with the target to remove NG tubes by day 5 after surgery (**Figure 2.2** and **Table 2.2**).

As the majority of controls patients were from a historical cohort, this could reflect a small change in practice around NG tube removal. Compliance with six out of the seven ERP elements in the matched analysis were comparable between the two groups, suggesting that there were not substantial differences in post-operative care to account for the lower rate of pneumonia and shorter hospital stay. In colorectal surgery, the use of a post-operative NG tube is thought to increase the risk of post-operative pneumonia by causing dysfunction of the gastro-oesophageal junction (132). Given this, higher compliance with the NG tube target, meaning that fewer patients in the prehabilitation group had NG tubes still in situ after day 5, could itself reduce the risk of developing a post-operative pneumonia. However, the applicability of that theory to this study population, who do not have a functioning gastro-oesophageal junction following surgery, is not known.

The relationship between ERP compliance and complications is complex; complications may result from poor compliance but complications themselves will also cause deviation from the protocol and lower compliance (133). For example, better compliance with the target for NG tube removal in the PREPARE group may occur because of the lower incidence of post-operative pneumonia. In clinical practice, an elevation in inflammatory markers will raise concerns about an anastomotic leak. Therefore, a rise in inflammatory markers from pneumonia may delay NG tube removal until an anastomotic leak has been excluded by other

investigations, and this could contribute the lower compliance with the target for NG tube removal in the control group.

Early post-operative mobilisation is encouraged to improve respiratory function, and it could be postulated that undertaking pre-operative exercise may positively impact on the patient's post-operative physical activity levels. Poor pain control can also lead to poor post-operative pulmonary function and reduced clearance of secretions, particularly in upper abdominal surgery, where pain limits deep breathing and cough. Both of these factors could therefore impact upon the risk of developing post-operative pneumonia. However, there was no significant difference in compliance with either the pain control or early post-operative mobilisation ERP targets.

The readmission rate in the prehabilitation patients was 18% in the unmatched comparison and 21% in the matched analysis. These figures are higher than recent benchmarking outcome data, which reported an 11% readmission rate (11). In the whole prehabilitation cohort, nine of the 13 readmissions were due to post-operative complications and four were due to symptom control or disease progression. These complications were included in the comparison of 60-day complications between the two study groups.

Although it is beyond scope of this thesis, the finding of a high rate of readmissions within the prehabilitation cohort is important and warrants further investigation elsewhere. The readmission rate in the prehabilitation cohort may be due to the shorter length of stay. Although the overall rate of pulmonary complications was lower in the PREPARE group, the incidence of post-operative complications after an oesophagectomy is still high (11,127). The prehabilitation cohort had a shorter length of stay and therefore complications that may otherwise have been managed during the index admission may have occurred in the community setting. Four of the readmissions were due to symptom control, which could suggest the patients were discharged before they had recovered sufficiently well to manage at home.

For prehabilitation to be a viable clinical intervention, the economic impact needs to be assessed, and whilst a reduction in post-operative pneumonia rates and shorter length of stay

may lead to significant economic benefits, this could be negated if the rate of readmission is subsequently higher. The psychological impact of re-admission on patients should be considered.

Ambulatory care for symptom control and low-grade complications, such wound infections, could be employed to prevent or limit readmission, which itself may serve to further delay post-operative functional recovery. The ethos of prehabilitation could be extended to recovery at home after surgery, with structured exercise and psychological interventions to facilitate supported self-management after surgery. Identifying ways to reduce readmission and provide more support following discharge should be examined in future research.

2.5.1 Study limitations

There are several limitations to this study. Firstly, it is an observational study and the intervention was not randomised between the two arms of this study. To reduce the impact of confounding factors between the two groups, a propensity score matched analysis was performed. Although this reduced the size of the study population, the significant differences in the incidence of pneumonia and length of stay remained. The number of cases and controls included in this study limited the number of variables that could be added to the propensity score. The number of controls was limited by the availability of data. It was not possible to add cases from before 2015 as a new ERP was implemented at this point and therefore significant differences occurred in other aspects of peri-operative care independent to the use of prehabilitation. The results of this study provide evidence to support a large-scale, multi-centre randomised controlled trial of prehabilitation in this patient population.

Measurements of baseline fitness and physical activity were not recorded for the control patients so this could not be added to the propensity score. Whilst there was no difference in comorbidities between the two groups (with the exception of a higher incidence of respiratory comorbidities in the prehabilitation group), cardio-respiratory fitness and lung function of the two groups could not be compared, and these factors could have impacted on

post-operative pneumonia. Lung function tests were performed only when indicated and cardio-pulmonary exercise testing was not routinely performed. Sub-maximal exercise testing was performed only in the prehabilitation group and thus was not available for the controls. Psychometric variables, such as anxiety or motivation, which may influence post-operative recovery were also not recorded for the control patients. However, there was no significant difference in known psychiatric co-morbidities between the two groups (**Table 2.1**).

2.5.2 Future studies

Given the finding of a trend for higher 30 day readmission in the prehabilitation group, further research is needed to understand the reasons for this. As well as quantitative research, this should include qualitative research with patients, carers and healthcare professionals to better the patient's post-operative recovery and to identify ways to support and manage patients in the community after surgery. It is also important to understand how decreased complications affects long term recovery from surgery, including psychological well-being and return to pre-diagnosis activities of daily living and social functioning.

The economic impact of prehabilitation should be studied. This study has shown reduced complications and a shorter length of stay, which may have significant economic advantages for the healthcare service. However, if the burden of care is being pushed to community providers, there economic benefit may not be significant. It is important to understand the patient's journey after discharge, including use of primary care and out of hours or emergency healthcare services. This will give a broader understanding of the economic impact of prehabilitation but also determine if there are other unintended consequences for the healthcare service in managing these patients. Other stakeholders who may wish to contribute to the design and delivery of prehabilitation programmes may also be identified by this process.

2.6 Conclusions

Patients undergoing an oesophagectomy have a high incidence of respiratory complications. Using a propensity score matched analysis, this study has found a lower rate of post-operative pneumonia and shorter length of stay in oesophageal cancer patients who have undergone home-based, multimodal prehabilitation.

CHAPTER 3

-

CARDIORESPIRATORY FITNESS AND ADHERENCE TO PRE-OPERATIVE EXERCISE

Work within this Chapter has already been published within a peer-reviewed journal:

Halliday LJ, Doganay E, Wynter-Blyth V, Osborn H, Buckley J, Moorthy K. Adherence to pre-operative exercise and the response to prehabilitation in oesophageal cancer patients. *Journal of Gastrointestinal Surgery.* 2020. Available from: DOI:10.1007/s11605-020-04561-2

3.1 Objectives and hypothesis

Objectives:

I. To characterise the changes that occur in cardiorespiratory fitness during prehabilitation in oesophageal cancer patients
II. To examine the relationship between adherence to pre-operative exercise, changes in cardiorespiratory fitness and the occurrence of post-operative pneumonia

Hypothesis: Prehabilitation improves cardiorespiratory fitness in the pre-operative period. Patients with higher adherence to their exercise programme will have greater improvements in fitness and a lower incidence of post-operative pneumonia.

3.2 Introduction

The current evidence base shows particularly strong evidence of a reduction in pulmonary complications after prehabilitation in patients undergoing intra-abdominal surgery (20). In keeping with this, the study in **Chapter 2** found that whilst there was a non-significant trend for a lower rate of overall complications in oesophageal cancer patients who underwent prehabilitation, there was a significant 77% reduction in the risk of post-operative pneumonia. Post-operative pneumonia is a well acknowledged complication after oesophagectomy and is reported in up to 50% of patients (125,127,128). There are multiple reasons for the particularly high rate of post-operative pulmonary complications following an oesophagectomy; intra-operative one lung ventilation, post-operative diaphragm dysfunction and upper abdominal pain limiting coughing and clearing of secretions.

Cardiorespiratory fitness is a risk factor for the development of post-operative pneumonia (49). Many oesophageal cancer patients are frail, with multiple comorbidities, poor cardiorespiratory fitness and poor physiological reserve (6,8,48). Patients frequently undergo neoadjuvant chemotherapy or chemoradiotherapy, which are associated with a further decrease in fitness (9,134). Improvements in cardiorespiratory fitness in response to pre-operative exercise represents a possible mechanism behind the effect of prehabilitation on the incidence of post-operative pneumonia. A study of prehabilitation in patients with oesophago-gastric cancer found a significant difference in the change in VO_2max after neoadjuvant therapy between prehabilitation and controls, with a larger fall in the control group (38).

As discussed in **Chapter 1**, other studies have demonstrated that pre-operative exercise can improve cardiorespiratory fitness prior to surgery, although when the pre-operative change in fitness compared with controls, the difference has not always statistically significant (18,26). A meta-analysis of studies into prehabilitation in patients undergoing resection of any gastrointestinal cancer found a significant improvement in 6 minute walk test (6MWT) compared with controls (27). This review included a study in oesophago-gastric cancer patients, which found a significant difference in the change in pre-operative 6MWT in

prehabilitation patients compared with controls (36). However, the 6MWT is a measure of functional walking capacity, rather than solely cardiorespiratory fitness, and whilst fitness will have a strong impact on the 6MWT result, other factors such as muscle strength, balance and co-ordination may also affect the result.

Failure to complete exercise as prescribed may limit the impact of the intervention. The real-world performance of prehabilitation is important when assessing its effectiveness and within this, patient adherence may have a significant impact of the effectiveness of prehabilitation. For example, widespread poor adherence may limit the effectiveness of the programme in improving outcomes at a population level, even if the intervention has the potential to cause a substantial improvement in outcomes when fully adhered to.

There is no standardised method for measuring adherence to exercise (121,135,136). Both in prehabilitation and the broader field of exercise medicine, it is typically assessed by attendance at exercise sessions (18,34). Using this measurement, the average adherence to supervised prehabilitation programmes is 98% but this falls to 70% in home-based prehabilitation programmes (34). This is comparable to the adherence seen in home-based exercise across broad range of interventions in a variety of clinical populations (137).

However, assessing adherence purely by attendance does not account for exercise volume. Incorporating duration and intensity of the exercise, along with the frequency, provides a more comprehensive measurement of exercise adherence. Even if a patient is exercising at the recommended frequency (and therefore would have 100% attendance), if they are not exercising at the correct intensity and/or duration, the amount of exercise they are undertaking will be substantially less than intended.

In trying to understand the underlying mechanisms behind how pre-operative exercise affects outcomes, the level of adherence may obscure the mechanisms. Poor adherence may reduce the magnitude of change that is seen in physiological parameters, such as cardiorespiratory fitness, and thereby mask the underlying relationships between the intervention and these measures. The changes in the physiological parameters should be considered alongside adherence. In this context, it is particularly important that the measurement of adherence

that is used is truly reflective of what the patient has done and how well they adhered to the intervention. Measurements of adherence that are derived solely from attendance do not provide adequate information for this purpose.

This study will examine the changes in cardiorespiratory fitness during prehabilitation in oesophageal cancer patients and how these are related to the incidence of post-operative pneumonia. Furthermore, using a comprehensive measurement of adherence to account for exercise volume, the effect of adherence on fitness and post-operative pneumonia will be explored.

3.3 Methods

3.3.1 Study population

Details of the PREPARE for Surgery programme have previously been described (**Chapter 2.3.1**). All patients who completed the programme and underwent surgery from January 2016 to December 2018 were included in this longitudinal study. Ethical approval for retrospective analysis of patient data was granted by the UK Health Research Authority (ref: 268837).

3.3.2 Measurement of cardiorespiratory fitness

Sub-maximal exercise testing using the Chester Step Test (CST) was used to measure pVO_2max and O_2 pulse (44,117). Sub-maximal exercise testing has been used in previous clinical studies and is appropriate for prescription of home-based exercises (44-46,117). The CST is validated method to estimate aerobic power and maximal oxygen uptake (pVO_2max) (44,138).

The full CST protocol is shown in **Appendix III**. The test was performed by a trained exercise therapist. Using the Inbar formula (205.8 – (0.685 x age)), the patient's maximum heart rate was calculated. If the patient was taking beta-blockers, 30 beats per minute were deducted

from the maximum heart rate calculated from the Inbar formula. The patient's resting heart rate was recorded prior to the test. The heart rate reserve (HRR) was then calculated (maximum heart rate – resting heart rate).

During the test, patients walked up and down a step at a predefined frequency using a metronome. Three different step heights were used dependent on the patient's abilities. Every two minutes, the speed of the metronome was increased. The test finished when the patient felt unable to continue, was unable to maintain the metronome speed or reached over 70% of HRR.

The final step height and step rate that was achieved during the CST was used to calculate the level of exercise intensity in METS that was achieved during the test (**Appendix III**). METS are the ratio of energy expenditure to the baseline metabolic ratio. One MET represents the resting baseline metabolic rate, whilst a METS value of 4 means the body is using four-times the energy expenditure that it does at rest.

The maximum heart rate the patient achieved during the final stage of the protocol was also recorded and this was used to calculate the percentage of HRR (%HRR) that was achieved during the CST. The achieved METS was divided by the %HRR to calculate the patients predicted METSmax (117). As one MET represents 3.5 ml kg^{-1} min^{-1} of oxygen consumption, the METSmax was multiplied by 3.5 to give the pVO_2max (ml kg^{-1} min^{-1}).

O_2 pulse is an indirect representation of stroke volume and demonstrates the central cardiac contribution to overall oxygen uptake (139). It was calculated with the following formula

$$O2\ pulse\ (ml) = \frac{Achieved\ METS\ x\ 3.5}{Mean\ HR\ during\ exercise\ (bpm)\ x\ 100}$$

The CST was undertaken at three time points during prehabilitation

- PREPARE 1 (P1) = diagnosis (baseline)
- PREPARE 2 (P2) = completion of neoadjuvant chemotherapy (NAC). For patients who did not receive NAC this was their baseline measurement (four to six weeks prior to surgery)
- PREPARE 3 (P3) = one week prior to surgery

In respect of the known estimate errors of the CST and effects of test-retest familiarity (44,138,140), and based on studies examining the clinical effects of improving pVO_2max (141), an improvement in fitness was defined as an increase of 10% or more in pVO_2max.

3.3.3 Measurement of adherence

Patients self-reported the frequency, duration and intensity with which they completed each exercise every week using exercise diaries (see **Appendix I**). Patients were trained to record their exercise intensity using the Borg RPE scale (118). RPE scores are a validated measure of the percentage of maximum intensity and therefore the percentage of METSmax at which they exercised (115,117). Each patient's METSmax was calculated from the CST, and using the percentage of METSmax derived from the RPE, the estimated achieved intensity in METS was calculated for each exercise session. The weekly exercise duration, intensity and frequency for each activity were multiplied to quantify the volume of physical activity (PA) in MET minutes $week^{-1}$ (**Figure 3.1**). Weekly adherence was calculated as a percentage of MET minutes $week^{-1}$ completed divided by the prescribed MET minutes $week^{-1}$.

As previously discussed, there is no standardised method for defining acceptable levels of adherence in exercise studies. Therefore, high adherence was pragmatically defined as an average weekly adherence of 75% or greater.

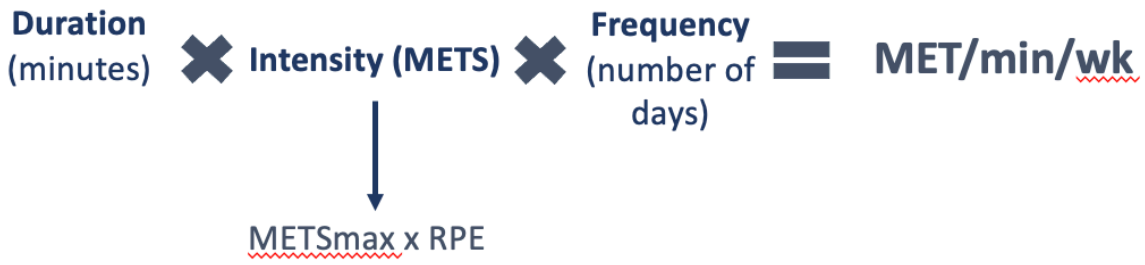


Figure 3.1 Weekly adherence calculation
METS = metabolic equivalent; RPE = rating of perceived exertion.

3.3.4 Definition of pneumonia

The diagnosis of post-operative pneumonia was defined according to the Esophagectomy Complication Consensus Group (ECCG) guidelines (**Appendix II**) (122) .

3.3.5 Statistical analysis

Changes in pVO_2max and O_2 pulse during prehabilitation were assessed using a repeated measures one-way analysis of variance (ANOVA) for patients who underwent NAC and had three measurements, and a paired T test for those who did not have NAC and therefore had two measurements. If significant difference was determined with the ANOVA, post-hoc paired T-tests with a Bonferroni correction were used to determine where the paired differences occurred.

Intra and inter-person coefficient of variances were calculated to assess the variability of self-reported exercise adherence, Binary logistic regression was used to determine the factors associated with achieving ≥10% improvement in pVO_2max and those associated with post-operative pneumonia. Chi squared tests were used to establish the effects of ≥10% improvement in pVO_2max and ≥75% adherence on the occurrence of post-operative pneumonia. Student's T tests were used to compare baseline fitness in patients with ≥75% adherence to the rest of the cohort, and to compare baseline fitness between patients who

did and did achieve ≥10% improvement in pVO_2max. To assess the relationship between baseline fitness and average weekly PA, a Pearson correlation test was used.

Two-tailed tests were used throughout with a significance level of $p<0.05$. Statistical analysis was performed using SPSS version 25 (IBM, New York, USA).

3.4 Results

Between January 2016 and December 2018, 79 patients with oesophageal or gastro-oesophageal junctional adenocarcinoma entered the PREPARE for Surgery programme. 10 patients did not complete the programme due to a change in clinical status precluding resection (disease progression, development of metastases or deterioration in medical co-morbidities). One patient declined to participate in the programme and one patient declined surgery after starting treatment. The remaining 67 patients who completed the programme and underwent surgery were included in this study. Characteristics for these patients are shown in **Table 3.1**. Of the 67 patients, 60 underwent NAC and had three pre-operative assessments of fitness (P1, P2 and P3). The remaining seven patients did not receive NAC and therefore had two pre-operative assessments (P2 and P3).

11 patients had a three stage oesophagectomy and 56 had a two-stage procedure. Both the abdominal and thoracic components were performed as open procedures in 62 patients (93%); five patients had a laparoscopic abdominal phase followed by an open thoracotomy.

The overall mean PA was 989 MET minutes $week^{-1}$ (SD 805); between P1 and P2 this was 848 MET minutes $week^{-1}$ (SD 667), and this rose to 1228 MET minutes $week^{-1}$ (SD 1236) between P2 and P3. Coefficient of variance for self-reported adherence within individual patients was 49% (intra-person variability) and between patients was 38% (inter-person variability).

	Study participants (n=67)
Age, years	**66 (9.7)**
ASA grade n (%)	
ASA1	0
ASA 2	57 (85%)
ASA 3	10 (15%)
ASA 4	0
Charlson Comorbidity Index [1]	5 (2 – 8)
Pre-operative T stage n (%)	
T1	5 (8%)
T2	11 (16%)
T3	44 (66%)
T4	7 (10%)
Pre-operative N stage n (%)	
N0	23 (34%)
N1	33 (50%)
N2	8 (12%)
N3	3 (4%)
NAC n (%)	60 (90%)
Baseline weight, kg	79.7 (19.4)
Baseline pVO_2max, ml kg^{-1} min^{-1}	23.8 (6.4)
Adherence	
Overall	64% (30.1)
P1-2	56% (30.1)
P2-P3 NAC patients	65% (36.3)
P2-3 non NAC patients	85% (22.5)
Post-operative pneumonia n (%)	22 (33%)
Overall complications n (%)	44 (66%)
Length of stay [1]	10 (8-16)

Table 3.1 Study participant characteristics
Continuous data presented as mean ± SD unless otherwise stated.[1] *Non-parametric data, displayed as median (interquartile range)*

3.4.1 Changes in fitness during prehabilitation

In patients who received NAC, both pVO_2max and O_2 pulse changed significantly during prehabilitation (**Figures 3.2a** and **3.3a** respectively). pVO_2max and O_2 pulse were preserved between P1 and P2, followed by a significant increase between P2 and P3: Δ $pV0_2max$ = +2.6 ml min^{-1} kg^{-1} (95% CI 1.2 - 4.0); ΔO_2 pulse = +1.4 ml $beat^{-1}$ (95% CI 0.5 - 2.3).

In the whole cohort (including those who did not undergo NAC), both $pV0_2max$ and O_2 pulse increased significantly between P2 and P3 (**Figures 3.2b** and **3.3b** respectively): Δ $pV0_2max$ = +3.0 ml min^{-1} kg^{-1} (95% CI = 2.0 - 4.0); ΔO_2 pulse = +1.6 ml $beat^{-1}$ (95% CI = 0.9 - 2.2).

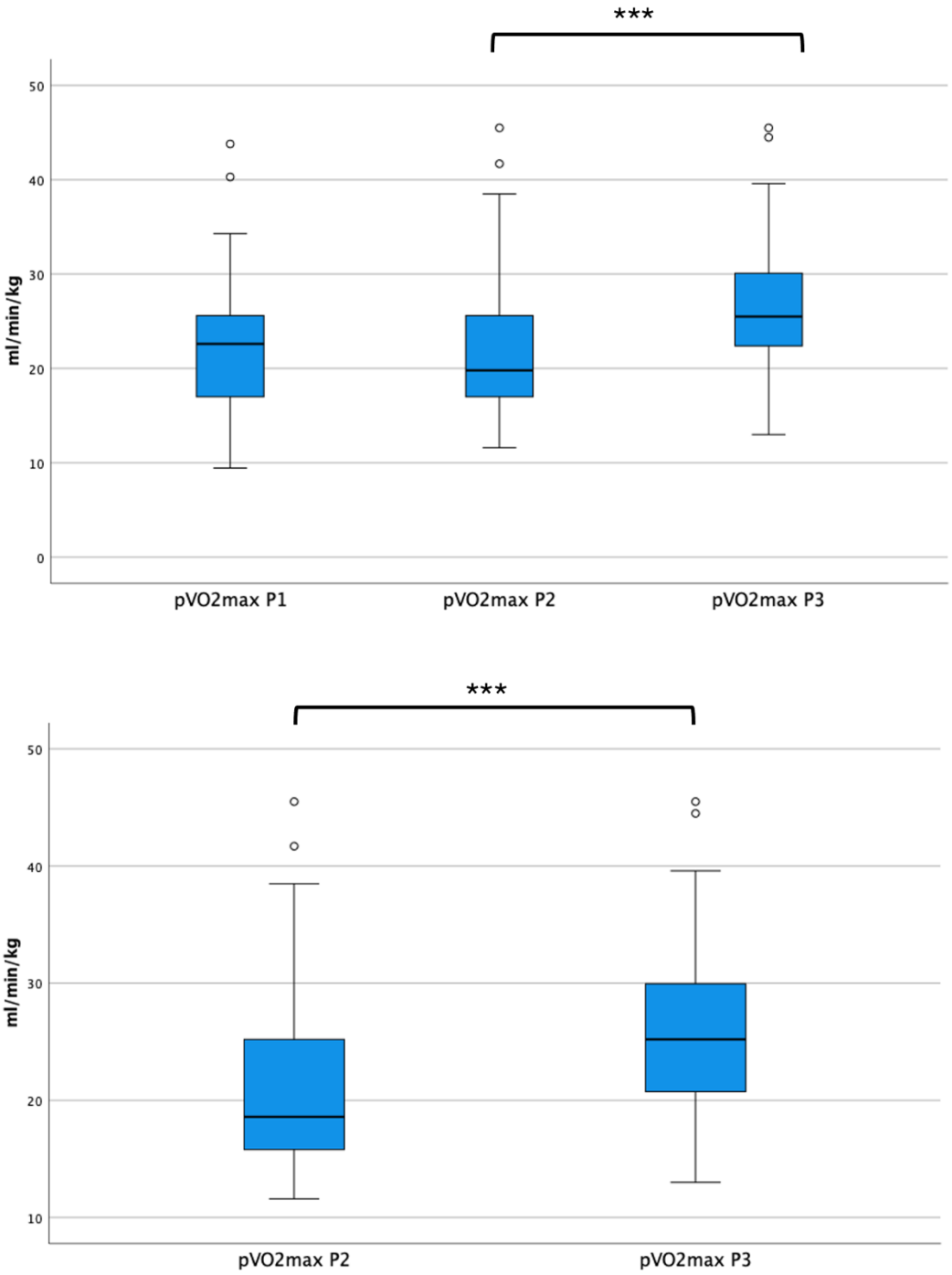
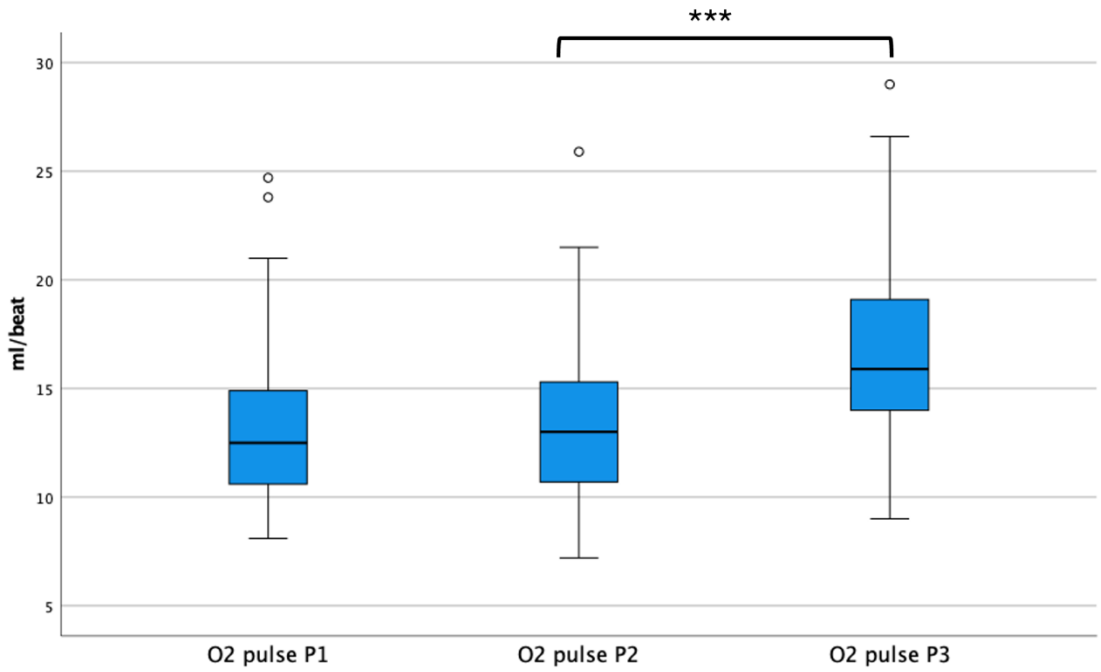


Figure 3.2 pVO_2max during prehabilitation (a) patients receiving neoadjuvant therapy (b) whole cohort

(A)



(B)

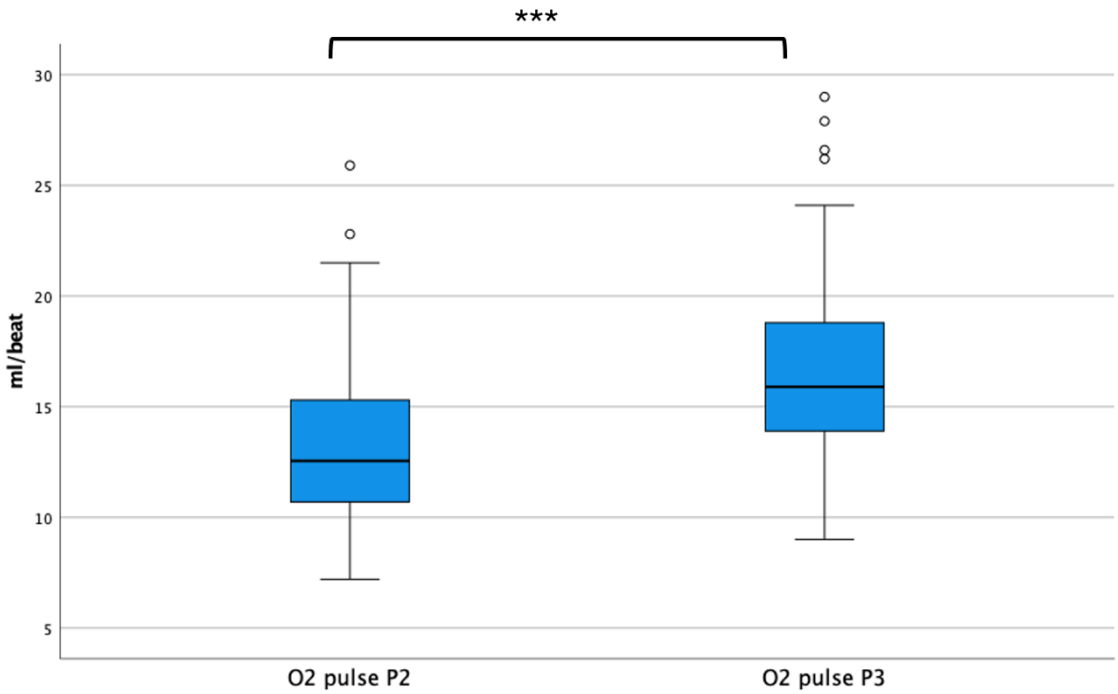


Figure 3.3 pVO_2max during prehabilitation (a) patients receiving neoadjuvant therapy (b) whole cohort

3.4.2 Factors predictive of improvement in cardiorespiratory fitness

21% of patients increased their pVO_2max by 10% or more between P1 and P2. There was no significant relationship between ≥10% increase in fitness between P1 and P2 and age, pre-operative stage, baseline fitness, adherence or average weekly PA completed between P1 and P2 ($p>0.05$).

52% of patients increased their pVO_2max by 10% or more between P2 and P3. Adherence with prescribed exercise was significantly associated with the chance of increasing pVO_2max ≥10% between P2 and P3 (**Table 3.4**; $p=0.048$). There was no significant effect of age, the use of NAC, pre-operative stage, baseline fitness or average weekly PA completed between P2 and P3.

Variable	Odds ratio (95% CI)	B	SE	p value
NAC	0.16 (0.00 to 2.28)	-4.14	2.54	0.999
Age	0.98 (0.88 to 1.09)	-0.18	0.56	0.752
Charlson comorbidity index	1.63 (0.67 to 4.02)	0.49	0.46	0.286
Clinical stage (II) [1]	0.15 (0.00 to 40.96)	-1.89	27.7	0.999
Clinical stage (II) [1]	0.10 (0.01 to 1.37)	-2.34	1.36	0.840
Clinical stage (IV) [1]	0.49 (0.84 to 2.82)	-0.72	0.90	0.423
Baseline pVO2max (ml min^{-1} kg^{-1})	0.99 (0.88 to 1.10)	-0.15	0.59	0.795
Total adherence (%)	49.38 (1.04 to 2356.0)	3.90	1.97	**0.048**
Average PA (MET min wk^{-1})	0.99 (0.99 to 1.00)	-0.002	0.001	0.126

Table 3.2 Factors associated with improvement in pVO_2max between P2 and P3.
[1] *Compared against clinical stage I*

3.4.3 Factors predictive of post-operative pneumonia

Baseline characteristics, adherence, PA and changes in fitness for patients who developed post-operative pneumonia are shown in **Table 3.5**. Average weekly PA over the whole programme was significantly associated with the risk of post-operative pneumonia (**Table 3.6**;

p=0.035). There was no significant effect of age, the use of NAC, pre-operative stage, baseline fitness or adherence to prescribed exercise.

Characteristics	**Patients who developed pneumonia n=22 (33%)**	**Patients who did not develop pneumonia n=45 (67%)**	**p-value**
Age, years	68.4 (10.0)	65.3 (9.4)	0.214
Pre-operative T stage n (%)			0.725
T1	2 (9%)	3 (7%)	
T2	3 (14%)	9 (20%)	
T3	15 (68%)	28 (62%)	
T4	2 (9%)	5 (11%)	
Pre-operative N stage n (%)			0.494
N0	5 (22%)	18 (40%)	
N1	13 (59%)	19 (43%)	
N2	3 (14%)	6 (13%)	
N3	1 (5%)	2 (4%)	
NAC n (%)	19 (86%)	41 (91%)	0.551
Baseline pVO_2max	23.9 (5.4)	23.7 (6.8)	0.911
Change in pVO_2max			
P1-2	-9.9 (16.7)	3.3 (27.6)	0.068
P2-P3	18.1 (22.8)	14.1 (17.8)	0.459
Adherence			
Overall	62% (26.3)	65% (32.0)	0.807
P1-2	55% (34.0)	57% (22.2)	0.790
P2-P3	67% (36.7)	69% (32.6)	0.813
Weekly PA, MET min wk^{-1}			
Overall	785 (528)	1084 (895)	0.184
P1-2	653 (349)	960 (779)	0.157
P2-P3	954 (699)	1332 (1381)	0.334
Laparoscopic abdominal phase n (%)	2 (9%)	3 (7%)	0.723

Table 3.3 Characteristics of patients who did and did not develop post-operative pneumonia
Continuous data presented as mean ± SD

Variable	Odds ratio (95% CI)	B	SE	p value
NAC	0.21 (0.01 to 28.32)	-1.57	2.51	0.531
Age	1.03 (0.92 to 1.15)	0.31	0.57	0.588
Charlson comorbidity index	1.35 (0.62 to 2.91)	0.30	0.39	0.449
Clinical stage (II) [1]	3.11 (0.13 to 734.1)	1.14	2.79	0.684
Clinical stage (II) [1]	0.20 (0.13 to 3.28)	-1.59	1.42	0.262
Clinical stage (IV) [1]	0.87 (0.14 to 5.33)	-1.42	0.93	0.878
Baseline pVO2max (ml min^{-1} kg^{-1})	1.11 (0.99 to 1.25)	0.10	0.61	0.083
Total adherence (%)	24.23 (0.82 to 715.6)	3.19	1.73	0.065
Average PA (MET min wk^{-1})	0.99 (0.95 to 0.99)	-0.02	0.01	**0.035**

Table 3.4 Factors associated with development of post-operative pneumonia
[1] *Compared against clinical stage I*

Patients with ≥75% adherence had a lower incidence of post-operative pneumonia, although this difference did not reach statistical significance (22% vs 39%, p=0.192; **Figure 3.2a**). Patients who increased pVO_2max between P1 and P2 had a lower incidence of post-operative pneumonia than patients who either maintained or had a fall in pVO_2max (9% vs 41%, p=0.045; **Figure 3.2b**). There was no significant difference in the incidence of pneumonia between patients who increased their pVO_2max between P2 and P3 and those who did not (32% vs 34%, p=0.855).

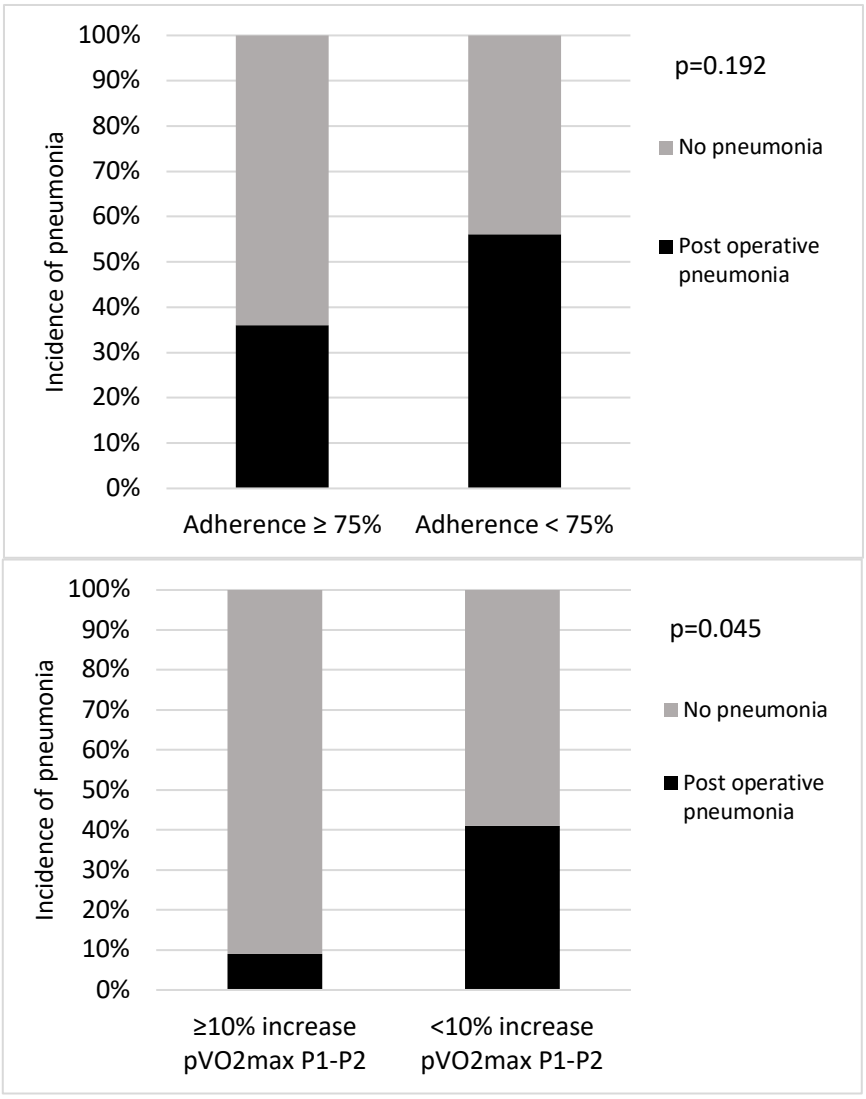


Figure 3.4 Incidence of post-operative pneumonia in patients subdivided by (a) ≥75% adherence and (b) those with ≥10% increase pVO_2max during chemotherapy

3.4.4 The relationships between baseline fitness and adherence, fitness and pneumonia

Patients who had ≥75% adherence had a higher baseline pVO_2max than those with less than 75% adherence (26.1 vs 22.3, p=0.028; **Figure 3.3a**). There was also a moderate correlation between baseline pVO_2max and average weekly PA completed throughout the programme, with higher levels of PA in patients with a higher baseline fitness (r=0.340, p=0.008).

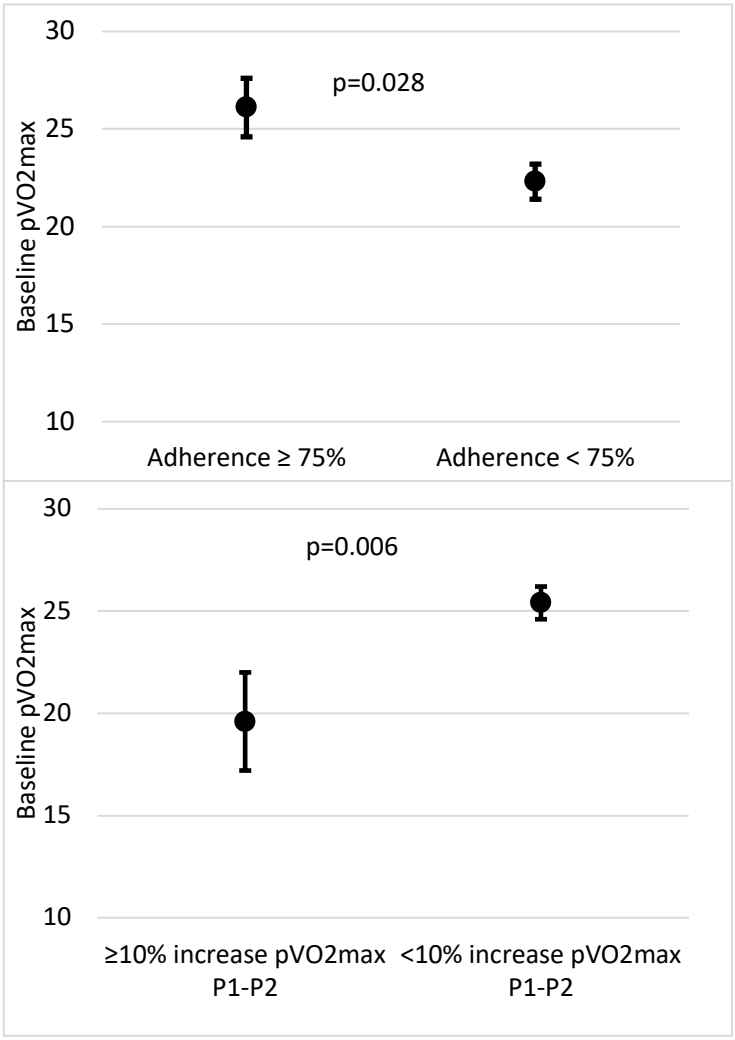


Figure 3.5 Baseline fitness in patients who had (a) ≥75% adherence and (b) those with ≥10% increase pVO_2max during chemotherapy.
Results displayed as mean ±SE

Patients who increased their $pV0_2max$ between P1 and P2 had a lower baseline fitness than those who either maintained or had a fall in pVO_2max during this time (19.6 vs 25.4, p=0.006; **Figure 3.3b**). Baseline pVO_2max was comparable between patients who did and did not increase their fitness between P2 and P3 (23.5 vs 24.4, p=0.620). There was no significant difference in baseline pVO_2max between patients who did and did not develop a post-operative pneumonia (23.9 vs 23.7, p=0.903).

3.5 Discussion

This three-year retrospective analysis of patients with oesophageal cancer has demonstrated that with prehabilitation cardiorespiratory fitness can be maintained during NAC, followed by an increase in fitness prior to surgery. Whilst a recovery in fitness following NAC could be anticipated, without prehabilitation the patient is recovering after a substantial fall in fitness from their baseline (10,134). This fall in fitness was not seen in patients in this study, suggesting that prehabilitation may counteract the effects of chemotherapy and then go on to facilitate an increase in fitness from baseline levels prior to surgery.

Allen *et al.* published an RCT in into prehabilitation in patients with oesophageal or gastric cancer. This found a smaller decrease in VO_2max after NAC in patients who received prehabilitation compared with controls (mean change -0.4 ml min^{-1} kg^{-1} in prehabilitation patients and -2.5 ml min^{-1} kg^{-1} in controls, p=0.022) (38). This in keeping with the changes in pVO_2max seen during NAC in the study presented in this chapter and adds further evidence to support the hypothesis that prehabilitation can prevent or limit a NAC-induced decline in fitness.

The prehabilitation patients included in the study presented in this chapter had a mean increase in pVO_2max of 2.6 ml min^{-1} kg^{-}after NAC. In the whole cohort, thus including those who did not receive NAC and joined the programme at the P2 assessment point, a mean increase in pVO_2max of 2.9 ml min^{-1} kg^{-1} was observed. This is comparable to changes seen after prehabilitation in a study of liver cancer patients (142). Change in pVO_2max of this magnitude are associated with clinical benefit in other patient populations, such as significant decreases in systolic blood pressure (143) and a lower risk of admission to hospital and lower all-cause mortality in patients with heart failure (141).

In the trial by Allen *et al*., despite the differences in VO_2max between prehabilitation patients and controls after NAC, there was no significant difference in VO_2max by the time of surgery (38). They found that the anaerobic threshold significantly increased from the end of NAC to time of surgery, but this was seen in both groups and there was no significant difference in

anaerobic threshold between the two groups at any time point. Therefore, changes in cardiorespiratory fitness alone may not solely explain the difference in post-op complications observed in **Chapter 2** and other mechanisms that could underlie the relationship should be explored.

The impact of adherence should also be considered. Decreasing adherence to prehabilitation over time could explain why the difference in VO_2max did not persist by time of surgery in the Allen *et al.* study. Average adherence in that study was 76% for supervised sessions and 65% for home-based sessions (38) but this was not broken down over time so this possible explanation cannot be further explored. In the study presented in this chapter, there was no evidence of waning adherence over time; for patients who received NAC, the observed compliance in the second section of the programme once NAC has been completed was slightly higher than during NAC (56% adherence before NAC and 65% after NAC).

For home-based programmes, adherence is commonly self-reported with a diary card or journal (18,136), as was used in this study. However, as previously discussed, most exercise studies use frequency of exercise to report adherence (18,34,144). Using this methodology, the average adherence to other published home-based prehabilitation patients is 70% (34). This is broadly comparable to the average adherence of 64% seen in this study. However, in this study, patients recorded the duration and frequency of which they performed each exercise, as well as the frequency. This method gives a more detailed reflection of how well the patient is complying with overall exercise programme, not just whether they are doing any exercise. Therefore, direct comparison of adherence rates is limited by the difference in the reporting of adherence.

The adherence percentage reflects whether patients completed the exercise as prescribed. These programmes are personalised and reviewed each week by an exercise therapist, with incremental increases as patients reach their targets. This study found that adherence to the prescriptions was significantly associated with improvement in cardiorespiratory fitness after NAC; as adherence increased, the chance of increasing pVO_2max by ≥10% after NAC increased. This association shows that adherence to the personalised prescriptions was

associated with improvements in fitness and supports the method of personalised exercise prescribing as a way to improve fitness.

Oesophageal cancer surgery has a high post-operative morbidity; the overall incidence of complications often exceeds 70% and post-operative pneumonia rates of up to 50% are reported (11,127,128,134). 66% of patients in this study experienced post-operative complications, with a particular high incidence of post-operative pneumonia. The amount of PA completed was significantly associated with the risk of pneumonia, with the incidence reducing as the volume of PA in MET min wk^{-1} increases.

The adherence percentage does not reflect the dose of exercise, as the amount of PA prescribed varies from patient-to-patient. Weekly PA in MET minutes $week^{-1}$ is a more objective and quantifiable measure of exercise dose, and it was this parameter that was associated with the occurrence of pneumonia, rather than adherence. Therefore, whilst personalised prescriptions may be a good way to improve cardiorespiratory fitness, the findings suggest that it is the actual volume of physical activity that is important to reduce the risk of post-operative pneumonia. Patients should be encouraged to be as active as possible, with review and escalation of exercise programmes to increase physical activity as much as possible throughout prehabilitation.

NAC had a negative impact on adherence and PA, with an average adherence of 56%. Following NAC, average adherence increased to 65% but remained lower than the 85% seen in patients who did not receive NAC. Whilst adherence was challenging for patients during NAC, the average amount of PA achieved exceeded the WHO recommendations of 600 MET minutes $week^{-1}$ (113). In the four to six-week period before surgery, the average weekly PA level increased by over 40% to more than twice the WHO target. However, these findings highlight the need for further research to better understand and evaluate ways to support and encourage behaviour change, especially during NAC.

The negative impact of chemotherapy on fitness is well documented (9,10,134). Overall the study population maintained their fitness during NAC. However, 21% of patients increased their pVO2max by 10% or more during NAC. These patients were less fit at baseline than

those who either saw no change or a fall in fitness over this period. Patients with a low baseline fitness may be more likely to be sedentary and have a greater capacity to incorporate PA in order to improve their fitness. Those who were already undertook high levels of PA may find it difficult to incorporate additional exercise, especially during NAC. However, patients who were able to improve their pVO2max by 10% or more during NAC had a lower rate of pneumonia than those who did not have this increase in fitness during NAC, despite their lower baseline fitness, highlighting the benefits of increasing fitness during this time and preventing a decline in fitness due to NAC.

Patients with a higher baseline fitness completed more physical activity and had higher adherence to exercise during prehabilitation. Therefore, it is possible that patients with higher baseline fitness may require less supervision and support to reach their exercise and fitness goals. This raises the possibility of a stratified approach to prehabilitation; as well as a personalised exercise prescription, the level of supervision could be tailored to the patient. In centralised services, such as oesophago-gastric cancer, this could have logistical and financial benefits for both the patient and the healthcare provider by minimising disruption for patients who can undertake prehabilitation independently and generating a more efficient use of resources to support those patients who need more supervision to achieve their exercise goals. Further research is needed to establish which patients benefit most and thus identify potential screening criteria for a stratified approach to the delivery of prehabilitation programmes.

3.5.1 Study limitations

There are a number of limitations to this study. It is an observational study of patients undergoing surgery in a single centre and therefore the results may not be comparable in other settings. Delivery of prehabilitation programme is complex, and the successful implementation of changes to the perioperative pathway can be challenging (145). Prehabilitation programmes need to integrate many different specialities from across the multi-disciplinary team. Future research must address the optimum way to roll out and

deliver prehabilitation across different surgical settings. Stakeholder engagement is important for both the development and implementation of prehabilitation protocols. Many barriers to implementation of prehabilitation will be specific to each individual centre and therefore a system of 'facilitated evolution' should be examined to translate and adjust solutions to the local setting (145,146).

Adherence in this study is based upon self-reported exercise behaviour. This therefore raises the risk of measurement bias. There was a high inter-patient and intra-patient variability of reported exercise levels, demonstrating that patients were reporting different amounts of PA each week, and this suggests that they were actively engaged in the process of self-reporting. However, it a subjective measurement and the accuracy of these reports cannot be verified.

Furthermore, the intensity of exercise was self-reported using RPE. Patients are trained on how to use the scale to self-assess and quantify the intensity of their exercise. During this training, the patient's heart rate is recorded whilst they exercise, and they are taught to understand and recognise how each heart rate zone feels and which RPE levels this corresponds to. However, the use of RPE to grade intensity during the programme may be subject to self-reported measurement bias and therefore may overestimate or underestimate the intensity that was reported. The use of RPE to grade exercise intensity has been not previously studied in this particular population. However, previous studies in both healthy adults and patients with chronic disease, self-assessed RPE ratings have been shown to accurately correspond to true exercise intensity (115,117,118).

3.5.2 Future studies

The use of heart rate monitors and activity trackers during exercise may provide a more accurate way to both assess intensity and measure the amount of exercise completed during prehabilitation. Activity monitors are increasingly being used in cancer patients to assess the impact of behaviour change interventions (147). Furthermore, the monitor itself can act as a positive behaviour change intervention; the provision of regular feedback from such a device

and actively monitoring adherence have been shown to have a positive impact upon adherence and exercise behaviour (135,137).

However, the use of activity monitors is not without possible limitations. The uptake and retention for activity monitors needs to be examined. The amount of time that a device needs to be worn to validate the recordings needs to be considered, and at present, there is no consensus on this within studies of such devices (147). A vast array of different activity monitors is available, and evaluation of the different models is needed to determine their suitability for this population. For example, the reliability of heart rate measurements in common conditions such as atrial fibrillation must be considered. Consideration should also be given to equity of access to prehabilitation, as the introduction of technology may deter some patients from participating in the programme. It is recognised that whilst prehabilitation may offer benefits for cancer patients, it also has potential to exacerbate inequalities in cancer care if equity of access to the programmes is not carefully addressed (148). Therefore, whilst the use of heart rate monitors and activity trackers offer great potential to improve the accuracy of recording exercise volume and exercise intensity, their use needs to be carefully examined and investigated before they are integrated within prehabilitation programmes. Although this is beyond the scope of this study, it is an important priority for future research in this field.

3.6 Conclusions

The time available to improve a patient's fitness prior to surgery is tightly limited and therefore it is important to use this time efficiently. This study has shown that sustained levels of PA can be achieved during NAC and that cardiorespiratory fitness can be preserved during this time, despite the negative impact that chemotherapy is otherwise seen to have on fitness. Increasing amounts of PA completed during prehabilitation was associated with a lower risk of post-operative pneumonia. Exercise goals should not be seen as a fixed concept during prehabilitation; instead, a personalised approach should encourage patients to continually escalate and maximise their PA to achieve the maximum benefit in the pre-

operative period. Patients with a higher baseline fitness completed more PA and had higher adherence. Patients with a higher baseline fitness completed more PA and had higher adherence. Further research is needed to establish which patients benefit most and thus identify potential screening criteria for a stratified approach to the delivery of prehabilitation programmes.

CHAPTER 4

-

PREHABILITATION AND CHANGES IN BODY COMPOSITION DURING NEOADJUVANT THERAPY FOR OESOPHAGEAL CANCER

Work within this Chapter has already been published within a peer-reviewed journal:

Halliday LJ, Boshier PR, Doganay E, Wynter-Blyth V, Buckley JP, Moorthy K. The effects of prehabilitation on body composition in patients undergoing multimodal therapy for oesophageal cancer. Diseases of the Esophagus 2023 DOI:10.1093/doac046

4.1 Objectives and hypothesis

Objectives:

I. To examine whether prehabilitation impacts upon changes in body composition during neoadjuvant therapy for oesophageal cancer

II. To establish how changes in body composition during prehabilitation are related to the amount of exercise completed and subsequent post-operative outcomes

Hypothesis: Prehabilitation is associated with improvements in muscle mass and loss of adipose tissue. Patients who complete more exercise during prehabilitation gain more muscle and lose more adipose tissue, and these changes in body composition are associated with a lower incidence of post-operative complications.

4.2 Introduction

Cachexia and sarcopenia are a common feature of oesophageal cancer (57), characterised by dysregulated energy metabolism and wasting of skeletal muscle. Predisposing factors include the burden of the tumour itself and the physiological effects of chemoradiotherapy (55,56), compounded by anorexia and mechanical obstruction of the oesophagus. Previous studies have identified sarcopenia as a negative prognostic indicator in patients with oesophageal cancer, predicative of chemotherapy toxicity, post-operative complications and worse overall survival (4,56-59).

Oesophageal cancer patients are notable for their high incidence of sarcopenia (57). This is compounded by the frequent administration of neoadjuvant chemotherapy or chemoradiotherapy, which is itself is associated with a fall in muscle mass (55,149). Pre-operative exercise may therefore have a particularly beneficial effects on muscle mass in this high-risk group of patients. Prehabilitation has been shown to reduce skeletal muscle loss in patients with oesophageal cancer during neoadjuvant therapy and increase skeletal mass in rectal cancer patients undergoing neoadjuvant chemoradiotherapy (38,150). However, the effects of prehabilitation on other body composition parameters have not been studied to date.

This primary aim of this study was to assess the impact of prehabilitation on changes in body composition in patients undergoing multimodal treatment for oesophageal cancer. Secondary aims of the study include identifying factors that are associated with changes in body composition in prehabilitation patients and examining the relationship between changes in body composition and post-operative outcomes.

4.3 Methods

4.3.1 Study population

This was a single centre retrospective cohort study. All patients who underwent oesophagectomy for oesophageal or gastro-oesophageal junction (GOJ) cancer at Imperial College NHS Healthcare Trust after neoadjuvant therapy between January 2015 and December 2018 were eligible for inclusion in this study. Ethical approval for retrospective analysis of patient data was granted by the UK Health Research Authority (ref: 268837).

From January 2016 to December 2018 all patients were invited to participate in a structured prehabilitation programme. Details of the PREPARE for Surgery programme have previously been described (**Chapter 2.3.1**). Patients who completed this programme were included in the prehabilitation study group. Patients who did not complete or declined the programme were excluded from this study. The control group comprised of patients who received treatment in 2015 (prior the introduction of the programme) and patients from 2016 to 2018 who underwent resection at the same centre as the prehabilitation cohort but either started their treatment at a different centre so not participate in the programme or were not included in the prehabilitation programme due to administrative constraints during the initial introduction of the programme. Other than the provision of prehabilitation, the peri-operative care of all patients was comparable.

4.3.2 Assessment of body composition

Patient's body composition was assessed at diagnosis (before neoadjuvant therapy) and after completion of neoadjuvant therapy (before surgery). Assessment was performed using a single contrast enhanced CT image, taken at the midpoint of the third lumbar (L3) vertebral body. The CT scans used for analysis had already been performed for clinical purposes for the staging of the patient's cancer and were analysed retrospectively.

CT images were exported from the Picture Archiving and Communication System (PACS) and saved as an anonymized Digital Imaging and Communications in Medicine (DICOM) file. Anonymization of CT images was confirmed using the MIRC DICOM Editor (Version 35. MIRC; http://mirc.rsna.org). Segmentation of skeletal muscle (-29 to +150 HU), visceral adipose tissue (VAT) (-150 to -50 HU) and subcutaneous adipose tissue (SAT) (-190 to -30 HU) was performed using Slice-O-Matic (Version 5.0, Tomovision, Magog, Canada) using the ABACS-L3 module (Version 1.0, Voronoi Health Analytics, Canada) (**Figure 4.1**). Two trained assessors, who were blinded to patient identity, image sequence and study group, performed subsequent manual correction of segmented images.

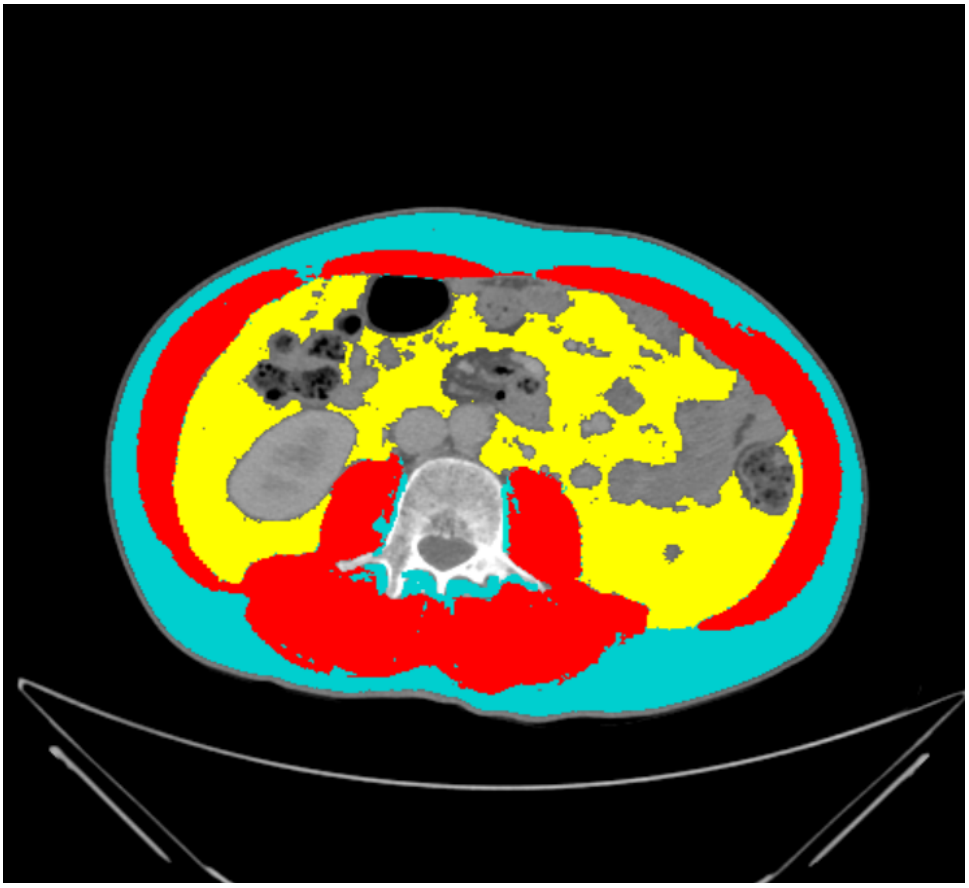


Figure 4.1 Assessment of body composition using a contrast enhanced CT image of L3 level
Skeletal muscle (-29 to +150 HU) shown in red, VAT (-150 to -50 HU) shown in yellow, and SAT (-190 to -30 HU) shown in blue

Skeletal muscle index (SMI) was calculated as the ratio of lumbar skeletal muscle area to height squared. Sarcopenia was defined using Prado's criteria for low muscle mass: SMI <52.4 cm^2/m^2 for men and <38.5 cm^2/m^2 for women (151). Visceral obesity was defined as a visceral fat area >163.8 cm^2 for men and >80.1 cm^2 for women (56).

4.3.3 Outcome measurements

The primary outcome measure of this study was change in parameters of body composition (weight, BMI, skeletal muscle, visceral adipose tissue, subcutaneous adipose tissue and total adipose tissue). Secondary outcome measures included hand-grip strength, adherence to pre-operative exercise, volume of physical activity completed during prehabilitation and 60-day post-operative complications. Complications were defined according to the Esophagectomy Complication Consensus Group (ECCG) guidelines (122).

Hand-grip strength was measured as a part of the prehabilitation programme to provide a validated assessment of muscle function (152). It was measured at the start of prehabilitation and again following completion of neoadjuvant therapy using a Takei digital hand grip dynamometer. Patients were asked to squeeze the dynamometer as tight as possible using their non-dominant hand and the highest of three repeated readings was recorded (153). As measurement of hand-grip strength was a part of the prehabilitation programme, and was otherwise not a routinely recorded clinical parameter, measurements are not available for the control group.

The methodology for the measurement of adherence to exercise and volume of physical activity for patients in the prehabilitation programme has previously been described (**Chapter 3.3.3**).

4.3.4 Statistical analysis

Statistical analysis was performed using SPSS version 26 (IBM, New York, USA). Normality of data was assessed visually and using the Kolmogorov-Smirnov (with Lilliefors correction) and the Shapiro-Wilk normality test. Dependant on their distribution, continuous variables are presented as either mean ± standard deviation or median [interquartile range, IQR]. Changes in continuous variables over time was assessed using a paired T test or Wilcoxon test respectively. Between group comparison of continuous variables was performed using the Independent-Samples T test or Mann-Whitney U test respectively. Categorical variables were compared using the chi-squared or Fisher's exact tests. Correlation between continuous variables was assessed using a Pearson's or Spearman's rank test, dependant on data distribution. Multiple regression analysis was used to determine the factors associated with change in body composition and binary logistic regression used to determine the factors associated with post-operative outcomes. Two-tailed tests were used throughout with a significance level of $p<0.05$.

4.4 Results

Between January 2016 and December 2018, 69 patients with oesophageal or GOJ cancer were invited to participate in the PREPARE programme prior to starting neoadjuvant therapy. Eighteen patients were excluded: declined to participate in the PREPARE programme (n=1); declined surgery (n=1); change in clinical status precluding resection (disease progression or medical co-morbidities) (n=8); and lack of availability of matched CT images pre- and post-neoadjuvant therapy (n=8). No patients dropped out of the prehabilitation programme. Consequently, 51 patients were included in prehabilitation group (figure 4.1). 39 control patients who underwent neoadjuvant therapy followed by surgery but did not complete prehabilitation were identified (**Figure 4.2**). Matched CT images were not available for 11 of these patients, and therefore 28 control patients were included in the analysis. Characteristics of study participants are presented in **Table 4.1**.

Within the prehabilitation group, 18 patients (35%) received oral nutritional supplementation during neoadjuvant therapy and four (8%) received supplemental feeding by either a nasogastric tube or jejunostomy. Seven patients in the control group received oral nutritional supplementation (25%) and one patient received jejunostomy feeding (4%). There was no significant difference in the use of nutritional interventions between the two groups (oral supplementation p=0.347, nasogastric or jejunostomy feeding p=0.456).

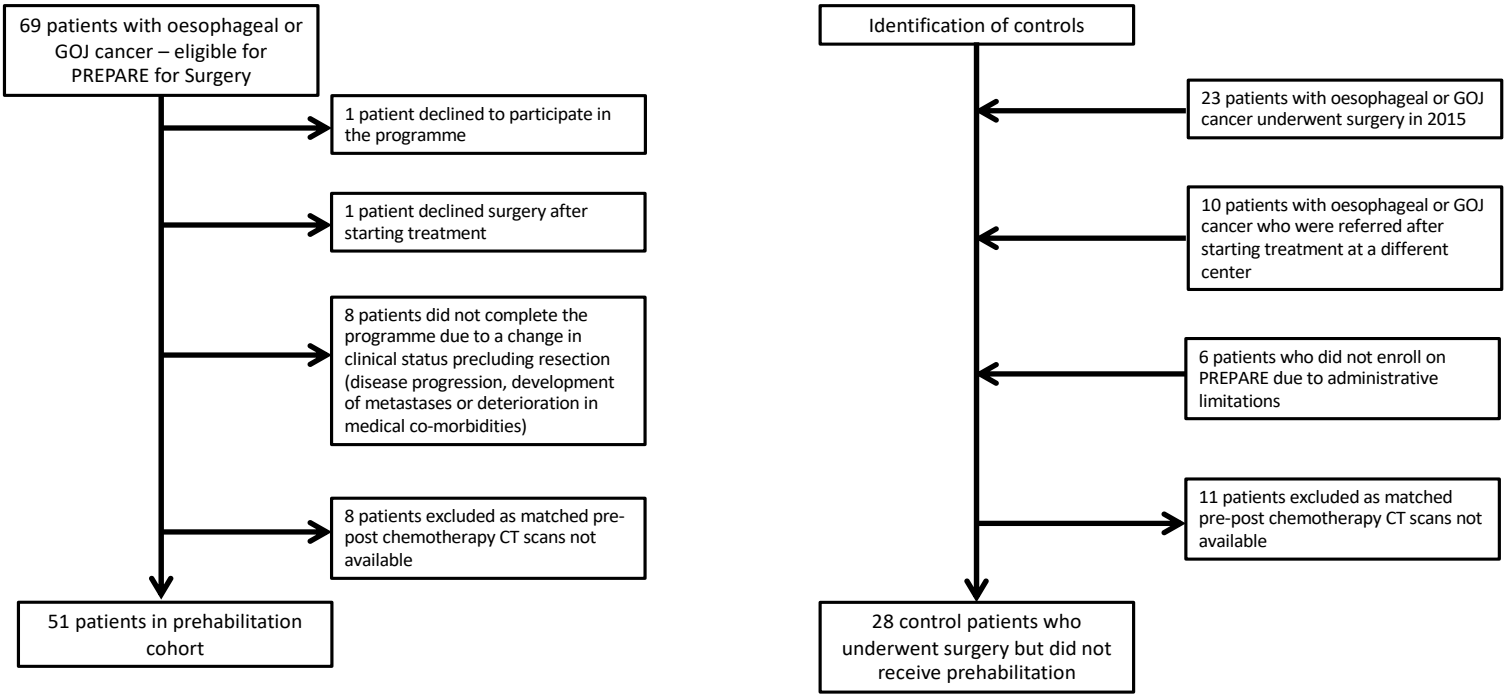


Figure 4.2 Study participant flow chart

4.4.1 Changes in body composition during neoadjuvant therapy

Baseline body composition characteristics are presented in **Table 4.1**. A significant decrease in weight, BMI, skeletal muscle (SM) area, skeletal muscle index (SMI), visceral adipose tissue (VAT) and total adipose tissue (TAT) was observed in both groups after neoadjuvant therapy (**Table 4.2**).

Comparing the change in body composition between the two groups, there was a significantly greater fall in SMI in the control group compared with the prehabilitation patients (**Table 4.2**; Δ SMI mean difference = -2.2 cm^2/m^2, 95% CI -4.3 to -0.1, p=0.038). There was also larger % decrease in SMI in the controls compared with the prehabilitation patients (Table 2; relative Δ SMI mean difference = -4.3%, 95% CI -8.5 to -0.2, p=0.05). There were no significant differences in changes in other body composition parameters between the two groups.

To adjust for the lower baseline SMI in the prehabilitation group, a propensity score was created using a multivariate logistical regression model, with SM area and SMI as co-variates. Using the propensity score, patients in the prehabilitation group were matched 1:1 to those in the control group, with a match tolerance of 0.05. This generated 28 patients in each group (**Table 4.3**). Both the absolute and relative changes in SMI remained significantly different between the two groups, with a larger fall in the control group (**Table 4.4**).

	Prehabilitation patients (n=51)	Controls (n=28)	p value
Age, years	66 2 ± 9.9	63.5 ± 9.6	0.245
Gender, male n (%)	37 (73%)	22 (76%)	0.556
Tumour location n (%)			
Oesophagus	32 (63%)	17 (61%)	0.859
GOJ	19 (37%)	11 (39%)	
Histological subtype n (%)			
Adenocarcinoma	43 (84%)	21 (75%)	0.313
Squamous cell carcinoma	8 (16%)	7 (25%)	
Neoadjuvant therapy n (%)			
Chemotherapy	37 (73%)	21 (75%)	0.814
Chemoradiotherapy	14 (27%)	7 (25%)	
Clinical stage n (%)			
I	1 (2%)	1 (3%)	0.357
II	7 (14%)	3 (11%)	
II	35 (69%)	15 (54%)	
IV	8 (15%)	9 (32%)	
ASA grade n (%)			
II	44 (86%)	21 (75%)	0.209
III	7 (14%)	7 (25%)	
Charlson Comorbidity Index	4.7 ± 1.3	4.4 ± 1.2	0.351
Time interval between scans days	97.6 ± 26.0	119.0 ± 39.5	0.014
Oesophagectomy			
2-stage	35 (68%)	15 (54%)	0.314
3-stage	9 (18%)	9 (32%)	
Thoracoabdominal	7 (14%)	4 (14%)	
Surgical approach			
Open	48 (94%)	25 (89%)	0.438
Hybrid minimally invasive [1]	3 (6%)	3 (11%)	
Baseline body composition			
Weight (kg)	80.7 ± 19.8	79.5 ± 13.3	0.772
BMI (kg/m^2)	27.6 ± 6.8	26.6 ± 3.5	0.394
SM area (cm^2)	133.8 ± 32.0	149.3 ± 26.7	0.033
SMI (cm^2/m^2)	45.4 ± 8.9	49.9 ± 6.8	0.024
TAT area (cm^2)	398.4 ± 192.4	403.6 ± 154.4	0.902
VAT area (cm^2)	171.3 ± 90.3	176.0 ± 102.7	0.834
SAT area (cm^2) [2]	200.1 (151.3, 278.8)	211.1 (165.1, 296.4)	0.580
Sarcopenia, n (%)	34 (66%)	14 (50%)	0.147
Visceral obesity, n (%)	33 (65%)	15 (54%)	0.332

Table 4.1 Study participant characteristics

Continuous data presented as mean ± SD unless otherwise stated.

GOJ = gastro oesophageal junction; ASA = American Society of Anesthesiologist physical status classification; NA-therapy = neoadjuvant therapy; SM = skeletal muscle; SMI = skeletal muscle index; TAT = total adipose tissue; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue. [1] *Laparoscopic abdominal stage, open thoracic stage;* [2] *Non-parametric data, displayed as median (interquartile range)*

	Prehabilitation patients (n=51)	Controls (n=28)	Mean difference (95% CI)	p value
Δ Weight (kg)	-1.6 ± 5.2*	-3.0 ± 4.5*	-1.5 (-3.8 to 0.9)	0.215
Δ BMI (kg/m^2)	-0.6 ± 1.9*	-1.1 ± 1.5**	-0.4 (-1.3 to 0.4)	0.313
Δ SM area (cm^2)	-8.7 ± 14.0***	-15.5 ± 11.3***	-6.8 (-12.9 to -0.6)	0.031
Δ SMI (cm^2/m^2)	-3.0 ± 4.8***	-5.2 ± 3.7***	-2.2 (-4.3 to -0.1)	0.038
Δ TAT area (cm^2)	-27.3 ± 81.0***	-33.3 ± 63.2**	-6.0 (-41.2 to 29.2)	0.735
Δ VAT area (cm^2)	-16.9 ± 48.0*	-19.4 ± 42.4*	-2.5 (-24.1 to 19.1)	0.818
Δ SAT area (cm^2) [1]	-5.6 (-31.0, 16.9)	-11.0 (-35.7, 4.8)	n/a	0.608
Relative changes in body composition				
Relative Δ Weight (%)	-1.5 ± 6.5	-3.9 ± 5.9	-2.5 (-5.3 to 0.5)	0.099
Relative Δ BMI (%)	-1.7 ± 7.0	-3.9 ± 5.9	-2.3 (-5.4 to 0.8)	0.151
Relative Δ SM area (%)	-6.1 ± 11.4	-10.6 ± 7.5	-4.5 (-8.7 to -0.2)	0.039
Relative Δ SMI (%)	-6.3 ± 11.6	-10.6 ± 7.5	-4.3 (-8.5 to -0.2)	0.050
Relative Δ TAT area (%) [1]	-6.1 (-21.2, 6.4)	-9.4 (-19.8, -0.1)	n/a	0.559
Relative Δ VAT area (%) [1]	-10.7 (-28.9, 2.9)	-12.4 (-30.5, 0.9)	n/a	0.731
Relative Δ SAT area (%) [1]	-3.9 (-18.0, 8.1)	-5.8 (-14.9, 1.6)	n/a	0.678

Table 4.2 Change in body composition parameters during neoadjuvant therapy

Continuous data presented as mean ± SD unless otherwise stated. Within group comparison of change before and after neoadjuvant therapy: * p<0.05; ** p<0.01; *** p<0.001

SM = skeletal muscle; SMI = skeletal muscle index; TAT = total adipose tissue; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; n/a = not applicable. [1] Non-parametric data, displayed as median (interquartile range)

	Prehabilitation patients (n=28)	Controls (n=28)	p value
Age, years	65.3 ± 9.6	63.5 ± 9.6	0.496
Gender, male n (%)	21 (75%)	22 (76%)	0.752
Tumour location n (%)			
Oesophagus	17 (61%)	17 (61%)	0.999
GOJ	11 (39%)	11 (39%)	
Histological subtype n (%)			
Adenocarcinoma	25 (89%)	21 (75%)	0.163
Squamous cell carcinoma	3 (11%)	7 (25%)	
Neoadjuvant therapy n (%)			
Chemotherapy	22 (79%)	21 (75%)	0.752
Chemoradiotherapy	6 (21%)	7 (25%)	
Clinical stage n (%)			
I	1 (3%)	1 (3%)	0.852
II	3 (11%)	3 (11%)	
II	18 (64%)	15 (54%)	
IV	6 (22%)	9 (32%)	
ASA grade n (%)			
II	25 (89%)	21 (75%)	0.163
III	3 (11%)	7 (25%)	
Charlson Comorbidity Index	4.8 ± 1.5	4.4 ± 1.2	0.371
Time interval between scans days	98.7 ± 22.9	119.0 ± 39.5	0.023
Oesophagectomy			
2-stage	35 (68%)	15 (54%)	0.314
3-stage	9 (18%)	9 (32%)	
Thoracoabdominal	7 (14%)	4 (14%)	
Surgical approach			
Open	27 (96%)	25 (89%)	0.299
Hybrid minimally invasive [1]	1 (4%)	3 (11%)	
Baseline body composition			
Weight (kg)	84.9 ± 18.2	79.5 ± 13.3	0.206
BMI (kg/m^2)	28.6 ± 5.2	26.6 ± 3.5	0.105
SM area (cm^2)	143.6 ± 31.8	149.3 ± 26.7	0.467
SMI (cm^2/m^2)	48.0 ± 7.3	49.9 ± 6.8	0.314
TAT area (cm^2)	421.8 ± 168.3	403.6 ± 154.4	0.675
VAT area (cm^2)	181.6 ± 87.3	176.0 ± 102.7	0.829
SAT area (cm^2) [2]	224.2 (173.3, 281.8)	211.1 (165.1, 296.4)	0.831
Sarcopenia, n (%)	17 (61%)	14 (50%)	0.420
Visceral obesity, n (%)	19 (68%)	15 (54%)	0.274

Table 4.3 Baseline comparison of propensity score matched groups

Continuous data presented as mean ± SD unless otherwise stated.

GOJ = gastro oesophageal junction; ASA = American Society of Anesthesiologist physical status classification; SM = skeletal muscle; SMI = skeletal muscle index; TAT = total adipose tissue; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; n/a = not applicable. [1] *Laparoscopic abdominal stage, open thoracic stage.* [2] *Non-parametric data, displayed as median (interquartile range)*

	Prehabilitation patients (n=28)	Controls (n=28)	Mean difference (95% CI)	p value
Δ Weight (kg)	-1.5 ± 5.3	-3.0 ± 4.5	-1.5 (-4.2 to 1.1)	0.248
Δ BMI (kg/m^2)	-0.5 ± 1.7	-1.1 ± 1.5	-0.5 (-1.4 to 0.3)	0.221
Δ SM area (cm^2)	-9.1 ± 10.9	-15.5 ± 11.3	-6.4 (-12.4 to -0.5)	0.035
Δ SMI (cm^2/m^2)	-2.9 ± 3.5	-5.2 ± 3.7	-2.3 (-4.3 to -0.3)	0.023
Δ TAT area (cm^2)	-30.3 ± 72.7	-33.3 ± 63.2	-3.0 (-39.5 to 33.5)	0.868
Δ VAT area (cm^2)	-14.5 ± 41.7	-19.4 ± 42.4	-4.9 (-27.5 to 17.6)	0.664
Δ SAT area (cm^2) †	-12.2 (-29.7, 9.1)	-11.0 (-35.7, 4.8)	n/a	0.987
Relative Δ Weight (%)	-1.4 ± 5.7	-3.9 ± 5.9	-2.5 (-5.6 to 0.6)	0.110
Relative Δ BMI (%)	-1.4 ± 5.7	-3.9 ± 5.9	-2.5 (-5.6 to 0.6)	0.110
Relative Δ SM area (%)	-5.9 ± 7.3	-10.6 ± 7.5	-4.7 (-8.6 to -0.7)	0.021
Relative Δ SMI (%)	-5.9 ± 7.3	-10.6 ± 7.5	-4.7 (-8.6 to -0.7)	0.021
Relative Δ TAT area (%) [1]	-7.1 (-15.7, 3.9)	-9.4 (-19.8, -0.1)	n/a	0.670
Relative Δ VAT area (%) [1]	-11.3 (-23.8, 2.7)	-12.4 (-30.5, 0.9)	n/a	0.629
Relative Δ SAT area (%) [1]	-5.2 (-15.5, 5.5)	-5.8 (-14.9, 1.6)	n/a	0.806

Table 4.4 Propensity score matched comparison of change in body composition parameters during neoadjuvant therapy

Continuous data presented as mean ± SD unless otherwise stated. *SM = skeletal muscle; SMI = skeletal muscle index; TAT = total adipose tissue; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; n/a = not applicable.* [1] *Non-parametric data, displayed as median (interquartile range)*

4.4.2 Hand grip strength

Hand-grip strength was measured in the prehabilitation group only. It did not vary significantly between assessment at diagnosis and after neoadjuvant therapy (30.7± 8.5 vs. 30.3 ± 8.3; p=0.491). Hand grip strength at diagnosis (R^2=0.576, p=0.001) and after neoadjuvant chemotherapy (R^2=0.554, p=0.001) was correlated to skeletal muscle area.

4.4.3 Changes in body composition and adherence to pre-operative exercise in prehabilitation patients

Data on exercise adherence and physical activity during prehabilitation was available for 47 patients in the prehabilitation cohort (92%). The mean amount of activity completed during neoadjuvant therapy was 858±727 MET minutes week^{-1}. The mean adherence to the personalised exercise prescriptions during neoadjuvant therapy was 55±31.3%.

Variation in body composition parameters based on patient adherence to the personalised exercise prescriptions are presented in **Table 4.5**. The decline in SMI was significantly less in patients with ≥75% adherence (Δ SMI mean difference = -3.2 cm^2/m^2, 95% CI -6.0 to -0.5 p=0.023). There were no significant differences in the changes in other body composition parameters between patients with ≥75% and <75% adherence. When the adherence threshold was decreased to ≥50%, compliance with the prescribed exercise programme was no longer protective for preservation of SM area and SMI (**Table 4.5**).

	Adherence ≥75% n=15	**Adherence <75% n=32**	**Mean difference (95% CI)**	**p value**
Δ Weight (kg)	0.3 ± 5.9	-2.2 ± 4.5	-2.4 (-6.0 to 1.1)	0.169
Δ BMI (kg/m^2)	0.1 ± 1.9	-0.9 ± 1.9	-1.0 (-2.1 to 0.2)	0.105
Δ SM area (cm^2)	-1.4 ± 13.3	-10.3 ± 12.3	-8.9 (-16.9 to -0.9)	0.040
Δ SMI (cm^2/m^2)	-0.4 ± 4.2	-3.7 ± 4.4	-3.2 (-6.0 to -0.5)	0.023
Δ TAT area (cm^2)	-32.0 ± 106.9	-31.5 ± 71.6	0.5 (-63.0 to 64.0)	0.987
Δ VAT area (cm^2)	-14.4 ± 65.4	-22.2 ± 39.2	-7.8 (-38.9 to 23.3)	0.616
Δ SAT area (cm^2) [1]	-5.6 (-25.8, 12.5)	-10.2 (-40.6, 16.9)	n/a	0.916
Δ Hand grip strength (kg)	-0.2 ± 3.2	-0.2 ± 3.5	n/a	0.970
Sarcopenia after NAC	13 (87%)	23 (72%)	n/a	0.336
Visceral obesity after NAC	7 (47%)	20 (63%)	n/a	0.249
	Adherence ≥50% n=28	**Adherence <50% n=19**	**Mean difference (95% CI)**	**p value**
Δ Weight (kg)	-0.9 ± 5.5	2.0 ± 4.3	1.2 (-1.7 to 4.0)	0.424
Δ BMI (kg/m^2)	-0.4 ± 1.9	-0.9 ± 2.0	0.6 (-0.6 to 1.7)	0.323
Δ SM area (cm^2)	-4.8 ± 13.3	-10.9 ± 12.2	-6.1 (-13.7 to 1.5)	0.114
Δ SMI (cm^2/m^2)	-1.6 ± 4.6	-3.9 ± 4.3	-2.2 (-4.9 to 0.4)	0.096
Δ TAT area (cm^2)	-25.0 ± 95.8	-38.7 ± 60.1	-13.7 (-59.8 to 32.4)	0.552
Δ VAT area (cm^2)	-11.7 ± 53.3	-29.5 ± 39.2	-17.7 (-44.9 to 9.5)	0.197
Δ SAT area (cm^2) [1]	-7.9 (-35.0, 19.0)	-9.3 (-40.6, 9.1)	n/a	0.897
Δ Hand grip strength (kg)	-0.2 ± 2.9	-0.1 ± 4.1	n/a	0.934
Sarcopenia after NAC	24 (86%)	12 (63%)	n/a	0.073
Visceral obesity NAC	15 (54%)	12 (63%)	n/a	0.514

Table 4.5 Change in body composition parameters stratified by adherence to personalised exercise prescriptions Continuous data presented as mean ± SD unless otherwise stated.
SM = skeletal muscle; SMI = skeletal muscle index; TAT = total adipose tissue; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; n/a = not applicable; NAC = neoadjuvant chemotherapy. [1] Non-parametric data, displayed as median (interquartile range)

On multivariate analysis, there was no relationship between the decrease in SMI during neoadjuvant therapy and age, ASA grade, Charlson Comorbidity Index (CCI), clinical stage, baseline fitness, adherence (%) or average weekly physical activity (**Table 4.6**). However, increasing amounts of average weekly physical activity was significantly associated with a greater loss of VAT during neoadjuvant therapy (**Table 4.6**, p=0.046).

	B coefficient (95% CI)	SE	p value
Loss of skeletal mass			
Age	0.52 (-0.13 to 1.17)	0.32	0.110
ASA	7.62 (-5.39 to 20.62)	6.37	0.241
CCI	-1.06 (-6.51 to 4.39)	2.67	0.693
Clinical stage	5.44 (-3.61 to 14.49)	4.43	0.229
Adherence (%)	-13.54 (-39.21 to 12.14)	12.57	0.290
Average PA (MET min wk^{-1})	0.01 (-0.01 to 0.02)	0.01	0.463
Loss of visceral adipose tissue			
Age	0.44 (-1.94 to 2.81)	1.16	0.709
ASA	36.78 (-10.96 to 84.52)	23.37	0.126
CCI	-8.98 (-28.98 to 11.02)	9.79	0.367
Clinical stage	-9.02 (-42.24 to 24.20)	16.27	0.583
Adherence (%)	-81.46 (-175.70 to 12.79)	46.15	0.088
Average PA (MET min wk^{-1})	0.04 (0.01 to 0.07)	0.02	0.046

Table 4.6 Factors associated with loss of skeletal mass and loss of visceral adipose tissue during prehabilitation
CCI = Charlson Comorbidity Index; PA = physical activity

4.4.4 Changes in body composition and post-operative outcomes

Thirty-three prehabilitation patients (65%) developed one or more post-operative complication, 13 of which were classified as severe complications (Clavien Dindo grade ≥3). The most frequent complications included: lower respiratory tract infection (n=16), pleural effusion requiring drainage (n=6), atrial arrythmia (n=5) and delayed conduit emptying requiring intervention (n=5). Twenty control patients (71%) developed one or more post-operative complications, 14 of which were severe complications (Clavien Dindo grade ≥3). There was no significant difference in overall complication rate between the two groups (p=0.543). There was, however, a trend for a lower incidence of lower respiratory tract infection in the prehabilitation group: 17 patients (33%) in the prehabilitation group, compared with 15 patients (54%) in the control group, p=0.080.

Patients who developed complications lost significantly less VAT during neoadjuvant therapy in comparison to patients who did not develop complications (**Table 4.7**, Δ VAT mean difference = = -23.7 cm^2, 95% CI -45.0 to -2.3, p=0.030). On multivariate analysis, loss of VAT during neoadjuvant therapy was associated with a lower risk of post-operative complications (**Table 4.8**, p=0.017).

	Any complication n=53	**No complications n=26**	**Mean difference (95% CI)**	**p value**
Δ Weight (kg)	-2.1 ± 5.3	-2.1 ± 4.4	0.0 (-2.4 to 2.4)	0.996
Δ BMI (kg/m^2)	-0.8 ± 1.9	-0.7 ± 1.5	0.1 (-0.8 to 1.0)	0.821
Δ SM area (cm^2)	-11.0 ± 12.7	-11.5 ± 15.1	-0.5 (-6.9 to 6.0)	0.882
Δ SMI (cm^2/m^2)	-3.7 ± 4.4	-3.8 ± 4.9	-0.1 (-2.3 to 2.1)	0.935
Δ TAT area (cm^2)	-16.2 ± 75.3	-56.4 ± 67.6	-40.1 (-74.9 to -5.4)	0.024
Δ VAT area (cm^2)	-10.0 ± 47.2	-33.7 ± 39.4	-23.7 (-45.0 to -2.3)	0.030
Δ SAT area (cm^2) [1]	-2.9 (-20.3, 16.8)	-16.3 (-44.4, 0.1)	n/a	0.055

Table 4.7 Variation in body composition in all study participants patients, stratified by post-operative complications

Continuous data presented as mean ± SD unless otherwise stated. *SM = skeletal muscle; SMI = skeletal muscle index; TAT = total adipose tissue; VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; [1] Non-parametric data, displayed as median (interquartile range)*

Variable	**Odds ratio (95% CI)**	**SE**	**p value**
Age	1.00 (0.91 to 1.09)	0.01	0.948
ASA	6.58 (0.98 to 44.04)	0.97	0.052
CCI	0.93 (0.44 to 1.96)	0.38	0.854
Clinical stage III [1]	1.07 (0.17 to 6.68)	0.93	0.939
Clinical stage IV [1]	1.31 (0.35 to 4.85)	0.67	0.685
SM loss (cm^2/m^2)	1.00 (0.97 to 1.05)	0.02	0.761
VAT loss (cm^2)	0.98 (0.96 to 0.99)	0.01	0.017

Table 4.8 Factors associated with post-operative complications

CCI = Charlson Comorbidity Index; SM= skeletal muscle; VAT = visceral adipose tissue. [1] Clinical stage against with stage II

4.5 Discussion

This study has observed that prehabilitation appears to preserve skeletal muscle during neoadjuvant therapy. It has also found some evidence of a dose-response effect, with greater preservation of skeletal muscle with higher levels of adherence to pre-operative exercise. Finally, it has observed that loss of VAT may be protective against post-operative complications.

The finding of a positive impact of prehabilitation on muscle mass is in keeping with previous studies; prehabilitation during neoadjuvant therapy has been shown to reduce muscle loss in oesophageal cancer patients and increase skeletal mass in rectal cancer patients (38,150). In keeping with a previous study of prehabilitation in oesophageal cancer patients (38), this study found a similar magnitude of change in muscle mass in our study, and also found that hand-grip strength was preserved in prehabilitation patients during neoadjuvant therapy, suggesting preservation of muscle function. However, in this study, hand grip strength was not recorded in the control group and therefore comparison of function between the two groups is not possible.

Not all studies into the effects of prehabilitation on muscle mass have shown a beneficial effect. Studies where patients did not receive neoadjuvant therapy have failed to show a significant impact of prehabilitation on muscle mass (154,155). Evidence to date of a beneficial effect of prehabilitation on muscle mass has only been seen in studies where participants received neoadjuvant therapy (38,150). Particular benefit may be derived from exercise during neoadjuvant treatment due to the deleterious effect of chemotherapy and chemoradiotherapy on muscle mass (38,55,149).

The prehabilitation patients in this study who had high adherence to their personalised exercise programme had greater preservation of skeletal muscle. This benefit was not preserved when the threshold for acceptable adherence was decreased, highlighting the importance of regular participation in exercise to limit loss of skeletal muscle. However, in the multivariate analysis of factors associated with loss of skeletal muscle within the

prehabilitation patients, the overall adherence percentage was not a significant factor. This may imply a non-linear relationship between exercise adherence and preservation of muscle, and high levels of adherence may be needed to limit muscle loss. More research is needed into ways to improve adherence to home based exercise during neoadjuvant therapy, such as wearable technology, video exercises, greater exercise personalisation and the incorporation of other behaviour change techniques.

Overall, this study saw a significant decrease in VAT during neoadjuvant therapy. A fall in VAT:SAT is seen in oesophageal cancer patients during neoadjuvant therapy (55), indicating that changes in adiposity may occur as a consequence of the underlying disease and oncological treatments. However, the amount of VAT lost in the pre-operative period was significantly related to the volume of exercise completed, with a greater decrease in VAT seen with increasing volumes of physical activity.

This is the first study to observe a relationship between changes in adiposity during neoadjuvant therapy and post-operative complications. There was a high incidence of visceral obesity in this study population (65%). Obesity is a risk factor for developing oesophageal cancer (156-158). It is also a poor prognostic factor in some cancers; for example, pancreatic cancer patients with a high VAT:SAT ratio have a lower overall survival and disease-free survival (159), and VAT:abdominal muscle area ratio is an independent risk factor for post-operative complications in patients with gastric cancer (62). In oesophageal cancer patients, high volumes of VAT after neoadjuvant therapy is associated with poorer overall survival (160). VAT is metabolically active and secretes a range of pro-inflammatory cytokines (65). Reducing adiposity reduces systemic inflammation and improves glycaemic control (64,67,71), which represents a possible mechanism by which reducing VAT may reduce the risk of post-operative complications. Future research is needed to examine these parameters in relation to changes in VAT during prehabilitation.

There is significant heterogeneity in the content of prehabilitation programmes, including substantial differences in the type and intensity of exercise (18,130). Given the relationship we have observed between VAT loss and complications, I propose that exercise programmes targeting VAT loss should be explored. High or moderate intensity exercise is associated with

VAT loss in overweight and obese patients (161,162). High intensity interval training (HIIT) in cancer survivors has also been shown to result in larger reductions in fat mass compared with low or moderate intensity continuous training (163,164). HIIT was not used in this study, but it has been trialled in patients undergoing prehabilitation and shown to be safe and feasible, with significant improvements in cardiorespiratory fitness (165). However, the effect of HIIT-based prehabilitation on body composition and post-operative outcomes has not been established, and the impact of HIIT has not been compared with moderate or low intensity exercise in the pre-operative setting.

Both dietary modifications and exercise can be used induce VAT loss (166,167). However, studies suggest that a reduction in VAT is not seen without overall weight loss when dietary interventions alone are used, whereas VAT loss can be achieved with exercise even when no significant weight loss occurs (167). Due to the metabolic effects of cancer, overall weight loss may not be desirable in all patients and therefore exercise may be a more suitable strategy to achieve VAT loss compared with calorie restriction.

The nutritional support needed by oesophageal patients is very variable. Whilst some patients may need to lose weight, others will need to gain weight, and some may have very poor oral intake due to dysphagia. In keeping with guidelines from Macmillan Cancer Support, nutritional support was a key component of the prehabilitation programme in this study (25) and patients were reviewed every two weeks by a specialist oesophagogastric cancer dietitian, using standardised guidelines to optimise nutrition. This proactive approach contrasts with the reactive approach to nutrition in the standard pre-operative cancer pathway used in the control patients. Whilst nutritional deficiencies may have been identified and addressed in the control patients, traditional pre-operative nutritional support is often ad-hoc, with variable nutritional input from a range of healthcare professionals. A higher proportion of patients in the prehabilitation group received oral supplementation or supplemental feeding by either a nasogastric tube or jejunostomy compared with the controls, and although these differences were not statistically significant, we believe that this reflects the proactive approach in the prehabilitation programme to identifying and managing nutritional deficiencies.

Body composition was measured in this study using CT scan images. Use of CT scans to measure muscle mass and adipositiy is well established in studies of patients with gastrointestinal malignancy, including oesophageal cancer patients (57,168). The most commonly used CT image for assessment of body composition is the L3 level (168), which was performed in this study. Dual energy x-ray absorptiometry (DEXA) is regarded in many fields as the gold standard for assessing body composition (169,170). It has a lower level of radiation exposure compared with CT imaging and provides measurements of total adipose tissue and muscle mass. Although it is not directly measured, estimates for VAT can be provided using validated computer algorithms (169). Bioelectrical impedance analysis (BIA) can also be used to estimate fat mass. It is widely used in research as it does not involve radiation exposure so can safely be used for repeated measurements (169,170).

CT image analysis allows measurement of multiple body composition domains based on the Hounsfield units of the imaged tissues and the use of analysis software allows independent measurement of outcomes. Strong correlation is seen between CT derived measurements of muscle mass and DEXA and BIA results, and between CT measurement of fat mass and DEXA results (170). Furthermore, CT and MRI scans are gold standards for the assessment of VAT as it allows direct measurement of the amount of VAT unlike other methods of analysis (169). Whilst exposure to radiation is an important limitation of its use in a purely research setting, secondary analysis of images obtained for clinical purposes provides a detailed insight into body composition.

4.5.1 Study limitations

There are several limitations to this study. The time interval between CT scans was longer in the control group than in the prehabilitation patients (**Table 4.1**), which may contribute to the differences in muscle loss. There are no studies to date assessing the rate of pre-operative muscle mass loss in oesophageal cancer patients, so it is not possible to definitively conclude what effect this time difference may have on changes in muscle mass. Nonetheless, the longer time interval in the control group may contribute to the differences in muscle loss between

the two groups and it is possible that the difference in change in muscle mass may be a result of this time discrepancy. However, the finding of less muscle loss with prehabilitation is in keeping with a previous study in this patient group (38).

All patients who completed the programme between January 2016 and December 2018 and underwent neoadjuvant chemotherapy were eligible for this study. Despite this, the sample size may be insufficient to detect the effect of changes in some body composition parameters, such as SMI, on post-operative outcomes. Other factors independent of the prehabilitation programme may have influenced both the changes in body composition and post-operative outcomes. This includes the use of neoadjuvant radiotherapy, the number of cycles of chemotherapy received and the side effects and toxicity from neoadjuvant therapy. Due to the sample size, it was not possible to undertake subgroup analyses to control for the effects of these factors.

Although post-operative outcomes have been quoted, this was not the primary outcome, and the study was not powered to detect a difference in complications. This topic has been addressed in **Chapter 2**. A large, multi-centre randomised controlled trial should be undertaken to provide a sufficient sample size to allow analysis of a broader range of outcomes and to control for the effects of different patient variables. Multi-centre studies are also particularly important to establish whether benefits seen in this and in other studies (38) can be replicated in wider clinical practice.

Finally, in this home-based prehabilitation programme, measurements of physical activity and adherence were self-reported, and their accuracy cannot be verified. The use of eHealth technology and activity trackers may provide a more accurate assessment of exercise volume.

4.5.2 Future studies

As discussed above, further studies in this field should include randomised controlled trials to remove the potential influence of any unmeasured confounding factors between the

prehabilitation patients and controls, and the use of activity trackers to independently quantify the amount of exercise completed. In this study, hand grip strength was measured in the prehabilitation cohort only. Further studies should address functional outcomes, such as changes in hand-grip strength, with comparison to controls.

Body composition was assessed in this study using analysis of CT images. Radiation exposure limits repetitive use of CT or DEXA tests. However, BIA could be used during prehabilitation to regularly monitor changes in muscle mass as the programme is being delivered. This data could potentially be used during prehabilitation to tailor the programme depending on response and this should be studied. BIA could also be used in the post-operative period to both assess how prehabilitation affects changes in body composition in response to surgery and how it affects long-term changes in body composition.

4.6 Conclusions

Through both limiting loss of skeletal mass and promoting loss of VAT before surgery, prehabilitation may have multiple beneficial effects on body composition in oesophageal cancer patients. The beneficial impact of pre-operative exercise on muscle mass has been seen in other cancer groups and may reflect a protective effect from the deleterious effects of neoadjuvant therapy. However, this is the first study to date to report a relationship between changes in VAT during prehabilitation and post-operative outcomes. Further research is needed to explore this association and the underlying mechanisms that may mediate the relationship between VAT loss and complications.

CHAPTER 5

-

EXERCISE AND INFLAMMATION IN PATIENTS UNDERGOING ONCOLOGICAL TREATMENT: A SYSTEMATIC REVIEW

5.1 Objective and hypothesis

Objective: To review the published literature on the effects of exercise on systemic inflammation in patients undergoing chemotherapy or radiotherapy.

Hypothesis: Prehabilitation reduces systemic inflammation in patients undergoing chemotherapy or radiotherapy.

5.2 Introduction

The presence of chronic inflammation is a poor prognostic factor in many types of cancer, including colorectal, lung, breast, prostate, gastric and oesophageal malignancies (4,72,73,171). It has been suggested that exercise can reduce systemic inflammation (71), and therefore may represent a potential intervention to target chronic inflammation.

A large number of studies have examined the effects of exercise on inflammation in both diseased and healthy populations, including different exercise modalities and intensities. Given this heterogeneity, it is unsurprising that results have been mixed. In particular, studies of short-term or high intensity exercise (102,172-174) or those in a healthy adult population (102,175), where underlying chronic inflammation may be low, have failed to demonstrate a significant anti-inflammatory effect from exercise. However, a number of systematic reviews

have demonstrated that exercise can lower inflammation in cancer survivors (98,99) and in elderly populations (176).

Given this, it is possible that some of the benefits from prehabilitation may be derived from modulating the patient's inflammatory response. A study of a post-operative exercise programme in patients after they had undergone an oesophagectomy found a significant decrease in serum IL-8, with non-significant falls in IL-1β, IL-6 and TNFα (100). However, there are no studies to date assessing the impact of prehabilitation on inflammation.

There are several reasons for a particular interest in exercise and inflammation in patients who are actively undergoing treatment for cancer. Firstly, cancerous tumours stimulate a pro-inflammatory response and therefore high levels of chronic inflammation are seen in this population (4). Secondly, the use of oncological therapies, either in a curative, neoadjuvant or adjuvant setting, will have a negative impact on many aspects of the body's physiology, such as cardiorespiratory fitness and muscle mass (10,56), and will significantly alter the inflammatory milieu through both direct immunosuppressive effects and as a response to cell death and tissue damage. Finally, inflammation is a strong driver of carcinogenesis and tumour spread in many cancer types (64,65) and so it is possible that interventions to limit inflammation may also impact upon oncological outcomes.

Most of the evidence on the effects of exercise on inflammation in cancer patients has been undertaken in cancer survivors who have completed treatment. However, a result of neoadjuvant treatment and the effect of the cancer itself, the inflammatory profile of pre-operative patients will be different to those of cancer survivors who have finished their treatment. Consequently, the effects of exercise may not be comparable. No systematic reviews have been published to look at the effects of exercise on inflammation during cancer treatment. This review will examine the effect of exercise interventions on markers of systemic inflammation in patients who are undergoing chemotherapy or radiotherapy to establish whether the effects of exercise on inflammation are seen in this patient group.

5.3 Methods

The systematic review protocol is in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guideline (177) and was established prior to the commencement of the study.

5.3.1 Search strategy

The following databases were searched to find eligible articles: MEDLINE (1946 – January 2020), EMBASE (1947 – January 2020) and CINAHL (1937 – January 2020). OpenGrey, ProQuest dissertation & theses, King's Fund, Google Scholar were also searched to identify any grey literature. The final search was conducted on 20th January 2020. The MeSH headings used included neoplasms AND exercise OR exercise therapy AND inflammatory mediators OR c-reactive protein OR tumour necrosis factor alpha. Free text words were also used to avoid excluding recently published articles. A detailed description of the search strategy is shown in **Appendix IV**.

5.3.2 Study selection

After removing duplicate articles, two reviewers independently screened and selected potentially eligible studies. The full text was obtained if either reviewer selected the study, or the abstract was unclear. Both reviewers independently reviewed the selected full text articles to determine suitability for inclusion in this review. A third independent reviewer was available to resolve any discrepancy in study selection if needed.

Articles were retrieved based on the following inclusion criteria: original research; English language; use of structured exercise programme; and participants with a current diagnosis of cancer (either solid tumour or haematological malignancy). Exercise was defined as structured physical activity comprising of aerobic and/or strength exercises using the upper and/or lower limbs. Both randomised controlled trials and observational studies were

included. Exclusion criteria included: commentary, opinion papers and reviews; papers without original data; single measurements of inflammation; and studies performed only in a cancer rehabilitation setting (participants who had finished treatment for cancer). If multiple studies had included results from the same dataset, the article with the largest dataset was selected.

5.3.3 Data extraction and analysis

A standardised data extraction sheet was used to collect information from the selected studies, including study name, year, participant demographics (sex, age, cancer type), oncological treatment, exercise intervention characteristics (type of exercise, duration of programme, frequency of sessions, intensity, adherence) and outcomes (marker of inflammation).

On preliminary data analysis, there was significant heterogeneity between the studies identified in the review, with substantial differences in the interventions, study endpoints, outcome selection and units used to measure outcomes. Therefore, a meta-analysis was not performed, and a critical review and narrative synthesis was undertaken. Specific values for inflammatory markers were included when given and presented in the format displayed in the paper (either mean ± standard deviation, mean difference and 95% confidence interval or median and interquartile range). Measurement units and P values were quoted when given.

5.3.4 Assessment of bias and therapeutic validity

The risk of bias in randomised controlled trials was assessed using Cochrane Risk of Bias tool and PEDro scale (177-179). These methods assess different domains of potential bias. The Cochrane Risk of Bias tool assesses randomisation, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result (180). Within each domain, an algorithm is used to assess the impact of

potential sources of bias, grading each domain as low risk, some concerns or high risk. The PEDro scale addresses bias in studies using physical therapy interventions (178,179). It assesses 10 domains and uses a binary 'yes' or 'no' scoring system for each item. The higher the score, the lower the risk of bias. Previous studies have identified poor agreement between Cochrane Risk of Bias and PEDro scales (181) so both scoring systems have been used in this review.

The CONTENT (Consensus on Therapeutic Exercise Training) scale was used to assess the quality and therapeutic validity of the exercise interventions in each study (182). This assesses nine areas of the exercise intervention itself, covering five domains: patient eligibility; competences & setting; exercise rationale; content; and adherence. High therapeutic validity is defined as an overall score of six or greater out of a maximum score of nine.

The risk of bias and therapeutic validity assessments were conducted independently by two reviewers and disagreements resolved by consensus with a third independent reviewer if needed.

5.4 Results

5.4.1 Selection of studies

643 articles were generated from the search (**Figure 5.1**). 75 abstracts were retrieved. Following abstract screening, 37 papers were retrieved and assessed, of which a further 29 studies excluded, leaving 8 papers to be included in the analysis.

The study characteristics of the eight papers are shown in **Table 5.1**: four studies with breast cancer patients (183-186), two studies with prostate cancer patients (187,188), one study with testicular cancer patients (189) and one study with patients who had any solid tumour (190). In four studies, patients received chemotherapy alone (182,183,186,187), in three

studies they received radiotherapy alone (181,184,185), and in one study they received either or both chemotherapy and radiotherapy (180).

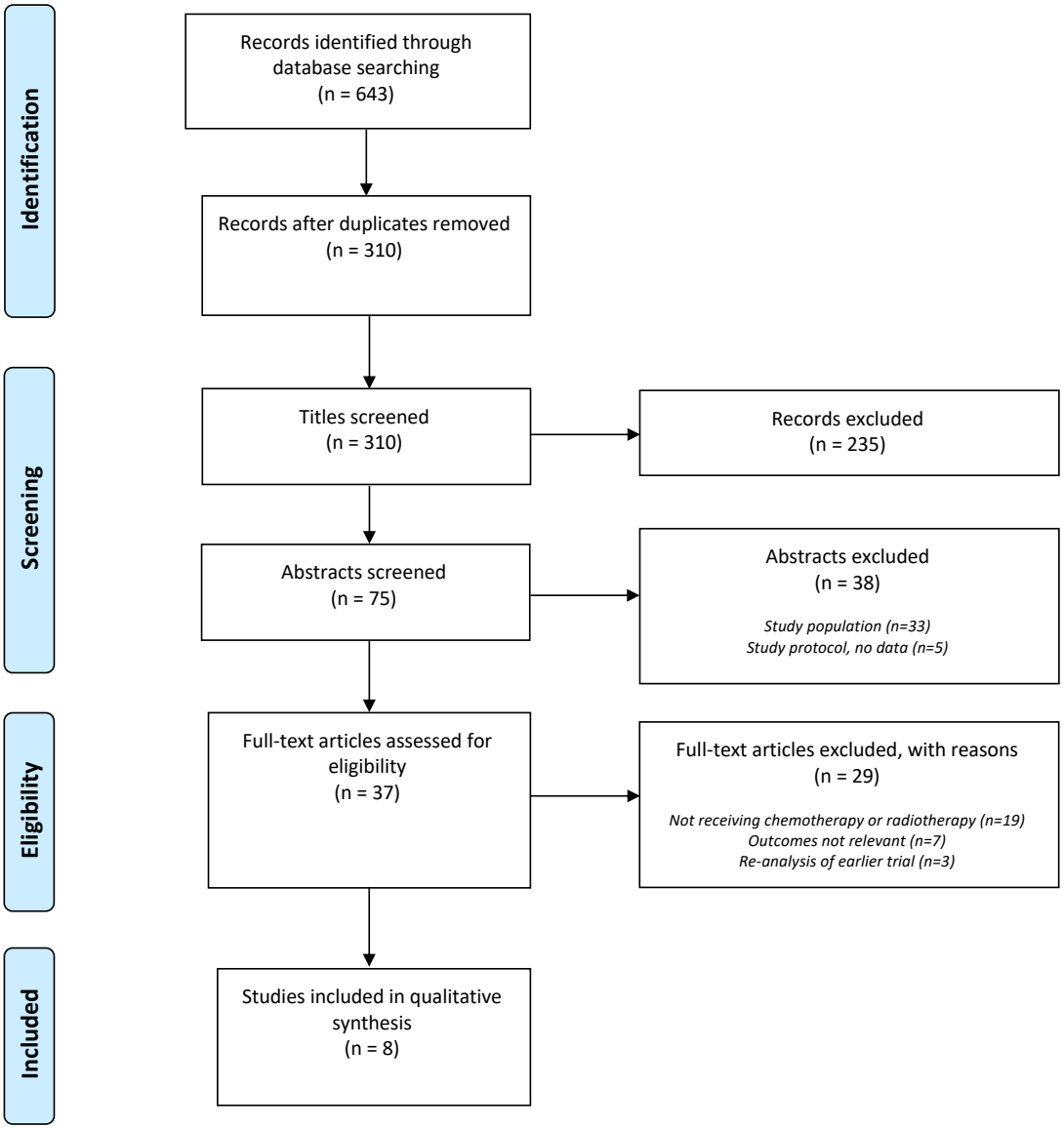


Figure 5.1 PRISMA flow chart

	Study design	Cancer diagnosis	n	Age (years; mean ± SD)	Oncological treatment	Exercise intervention	Duration of intervention	Outcomes	Study end point
Christensen *et al.,* 2014 (186)	RCT	Testicular germ cell tumour	Intervention = 15 Controls = 15 Healthy participants = 19	Intervention = 34.4 ± 7.6 Controls = 35.8 ± 8.9	Chemotherapy	Resistance training Escalating number of reps and sets; three sessions a week	9 weeks	Cytokines: IL6, IL8, IL10, TNFa, IFNy	30 weeks for two cancer arms; 9 weeks for healthy controls receiving intervention
Glass *et al.*, 2015 (187)	RCT	Solid tumour	Intervention = 21 Controls = 23	Intervention = 56 ± 10 Controls = 54 ± 11	Chemotherapy	Aerobic exercise 20-45 mins cycle ergometry; three sessions a week (intensity increased after first 6 weeks)	12 weeks	Cytokines: IL4, TNFa, MIP 1b Immune cells: CD4 cells, CD8 cells, B cells, NK cells, monocytes Other: leptin, IGF1	End of exercise intervention
Hojan *et al.*, 2016 (184)	RCT	Prostate cancer	Intervention = 27 Controls = 27	Intervention = 67.4 ± 8.3 Controls = 69.9 ± 7.2	Radiotherapy	Aerobic & resistance exercises 30 mins aerobic exercise and 15mins resistance exercises; five sessions a week	8 weeks	Cytokines: IL1b, IL6, TNFa Immune cells: total WCC, lymphocyte	End of exercise intervention
Hojan *et al.*, 2017 (185)	RCT	Prostate cancer	Intervention = 36 Controls = 36	Intervention = 65.7 ± 6.2 Controls = 67.9 ± 4.9	Radiotherapy	Aerobic & resistance exercises During radiotherapy: 30 mins aerobic exercise and 25 mins resistance exercises; five sessions a week After radiotherapy: 40 mins aerobic exercise and 35 mins resistance exercise; two sessions a week	During radiotherapy – 8 weeks Post-radiotherapy exercise programme – 44 weeks	Cytokines: IL1b, IL6, TNFa	End of 12 month programme

Kim *et al.*, 2015 (180)	Observational	Breast cancer	Intervention = 20	47.8 ± 6.8	Radiotherapy and/or chemotherapy	Aerobic exercise 30-40 mins walking; five sessions a week (intensity increased after first 6 weeks)	12 weeks	Immune cells: total WCC, lymphocyte, CD4 cells, CD8 cells, NK cells	End of exercise intervention
Schmidt *et al.*, 2016 (181)	RCT	Breast cancer	Intervention = 54 Controls = 49	Intervention = 57.1 ± 8.9 Controls = 57.3 ± 8.8	Radiotherapy	Resistance training 1 hour sessions with 3 sets of 3-12 reps; two sessions a week	12 weeks	Cytokines: IL6, IL1RA	End of exercise intervention
Schmidt *et al.*, 2018 (182)	RCT	Breast cancer	Aerobic exercise = 20 Resistance exercise = 21 Controls = 26	Aerobic exercise = 56 ± 10.15 Resistance exercise = 53 ± 12.55 Controls = 54 ± 11.19	Chemotherapy	Aerobic & resistance exercises Aerobic protocol: 30 mins of aerobic activity; two sessions a week Resistance protocol: 1 hour of 10 exercises, with 1 set of 20 reps; two sessions a week	12 weeks	Immune cells: CD3 cells, CD4 cells, CD8 cells, B cells, NK cells	End of exercise intervention
Van Vulpen *et al., 2018* (183)	RCT	Breast cancer	Intervention = 64 Controls = 66	Intervention = 50.8 ± 9.1 Controls = 52.3 ± 4.8	Chemotherapy	Protocol one = Resistance training. Twice weekly 1 hour sessions with 3 sets of 8-12 reps Protocol two = Resistance & aerobic training. Twice weekly 1 hour sessions (20 mins aerobic exercise and increasing intensity of resistance exercises)	Protocol one = 12 weeks Protocol two = 18 weeks	Cytokines: IL6, IL1RA, TNFa Other: CRP, leptin, adiponectin	End of exercise intervention

Table 5.1 Characteristics of included studies

Seven of the eight studies were randomised controlled trials, and one was a longitudinal observational study with no control group (180). One of the studies was a pooled analysis of two randomised trials (183). The original papers reporting the trials separately did not include measurements of inflammatory markers within their results and therefore the pooled paper was included in this review as it was the only paper reporting these outcomes.

Sample sizes ranged from 20 patients in the longitudinal observational study to 130 in the largest RCT. The inclusion and exclusion criteria for the studies are shown in **Table 5.2**. Medical co-morbidities were listed in the exclusion criteria in all studies: one study excluded any chronic disease (186), one excluded common co-morbidities, such as diabetes mellitus and cardiac disease (180), whilst four others excluded poorly controlled chronic disease (182-185,187). Three studies also excluded patients who had contraindications to exercise testing or were not fit to exercise (182,183,187), although further details on how this was defined were not given. Two other studies excluded patients who were previously participated in regular exercise (180,183). An upper age limit was applied to three studies and was set at 50 years old (186), 70 years old (184) and 75 years old (182).

5.4.2 Exercise interventions

A variety of exercise interventions were used in the eight studies and are summarised in **Table 5.1**. Two studies used only aerobic exercise (180,187), two used only resistance training (181,186) and the remaining four studies used combined aerobic and resistance exercise programmes. The two protocols used within the study by Van Vulpen et al. had different exercise protocols; one used resistance only and one used both resistance and aerobic exercise (183). Therefore, in this review, it has been classified as a mixed aerobic/resistance programme as aerobic exercise was not used in isolation in all participants. The intervention duration ranged from 8 to 44 weeks; the median and mode duration was 12 weeks.

	Inclusion criteria	Exclusion criteria
Christensen *et al.,* 2014 (186)	For seminoma: any primary tumour site, any tumour marker level For non-seminoma: testis or retroperitoneum primary tumour site, serum alpha-fetoprotein between 14 and 1000 ng/mL, serum human chorionic gonadotropin between 2 and 5000 IU/L, lactate dehydrogenase < 1.5 times upper normal limit No non-pulmonary visceral metastases Scheduled to receive three cycles BEP chemotherapy	Age younger than 18 years or older than 50 years Presence of clinically important cardiovascular disease Presence of chronic disease (eg, diabetes mellitus, chronic obstructive pulmonary disease) Inability to read and understand Danish
Glass *et al.*, 2015 (187)	Histologically confirmed diagnosis of a solid malignancy Haemoglobin (Hb) level between 80 and 100gl-1, Expected survival of >3 months.	Iron deficiency (ferritin <12 µg/l) Received an Erythropoiesis-stimulating agent within 4 weeks of randomization Uncontrolled hypertension, cardiac abnormalities, a psychiatric illness, a known hematologic disorder causing anaemia, substantial lung, pleural, or pericardial disease, pre-existing bone metastases at high risk for fracture, or contraindications to maximal exercise testing.
Hojan *et al.*, 2016 (184)	Age between 18 and 75 years Scheduled ADT (LH-analogue 10.8 mg every 3 months) planned to continue for a total period of 36 months Total RT dose of 76 Gy in 38 fractions ECOG performance status 0-1	Distant metastases and/or disease progression resulting in RT or the introduction of chemotherapy Insufficiently controlled arterial hypertension or cardiac disease resulting in circulation failure (above stage II NYHA heart failure Insufficiently controlled metabolic disease; endocrinological, rheumatic, and absorption disorders; and tumours outside of the prostate.
Hojan *et al.*, 2017 (185)	Histologically confirmed diagnosis of high risk or intermediate risk prostate cancer ADT (LH analogue, 10.8 mg every 3 months) scheduled for a total period of 36 months (3 to 5 months prior to RT, during and after completion) Due to start RT 76 Gy in 38 fractions ECOG performance status 0– 1 Over 18 years old	Distant metastases and/or disease progression resulting in RT or the introduction of chemo therapy Insufficiently controlled arterial hypertension or cardiac diseases resulting in circulation failure (heart failure above class II NYHA) or uncontrolled asthma; with insufficiently controlled metabolic diseases or endocrine, rheumatic, and absorption disorders, as well as other tumours; with pre-existing bone metastases at high risk for fracture; or with a psychiatric illness or dementia or organic brain disease.

Kim *et al.*, 2015 (180)	Histologically confirmed stage I to III breast cancer along with radiotherapy and/or chemotherapy Sedentary lifestyle and had not exercised regularly in the last 6 months.	Cardiac disease, uncontrolled hypertension, thyroid disease, lymphatic complications, diabetes mellitus, or mental illness
Schmidt *et al.*, 2016 (181)	Age >18 years, body mass index (BMI) >18 kg/m^2 No contraindications for resistance training (eg, acute infectious disease, severe cardiac disease, severe respiratory insufficiency), and no other concomitant malignant diseases.	
Schmidt *et al.*, 2018 (182)	Primary moderate or high risk breast cancer, planned adjuvant or neoadjuvant chemotherapy 18–70 years old women Fitness to exercise	Acute infectious disease, severe cardiac disease (NYHA functional class III; myocardial infarction < 3 months), severe pulmonary or renal insufficiency (glomerular filtration rate < 30%), serious neurological disorders, less than 10,000 platelets per ml, haemoglobin < 8 g/dl Planned radiotherapy during the study
Van Vulpen *et al., 2018* (183)	Protocol one: Histologically confirmed primary breast cancer after lumpectomy or mastectomy Scheduled for adjuvant chemotherapy Age ≥ 18 years Body mass index ≥ 18 kg/m^2 Ability to understand and follow the study protocol Willingness to come to the Heidelberg exercise facilities	Protocol one: Contraindications for training Concurrent malignant diseases (except carcinoma in situ of skin or cervix) Already participating in systematic intensive resistance or aerobic training (≥ 2 × 1 h/week)

	Protocol two: Histologically confirmed primary breast cancer less than 6 weeks before recruitment (or 10 weeks in case of immediate use of a tissue expander after surgery) Scheduled for adjuvant chemotherapy Age 25–75 years Stage M0 Ability to read and understand the Dutch language Karnofsky performance status ≥ 60 and ability to walk ≥ 100 m	Protocol two: Contraindications for physical activity Treatment for malignancies in the 5 years preceding recruitment (except basal skin cancer)

Table 5.2 Inclusion and exclusion criteria for each study

5.4.3 Assessment of bias

The Cochrane risk of bias and PEDro scales were applied to the seven randomised controlled trials. Based on the Cochrane risk of bias assessment, three studies had a moderate risk of bias (182,183,186) and four studies had a low risk of bias (181,184,185,187) (**Figure 5.2**). The PEDro scale scoring is shown in **Table 5.3**. Four studies scored seven points (181-183,186), one study scored eight points (187) and two studies scored nine points (184,185).

The observational longitudinal study by Kim et al did not provide information about how participants were recruited for the study (180). The outcomes were well defined with a standardised protocol for measuring outcomes, there was no loss to follow up and data reporting was complete.

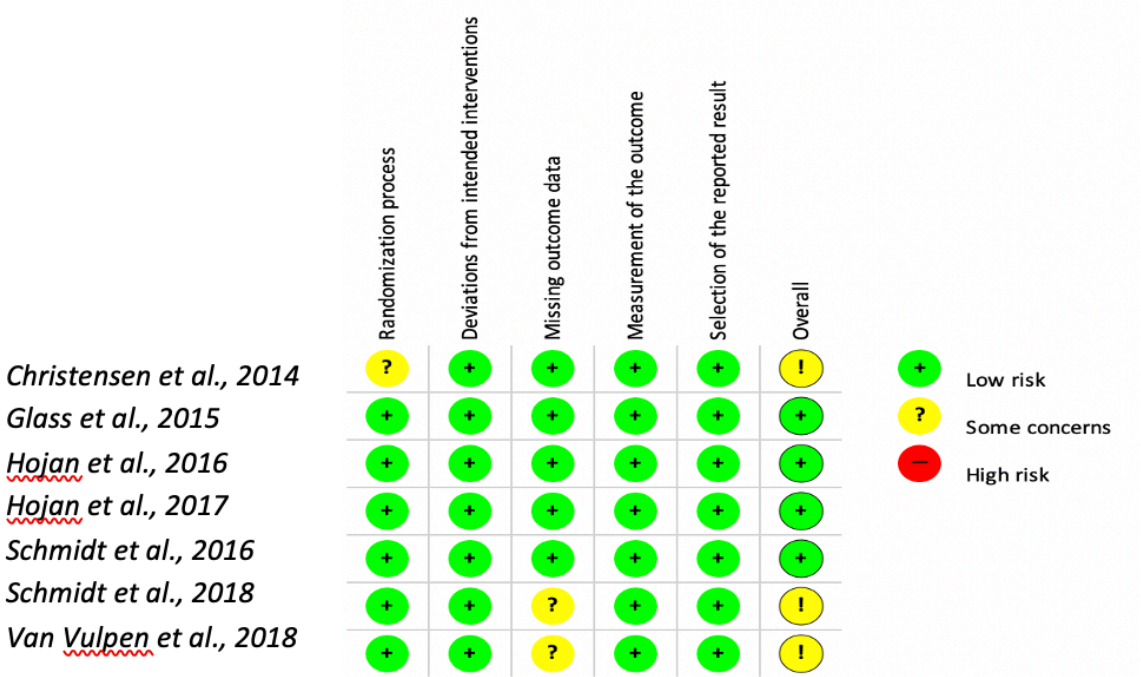


Figure 5.2 Cochrane Risk of Bias assessment for included studies

	Eligibility criteria	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	<15% dropout	Intention-to-treat analysis	Between group differences reported	Point estimate and variability reported	Total (0-11)
Christensen et al., 2014 (186)	✓	✓	×	✓	×	×	✓	×	✓	✓	✓	7
Glass et al., 2015 (187)	✓	✓	✓	✓	×	×	×	✓	✓	✓	✓	8
Hojan et al., 2016 (184)	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	9
Hojan et al., 2017 (185)	✓	✓	✓	✓	×	×	✓	✓	✓	✓	✓	9
Schmidt et al., 2016 (181)	✓	✓	✓	✓	×	×	×	×	✓	✓	✓	7
Schmidt et al., 2018 (182)	✓	✓	✓	✓	×	×	×	×	✓	✓	✓	7
Van Vulpen et al., 2018 (183)	✓	✓	✓	✓	×	×	×	×	✓	✓	✓	7
	100%	100%	100%	100%	0%	0%	43%	43%	100%	100%	100%	

Table 5.3 PEDro scale assessment of bias for included studies

	Description of patient selection	**Adequate patient selection**	**Eligibility criteria for therapist/ setting determined & adequate**	**Exercise based in *a priori* aims & intentions**	**Rationale for content & intensity**	**Intensity described**	**Exercise monitored & adjusted where necessary**	**Exercises personalised & contextualised to individual**	**Adherence determined & acceptable**	**Conclusion therapeutic validity**
Christensen et al., 2014 (186)	✓	✓	✓	✓	✓	✓	✓	×	✓	High
Glass et al., 2015 (187)	✓	✓	✓	✓	✓	✓	✓	×	✓	High
Hojan et al., 2016 (184)	✓	✓	✓	✓	✓	✓	×	✓	✓	High
Hojan et al., 2017 (185)	✓	✓	✓	✓	✓	✓	×	✓	✓	High
Kim et al., 2015 (180)	✓	✓	✓	✓	✓	✓	✓	×	×	High
Schmidt et al., 2016 (181)	✓	✓	✓	✓	✓	✓	✓	×	×	High
Schmidt et al., 2018 (182)	✓	✓	✓	✓	✓	✓	×	×	×	High
Van Vulpen et al., 2018 (183)	✓	✓	✓	✓	✓	✓	✓	×	×	High

Table 5.4 CONTENT scale assessment of therapeutic validity for included studies

5.4.4 Therapeutic validity of exercise interventions

Using the CONTENT scale, all eight studies were deemed to have a high therapeutic validity (**Table 5.4**). All the interventions had a clear rationale, well defined aims and provided a stated intensity for the exercises. Adherence to the intervention was reported in four studies and this ranged from 70% to 95% (184-187). Two of the studies offered a personalised exercise programme (184,185).

5.4.5 Effects of exercise on inflammation

The outcome measures used to assess systemic inflammation included pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, TNFα, IFNγ and CCL4), anti-inflammatory cytokines (IL-1RA and IL-10), immune cell counts (total white cell, lymphocyte, monocyte, CD3, CD4, CD8, B cell and NK cell), adipokines (adiponectin and leptin), IGF-1 and C-reactive protein (CRP). All studies measured these markers from plasma samples.

IL-6

Five studies measured IL-6 (181,183-186) and the results are summarised in **Table 5.5**. In all studies there was an increase in IL-6 in control patients. Two of the studies found a significant difference in Δ IL-6 between the exercise group and controls, with either no increase or a smaller increase found in the exercise groups (181,185). A third study reported a significant increase in IL-6 during radiotherapy in the controls, which was not seen in the exercise group; however, the between group difference was not significant (184).

TNFα

Five studies measured TNFα (183-187) and the results are summarised in **Table 5.6**. Two of the five studies reported significant increase in TNFα in the control groups (185,187). Only

one of the five studies found a significant increase in TNFα in the exercise group (185). One study reported a significant between group difference in Δ TNFα, with a significant increase in the control group compared to no change in the exercise group (187). A second found a larger increase in TNFα in the controls compared to the exercise group but the difference was not statistically significant (184).

IL-1β

Two studies reported IL-1β as an outcome (184,185). Both studies showed an increase in IL-1β in controls: mean 87.4 ± 179.6 ft/ml to 210.8 ± 494.4 ft/ml, p>0.05 (184) and 117.1 ± 212.6 ft/ml to 147.2 ± 186.8 ft/ml, p<0.05 (185). The former study reported a non-significant fall in the exercise group (mean 98.6 ± 180.1 ft/ml to 96.7 ± 134 ft/ml, p>0.05) (184), whilst the latter found significant increase in the exercise group (106.2 ± 1675.2 ft/ml to 142.9 ± 196.9 ft/ml, p<0.05) (185). Neither study found a significant between group difference in Δ IL-1β.

	Δ IL-6 in exercise group	Δ IL-6 in controls	Between group comparison	Other findings
Resistance training				
Schmidt et al., 2016 (181)	No significant change during radiotherapy: mean difference = 0.16, 95% CI -0.28 to 0.60 (log transformed values)	Non-significant increase during radiotherapy: mean difference = 0.42, 95% CI -0.01 to 0.85 (log transformed values)	Significantly smaller increase in exercise vs controls: between group mean difference = -0.26, 95%CI -0.46 to -0.06, p=0.01 (log transformed values)	Effects of exercise on fatigue and pain after radiotherapy were significantly mediated by IL6 level at end of treatment: 22% of fatigue variance (p=0.023); 24% of pain variance (p<0.001)
Christensen et al., 2014 (186)	Increased during chemotherapy: 2.3-fold increase, 95%CI 1.3 to 3.7 (mean 0.75 ± 0.62 pg/ml to mean 2.43 ± 3.68 pg/ml)	Increased during chemotherapy: 1.9-fold increase, 95% CI 1.1 to 3.2 (mean 1.08 ± 0.66 pg/ml to mean 2.35 ± 2.15 pg/ml)	No significant difference in ΔIL6 between exercise and controls (p=0.336)	Both exercise and control groups had significantly higher baseline levels than healthy population comparison group: 1.8-fold and 3.0-fold respectively
Combined aerobic & resistance				
Van Vulpen et al., 2018 (183)	Increased during chemotherapy: TER 2.11, 95% CI 1.26 to 3.52	Increased during chemotherapy: TER 1.69, 95% CI 1.04 to 2.74	No significant difference in ΔIL6 changes between exercise and controls	Baseline to post exercise intervention changes in IL-6 correlated with change in cancer related fatigue (r=0.21)
Hojan et al., 2016 (184)	No significant change during radiotherapy: mean difference = 1446.2, p>0.05 (mean 3461.4 ± 1824.8 ft/ml to mean 4907.5 ± 2460.7 ft/ml)	Increased during radiotherapy: mean difference = 2126.3, p<0.05 (mean 3415.7 ± 1983.5 ft/ml to mean 5542.4 ± 3106.1 ft/ml)	No significant difference in ΔIL6 changes between exercise and controls	
Hojan et al., 2017 (185)	Increased during radiotherapy: mean 3158.1 ± 1675.6 ft/ml to mean 5306.1 ± 5055.1 ft/ml, p<0.05	Increased during radiotherapy: mean 3249.4 ±2044.8 ft/ml to mean 5883.7 ± 3050.7 ft/ml, p<0.05	Significant between group difference in ΔIL6 over 1 year follow up (p<0.001) 12 month follow up: mean 3095.9 ± 2623.1 ft/ml, in exercise; mean 3618.2 ± 2227.1 ft/ml, in controls	

Table 5.5 Effect of exercise on plasma IL-6 levels

	ΔTNFa in exercise group	ΔTNFa in controls	Between group comparison
Aerobic training			
Glass et al., 2015 (187)	No change during chemotherapy: median 1 pg/ml (IQR 1-3) to median 1 pg/ml (IQR 1-3)	Increase during chemotherapy: median 2 pg/ml (IQR 1-3) to median 3 pg/ml (IQR 1-5)	Significant between group difference in ΔTNFα between exercise and controls (p=0.046).
Resistance training			
Christensen et al., 2014 (186)	No significant change during chemotherapy: mean 4.3 ± 1.85 pg/ml to 3.87 ± 1.04 pg/ml, p=0.105	No significant change during chemotherapy: mean 4.0 ± 2.70 pg/ml to 4.08 ± 1.58 pg/ml, p=0.575	No significant difference in Δ TNFα between exercise and controls (p=0.575)
Combined aerobic & resistance			
Van Vulpen et al., 2018 (183)	No significant change during chemotherapy: TER 1.24 (95% CI 0.90 to 1.74)	No significant change during chemotherapy: TER 1.00 (95% CI 0.75 to 1.33)	No significant difference in Δ TNFα between exercise and controls: TER 1.28 (95% CI 0.91 to 1.79)
Hojan et al., 2016 (184)	Non-significant increase during radiotherapy: mean difference 11.72 ft/ml (mean 50.0 ± 20.6 ft/ml to mean 61.7 ± 39.4 ft/ml)	Non-significant increase during radiotherapy: mean difference 60.68 ft/ml (mean 34.87 ± 26.2 ft/ml to mean 95.0 ± 38.8)	Increase larger in controls than exercise group but no significant between group difference in ΔTNFα
Hojan et al., 2017 (185)	Increase during radiotherapy: mean 32.8 ± 161.1 ft/ml to 51.3 ± 186.1 ft/ml (p<0.05)	Increase during radiotherapy: mean 32.9 ± 96.2 ft/ml to 67.8 ± 196.8 ft/ml (p<0.05)	No significant difference in Δ TNFα between exercise and controls (p=0.71)

Table 5.6 Effects of exercise on plasma TNFα levels

IL-4

One study reported IL-4 (187). IL-4 decreased in the exercise group during chemotherapy (median 115 pg/ml, IQR 77-120 to median 111 pg/ml, IQR 74-90) and increased in controls (median 117 pg/ml, IQR 77-122 to median 120 pg/ml, IQR 79-138). The difference in Δ IL-4 between the exercise and control group was statistically significant (p=0.012).

IL-8

One study reported IL-8 (186). IL-8 increased during chemotherapy in both the control and exercise group (controls 1.9-fold increase, 95% CI 1.5 to 2.4, p<0.001; exercise 1.4-fold increase, 95% CI 1.1 to 1.8 p<0.01). There was no significant difference in Δ IL-8 between the two groups (p=0.272).

IFNγ

One study reported IFNγ (186). There was no significant difference in IFNγ after chemotherapy in either the exercise or control group (controls mean 2.96 $\pm$ 1.73 pg/ml to mean 2.31 $\pm$ 1.38 pg/ml; exercise mean 2.01 $\pm$ 2.30 pg/ml to mean 1.87 $\pm$ 1.27 pg/ml) and no significant difference in Δ IFNγ between the two groups (p=0.161).

CCL4

One study reported CCL4 (187). CCL4 decreased during chemotherapy in exercise group (median 177 pg/ml IQR 123-265 to median 163 pg/ml IQR 114-205) and increased in controls (median 152 pg/ml IQR 125-199 to median 159 pg/ml IQR 136-217). There was a significant difference in Δ CCL4 between the exercise and control group (p=0.034).

IL1-RA

Two studies reported IL-1RA as an outcome (181,183). One study found a non-significant fall in IL1-RA in both exercise and control groups (mean difference -0.11, 95% CI -0.34 to 0.12 in exercise; mean difference -0.11, 95% CI -0.33 to 0.12 in controls, log transformed values) (181). The other study found a significant increase from baseline to mid chemotherapy in controls (treatment effect ratio 1.44, 95% CI 1.11 to 1.86, $p<0.01$), which was not seen in the exercise group (treatment effect ratio 1.27, 95% CI 0.99 to 1.62, $p>0.05$) (183). Neither study showed a significant between group difference in Δ IL-1RA.

IL-10

One study reported IL-10 (186). IL-10 increased during chemotherapy in both the control and exercise group (controls mean 1.3-fold increase, 95% CI 1.0 to 1.6, $p<0.05$; exercise mean 1.3-fold increase, 95% CI 1.1 to 1.6, $p<0.01$). There was no significant between group difference in Δ IL-10 ($p=0.194$).

Immune cell parameters

Four studies measured changes in immune cell parameters (180,182,184,187). The results are summarised in **Table 5.7**. In the control groups, the studies reported a fall in total white cell count, lymphocyte count, CD3 count, CD4 count and CD8 count, with an increase in the monocyte count. Two studies assessed changes in B cell counts and reported different results in their control groups, with one reporting an increase (187) and the other a decrease (182).

There were no significant between group differences in the change in any of these parameters. In most of the studies, the changes seen in the exercise group mirrored that seen in the control patients (**Table 5.7**). However, Glass et al reported an increase in CD8 and no change in CD4 in the exercise group, in comparison to a decrease in both parameters in controls, but this difference was not statistically significant (187). Kim et al did not provide a control group for comparison but reported no change in total white cell and lymphocyte

counts, a non-significant increase in CD4 and CD8 counts and a non-significant decrease in NK cell in patients who underwent exercise (180).

Adipokines and other markers of inflammation

Other markers of inflammation were included in two studies: adiponectin, leptin, IGF-1 and CRP (183,187). The results are summarised in **Table 5.7**. Both studies measured leptin. One found a significant between group difference in Δ leptin, with a non-significant increase in the exercise group and non-significant decrease in the controls (183). The between group difference lost significance after controlling for changes in BMI. The other study found a decrease in leptin in both the exercise and control groups, and the between group difference in Δ leptin was not significant (187).

Van Vulpen *et al* reported a decrease in adiponectin in both exercise and groups, with no significant difference in Δ adiponectin between the groups (183). This study also measured CRP and found a significant decrease at 6-9 month follow up in the exercise, with no change at 6-9 month follow up in controls, but there was no significant difference in Δ CRP between the groups (183). Glass *et al* reported a decrease in IGF-1 in the exercise group, with no change in the control group, but again the difference in Δ IGF-1 between the groups was not significant (187).

Outcome	Study	Δ outcome in exercise group	Δ outcome in controls	Between group comparison
Total WCC	Hojan et al., 2016 (184)	Significant decrease during radiotherapy: mean difference -1.73 ($x10^9$/l), p<0.05 (mean 7.09 ± 1.70 to mean 5.35 ± 1.43)	Significant decrease during radiotherapy: mean difference -0.99 ($x10^9$/l), p<0.05 (mean 7.61 ± 1.70 to mean 5.68 ± 1.68)	No significant between group difference in ΔWCC
	Kim et al., 2015 (180)	No change from baseline to end of intervention: mean 4.89 ± 2.23 ($x10^3$/ul) to mean 5.00 ± 1.64 $x10^3$/ul, p=0.805	N/A – no control group	N/A – no control group
Lymphocyte	Hojan et al., 2016 (184)	Significant decrease during radiotherapy: mean difference -0.67 ($x10^9$/l), p<0.05 (mean 1.84 ± 0.58 to mean 1.11 ± 0.43)	Significant decrease during radiotherapy: mean difference -0.99 ($x10^9$/l), p<0.05 (mean 2.10 ± 0.58 to mean 1.11 ± 0.43)	No significant between group difference in Δ lymphocyte count
	Kim et al., 2015 (180)	No change from baseline to end of intervention: mean 1.31 ± 0.57 ($x10^3$/ul) to mean 1.18 ± 0.41 $x10^3$/ul, p=0.349	N/A – no control group	N/A – no control group
Monocyte	Glass et al., 2015 (187)	Increased during chemotherapy: 7.9% to 11.8%	Increased during chemotherapy: 8.4% to 13.2%	No significant between group difference in Δ monocyte (p=0.949)
CD3	Schmidt et al., 2018 (182)	Significant reduction during chemotherapy in aerobic group: Δ-25.8%, p=0.001 Non-significant reduction in resistance group: Δ-19.3%, p=0.46	Significant reduction during chemotherapy: Δ-21.5%, p=0.001	No significant between group difference in Δ CD3 (p=0.91)
CD4	Glass et al., 2015 (187)	No change during chemotherapy: 23.6% to 22.4%	Decrease during chemotherapy: 22.2% to 19.0%	No significant between group difference in Δ CD4 (p=0.063)
	Kim et al., 2015 (180)	Non-significant increase from baseline to end of intervention: mean 36.76% ± 13.90 to mean 40.36% ± 17.03, p=0.160	N/A – no control group	N/A – no control group
	Schmidt et al., 2018	Significant reduction during chemotherapy in aerobic group: Δ-35.1%, p=0.001 Significant reduction in resistance group: Δ-32.0%, p=0.001	Significant reduction during chemotherapy: Δ-29.2%, p=0.001	No significant between group difference in Δ CD4 (p=0.8)

CD8	Glass et al., 2015 (187)	Increase during chemotherapy: 42.9% to 46.7%	Decrease during chemotherapy: 48.8.2% to 42.6%	No significant between group difference in Δ CD8 (p=0.101)
	Kim et al., 2015 (180)	Non-significant increase from baseline to end of intervention: mean 19.22% ± 8.27 to mean 22.22% ± 6.60, p=0.149	N/A – no control group	N/A – no control group
	Schmidt et al., 2018 (182)	Significant reduction during chemotherapy in aerobic group: Δ-16.9%, p=0.04 Non-significant reduction in resistance group: Δ-10.9%, p=0.41	Non-significant reduction during chemotherapy: Δ-4.0%, p=0.41	No significant between group difference in Δ CD8 (p=0.41)
B cell	Glass et al., 2015 (187)	Increase during chemotherapy: 41.8% to 43.0%	Increase during chemotherapy: 41.0% to 46.5%	No significant between group difference in Δ B cell (p=0.852)
	Schmidt et al., 2018	Significant reduction during chemotherapy in aerobic group: Δ-92.6%, p=0.001 Significant reduction in resistance group: Δ-86.6%, p=0.001	Significant reduction during chemotherapy: Δ-88.8%, p=0.001	No significant between group difference in Δ B cell (p=0.97)
NK cell	Glass et al., 2015 (187)	No change during chemotherapy: 8.2% to 9.7%	No change during chemotherapy: 8.8% to 9.8%	No significant between group difference in Δ B NK cell (p=0.929)
	Kim et al., 2015 (180)	Non-significant decrease from baseline to end of intervention: mean 16.48% ± 8.23 to mean 15.82% ± 9.36, p=0.729	N/A – no control group	N/A – no control group
	Schmidt et al., 2018 (182)	Significant reduction during chemotherapy in aerobic group: Δ-40.1%, p=0.001 Non-significant reduction in resistance group: Δ-22.9%, p=0.53	Significant reduction during chemotherapy: Δ-19.4%, p=0.05	No significant between group difference in Δ NK cell (p=0.07)
Adiponectin	Van Vulpen et al., 2018 (183)	Non-significant decrease from baseline to end of chemotherapy: TER 0.91, 95% CI 0.71 to 1.15	Decrease from baseline to end of chemotherapy: TER 0.79, 95% CI 0.65 to 0.97, p<0.05	No significant between group difference in Δ adiponectin (TER 1.13, 95% CI 0.85 to 1.50)

Leptin	Glass et al., 2015 (187)	Decrease during chemotherapy: median 7795 pg/ml (IQR 4067-18508) to median 6255 pg/ml (IQR 3508-12308)	Decrease during chemotherapy: median 12265 pg/ml (IQR 2195-28808) to median 9072 pg/ml (IQR 3663-14704)	No significant between group difference in Δ leptin (p=0.848)
	Van Vulpen et al., 2018 (183)	Non-significant increase: TER 1.12, 95% CI 0.82 to 1.52	Non-significant decrease: TER 0.80, 95% CI 0.62 to 1.05	Significant between group differences in Δ leptin: TER 1.40, 95% CI 1.01 to 1.93, p<0.05 After controlling for changes in BMI: TER 1.19, 95% CI 0.88 to 1.62
IGF-1	Glass et al., 2015 (187)	Decrease during chemotherapy: median 172 pg/ml (IQR 113.5-207.5) to median 149 pg/ml (IQR 119-182.5)	No change during chemotherapy: median 150 pg/ml (IQR 119-199) to median 159 pg/ml (IQR 101-195)	No significant between group difference in Δ IGF-1 (p=0.879)
CRP	Van Vulpen et al., 2018 (183)	Significant decrease from baseline to 6-9 month follow up: TER 0.54, 95% CI 0.30 to 0.96, p<0.01	No significant change from baseline to 6-9 month follow up: TER 0.74, 95% CI 0.46 to 1.21	No significant difference in Δ CRP between two groups: TER 0.86, 95% CI 0.52 to 1.40

Table 5.7 Effects of exercise on immune cell parameters, plasma adipokines, IGF-1 and CRP

5.5 Discussion

In this review, three studies found a significant difference in the change in cytokine levels between exercise and control groups, with either a decrease or smaller increase in IL-4, IL-6, TNFα and CCL4 in the exercise group compared to controls (181,185,187). The strongest evidence is of an effect of exercise on IL-6 levels, with two studies out of five that measured this cytokine showing a significant difference (181,185).

The finding of a significant between group differences in IL-6 and TNFα are in keeping with previous meta-analyses of exercise studies in cancer survivors (98,99). IL-6 and TNFα are acute phase reactants that are secreted in response to trauma or cellular injury (191,192). TNFα is predominantly secreted by activated macrophages and plays a key role in regulating immune cells (191-193). It also mediates cell apoptosis, cachexia and fever, and stimulates the production of other pro-inflammatory cytokines, such as IL-6 (192,193).

IL-6 is a key mediator of the acute phase response and is secreted by, amongst other cells, macrophages and adipocytes. Its pro-inflammatory effects include stimulating the recruitment of neutrophils, T cell differentiation and B cell maturation (191,194). IL-6 is also regarded as a 'myokine' as it is also secreted by skeletal muscle in response to muscle contraction and rises in response to an acute episode of exercise (195). However, high levels of IL-6 are associated with muscle atrophy and inhibition of IL-6 is associated with preservation of muscle mass in murine models (192).

CCL4, also known as macrophage inflammatory protein 1β, is secreted by B cells, T cells, neutrophils and monocytes, and is a potent chemoattractant for CD4 cells, monocytes and NK cells (196). IL-4 stimulates CD4 differentiation, which in turn produce further IL-4 in a positive feedback loop (191,197). It also promotes the differentiation of B cells into plasma cells (188,194) and has been implicated in macrophage differentiation, promoting the development of the 'anti-inflammatory' M2 subtype, which is associated with tissue repair and fibrosis (194).

Many markers of inflammation were used in the studies included in this review. Whilst some markers, such as IL-6 and TNFα, were reported in five out of the eight included studies, the others were only measured in one or two studies. IL-1β and IL-1RA were both measured in two studies, and although a significant between group difference in the change in these parameters was not found, there was evidence of an increase in control groups, which was not seen in the exercise groups (183,184). CRP was measured in only one study; this found a significant decrease in CRP in the exercise group, which was not seen in the controls, but the difference between the groups was not significant (183). Due to the small number of studies that measured these markers, and the sample size of the studies, it is possible that the studies are not adequately powered to detect significant differences between the groups. These observed trends warrant further investigation with studies targeting a narrower range of markers and with sample size calculations based upon these specific markers.

A rise in pro-inflammatory cytokines, including IL-1β, IL-4, IL-6, IL-8, TNFα and CCL4, was seen in all studies in the control patients who were undergoing chemotherapy or radiotherapy (183-187), highlighting the presence of inflammatory stimulus from these oncological treatments and/or the cancer itself. An increase in IL-10 was also found during chemotherapy (186). This anti-inflammatory cytokine is released in response to a rise in IL-6 as an attempt to regulate and balance the systemic inflammatory response.

High levels of systemic inflammation are associated with catabolic effects of cancer and the occurrence of sarcopenia (3,4), and pro-inflammatory cytokines such as IL-6, TNF α and CCL4 are involved in both stimulating and magnifying this inflammatory response (4). It is therefore possible that a reduction in these cytokines may negate the negative effects of cancer and oncological therapies on body composition. High levels of pre-operative inflammation are also associated with a greater risk of developing post-operative complications (82,84,86)) and thus it is also possible that lower inflammation in cancer patients preparing for surgery may have a beneficial effect on post-operative outcomes. However, the regulation of interleukins is a complex, with many cytokines have intrinsic negative feedback loops (188), and as highlighted by the role of IL-4 in promoting M2 macrophage differentiation (194), cytokines can exert both pro- and anti-inflammatory effects. Consequently, it is challenging to predict

the effects of changes in serum interleukins on the wider inflammatory milieu, yet alone the draw conclusions on the effects of changes of serum interleukins on clinical outcomes.

There was no evidence of a significant difference in the changes in leucocyte numbers between the exercise groups and the controls. Therefore, whilst there is evidence of an effect of exercise on some cytokine levels, there is no evidence that this translates to an effect on immune cell number. There may be other factors related to the effects of chemotherapy or radiotherapy on the immune system which negate or overcome the influence of these cytokines on immune cell populations. As many of the studies have a small sample size and do not provide sample size calculations, it is possible the studies are not adequately powered to detect differences in immune cell populations. Further research into the effects of exercise on immune cell number and activity is needed. The clinical significance of changes in cytokines is complex so the effect of exercise on immune cells is a clinically important outcome to address.

A significant difference in the change in leptin levels was seen between the exercise and control groups in one study, with a non-significant increase in the exercise group and a decrease in the control group (183). This difference was mediated by changes in BMI in the two groups and was not statistically significant once changes in BMI were controlled for. Visceral adipose tissue is metabolically active, and adipocytes secrete a range of cytokines and adipokines, including IL-6, IL-8, TNFα, adiponectin and leptin (65). Leptin potentiates chronic inflammation through stimulating production of IL-1, IL-6, IL-12 and TNFα, and it has also been shown to increase cell survival in a range of cancer cell lines, including oesophageal cancer cells (198).

Adiposity is a key driver of inflammation and high levels of leptin are found in obese patients (64). An exercise induced reduction in adiposity may therefore reduce inflammation. However, this hypothesis would expect a fall in leptin with exercise, rather than a rise as was observed in the study by Van Vulpen et al (183). In this study, baseline BMI in the exercise and control groups was comparable (26.1 ± 4.8 kg/m^2 and 26.6 ± 4.8 kg/m^2 respectively) but the change in BMI, which attenuated the between group difference in change in leptin, is not

provided. It is possible that is a greater fall in BMI occurred in the controls during chemotherapy, in comparison to the exercise group. This may account for the fall in leptin in the control group but as the change is BMI is not provided, this cannot be substantiated.

The studies in this review included a range of malignancies: breast (four studies), prostate (two studies), testicular (one study) and any solid malignancy (one study). Over 50% of the participants in the latter study had breast cancer; others included lung, bladder, uterine, rectal, peritoneal and nasopharyngeal cancers (187). Therefore, the majority of the patients who have been included in the studies in this review had breast cancer. The link between adiposity, chronic inflammation and poor outcomes in breast cancer is well described (71,105,64). Two of the studies in this review that found a significant benefit from exercise in reducing inflammation included breast cancer patients (181,187). This is in keeping with the large number of studies that have found a significant reduction in inflammation with exercise in patients who have recovered from breast cancer (98,101,103,108). However, in this review evidence of an effect of exercise on inflammation was also seen studies of prostate cancer patients (185) and those with other solid tumours (187), suggesting the benefits of exercise on inflammation are not limited to breast cancer patients only.

The exercise interventions in the studies including in this review lasted between 8 and 52 weeks. The majority lasted for 12 weeks, which is comparable to the duration of prehabilitation in oesophageal cancer patients undergoing neoadjuvant chemotherapy or radiotherapy. The mean age of participants in the studies ranged from 34 to 67 years old in the exercise groups and 35 to 69 years old in the controls (median 52 and 54 years old respectively). Two studies excluded common chronic diseases in their study populations (180,186), and in a further three studies the contraindications to exercise training were poorly defined (182,183,187). Therefore, the results of this review are most applicable to a middle-aged population who do not have significant co-morbidities in addition to their diagnosis of cancer. This limits the external validity of these findings, and the results may not be comparable in patients with oesophageal cancer, who are often more elderly, frail and have multiple comorbidities (199).

The type of oncological treatments that were used during the study period varied considerably. However, significant differences in the change in cytokines between exercise and control groups were seen both in studies with chemotherapy and radiotherapy. The timing of the oncological treatments was also variable. Patients in two studies received adjuvant chemotherapy or radiotherapy (181,183), one included patients receiving either adjuvant or neoadjuvant chemotherapy (182), but in other five studies in this review it is unclear whether the oncological treatments were curative, neoadjuvant or adjuvant therapies. The timing of the studies in relation to other treatments, such as surgery, is important as this may affect the patient's systemic inflammatory state. None of the studies reported whether participants used other treatments or medications that may affect inflammation.

There was a high drop-out rate in several studies, with a high proportion of drop out-after randomisation in three studies (181-183), a high proportion of loss to follow up in one study (186) and incomplete reporting at all assessment points in one study (183). The high drop-out after randomisation appears to be due to the application of exclusion criteria after randomisation or performing a secondary analysis of data from a previous study. Although all three studies show the study groups after the drop-out were comparable for key demographic factors, the two groups are only truly comparable at the point of randomisation so there is a risk of selection bias due to unmeasured cofounding factors. There was no evidence of assessor blinding in four studies (181-183,187). However, the outcome measurements in these studies are objective with clearly defined protocols so there is less risk of measurement bias if indeed they were not blinded to group allocation.

The CONTENT scale scores demonstrate that the interventions were generally very well reported, with detailed study protocols and appropriate rationale to support the type of exercises used in the protocols. However, only half of the studies reported adherence to the exercise protocols (184-187). It is possible that poor adherence to exercise may lead to a type 2 error and the failure to detect an effect of exercise on markers of inflammation. Only two studies offered personalisation of the exercise protocols (184,185). Personalisation could allow less stringent exclusion criteria, which in many of these studies excluded patients with comorbidities (180,182,184-187). This would improve the external validity of the study

findings and better reflect true clinical population that may receive these exercise interventions in practice.

A previous meta-analysis of exercise interventions in cancer survivors found that combined aerobic and resistance training programmes had the greatest impact on levels of systemic inflammation (99). In this review, there is evidence of an anti-inflammatory effect of exercise in studies using aerobic exercise, resistance exercise and those with a combination of both (181,185,187). Due to the small number of studies and heterogeneity in both exercise intervention and the study populations, comparison between studies is difficult and subgroup analysis is not possible. Furthermore, the studies used different units, measurement scales and data transformations for reporting same outcomes. Therefore, it is not possible to conclude whether particular types of exercise may have the most beneficial effects on inflammation or which study populations may benefit most.

5.6 Conclusions

This review has identified some evidence of a beneficial effect of exercise on inflammation during chemotherapy or radiotherapy treatments. The changes seen in IL-4, IL-6, TNFα, CCL4 and leptin highlight these inflammatory markers as candidates for future research in this field. However, not all the studies showed benefit from exercise and a large range of markers of inflammation were used, often with conflicting results. Larger studies are needed with focused outcomes and specific power calculations to reduce risk of both type 1 and type 2 errors arising from multiple testing and underpowered studies respectively.

CHAPTER 6

-

REHABILITATION AND SYSTEMIC INFLAMMATION IN PATIENTS WITH OESOPHAGO-GASTRIC CANCER

6.1 Objectives and hypothesis

Objectives:

I. To characterise changes in systemic inflammation between diagnosis and surgery in patients with oesophago-gastric cancer

II. To examine whether prehabilitation impacts upon pre-operative changes in systemic inflammation

Hypothesis: Systemic inflammation increases during neoadjuvant therapy and prehabilitation attenuates this increase in inflammation.

6.2 Introduction

Exercise can reduce systemic inflammation in cancer survivors (98,99). A meta-analysis into the effects of exercise programmes on inflammation in breast cancer survivors found that exercise is associated with a significant reduction of IL-6, IL-8 and TNFα, and a significant increase in the anti-inflammatory cytokine IL-2 (98). Building on these findings, a second meta-analysis included studies from all cancer survivors and again found a significant decrease in pro-inflammatory cytokines with exercise training (99). The greatest effect on inflammation was seen with combined aerobic and resistance exercise programmes, and in studies with breast or prostate cancer patients (99).

Only one study to date has looked at exercise in oesophageal cancer survivors; a study of 12 patients who had completed treatment for oesophageal cancer found a significant reduction in serum IL-8 after a 12-week exercise programme (100). This study did not include a control group comparison so the conclusions that can be drawn are limited. It does, however, support the need for further research into the effects of exercise in patient group. As over 80% of published studies into exercise and inflammation in cancer survivors have focused on breast or prostate cancers (99), it provides an important indication that the anti-inflammatory benefits of exercise may extend beyond hormone driven cancer groups.

The systematic review undertaken in **Chapter 5** found evidence that exercise can reduce inflammation in patients actively undergoing chemotherapy and/or radiotherapy, suggesting that the beneficial effects of exercise on inflammation can be seen during treatment as well as in cancer survivors. However, the inflammatory profile of patients undergoing neoadjuvant treatment for oesophago-gastric (OG) cancer is not known and no studies to date have examined the effects of prehabilitation on inflammation in any patient group. Therefore, this study aims to characterise the changes in inflammation in patients undergoing neoadjuvant treatment for OG cancer and to examine the impact that prehabilitation may have on inflammation during this time.

6.3 Methods

6.3.1 Study population

All patients who were discussed at the North-West London OG cancer multidisciplinary team (MDT) meeting between May 2019 and March 2020 and between August 2020 and September 2021 were eligible for inclusion in this study. All research activities were suspended between March 2020 and August 2020 due to the Covid-19 pandemic and therefore patients starting their cancer treatment during this period were not included in this study. Patients were referred to the MDT meeting from Imperial College Healthcare NHS

Trust, Bedfordshire Hospitals NHS Trust, East and North Hertfordshire Hospitals NHS Trust and West Hertfordshire Hospitals NHS Trust. Patients from all three NHS Trusts underwent surgery at the same specialist OG cancer centre at Hammersmith Hospital, London.

All patients from Imperial College Healthcare NHS Trust were invited to participate in the PREPARE for Surgery prehabilitation programme. Patients from Bedfordshire Hospitals, East and North Hertfordshire Hospitals and West Hertfordshire Hospitals NHS Trusts who underwent treatment prior to February 2021 did not receive any prehabilitation and were invited to participate in this study as a control group. From February 2021, patients from these NHS Trusts were invited to participate in a digital prehabilitation programme and were therefore included in the prehabilitation group (**Figure 6.1**).

Other than the provision of prehabilitation, all patients in this study received the same pre-operative care, co-ordinated by the same MDT. The same chemotherapy and chemo-radiotherapy protocols were used for all patients. Patients undergoing neoadjuvant chemotherapy received fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT), epirubicin, cisplatin and capecitabine (ECX), or epirubicin, oxaliplatin and capecitabine (EOX). Paclitaxel and carboplatin alongside 41.4Gy radiotherapy in 23 fractions was given to patients requiring neoadjuvant chemoradiotherapy.

Ethical approval for this study was granted by the UK Health Research Authority (reference 19/LO/1604).

6.3.2 Prehabilitation programme 2020-2021

Two different types of prehabilitation were provided during this study period (**Figure 6.1**).

Between May 2019 and March 2020, patients from Imperial College Healthcare NHS Trust were invited to participate in the PREPARE for Surgery prehabilitation programme, as described in **Chapter 2.3.1**. Patients attended an initial face-to-face appointment at the multidisciplinary prehabilitation clinic to assess their needs and prescribe their personalised

interventions. The programme was home-based, with weekly telephone appointments with the exercise therapist. Further face-to-face appointments were undertaken at the end of neoadjuvant therapy and immediately before surgery to reassess the patient's cardiorespiratory fitness (as described in **Chapter 3.3.2**).

From March 2020 onwards, the provision of prehabilitation was interrupted due to the Covid-19 pandemic. A digital version of the prehabilitation programme was introduced in August 2020 to provide prehabilitation whilst minimising visits to the hospital and reducing the risk of exposure to SARS-CoV-2. To avoid excluding patients who were unable to or did not wish to participate in the digital version of the programme, the previous model of a home-based prehabilitation with telephone appointments and face-to-face assessments was also reintroduced when it was operationally possible to do so, which occurred in February 2021. Therefore, from February 2021 onwards, patients were given the choice of which model of prehabilitation they wished to participate in.

The introduction of a digital model of the prehabilitation programme enabled prehabilitation to be extended to patients from Bedfordshire Hospitals NHS Trust, East and North Hertfordshire Hospitals NHS Trust and West Hertfordshire Hospitals NHS Trust from February 2021, as this model did not require face-to-face appointments. These patients were only offered the digital prehabilitation model as they were drawn from a wide geographical area so could not attend the prehabilitation clinics that are needed for assessment in the face-to-face prehabilitation model.

In the digital prehabilitation model, a free downloadable digital application (app) was created, available on both iOS and Android platforms. The app included an integrated video platform for remote assessments and consultations, a screening survey to measure baseline health behaviours and a 'to-do' list with the patient's personalised exercise and nutritional interventions. These interventions were personalised according to each patient's individual needs, as occurred in the face-to-face prehabilitation model.

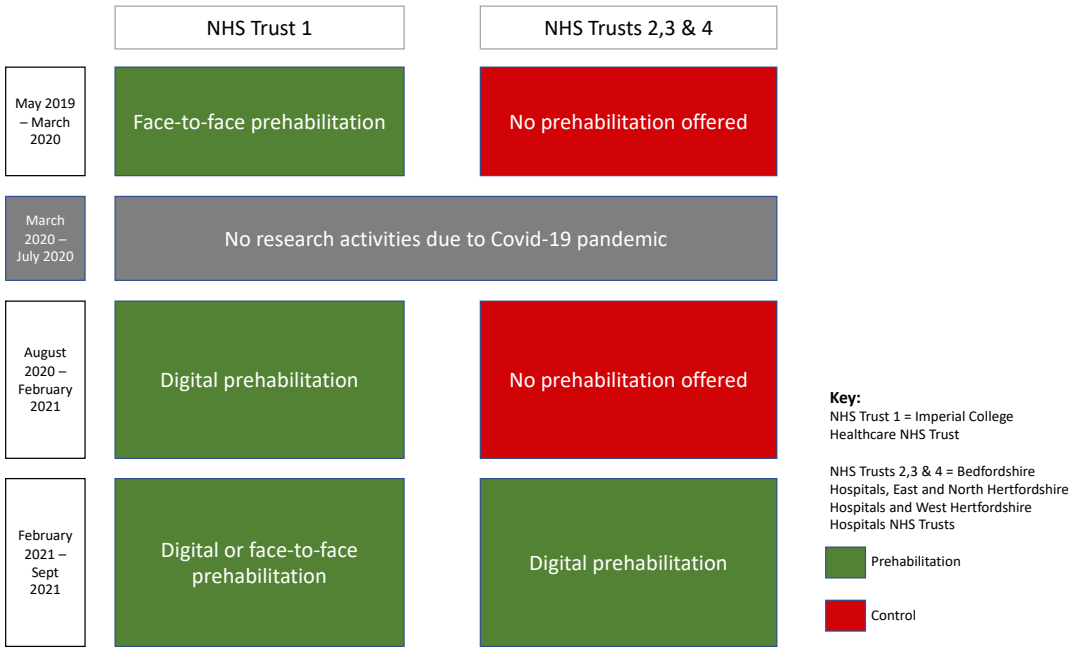


Figure 6.1 Types of prehabilitation used during the study period

As different models of prehabilitation were used during this study period, different methods were used to monitor adherence to the prehabilitation programme. These also changed over time as the programme continually had to adapt and respond to the changing clinical environment during the Covid-19 pandemic. Consequently, there was no consistent measure of adherence to use for the prehabilitation patients in this study. Therefore, to measure the amount of exercise that study participants had completed, patients in this study were asked to self-assess their activity using the Godin-Shephard Leisure Time Physical Activity Questionnaire (200) (**Appendix V**). Participants completed this questionnaire on the day the samples were taken to assess their level of physical activity.

The Godin-Shephard Leisure Time Physical Activity Questionnaire is a validated tool for quantifying levels of physical activity, and has been used in studies involving cancer patients and prehabilitation patients (201,202). In this assessment, patients state how many times they have undertaken mild, moderate and strenuous activities for at least a 15-minute duration in a typical week. Examples of each category of activity are provided in the questionnaire, along with a description of how that level of intensity would feel whilst it was

being undertaken. Mild activities are those with a METS value of 3, moderate activities have a METS value of 5, and strenuous activities are those with a METS value of 9. A description of METS values has previously been provided in **Chapter 3.3.2**.

The frequency with which the patient undertook each category of activity was multiplied by the respective METS value and the results added together for to give an overall Leisure Score Index (LSI) value. The total METS values for the moderate and strenuous activities are calculated to give a Godin Scale Score (GSS), which can then be used to stratify the amount of activity (203):

- <14: insufficient activity
- 14-23: moderate activity
- ≥24: active

A GSS of ≥24 is in keeping with WHO guidelines for recommended levels of physical activity (113,200) and has been shown to be associated with health benefits, such as a higher pVO2max and lower body fat percentage (200).

6.3.3 Measurement of inflammation

Blood samples were taken at the time of the staging laparoscopy and the time of the cancer resection. **Figure 6.2** shows these sampling time-points with reference to the pre-operative pathway in the two groups.

To ensure that as many study participants as possible had matched samples from both diagnosis and the time of resection, plasma samples collected by the Imperial College Healthcare Tissue Bank (ICHTB) were also used for patients who had consented to participate in this study. These samples were collected at the time of the staging laparoscopy, before any treatment had started. ICHTB is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and

Imperial College London. ICHTB is approved by Wales REC3 to release human material for research (17/WA/0161).

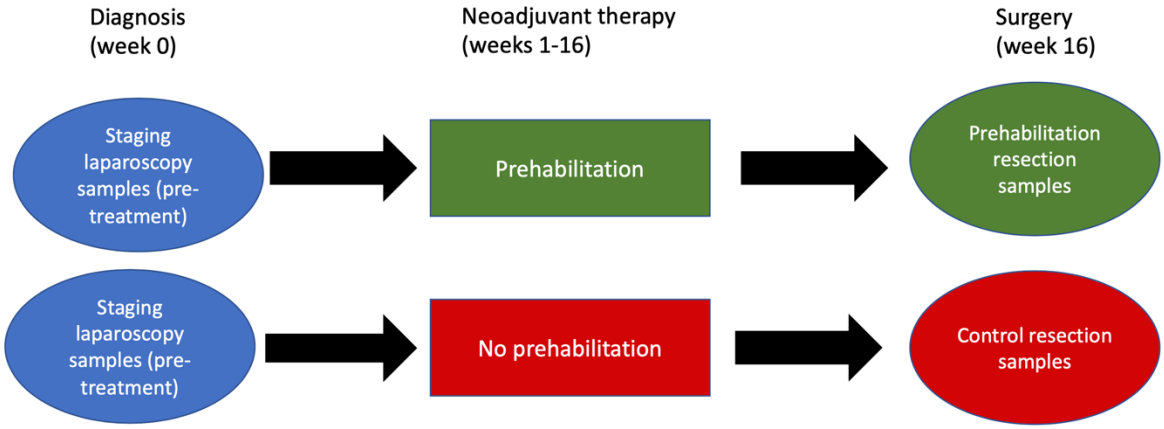


Figure 6.2 Timing of plasma sample collection.
The exact duration of the programme was determined by the time between the start of their curative pathway and the time of surgery; this was a clinical decision, unaffected by the prehabilitation programme, and the programme was provided to the patients for the whole duration of their pre-operative period

The samples were collected in 15ml Vacutainer EDTA tube and centrifuged at 2500 rpm for 10 min at 4 °C to extract the plasma, which was then stored at -80°C until the assays were performed. Measurement of human IL-1β, IL-6, IL-10 and TNFα was performed using sandwich enzyme linked immunosorbent assays (ELISA) following the manufacturer's recommendations (Invitrogen). All tests were performed with technical duplicates. For each experiment, a standard curve was generated from serial dilutions of the recombinant form of the relevant cytokine. Light absorbance was measured at 450nm and 570nm using Multiskan Ascent (Thermofisher) and the values of 570nm were subtracted from the values of 450nm for wavelength correction. The detection limit was 2pg/ml for the IL-1β, IL-6, IL-10 assays, and 4pg/ml for the TNFα assay.

IL-4 and CCL-4 were identified in Chapter 5 as markers that may be affected by exercise during ontological therapy. It was not possible to obtain ELISA testing kits for these markers due to a lack of availability during the study period, and therefore these markers could not be assessed.

6.3.4 Statistical analysis

There are no previous studies of changes in serum inflammation in oesophageal or gastric cancer patients who are undergoing multimodal treatment upon which to base a sample size calculation for this study. Therefore, data was used from a study comparing exercise and standard care in patients undergoing oncological treatment for any type of solid tumour (187). Based upon their findings (control mean TNFα = 3, exercise mean TNFα = 1, SD 2.2), 19 patients prehabilitation patients and 19 control patients would be needed to detect a significant difference in change in TNFα levels with 80% power and a significance level of 0.05.

Normality of data was assessed visually and using the Kolmogorov-Smirnov (with Lilliefors correction) and the Shapiro-Wilk normality test. Dependant on their distribution, continuous variables are presented as either mean ± standard deviation or median [interquartile range, IQR]. Changes in plasma cytokine levels between the time of the staging laparoscopy and time of surgery were assessed using a Wilcoxon test and the changes in the prehabilitation and non-prehabilitation groups were compared using a Mann-Whitney U test.

Physical activity levels between the prehabilitation and control groups were compared using an Independent-Samples T test. To assess the relationship between physical activity scores and cytokine levels, a Spearman's rank correlation test was used. Participants were categorised according to the change in cytokine levels and activity levels were compared between these groups using Independent Sample T-tests. Two-tailed tests were used throughout with a significance level of $p<0.05$. Statistical analysis was performed using SPSS version 28 (IBM, New York, USA).

6.4 Results

During the study period, matched plasma samples from pre-treatment and the time of resection were obtained from 25 patients who underwent prehabilitation and 14 controls (**Figure 6.3**). Characteristics of these study participants are shown in **Table 6.1**. There was a significantly higher BMI in prehabilitation group at baseline compared with the control group: mean difference 4.0 kg/m^2 (95% CI 0.2 to 7.9). At the time of resection, the prehabilitation group had a significantly higher weight and BMI compared with the control group: mean difference 12.4 kg (95% CI 2.4 to 22.3) and mean difference 2.9 kg/m^2 (95% CI 0.2 to 5.7) respectively. There was no significant difference in change in weight or BMI during the study in either group (prehabilitation group p=0.861 and p=0.932 respectively, control group p=0.994 and p=0.980 respectively).

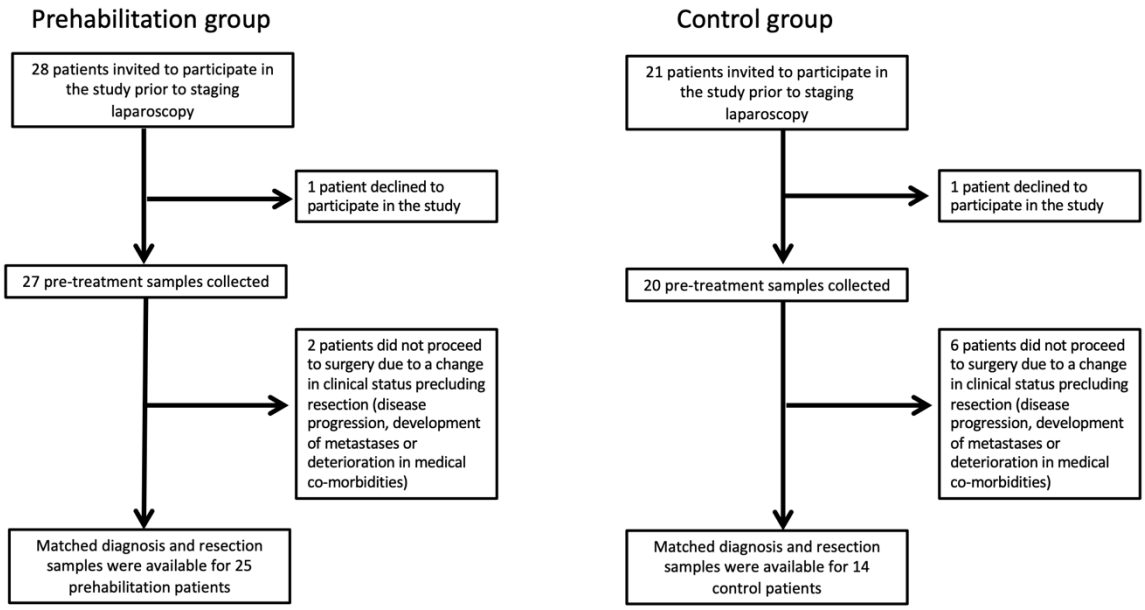


Figure 6.3 Study participant flow chart

	Prehabilitation group n=25	Control group n=14	p-value
Baseline			
Age (years)	69.4 ± 10.9	70.7 ± 8.9	0.695
Gender, male n (%)	21 (84%)	12 (86%)	0.887
Tumour location n (%)			0.824
Oesophagus/GOJ	17 (68%)	10 (71%)	
Stomach	8 (32%)	4 (29%)	
Histology, n (%)			0.448
Adenocarcinoma	24 (96%)	14 (100%)	
Squamous cell carcinoma	1 (4%)	0 (0%)	
Clinical stage, n (%)			0.650
I	1 (4%)	0 (0%)	
II	4 (16%)	1 (7%)	
II	17 (68%)	10 (72%)	
IV	3 (12%)	3 (21%)	
ASA grade, n (%)			0.673
II	16 (64%)	8 (57%)	
III	9 (36%)	6 (43%)	
Charlson Comorbidity Index	4.7 ± 1.3	5.6 ± 1.7	0.075
Comorbidities, n (%)			
Cardiac	5 (20%)	4 (29%)	0.542
Respiratory	3 (12%)	63 (21%)	0.434
Neurological	1 (4%)	1 (7%)	0.669
Endocrine	3 (12%)	3 (21%)	0.434
Psychiatric	5 (20%)	1 (7%)	0.286
Previous malignancy	2 (8%)	3 (21%)	0.229
Autoimmune	1 (4%)	0 (0%)	0.448
Weight (kg)	84.4± 16.5	70.0± 16.9	0.081
BMI (kg/m^2)	28.0± 3.8	24.0± 4.1	0.041
Neoadjuvant therapy n (%)			0.176
Chemotherapy	25 (100%)	13 (93%)	
Chemoradiotherapy	0 (0%)	1 (7%)	
At time of resection			
Weight (kg)	82.7± 13.9	70.3± 13.1	0.017
BMI (kg/m^2)	27.4± 3.9	24.4± 3.3	0.035
Physical activity			
Leisure Score Index [1]	44.7 ± 16.6	16.4 ± 13.1	0.001
Godin Scale Score [2]	28.6 ± 14.8	7.0 ± 10.8	0.001

Table 6.1. Study participant characteristics

Continuous data presented as mean ± SD. BMI = body mass index; GOJ = gastro-oesophageal junction. [1] Leisure Score Index includes all physical activity; [2] Godin Scale Score includes moderate and strenuous intensity exercise only

There was non-significant trend for a lower Charlson Co-morbidity Index in the prehabilitation patients compared with the controls. All other baseline demographics were comparable between the two groups. One patient in the prehabilitation group was taking regular immunosuppressive medication; no patients in the control group were taking immunosuppressive medication (p=0.448).

Within the prehabilitation group, 15 patients (60%) underwent the face-to-face prehabilitation model, and 10 patients (40%) underwent the digital model.

	Prehabilitation group n=25			**Control group n=14**			**Between group comparison**
	Baseline	**Resection**	**p-value**	**Baseline**	**Resection**	**p-value**	**p-value**
IL-1β (pg/ml)	5.43 (4.89 – 9.79)	5.12 (4.89 – 9.65)	0.435	7.32 (5.05 – 10.14)	5.62 (4.99 – 9.94)	0.510	0.930
TNFα (pg/ml)	36.35 (15.54 – 89.14)	20.94 (12.78 – 41.73)	0.011	33.11 (13.86 – 72.73)	27.83 (13.17 – 100.02)	0.397	0.033
IL-6 (pg/ml)	7.00 (4.33 – 9.03)	9.18 (4.43 – 13.27)	0.007	6.68 (4.21 – 11.99)	8.69 (5.20 – 13.14)	0.638	0.747
IL-10 (pg/ml)	15.04 (7.18 – 16.70)	12.04 (6.46 – 16.01)	0.382	16.16 (5.71 – 17.43)	16.45 (6.26 – 20.67)	0.433	0.464

Table 6.2 Changes in inflammatory markers
Continuous data presented as median (interquartile range).

6.4.1 Changes in inflammatory markers

Baseline levels of inflammation were comparable between the prehabilitation and control groups (IL-1β p=0.529, TNFα p=0.639, IL-6 p=0.501, IL-10 p=0.501).

There was a significant difference in the change in TNFα between the two groups (**Table 6.2**). Within the prehabilitation group there was a significant decrease in TNFα, which was not seen in the control group: median Δ TNFα -12.28 pg/ml (IQR -50.68 to +3.11) and median Δ TNFα +5.73 pg/ml (IQR -13.42 to +30.73) respectively.

Within the prehabilitation group there was a significant increase in IL-6 (Table 6.2): median Δ IL-6 +1.03 pg/ml (IQR -0.08 to 4.74). There was no significant change in IL-6 in the control group. However, when the two groups were compared, there was no significant difference in the change in IL-6 between the two groups. There were no significant changes in IL-1β or IL-10 in either group during the study period.

6.4.2 Changes in inflammation and physical activity levels

Self-reported levels of physical activity were recorded for all study participants. Physical activity scores were higher in the prehabilitation group compared with the control group (**Table 6.1**): mean difference LSI 28.3 (95% CI 17.8 to 38.7) and mean difference GSS 21.6 (95% CI 12.4 to 30.8).

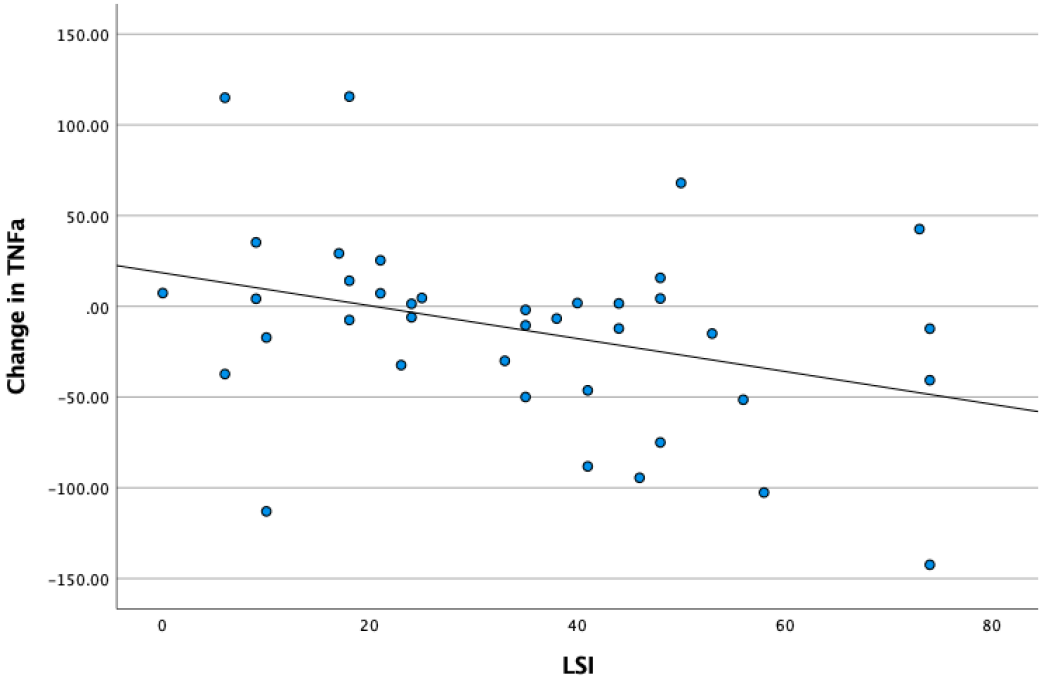
There was a weak negative correlation between change in plasma TNFα and LSI (**Figure 6.4a**; R^2 =-0.120, p=0.031) and change in plasma TNFα and GSS (**Figure 6.4b**; R^2 =-0.170, p=0.009).

Patients who had a decrease in TNFα had a significantly higher GSS than those who had a rise in TNFα: mean difference GSS 12.9 (95% CI 2.4 to 23.3), p=0.017. There was a non-significant trend for a higher LSI in those with a decrease in TNFα compared to those with a rise in TNFα: mean difference LSI 12.1 (95% CI -0.9 to 25.1), p=0.067.

Patients who had an increase in IL-6 had a higher GSS compared to those with a fall in IL-6: mean difference GSS 11.6 (95% CI 0.9 to 23.1), p=0.048. There was no significant difference in LSI between patients with an increase in IL-6 and those with a decrease in IL-6.

There were no significant associations between physical activity levels and the change in IL-1β or IL-10.

(a)



(b)

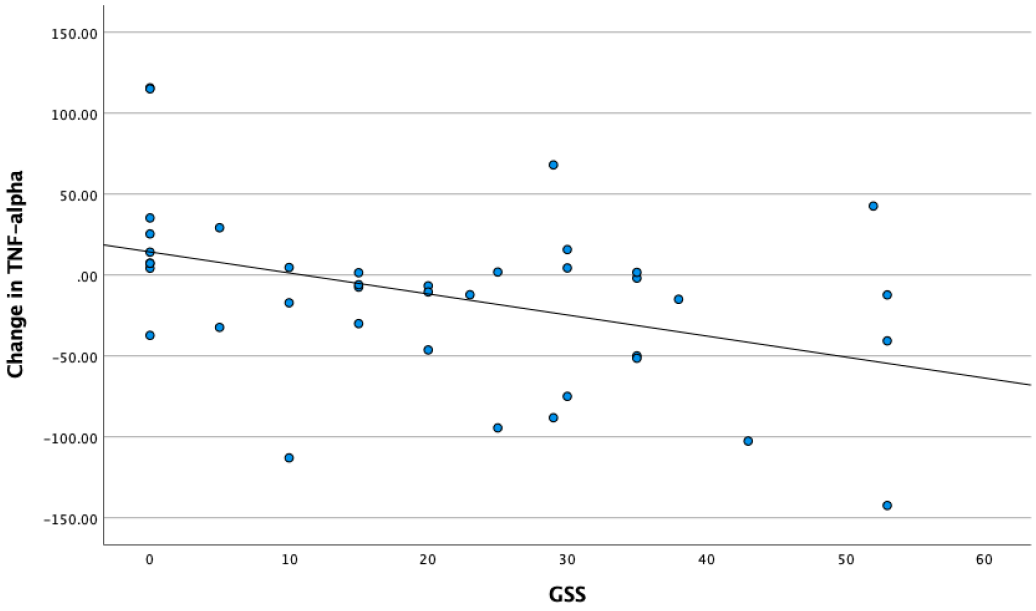


Figure 6.4 Correlation between changes in TNFα and physical activity levels, measured by (a) Leisure Score Index (LSI) and (b) Godin Score Scale (GSS).

6.5 Discussion

This is the first study to date to identify a significant reduction in systemic inflammation in patients undergoing prehabilitation. Furthermore, it observed a relationship between the reduction in plasma markers of inflammation and the amount of exercise that patients completed in the pre-operative period.

TNFα is emerging as a key mediator of interest in the study of the effects of exercise on inflammation. This study's finding of a significant reduction in plasma TNFα during prehabilitation is in keeping with previous research showing a fall in TNFα with exercise in cancer survivors (98-100). Furthermore, it is also in keeping with the findings in the systematic review in **Chapter 5**, which found evidence of a fall in plasma TNFα in patients participating in exercise during oncological treatments.

The main source of TNFα production are cells from the monocyte-macrophage lineage (190). However, a large number of cell types are also capable of producing TNFα, including B and T lymphocytes, natural killer cells, neutrophils, endothelial cells and smooth muscle cells (189,190). It acts via two receptors subtypes triggering a range of signalling pathways; the type 1 receptors triggers cytotoxic and pro-inflammatory responses, whilst activation of the type 2 receptors triggers cell activation, migration and proliferation (204).

TNFα is a crucial part of the normal immune response. However, inappropriate or excessive production of TNFα is strongly associated with a range of disease states, including cancer, as well as autoimmune diseases, such as inflammatory arthritis and inflammatory bowel disease (188,189, 201). The key role of TNFα in many of these inflammatory diseases is demonstrated by the ever-growing use of anti- TNFα monoclonal antibodies as treatments for these conditions.

TNFα is a poor prognostic factor in many cancers (205). It is overexpressed within tissue samples of oesophageal and gastric cancer (206) and cell line studies have demonstrated the

TNFα can promote proliferation in oesophageal cancer cells (207). High levels of soluble type 2 TNFα receptors are significantly associated with the risk of developing oesophageal cancer (208).

In this study, there was stronger evidence of a relationship between the change in plasma TNFα and GSS (which represents moderate and high intensity activity) compared to that between change in plasma TNFα and LSI (which includes all intensities of physical activity). For example, the correlation between GSS and change in plasma TNFα was stronger than that between LSI and change in plasma TNFα. Additionally, patients who had a decrease in TNFα had a significantly higher GSS compared to those with no change or a rise in TNFα, whilst the difference in LSI did not reach statistical significance. These findings suggest that moderate and high intensity exercise may have a stronger relationship with changes in TNFα and therefore moderate and high intensity exercise may offer greater potential anti-inflammatory effects. This highlights the need for further research to understand the effects of different exercise modalities and intensities on changes in inflammation.

In addition to these observed changes in TNFα, a significant increase in IL-6 was observed in the prehabilitation group, which was not seen in the control group. The evidence for a significant impact of prehabilitation on serum IL-6 levels from these study findings is not as strong as that observed with TNFα. Although there was a significant change in IL-6 in the prehabilitation group, the difference in the change in IL-6 between the prehabilitation group and the controls was not significant. The changes observed in IL-6 in the prehabilitation group, however, do warrant further research. This finding contrasts with previous studies that found a decrease in IL-6 in cancer survivors who participated in exercise (98,99). Furthermore, the systematic review in **Chapter 5** also found a fall in IL-6 in patients who participated in exercise during cancer treatment.

The relationship between IL-6 and exercise is likely to be complex. IL-6 is released by a large number of cells in response to a variety of stimuli that signal cellular distress (191). It plays a major role in regulating and amplifying both innate and adaptative immune responses and is also a mediator of chronic inflammatory effects, such as fibrosis and insulin resistance (188191,192). In addition to the proinflammatory effects IL-6 stimulates the release of anti-

inflammatory cytokines and prostaglandins, and it has a roll in both the immediate pro-inflammatory response to trauma as well as the subsequent immunosuppressive phase of the stress response (209). IL-6 also acts as a 'myokine' and is secreted by skeletal muscle in response to muscle contraction (104). Studies have shown an acute rise in IL-6 occurs following episodes of exercise (104).

Muscle induced IL-6 release is a possible explanation for the observed rise in IL-6 during prehabilitation in this study. Levels of moderate and high intensity activity were significantly higher in patients with an increase in IL-6 compared to those who did not have an increase in IL-6. However, there was no significant linear correlation between the change in IL-6 and either GSS or LSI. This does not preclude a relationship between IL-6 release and exercise intensity but does imply that if such a relationship does exist, it is not a simple linear one. For example, a threshold of exercise intensity may be required before observing a link between exercise and IL-6. It is also possible that the type of exercise itself, rather than just the intensity, impacts upon the relationship. Other factors, such as age, co-morbidities and previous exercise history, should also be considered. The limited sample size in this study was insufficient to perform such analyses but this must be considered in future research in this field.

Within the control group, there was no significant changes in any of the measured cytokines during neoadjuvant therapy. This contrasts with the finding of the systematic review in **Chapter 5**, which highlighted a rise in IL-6 and TNFα in the control groups during oncological therapy. A study of oesophageal cancer patients also noted that TNFα was significantly elevated in patients compared with healthy controls and significantly rose during radiotherapy (210). These studies all had substantially bigger sample sizes than the study presented here, and therefore it is possible that the small sample size for the controls (n=14) has created a type II error and failure to detect a significant rise in these cytokines during neoadjuvant therapy.

The effect that changes in pre-operative inflammation will have on clinical outcomes is not known. It is recognised that pre-operative inflammation is associated with poor outcomes;

pre-operative CRP, alone or in combination with albumin, are associated with overall post-operative complications and respiratory complications (81-84). CRP and albumin are acute phase reactants and levels rise and fall respectively in the presence of inflammation.

As previously discussed, an amplified surgical stress response is associated with an increased risk of post-operative complications (90,95). Preoperative morbidity impacts upon the surgical stress response and higher pre-operative inflammation is associated with higher peri-operative stress response (95,211). IL-6 and TNFα stimulate the HPA axis leading to a rise in cortisol and, if persistent, this causes subsequent hypothalamic-pituitary-adrenal axis dysregulation (95,209). Elevated plasma levels of IL-6 and TNFα before surgery and in the first 72 hours after surgery is associated with a higher risk of post-operative complications in patients undergoing open aortic aneurysm repair and colorectal cancer surgery respectively (94,212). IL-6 is the predominant cytokine in the early post-operative stress response and levels correlate strongly with the acute phase reactants, such as CRP (206). Elevated IL-6 on post-operative day 1 is associated with a higher risk of complications after major abdominal surgery (213). Furthermore, in a study of patients undergoing a gastrectomy, elevated IL-6 on post-operative day 1 was associated with a higher risk of overall post-operative complications and infectious complications in particular (214).

Therefore, the possibility that reducing pre-operative inflammation could reduce the magnitude of the surgical stress should be considered. It has been hypothesised that the peri-operative use of steroids to suppress release of cytokines may improve post-operative outcomes, with evidence of a reduction in respiratory failure and acute kidney injury following both cardiac and non-cardiac surgery, and a reduction in infectious complications after cardiac surgery (206). Suppressing pre-operative inflammation is unlikely to have a negative impact on post-operative outcomes. For example, a meta-analysis of use of anti TNFα therapies prior to surgery for inflammatory bowel disease found no increased risk of infectious complications due to immune suppression (215).

The findings of most studies in the existing literature suggests that reducing TNFα and IL6 may improve outcomes. However, whilst this study did find a significant fall in TNFα during prehabilitation, a rise in IL-6 was observed. This could potentially have a detrimental impact

on post-operative outcomes. IL-6 promotes proliferation, migration and invasion of cancer cells, including oesophageal cancer cells (74,207) and elevated IL-6 is associated with a poor response to neoadjuvant therapy and a lower post-operative survival in oesophageal cancer patients (74,216). High levels of IL-6 are also associated with muscle atrophy and inhibition of IL-6 has been demonstrated to preserve muscle mass in murine models (104). Given that high levels of IL-6 are associated with many detrimental outcomes, further research into IL-6 and exercise in cancer patients is essential, as if a rise does occur during prehabilitation, it may not be a positive benefit to patients.

In this study there was a large amount of variation in cytokine levels in all patients at both time points, and this was particularly apparent in the measured TNFα levels. It is difficult to compare the magnitude of the change and the variation in cytokines levels between previous studies as a large number of different techniques, different assays and different units of measurement are used.

6.5.1 Study limitations

The sample size in this study was significantly limited by the Covid-19 pandemic. All research was suspended between March and July 2020 which prevented any patient recruitment during this time. Whilst treatment of cancer patients did continue during this time, those participants who were recruited prior to the pandemic but underwent surgery between March and July 2020 were not able to be sampled prior to surgery and therefore were not included in this study. Throughout the latter half of 2020 and early 2021, some operations were performed at hospitals outside of the NHS and therefore it was not possible to collect samples. Following the resumption of research activities, recruitment to the study prior to the staging laparoscopy was also more challenging due to remote consultations. Samples from the ICHTB were also used in this study to obtain staging laparoscopy samples for those patients who were subsequently recruited to the study before starting treatment.

The delivery of the prehabilitation was substantially affected by the Covid-19 pandemic. A digital programme was introduced to facilitate the programme delivery during the pandemic. The study in **Chapter 2** demonstrated the efficacy of the face-to-face programme in reducing the risk of post-operative pneumonia. A direct comparison of the two models has not been undertaken. However, the feasibility of the digital model has been demonstrated, with 75% uptake of the programme and a 90% retention rate, and with comparable improvements in pre-operative physical and psychological parameters to those seen in the face-to-face model (217). There is growing evidence that eHealth technology can facilitate behaviour change in patients; positive changes seen with the use of eHealth technology include weight loss, healthy eating, increasing activity, improved medication compliance and better appointment attendance (218). A growing number of prehabilitation programme are investigating the role of digital interventions (219,220). It is increasingly recognised that a dynamic approach to prehabilitation is needed, personalising not just the individual interventions being offered but the way it is delivered (221).

Patient behaviour will also have between impacted as a consequence of the Covid-19 pandemic. Patients undergoing chemotherapy and chemoradiotherapy were advised to limit contacts with people to reduce the risk of infection with SARS-CoV-2 and this will have impacted upon exercise behaviour. The exercise interventions were personalised in the programme and therefore could adapt to this but many forms of recreational exercise were not possible for large parts of the study period. Furthermore, the psychological stress and worry about having cancer treatment during the Covid-19 pandemic may also impact upon prehabilitation adherence and treatment outcomes.

It is not possible to directly compare physical activity levels in this study to those in the previous chapters (before the Covid-19 pandemic) as different methods for recording physical activity. As previous discussed, different methods were used to monitor adherence in the two prehabilitation models and these changed over time as the programme responded to the changing clinical environment. The Godin-Shephard Leisure Time Physical Activity Questionnaire was used in this study. This quantified the amount of activity over a seven-day period but does not account for intra-person variation, which was found to be high in the

previous study (**Chapter 3.4**). Furthermore it is a self-reported measure, and so is subject to reporting bias.

This study included both oesophageal and gastric cancer patients. Due to the small sample size, it was not possible to do a subgroup analysis to compare the findings in the two cancer types. It is possible, however, that the two patient groups may have different response to prehabilitation due to differences in both the underlying disease itself and/or differences in the neoadjuvant regimes. An increase in late and emergency presentations of oesophago-gastric cancer was noted during the Covid-19 pandemic and delays in treatment were also noted as services struggled to reorganise their treatment pathways (222). However, this would have affected both study arms equally and there was no significant difference in staging between the prehabilitation and control patients in this study.

The prehabilitation patients were noted to have a significantly higher BMI at both time points than the control patients. There is a strong link between obesity and chronic inflammation (64). However, there was no significant difference in baseline inflammatory markers between the two groups. A small fall in weight and BMI were seen in the prehabilitation group, compared with very little change in the control group. Although these differences were not significant, it is possible that loss of weight and VAT may be mediating the reduction in TNFα in the prehabilitation group.

6.5.2 Future studies

The relationship between the changes in TNFα observed in this study and clinical outcomes should be studied. This should include the relationship between pre-operative changes in TNFα and cardiorespiratory fitness and post-operative complications. A large sample size is likely to be needed to detect clinically significant differences but the results from this study suggest a significant impact of prehabilitation on inflammation and therefore further research is justified to better understand then significance of these changes.

TNFα is pro-inflammatory marker and is a key mediators of the inflammatory cascade. This study found that levels of TNFα did not change significantly during neoadjuvant therapy in controls, with a significant fall in prehabilitation patients. However, as a large number of factors can both stimulate and inhibit inflammation and the cascade can be further complicated by negative feedback mechanism, a more detailed study of changes in TNFα during neoadjuvant therapy should be undertaken. Repeated measurements, for example every week, may help to highlight what aspects of prehabilitation have anti-inflammatory effects and what effect chemotherapy cycles have on inflammation. If an anti-inflammatory impact of prehabilitation is found to play a significant role in the benefits of prehabilitation, then better understanding the inflammatory profile during the pre-operative period may help to target interventions more effectively.

Other inflammatory mediators should also be studied. IL-4 and CCL-4 were identified in **Chapter 5** as markers that may be affected by exercise during oncological treatment and therefore these should be examined. Finally, the role of activity trackers to quantify exercise volume and intensity should be studied alongside changes in inflammatory markers to give a more detailed understanding of the relationship between exercise and inflammation.

6.6 Conclusions

A significant reduction in TNFα has been demonstrated in this study, indicating that prehabilitation does have some anti-inflammatory effects. However, a rise in IL-6 was also seen in the prehabilitation group, and although the difference in the change in IL-6 between the two groups was not significant, it indicates that the effects of prehabilitation on inflammation are likely to be complex. Further research is needed to understand the mechanisms behind the changes observed in systemic inflammation.

CHAPTER 7

-

PREHABILITATION AND INFLAMMATION WITHIN VISCERAL ADIPOSE TISSUE IN PATIENTS WITH OESOPHAGO-GASTRIC CANCER

7.1 Objective and hypothesis

Objective: To examine whether prehabilitation impacts upon levels of inflammation within visceral adipose tissue in patients with oesophago-gastric cancer.

Hypothesis: Prehabilitation reduces inflammation within visceral adipose tissue in patients with oesophago-gastric cancer.

7.2 Introduction

The study in **Chapter 6** found a significant decrease in pre-operative plasma TNFα levels in patients who underwent prehabilitation, and that the levels of inflammation were related to the amount of exercise that patients completed. This suggests that there may be some anti-inflammatory effects from exercise in this population.

A reduction in adipose tissue derived inflammation due to exercise is one possible mechanism that could underlie this association. The study in **Chapter 4** found that the amount of physical activity completed by patients during prehabilitation was related to the amount of visceral adipose tissue (VAT) lost during the programme. VAT secretes a range of pro-inflammatory mediators and hormones, such as IL-6, IL-8, TNFα, leptin and IGF-1 (64,65). VAT secretory activity is higher than that of subcutaneous adipose tissue (SAT) and is higher in is the obese state (65). In colorectal cancer patients, VAT area has been found to correlate with serum CRP levels (65).

In normal conditions and within normal weight ranges, VAT contains anti-inflammatory immune cells and mediators (223). The accumulation of VAT stimulates chronic inflammation through several mechanisms: secretion of pro-inflammatory mediators by adipocytes and adipose stromal cells; recruitment and proliferation of pro-inflammatory immune cells; adipose tissue remodelling and adipocyte hypertrophy; and formation of crown-like structures (dead or dying adipocytes surrounded by macrophages) (65,220). These changes lead to further secretion of pro-inflammatory cytokines by immune cells, the development of insulin resistance and an amplified systemic inflammatory response to trauma or other stimuli (65,67)

Exercise has been shown to decrease IGF-1 secretion, improve insulin sensitivity, decrease pro-inflammatory adipokines (such as leptin), increase anti-inflammatory adipokines (such as adiponectin) and improve immune cell function (102,105). It is thought that some of these changes may be triggered by a reduction in VAT and thus a reduction in the secretion of pro-inflammatory cytokines and adipokines from VAT (65, 105).

Adipocytes produce chemoattractants to stimulate recruitment and activation of macrophages, which are the key mediators of VAT inflammation (224). Macrophages are a heterogeneous immune cell population, and they can exist in different pro- and anti-inflammatory phenotypes (**Figure 7.1**). VAT contains higher levels of the pro-inflammatory M1 macrophages than SAT (225). The presence of inflammation stimulates activation of M1 macrophages, which in turn secrete pro-inflammatory cytokines leading to further recruitment and activation of immune cells and an amplification of the inflammatory response (226-228). In contrast, the presence of anti-inflammatory cytokines, such as IL-10, stimulate the development of M2 macrophages, which themselves have anti-inflammatory properties and secrete anti-inflammatory cytokines (224,228). A study in breast cancer survivors found that exercise can decrease levels of pro-inflammatory M1 macrophages within adipose tissue and increase levels of the anti-inflammatory M2 phenotype (101).

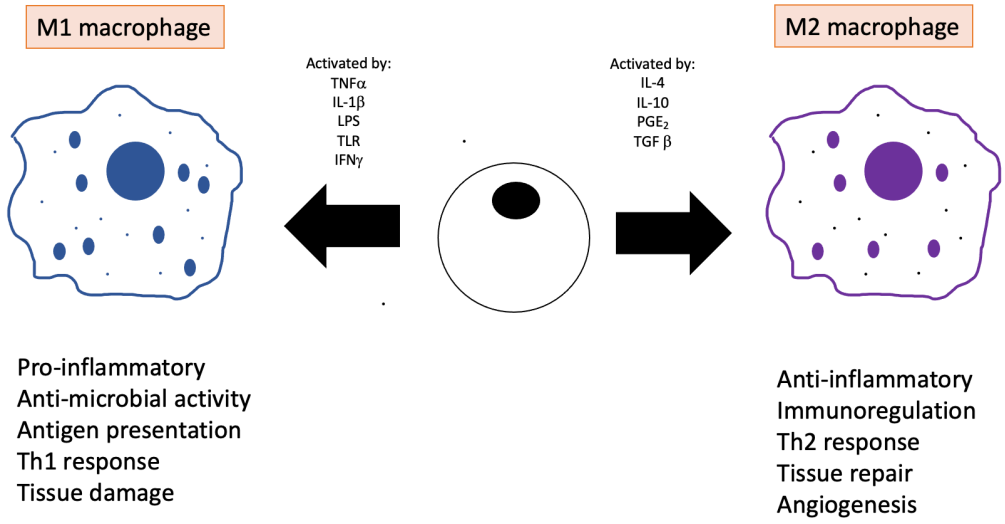


Figure 7.1 Macrophage polarisation
IFN = interferon; IL= interleukin; LPS = lipopolysaccharide; TGF = transforming growth factor; TLR = toll like receptor; TNF = tumour necrosis factor; PGE_2 = prostaglandin E_2

Pre-operative inflammation is associated with the risk of complications following colorectal, hepatic and cardiac surgery (81-84). In **Chapter 4**, the study found that the amount of physical activity completed by patients during prehabilitation was related to the amount of VAT lost during the programme, and in turn, the amount of VAT lost was related to the risk of post-operative complications, with a fall in the risk of complications as more VAT was lost. These relationships between physical activity, VAT loss and complications are in keeping with a hypothesis that exercise-derived VAT loss during prehabilitation contributes to improved post-operative outcomes through a reduction in inflammation generated from VAT.

This exploratory study will examine the levels of inflammation within VAT in patients with oesophago-gastric (OG) cancer and investigate whether prehabilitation affects VAT inflammation.

7.3 Methods

7.3.1 Study population

All patients who were discussed at the North West London OG cancer multidisciplinary team (MDT) meeting between May 2019 and March 2020 and between July 2020 and September 2021 were eligible for inclusion in this study. All research activities were suspended between March 2020 and July 2020 due to the Covid-19 pandemic and therefore patients starting their cancer treatment during this period were not included in this study. This is the same study population as described in the previous chapter; full details of the study population and the prehabilitation programmes used during the study period are given in **Chapter 6.3.1** and **Chapter 6.3.2** respectively. All patients who consented to participate in the study in **Chapter 6** were invited to participate in this study.

VAT samples were taken at the time of the staging laparoscopy or the time of the cancer resection. Patients were divided into three groups, based upon the timing of the sample and whether prehabilitation was given: pre-treatment group, prehabilitation resection group and no prehabilitation resection group (**Figure 7.2**).

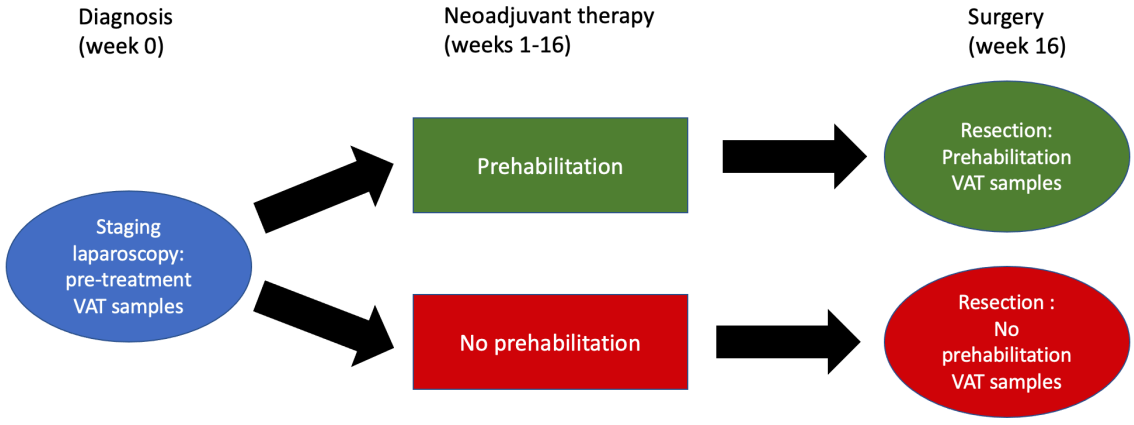


Figure 7.2 Timing of VAT sample collection.
The exact duration of the programme was determined by the time between the start of their curative pathway and the time of surgery; this was a clinical decision, unaffected by the prehabilitation programme, and the programme was provided to the patients for the whole duration of their pre-operative period

7.3.2 Study outcomes

The primary outcome of this study was expression of TNFα within VAT. The following other markers were also assessed: cytokines IL-1β, IL-6, IL-10, and CCL3; adipokines leptin and adiponectin; and macrophage markers CD68, CD163 and CD206.

Other secondary outcomes included macrophage number, adipocyte size, physical activity scores (Leisure Score Index and Godin Score Scale) and body composition parameters. Details of how the Leisure Score Index (LSI) and Godin Score Scale (GSS) were derived is described in **Chapter 6.3.2**. Measurement of body composition was derived from CT scans performed at diagnosis and after the completion of neoadjuvant therapy, as previously described in **Chapter 4.3.2**.

7.3.3 Measurement of inflammation

Samples of omental VAT were taken at the time of the staging laparoscopy and/or cancer resection. Each sample was approximately 1g and was taken by the operating surgeon. The sample was dissected into two pieces: one piece was snap frozen and stored at -80°C and the other fixed in formalin fixation for paraffin tissue embedding. Two techniques were used to quantify the inflammation within the VAT: quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemistry.

qRT-PCR was used to quantify the expression of inflammatory cytokines and macrophage markers within the VAT samples. Total RNA was extracted from the VAT samples using Trizol (Ambion Life technology) and mechanical homogenisation. 200µl chloroform was added to the solution, which was incubated at room temperature for 5 minutes and then centrifuged for 20 minutes at 12000 rpm. Total RNA was extracted from the solution using RNA extraction kit (Qiagen), according to the manufacturer's instructions, and then complementary DNA (cDNA) was obtained from 1mg of mRNA using iScript (Bio-Rad), according to manufacturer instructions.

qRT-PCR was performed using the Viaa 7 Real-Time PCR system (Life Technologies). 10ug of cDNA from each sample was used for each reaction, using Brilliant II SYBR Green QPCR Master Mix (Agilent). qRT-PCR reactions were performed with technical replicates using a 384-well configuration. Ct values were measured using Viia 7 RUO Software and the comparative Ct method was used to analyse the results, normalised to HPRT gene. The forward and reverse primer sequences used are provided in **Appendix VI**.

CD68 immunostaining was performed to detect macrophages within the VAT samples. 5μm thick paraffin sections were cut and then dewaxed and rehydrated for testing. Sodium citrate buffer (pH 6) was used for antigen retrieval, following by blocking. The sections were incubated with primary antibodies against CD68 (Bio-Rad, MCA5709) in phosphate-buffered saline (PBS) for 1 hour 30 minutes, then washed in PBS and incubated with horseradish peroxidase-labelled secondary antibody (1:10,000) for 30 minutes at room temperature (DAKO EnVision™+; Agilent Technologies). Following this, the slides were washed in PBS and further incubated with diaminobenzidine (DAB) chromogen for 30 minutes. The slides were visualized using brightfield images taken on a Leica DM4B microscope. The number of CD68+ macrophages were measured using 40X images (**Figure 7.3**). and the mean values were calculated from 10 images.

Haemotoxylin and eosin staining was also performed on the paraffin sections. Adipocyte size was measured by calculating the mean adipocyte area using 10X brightfield images taken on a Leica DM4B microscope. Mean area was calculated across 4 images using Image J Adiposoft plug-in (MathWorks, Natick MA) (**Figure 7.4**). The scale was set using a scale bar and the minimum and maximum areas were set to 20 and 10000 μm^2 respectively.

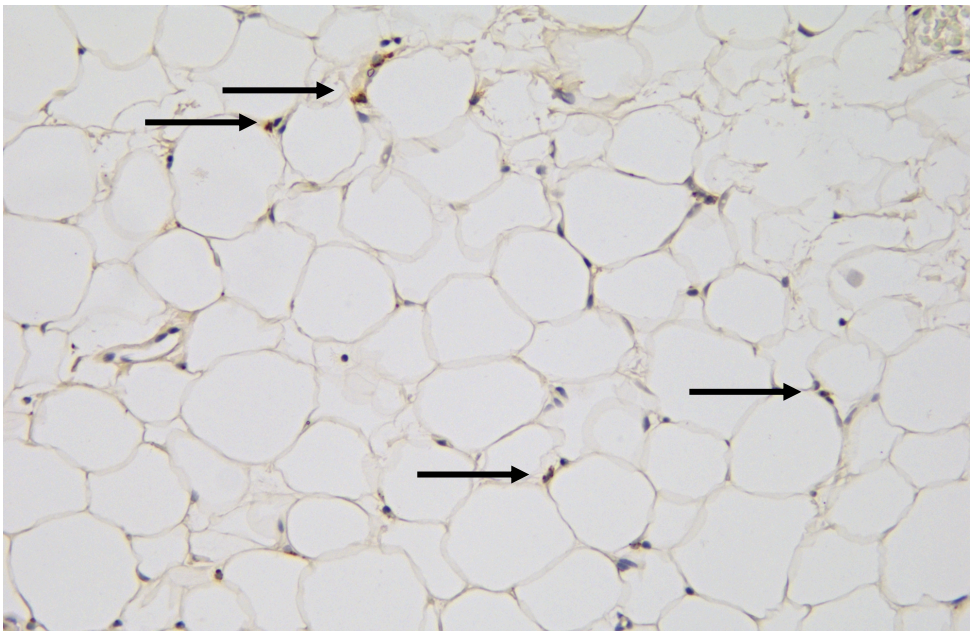


Figure 7.3 CD68+ macrophage staining in VAT samples.
CD68+ cells are located in between adipocyte cells (see arrows)

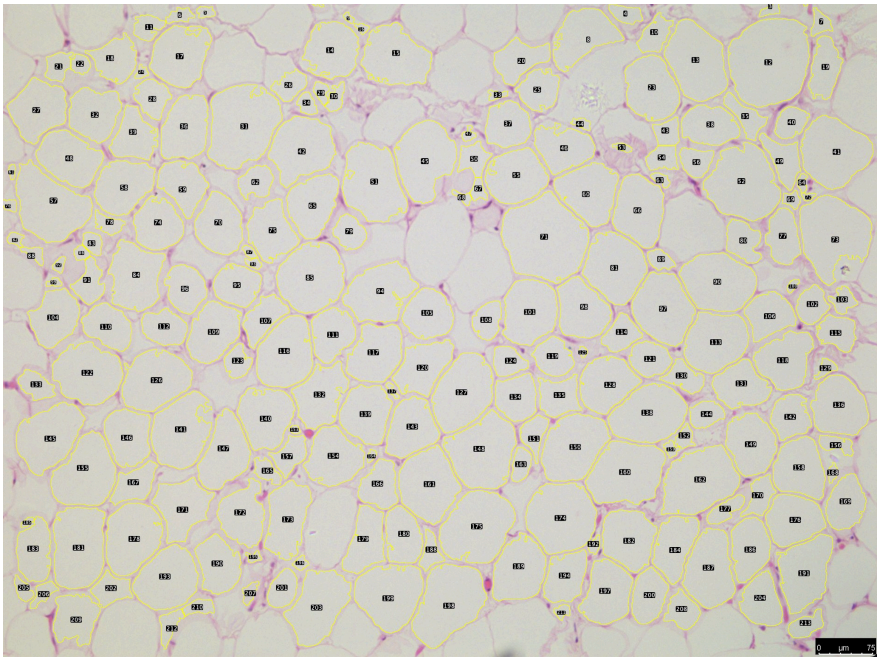


Figure 7.4 Calculation of adipocyte size using Image J Adiposoft

7.3.4 Statistical analysis

Normality of data was assessed visually and using the Kolmogorov-Smirnov (with Lilliefors correction) and the Shapiro-Wilk normality test. Dependant on their distribution, continuous variables are presented as either mean ± standard deviation or median [interquartile range, IQR]. Cytokine levels, adipokine levels, macrophage markers and adipocyte size were compared between the three study groups using a Kruskal-Wallis test for non-parametric variables or a one-way analysis of variance (ANOVA) for parametric variables. If significant differences were found, post-hoc analyses with Mann-Whitney U-tests or Independent-Samples T test respectively were performed with a Bonferroni correction to determine where the differences occurred.

A Spearman's rank correlation test was used to assess the relationships between the inflammatory parameters and physical activity scores, and between inflammatory parameters and body composition parameters. Finally, Mann-Whitney U-tests were used to compare the inflammatory parameters between patients who achieved a GSS of ≥24 and those who completed lower levels of physical activity. Two-tailed tests were used throughout with a significance level of $p<0.05$. Statistical analysis was performed using SPSS version 28 (IBM, New York, USA).

7.4 Results

During the study period, 13 pre-treatment VAT samples were collected, 23 from patients at the time of resection after completing prehabilitation and 23 from patients at the time of resection who did not have any prehabilitation (**Figure 7.5**).

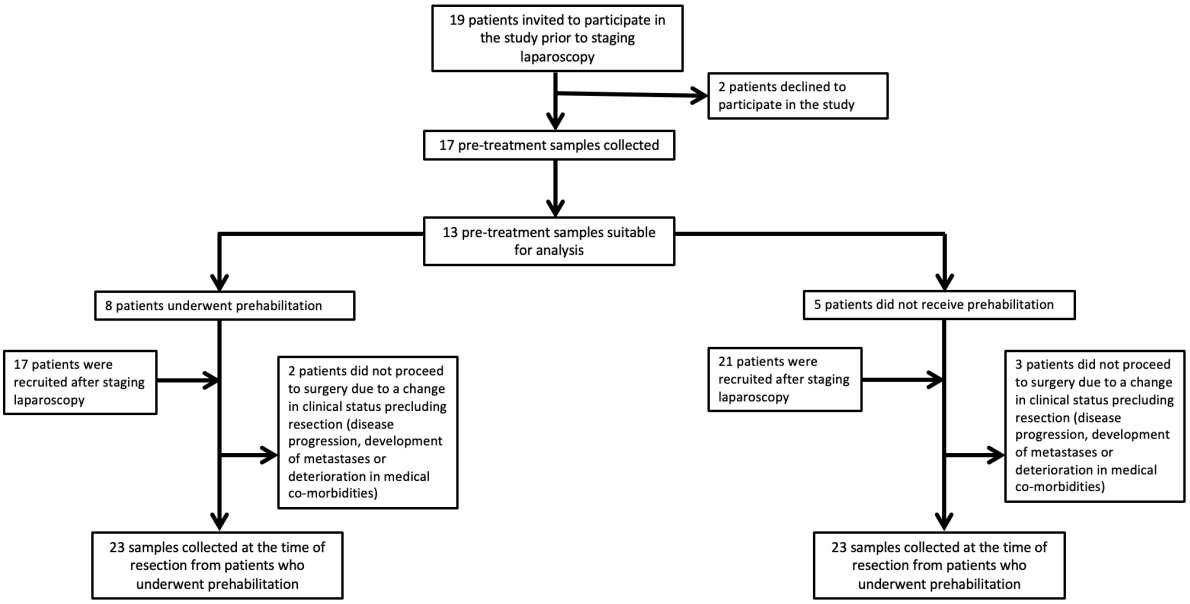


Figure 7.5 Study participant flow chart

Characteristics of these study participants are shown in **Table 7.1**. All demographic parameters were comparable between the three groups, except for TAT area. There was a significantly lower TAT area in no prehabilitation group compared with the pre-treatment and prehabilitation groups: mean difference -117.2cm^2 (95% CI -255.1 to -20.6) and mean difference -113.9cm^2 (95% CI -236.3 to -8.4) respectively.

Two patients in the prehabilitation group were taking regular steroid medications; no patients in the other two groups took steroid medications (p=0.184). One patient in both the prehabilitation and no-prehabilitation groups were taking other immunosuppressant medications; no patients in the pre-treatment group took immunosuppressant medications (p=0.746).

Physical activity levels were significant lower in the no prehabilitation group compared with the pre-treatment and prehabilitation groups: LSI mean difference -15.6 (95% CI -29.9 to -1.4) and -29.8 (95% CI -41.9 to -17.7) respectively; GSS mean difference -13.6 (95% CI -25.8 to -1.4) and -24.5 (95% CI -34.9 to -14.1) respectively.

	Pre-treatment n=13	Prehabilitation n=23	No prehabilitation n=23	p-value
Age (years)	65.7 ± 11.9	69.2 ± 12.3	69.6 ± 10.4	0.596
Gender, male n (%)	7 (54%)	18 (78%)	17 (74%)	0.279
Tumour location n (%)				0.168
Oesophagus/GOJ	9 (69%)	18 (78%)	12 (52%)	
Stomach	4 (31%)	5 (22%)	11 (48%)	
Histology, n (%)				0.324
Adenocarcinoma	12 (92%)	19 (83%)	22 (96%)	
Squamous cell carcinoma	1 (8%)	4 (17%)	1 (4%)	
Clinical stage, n (%)				0.491
I	0 (0%)	4 (17%)	2 (9%)	
II	0 (0%)	4 (17%)	4 (17%)	
II	10 (77%)	13 (57%)	13 (57%)	
IV	3 (23%)	2 (9%)	4 (17%)	
ASA grade, n (%)				0.328
II	10 (77%)	13 (57%)	12 (52%)	
III	3 (23%)	10 (43%)	11 (48%)	
Charlson Comorbidity Index	4.4 ± 1.3	4.8 ± 1.5	5.4 ± 1.7	0.158
Comorbidities, n (%)				
Cardiac	2 (15%)	2 (9%)	6 (26%)	0.287
Respiratory	0 (0%)	5 (22%)	6 (26%)	0.138
Neurological	0 (0%)	3 (13%)	1 (4%)	0.274
Endocrine	2 (15%)	3 (13%)	3 (13%)	0.977
Psychiatric	3 (23%)	3 (13%)	1 (4%)	0.242
Previous malignancy	2 (15%)	2 (9%)	4 (17%)	0.674
Autoimmune	0 (0%)	2 (9%)	1 (4%)	0.511
Weight (kg)	78.1 ± 24.3	81.2± 16.1	70.9± 14.9	0.083
BMI (kg/m^2)	27.2 ± 7.2	27.3± 4.0	24.4± 3.2	0.289
Neoadjuvant chemotherapy, n (%)	N/A	16 (70%)	16 (70%)	0.999
Body composition				
SM area (cm^2)	148.2 ± 36.7	149.0 ± 31.5	137.8 ± 39.9	0.572
SMI (cm^2/m^2)	51.4 ± 9.0	50.8 ± 7.7	47.6 ± 8.7	0.377
TAT area (cm^2)	380.6 ± 226.0	377.3 ± 154.6	263.4 ± 89.7	0.042
VAT area (cm^2)	155.6 ± 90.1	187.3 ± 120.4	122.9 ± 67.0	0.115
SAT area (cm^2)	225.0 ± 170.0	190.0 ± 86.6	140.5 ± 40.9	0.067
Physical activity				
Leisure Score Index [1]	31.2 ± 18.4	45.4 ± 20.6	15.5 ± 9.9	0.001
Godin Scale Score [2]	18.7 ± 16.3	29.6 ± 17.7	5.1 ± 7.7	0.001

Table 7.1. Study participant characteristics

Continuous data presented as mean ± SD. BMI = body mass index; GOJ = gastro-oesophageal junction.

[1] Leisure Score Index includes all physical activity; [2] Godin Scale Score includes moderate and strenuous intensity exercise only

7.4.1 Differences in inflammatory markers

	Pre-treatment n=13	Prehabilitation n=23	No prehabilitation n=23	p-value
IL-1β	1.59 (1.22 – 4.27)	1.83 (0.74 – 4.69)	8.96 (2.13 – 17.37)	0.011
IL-6	1.33 (0.57– 3.52)	3.47 (0.89 – 22.15)	14.08 (1.95 – 42.84)	0.109
TNFα	1.73 (0.49 – 4.25)	0.97 (0.33 – 1.41)	3.29 (0.33 – 17.70)	0.102
IL-10	0.97 (0.31 – 3.55)	0.56 (0.20 – 2.87)	2.52 (0.28 – 5.95)	0.283
Leptin	1.13 (0.62 – 4.35)	0.92 (0.50 – 1.70)	1.86 (0.88 – 8.68)	0.062
Adiponectin	1.10 (0.57 – 2.38)	0.93 (0.53 – 1.81)	0.83 (0.32 – 2.18)	0.758
CCL3	0.57 (0.12 – 0.90)	0.52 (0.28 – 2.34)	1.63 (0.50 – 3.42)	0.030
CD68	1.83 (0.65 – 3.41)	0.47 (0.09 – 1.86)	0.74 (0.31 – 6.90)	0.054
CD163	1.97 (0.77 – 11.10)	3.73 (0.72 – 9.93)	0.72 (0.14 – 2.59)	0.024
CD206	2.08 (0.88 – 3.65)	0.83 (0.26 – 4.18)	1.04 (0.15 – 5.92)	0.402

Table 7.2. Comparison of inflammatory markers
Continuous data presented as median (interquartile range). Units = relative expression to HPRT

There were significant differences between the three groups in expression of IL-1β, CCL3 and CD163 (**Table 7.2**).

IL-1β expression was significantly higher in the no-prehabilitation group compared with both the pre-treatment and prehabilitation groups (p=0.016 and p=0.008 respectively, **Figure 7.6**). There was no significant difference in IL-1β expression between the pre-treatment and prehabilitation groups (p=0.745).

CCL3 expression was significantly higher in the no-prehabilitation group compared with the pre-treatment group (p=0.007, **Figure 7.7**). There were no significant differences in CCL3 expression between the pre-treatment and prehabilitation groups (p=0.242) or the prehabilitation and no-prehabilitation groups (p=0.135).

CD163 expression was significantly lower in the no prehabilitation group compared with both the pre-treatment and prehabilitation groups (p=0.031 and p=0.015 respectively, **Figure 7.8**).

There was no significant difference in CD163 expression between the pre-treatment and prehabilitation groups (p=0.805).

There were non-significant trends for higher expression of IL-6, TNFα and leptin in the no prehabilitation group compared with the prehabilitation group, and for lower expression of CD68 in the prehabilitation group compared with the other two groups.

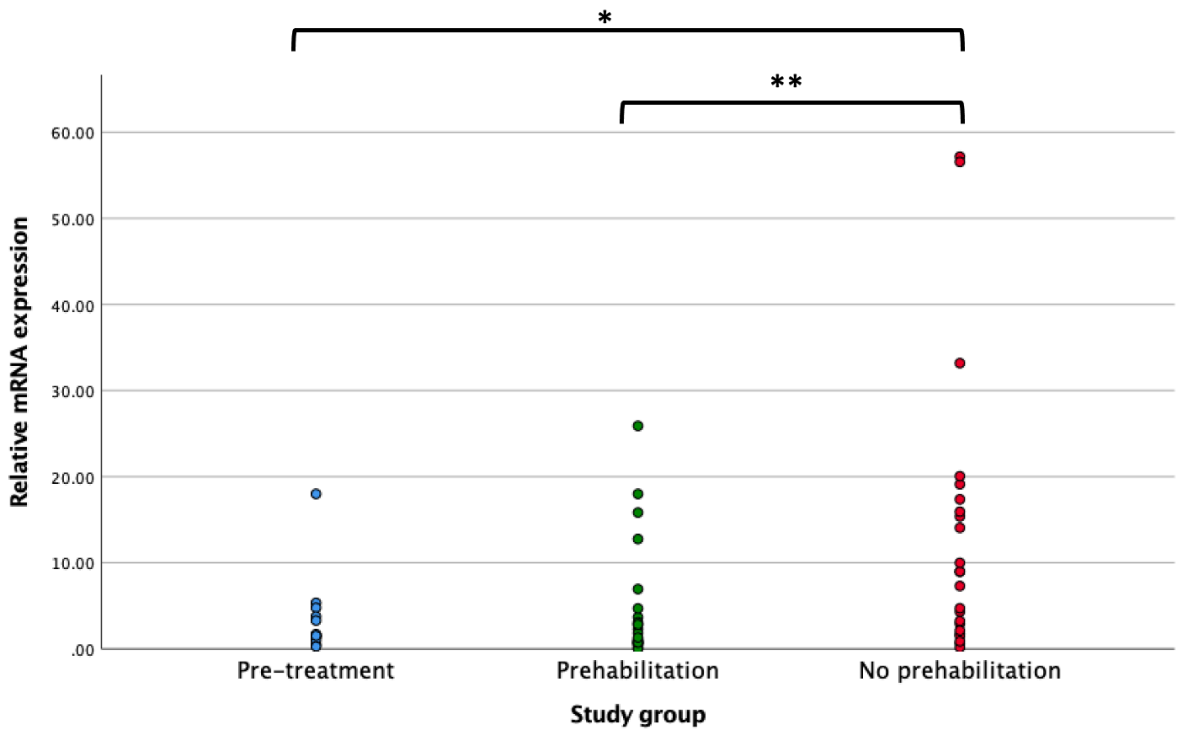


Figure 7.6 Comparison of expression of IL-1β mRNA
mRNA expression measured relative to HPRT expression. * p<0.05; ** p<0.01; *** p<0.001

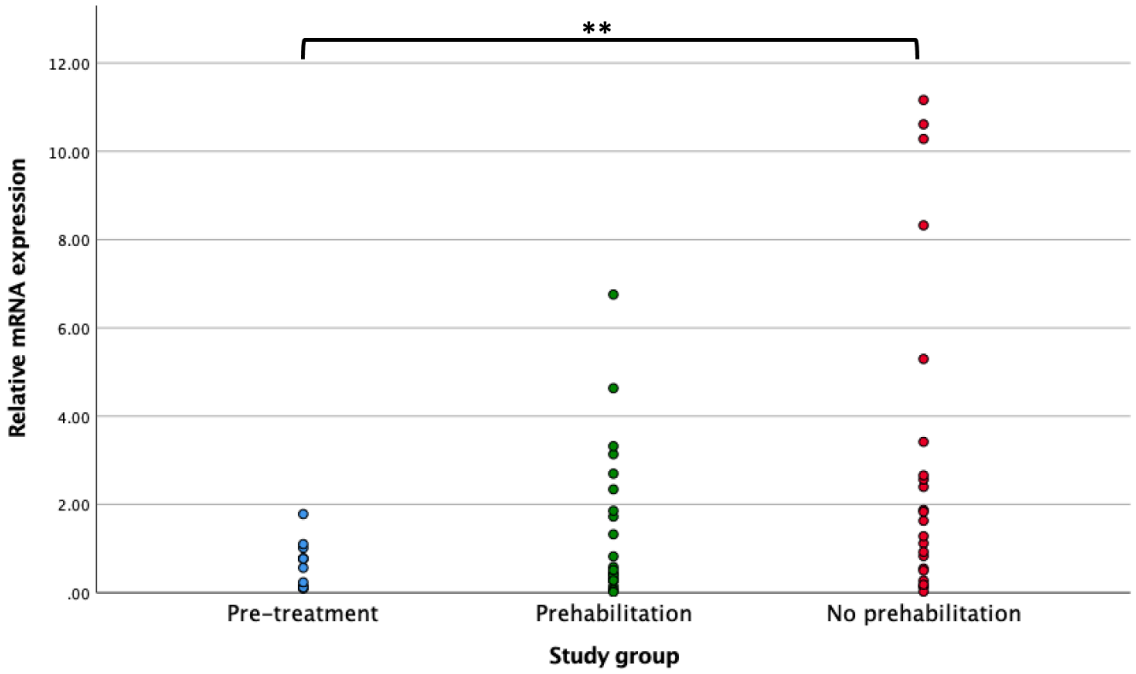


Figure 7.7 Comparison of expression of CCL3 mRNA
mRNA expression measured relative to HPRT expression. * p<0.05; ** p<0.01; *** p<0.001

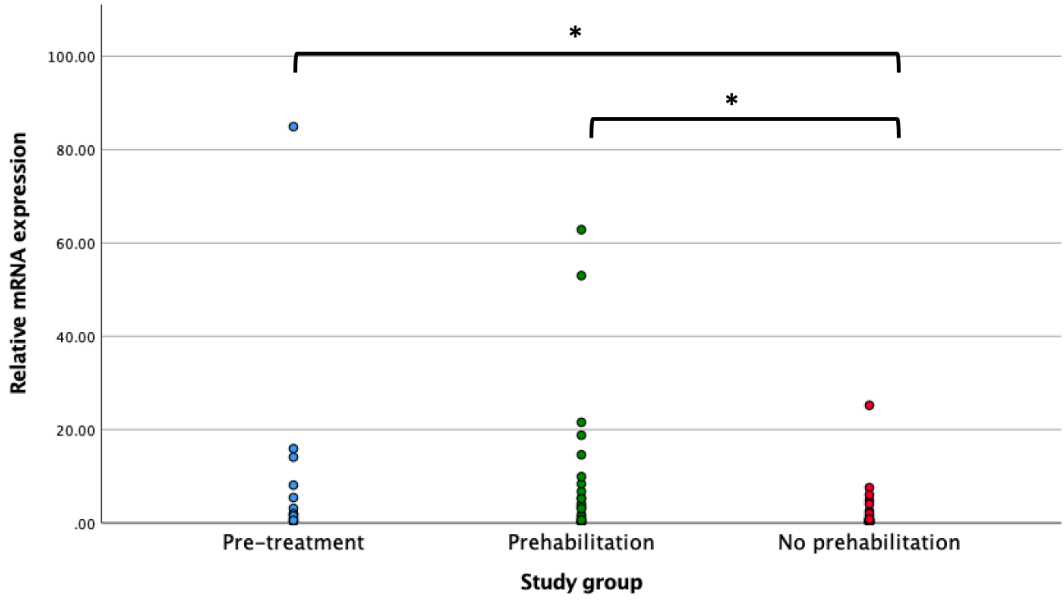


Figure 7.8 Comparison of expression of CD163 mRNA
mRNA expression measured relative to HPRT expression. * p<0.05; ** p<0.01; *** p<0.001

7.4.2 Exercise and inflammatory markers

There was weak negative correlation between LSI and TNFα (R^2 =-0.294, p=0.025), GSS and TNFα (R2 =-0.261, p=0.048), LSI and IL-10 (r=-0.326, p=0.012), and GSS and IL-10 (R^2 =-0.338, p=0.009). There was no correlation between the other inflammatory markers and exercise scores. IL-10 expression was significantly lower in patients with GSS ≥ 24 (in keeping with WHO guidelines for recommended levels of physical activity) compared to those who did not achieve this level of activity (p=0.029, **Figure 7.9**).

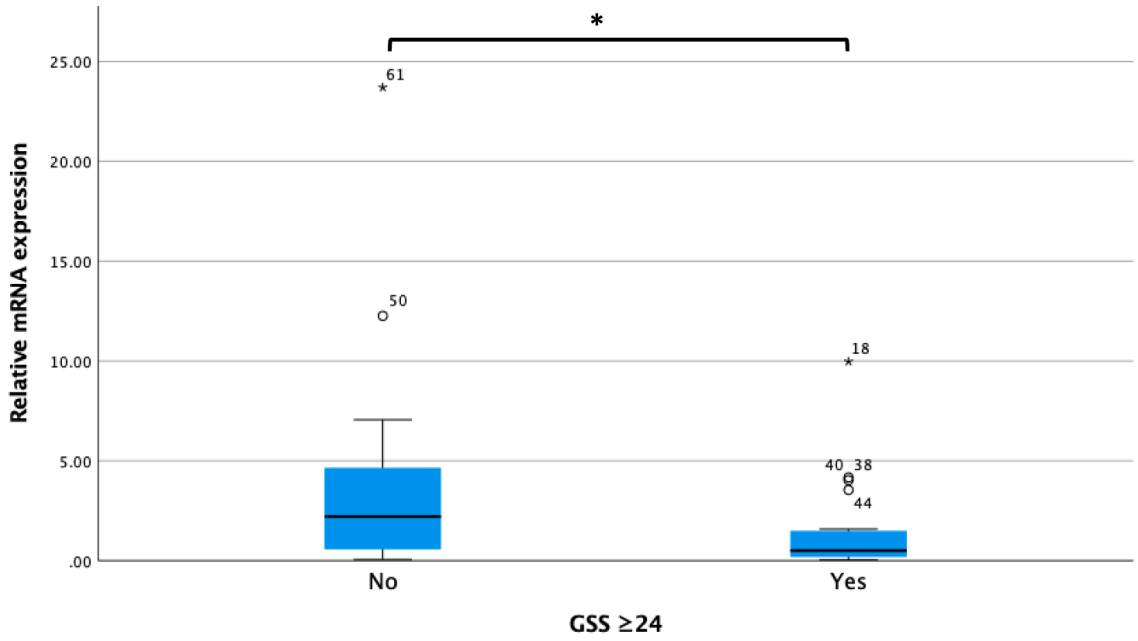


Figure 7.9 IL-10 expression and Godin Score Scale
A GSS of ≥24 is in keeping with WHO guidelines for recommended levels of physical activity. *mRNA expression measured relative to HPRT expression.* * p<0.05; ** p<0.01; *** p<0.001

7.4.3 Body composition and inflammatory markers

There was a weak positive correlation between VAT area and CCL3 (r=0.292, p=0.034) and between TAT area and CCL3 (r=0.281, p=0.041). There was no correlation between the other inflammatory markers and body composition results.

7.4.4 Macrophage infiltration within VAT

23 samples were available for immunohistochemical analysis: 9 pre-treatment samples, 10 prehabilitation samples and 14 no prehabilitation samples. Characteristics of these study participants are shown in **Table 7.3**. All demographic parameters were comparable between the three groups.

One patient in the prehabilitation group was taking regular steroid medications; no other patients took steroid medications (p=0.305). No other immunosuppressant medications were taken by any patients in this study.

Physical activity levels were significant lower in the no prehabilitation group compared with the pre-treatment and prehabilitation groups: LSI mean difference -21.0 (95% CI -37.8 to -4.2) and -29.6 (95% CI -45.9 to -13.3) respectively; GSS mean difference -17.8 (95% CI -32.7 to -2.9) and -25.7 (95% CI -40.1 to -11.3) respectively.

	Pre-treatment n=9	Prehabilitation n=10	No prehabilitation n=14	p-value
Age (years)	68.4 ± 9.4	64.3 ± 11.7	67.2 ± 10.4	0.676
Gender, male n (%)	7 (78%)	6 (60%)	11 (79%)	0.556
Tumour location n (%)				0.270
Oesophagus/GOJ	6 (67%)	9 (90%)	9 (64%)	
Stomach	3 (33%)	1 (10%)	5 (36%)	
Histology, n (%)				0.085
Adenocarcinoma	8 (89%)	7 (70%)	14 (100%)	
Squamous cell carcinoma	1 (11%)	3 (30%)	0 (0%)	
Clinical stage, n (%)				0.177
I	0 (0%)	2 (20%)	2 (14%)	
II	0 (0%)	3 (30%)	1 (7%)	
II	6 (67%)	5 (50%)	8 (57%)	
IV	3 (33%)	0 (0%)	3 (21%)	
ASA grade, n (%)				0.953
II	6 (67%)	6 (60%)	9 (64%)	
III	3 (33%)	4 (40%)	5 (36%)	
Charlson Comorbidity Index	4.7 ± 1.0	4.4 ± 1.6	4.9 ± 1.6	0.697
Comorbidities, n (%)				
Cardiac	2 (22%)	1 (10%)	3 (21%)	0.723
Respiratory	0 (0%)	2 (20%)	2 (14%)	0.390
Neurological	0 (0%)	1 (10%)	0 (0%)	0.305
Endocrine	2 (22%)	1 (10%)	2 (14%)	0.754
Psychiatric	2 (22%)	2 (20%)	1 (7%)	0.540
Previous malignancy	1 (11%)	2 (20%)	2 (14%)	0.858
Autoimmune	0 (0%)	1 (10%)	0 (0%)	0.305
Weight (kg)	70.7 ± 16.4	81.8± 22.3	73.2± 12.4	0.319
BMI (kg/m^2)	24.7 ± 5.6	27.6± 5.2	24.9± 3.1	0.289
Neoadjuvant chemotherapy, n (%)	N/A	6 (60%)	11 (79%)	0.324
Body composition				
SM area (cm^2)	139.4 ± 24.9	150.6 ± 41.8	145.1 ± 43.2	0.823
SMI (cm^2/m^2)	48.8 ± 9.4	50.7 ± 8.4	48.7 ± 10.3	0.867
TAT area (cm^2)	330.5 ± 184.4	398.6 ± 182.1	275.7 ± 75.8	0.146
VAT area (cm^2)	146.8 ± 79.2	183.1 ± 131.3	128.4 ± 56.5	0.357
SAT area (cm^2)	183.7 ± 115.2	215.6 ± 100.0	147.3 ± 38.7	0.164
Physical activity				
Leisure Score Index [1]	36.0 ± 16.8	44.6 ± 19.7	15.0 ± 10.7	0.001
Godin Scale Score [2]	22.3 ± 17.6	30.2 ± 16.7	4.5 ± 7.3	0.001

Table 7.3. Study participant characteristics

Continuous data presented as mean ± SD. BMI = body mass index; GOJ = gastro-oesophageal junction.

[1] Leisure Score Index includes all physical activity; [2] Godin Scale Score includes moderate and strenuous intensity exercise only

	Pre-treatment n=9	Prehabilitation n=10	No prehabilitation n=14	p-value
CD68 count per slide[1]	1.7 (1.3-3.6)	1.3 (1.0-1.7)	2.9 (2.4-3.9)	0.006
Adipocyte size (um^2)	2029.2 ± 700.2	3812.4 ± 1479.7	3552.7 ± 1645.5	0.019

Table 7.4. Comparison of CD68+ cell count and adipocyte size
Continuous data presented as mean ± SD unless otherwise stated. [1]Non-parametric data, displayed as median (interquartile range)

There were significant differences in CD68 count and adipocyte size between the three groups (**Table 7.4** & **Figure 7.10**). The prehabilitation group had significantly lower CD68 count per slide in comparison to the no-prehabilitation group: mean difference = -2.1, 95% CI = -3.6 to -0.6, p=0.005; There were no significant differences between the pre-treatment and prehabilitation groups in CD68 count per slide (p=0.337).

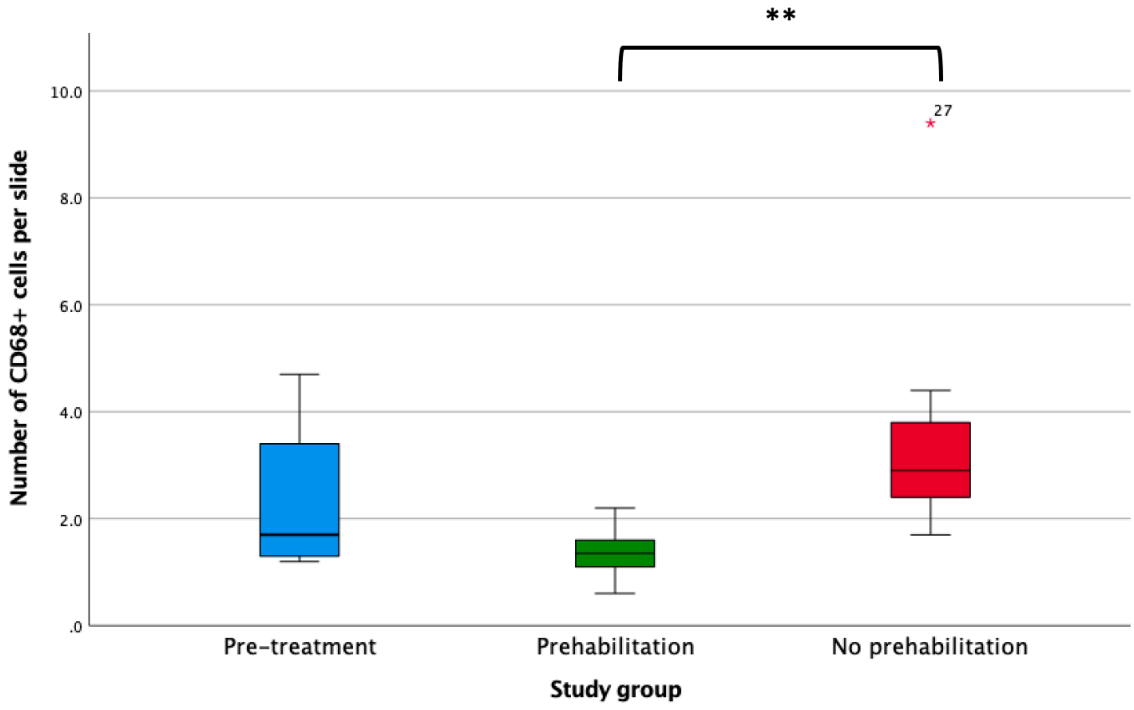


Figure 7.10 Comparison of CD68+ cell count

The pre-treatment group had significantly smaller adipocytes than both the prehabilitation and no-prehabilitation groups: mean difference = -1783.2 um^2 (95% CI = -3414.7 to -151.6, p=0.028) and mean difference = -1523.5 um^2 (95% CI = --3040.6 to -6.4, p=0.049) respectively.

There was no significant difference in adipocyte size between the prehabilitation and no-prehabilitation groups (p=0.999).

There was a weak negative correlation between LSI and CD68 count per slide (R^2 =-0.361, p=0.001) and between GSS and CD68 count per slide (R^2=-0.343, p=0.001). Patients who had a GSS ≥ 24 had a significantly lower CD68 count per slide than patients with GSS <24: GSS ≥ 24 median 1.4 (IQR 1.2 to 1.8) and GSS < 24 median 2.5 (IQR 1.8 to 3.8), p=0.006 (**Figure 7.11**).

There was no association between adipocyte size and physical activity scores.

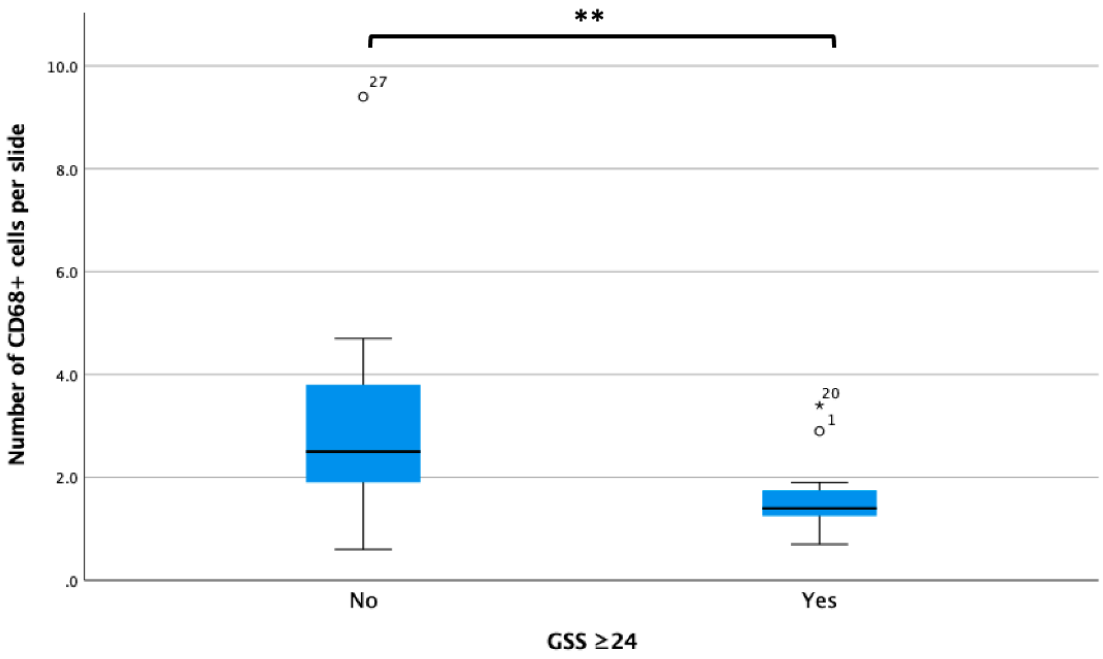


Figure 7.11 CD68+ cell count and Godin Score Scale
A GSS of ≥24 is in keeping with WHO guidelines for recommended levels of physical activity. *mRNA expression measured relative to HPRT expression.* * p<0.05; ** p<0.01; *** p<0.001

There was a positive correlation between adipocyte size and VAT area (r=0.388, p=0.026), SAT area (r=0.396, p=0.022) and TAT area (r=0.427, p=0.013). There was no association between CD68+ counts and body composition parameters.

7.5 Discussion

This study is the first to date to observe evidence of an effect of prehabilitation on the expression of inflammatory cytokines and macrophage markers in patients with oesophago-gastric cancer. Samples taken from patients at the time of surgery who did not receive prehabilitation had significantly higher expression of the pro-inflammatory cytokines IL-1β and CCL3, and lower expression of the anti-inflammatory M2 macrophage marker CD163, in comparison to pre-treatment samples; these differences in inflammation was not seen between the pre-treatment group and patients who had completed prehabilitation. Furthermore, there were non-significant trends for higher expression of the pro-inflammatory cytokines IL-6, TNFα and leptin in the no prehabilitation group compared with the prehabilitation group.

The findings indicate that VAT in patients who did not receive prehabilitation had a more pro-inflammatory environment compared with patients before starting treatment and with those who have received prehabilitation. There have been no previous studies examining changes in the VAT microenvironment during neoadjuvant therapy. The findings of this study may reflect an increase in VAT mediated during neoadjuvant therapy, as demonstrated with the differences between the baseline and no-prehabilitation resection samples. This increase may be attenuated in patients who undergo prehabilitation, as the difference was not seen between the baseline and prehabilitation resection samples.

IL-1β is expressed by macrophages, both within lymphoid tissue and within other tissues, such as the GI tract (229). It promotes the maturation of monocytes into the pro-inflammatory M1 macrophage subtype and B lymphocytes into plasma cells (226). IL-1β is essential in triggering the acute phase response to trauma or other stimuli (230). It has both pro- and anti-inflammatory effects, depending on whether its acts upon IL-1R1 or IL-1R2 respectively, and therefore has a significant role in both regulating inflammation and the subsequent response to acute inflammation (191,229,230).

CCL3 is only detectable at very low levels under normal conditions but is released from a range of immune cells, including macrophages, in response to IL-1β or endotoxins (231). It is involved in potentiating acute inflammation, through attracting recruitment of macrophages, neutrophils and eosinophils, in wound heading via its action on macrophages, and in tumour cell migration and metastasis (228). CD163 is membrane protein that is specific to the M2 macrophage subtype (232). The M2 macrophage is activated by the release of anti-inflammatory cytokines, such as IL-4 and IL-10, and acts to promote wound healing and further limit acute inflammation through secretion of anti-inflammatory cytokines (90,220,229).

In this study, there were also non-significant trends for higher expression of IL-6, TNFα and leptin in the no prehabilitation group and lower expression of CD68 in the prehabilitation group. The pro-inflammatory effects of IL-6 and TNFα have previously been discussed in **Chapter 6.5**. Leptin is primarily secreted by adipocytes and high levels of leptin potentiates chronic inflammation through stimulating production of pro-inflammatory cytokines (64,65,195).

The no prehabilitation group had a significantly lower total adipose tissue area compared with the other two groups. Normal volumes of adipose tissue are not usually associated with pro-inflammatory changes and under normal conditions, VAT contains anti-inflammatory cytokines and anti-inflammatory immune cells (220). However, as VAT mass increases, chronic inflammatory changes are seen (64). A positive correlation was noted in this study between CCL3 and both VAT area and total adipose tissue area, in keeping with known link between increasing adiposity and macrophage associated inflammation (64).

In the obese state, adipose tissue becomes dysfunctional and cannot adequately store the excess energy, resulting in adipocyte hypertrophy and decreased adipogenesis (233), which is in keeping with this study's finding of a significant correlation between adipocyte size and VAT area. Hypertrophic adipocytes are associated with chronic inflammation via adipocyte cell death, rupture of the cell membrane and release of cell contents, which in turn triggers macrophage recruitment and activation (220). In this study, the adipocytes were significantly

smaller in the pre-treatment samples compared with either of the two groups of resection samples, but there was no significant difference between the prehabilitation and no prehabilitation groups. Therefore, there is no evidence from this preliminary study that prehabilitation impacts upon adipocyte dysfunction. However, the differences in adipocyte size between the baseline and resection samples may indicate some impact of either the neoadjuvant therapy or the developing cancer itself on the adipose tissue microenvironment.

CD68 is a pan-macrophage marker that is non-specific and will identify both the M1 and M2 macrophage subtypes (234). In this study there was a trend for a significant difference in the expression of CD68 mRNA, with a lower expression of CD68 in the prehabilitation samples compared with the baseline samples, and a higher expression in the no prehabilitation samples compared with the baseline samples. Building on this trend, within the subset of samples that were available for immunohistochemistry, the prehabilitation cohort had a significantly lower CD68 count within the VAT compared with the no prehabilitation group. Although the findings of the immunohistochemistry are limited by the small sample size, taken alongside the trends in the CD68 mRNA, it is in keeping with the hypothesis of prehabilitation attenuating inflammation.

There was a significant negative correlation between the measurements of physical activity and the expression of both TNFα and IL-10. This correlation between TNFα and physical activity is in keeping with the findings from the plasma samples described in **Chapter 6**. However, IL-10 is known to have predominantly anti-inflammatory actions (188). The main source of IL-10 secretion is macrophages and it plays an important immunoregulatory role (235). Secretion of IL-10 often occurs at the same time as secretion of pro-inflammatory cytokines, and it acts as a negative feedback loop to prevent over-activation of macrophages and an excessive inflammatory response (236). Therefore, the finding of lower expression of IL-10 in patients with higher excess volumes may reflect less overall activation of inflammatory response as there is less overall macrophage activation.

7.5.1 Study limitations

There are several limitations to this study. The limitations resulting from changes imposed by the Covid-19 pandemic are the same as those previously been discussed in **Chapter 6.4**. There were fewer pre-treatment samples compared with the number of samples taken at the time of resection. Some staging laparoscopies were performed at different hospitals sites due to the pandemic and it was not possible to collect samples for these cases. Furthermore, four of the 17 pre-treatment samples were not suitable for analysis. This was due to difficulty extracting the VAT samples through the laparoscopic port sites and damage to the small samples caused by the diathermy used to take the sample of omentum. The tissue damage to these samples meant that adequate levels of mRNA could not be extracted from the tissue. As the study progressed, the technique to improve extraction of samples was refined to prevent this occurring.

It was not possible to obtain enough VAT from all patients to allow both mRNA extraction for qRT-PCR and immunohistochemistry. As the qRT-PCR allowed the measurement of a number of cytokines and markers, and the immunohistochemistry only provided a CD68 count, mRNA extraction was prioritised. Only a subset of samples provided enough tissue for immunohistochemistry as well. However, although the number of samples in each group is smaller, the three groups were still comparable for all demographic factors.

Finally, on post-hoc analysis of the markers that showed a significant difference between the three group, the differences were not the same. For example, some of the markers. For example, IL-1β and CCL3 expression was significantly different between the no-prehabilitation group compared with both the pre-treatment and prehabilitation groups. However, CCL3 expression was only significantly difference between the no-prehabilitation and pre-treatment groups. This may be due exercise having different effects on different components of the inflammatory cascade. It may also be due to a relatively small sample size in this study. As there were no previous studies looking at VAT inflammation in this patient group, it was not possible to do a sample size calculation for this study.

6.5.2 Future studies

Building from this preliminary study, further research is needed with a larger sample size, and with paired pre-treatment and resection samples, to more comprehensively delineate the changes in VAT inflammation during neoadjuvant therapy. With this, comparison of the changes in VAT inflammation between patients with and without prehabilitation will characterise whether prehabilitation does have a significant effect on VAT inflammation.

Flow cytometry should also be examined to look at the effect of prehabilitation on other cell types, including other leukocyte populations. Mass spectrometry could be used to confirm changes seen in this study. Mass spectrometry opens the field to studying a vast array of secretory proteins in adipose microenvironment. This would give a better understanding of the changes in VAT microenviroment both during neoadjuvant therapy and in response to prehabilitation.

6.6 Conclusions

Inflammation in VAT is higher in patients who have completed neoadjuvant therapy, with increased expression of IL-1β and CCL3, and lower expression of the anti-inflammatory CD163. There was no significant difference in inflammation between the pre-treatment and post-prehabilitation samples, suggesting that the pro-inflammatory effects may be attenuated by prehabilitation. Furthermore, TNFα and IL-10 expression was significantly associated with exercise volume. However, these markers were not significantly different overall between the three groups. It is possible that the exercise amount may not be the only factor contributing to change in VAT microenvironment and the impact of other prehab components should be considered.

CHAPTER 8

-

FINAL CONCLUSIONS AND FUTURE DIRECTIONS

8.1 Key findings

The studies presented within this thesis have provided evidence to support the hypothesis that pre-operative exercise reduces post-operative complications in patients undergoing surgery for oesophago-gastric cancer and the mechanisms by which it has this effect are multifactorial, with multiple impacts upon cardiorespiratory fitness, body composition and systemic inflammation.

The key findings of this thesis are shown in Figure 8.1. Prehabilitation was associated with a lower incidence of pulmonary complications and the risk of post-operative pneumonia was related to the amount of physical activity completed. It has been demonstrated that prehabilitation has positive effects on cardiorespiratory fitness (**Chapter 3**), body composition (**Chapter 4**) and on inflammation (**Chapters 6** and **7**). Changes in cardiorespiratory fitness and changes in visceral adipose tissue (VAT) mass have been shown to be directly related to improvements in post-operative outcomes. Due to the comparatively small sample sizes in the inflammation studies (**Chapters 6** and **7**), it was not possible to assess the relationship between either systemic or VAT inflammation and post-operative outcomes. However, given that it has been demonstrated that prehabilitation can reduce inflammation, it is important that future research is undertaken with a larger sample size to examine the relationship between changes in inflammation and post-operative outcomes.

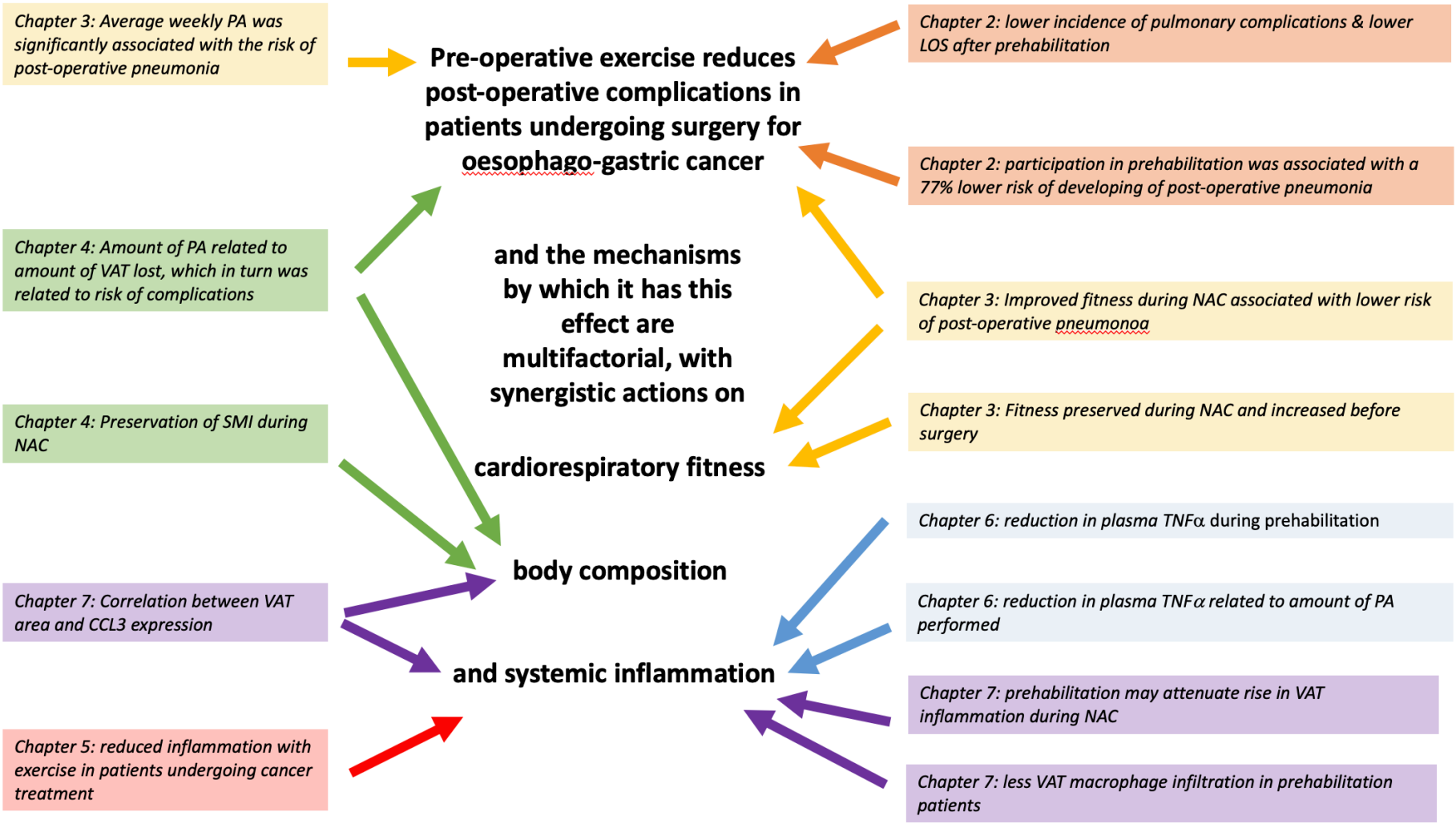


Figure 8.1 Thesis hypothesis and key findings
CCL3 = Chemokine C-C motif ligand 3; LOS = length of stay; NAC = neoadjuvant chemotherapy; PA = physical activity; SMI = skeletal muscle index; TNFα = tumour necrosis factor α; VAT = visceral adipose tissue

The interplay of the mechanisms involved in reducing post-operative complications is likely to be complex. There was evidence of a relationship between the changes in body composition and VAT inflammation (**Chapter 7**). However, other relationships between potential mechanisms by which prehabilitation works have not been identified, and therefore whilst this thesis has established that changes in fitness, body composition and inflammation occur during prehabilitation, further research is needed to better understand how changes in one mechanistic domain impact upon another.

Exercise is a key component of prehabilitation programmes (22) and this has been the focus of this thesis. However, it is increasingly recognised that prehabilitation should be multimodal (25), and as outlined in **Chapter 2.3.1** and **Figure 2.1**, the PREPARE for Surgery programme that was utilised in these studies involved nutritional optimisation and psychological support in addition to exercise.

With these interventions being delivered simultaneously, it is difficult to isolate the respective contributions of each intervention. However, as the amount of exercise that patients completed was quantified in each study, it was possible to identify relationships between the amount of exercise completed and various outcomes. It was shown that the volume of physical activity was significantly related to the risk of post-operative pneumonia (**Chapter 3**), and that the volume of physical activity was related to the volume of VAT lost, which in turn was related to the risk of post-operative complications (**Chapter 4**). Furthermore, the amount of exercise completed by patients was also related to changes in plasma TNFα during prehabilitation (**Chapter 6**) and to TNFα expression within VAT (**Chapter 7**).

This, however, does not necessarily indicate that increasing exercise volume alone in the absence of the other interventions used in the PREPARE for Surgery programme would have similar benefits. Optimising nutrition may benefit fitness in many ways, such as optimising energy intake and addressing vitamin and mineral deficiencies to improve metabolism. Additionally, helping with psychological distress may also increase patient motivation and improve exercise adherence. This thesis has focused on the mechanisms behind how exercise can improve post-operative outcomes. Although beyond the scope of this work, it is

important to also look at the mechanisms behind how nutritional and psychological interventions improve post-operative outcomes and how these interventions work together.

8.2 Future research

8.2.1 Clinical studies

In addition to the proposed topics for future research discussed within each chapter, several other channels of research should be considered. Firstly, the PREPARE for Surgery programme has been utilised in each of the studies. It remains to be seen how replicable these findings are in other clinical settings and institutions, and therefore future research must include multicentre trials. To aid the successful rollout of prehabilitation, implementation research techniques should be employed. Implementation science research focuses on delivering research findings into routine clinical practice, the barriers and enabling factors for implementation, and the study of organisational and individual behaviour change (237). It is important that clinical interventions are adapted to the context of the local environment (238), and therefore the methods that are used to deliver prehabilitation successfully at one site may not work as well in another. Throughout this thesis, the importance of personalisation of prehabilitation has been stressed. The methods for implementing and delivering these programmes similarly need to be personalised to the physical environment, the skills and abilities of the staff and the demographics of the patient group.

Although two meta-analyses have previously found a significant reduction in the risk of post-operative complications after intra-abdominal surgery with prehabilitation (20,33), the results shown in **Chapter 2** are the first to demonstrate a reduction in complications after oesophageal cancer surgery. This thesis has shown that prehabilitation can preserve fitness (**Chapter 3**), preserve muscle mass loss (**Chapter 4**), and attenuate a rise in systemic TNFα (**Chapter 6**) during neoadjuvant therapy. It is possible that many of the benefits of prehabilitation in oesophageal cancer patients derives from diminishing some of the negative

effects of neoadjuvant therapy. Therefore, I propose that future research in prehabilitation should focus on other patient groups who receive neoadjuvant therapy, such as breast and rectal cancer patients. Prehabilitation has already been shown to prevent muscle loss and a decline in cardiorespiratory fitness during neoadjuvant therapy in rectal cancer patients (9,30), and exercise to reduce inflammation in breast cancer patients (98). It remains to be seen whether prehabilitation can improve post-operative outcomes in these patient groups; however, given that benefits of prehabilitation and exercise have already been demonstrated in these groups, more detailed research into prehabilitation in these populations is needed.

However, this potential link between neoadjuvant therapy and improved outcomes from prehabilitation does not mean that only cancer patients could benefit from these interventions. In **Chapter 4** it was found that the amount of VAT lost during prehabilitation increased incrementally with the increase in the amount of physical activity completed, and also that the more VAT that was lost, the lower the subsequent risk of post-operative complications. Given this link between exercise, VAT area and post-operative findings, the impact of prehabilitation on clinically obese patients undergoing other major surgery must be explored.

To date, most prehabilitation research has focused on short-term outcomes, such as changes in pre-operative fitness, post-operative complications and fitness in the first few weeks after surgery (21). It is important that research is undertaken to assess the long-term impacts of prehabilitation on psychological recovery and patient reported outcome measures. Whilst psychological interventions were included within the programme, further work is needed to optimise the interventions offered and elucidate which interventions are most efficacious in this setting and how to identify the amount of support needed by individual patients. Furthermore, more research is needed to understand how psychological intervention impact on adherence to other prehabilitation interventions, such as exercise, and how they affect post-operative recovery.

The effect of prehabilitation on oncological outcomes must also be assessed. In oesophageal and rectal cancer patients, prehabilitation has been shown to be associated with greater response to neoadjuvant chemotherapy and chemoradiotherapy respectively (9,112).

Furthermore, in both murine and human studies of pancreatic cancer, vascular remodelling within the tumour was noted when exercise was delivered during neoadjuvant therapy (239).

There is substantial evidence that inflammation is associated with a poor prognosis in many cancer types (64,72,73,202), including oesophageal cancer (4,203,205). Adipose tissue mediated inflammation has particularly been shown to be associated with carcinogenesis (65,71). Within **Chapter 7**, differences in VAT inflammation were noted between pre-treatment patients and those who had and had not received prehabilitation. It is possible that these changes in VAT inflammation may impact on the biological behaviour of the cancer and its chance of progression or responding to neoadjuvant therapy. As previously discussed, it is important that future research moves towards larger, multicentre studies. As well as providing more information of the generalisability of the findings, the much larger sample size will improve the power of the studies and make it more feasible to study oncological outcomes such as disease-free survival and overall survival.

In the prehabilitation programme studied in this thesis, a combination of aerobic and strength exercises were used. As discussed, the studies have demonstrated important relationships between the amount of physical activity and the risk of developing post-operative pneumonia, and the amount of physical activity and the loss of VAT, which in turn was related to post-operative complications. Every extra MET/min/week makes a difference to the patient's outcome. However, it is unclear what the impact is of different types of aerobic and strength exercise are. Does the type of exercise also have an impact on outcomes, as well as exercise volume? In these studies, the type of exercises was personalised according to the results of submaximal exercise testing, previous exercise behaviour, patient preference and medical co-morbidities, and consequently a wide range of exercise modalities was used. Building on the findings of this thesis, future research should compare different aerobic modalities, different exercise intensities and different combinations of aerobic and strength exercise. These studies would again require multi-centre collaboration to ensure adequate sample sizes and outcomes should include both physiological measures, such as fitness and body composition, as well as clinical outcomes.

Another important topic for research is how to best measure response to prehabilitation in real-time whilst the programmes are being delivered. This thesis identified that both amount of physical activity and loss of VAT during the programme were associated with the risk of post-operative complications, so these are important markers of response to explore. The PREPARE for Surgery programme monitored adherence during the programme, and adjusted the programme accordingly to increase the interventions when possible or adjust the type of interventions if adherence was poor. As extensively discussed throughout these studies, the adherence was self-reported and wearable technology, such as pedometers, could be used to provide a more reliable measure of activity. This also has the potential to feed real-time data into an artificial intelligence model to automatically make changes to the exercise programme, thus reducing the staffing demands of the programme. In this model, the artificial intelligence model could also be programmed to flag up ay participants who are repeatedly not meeting their targets and need a more comprehensive assessment for the reasons behind poor adherence.

Since the Covid-19 pandemic, a growing number of healthcare interventions are being delivered digitally (219-222). In Chapters 6 and 7, a digital programme programme was used. Further research is needed to optimise the delivery of digital prehabilitation. This must include research into the role that artificial intelligence can play. Artificial intelligence algorithms could be used to design the patient's personalised programme, to monitor their progress and adapt the programme accordingly. This may have substantial economic savings by reducing the time healthcare staff have to spend on each patient's programme, and consequently could open up the delivery of prehabilitation to a larger number of patient groups undergoing different types of surgery, where the high patient volumes and low baseline complication rate can make the economic justification for prehabilitation difficult. Alongside research to establish the feasibility and effectiveness of an artificial intelligence assisted prehabilitation programme, it would be essential to undertake qualitative research to determine the acceptability of these methods to patients and healthcare workers.

The final area of clinical research that I propose is to look at stratifying the level of support and interventions used based upon a prehabilitation score. Programmes such as the one studied in this thesis with a high degree of personalisation and regular reviews are labour

intensive to run and this may pose a logistical and economic limitation to the roll out of prehabilitation, especially if extended to conditions with larger patient populations. A score could be used to identify two key features; those who are most in need of intervention (have the highest risk of complications) and those who are likely to need the most support with adherence to the programme.

The first step in this process would be to identify the factors associated with complications and with adherence to include in the score. Many of the factors associated with post-operative complications following oesophageal cancer surgery have previously been discussed in **Chapter 1** and includes baseline VO_2max, sarcopenia and chronic inflammation. In **Chapter 3**, it was noted that both baseline fitness and the use of neoadjuvant therapy were associated with physical activity volumes and adherence; patients had lower adherence and completed less physical activity during neoadjuvant therapy, whilst patients with a high baseline fitness had a higher adherence.

These factors could be incorporated into a scoring system. In addition, other factors must be explored. Retrospective analysis of multi-centre data sets could be used to establish other factors associated with complications and with adherence to prehabilitation. This may include specific comorbidities, psychological wellbeing, social factors and frailty scores. Once potential factors have been identified, again multi-centre data sets could be used to test and optimise the marking and weighting within the score system. Then finally it could be tested to identify the level of support that it optimal for different scoring levels. Whilst this would be a large project, requiring significant collaboration and co-ordination, this type of research is likely to be very important to aid the implementation and delivery of prehabilitation within routine clinical practice.

8.2.2 Laboratory studies

In addition to clinical studies, I also propose that other laboratory studies into prehabilitation should be considered. Firstly as discussed in **Chapters 6** and **7**, larger studies are needed to assess the relationship between changes in VAT and systemic inflammation and clinical outcomes. However, other areas of research should also be explored. Flow cytometry techniques could be used to both validate the findings in **Chapters 6** and **7**, and also look at other haematological cell types and how these change during prehabilitation. Mass spectrometry could also be used to study a vast array of proteins within the adipose tissue microenviroment, including adipokines, cytokines, markers of cell turnover and the lipid composition of the tissue. There is growing commercial interest in the development of point-of-care mass spectrometers (240), and whilst this is many years from widespread clinical application, it could allow inflammation to be regularly assessed during prehabilitation, giving real-time feedback on the effect of the intervention on the tissue and cellular microenvironment.

Identifying markers of response to prehabilitation in real-time as it is being delivered is important. The laboratory techniques used to quantify haematological markers of inflammation in **Chapter 6** are not used in routine clinical practice. Routinely measured inflammatory markers, such as white cell count and C-reactive protein, could be explored as potential markers of response.

VAT mediated chronic inflammation is known to be associated with increasing insulin resistance (65,67). The impact of prehabilitation on insulin resistance could also be examined. These studies could include measuring fasting insulin and glucose levels to calculate the homeostatic model assessment for insulin resistance (HOMA-IR) and undertaking oral glucose tolerance tests to assess the impact of prehabilitation on these parameters.

Finally, research should be undertaken to assess and quantify the peri-operative stress response and compare the immediate physiological response to surgery between patients

who have completed prehabilitation and those who have not. This could be achieved by measuring cortisol and ACTH levels. Potential studies which should be considered include comparing pre-operative HPA axis function in prehabilitation patients and controls through a short synacthen test. ACTH levels and cortisol levels could also be recorded prior to surgery, at regular intervals in the first twenty-four hours after surgery, and then followed by daily measurements of cortisol in the first week after surgery.

When studying cortisol in the early post-operative period, the use of mass spectrometry to measure free cortisol levels should be examined in addition to measuring total plasma cortisol through techniques such as immunoassays. This is because levels of albumin and cortisol binding globulin decrease after surgery and therefore there are higher levels of the biological activity free cortisol during this time (95). Due to the circadian rhythms that regulate cortisol, a strict timing of sample collection would be needed. The trauma of a major operation can disrupt the usual circadian cycle (89,95). Multiple cortisol readings throughout the first few days after surgery in both prehabilitation patients and controls could provide a valuable insight into whether prehabilitation could impact upon this disruption in cortisol regulation in the post-operative period.

8.3 Summary

This thesis has demonstrated that prehabilitation can reduce the risk of post-operative pneumonia after oesophageal cancer surgery and is associated with a shorter length of stay. In keeping with this, multiple beneficial effects of prehabilitation have been observed during neoadjuvant therapy including preservation of cardiorespiratory fitness, protection from skeletal muscle loss, promotion of VAT loss and an attenuation in the pro-inflammatory response to neoadjuvant treatment.

Time in the pre-operative period is limited and must be used wisely. The findings of this thesis have demonstrated the benefits of prehabilitation for oesophageal cancer patients. I believe that prehabilitation should be considered a key component of peri-operative care and should be fully integrated within the peri-operative pathway for patients undergoing oesophageal cancer surgery. The importance of and benefits of prehabilitation should be emphasised from the point of diagnosis, highlighting that what patients do in the pre-operative period will impact upon their recovery.

Every patient is an individual. What they can gain from prehabilitation and how they need prehabilitation to be delivered will vary. The challenge now for clinicians and researchers is to match the effort that patients are putting into completing prehabilitation and ensure we are providing them with the most comprehensive and evidence based programmes. Ongoing research into prehabilitation is essential to allow continued optimisation of the interventions and to allow more efficient targeting of resources to those most at need and those who will benefit most, which in turn may greatly improve the benefits that can be accrued.

Given the observed direct relationships in this thesis between the volume of physical activity and both the risk of post-operative pneumonia and the amount of VAT loss, every extra MET/min/wk has been shown to have benefits for patients. Exercise must be a key feature of pre-operative care.

In the pre-operative period, every extra step counts.

REFERENCES

(1) Desborough JP. The stress response to trauma and surgery. *British Journal of Anaesthesia*. 2000; 85 (1): 109-117.

(2) Gutierrez T, Hornigold R, Pearce A. The systemic response to surgery. *Surgery (Oxford*). 2011; 29 (2): 93-96.

(3) Vigano A, Kasvis P, Di Tomasso J, Gillis C, Kilgour R, Carli F. Pearls of optimizing nutrition and physical performance of older adults undergoing cancer therapy. *Journal of Geriatric Oncology*. 2017; 8 (6): 428-436.

(4) Anandavadivelan P, Lagergren P. Cachexia in patients with oesophageal cancer. *Nature Reviews Clinical Oncology*. 2016; (13): 185-196.

(5) Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. *Gut*. 2011; 60 (11): 1449-1473.

(6) Backemar L, Lagergren P, Johar A, Lagergren J. Impact of co- morbidity on mortality after oesophageal cancer surgery. *British Journal of Surgery*. 2015; 102 (9): 1097-1105.

(7) McIsaac DI, Bryson GL, van Walraven C. Association of Frailty and 1- Year Postoperative Mortality Following Major Elective Noncardiac Surgery: A Population-Based Cohort Study. *JAMA Surgery*. 2016; 151 (6): 538-545.

(8) Varagunam M, Park MH, Sinha S, Cromwell D, Maynard N, Crosby T, et al. *National Oesophago-Gastric Cancer Audit 2018*. Royal College of Surgeons; 2019.

(9) West MA, Astin R, Moyses HE, Cave J, White D, Levett DZH, et al. Exercise prehabilitation may lead to augmented tumor regression following neoadjuvant chemoradiotherapy in locally advanced rectal cancer. *Acta Oncologica*. 2019; 58 (5): 588-595.

(10) Hoppe S, Rainfray M, Fonck M, Hoppenreys L, Blanc J, Ceccaldi J, et al. Functional decline in older patients with cancer receiving first- line chemotherapy. *Journal of Clinical Oncology*. 2013; 31 (31): 3877-3882.

(11) Low DE, Kuppusamy MK, Alderson DC, Cecconello IB, Chang AC., Darling G, et al. Benchmarking Complications Associated with Esophagectomy. Annals of Surgery. 2019; 269 (2): 291-298.

(12) Barbour AP, Lagergren P, Hughes R, Alderson D, Barham CP, Blazeby JM. Health- related quality of life among patients with adenocarcinoma of the gastro- oesophageal junction treated by gastrectomy or oesophagectomy. *British Journal of Surgery*. 2008; 95 (1): 80-84.

(13) Akkerman RDL, Haverkamp L, van Rossum PSN, van Hillegersberg R, Ruurda JP. Long- term quality of life after oesophagectomy with gastric conduit interposition for cancer. *European Journal of Cancer*. 2015; 51 (12): 1538-1545.

(14) Fearon KCH, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CHC, Lassen K, et al. Enhanced recovery after surgery: A consensus review of clinical care for patients undergoing colonic resection. *Clinical Nutrition*. 2005; 24 (3): 466-477.

(15) Findlay JM, Gillies RS, Millo J, Sgromo B, Marshall REK, Maynard ND. Enhanced recovery for esophagectomy: a systematic review and evidence- based guidelines. *Annals of Surgery*. 2014; 259 (3): 413-431.

(16) Lee L, Li C, Robert N, Latimer E, Carli F, Mulder DS, et al. Economic impact of an enhanced recovery pathway for oesophagectomy. *British Journal of Surgery*. 2013; 100 (10): 1326-1334.

(17) Carli F, Silver JK, Feldman LS, McKee A, Gilman S, Gillis C, et al. Surgical Prehabilitation in Patients with Cancer: State-of-the-science and recommendations for future research from a panel of subject matter experts. *Physical Medicine and Rehabilitation Clinics of North America*. 2017; 28 49-64.

(18) Vermillion SA, James A, Dorrell RD, Brubaker P, Mihalko SL, Hill AR, et al. Preoperative exercise therapy for gastrointestinal cancer patients: a systematic review. *Systematic Reviews*. 2018; 7 (1): 1-10. Available from: doi: 10.1186/s13643-018-0771-0

(19) Levett DZH, Edwards M, Grocott M, Mythen M. Preparing the patient for surgery to improve outcomes. *Best Practice & Research Clinical Anaesthesiology*. 2016; 30 (2): 145-157.

(20) Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation Before Major Abdominal Surgery: A Systematic Review and Meta-analysis. *World Journal of Surgery*. 2019. Available from: doi: 10.1007/s00268-019-04950-y

(21) Minnella EM, Carli F. Prehabilitation and functional recovery for colorectal cancer patients. *European Journal of Surgical Oncology*. 2018; 44 (7): 919-926.

(22) Bloom E. *Prehabilitation evidence and insight review.* Macmillan Cancer Support; 2017.

(23) Levett DZH, Grimmett C. Psychological factors, prehabilitation and surgical outcomes: evidence and future directions. *Anaesthesia*. 2019; 74: 36-42.

(24) Scheede-Bergdahl C, Minnella EM, Carli F. Multi-modal prehabilitation: addressing the why, when, what, how, who and where next? *Anaesthesia*. 2019; 74: 20-26.

(25) Macmillan Cancer Support. *Prehabilitation for people with cancer: principles and guidance for prehabilitation within the management and support of people with cancer.* Available from: https://www.macmillan.org.uk/healthcare-professionals/news-and-resources/guides/principles-and-guidance-for-prehabilitation [Accessed 10th December 2020]

(26) Piraux E, Caty G, Reychler G. Effects of preoperative combined aerobic and resistance exercise training in cancer patients undergoing tumour resection surgery: A systematic review of randomised trials. *Surgical Oncology*. 2018; 27 (3): 584-594.

(27) Lau CSM, Chamberlain RS. Prehabilitation Programs Improve Exercise Capacity Before and After Surgery in Gastrointestinal Cancer Surgery Patients: A Meta-Analysis. *Journal of Gastrointestinal Surgery*. 2019. Available from: doi: 10.1007/s11605-019-04436-1

(28) Blackwell JEM, Doleman B, Boereboom CL, Morton A, Williams S, Atherton P, et al. High-intensity interval training produces a significant improvement in fitness in less than 31 days before surgery for urological cancer: a randomised control trial. *Prostate Cancer and Prostatic Diseases*. 2020; 23 (4): 696-704.

(29) Minnella EM, Awasthi R, Bousquet-Dion G, Ferreira V, Austin B, Audi C, et al. Multimodal Prehabilitation to Enhance Functional Capacity Following Radical Cystectomy: A Randomized Controlled Trial. *European Urology Focus.* 2019. Available from: doi: 10.1016/j.euf.2019.05.016

(30) Moug SJ, Mutrie N, Barry SJE, Mackay G, Steele RJC, Boachie C, et al. Prehabilitation is feasible in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy and may minimize physical deterioration: results from the REx trial. *Colorectal Disease*. 2019; 21 (5): 548-562.

(31) Carli F, Bousquet-Dion G, Awasthi R, Elsherbini N, Liberman S, Boutros M, et al. Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial. *JAMA Surgery*. 2020; 155 (3): 233-242.

(32) Santa Mina D, Clarke H, Ritvo P, Leung YW, Matthew AG, Katz J, et al. Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. *Physiotherapy*. 2014; 100 (3): 196-207.

(33) Moran J, Guinan E, Mccormick P, Larkin J, Mockler D, Hussey J, et al. The ability of prehabilitation to influence postoperative outcome after intra- abdominal operation: A systematic review and meta-analysis. *Surgery*. 2016; 160 (5): 1189-1201.

(34) Thomas R, G., Tahir C, M., Bongers L, B., Kallen D, V., Slooter L, G., Van Meeteren L, Nico. Prehabilitation before major intra-abdominal cancer surgery: A systematic review of randomised controlled trials. *European Journal of Anaesthesiology*. 2019; 36 (12): 933-945.

(35) Santa Mina D, Hilton WJ, Matthew AG, Awasthi R, Bousquet-Dion G, Alibhai SMH, et al. Prehabilitation for radical prostatectomy: A multicentre randomized controlled trial. *Surgical Oncology*. 2018; 27 (2): 289-298.

(36) Minnella EM, Awasthi R, Loiselle S, Agnihotram RV, Ferri LE, Carli F. Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial. *JAMA Surgery*. 2018; 153 (12): 1081-1089.

(37) Dewberry LC, Wingrove LJ, Marsh MD, Glode AE, Schefter TE, Leong S, et al. Pilot Prehabilitation Program for Patients With Esophageal Cancer During Neoadjuvant Therapy and Surgery. *Journal of Surgical Research*. 2019; 235 66-72.

(38) Allen SK, Brown V, White D, King D, Hunt J, Wainwright J, et al. Multimodal Prehabilitation During Neoadjuvant Therapy Prior to Esophagogastric Cancer Resection: Effect on Cardiopulmonary Exercise Test Performance, Muscle Mass and Quality of Life—A Pilot Randomized Clinical Trial. Annals of *Surgical Oncology*. 2021. Available from: doi: 10.1245/s10434-021-11002-0

(39) Ngo-Huang A, Parker N, Wang X, Petzel M, Fogelman D, Schadler K, et al. Home-based exercise during preoperative therapy for pancreatic cancer. *Langenbeck's Archives of Surgery*. 2017; 402 (8): 1175-1185.

(40) Tatematsu N, Park M, Tanaka E, Sakai Y, Tsuboyama T. Association between Physical Activity and Postoperative Complications after Esophagectomy for Cancer: A Prospective Observational Study. *Asian Pacific Journal of Cancer Prevention*. 2013; 14 (1): 47-51.

(41) Feeney C, Reynolds JV, Hussey J. Preoperative physical activity levels and postoperative pulmonary complications post-esophagectomy. *Diseases of the Esophagus*. 2011; 24 (7): 489-494.

(42) Dronkers JJ, Chorus AMJ, Meeteren NLU, Hopman-Rock M. The association of pre-operative physical fitness and physical activity with outcome after scheduled major abdominal surgery. *Anaesthesia*. 2013; 68 (1): 67-73.

(43) Nilsson H, Angerås U, Bock D, Börjesson M, Onerup A, Fagevik Olsen M, et al. Is preoperative physical activity related to post-surgery recovery? A cohort study of patients with breast cancer. *BMJ Open.* 2016; 6 (1): e007997. Available from: doi: 10.1136/bmjopen-2015-007997

(44) Sykes K, Roberts A. The Chester step test—a simple yet effective tool for the prediction of aerobic capacity. *Physiotherapy*. 2004; 90 (4): 183-188.

(45) Du H, Newton PJ, Salamonson Y, Carrieri-Kohlman V, Davidson PM. A Review of the Six- Minute Walk Test: Its Implication as a Self- Administered Assessment Tool. *European Journal of Cardiovascular Nursing*. 2009; 8 (1): 2-8. Available from: doi: 10.1016/j.ejcnurse.2008.07.001

(46) Grove T. Incremental shuttle walk test in cardiac rehabilitation. *British Journal of Cardiac Nursing*. 2013; 8 (1): 31-37.

(47) Older PO, Levett DZH. Cardiopulmonary Exercise Testing and Surgery. *Annals of the American Thoracic Society*. 2017; 14: S74. Available from: doi: 10.1513/AnnalsATS.201610-780FR

(48) Patel N, Powell AG, Wheat JR, Brown C, Appadurai IR, Davies RG, et al. Cardiopulmonary fitness predicts postoperative major morbidity after esophagectomy for patients with cancer. *Physiological Report*s. 2019; 7 (14): e14174. Available from: doi: 10.14814/phy2.14174

(49) Sankar A, Thorpe KE, Gershon AS, Granton JT, Wijeysundera DN. Association of preoperative spirometry with cardiopulmonary fitness and postoperative outcomes in surgical patients: A multicentre prospective cohort study. *EClinicalMedicine*. 2020; 23: 100396. Available from: doi: 10.1016/j.eclinm.2020.100396

(50) West MA, Lythgoe D, Barben CP, Noble L, Kemp GJ, Jack S, et al. Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. *British Journal of Anaesthesia*. 2014; 112 (4): 665-671.

(51) McCullough PA, Gallagher MJ, de Jong AT, Sandberg KR, Trivax JE, Alexander D, et al. Cardiorespiratory Fitness and Short-term Complications After Bariatric Surgery. *Chest*. 2006; 130 (2): 517-525.

(52) Snowden CP, Prentis J, Jacques B, Anderson H, Manas D, Jones D, et al. Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. *Annals of Surgery.* 2013; 257 (6): 999. Available from: doi: 10.1097/SLA.0b013e31828dbac2

(53) Stubbs DJ, Grimes LA, Ercole A. Performance of cardiopulmonary exercise testing for the prediction of post-operative complications in non cardiopulmonary surgery: A systematic review. *PloS One.* 2020; 15 (2): e0226480. Available from: doi: 10.1371/journal.pone.0226480

(54) Avendano CE, Flume PA, Silvestri GA, King LB, Reed CE. Pulmonary complications after esophagectomy. *The Annals of Thoracic Surgery*. 2002; 73 (3): 922-926.

(55) Yip C, Goh V, Davies A, Gossage J, Mitchell-Hay R, Hynes O, et al. Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer. *European Radiology*. 2014; 24 (5): 998-1005.

(56) Elliott A, J., Doyle L, S., Murphy F, C., King M, S., Guinan V, E., Beddy V, P., et al. Sarcopenia: Prevalence, and Impact on Operative and Oncologic Outcomes in the Multimodal Management of Locally Advanced Esophageal Cancer. *Annals of Surgery*. 2017; 266 (5): 822-830.

(57) Boshier PR, Heneghan R, Markar SR, Baracos VE, Low DE. Assessment of body composition and sarcopenia in patients with esophageal cancer: a systematic review and meta-analysis. *Diseases of the Esophagus.* 2018. Available from: doi: 10.1093/dote/doy047 .

(58) Makiura D, Ono R, Inoue J, Kashiwa M, Oshikiri T, Nakamura T, et al. Preoperative sarcopenia is a predictor of postoperative pulmonary complications in esophageal cancer following esophagectomy: A retrospective cohort study. *Journal of Geriatric Oncology*. 2016; 7 (6): 430-436.

(59) Tan BHL, Brammer K, Randhawa N, Welch NT, Parsons SL, James EJ, et al. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. *European Journal of Surgical Oncology.* 2015; 41 (3): 333-338.

(60) Dirks RC, M.D., Edwards BL,M.D.M.S., Tong E, M.D., Schaheen B, M.D., Turrentine FE,PhD.R.N., Shada A, M.D., et al. Sarcopenia in emergency abdominal surgery. *The Journal of Surgical Research*. 2017; 207: 13-21.

(61) Chen W, Chen X, Ma L, Zhang F, Lin J, Zhuang C, et al. Impact of Visceral Obesity and Sarcopenia on Short-Term Outcomes After Colorectal Cancer Surgery. *Digestive Diseases and Sciences*. 2018; 63 (6): 1620. Available from: doi: 10.1007/s10620-018-5019-2

(62) Huang D, Zhou C, Wang S, Mao S, Zhou X, Lou N, et al. Impact of different sarcopenia stages on the postoperative outcomes after radical gastrectomy for gastric cancer. *Surgery*. 2017; 161 (3): 680-693.

(63) Dean D, Tan BH, Wigmore SJ, Ross JA, De Beaux A,C., Paterson-Brown S, et al. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. *British Journal of Cancer*. 2009; 100 (1): 63-69.

(64) Hopkins BD, Goncalves MD, Cantley LC. Obesity and Cancer Mechanisms: Cancer Metabolism. *Journal of Clinical Oncology*. 2016; 34 (35): 4277-4283.

(65) Himbert C, Delphan M, Scherer D, Bowers LW, Hursting S, Ulrich CM. Signals from the Adipose Microenvironment and the Obesity-Cancer Link-A Systematic Review. *Cancer Prevention Research*. 2017; 10 (9): 494-506.

(66) Bruun JM, Lihn AS, Pedersen SB, Richelsen B. Monocyte Chemoattractant Protein-1 Release Is Higher in Visceral than Subcutaneous Human Adipose Tissue (AT): Implication of Macrophages Resident in the AT. *The Journal of Clinical Endocrinology and Metabolism*. 2005; 90 (4): 2282-2289.

(67) Carli F. Physiologic considerations of Enhanced Recovery After Surgery programs: implications of the stress response. *Canadian Journal of Anesthesia*. 2015; 62 (2): 110. Available from: doi: 10.1007/s12630-014-0264-0

(68) Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006; 444 (7121): 840-846.

(69) Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? *Current opinion in endocrinology, diabetes, and obesity.* 2012; 19 (2): 81-87.

(70) Majorczyk M, Smoląg D. Effect of physical activity on IGF-1 and IGFBP levels in the context of civilization diseases prevention. *Roczniki Państwowego Zakładu Higieny.* 2016; 67 (2): 105-111.

(71) McTiernan A. Mechanisms linking physical activity with cancer. *Nature Reviews Cancer.* 2008; 8 (3): 205-211. Available from: doi: 10.1038/nrc2325

(72) Ma Y, Ren Y, Dai Z, Wu C, Ji Y, Xu J. IL-6, IL-8 and TNF-α levels correlate with disease stage in breast cancer patients. *Advances in Clinical and Experimental Medicine.* 2017; 26 (3): 421-426. Available from: doi: 10.17219/acem/62120

(73) Michalaki V, Syrigos K, Charles P, Waxman J. Serum levels of IL-6 and TNF-α correlate with clinicopathological features and patient survival in patients with prostate cancer. *British Journal of Cancer.* 2004; 90 (12): 2312-2316.

(74) Kishimoto T. Interleukin-6: from basic science to medicine--40 years in immunology. *Annual Review of Immunology.* 2005; 23 (1): 1-21.

(75) Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. *Diabetology and Metabolic Syndrome.* 2011; 3 (1): 12. Available from: doi: 10.1186/1758-5996-3-12

(76) Sultan P, Edwards MR, Gutierrez del Arroyo A, Cain D, Sneyd JR, Struthers R, et al. Cardiopulmonary exercise capacity and preoperative markers of inflammation. *Mediators of Inflammation.* 2014. Available from: doi: 0.1155/2014/727451

(77) McSorley ST, Roxburgh CSD, Horgan PG, McMillan DC. The relationship between cardiopulmonary exercise test variables, the systemic inflammatory response, and complications following surgery for colorectal cancer. *Perioperative Medicine.* 2018. Available from: doi: 10.1186/s13741-018-0093-8

(78) Madssen E, Skaug E, Wisløff U, Ellingsen Ø, Videm V. Inflammation Is Strongly Associated With Cardiorespiratory Fitness, Sex, BMI, and the Metabolic Syndrome in a Self-reported Healthy Population: HUNT3 Fitness Study. *Mayo Clinic Proceedings.* 2019; 94 (5): 803-810.

(79) Arsenault BJ, Cartier A, Côté M, Lemieux I, Tremblay A, Bouchard C., et al. Body Composition, Cardiorespiratory Fitness, and Low-Grade Inflammation in Middle-Aged Men and Women. *The American Journal of Cardiology.* 2009; 104 (2): 240-246.

(80) Wedell-Neergaard A, Krogh-Madsen R, Petersen GL, Hansen ÅM, Pedersen BK, Lund R, et al. Cardiorespiratory fitness and the metabolic syndrome: Roles of inflammation and abdominal obesity. *PloS One.* 2018; 13 (3): e0194991. Available from: doi: 10.1371/journal.pone.0194991

(81) Fujiwara Y, Shiba H, Furukawa K, Iida T, Haruki K, Gocho T, et al. Glasgow prognostic score is related to blood transfusion requirements and post-operative complications in hepatic resection for hepatocellular carcinoma. *Anticancer Research.* 2010; 30 (12): 5129.

(82) De Magistris L, Paquette B, Orry D, Facy O, Di Giacomo G, Rat P, et al. Preoperative inflammation increases the risk of infection after elective colorectal surgery: results from a prospective cohort. *International Journal of Colorectal Disease.* 2016; 31 (9): 1611-1617. Available from: doi: 10.1007/s00384-016-2620-8

(83) Mezzomo A, Bodin J,Odemir L., Lucia V. Preoperative C-reactive protein predicts respiratory infection after coronary artery bypass graft surgery. *Arquivos Brasileiros de Cardiologia.* 2011; 97 (5): 365. Available from: doi: 10.1590/S0066-782X2011005000092

(84) Moyes L, Leitch EF, McKee RF, Anderson JH, Horgan PG, McMillan DC. Preoperative systemic inflammation predicts postoperative infectious complications in patients undergoing curative resection for colorectal cancer. *British Journal of Cancer.* 2009; 100 (8): 1236-1239.

(85) Neal CP, Mann CD, Garcea G, Briggs CD, Dennison AR, Berry DP. Preoperative Systemic Inflammation and Infectious Complications After Resection of Colorectal Liver Metastases. *Archives of Surgery.* 2011; 146 (4): 471-478.

(86) Miskovic A, Lumb AB. Postoperative pulmonary complications. *British Journal of Anaesthesia.* 2017; 118 (3): 317-334.

(87) Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *British Journal of Anaesthesia.* 1997; 78 (5): 606.

(88) Iwasaki M, Edmondson M, Sakamoto A, Ma D. Anesthesia, surgical stress, and "long-term" outcomes. *Acta Anaesthesiologica Taiwanica.* 2015; 53 (3): 99-104.

(89) Prete A, Yan Q, Al-Tarrah K, Akturk HK, Prokop LJ, Alahdab F, et al. The cortisol stress response induced by surgery: A systematic review and meta-analysis. *Clinical Endocrinology..* 2018; 89 (5): 554-567.

(90) de Bois J, Moor D, Aggarwal G. Systemic response to surgery. *Surgery).* 2023; 41 (2): 117-121. Available from: doi: 10.1016/j.mpsur.2022.12.001

(91) Chevrollier GS, Rosato MC, Zilberman BG, Giugliano DN, Taleb M, Palazzo F, et al. Persistently Elevated Serum Lactate Levels 48 Hours Postoperatively Predict Increased Complications after Esophagectomy. *Journal of the American College of Surgeons.* 2018; 227 (4): e74. Available from: doi: 10.1016/j.jamcollsurg.2018.08.199

(92) Pitter SET, Kehlet H, Hansen CP, Bundgaard-Nielsen M, Storkholm J, Aasvang EK. Persistent severe post-operative hypotension after pancreaticoduodenectomy is related to increased inflammatory response. *Acta Anaesthesiologica Scandinavica.* 2020; 64 (4): 455-463.

(93) Mokart D, Leone M, Sannini A, Brun JP, Tison A, Delpero JR, et al. Predictive perioperative factors for developing severe sepsis after major surgery. *British Journal of Anaesthesia.* 2005; 95 (6): 776-781.

(94) Lu JJ, Yang MS, Cen CQ, Xu C, Yuan H. Surgical stress biomarkers as early predictors of postoperative infectious complications in patients with colorectal cancer. *Translational Cancer Research.* 2018; 7 (3): 668-675.

(95) Manou-Stathopoulou V, Korbonits M, Ackland GL. Redefining the perioperative stress response: a narrative review. *British Journal of Anaesthesia.* 2019; 123 (5): 570-583.

(96) Kapritsou M, Korkolis DP, Giannakopoulou M, Katsoulas T, Bastaki M, Konstantinou EA. Factors Affecting Stress Levels in Hospitalized Patients after Implementation of Fast-Track Protocol in

Hepatopancreatobiliary Surgery. *Asia-Pacific Journal of Oncology Nursing.* 2020; 7 (1): 44-48. Available from: doi: 10.4103/apjon.apjon_24_19

(97) Barberan-Garcia A, Ubré M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. *Annals of Surgery.* 2018; 267 (1): 50-56.

(98) Meneses-Echavez JF, Correa-Bautista JE, Gonzalez-Jimenez E, Schmidt Rio-Valle J, Elkins MR, Lobelo F, et al. The Effect of Exercise Training on Mediators of Inflammation in Breast Cancer Survivors: A Systematic Review with Meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention.* 2016; 25 (7): 1009-1017.

(99) Khosravi N, Stoner L, Farajivafa V, Hanson ED. Exercise training, circulating cytokine levels and immune function in cancer survivors: A meta-analysis. *Brain, Behavior, and Immunity.* 2019; 81 92-104.

(100) Guinan EM, Doyle SL, O'Neill L, Dunne MR, Foley EK, O'Sullivan J, et al. Effects of a multimodal rehabilitation programme on inflammation and oxidative stress in oesophageal cancer survivors: the ReStOre feasibility study. *Supportive Care in Cancer.* 2017; 25 (3): 749-756.

(101) Dieli-Conwright C, Courneya KS, Demark-Wahnefried W, Sami N, Lee K, Buchanan TA, et al. Effects of Aerobic and Resistance Exercise on Metabolic Syndrome, Sarcopenic Obesity, and Circulating Biomarkers in Overweight or Obese Survivors of Breast Cancer: A Randomized Controlled Trial. *Journal of Clinical Oncology.* 2018; 36 (9): 875-883.

(102) Dethlefsen C, Pedersen K, Hojman P. Every exercise bout matters: linking systemic exercise responses to breast cancer control. *Breast Cancer Research and Treatment.* 2017; 162 (3): 399-408.

(103) Winters-Stone KM, Wood LJ, Stoyles S, Dieckmann NF. The Effects of Resistance Exercise on Biomarkers of Breast Cancer Prognosis: A Pooled Analysis of Three Randomized Trials. *Cancer Epidemiology, Biomarkers & Prevention.* 2018; 27 (2): 146-153.

(104) Lee JH, Jun H. Role of Myokines in Regulating Skeletal Muscle Mass and Function. *Frontiers in Physiology.* 2019; 10: 42. Available from: doi: 10.3389/fphys.2019.00042

(105) Campbell KL, McTiernan A. Exercise and Biomarkers for Cancer Prevention Studies. 2007; 137: S161-S169.

(106) Markofski MM, Carrillo AE, Timmerman KL, Jennings K, Coen PM, Pence BD, et al. Exercise Training Modifies Ghrelin and Adiponectin Concentrations and Is Related to Inflammation in Older Adults. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences.* 2014; 69 (6): 675-681.

(107) Kang D, Lee J, Suh S, Ligibel J, Courneya KS, Jeon JY. Effects of Exercise on Insulin, IGF Axis, Adipocytokines, and Inflammatory Markers in Breast Cancer Survivors: A Systematic Review and Meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention.* 2017; 26 (3): 355-365.

(108) Dieli-Conwright C, Parmentier J, Sami N, Lee K, Spicer D, Mack W, et al. Adipose tissue inflammation in breast cancer survivors: effects of a 16-week combined aerobic and resistance exercise training intervention. *Breast Cancer Research and Treatment.* 2018; 168 (1): 147-157.

(109) Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop N, et al. Immune function and exercise. *Exercise Immunology Review.* 2011; 17 6-63.

(110) Pedersen BK, Ullum H. NK cell response to physical activity: possible mechanisms of action. *Medicine and Science in Sports and Exercise.* 1994; 26 (2): 140-146.

(111) Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. *Cell Metabolism.* 2016; 23 (3): 554-562.

(112) Zylstra J, Boshier P, Whyte GP, Low DE, Davies AR. Peri-operative patient optimization for oesophageal cancer surgery – From prehabilitation to enhanced recovery. *Best Practice & Research Clinical Gastroenterology.* 2018; 36 61-73.

(113) *Global recommendations on physical activity for health.* World Health Organisation; 2010.

(114) American College of Sports Medicine. *ACSMs Guidelines for Exercise Testing and Prescription.* Philadelphia: Lippincott, Williams & Wilkins; 2010.

(115) Colberg SR, Swain DP, Vinik AI. Use of heart rate reserve and rating of perceived exertion to prescribe exercise intensity in diabetic autonomic neuropathy. *Diabetes Care.* 2003; 26 (4): 986-990.

(116) Borg G. *Borg's Perceived Exertion and Pain Scales.* Illinois: Human Kinetics; 1998.

(117) Buckley J, Jones J. *Tables for assessing, monitoring and guiding physical activity/exercise intensity in programmes for cardiovascular disease prevention and rehabilitation.* British Association for Cardiovascular Prevention and Rehabilitation; 2012.

(118) Borg GA. Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise.* 1982; 14 (5): 377-381.

(119) Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: Clinical Nutrition in cancer. *Clinical Nutrition.* 2021; 40 (5): 2898-2913.

(120) Rollnick S, Butler CC, Kinnersley P, Gregory J, Mash B. Motivational interviewing. *British Medical* Journal. 2010; 340 (7758). Available from: doi: 10.1136/bmj.c1900

(121) Hawley-Hague H, Horne M, Skelton DA, Todd C. Review of how we should define (and measure) adherence in studies examining older adults' participation in exercise classes. *BMJ Open* 2016. Available from: doi: 10.1136/bmjopen-2016-011560.

(122) Low DE, Alderson DC, Cecconello IE, Chang AB,, Darling GM, D'journo XH, et al. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Annals of Surgery.* 2015; 262 (2): 286-294.

(123) Streiner DL, Norman GR. The Pros and Cons of Propensity Scores. *Chest.* 2012; 142 (6): 1380-1382.

(124) D' Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Statistics in Medicine.* 1998; 17 (19): 2265-2281.

(125) Sinclair RCF, Phillips AW, Navidi M, Griffin SM, Snowden CP. Pre-operative variables including fitness associated with complications after oesophagectomy. *Anaesthesia.* 2017; 72 (12): 1501-1507.

(126) Chadwick G, Varagunam M, Groene O, Cromwell D, Hardwick R, Maynard N, et al. *National Oesophago-Gastric Cancer Audit 2015.* Royal College of Surgeons; 2015.

(127) Paul S, Altorki N. Outcomes in the management of esophageal cancer. *Journal of Surgical Oncology.* 2014; 110 (5): 599-610.

(128) Goense L, van Rossum PSN, Tromp M, Joore HC, van Dijk D, Kroese AC, et al. Intraoperative and postoperative risk factors for anastomotic leakage and pneumonia after esophagectomy for cancer. *Diseases of the Esophagus.* 2017; Available from: DOI: 10.1111/dote.12517

(129) Xiong W, Li R, Lei H, Jiang Z. Comparison of outcomes between minimally invasive oesophagectomy and open oesophagectomy for oesophageal cancer. *ANZ Journal of Surgery.* 2017; 87 (3): 165-170.

(130) Hughes M, Hackney R, Lamb P, Wigmore S, Deans C, Skipworth R. Prehabilitation before Major Abdominal Surgery: A Systematic Review and Meta-Analysis. *International Journal of Surgery.* 2018; 55: S5. Available from: doi: 10.1016/j.ijsu.2018.05.692

(131) Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity levels in women attending breast screening, receiving chemotherapy and post-breast cancer treatment; a cross-sectional study. *International Journal of Environmental Research and Public Health.* 2014; 11 (5): 5487-5496.

(132) Bauer VP. The Evidence against Prophylactic Nasogastric Intubation and Oral Restriction. *Clinics in Colon and Rectal Surgery.* 2013; 26 (3): 182-185. Available from: doi: 10.1055/s-0033-1351136

(133) Thorn C, White I, Burch J, Malietzis G, Kennedy R, Jenkins J. Active and passive compliance in an enhanced recovery programme. *International Journal of Colorectal Disease; Clinical and Molecular Gastroenterology and Surgery.* 2016; 31 (7): 1329-1339.

(134) Sinclair R, Navidi M, Griffin SM, Sumpter K. The impact of neoadjuvant chemotherapy on cardiopulmonary physical fitness in gastro-oesophageal adenocarcinoma. *Annals of the Royal College of Surgeons of England.* 2016; 98 (6): 396-400.

(135) Room J, Hannink E, Dawes H, Barker K. What interventions are used to improve exercise adherence in older people and what behavioural techniques are they based on? A systematic review. *BMJ Open.* 2017; 7 (12): e019221. Available from: doi: 10.1136/bmjopen-2017-019221

(136) Levy T, Laver K, Killington M, Lannin N, Crotty M. A systematic review of measures of adherence to physical exercise recommendations in people with stroke. *Clinical Rehabilitation.* 2019; 33 (3): 535-545.

(137) Argent R, Daly A, Caulfield B. Patient Involvement With Home-Based Exercise Programs: Can Connected Health Interventions Influence Adherence? *JMIR mHealth and uHealth..* 2018; 6 (3): e47. Available from: doi: 10.2196/mhealth.8518

(138) Buckley JP, Sim J, Eston RG, Hession R, Fox R. Reliability and validity of measures taken during the Chester step test to predict aerobic power and to prescribe aerobic exercise. *British Journal of Sports Medicine.* 2004; 38 (2): 197-205.

(139) Ridgway A, Z., Howell J, S. Cardiopulmonary exercise testing: a review of methods and applications in surgical patients. *European Journal of Anaesthesiology.* 2010; 27 (10): 858-865.

(140) Nevill AM, Atkinson G. Assessing agreement between measurements recorded on a ratio scale in sports medicine and sports science. *British Journal of Sports Medicine.* 1997; 31 (4): 314-318.

(141) Swank AM, Horton JL, Fleg JC, Fonarow GM, Keteyian SE, Goldberg LE, et al. Modest Increase in Peak VO2 Is Related to Better Clinical Outcomes in Chronic Heart Failure Patients: Results From Heart Failure and a Controlled Trial to Investigate Outcomes of Exercise Training. *Circulation: Heart Failure.* 2012; 5 (5): 579-585.

(142) Dunne DFJ, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, et al. Randomized clinical trial of prehabilitation before planned liver resection. *British Journal of Surgery.* 2016; 103 (5): 504-512.

(143) Petrella RJ, Lattanzio CN, Shapiro S, Overend T. Improving aerobic fitness in older adults: effects of a physician-based exercise counseling and prescription program. *Canadian Family Physician.* 2010; 56 (5): 191-200.

(144) Kampshoff CS, Jansen F, van Mechelen W, May AM, Brug J, Chinapaw MJM, et al. Determinants of exercise adherence and maintenance among cancer survivors: a systematic review. *International Journal of Behavioral Nutrition and Physical Activity.* 2014; 11 (1): 80. Available from: doi: 10.1186/1479-5868-11-80

(145) Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implementation Science.* 2009; 4 (1): 50. Available from: doi: 10.1186/1748-5908-4-50

(146) Ovretveit J. Understanding the conditions for improvement: research to discover which context influences affect improvement success. *BMJ Quality & Safety.* 2011; 20: i18-i23.

(147) Gresham G, Schrack J, Gresham LM, Shinde AM, Hendifar AE, Tuli R, et al. Wearable activity monitors in oncology trials: Current use of an emerging technology. *Contemporary Clinical Trials.* 2018; 64: 13-21.

(148) Giles C, Cummins S. Prehabilitation before cancer treatment. *British Medical Journal.* 2019; 366: l5120. Available from: doi: 10.1136/bmj.l5120

(149) Mayanagi S, Tsubosa Y, Omae K, Niihara M, Uchida T, Tsushima T, et al. Negative Impact of Skeletal Muscle Wasting After Neoadjuvant Chemotherapy Followed by Surgery on Survival for Patients with Thoracic Esophageal Cancer. *Annals of Surgical Oncology.* 2017; 24 (12): 3741-3747.

(150) Moug SJ, Barry SJE, Maguire S, Johns N, Dolan D, Steele RJC, et al. Does prehabilitation modify muscle mass in patients with rectal cancer undergoing neoadjuvant therapy? A subanalysis from the REx randomised controlled trial. *Techniques in Coloproctology.* 2020; 24 (9): 959-964.

(151) Prado CMM, Lieffers JR, Mccargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncology.* 2008; 9 (7): 629-635.

(152) Norman K, Stobäus N, Gonzalez MC, Schulzke J, Pirlich M. Hand grip strength: Outcome predictor and marker of nutritional status. *Clinical Nutrition.* 2011; 30 (2): 135-142.

(153) Innes E. Handgrip strength testing: A review of the literature. *Australian Occupational Therapy Journal.* 1999; 46 (3): 120-140.

(154) Gillis C, Fenton TR, Sajobi TT, Minnella EM, Awasthi R, Loiselle S, et al. Trimodal prehabilitation for colorectal surgery attenuates post-surgical losses in lean body mass: A pooled analysis of randomized controlled trials. *Clinical Nutrition.* 2019; 38 (3): 1053-1060.

(155) Yamamoto K, Nagatsuma Y, Fukuda Y, Hirao M, Nishikawa K, Miyamoto A, et al. Effectiveness of a preoperative exercise and nutritional support program for elderly sarcopenic patients with gastric cancer. *Gastric Cancer.* 2016; 20 (5): 913-918.

(156) Lagergren J. Influence of obesity on the risk of esophageal disorders. *Nature Reviews. Gastroenterology & Hepatology.* 2011; 8 (6): 340-347.

(157) Sogabe M, Okahisa T, Kimura T, Okamoto K, Miyamoto H, Muguruma N, et al. Influence of metabolic syndrome on upper gastrointestinal disease. *Clinical Journal of Gastroenterology.* 2016; 9 (4): 191-202.

(158) Di Caro S, Cheung WH, Fini L, Keane MG, Theis B, Haidry R, et al. Role of body composition and metabolic profile in Barrett's oesophagus and progression to cancer. *European Journal of Gastroenterology & Hepatology.* 2016; 28 (3): 251-260.

(159) Okumura S, Kaido T, Hamaguchi Y, Kobayashi A, Shirai H, Yao S, et al. Visceral Adiposity and Sarcopenic Visceral Obesity are Associated with Poor Prognosis After Resection of Pancreatic Cancer. *Annals of Surgical Oncology.* 2017; 24 (12): 3732-3740.

(160) Hagens E, Feenstra M, Egmond M, Laarhoven H, Hulshof M, Boshier P, et al. Influence of body composition and muscle strength on outcomes after multimodal esophageal cancer treatment. *Journey of Cachexia, Sarcopenia & Muscle.* 2020; 11 (3). Available from: doi.10.1002/jcsm.12540

(161) Vissers, Hens. The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. PloS one; PLoS One. 2013; 8 (2): e56415. Available from: doi: 10.1371/journal.pone.0056415 .

(161) Vissers D, Hens W, Taeymans J, Baeyens J, Poortmans J, Van Gaal L. The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. *PloS One.* 2013; 8 (2): e56415. Available from: doi: 10.1371/journal.pone.0056415

(162) Maillard F, Pereira B, Boisseau N. Effect of High-Intensity Interval Training on Total, Abdominal and Visceral Fat Mass: A Meta-Analysis. *Sports Medicine.* 2017; 48 (2): 269-288.

(163) Devin JL, Jenkins DG, Sax AT, Hughes GI, Aitken JF, Chambers SK, et al. Cardiorespiratory Fitness and Body Composition Responses to Different Intensities and Frequencies of Exercise Training in Colorectal Cancer Survivors. *Clinical Colorectal Cancer.* 2018; 17 (2): e269-e279. Available from: doi: 10.1016/j.clcc.2018.01.004

(164) Toohey K, Pumpa KL, Arnolda L, Cooke J, Yip D, Craft PS, et al. A pilot study examining the effects of low-volume high-intensity interval training and continuous low to moderate intensity training on quality of life, functional capacity and cardiovascular risk factors in cancer survivors. *PeerJ.* 2016; 4 e2613. Available from: doi: 10.7717/peerj.2613

(165) Palma S, Hasenoehrl T, Jordakieva G, Ramazanova D, Crevenna R. High-intensity interval training in the prehabilitation of cancer patients—a systematic review and meta-analysis. *Supportive Care in Cancer.* 2020; 29 (4): 1781-1794.

(166) Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in the regulation of human adipose tissue physiology. *Physiological Reviews.* 2012; 92 (1): 157-191.

(167) Verheggen RJHM, Maessen MFH, Green DJ, Hermus ARMM, Hopman MTE, Thijssen DHT. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue: Effects of exercise versus diet on visceral fat. *Obesity Reviews.* 2016; 17 (8): 664-690.

(168) Tolonen A, Pakarinen T, Sassi A, Kytta J, Cancino W, Rinta-Kiikka I, et al. Methodology, clinical applications, and future directions of body composition analysis using computed tomography (CT) images: A review. *European Journal of Radiology*. 2021; 145 109943. Available from: doi: 10.1016/j.ejrad.2021.109943

(169) Marra M, Sammarco R, De Lorenzo A, Iellamo F, Siervo M, Pietrobelli A, et al. Assessment of Body Composition in Health and Disease Using Bioelectrical Impedance Analysis (BIA) and Dual Energy X-Ray Absorptiometry (DXA): A Critical Overview. *Contrast Media and Molecular Imaging*. 2019. Available from: doi: 10.1155/2019/3548284

(170) Kroll L, Mathew A, Baldini G, Hosch R, Koitka S, Kleesiek J, et al. CT-derived body composition analysis could possibly replace DXA and BIA to monitor NET-patients. Scientific Reports. 2022; 12 (1): 13419. Available from: doi: 10.1038/s41598-022-17611-3

(171) Zeng D, Zhou R, Yu Y, Luo Y, Zhang J, Sun H, et al. Gene expression profiles for a prognostic immunoscore in gastric cancer. *British Journal of Surgery.* 2018; 105 (10): 1338-1348.

(172) Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. *Cell Metabolism.* 2018; 27 (1): 10-21. Available from: doi: 10.1016/j.cmet.2017.09.015

(173) Sellami M, Gasmi M, Denham J, Hayes LD, Stratton D, Padulo J, et al. Effects of Acute and Chronic Exercise on Immunological Parameters in the Elderly Aged: Can Physical Activity Counteract the Effects of Aging? *Frontiers in Immunology.* 2018; 9: 2187. Available from: doi: 10.3389/fimmu.2018.02187 .

(174) McDermott L, Murphy M, McNeilly A, Rankin J, Gracey J. Biological markers as an outcome measure of exercise in cancer rehabilitation: A systematic review. *Journal of Cancer Research and Therapeutics.* 2018; 14 (2): 267-277.

(175) Sloan RP, Shapiro PA, McKinley PS, Bartels M, Shimbo D, Lauriola V, et al. Aerobic Exercise Training and Inducible Inflammation: Results of a Randomized Controlled Trial in Healthy, Young Adults. *Journal of the American Heart Association.* 2018; 7 (17): e010201. Available from: doi: 10.1161/JAHA.118.010201

(176) Zheng G, Qiu P, Xia R, Lin H, Ye B, Tao J, et al. Effect of Aerobic Exercise on Inflammatory Markers in Healthy Middle-Aged and Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Frontiers in Aging Neuroscience.* 2019; 11: 98. Available from: doi: 10.3389/fnagi.2019.00098 .

(177) Moher D, Liberati A, Tetzlaff J, Altman DG. Reprint—Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Physical Therapy.* 2009; 89 (9): 873-880.

(178) Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro Scale for Rating Quality of Randomized Controlled Trials. *Physical Therapy.* 2003; 83 (8): 713-721.

(179) de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Australian Journal of Physiotherapy.* 2009; 55 (2): 129-133.

(180) Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *British Medical Journal.* 2019; 366: l4898. Available from: doi: 10.1136/bmj.l4898

(181) Armijo-Olivo S, da Costa B,R., Cummings GG, Ha C, Fuentes J, Saltaji H, et al. PEDro or Cochrane to Assess the Quality of Clinical Trials? A Meta-Epidemiological Study. *PloS One.* 2015; 10 (7): e0132634. Available from: doi: 10.1371/journal.pone.0132634

(182) Hoogeboom TJ, Oosting E, Vriezekolk JE, Veenhof C, Siemonsma PC, de Bie R,A., et al. Therapeutic Validity and Effectiveness of Preoperative Exercise on Functional Recovery after Joint Replacement: A Systematic Review and Meta-Analysis. *PloS One.* 2012; 7 (5): e38031. Available from: doi: 10.1371/journal.pone.0038031

(183) Kim JJ, Shin YA, Suk MH. Effect of a 12-week walking exercise program on body composition and immune cell count in patients with breast cancer who are undergoing chemotherapy. *Journal of Exercise Nutrition & Biochemistry.* 2015; 19 (3): 255-262.

(184) Schmidt ME, Meynkohn A, Habermann N, Wiskemann J, Oelmann J, Hof H, et al. Resistance Exercise and Inflammation in Breast Cancer Patients Undergoing Adjuvant Radiation Therapy: Mediation Analysis From a Randomized, Controlled Intervention Trial. *International Journal of Radiation Oncology, Biology, Physics.* 2016; 94 (2): 329-337.

(185) Schmidt T, Jonat W, Wesch D, Oberg H, Adam-Klages S, Keller L, et al. Influence of physical activity on the immune system in breast cancer patients during chemotherapy. *Journal of Cancer Research & Clinical Oncology.* 2018; 144 (3): 579-586.

(186) van Vulpen JK, Schmidt ME, Velthuis MJ, Wiskemann J, Schneeweiss A, Vermeulen RCH, et al. Effects of physical exercise on markers of inflammation in breast cancer patients during adjuvant chemotherapy. *Breast Cancer Research & Treatment.* 2018; 168 (2): 421-431.

(187) Hojan K, Kwiatkowska-Borowczyk E, Leporowska E, Gorecki M, Ozga-Majchrzak O, Milecki T, et al. Physical exercise for functional capacity, blood immune function, fatigue, and quality of life in high-risk prostate cancer patients during radiotherapy: a prospective, randomized clinical study. *European journal of Physical & Rehabilitation Medicine.* 2016; 52 (4): 489-501.

(188) Hojan K, Kwiatkowska-Borowczyk E, Leporowska E, Milecki P. Inflammation, cardiometabolic markers, and functional changes in men with prostate cancer. A randomized controlled trial of a 12-month exercise program. *Polish Archives Of Internal Medicine.* 2017; 127 (1): 25-35.

(189) Christensen JF, Tolver A, Andersen JL, Rorth M, Daugaard G, Hojman P. Resistance training does not protect against increases in plasma cytokine levels among germ cell cancer patients during and after chemotherapy. *Journal of Clinical Endocrinology & Metabolism.* 2014; 99 (8): 2967-2976.

(190) Glass OK, Inman BA, Broadwater G, Courneya KS, Mackey JR, Goruk S, et al. Effect of aerobic training on the host systemic milieu in patients with solid tumours: an exploratory correlative study. *British Journal of Cancer.* 2015; 112 (5): 825-831.

(191) Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases. *Journal of Allergy and Clinical Immunology.* 2016; 138 (4): 984-1010.

(192) Sedger LM, McDermott MF. TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants – past, present and future. *Cytokine & Growth Factor Reviews.* 2014; 25 (4): 453-472.

(193) Bradley JR. TNF-mediated inflammatory disease. *Journal of Pathology.* 2008; 214 (2): 149-160.

(194) Choy E, Rose-John S. Interleukin-6 as a Multifunctional Regulator: Inflammation, Immune Response, and Fibrosis. *Journal of Scleroderma and Related Disorders.* 2017; 2 (2): S1-S5. Available from: doi: 10.5301/jsrd.5000265

(195) Lee JH, Jun H. Role of Myokines in Regulating Skeletal Muscle Mass and Function. *Frontiers in Physiology.* 2019; 10:42. Available from: doi: 10.3389/fphys.2019.00042 .

(196) Bystry RS, Aluvihare V, Welch KA, Kallikourdis M, Betz AG. B cells and professional APCs recruit regulatory T cells via CCL4. *Nature Immunology.* 2001; 2 (12): 1126-1132.

(197) Luzina IG, Keegan AD, Heller NM, Rook GAW, Shea-Donohue T, Atamas SP. Regulation of inflammation by interleukin-4: a review of "alternatives". *Journal of Leukocyte Biology.* 2012; 92 (4): 753-764.

(198) Beales ILP, Garcia-Morales C, Ogunwobi OO, Mutungi G. Adiponectin inhibits leptin-induced oncogenic signalling in oesophageal cancer cells by activation of PTP1B. *Molecular and Cellular Endocrinology.* 2014; 382 (1): 150-158.

(199) van Deudekom FJ, Klop HG, Hartgrink HH, Boonstra JJ, Lips IM, Slingerland M, et al. Functional and cognitive impairment, social functioning, frailty and adverse health outcomes in older patients with esophageal cancer, a systematic review. *Journal of Geriatric Oncology.* 2018; 9 (6): 560-568.

(200) Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Canadian Journal of Applied Sport Sciences.* 1985; 10: 141-146.

(201) Doganay E, Wynter-Blyth V, Halliday L, MacKinnon T, Osborn H, Moorthy K. Study of Long-Term Follow-up of Exercise Levels Following Participation in a Prehabilitation Program in Esophagogastric Cancer. *Rehabilitation Oncology.* 2020; 38 (3): 110-115.

(202) Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. *BMC medical research methodology; BMC Med Res Methodol.* 2015; 15 (1): 60. Available from: doi: 10.1186/s12874-015-0045-7 .

(203) Amireault S, Godin G. The Godin-Shephard Leisure-Time Physical Activity Questionnaire: Validity Evidence Supporting its Use for Classifying Healthy Adults into Active and Insufficiently Active Categories. *Perceptual and Motor Skills.* 2015; 120 (2): 604-622. Available from: doi: 10.2466/03.27.PMS.120v19x7

(204) Jang D, Lee A, Shin H, Song H, Park J, Kang T, et al. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. *International Journal of Molecular Sciences.* 2021; 22 (5): 2719. Available from: doi: 10.3390/ijms22052719

(205) Il'yasova D, Colbert LH, Harris TB, Newman AB, Bauer DC, Satterfield S, et al. Circulating Levels of Inflammatory Markers and Cancer Risk in the Health Aging and Body Composition Cohort. *Cancer Epidemiology, Biomarkers & Prevention.* 2005; 14 (10): 2413-2418.

(206) Deans DAC, Wigmore SJ, Gilmour H, Paterson-Brown S, Ross JA, Fearon KCH. Elevated tumour interleukin-1b is associated with systemic inflammation: a marker of reduced survival in gastro-oesophageal cancer. *British Journal of Cancer.* 2006; 95 (11): 1568-1575.

(207) O'Mahony L. Cellular source and significance of proinflammatory cytokine production in oesophageal cancer. *Immunology Letters.* 1997; 56 (1-3): 337-338.

(208) Cook MB, Barnett MJ, Bock CH, Cross AJ, Goodman PJ, Goodman GE, et al. Prediagnostic circulating markers of inflammation and risk of oesophageal adenocarcinoma: a study within the National Cancer Institute Cohort Consortium. *Gut*. 2019; 68 (6): 960-968.

(209) Bain CR, Myles PS, Corcoran T, Dieleman JM. Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. *Anaesthesia.* 2023; 78 (3): 356-370.

(210) Wang X, Wu D, Chen W, Liu J, Ju Y. Impact of radiotherapy on immunological parameters, levels of inflammatory factors, and clinical prognosis in patients with esophageal cancer. *Journal of Radiation Research.* 2019; 60 (3): 353-363.

(211) Hirose M, Okutani H, Hashimoto K, Ueki R, Shimode N, Kariya N, et al. Intraoperative Assessment of Surgical Stress Response Using Nociception Monitor under General Anesthesia and Postoperative Complications: A Narrative Review. *Journal of Clinical Medicine.* 2022; 11 (20): 6080. Available from: doi: 10.3390/jcm11206080

(212) Lv X, Lin Y, Wu Q, Wang L, Hou Y, Dong Y, et al. Plasma interleukin-6 is a potential predictive biomarker for postoperative delirium among acute type a aortic dissection patients treated with open surgical repair. *Journal of cardiothoracic surgery.* 2021; 16 (1): 1-146. Available from: doi: 10.1186/s13019-021-01529-4 .

(213) Rettig TCD, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde E,M.W., Noordzij PG. Postoperative Interleukin-6 Level and Early Detection of Complications After Elective Major Abdominal Surgery. *Annals of Surgery.* 2016; 263 (6): 1207-1212.

(214) Szczepanik AM, Scislo L, Scully T, Walewska E, Siedlar M, Kolodziejczyk P, et al. IL-6 serum levels predict postoperative morbidity in gastric cancer patients. *Gastric Cancer.* 2011; 14 (3): 266-273.

(215) Qiu Y, Zheng Z, Liu G, Zhao X, He A. Effects of preoperative anti-tumour necrosis factor alpha infusion timing on postoperative surgical site infection in inflammatory bowel disease: A systematic

review and meta-analysis. *United European Gastroenterology Journal.* 2019; 7 (9): 1198-1214. Available from: doi: 10.1177/2050640619878998

(216) Maeda Y, Takeuchi H, Matsuda S, Okamura A, Fukuda K, Miyasho T, et al. Clinical significance of preoperative serum concentrations of interleukin-6 as a prognostic marker in patients with esophageal cancer. *Esophagus.* 2020; 17 (3): 279-288. Available from: doi: 10.1007/s10388-019-00708-6

(217) Moorthy K, Halliday LJ, Noor N, Peters CJ, Wynter-Blyth V, Urch CE. Feasibility of Implementation and the Impact of a Digital Prehabilitation Service in Patients Undergoing Treatment for Oesophago-Gastric Cancer. *Current Oncology.* 2023; 30 (2): 1673-1682.

(218) Sawesi S, Rashrash M, Phalakornkule K, Carpenter JS, Jones JF, Rashrash M, et al. The Impact of Information Technology on Patient Engagement and Health Behavior Change: A Systematic Review of the Literature. *JMIR Medical Informatics.* 2016; 4 (1): e1. Available from: 10.2196/medinform.4514

(219) Sell NM, Silver JK, Rando S, Draviam AC, Mina DS, Qadan M. Prehabilitation Telemedicine in Neoadjuvant Surgical Oncology Patients During the Novel COVID-19 Coronavirus Pandemic. *Annals of Surgery.* 2020; 272 (2): e81. Available from: doi: 10.1097/SLA.0000000000004002

(220) Barberan Garcia A, Cano Franco I, Bongers BC, Seyfried S, Ganslandt T, Herrle F, et al. Digital Support to Multimodal Community-Based Prehabilitation: Looking for Optimization of Health Value Generation. *Frontiers in* Oncology. 2021. Available from: doi: 10.3389/fonc.2021.662013

(221) Durrand JW, Moore J, Danjoux G. Prehabilitation and preparation for surgery: has the digital revolution arrived? *Anaesthesia.* 2022; 77 (6): 635-639.

(222) Baxter MA, Khan KS, Gall LS, Samuelson C, McCollum C, Chuntamongkol R, et al. Diagnosis, treatment, and outcome of patients with oesophagogastric cancer during the COVID-19 pandemic: national study. *British Journal of Surgery.* 2023; 110 (4): 456-461.

(223) Quail DF, Dannenberg AJ. The obese adipose tissue microenvironment in cancer development and progression. *Nature Reviews Endocrinology.* 2019; 15 (3): 139-154.

(224) Boutens L, Stienstra R. Adipose tissue macrophages: going off track during obesity. *Diabetologia.* 2016; 59 (5): 879-894.

(225) Kralova Lesna I, Kralova A, Cejkova S, Fronek J, Petras M, Sekerkova A, et al. Characterisation and comparison of adipose tissue macrophages from human subcutaneous, visceral and perivascular adipose tissue. *Journal of Translational Medicine.* 2016; 14 (1): 208. Available from: doi: 10.1186/s12967-016-0962-1

(226) Bruun JM, Lihn AS, Pedersen SB, Richelsen B. Monocyte Chemoattractant Protein-1 Release Is Higher in Visceral than Subcutaneous Human Adipose Tissue (AT): Implication of Macrophages Resident in the AT. *The Journal of Clinical Endocrinology and Metabolism.* 2005; 90 (4): 2282-2289.

(227) Suganami T, Nishida J, Ogawa Y. A Paracrine Loop Between Adipocytes and Macrophages Aggravates Inflammatory Changes: Role of Free Fatty Acids and Tumor Necrosis Factor α. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2005; 25 (10): 2062-2068.

(228) Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, et al. Macrophage Activation and Polarization: Nomenclature and Experimental Guidelines. *Immunity.* 2014; 41 (1): 14-20. Available from: doi: 10.1016/j.immuni.2014.06.008

(229) Kaneko N, Kurata M, Yamamoto T, Morikawa S, Masumoto J. The role of interleukin-1 in general pathology. *Inflammation and regeneration.* 2019; 39: 12. Available from: doi: 10.1186/s41232-019-0101-5

(230) Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological Reviews.* 2018; 281 (1): 8-27. Available from: doi: 10.1111/imr.12621

(231) Bhavsar I, Miller CS, Al-Sabbagh M. Macrophage Inflammatory Protein-1 Alpha (MIP-1 alpha)/CCL3: As a Biomarker. *General Methods in Biomarker Research and their Applications.* Dordrecht: Springer Netherlands; 2015. pp. 223-249.

(232) Jayasingam SD, Citartan M, Thang TH, Mat Zin AA, Ang KC, Ch'ng ES. Evaluating the Polarization of Tumor-Associated Macrophages Into M1 and M2 Phenotypes in Human Cancer Tissue: Technicalities and Challenges in Routine Clinical Practice. *Frontiers in Oncology.* 2020; 9: 1512. Available from: doi: 10.3389/fonc.2019.01512

(233) Longo M, Zatterale F, Naderi J, Parrillo L, Formisano P, Raciti GA, et al. Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. *International Journal of Molecular Sciences.* 2019; 20 (9): 2358. Available from: doi: 10.3390/ijms20092358

(234) Chistiakov DA, Killingsworth MC, Myasoedova VA, Orekhov AN, Bobryshev YV. CD68/macrosialin: not just a histochemical marker. *Laboratory investigation.* 2017; 97 (1): 4-13. Available from: doi: 10.1038/labinvest.2016.116

(235) Trifunović J, Miller L, Debeljak Ž, Horvat V. Pathologic patterns of interleukin 10 expression--a review. *Biochemia Medica.* 2015; 25 (1): 36-48.

(236) O'Garra A, Saraiva M. The regulation of IL-10 production by immune cells. *Nature reviews Immunology.* 2010; 10 (3): 170-181.

(237) Eccles MP, Armstrong D, Baker R, Cleary K, Davies H, Davies S, et al. An implementation research agenda. *Implementation Science.* 2009; 4 (1): 18. Available from: doi: 10.1186/1748-5908-4-18

(238) Berwick DM. The science of improvement. *Journal of the American Medical Association.* 2008; 299 (10): 1182. Available from: doi: 10.1001/jama.299.10.1182

(239) Florez Bedoya CA, Cardoso ACF, Parker N, Ngo-Huang A, Petzel MQ, Kim MP, et al. Exercise during preoperative therapy increases tumor vascularity in pancreatic tumor patients. *Scientific Reports.* 2019; 9 (1): 13966-8.

(240) Zhai Y, Fu X, Xu W. Miniature mass spectrometers and their potential for clinical point-of-care analysis. *Mass Spectrometry Reviews*. 2024; 43 (5): 1172–1191.

APPENDIX I

-

Example of personalised exercise prescription and diary card used to record adherence

EXERCISE PRESCRIPTION CARD

Name: **Week Number:** **Date at start of the week:**

Activity		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Bike	Duration							
15mins, 5x a week	Intensity RPE							
RPE 14								
Walking	Duration							
30mins, 5x a week	Intensity RPE							
RPE 14								
Seat to stand	Duration							
2x 15 reps, 5x a week	Intensity RPE							
Squat	Duration							
3x 15 reps, 5x a week	Intensity RPE							
Stair climbing	Duration							
6 mins, 5x a week	Intensity RPE							
Press ups	Duration							
3 x 15 reps, 5x a week	Intensity RPE							

APPENDIX II

-

Esophagectomy Complication Consensus Group (ECCG) guidelines

Pulmonary
- Pneumonia (Definition: American Thoracic Society and Infectious Diseases Society of America)[19,20]
- Pleural effusion requiring additional drainage procedure
- Pneumothorax requiring treatment
- Atelectasis mucous plugging requiring bronchoscopy
- Respiratory failure requiring reintubation
- Acute respiratory distress syndrome (Berlin Definition)[21]
- Acute aspiration
- Tracheobronchial injury
- Chest tube maintenance for air leak for >10 d postoperatively

Cardiac
- Cardiac arrest requiring CPR
- Myocardial infarction (Definition: World Health Organization)[22]
- Dysrhythmia atrial requiring treatment
- Dysrhythmia ventricular requiring treatment
- Congestive heart failure requiring treatment
- Pericarditis requiring treatment

Gastrointestinal
- Esophagoenteric leak from anastomosis, staple line, or localized conduit necrosis. See "Definitions," Table 5
- Conduit necrosis/failure. See "Definitions," Table 5
- Ileus defined as small bowel dysfunction preventing or delaying enteral feeding
- Small bowel obstruction
- Feeding J-tube complication
- Pyloromyotomy/pyloroplasty complication
- *Clostridium difficile* Infection
- Gastrointestinal bleeding requiring intervention or transfusion
- Delayed conduit emptying requiring intervention or delaying discharge or requiring maintenance of NG drainage >7 d postoperatively
- Pancreatitis
- Liver dysfunction

Urologic
- Acute renal insufficiency (defined as doubling of baseline creatinine)
- Acute renal failure requiring dialysis
- Urinary tract infection
- Urinary retention requiring reinsertion of urinary catheter, delaying discharge, or discharge with urinary catheter

Thromboembolic
- Deep venous thrombosis
- Pulmonary embolus
- Stroke (CVA)
- Peripheral thrombophlebitis

Neurologic/psychiatric
- Recurrent nerve injury. See "Definitions," Table 5
- Other neurologic injury
- Acute delirium (Definition: Diagnostic and Statistical Manual of Mental Disorders, 5th ed)[23]
- Delirium tremens

Infection
- Wound infection requiring opening wound or antibiotics
- Central IV line infection requiring removal or antibiotics
- Intrathoracic/intra-abdominal abscess
- Generalized sepsis (Definition: CDC)[24]
- Other infections requiring antibiotics

Wound/diaphragm
- Thoracic wound dehiscence
- Acute abdominal wall dehiscence/hernia
- Acute diaphragmatic hernia

Other
- Chyle leak. See "Definitions," Table 5
- Reoperation for reasons other than bleeding, anastomotic leak, or conduit necrosis
- Multiple organ dysfunction syndrome (Definition: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee)[25]

All complications/adverse events occurring within 30 days of surgery or during the in-hospital stay after surgery should be included.
CDC indicates Centers for Disease Control and Prevention; CPR, cardiopulmonary resuscitation; CVA, cerebrovascular accident; IV, intravenous; NG, nasogastric tube.

Taken from Low et al, 2015 (11)

APPENDIX III
-
Chester Step Test protocol

Step Heights:

10” (25cm) Step – is generally suitable for those over 40 years of age who regularly take physical exercise and are used to moderately vigorous exertion.

8” (20cm) Step – is generally suitable for those under 40 years of age who take little or no regular physical exercise and for those under-40’s who are moderately overweight.

6” (15cm) Step – is generally suitable for those over 40 years of age who take little or no regular physical exercise and for those under-40’s who are moderately overweight.
Note: For testing over 60’s, the lower step height of 15-20 cm is generally best suited.

Prior to starting the test:

Record resting HR

Calculate 70% Max HR (205.8 – (0.685 x age). Subtract 30bpm if taking beta-blockers

Calculate heart rate reserve (HRR) (maximum heart rate – resting heart rate)

Explain: “*This is the Chester Step Test which is designed to measure your aerobic fitness. You’ll be asked to step onto and off the step at a set rate. Every 2 minutes your heart rate and exertion level will be checked and the stepping rate will be increased slightly. You can change your lead leg if you wish. The test will continue in this progressive manner until your heart rate reaches around 70% of its maximum heart rate reserve or until you feel unable to continue. You should then stop and recover. If at any time you feel overtired, breathless or dizzy then please stop and recover.”*

Demonstrate how to perform the test by stepping up and down on the step keeping in time with the beat of the metronome

The applicant can lead with either foot and is able to change the leading leg during testing, but MUST stay in time with the metronome.

The stepping must be UP / UP / DOWN / DOWN
Applicant’s should not be holding on to a railing / wall during the test

Conduct testing:

Have the applicant start testing at the same time as starting the stop watch

Watch for uneven weight bearing between left / right legs, use of hands on thighs for support, forward flexed posture, signs of fatigue etc

If the applicant deviates from the beat, instruct them a few times but if they keep slowing down due to fatigue, cease testing

Metronome pace increases every 2 minutes

At the conclusion of each 2 minute stage obtain RPE and HR

Metronome pacing:

Stage 1 = 15 steps per minute = 60 BPM

Stage 2 = 20 steps per minute = 80 BPM

Stage 3 = 25 steps per minute = 100 BPM

Stage 4 = 30 steps per minute = 120 BPM

Stage 5 = 35 steps per minute = 140 BPM

The final step height and step rate that was achieved during the CST is used to calculate the level of exercise intensity in METS achieved during the test

Stage	15cm step	20cm step	25cm step
1	3.0 METS	3.6 METS	4.2 METS
2	4.0 METS	4.8 METS	5.5 METS
3	5.0 METS	5.5 METS	6.9 METS
4	6.0 METS	7.2 METS	8.3 METS
5	7.0 METS	7.8 METS	9.1 METS

Maximum heart rate achieved during the final stage of the protocol is used to calculate the percentage of HRR (%HRR) achieved

$$\%HRR = \frac{Maximum\ HR\ during\ exercise\ (bpm) - Resting\ HR\ (bpm)}{Maximum\ HRR\ (bpm)}$$

The achieved METS was divided by the %HRR to calculate predicted METSmax

Date	Test 1: ___/___/___	Test 2: ___/___/___
PRE-TEST MEASUREMENTS		
Pre HR		
BP		
Predicted HR Max (220-age)		
70% HRR		
Step Height	15cm ☐ 20cm ☐ 25cm ☐	15cm ☐ 20cm ☐ 25cm ☐

Level	Mins	Step Rate	HR	RPE	Mins	Step Rate	HR	RPE	METS 15cm	METS 20cm	METS 25cm
1	1	15			1	15			3.0	3.6	4.2
	2				2						
2	3	20			3	20			4.0	4.8	5.5
	4				4						
3	5	25			5	25			5.0	5.5	6.9
	6				6						
4	7	30			7	30			6.0	7.2	8.3
	8				8						
5	9	35			9	35			7.0	7.8	9.1
	10				10						
	HR		BP		HR		BP				
2min rec.											
Comments											

TEST SUMMARY		
Completed Stages		
Total Minutes		
Mets Achieved		
Reason for stopping	☐ Unable to maintain speed ☐ Achieved 70%HRR ☐ RPE 14 ☐ Chest Pain ☐ Marked shortness of breath ☐ Leg fatigue ☐ Other (please specify) _____	☐ Unable to maintain speed ☐ Achieved 70%HRR ☐ RPE 14 ☐ Chest Pain ☐ Marked shortness of breath ☐ Leg fatigue ☐ Other (please specify) _____

APPENDIX IV
-
Systematic review search strategy

1	exp Neoplasms/
2	(Neoplasm* or Cancer* or malignanc*).mp
3	1 or 2
4	exp Exercise Therapy/
5	exp Exercise/
6	exercis*
7	((physical or resistance or strength or endurance) adj3 (train* or program* or activit* or exercise*)).mp
8	4 or 5 or 6 or 7
9	exp Inflammation Mediators/
10	exp C-Reactive Protein /
11	exp Tumor Necrosis Factor-alpha/
12	(c reactive protein or interleukin* or tum?or necrosis factor or inflammation* or CRP or TNF*or IL* or immune cell* or white cell* or macrophag* or mononuclear cell*).mp
13	9 or 10 or 11 or 12
14	randomized controlled trial.pt.
15	controlled clinical trial.pt
16	randomi?ed.ab.
17	placebo.ab.
18	randomly.ab.
19	trial.ab.
20	groups.ab.
21	14 or 15 or 16 or 17 or 18 or 19 or 20
22	3 and 8 and 13 and 21

APPENDIX V
-
Godin-Shephard Leisure Time Physical Activity Questionnaire

	Times per week		Totals
STRENUOUS ACTIVITY Heart beats rapidly (e.g. running, jogging, football, squash, vigorous swimming, vigorous cycling)		**X9**	
MODERATE EXERCISE Not exhausting (e.g. fast walking, easy cycling, easy swimming, badminton, dancing)		**X5**	
MILD/LIGHT EXERCISE Minimal effort (e.g. yoga, golf, easy walking, fishing)		**X3**	
WEEKLY LEISURE TIME ACTIVITY SCORE			

Worked example

Reported exercise – Strenuous exercise 1 times/week, moderate exercise 2 times/week, light exercise 4 times/week

Weekly leisure time activity score = (9 x 1) + (2 x 5) + (4 x 3) = 9 + 10 + 12
= **31**

Available at https://www.ons.org/sites/default/files/Godin%20Leisure-Time%20Exercise%20Questionnaire_070815.pdf

APPENDIX VI
-
qRT PCR forward and reverse primers

Primer	Forward Primer (5' - 3')	Reverse Primer (3' - 5')
IL-1β	GGAGAATGACCTGAGCACCT	GGAGGTGGAGAGCTTTCAGT
IL-6	AGTCCTGATCCAGTTCCTGC	AAGCTGCGCAGAATGAGATG
IL-10	TGTTTTCCCTGACCTCCCTC	AGTGGTTGGGGAATGAGGT
TNFα	TCCTTCAGACACCCTAAACC	AGGCCCCATTTGAATTCTT
Leptin	ACCAAGGTCTTCAGCCATCA	CTTGTGTTGCTGGGAGTTCC
Adiponectin	ATGGCCCCTGCACTACTCTA	CAGGGATGAGTTCGGCACTT
CD68	CCTCCAAGCCCAGATTCAGA	CATTGTACTCCACCGCCATG
CCL3	TGCAACCAGTTCTCTGCATC	TTTCTGGACCCACTCCTCAC
CD163	GGAGGAACAGACAAGGAGCT	AATCACAGAGACCGCTTCCA
CD206	AACGGACTGGGTTGCTATCA	CCCGATCCCTTGTAGAGCAT