An investigation into the utility of home-based, exercise intervention in maintaining cardiopulmonary fitness during neoadjuvant chemotherapy for oesophago-gastric cancer

Jakub Chmelo

Submitted in fulfilment of the requirements for the degree of Doctor of Medicine

Translational and Clinical Research Institute, Newcastle University

March 2022

Abstract

Background

Neoadjuvant chemotherapy (NAC) is a key component of treatment for locally advanced oesophago-gastric adenocarcinoma (OGA). However, it has a negative impact on patient fitness. Using prehabilitation to increase patients' fitness may positively affect patients' recovery from surgery, postoperative outcomes and quality of life (QoL). This study was designed to evaluate feasibility of a home-based prehabilitation programme and explore the effect of this regimen on cardiorespiratory fitness, sarcopenia and QoL.

Methods

This study (ChemoFit) recruited patients with OGA to a pragmatic home-based prehabilitation programme during NAC and prior to surgery. Participants completed daily aerobic sessions to a targeted step-count and daily strengthening exercises, under weekly telephone supervision. Cardiorespiratory fitness, sarcopenia and QoL were measured before and after the intervention utilising cardiopulmonary exercise testing (CPET), computed tomography measured muscle mass and hand-grip strength, and QoL questionnaires.

Results

A total of 42/58 (72%) patients approached were recruited and 36/39 (92%) participants completed the programme. Median compliance with wearing a pedometer and recording step count, engagement with telephone contacts, compliance with aerobic sessions and compliance with strengthening exercises were 98%, 100%, 70% and 69% respectively. Nineteen participants had a pre and post intervention CPET with no significant difference in anaerobic threshold (mean difference -0.5 $ml.kg^{-1}.min^{-1}$, 95% CI -1.6 to +0.6, p=0.387) or VO_2peak (mean difference -0.1 $ml.kg^{-1}.min^{-1}$, 95% CI -1.6 to +1.4, p=0.952). Radiological sarcopenia increased from 47% to 72% of participants during the intervention (p<0.001). There was no significant difference in mean grip strength observed (p=0.386). Global quality of life significantly improved during this period (p<0.001).

Conclusions

This study demonstrated that recruitment to the ChemoFit programme is feasible and achieved good patient compliance and engagement. This regimen permitted a potential maintenance of

the objectively measured cardiopulmonary fitness and a potential improvement to QoL during and after neoadjuvant chemotherapy, prior to surgery.

Acknowledgements

I would like to express my thanks to all the participants of the ChemoFit study who allowed this work to happen. Their enthusiasm to participate in this research and their altruism to help other patients in the future was very motivational to me.

I would like to express my gratitude to the Jon P. Moulton Charitable Foundation for their generous contribution of £111,031.26, which played a pivotal role in funding this study. Their support has been instrumental in advancing my research endeavours.

I am hugely thankful to all three of my supervisors.

Dr Rhona Sinclair who was the principal investigator of the study was very supportive, encouraging and showed patience with me. Her organisational leadership enabled this study to happen and I am grateful that she allowed me to be a part of this.

Mr Alexander Phillips showed great interest and trust in me. He has always made time for me. I enjoyed all our discussions (especially over coffee) talking about the endless number of research ideas he always has. He is a great motivator and his drive is truly inspirational. I am immensely grateful to have him as my mentor.

I am thankful for a guidance and support by Dr Alastair Greystoke. His opinions and navigation during every stage of this research were very valuable and his critique of the work was important during the writing of the manuscripts and this thesis.

Members of my panel Prof Colin Rees and Mr Colin Wilson were very helpful and I am grateful for their time where we discussed my progress. They always had new insights into this research and valuable comments.

The assistance provided by Dr Sarah Charman and Dr Kate Hallsworth with initial design of the study intervention is greatly appreciated.

I am very thankful to Ms Jenny Welford who was helping me to conduct this study and to specialty nurses Maria Bliss and Claire Sedgwick who were very helpful with tasks around patient identification and coordination of the consent process and tests.

My appreciation also goes to Dr George Petrides who kindly spent time with me to teach me how to perform radiological sarcopenia readings and to Mr Chris O'Neill who spent many hours in the cardiopulmonary exercise testing lab supervising and teaching me how to conduct these tests. Chris, who is very passionate about CPET, was extremely helpful and we always had a good time talking – not only about cycling and sports medicine.

Lastly, but most importantly, I am very grateful to all my family. Especially my wife Kristina and my parents. Kristina has been incredibly supportive, caring and always stood by me. My parents have been a continual source of inspiration, motivating me and supporting me throughout my childhood and my professional career.

Table of contents

List of tables

List of figures

List of abbreviations

6MWT	6-min walk test
AAA	abdominal aortic aneurysm
ACA	adenocarcinoma
AIO	Arbeitsgemeinschaft Internistische Onkologie
AT	anaerobic threshold
BMI	body mass index
CF	cisplatin, fluoruracil
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CT	computed tomography
CRT	chemoradiotherapy
DCF	docetaxel, cisplatin, fluoruracil
DNA	deoxyribonucleic acid
DXA	dual energy X-ray absorptiometry
ECF	epirubicin, cisplatin, fluoruracil
ECG	electrocardiogram
ECX	epirubicin, cisplatin, capecitabine
EORTC	European organization for research and treatment of cancer
ERAS	enhanced recovery after surgery
EUS	endoscopic ultrasound
FDG	[18F]2-fluoro-2-deoxy-D-glucose
FEV1	forced expiratory volume in 1s
FVC	forced vital capacity
H. pylori	Helicobacter pylori
HIIT	high intensity interval training
HR	hazard ratio
ICC	intraclass correlation coefficient

IMT	inspiratory muscle training
IQR	interquartile range
IRAS	Integrated research application system
LBM	lean body mass
LOA	limit of agreement
LTA	lean tissue area
MDT	multidisciplinary team
MET	metabolic equivalents
MRI	magnetic resonance imaging
N/A	not applicable
NAC	neoadjuvant chemotherapy
NACRT	neoadjuvant chemoradiotherapy
NHS	National Health Service
NOGU	Northern oesophagogastric unit
OGJ	oesophago-gastric junction
OR	odds ratio
PET	positron emission tomography
PIS	patient information sheet
PPI	patient and public involvement
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomised controlled trial
REC	Research ethical committee
RPE	rating of perceived exertion
SCC	squamous cell carcinoma
SD	standard deviation
SEM	standard error of mean
SMI	skeletal muscle index
SPPB	short physical performance battery
STG	subtotal gastrectomy
STO	subtotal oesophagectomy

TG	total gastrectomy
TNM	tumour, node, metastases
UK	United Kingdom
USA	United States of America
VE	minute ventilation
VE/VCO_2	ventilatory equivalents for carbon dioxide
VO_2	oxygen uptake
VO_2peak	peak oxygen uptake

Chapter 1. Introduction

1.1 Oesophago-gastric cancer

1.1.1 Symptoms and signs

Oesophago-gastric cancer often remains asymptomatic during its initial stages, with the manifestation of signs and symptoms becoming more pronounced in the later stages of the disease. Typical indicators of oesophageal cancer encompass dysphagia or odynophagia, while weight loss, a common occurrence also in gastric cancer, may be attributed to factors such as compromised oral intake due to dysphagia or the cancer related poor appetite and the catabolic nature of the disease. Patients may rarely present with a hoarse voice or a persistent cough. Both oesophageal and gastric cancers can lead to vomiting and bleeding, potentially resulting in the passage of melena or vomiting blood. Iron deficiency anaemia is a prevalent sign. As with other cancer types, fatigue, stemming from anaemia or simply cancer-related is frequently encountered in individuals with oesophago-gastric cancer.

Nonspecific symptoms, such as nausea and epigastric pain, typically emerge in the advanced stages of gastric cancer. Noteworthy are palpable lymph nodes, often mentioned in the supraclavicular or periumbilical regions, which may serve as signs of gastric cancer. Abdominal examination might unveil palpable masses or ascites, suggesting the likelihood of metastatic gastric cancer.

1.1.2 Epidemiology

Oesophago-gastric cancer affects more than 1.4 million people globally each year [1, 2]. Two main histological types are recognised. Squamous cell carcinoma (SCC) arising from squamous cell epithelium lining of the oesophagus and adenocarcinoma (ACA) which can be located either in the oesophagus proper, at the oesophago-gastric junction (OGJ) or in the stomach. The incidence of adenocarcinoma has been on the rise in Western countries [3]. The main contribution to this increase is a higher rate of tumours that are located at oesophago-gastric junction and gastric cardia [4]. SCC rates, in contrary, have been steadily decreasing in the same geographical areas [5].

Approximately 80% of the 450,000 oesophageal cancer cases diagnosed each year are SCC [1]. However, the predominant sub-type in Western countries is adenocarcinoma, and paradoxically this makes up 80% of cases in these regions [6]. Overall Asia and South East Africa have the highest rates of SCC [7].

Adenocarcinoma is usually found in the lower third of the oesophagus and at the oesophago-gastric junction. It has superseded SCC as the most common histological type of oesophageal cancer in the West approximately 30 years ago. One cause that is thought to have contributed towards this change is the increasing incidence of obesity which is a risk factor for adenocarcinoma [8].

The incidence of gastric cancer has been falling in the last few decades worldwide [9, 10]. There are some theories which are related to a reduction of risk factors for gastric cancer. Discovery and the treatment of Helicobacter pylori (H. pylori) and improved storage of food with the increase use of refrigerators, decrease in the consumption of salt preserved food may have played an important role in this [11, 12]. The incidence of the adenocarcinoma of the stomach is high in Eastern Asia, Eastern Europe and South America [13]. Japan has one of the highest incidences in the world of gastric cancer with the disease affecting 80 men per 100 000 annually [14]. Despite the fact that the incidence of distal gastric adenocarcinoma being on the decline in North America and Europe, adenocarcinomas of the gastric cardia and the oesophago-gastric junction are increasingly encountered [15].

1.1.3 Aetiology

The aetiology differs significantly depending on the histological sub-type of cancer and on site of cancer. Whilst strong risk factors for SCC of the oesophagus include smoking, alcohol consumption and low socio-economic status in the West and poor nutritional status, low intake of fruit and vegetables and smoking in the Asia and Africa [16], risk factors for the development of adenocarcinoma are different.

Gastro-oesophageal reflux symptoms are associated with an increased risk of oesophageal adenocarcinoma [17]. Intestinal metaplasia in the form of Barrett's oesophagus, which is caused by prolonged exposure of gastric refluxate which is of a low pH due to the secretion of hydrochloric acid, is considered a precancerous state for oesophageal adenocarcinoma. It is thought that most oesophageal cancers arise from a region of Barrett's metaplasia [18]. Smoking

is a risk factor for both SCC and adenocarcinoma [19]. In addition, high body mass index (BMI) and diet with high fat content is also associated with an increased risk of developing oesophageal and OGJ adenocarcinoma [20]. H. pylori infection may have a protective effect against oesophageal SCC and adenocarcinoma as suggested by one meta-analysis [21].

Histological type	Regional risk factors	
	'west'	Asia, Africa
SCC	• smoking • alcohol consumption • low vegetable and fruit diet	• smoking • alcohol consumption • low vegetable and fruit diet • poor nutritional status • high temperature beverages drinking • intake of foods containing N-nitroso compounds (pickled food) • chewing areca nuts or betel quid • zinc or selenium deficiency • low intake of folate
ACA	• gastro-oesophageal reflux • smoking • obesity	

Table 1 Oesophageal cancer risk factors

H. pylori infection plays an important role in the development of gastric cancer. It causes inflammation which leads to intestinal metaplasia followed by dysplasia and ultimately adenocarcinoma [22]. This has been demonstrated in epidemiological studies but also in the studies demonstrating that the eradication of H. pylori led to the lower rates of gastric cancer [23]. Obesity is associated with an increased risk of gastric cancer. Risk seems to be increased with a higher BMI [24]. Atrophic gastritis leading to an increase in gastric pH and microbial colonization of the stomach is an autoimmune condition associated with an increased risk of gastric cancer [25]. Other risk factors include pernicious anaemia, diets that are high in salt content including salt preserved food [26] and smoking [27].

1.2 Investigations and staging of oesophago-gastric cancer

The diagnosis of oesophago-gastric cancer is confirmed through endoscopy accompanied by histological sampling. Subsequently, staging is performed according to the American Joint

Committee on Cancer tumour, node, metastases (TNM) staging system, with the 8th edition currently being the latest [28, 29]. This edition recommends staging junctional tumours similarly to oesophageal tumours.

To stage the disease in terms of tumour, lymph nodes, and potential metastatic spread, contrast-enhanced computed tomography of the thorax, abdomen, and pelvis is conducted. Positron emission tomography (PET) CT with [18F]2-fluoro-2-deoxy-D-glucose (FDG) is employed for patients with oesophageal and junctional cancer suitable for radical treatment to rule out metastatic spread. However, there is not enough evidence to support routine use of PET CT for patients with gastric cancer [30].

Endoscopic ultrasound (EUS) is commonly utilised for oesophageal and junctional cancer to assess tumour and lymph node stage in patients with potentially resectable disease. EUS is recognized to have low accuracy for T1 tumours but enables sampling of suspicious lymph nodes located outside surgical resection or radiation fields [31].

Bronchoscopy and endobronchial ultrasound can be complementary to EUS, assessing tumour growth towards the airways. For patients with gastric cancer or junctional cancer extending to the gastric cardia who are suitable for curative treatment, staging laparoscopy with the collection of peritoneal washings for cytology testing is recommended [30]. This procedure can unveil metastatic spread undetected by CT in the abdominal cavity and assess the tumour stage.

1.3 Treatment of oesophago-gastric cancer

Most patients (50-60%) present with the disease too advanced to consider curative treatment [32, 33]. For the rest, whether cure can be considered depends on several factors including the patient's wishes, and their underlying fitness. Surgery remains the core treatment for those being managed with curative intent [30, 34]. However, the treatment strategy may involve other modalities such as radiotherapy, chemotherapy or a combination of these either as neoadjuvant (before surgery) or adjuvant (after surgery) interventions [30, 34].

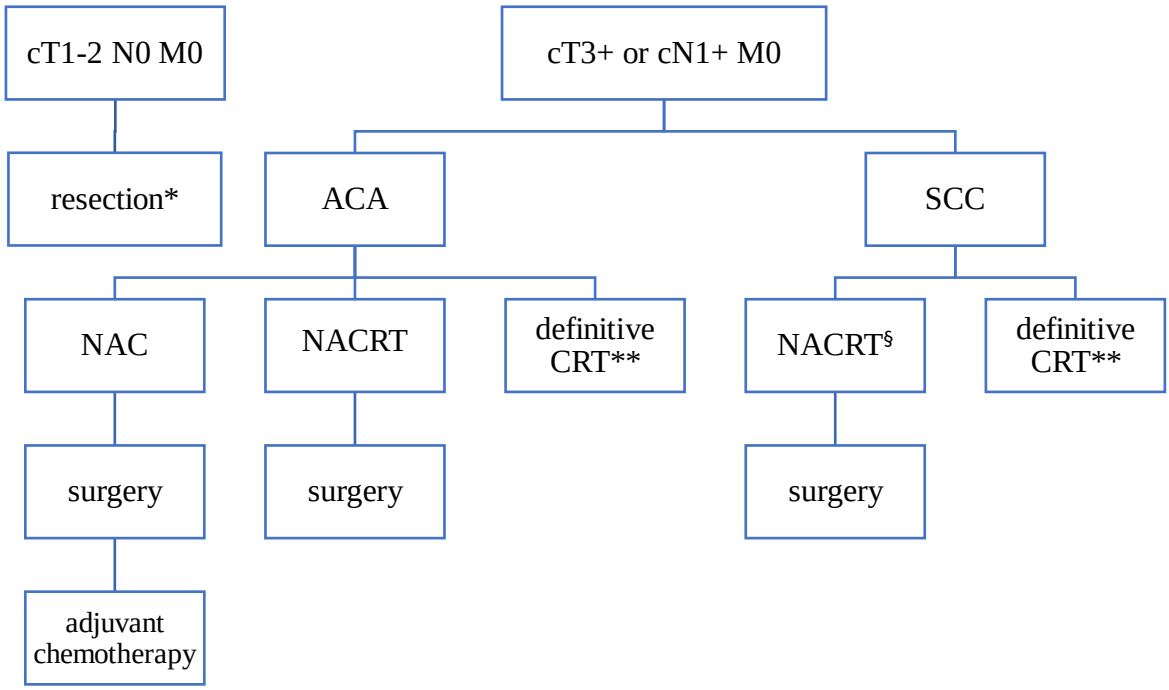


Figure 1 Treatment algorithm with curative intent for patients with oesophageal or oesophago-gastric junction cancer

* endoscopic resection or surgery depending on depth of tumour invasion, other risks factors and histological subtype [34]

** usually reserved for patients who are unwilling to undergo surgery or unfit for surgery [34]

§ if the length of the disease permits, otherwise NAC is used

ACA, adenocarcinoma. SCC, squamous cell carcinoma. NAC, neoadjuvant chemotherapy. NACRT, neoadjuvant chemoradiotherapy. CRT, chemoradiotherapy.

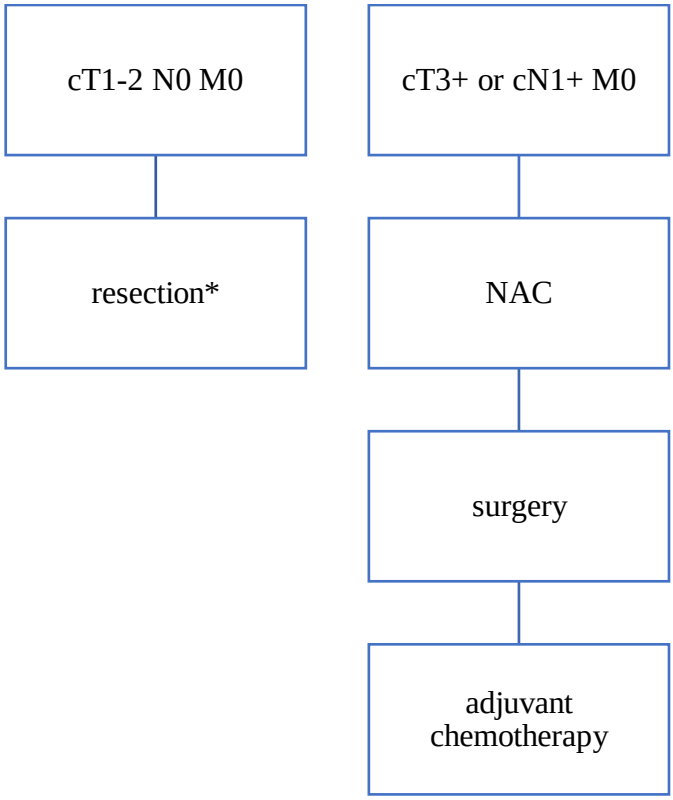


Figure 2 Treatment algorithm with curative intent for patients with gastric cancer
* endoscopic resection or surgery depending on depth of tumour invasion and other risks factors [30]
NAC, neoadjuvant chemotherapy.

1.3.1 Unimodality treatment

For those staged with early disease (T1/2 N0) unimodality surgery may be considered for both oesophageal and gastric cancer [30, 34]. Debate remains regarding any potential benefit for those staged T2 N0 with regards to neoadjuvant therapy [35, 36].

1.3.2 Multimodality treatment

There have been significant changes over the last two decades in the management of patients with locally advanced disease. The Medical research council adjuvant gastric infusional chemotherapy (MAGIC) trial [37], The United Kingdom Medical research council oesophageal cancer trial (OEO2) [38] and Chemoradiotherapy for oesophageal cancer followed by surgery study (CROSS) [39] demonstrated a significant advantage in neoadjuvant chemo(radio) therapy in those with locally advanced disease compared to unimodality surgery. More recent FLOT4-Arbeitsgemeinschaft Internistische Onkologie (AIO) trial has further improved survival for patients with locally advanced junctional and gastric adenocarcinoma [40].

The MAGIC trial [37] included 503 patients with potentially resectable adenocarcinoma of the lower oesophagus, OGJ and stomach. Patients were randomised to receive surgery alone or perioperative chemotherapy in the form of three pre-operative and three post-operative cycles of ECF (epirubicin, cisplatin and fluoruracil). Overall, there was a significant survival advantage in those receiving perioperative chemotherapy. Patients who received perioperative chemotherapy had a higher likelihood of overall survival (hazard ratio for death 0.75, 95% confidence interval 0.60-0.93, p 0.009), better five-year survival rate (36% vs 23%) and higher likelihood of progression-free survival (hazard ratio for progression 0.66, 95% confidence interval, 0.53-0.81, p<0.001). Similar results were seen in Dutch CROSS trial [39]. This study investigated 366 patients with potentially resectable SCC and adenocarcinoma of oesophagus and oesophago-gastric junction. Patients were assigned either to neoadjuvant chemoradiotherapy (paclitaxel and carboplatin plus concurrent radiotherapy) or surgery alone. Overall survival was higher in the neoadjuvant group with low toxicity rates (hazard ratio for death 0.66, 95% confidence interval 0.50-0.87, p 0.003). The UK OE02 trial [38] compared 400 patients who received pre-operative chemotherapy in the form of cisplatin and fluoruracil followed by surgery with 402 patients who received surgery only as a treatment of their oesophageal cancer. Patients treated with multimodal treatment demonstrated better overall survival (hazard ratio for death 0.79, 95% confidence interval 0.67-0.93, p 0.004) and better 5-year survival (23% vs 17%).

Trial name	Tumour types (number of patients)	Treatment arms (number of patients)	5-year survival	Overall survival
OE02 (2002)	ACA (533), SCC (247) and undifferentiated carcinoma (21)* of oesophagus (802)	pre-operative chemotherapy and surgery (400)	23%	HR for death 0.79, 95% CI 0.67 to 0.93, p 0.004
		surgery only (402)	17%	
MAGIC (2006)	ACA of lower oesophagus (73), OGJ (58), stomach (372)	perioperative chemotherapy and surgery (250)	36%	HR for death 0.75, 95% CI 0.60 to 0.93, p 0.009
		surgery only (253)	23%	
CROSS (2012)	ACA (275), SCC (84) and large cell undifferentiated carcinoma (7) of oesophagus (268) and OGJ (88)**	pre-operative chemoradiotherapy and surgery (178)	47%	HR for death 0.66, 95% CI 0.50 to 0.87, p 0.003
		surgery only (188)	34%	
FLOT (2019)	ACA of OGJ (398) and stomach (318)	perioperative chemotherapy and surgery FLOT (356)	45%	HR for death 0.77, 95% CI 0.63 to 0.94, p 0.012
		perioperative chemotherapy and surgery ECF/ECX (360)	36%	

Table 2 Major trials comparing various multimodality treatment regimens for oesophago-gastric cancer.
* one patient unknown histology
** ten patients unknown tumour site
ACA, adenocarcinoma. SCC, squamous cell carcinoma. OGJ, oesophago-gastric junction. ECF, epirubicin and cisplatin and fluoruracil. ECX, epirubicin and cisplatin and capecitabine. HR, hazard ratio.

These trials included various histological subtypes and location of tumours differed as well. Also, modalities, their deliveries and their timing varied. The results however convey the same message – neoadjuvant therapy prior to surgery leads to increased survival of these patients. The current UK gold standard for the treatment of locally advanced potentially resectable adenocarcinoma is a neoadjuvant chemotherapy followed by surgery usually followed by adjuvant chemotherapy as per MAGIC and FLOT regimens. Results from the multicentre "Neoadjuvant trial in adenocarcinoma of the oesophagus and oesophago-gastric junction international study" (Neo-AEGIS – NCT01726452) trial comparing neoadjuvant chemotherapy to neoadjuvant chemoradiotherapy and similar "Perioperative chemotherapy compared to

neoadjuvant chemoradiation in patients with adenocarcinoma of the esophagus" (ESOPEC – NCT02509286) trial are awaited.

1.3.3 Chemotherapy

Various chemotherapy regimens are currently used in the treatment of oesophageal and gastric cancer. The OE05 trial was a large, randomised control trial (RCT) which included 897 patients [41]. This study was designed to assess the difference between four cycles of neoadjuvant ECX (epirubicin, cisplatin, capecitabine) and two cycles of neoadjuvant CF (cisplatin and 5-fluoruracil) followed by oesophagectomy with two-field lymphadenectomy for T3N0/1 lower oesophageal and junctional adenocarcinomas. The median survival was not statistically different between both groups, 23.4 months with CF vs. 26.1 months with ECX. More recently the results of the phase III FLOT4-AIO trial became available [42]. This trial compared the FLOT regimen (docetaxel, oxaliplatin, leucovorin, fluoruracil – four two-week pre-operative cycles and four 2-week post-operative cycles) with ECX or ECF (Capecitabine is an oral pro-drug of 5-fluoruracil). This study included 716 patients with potentially curable gastric or junctional adenocarcinoma. The FLOT regimen led to a significantly better overall survival and significantly greater median overall survival (50 months in FLOT group vs. 35 months in ECX/ECF group). These results have already had an impact with many centres increasingly employing this regimen.

Chemotherapeutic agents used in the treatment of oesophago-gastric cancer have various mechanisms of action. Cisplatin and oxaliplatin are platinum-based compounds which damage the cell DNA. Cisplatin is activated intracellularly and binds to DNA to form DNA adducts. These then activate several complex signal-transduction pathways which are involved in cell cycle arrest, DNA-damage recognition and repair and apoptosis. This process ultimately leads to cell death [43].

Epirubicin, used in ECX/ECF triplets, belongs to the family of anthracyclines. These have several mechanisms of action which lead to cancer cell death [44]. First, it acts as a topoisomerase II poison which causes DNA cleavage. Second, it intercalates DNA strands and creates free radicals. Epirubicin is preferred over doxorubicin, one of the first anthracyclines used in cancer treatment, due to its lower cardiotoxicity [44].

Fluoruracil and its prodrug capecitabine are fluoropyrimidines which mis-incorporate into RNA and DNA [45]. They also inhibit the nucleotide synthetic enzyme thymidylate synthase. This leads to inhibition of DNA synthesis and mitosis but also impedes protein synthesis. Leucovorin is used as a modulation agent in treatment which uses fluoruracil. Leucovorin increases inhibition of thymidylates synthase and therefore enhances the toxicity and efficacy of fluoruracil [45].

Docetaxel belongs to group of taxanes. Similar to vinca alkaloids, their mechanism of action lies in binding to tubulin and stabilising microtubules. This binding blocks cell processes where microtubules play crucial part, such as mitosis. Apoptosis, mitotic catastrophe are then major mechanisms of cell death [46].

The use of oxaliplatin instead of cisplatin in the FLOT regimen was suggested due to the high toxicity of cisplatin combined with docetaxel and fluoruracil (DCF) [40], a regimen tested in metastatic gastric cancer [47]. Toxicity of chemotherapeutics however is common. General chemotherapy toxicity includes myelosuppression, diarrhoea, vomiting, nausea, constipation. Agent specific toxicities include nephrotoxicity and neurotoxicity of platinum-based drugs or cardiotoxicity which anthracyclines are known for. It has to be mentioned that participants receiving FLOT chemotherapy in FLOT4-AIO trial experienced significantly higher rates of grade 3 or 4 neutropenia compared to participants who received ECX/ECF chemotherapy [40].

1.3.4 Definitive radiotherapy or chemoradiotherapy

There are potentially alternative curative treatments to surgery with regards to oesophageal and junctional cancers. In some patients, if their performance status and the extent and length of disease allow, chemoradiotherapy or radiotherapy may be potential options. However, definitive chemoradiotherapy appears to have inferior outcomes compared to surgery with neoadjuvant chemoradiotherapy as demonstrated by a recent propensity matched study [48]. This retrospective study investigated difference between two mentioned treatment strategies on a large number of patients from American National Cancer Database. Neoadjuvant chemoradiotherapy was associated with significantly better survival compared to definitive radiotherapy in patients with both oesophageal ACA and SCC. Previous RCTs studying this comparison are old with methodological quality not sufficiently good enough to inform clinical practice [49, 50]. Future prospective studies are needed to fully answer this question in the era of oesophago-gastric surgery in high-volume centres.

1.3.5 Surgery

Surgery still remains the key component in the curative treatment of invasive cancer. Although mortality of the surgery has been on the decline and currently is around 3% in the United Kingdom (UK) [33], operations for oesophago-gastric cancer still remain procedures with high morbidity. Various approaches have been adopted.

Oesophageal and some oesophago-gastric junctional tumours are managed with a subtotal oesophagectomy, an operation where a significant portion of the oesophagus is resected. There are three main ways in how to achieve this. Ivor Lewis oesophagectomy combines a laparotomy and a right thoracotomy. It is commonly used for the tumours located in mid or lower oesophagus as well as junctional tumours. The anastomosis is formed in the chest by pulling up the tubulised stomach which was mobilised during the laparotomy stage of the operation. Transhiatal oesophagectomy combines laparotomy with a neck incision. Dissection of the thoracic oesophagus is achieved bluntly from both laparotomy and neck incisions and again the tubulised stomach is pulled towards the neck where a cervical anastomosis is formed. The limitation of this approach is the inability to perform a full lymphadenectomy in the chest however advantage is that it avoids a thoracotomy which may contribute to significant morbidity. Patients also need to be able to tolerate one lung ventilation. Three stage oesophagectomy combines a right thoracotomy, laparotomy and cervical incision. This may be the preferred place to create the anastomosis particularly for those employing minimally invasive techniques to operate in the chest, with a neck anastomosis being easier to create. Other surgeons may employ this for tumours located in upper oesophagus. It enables a adequate lymphadenectomy of each neck, chest and abdominal fields (see later). Modifications of these operations exist. Patients with the junctional tumours can be resected either with an oesophagectomy and partial gastrectomy or with an extended gastrectomy.

Tumours located at the junction between oesophagus and stomach can be divided according to the Siewert classification which has three groups. This classification was introduced to guide the treatment of tumours in this location [51]. Cancer which has an epicentre that arises at the distal oesophagus close to the junction is classified as Siewert I, cancer with the epicentre at the true junction is classified Siewert II and lastly cancer located at the proximal cardia is considered as Siewert III. Siewert I tumours are usually managed with an oesophagectomy whereas Siewert III tumours require a gastrectomy. Debate exists about which operation is needed for tumours arising from the true junction. These neoplasms are usually treated with an

oesophagectomy at the Northern Oesophagogastric Unit (NOGU). International survey however demonstrated that 66% respondents preferred to perform extended gastrectomy for this type of tumours [52].

Two main operations are used in the treatment of gastric cancer. Broadly speaking, total gastrectomy is used for the tumours located in the proximal stomach and subtotal gastrectomy is used for tumours located distally in the stomach [53]. Continuity of the alimentary tube is reconstructed using small bowel.

Removal of local lymph nodes (lymphadenectomy) is important to achieve loco-regional control of the disease. Several fields have been described to delineate the extent of lymphadenectomy [54]. One-field lymphadenectomy is the removal of lymph nodes in the upper abdomen, which includes diaphragmatic and paracardial lymph nodes, together with lymph nodes alongside the lesser curve, the left gastric artery, common hepatic artery, coeliac artery, splenic hilum, and splenic artery. Two-field lymphadenectomy includes the removal of the above-mentioned nodes together with paraoesophageal, para-aortic, paratracheal, subcarinal, and hilar nodes. Three-field lymphadenectomy adds the removal of nodes in the neck, more specifically, brachiocephalic, deep lateral, external cervical nodes, and deep anterior cervical nodes.

Extent of the lymphadenectomy is debatable. For oesophageal cancer many of the centres in the West perform routinely two-field lymphadenectomy whereas in Asia three-field lymphadenectomy is routinely performed for the upper thoracic tumours. It is unknown which of these approaches lead to an extended survival [55, 56]. The number of lymph nodes removed has been shown to be independent predictor of survival after oesophagectomy [57, 58] however low incidence of cervical recurrence after two-field lymphadenectomy for the tumours in mid or low oesophagus [59] might suggest that more extensive three-field lymphadenectomy is unlikely to improve survival.

For gastric cancer D2 lymphadenectomy (regional lymph nodes plus lymph nodes alongside the left gastric artery, common hepatic artery, coeliac artery, splenic hilum, and splenic artery) has been proven to be better in terms of survival comparing to D1 lymphadenectomy (regional lymph nodes only). D3 lymphadenectomy (including paraaortic nodes) does not lead to better

survival comparing to D2 lymphadenectomy [60]. Similarly, to oesophageal cancer, more lymph nodes resected lead to better stage-specific survival in gastric cancer.

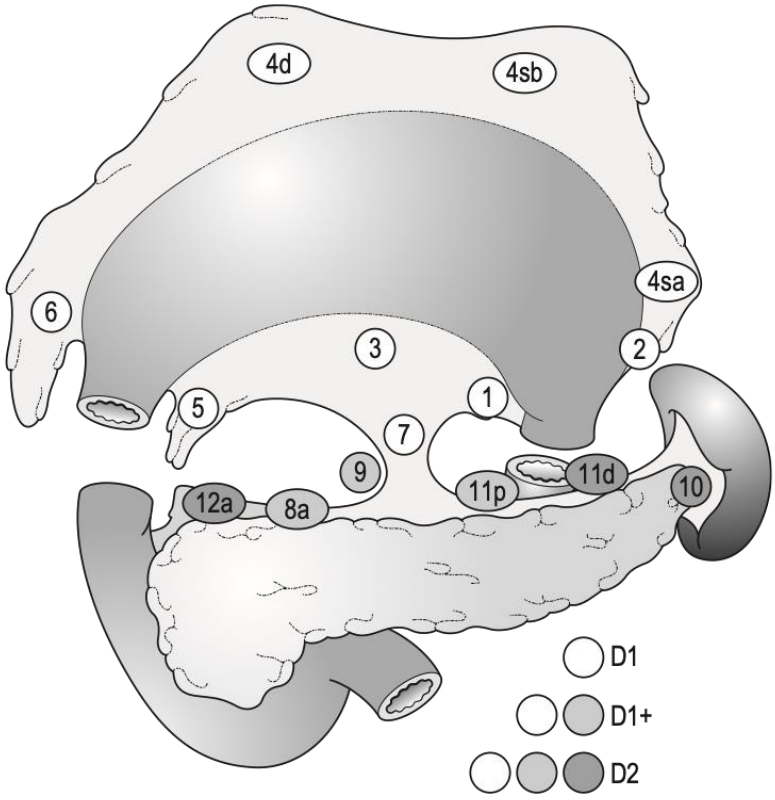


Figure 3 Gastric lymph node stations.
Adapted from 'A Companion to Specialist Surgical Practice, Oesophagogastric Surgery' [61].

1.4 Importance of fitness in surgery

Physical fitness can be defined as a set of health and skill related components which include cardiorespiratory endurance/fitness, muscular endurance and strength, body composition, flexibility, balance, agility, power and reaction time [62]. Cardiopulmonary fitness, which is a part of physical fitness, is defined as one's ability to deliver and use oxygen in tissues to perform work [63]. Part of this is genetically determined but another part is trainable [64, 65]. Cardiopulmonary fitness is associated with cardiovascular morbidity [66] and mortality [67] and it has been found to be an independent predictive factor for this in healthy individuals. The level of fitness is also associated with mortality from other causes [67-69]. Interventions employing physical activity which lead to improved physical fitness have been shown to improve outcomes for cancer survivors such as physical function, quality of life (QoL), psychological outcomes, physiology and body composition [70]. The stress from major surgery and general anaesthesia

demands a high level of cardiorespiratory fitness from the patient and therefore it is unsurprising that the patient's level of fitness is related to the outcomes after major surgery. Older et al. were one of the first to demonstrate that cardiopulmonary fitness measured by cardiopulmonary exercise testing (CPET) is associated with the non-surgical mortality after major elective surgery [71]. In their study patients tested by CPET prior to surgery with the anaerobic threshold (AT) of <11 $ml.kg^{-1}.min^{-1}$ had a mortality of 18% comparing to patients with anaerobic threshold of >11 $ml.kg^{-1}.min^{-1}$ who had a mortality rate of 0.8%. These results were later repeated for numerous treatment outcomes in patients undergoing intra-abdominal [72], vascular [73], colorectal [74, 75], hepatobiliary [76] and liver transplant procedures [77]. Various CPET related variables, mainly AT, peak oxygen uptake (VO_2peak) and ventilatory equivalents for carbon dioxide (VE/VCO_2), have been linked to outcomes such as critical care length of stay [77], morbidity [73, 78] and mortality [74, 76, 79]. It is understood that high level of fitness reduces complications, improves recovery and patients' functioning in postoperative period.

1.4.1 Cardiopulmonary exercise testing

CPET is a dynamic method of assessing cardiopulmonary fitness. It provides assessment of each system involved in the delivery of oxygen to the tissues - pulmonary, cardiovascular, haematological and metabolic. This is achieved through the measurement of pulmonary gas exchange by recording breath-by-breath expired gas values during incremental exercise. Concentration of respired O_2 and CO_2 is measured together with measurements of ventilatory flow. This allows calculation of uptake of O_2 and output of CO_2. These measurements are carried out in the background of exercise. This exercise involves a continuously ramped increase in workload which lasts until the patient is fatigued and unable to exercise anymore. A cycle ergometer is commonly used as an exercise machine. Patients use a non-rebreathing mask for the measurement of pulmonary gas exchange. A 12-lead electrocardiogram trace (ECG) and pulse oximetry are also used for monitoring. CPET is a safe test, major cardiac events were reported to be 1.2 per 10 000 tests [80] and mortality of 2-5 per 100 000 tests [81]. Contraindications to CPET can be divided between relative and absolute contraindications. Absolute contraindications include unstable angina, uncontrolled arrhythmia, syncope, acute myocardial infarction, active endocarditis, acute myocarditis and pericarditis, symptomatic severe aortic stenosis, uncontrolled heart failure, suspected dissecting or leaking aortic aneurysm, uncontrolled asthma or arterial desaturation at rest on room air below 85%. Findings described in the previous paragraph led to the routine use of CPET in clinical practice. Nowadays CPET is used to risk stratify patients, guide perioperative care and triage patients to

ward versus intensive care unit. The main variables reported during CPET are VO_2peak, AT, VE/VCO_2.

The highest amount of oxygen which can be utilised by a patient is described as the VO_2max. After this is reached, no increase in exercise will lead to an increase in oxygen utilisation. This value reflects the patient's maximal effort and is demonstrated by the VO_2 level plateauing despite the increase in workload. This value is however not always reached during CPET. VO_2peak is therefore defined as a highest oxygen uptake observed during incremental exercise [82]. This definition also explains why good patient effort during CPET is important to establish a value, which is close to, or representative of patient's physiological limit. The VO_2peak is usually expressed as an absolute value ($ml.min^{-1}$) or per kilogram of body weight ($ml.min^{-1}.kg^{-1}$). Any pathology of the systems involved in the delivery and utilisation of the oxygen from air to human cell and subsequently to mitochondria will result in a lower VO_2peak. Values of VO_2peak range from almost 70-80 $ml.min^{-1}.kg^{-1}$ in top world-class sport athletes [83] through 30-50 $ml.min^{-1}.kg^{-1}$ in healthy individuals [84] to around 16-22 $ml.min^{-1}.kg^{-1}$ in patients with oesophago-gastric cancer [85]. Several factors likely contribute to the observed values in patients with oesophago-gastric cancer. These can be linked to various aspects, including the age of the patients, the presence of comorbidities and in some patients their obesity, sedentary behaviour and smoking. Additionally, signs such as anaemia or general deconditioning due to dysphagia or the catabolic effects of cancer, also play a significant role in influencing these values.

Anaerobic threshold or lactate threshold is the VO_2 level at which the lactate level starts to gradually increase during exercise. It equals the start of anaerobic metabolism when the oxygen demand by muscles due to increased work is not met and cells need to adapt anaerobic glycolysis to produce enough ATP. This leads to metabolic acidosis. In sports medicine, sequential measurement of lactate from blood during exercise is commonly used to obtain value of AT. In the clinical setting, this is commonly established by three point discrimination technique [86], by V-slope method or modified V-slope method [82]. V-slope methods establishes AT from $VCO_2 - VO_2$ relationship which is changing during the incremental part of the exercise (Figure 2). AT seems to predict postoperative complications with more precision that other CPET derived variables [72].

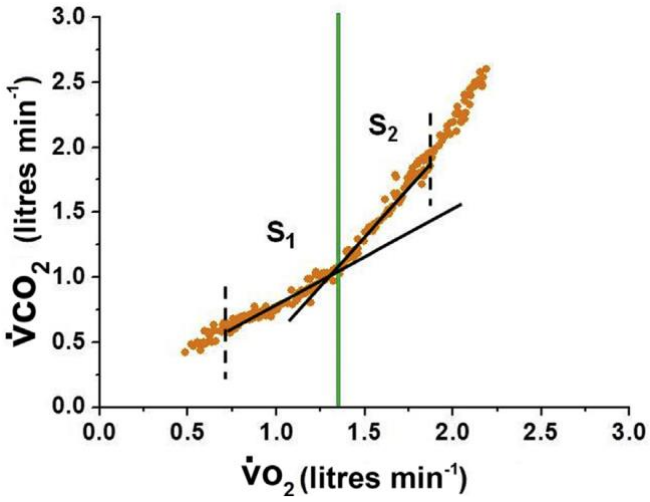


Figure 4 V-slope estimation.
Adapted from Levett et al. [82]. S1 and S2 are slopes representing VCO_2 – VO_2 relationship during initial part of exercise test (S_1) when increase in VO_2 is higher than in VCO_2 and at later stage (S_2) when excess of VCO_2 develops and slope becomes steeper. Crossing of these two slopes represents estimated AT.

Ventilatory equivalents for carbon dioxide are described as the ratio between minute ventilation and CO_2 output. It represents the efficiency in ability to clear carbon-dioxide from an organism. A high ratio can be seen in cardiac failure, pulmonary hypertension or in respiratory disease representing a poor ventilation-perfusion match or poor efficiency of gas exchange. VE/VCO_2 has been shown to have an impact on postoperative outcomes [87].

1.4.2 CPET in oesophago-gastric surgery

A relatively high number of studies have tried to establish the relationship between variables derived from CPET and surgical outcomes – in particular morbidity, mortality and length of stay.

There is a conflicting evidence in regard to the association of CPET variables and morbidity after oesophago-gastric surgery. Sinclair et al. found an association between preoperative VE/VCO_2 and postoperative complications graded with the Accordion classification [85]. This study involved 240 patients undergoing open transthoracic oesophagectomy. Another large study by Benington et al. involved 200 patients who underwent oesophagectomy [88]. In this cohort, patients who developed severe complications (classified grade III-V according to Clavien-Dindo grading of surgical complications system [89]) had significantly lower VO_2peak than those without a complication or with minor complications (Clavien-Dindo grade 0-II).

Patel et al. found an association between both VO_2peak and complications graded by Clavien-Dindo system on 120 patients having oesophagectomy [90]. Forshaw et al. included 78 patients undergoing oesophagectomy [91]. They found that VO_2peak was significantly lower (p 0.04) in those patients who had cardiopulmonary complications and Moyes et al. almost demonstrated similar association with AT (p 0.05) on a group of 108 patients after oesophagectomy and gastrectomy [92]. In contrast, another study by Lam et al. which included 206 patients post oesophagectomy failed to identify any relationships between AT or VO_2peak and postoperative complications graded according to the Clavien-Dindo classification [93]. Similar findings of no association between CPET variables and complications graded by the Clavien-Dindo classification were reported by Drummond et al. on 42 patients undergoing both oesophagectomy and gastrectomy and by Thomson et al. on 38 patients after oesophagectomy [94, 95]. Whibley et al. studied 81 patients undergoing both gastrectomy and oesophagectomy and they did not observe any correlation in CPET parameters and postoperative pulmonary complications [96]. These results are demonstrated in table 3.

Authors	Centre	Type of surgery (number of patients)	Sample size	NAC	Outcomes	Analysis	Variable	Results
Studies with some association or significant findings demonstrated in regard to CPET variables and morbidity								
Sinclair et al. (2017)	United Kingdom, Newcastle	open STO (majority Ivor Lewis – unclear how many) (240)	240	70%	Any postoperative complication	Multivariable logistic regression	VE/VCO_2 (continuous)	OR 1.088 p 0.018
Bennington et al. (2019)	United Kingdom, Manchester	open Ivor Lewis STO (57%) laparoscopic Ivor Lewis STO (33%) thoracoscopic Ivor Lewis (open or laparoscopic abdomen) STO (10%)	200	70%	Clavien-Dindo grade III-V	Univariable tests	VO_2peak VE/VCO_2	18.2 vs 19.7 p 0.01 32.9 vs 30.4 p<0.001
Patel et al. (2019)	United Kingdom, Cardiff	open Ivor Lewis STO (44) open transhiatal STO (76)	120	50%	Clavien-Dindo grade III-V	Multivariable logistic regression	VO_2peak (continuous)	OR 0.85 p 0.018
Forshaw et al. (2008)	United Kingdom, London	open transhiatal STO (39) laparoscopic Ivor Lewis STO (23) open Ivor Lewis STO (6) three stage STO (5) thoracoabdominal STO (5)	78	64%	Cardiopulmonary complications	Univariable tests	VO_2peak AT	mean 19.2 vs 21.4 p 0.04 mean 13.2 vs 14.4 p 0.07
Moyes et al. (2013)	United Kingdom, Glasgow	transthoracic STO (24) transhiatal STO (40) TG (15) STG (24)	108	72%	Cardiopulmonary complications	Univariable test	AT	mean 9.9 vs 11.2 p 0.05

Nagamatsu et al. (2001)	Japan, Kitakyushu	three stage STO (91)	91	0%	Cardiopulmonary complications (author defined)	Multivariable logistic regression	VO_2max (continuous; $ml.min^{-1}.m^{-2}$)	OR not reported p 0.0001
Studies without any association or significant findings demonstrated in regard to CPET variables and morbidity								
Lam et al. (2019)	United Kingdom, Norwich	laparoscopic Ivor Lewis (109) open or partially laparoscopic assisted Ivor Lewis STO (83) open three stage STO (14)	206	79%	Clavien-Dindo grade II-V (30 days)	Multivariable logistic regression	VO_2peak (continuous) AT (continuous)	OR 1.00 p 0.862 OR 0.98 p 0.769
Drummond et al. (2018)	United Kingdom, Glasgow	Ivor Lewis STO (12) transhiatal STO (11) thoracoabdominal STO (2) three stage STO (5) TG (4) STG (5) inoperable (3)	42	100%	Clavien-Dindo grade II-V	Univariable test (chi squared)	AT (categorical)	p 0.914
Whibley et al. (2018)	United Kingdom, London	STO (41) STG or TG (40)	81	Not reported	Respiratory complications	Univariable test (chi squared)	AT (categorical) VO_2peak (categorical)	p 0.24 p 0.65

Table 3 CPET variables and their association with postoperative morbidity after oesophago-gastric surgery.
NAC, neoadjuvant chemotherapy. STO, subtotal oesophagectomy. TG, total gastrectomy. STG, subtotal gastrectomy. AT, anaerobic threshold. VO_2peak, peak oxygen uptake. OR, odds ratio.

Relationships between CPET variables and postoperative mortality after oesophago-gastric surgery has also been studied. Jack et al. demonstrated a relationship between preoperative AT and one year mortality on 39 patients who completed neoadjuvant chemotherapy and progressed to oesophagectomy [97]. Benington et al., (in the study previously mentioned) found an association between AT of less than 11ml.min^{-1}.kg^{-1} and VO_2peak of less than 15ml.min^{-1}.kg^{-1} and mortality at 90 days [88]. Sinclair et al. reported that the ratio of expected-to-observed VE/VCO_2 is associated with survival [85]. Whibley et al. reported that survival in patients with an AT <10ml.min^{-1}.kg^{-1} is significantly worse than those above this threshold [96]. This was also demonstrated with a VO_2max of <14ml.min^{-1}.kg^{-1}. Patel et al. however have not found any association between any of CPET variables and mortality [90]. Only the study by Sinclair et al. reported some association between preoperative AT and VO_2peak and postoperative length of stay [85].

These studies have several limitations. They are retrospective in nature and include a great deal of heterogeneity in surgical procedures and outcome measures. Also, results are conflicting. Trends show that less fit patients experience worse postoperative outcomes. Substantial evidence from studies designed prospectively with large sample sizes is needed to establish the role of CPET in predicting postoperative outcomes after oesophago-gastric surgery. Until then, these results have to be interpreted with caution.

1.5 Sarcopenia and frailty

Sarcopenia is a syndrome characterised by the loss of muscle mass and strength or physical performance [98]. It is associated with a disability and with increased mortality [99]. Typically, the prevalence of sarcopenia increases with older age. In a population over 60 years of age, the prevalence was found to be 10% for both women and men measured by dual energy X-ray absorptiometry and by bio-electrical impedance analysis [100]. However, sarcopenia can be observed in younger individuals. Apart from ageing, there are several other causes which can lead to its development. The main cause is inactivity and a sedentary lifestyle, other causes include deconditioning, malignancy, chronic diseases and an inadequate dietary intake [98]. Increased apoptosis, mitochondrial dysfunction, increase in pro-inflammatory cytokines, reduction of sex-hormones, oxidative stress and decline of alpha motoneurons have been mentioned as internal pathophysiological processes which lead to this syndrome [98]. Sarcopenia is different to cachexia which is a syndrome associated with an underlying illness and

characterised by increased catabolism leading to weight loss, and muscle loss with or without loss of fat tissue [101]. Sarcopenia is a major component in the development of frailty as a condition of age-related decrease of reserve and resistance to stressors due to declines of multiple physiologic systems [102].

Several techniques are described to assess and recognise sarcopenia. Muscle mass which is the main criterion in the definition of sarcopenia can be measured by computed tomography (CT), magnetic resonance imaging (MRI) or by the dual energy X-ray absorptiometry (DXA) [98]. CT and MRI imaging are recognised to be the gold standard method for estimating muscle mass, mainly due to the precision in separating muscles from fat and other tissue. Muscle strength is the next criterion in the definition of sarcopenia and can be assessed measuring handgrip strength [98, 103]. Low muscle strength measured by handgrip strength has been associated with poor mobility and predicts disability [104, 105]. Correlation between muscle strength and poor mobility is stronger than the correlation between muscle mass (measured by calf muscle cross-sectional area) and poor mobility [103]. Handgrip strength correlates with leg strength and it is easy, quick, inexpensive and simple to measure. Values of less than 30kg in men and less than 20kg in women have been described as a diagnostic threshold for patients with mobility limitations [103]. Physical performance which is the last criterion in the definition of sarcopenia can be measured with various tests: these include the short physical performance battery (SPPB), usual gait speed, 6-min walk test (6MWT) and the stair climb power test [98].

Sarcopenia has been found to be associated with adverse outcomes in the cancer patient population [106, 107]. Patients with oesophago-gastric cancer suffer commonly with malnutrition as a result of cancer cachexia and dysphagia which this cancer is commonly associated with. This might explain why the prevalence is high in this group of patients [108, 109]. A systematic review and meta-analysis from 2020 looking at the impact of sarcopenia (defined by skeletal muscle index calculated from CT scans) on postoperative outcomes of patients undergoing oesophagectomy analysed 11 single-centre, non-randomized retrospective studies with 1979 patients included in total [110]. Low pre-operative skeletal muscle index was associated with an increased risk of overall morbidity rate, increased risk of postoperative respiratory complication and increased risk of anastomotic leak. Another systematic review and meta-analysis of sarcopenic patients with oesophageal cancer included other definitions of sarcopenia however demonstrated similar results including impact on long term outcomes after oesophagectomy [111]. Similar findings were observed in patients with gastric cancer [112].

Overall, the decreased mobility, poor nutrition and increasing sarcopenia can contribute to the development of frailty. Frailty is recognised as a distinct syndrome which affects approximately 10% of 65-year-olds and up to half of individuals >85 years [113]. Frail individuals are disproportionately vulnerable to reductions in functional status in response to minor stressors. The prevalence of frailty in cancer patients is high and independently associated with an increased risk of mortality and treatment complications [114].

1.6 Health economics of oesophago-gastric cancer

Oesophago-gastric cancer is acknowledged as one of the most costly cancers to treat [115]. The cost of treating oesophageal cancer has been noted to be highest during the terminal phase, followed by the staging or surgery phase, and subsequently the initial and continuing phases, according to Tramontano et al. [116]. Similar findings were reported for oesophageal adenocarcinoma by Thein et al. [117]. The study identified several strong predictors of higher net costs, including the delivery of chemotherapy and radiotherapy, surgery and chemotherapy, surgery alone, radiotherapy alone, stage III and IV of the disease, and comorbidities coupled with older age.

The health economics literature related to the diagnosis and treatment of oesophago-gastric cancer is limited. NICE guidelines offer some health economics evidence for various staging and treatment modalities related to oesophago-gastric cancer [118]. However, only seven studies were considered appropriate for inclusion in the NICE evidence review, as some lacked methodological quality or did not meet the applicability and quality criteria set out by NICE. Furthermore, only four studies specifically addressed the curative treatment of the disease.

Russell et al. concluded that staging using EUS was less costly and more effective than non-EUS alternatives for patients whose diagnosis was confirmed with endoscopy and CT [119]. Hisashige et al. demonstrated that curative treatment of gastric cancer with adjuvant chemotherapy in comparison to surgery alone is cost-effective [120]. However, the Japanese study's applicability to the treatment of patients in the UK or the broader Western context is limited. Similarly, in patients with resectable gastric adenocarcinoma or GOJ cancer, the addition of chemoradiotherapy to surgery alone was found to have a 67% probability of being cost-effective at a threshold of $50,000 per quality-adjusted life year (QALY) in a US study

from 2008 by Wang et al. [121] Lee et al. conducted a study on open and minimally invasive oesophagectomy from a cost-effectiveness perspective [122]. They concluded that the minimally invasive approach is more effective and less costly than the open approach.

Further research is needed to compare the cost-effectiveness of commonly used treatment modalities in oesophago-gastric cancer. Nevertheless, it is evident that efforts to promote lifestyle modifications, screening programs, and early detection strategies can be cost-effective in the long run, potentially reducing the need for expensive treatments in advanced stages of the disease.

1.7 Quality of life

Traditionally mortality and morbidity have been always considered as important outcome measures to assess the success of the treatment. However, patients' reported health related quality of life (QoL) and their perception of the treatment is equally important. Oesophago-gastric cancer has a significant impact on patients' QoL [123]. Some patients might not accept aggressive treatment strategies if this does not lead to significant improvement in their chance of cure and impacts negatively on their life and wellbeing. As already mentioned, many patients present with dysphagia, weight loss and fatigue. Difficulties for example with swallowing lead not only to weight loss and fatigue but also to social isolation which is perceived negatively.

Various instruments to assess QoL exist. In oesophago-gastric cancer one of the most commonly used tools are European organization for research and treatment of cancer (EORTC) quality of life questionnaires. EORTC QLQ-C30 was developed to assess QoL in cancer patients in general [124]. A more specific oesophago-gastric EORTC QLQ-OG25 questionnaire exists as well [125]. Both of these questionnaires have been validated and are recommended to be used in conjunction to assess health related QoL of patients with oesophago-gastric cancer [125].

Oesophago-gastric surgery has a significant impact on QoL especially during the first weeks after surgery. This tends to recover to baseline levels usually 6 to 9 months after surgery [126]. Poor QoL score at 6 months postoperatively was found to be predictive of long-term survival in oesophageal cancer [127]. It was also demonstrated that although neoadjuvant chemoradiotherapy delivered as part of the CROSS regimen has got negative impact on QoL, this is restored to baseline levels prior to surgery [128]. This mean that poor QoL scores after

surgery are probably related to the operation itself rather than neoadjuvant treatment. QoL might be taken into consideration when two heterogenous treatment strategies with similar morbidity, mortality and survival outcomes are compared. A different QoL score might influence which of the strategies will be employed. National institute for health and care excellence also uses QoL measures to assess cost-effectiveness [129]. Effect of the treatment strategy and its impact on QoL can be assessed when QoL tools are compared before and after treatment. It is however important to mention that this might be confounded as the patients' perception of their QoL change during the time due to the changes in their priorities and expectations [130].

1.8 Exercise

Physical activity can be defined as any sustained body movement that increases energy expenditure and exercise as a subcategory of physical activity that is planned, purposeful, and repeated on a regular basis in order to improve or maintain health and fitness [62]. Exercise can be divided into one of four categories. Aerobic (sometimes termed endurance) exercise which can improve cardiopulmonary fitness, strengthening (sometimes termed resistance) exercise which can increase muscular strength and also mobility and balance exercises.

1.8.1 Exercise physiology

Training and regular exercise leads to adaptation of several systems involved in the delivery and utilization of oxygen to compensate for the stress of exercising. Endurance training leads to many cardiovascular changes, this includes cardiac muscle fibre hypertrophy which may progress in the well-trained to enlargement of the left ventricle. This causes an increase in cardiac output. Peripheral capillary resistance is lower which allows better oxygen delivery to tissues [131]. A decrease in minute ventilation (VE) to achieve a given VO_2 or VCO_2 is a typical training response of the respiratory system. Training of the musculoskeletal system leads to various adaptations depending on the type of training [132]. Endurance training leads to changes of the type of muscle fibres from fast to slow-twitch fibres, mitochondrial biogenesis and changes in substrate metabolism. Resistance training in contrary leads to muscular hypertrophy to increase the maximal contractile output force. The degree of adaptation is individual to every subject. Metabolic adaptations to endurance training include increase in the number and size of

mitochondria, increase in the storage capacity of glycogen by muscles and better fat utilization of muscles [133].

As a consequence of the above, endurance training leads to increase in lactate threshold and maximal oxygen uptake. Lactate threshold occurs at above 50% of predicted maximal oxygen uptake in normal individuals [134]. This percentage increases when the individual is trained.

1.8.2 Benefits of exercise

Physical activity and exercise are beneficial for health. People who regularly exercise have a lower risk of all-cause mortality compared to those leading a sedentary lifestyle [135]. Regular exercise improves quality of life and sleep and reduces anxiety [136, 137]. People who are active have been found to have a lower incidence of cancer [138-140]. An umbrella review from 2018 by Rezende et al. included multiple systematic reviews, meta-analyses and original works about physical activity and cancer incidence and mortality [141]. This review included 770 000 cancer cases. The authors concluded that physical activity was inversely associated with a risk of multiple types of cancer. The association was particularly strong in colon and breast cancer. Sedentary behaviour was found to be independently associated with increased risk of various types of cancer [142]. There is also an association between physical activity before the diagnosis of cancer and cancer-related mortality with the dose-response effect as concluded in one meta-analysis [143]. These associations have however never been demonstrated in an RCT setting. Another limitation of these studies is the fact that the majority included self-reported activity by subjects instead of using for example accelerometers as a more objective measurement of physical activity. Biological principles explaining why there is an association between physical activity and cancer incidence are not fully understood. Some have highlighted the changes in immune response due to physical exercise or changes of the circulating levels of insulin and inflammation [144].

Exercise plays an important role in the cancer related outcomes even after the diagnosis of cancer. Several systematic reviews and meta-analyses amongst cancer survivors reported an association between physical exercise and survival data [145]. This might suggest that physical activity plays an important role in cancer recurrence and/or disease progression. Furthermore, recent laboratory work has linked the activity levels of patients during chemotherapy to improved chemotoxic drug delivery to tumour cells and potential improvements in cancer treatment and survival [146].

1.8.3 How much exercise

The UK government physical activity guidelines recommend a certain amount of exercise for adults in order to obtain physical and mental health benefit and to reduce the risk of many non-communicable disease [147]. The current recommendation is for every adult to perform at least 150 minutes of moderate intensity activity or 75 minutes of vigorous intensity activity or a combination of moderate, vigorous and very vigorous intensity activity weekly. Evidence suggests that this amount of activity can be achieved almost in any number of bouts of activity [148]. A short duration of very vigorous exercise can be a time efficient way to gain health benefits. Muscle strengthening exercises are recommended to be done on at least two days a week and should use all major muscle groups of lower and upper body. Importantly, any activity is still better than no activity. Unfortunately, it is well recognised that these targets are not met by most of the UK population [149].

When prescribing exercise (usually as a training programme for any reason), The American College of Sports Medicine looks at six main domains – frequency, intensity, time, type, volume and progression [150]. Frequency is the amount of exercise sessions per time unit, usually one week. Intensity is the amount of energy used to exercise or in other words, how hard one needs to exercise. Time is usually defined as the number of minutes per one exercise session. Type of exercise is one of the main four types of exercise – aerobic, strengthening, mobility and balance. Volume is the total amount of exercise performed during the time period taken into account frequency, intensity and duration of the exercise. Progression refers to the process of increasing the amount of exercise during the long term. This is mainly because body systems adapt to the load of exercise and in order to stress these systems, the amount of exercise needs to be increased.

1.8.4 Intensity

In order to improve fitness, exercise need to be performed at a certain level of intensity. This can be expressed in various ways using objective or subjective measures. One of them is metabolic equivalents (METs). One MET is the rate of energy expenditure while sitting at rest. It is taken by convention to be an oxygen uptake of 3.5 $ml.min^{-1}.kg^{-1}$ [151].

Another way to express intensity is to use the percentage of a person's maximal aerobic capacity derived from CPET [152]. For practical reasons this can be then translated into the amount of power expenditure on various exercise machines like stationary bikes, treadmills or rowing machines. It is important to mention that the amount of power generated on one machine by an individual (rowing) can be different to the percentage of the individual's maximal oxygen uptake generated by same amount of power on a different machine (e.g., stationary bike). This relates to different muscle groups involved on different exercise machines.

Intensity can be also expressed by the percentage of a person's maximal heart rate. Again, this can be measured by CPET or predicted by age using the Karvonen formula [153]. This is based on the linear relationship between heart rate and oxygen consumption. Use of the heart rate to monitor intensity is however disadvantaged by several factors. For instance, patients with a permanent pacemaker or patients with beta blockers do not respond to variations in the intensity of exercise with a change in their heart rate. The use of caffeine can also influence heart rate [154].

The Borg rating of perceived exertion scale represents a subjective tool to measure exercise intensity [155]. This is done by measuring an individual's exertion, breathlessness and fatigue. Individuals are asked to rate the feeling they are experiencing when exercising on the numerical scale. The original scale ranges from 6 to 20 with 6 being 'no exertion at all' and 20 being 'maximal exertion'. Borg also developed an alternative Borg's CR-10 scale. This rates perceived exertion from 0 which represents 'nothing at all' effort through 3 which is 'moderate' towards 10 which equates to 'maximal' effort. The Borg scale, although subjective, remains a valuable and simple tool to prescribe intensity in the clinical setting if used correctly. These scales are often used in research [156].

It is important when prescribing intensity that the prescription is relative to the individual's maximal values rather than absolute values. This allows reproducibility of one prescription to multiple individuals as everyone's physical fitness is different.

1.9 Prehabilitation

Implementation of enhanced recovery after surgery pathways (ERAS) in the optimisation of the peri-operative care of surgical patients has led to improvements of peri-operative outcomes.

This multidisciplinary and multimodal approach to the care and recovery of patients came to life in the 1990s in a group of patients undergoing major colorectal surgery [157]. This strategy was later introduced in the treatment of other surgical cohorts including patients with oesophago-gastric cancer [158].

Focus has however now moved towards improving patients' physiology in the preoperative period. Work demonstrating a relationship between cardiopulmonary fitness and postoperative outcomes led to the development of preoperative programmes where the primary aim is to improve fitness with exercise. *Prehabilitation* could be defined as "an intervention to enhance functional capacity in anticipation of a forthcoming stressor" [159]. The stressor mentioned in this definition is the surgery and general anaesthetic. This intervention is usually delivered in the form of aerobic or strength training, sometimes combined with nutritional and psychological support [160, 161]. There are also other forms of preoperative exercises namely inspiratory muscle training (IMT) where emphasis is on improving lung function to reduce pulmonary postoperative complications [162]. Correction of anaemia or other comorbidities like diabetes and alcohol and smoking cessation are other pre-operative interventions which some authors tend to include when talking about prehabilitation [163].

Prehabilitation has been shown to have an impact on the functional capacity of patients demonstrated by CPET variables like anaerobic threshold or VO_2peak [164-166], or 6MWT [160]. This was demonstrated on patients undergoing orthopaedic, cardiothoracic and major abdominal surgery, both for benign and malignant disease. As preoperative cardiopulmonary fitness represented by variables from CPET is known to have an impact on postoperative outcomes [72] it could be postulated that improving functional reserve must have impact on outcomes of the patients after surgery.

1.9.1 Current prehabilitation evidence

Jones et al. were amongst the first to demonstrate in a group of 18 patients undergoing pulmonary resection for malignant lesions, that exercise in the preoperative period can lead to improvement of cardiopulmonary fitness [167]. Similar improvements in fitness were seen in a group of 15 patients with lower or upper gastrointestinal cancers [168].

Li and Carli (2013) studied colorectal cancer patients undergoing surgical resection of their tumours [159, 160]. When these patients were enrolled into a tri-modal prehabilitation programme their functional walking capacity prior to surgery improved [160]. More importantly, postoperative

functional recovery was better comparing to a cohort without prehabilitation. Their programme, with a median duration of 33 days, consisted of aerobic and resistance exercise, nutritional counselling and psychological support.

The above-mentioned studies were designed as prospective cohort studies. An Italian RCT compared patients undergoing an intensive pulmonary prehabilitation programme consisting of high-intensity aerobic exercise prior to lung resection with a group undergoing lobectomy only [164]. Patients in the prehabilitation group showed a significant improvement of their VO_2peak during the pre-operative period. Another RCT on prehabilitation of patients with abdominal aortic aneurysms (AAA) demonstrated similar improvement of VO_2peak and also in anaerobic threshold [165]. An RCT conducted in the UK on 35 patients undergoing elective liver resection for colorectal metastases demonstrated significant improvement in fitness of patients who were randomised into 4-week high intensity cycle programme [166]. This was one of the first RCTs demonstrating the fitness benefit of prehabilitation on cancer patients. Participants had significantly improved their AT by 1.5ml.kg.min and VO_2peak by 2.0ml.kg.min and had significantly higher scores in their quality of life questionnaires postoperatively.

Barakat et al. in a subsequent RCT but on a much larger sample size of 124 patients demonstrated that preoperative exercise on patients undergoing AAA repair can lead to fewer postoperative complications and patients in the exercise group were discharged from hospital one day earlier [169]. This is the first trial in the field of major abdominal surgery that was able to translate improvements in cardiopulmonary fitness into an improvement in postoperative outcomes.

The breakthrough study was published in 2018 in Annals of Surgery by Barberan-Garcia et al. [161]. This study reports results of 125 patients who were randomised either to a prehabilitation arm or to routine care. The study population were high risk patients expecting to undergo major abdominal surgery mainly oesophageal, gastric, pancreatic, liver and colorectal resections. The intervention was an individualised mix of home-based increased physical activity by walking and supervised high-intensity endurance programmes. Results showed that the prehabilitation group had 51% fewer complications. Although single-centre, this single-blinded study represents high quality evidence demonstrating that a prehabilitation intervention can influence postoperative outcomes.

A recent systematic review and meta-analysis of prehabilitation prior to major abdominal surgery included 15 RCTs [170]. Some of the studies used IMT as the only prehabilitation intervention. Five trials did not include patients undergoing operations for cancer. Nine RCTs with 354 patients in total undergoing a prehabilitation intervention were compared to 354 patients in the control group. The meta-analysis looked at postoperative morbidity. Overall morbidity was reduced significantly in the prehabilitation group (OR 0.63 95% CI 0.46–0.87 I2 = 34%, p = 0.005) and composite pulmonary morbidity was significantly reduced as well (OR 0.40 95% CI 0.23–0.68, I2 = 0%, p = 0.0007). The quality of life of cancer patients undergoing prehabilitation has been assessed in different systematic reviews [171]. These have produced conflicting results.

The downside of any conducted prehabilitation meta-analysis is that there is no clear and accepted definition of prehabilitation. Interventions, study populations and reported outcomes vary significantly. It is therefore difficult to draw valid conclusions from these.

1.9.2 Prehabilitation of patients with oesophago-gastric cancer

Evidence of exercise prehabilitation studies in the field of oesophago-gastric surgery are not robust and are limited to a small number of very heterogenous studies assessing a wide variety of outcomes.

A Japanese prospective cohort study with matched pair analysis from 2014 in stage I gastric cancer patients with metabolic syndrome showed that patients undergoing preoperative exercises in the form of aerobic exercises and resistance training prior to gastrectomy benefit from lower incidence of postoperative complications [172]. There were however only 18 patients included in the exercise group and all of the patients had early disease.

Xu et al. conducted an RCT on patients with locally advanced oesophageal cancer undergoing neoadjuvant chemoradiotherapy [173]. Participants in the intervention arm entered a nurse-led programme consisting of nurse supervised walking three times a week and weekly nutrition advice. The majority (96.4%) of patients had a histological diagnosis of SCC. Results showed that patients in the walk-and-eat programme had a lower decline in walked distance during 6MWT and lower decrease in handgrip strength.

Another Japanese pilot study looking into preoperative exercise and nutritional support of elderly patients with gastric cancer showed that total calorie and protein intakes were significantly higher after the program than before and handgrip strength significantly increased after the program [174].

An RCT conducted by Minnella et al. provided statistically significant results [175]. In this study 51 patients with oesophageal or gastric SCC or adenocarcinomas were randomized into a home-based prehabilitation programme versus routine care. Patients in the prehabilitation arm had significantly better functional capacity demonstrated by 6MWT both before and after surgery. There were no differences in postoperative outcomes between the two groups.

IMT alone in the preoperative period before oesophagectomy has been evaluated in two studies. Dettling et al. in a non-randomized controlled trial compared 44 patients receiving IMT with 39 patients without this intervention [176]. They found that maximal inspiratory pressure was influenced by this training in intervention group however this did not lead to lower rate of pneumonia or shorter length of hospital stay. A similar conclusion was reported by Valkenet et al. who conducted a multicentre RCT on 241 patients prior to surgery for oesophageal cancer [177].

Apart from the already mentioned study conducted by Barberan-Garcia et al. [161] which included 13 patients undergoing oesophagectomy and five patients undergoing gastrectomy, there is no other evidence published to show that prehabilitation can have an influence on postoperative outcomes in patients with oesophago-gastric cancer.

1.9.3 Impact of neoadjuvant chemotherapy on fitness

Neoadjuvant chemotherapy provides a survival benefit to patients with oesophago-gastric cancer. This type of treatment is also indicated in other cancer types. One example of this is in locally advanced rectal cancer. This intense treatment poses a major challenge to the patients receiving it. Apart from chemotherapy related toxicity, patients have to face fatigue, poor sleep quality and overall reduced quality of life [128]. It is not surprising that neoadjuvant chemotherapy has been associated with reduced fitness after this treatment.

A UK study demonstrated this on a group of patients receiving neoadjuvant chemoradiotherapy for rectal cancer [178]. In this study patients' AT decreased by 1.5 $ml.min^{-1}.kg^{-1}$ and VO_2peak

decreased by 1.4 $ml.min^{-1}.kg^{-1}$ during neoadjuvant treatment. Similar results were demonstrated in another UK study on a group of patients with oesophago-gastric cancer [97]. After neoadjuvant chemotherapy, AT of these patients were decreased by 2.2 $ml.min^{-1}.kg^{-1}$ and their VO_2peak by 2.5 $ml.min^{-1}.kg^{-1}$. Decrease in both of these variables was associated with increased one-year mortality. These results were confirmed in a local study on the participants with oesophageal or gastric cancer [179]. A drop in these CPET variables was even more evident. The AT of this group of patients decreased by 3.5 $ml.min^{-1}.kg^{-1}$ and VO_2peak decreased by 4.2 $ml.min^{-1}.kg^{-1}$ during neoadjuvant treatment. Importantly, these values did not recover to baseline levels during the time window between end of chemotherapy and surgery.

This decline in cardiorespiratory reserve means that some patients may not be deemed fit enough to proceed to surgery and therefore a proportion of high-risk patients might not be given the option of neoadjuvant chemotherapy due to concerns that the deleterious effect of the treatment may render them unfit to proceed to surgery. Prehabilitation could provide a method for reversing this impact or preventing the decline in fitness.

West et al. conducted a feasibility and pilot study on a cohort of patients with advanced rectal cancer receiving neoadjuvant chemoradiotherapy [180]. They compared 22 patients who received an exercise programme after they finished neoadjuvant treatment (but prior to surgery) with a control group of 17 contemporaneous patients without any prescribed exercises. They demonstrated that within six weeks the exercise group significantly improved their anaerobic threshold by 2.1 $ml.min^{-1}.kg^{-1}$ whereas the control group values remained unchanged. These results are very promising and bring hope that preoptimization of cardiopulmonary reserve in this group of patients might be possible.

1.9.4 Key concepts of prehabilitation

It is clear that prehabilitation may have a major role in elective surgery. Patients that are planned for major elective surgery, are likely to have sufficient time to permit optimisation of their fitness. Although some changes in fitness have been reported after four or even two weeks of exercise [181], there are areas of elective surgery where adopting prehabilitation is challenging. A good example of this are patients with cancer where the emphasis in the treatment pathways is on the quick treatment of malignant disease. There are however some treatment strategies for various cancer types where chemotherapy is used in the neoadjuvant setting. This strategy provides a window of opportunity where prehabilitation can be adopted. A new diagnosis of

cancer is an important teachable moment [182] for patients where motivation is high, new habits can be embraced and patients have got the opportunity to play an active role in the preparation for their surgery.

Multiple authors stress the importance of individualising prehabilitation, therefore an initial assessment of patients is needed [161, 183]. Age, physical fitness, social status, comorbidities, disabilities and previous exercise behaviour are all important factors which have to be addressed when exercise programmes are prescribed. A baseline period of monitoring is advisable as this time acts as an observation period where information mainly about routine physical activity can be obtained.

The majority of studies employ the use of aerobic exercises in combination with resistance training. Some researchers use other modalities. IMT is used mainly in thoracic surgery regimens. Many investigators emphasize importance of nutritional advice. Li et al. found that only when their prehabilitation aerobic regimen was enhanced by other modalities like psychological and nutritional support did this lead to the improvement in cardiopulmonary fitness [160].

1.9.5 Frequency, intensity, time, type, volume and progression

It is unclear what is the best prescription in terms of how often, how much, and how intense exercise should be. As already mentioned, every individual has different needs. The current evidence is very heterogeneous and there are many studies with a variety of different exercise programmes reported which can lead to success. There is a dose related benefit from the exercise which means that the more exercise patients do, the more stress is put on their bodies and adaptations to higher fitness can occur. Clearly some exercise is still better than no exercise [147] at all and therefore for some patients who are sedentary even a small amount of increased physical activity can lead to the improvement of their fitness. Patients who are inactive and sedentary might experience the most benefit from prehabilitation. Progression of exercise intensity is another important consideration when programmes are designed as the body adapts to the current level of exercise stress, and in order to achieve a continuous improvement in fitness, there has to be ongoing increment in intensity [150].

Hughes et al. in their systematic review of prehabilitation before major abdominal surgery reported the length of programmes to be between two to six weeks [170]. Weekly frequency of

exercises varied between daily exercise to once a week session. Similar findings were reported in a systematic review looking at prehabilitation of gastrointestinal cancer patients by Vermillion et al. [171]. These authors also reported that single session duration of the studies included in their systematic reviews ranged from 20-60 minutes. Authors are rarely specific when reporting what type of aerobic exercise patients are asked to do. This applies mainly to home-based regimes. For a supervised hospital-based regimen, treadmills or stationary bikes are commonly used.

The majority of preoperative exercise programmes focus on achieving moderate-intensity prescriptions. There are however some new strategies which employ exercises at higher intensities.

1.9.6 High intensity interval training

Many of the researchers were inspired by sports science when adopting preoperative exercise strategies. This led to the use of similar strategies which are used in the training of professional athletes. High intensity interval training (HIIT) can be defined as a programme which utilises brief bouts of intense exercise and rest or active recovery periods in between them [63]. Actual prescriptions of intensity vary but the typical prescription would be an exercise performed at the intensity of more than 90% of maximal heart rate [63].

HIIT can lead to a significant improvement in the fitness in a relatively short time [184-186]. There is however a question of whether the similar strategy which is primarily used for healthy individuals like professional athletes can be used to exercise cancer patients. The ability to tolerate high intensity (even when relative rather than an absolute measure of intensity is used) by patients whose baseline fitness is far worse, who are frail and sarcopenic and who are fatigued from undergoing treatment like chemotherapy is debatable. Intense physical efforts are necessarily followed by fatigue and this can also have a negative impact on patients' willingness to participate in this form of training [187].

There is no doubt that adopting HIIT requires significant resources. Patients need to be supervised by a trained physiotherapist/physiologist. Equipment needed for this type of training usually includes stationary exercise bikes or treadmills but also devices required to monitor intensity of exercise which adds to the total cost of these regimens. It seems very unlikely that HIIT training can be effectively used by patients at homes.

1.9.7 Home-based vs hospital-based exercise

There are two main approaches on where to exercise patients. It is not clear so far if it is better to prehabilitate a patient in the hospital or gym under direct supervision or at home with distant supervision or no supervision at all. Hospital-based exercise regimens require more resources, but some proponents feel that this type of programme could provide a more intense "HIIT-like" effect and therefore produce better results [63].

Home-based regimens, in contrast, do not require multiple visits to hospital and costly staff input. Qualitative research on a group of 52 cancer patients undergoing prehabilitation [188] showed that the preferred method of exercise was home-based and the biggest barrier to participation was related to transportation. So far there are no trials looking at the difference between these two approaches. It seems to be the case that some sort of supervision will always be required in order to keep patients motivated [189].

1.9.8 Compliance and adherence of prehabilitation

There have been various data published with regards to the compliance of both home-based and hospital-based exercise. Some authors have reported compliance to home-based programmes for cancer patients as low as 16% [159] but also as high as 98% [190]. Data varies significantly. This is related to the high heterogeneity of the prehabilitation programmes and also due to various definitions of the compliance which differ from willingness to participate to accurate monitoring of attendance of each session or achievement of exercise targets. Patients with higher baseline cardiopulmonary fitness tend to be more adherent to exercise regimen as observed in one study [191]. Also, adherence led to better outcome of exercise regimen. Prehabilitation for cancer patients can also make use of the power of a teachable moment mentioned previously. Prehabilitation allows patients to be more actively involved in their treatment. It has been suggested that behavioural techniques and interventions as part of prehabilitation regimens can potentially lead to better compliance and consequently better outcomes of treatment [192].

1.9.9 Ideal regimen

The ideal prehabilitation regimen is yet to be established. This also applies to the target population. However, it is clearly important for cancer patients as these are commonly malnourished, cachectic and sarcopenic. It is evident that generalizability of the regimen will

not be possible, and the regimen will have to be not only disease specific but also specific to every individual if the greatest effect of the prehabilitation is to be achieved.

Chapter 2. Developing the ChemoFit study

Prehabilitation regimens have been the focus of research to improve patient outcomes in recent years for several reasons. Surgical treatment of advanced oesophago-gastric adenocarcinoma is associated with high morbidity and mortality. Patients with oesophago-gastric cancer undergoing neoadjuvant chemotherapy experience a significant and sustained reduction in fitness during this treatment, which not only affects both daily activities and quality of life, but also decreases the physical reserve of the patient before they undergo major surgery. Poor fitness can lead to development of postoperative complications. It can also make it harder for patients to recover from the complications or suffer a more profound impact of complications. Complications are associated with worse quality of life in the short-term and a worse prognosis. Poorer fitness and an inability to recover from complications can potentially delay or prevent administration of any planned adjuvant chemotherapy, and consequently this may impact on overall prognosis.

If cardiorespiratory fitness prior to surgery is related to postoperative outcomes, it must be hypothesised that improving fitness will lead to improvement of postoperative outcomes. Preventing complications may improve surgical outcomes and patient health or survival from oesophago-gastric cancer. This is the aim of prehabilitation interventions described in the previous chapter. In addition, exercise may have beneficial effects on improving immune surveillance and reducing inflammation; reversing abnormalities that may be associated with tumour recurrence and growth.

This has fuelled interest in developing this type of intervention that can ultimately be incorporated into the usual treatment pathway for patients at NOGU in Newcastle upon Tyne, UK. Several requirements that were considered to be important for the local population and institutional facilities were formulated in designing this prehabilitation regimen. A regimen which would be applicable to the local patient population needed to be developed.

There was a desire to avoid high intensity exercise interventions. These have already demonstrated the ability to prevent the decline in health observed in other patient groups undergoing chemotherapy [184-186]. However, these programmes require large personal and financial resources. There is no evidence that they can be instituted in larger patient cohorts and

are largely impractical within the National Health Service (NHS). The aim was for this regimen to be low cost and achievable at home or remotely from a tertiary referral centre (NOGU).

The ChemoFit study was then designed to test safety and feasibility of this prehabilitation regimen on a small group of patients. The secondary aim was also to explore the effect of this regimen on cardiorespiratory fitness and sarcopenia as this might provide information about the effectiveness of this regimen. This would enable statistical power calculations and justify funding for future studies.

2.1 Designing the intervention

2.1.1 Population

The majority of patients with potentially curable oesophago-gastric cancer, present with locally advanced disease. As such, the optimum treatment to achieve "cure" involves neoadjuvant treatment (with surgery). This group was therefore decided to be the target population. Neoadjuvant treatment also presents a time opportunity to employ prehabilitation regimens as explained in the previous chapter. Furthermore, a local study with a similar target population has demonstrated that neoadjuvant chemotherapy has a deleterious effect on patients' fitness.

As already mentioned, many of the inclusion criteria were chosen in order to mirror the target population of the previous study at the unit [179]. In order to have a homogenous group of patients undergoing similar neoadjuvant treatment and therefore reduce confounders, patients with SCC were decided not to be included. This study was not intended to investigate any postoperative outcomes and therefore, it was decided that, both tumours of the oesophagus and tumours of the stomach should be included.

The recent FLOT4 study [40] has led to a change in the type of neoadjuvant chemotherapy that is now regarded as the first-choice regimen for patients with ACA of stomach and OGJ. At the time of the recruitment into the ChemoFit study especially patients with ACA of oesophagus tended to receive treatment with ECX or ECX variant. Both chemotherapy regimens were therefore included in the ChemoFit study.

2.1.2 Study type

The ChemoFit was designed as a feasibility study due to pragmatic reasons. It was needed to be established whether it is actually feasible to run this intervention from a unit and patients' perspective. It was not known whether patients would be interested in such an intervention and whether they would comply with it.

2.1.3 Primary and secondary outcomes

The main hypothesis question stood as:
'Will patients participate in a home-based exercise programme during and after neoadjuvant chemotherapy for oesophago-gastric cancer?'

Secondary outcomes were chosen to see if this prehabilitation regimen has any impact on cardiopulmonary fitness, sarcopenia and quality of life. Only a regimen that is feasible and effective could potentially be embedded into clinical practice.

2.1.4 Intervention

The exercise intervention was developed with the help of exercise physiologists and physiotherapists from Newcastle University with prior experience in developing exercise interventions within a research setting. The aim was to have a relatively simple and low-cost intervention which could be carried out without supervision and without a need of frequent hospital visits. It was decided that an intervention based around improving daily step count could be both achievable and well-tolerated by this group of patients. This intervention was inspired by a previous study from Newcastle University on patients with chronic heart failure [193].The importance of patients' individualisation, a term much mentioned in previously published prehabilitation studies, was also strongly considered. Strengthening exercises were chosen to reverse the negative impact of chemotherapy on muscle mass. Exercises were chosen to be simple, easy to follow and to comprise all major muscle groups of the body.

Previous successful prehabilitation studies were also inspirational in the process of the development of the ChemoFit intervention and its monitoring. It was decided that weekly telephone reinforcement and encouragement is the key part of this intervention. The research team relied on the patients' self-reported activity recording and monitoring. Telephone conversation was decided also to be used for physical activity data collection.

The ChemoFit study design was developed by me with the help of my supervisors and other specialists involved in the care of the patients with oesophago-gastric cancer. Surgeons, anaesthetists, oncologists, physiotherapists, psychologists, cancer nurse specialists and local research nurses were all approached, and the key areas and design was discussed with them. The research and development team of Newcastle upon Tyne Hospitals NHS Foundation Trust was involved in the design and the process of costing the study. The Trust acted as the research study sponsor.

I conducted a thorough literature review of the management of the oesophago-gastric cancer, importance of the cardiopulmonary fitness of surgical patients and prehabilitation (this is summarised in Chapter 1 of this work). My knowledge gained in this process was instrumental in the ChemoFit study design development.

2.2 Patient and public involvement (PPI) in study design

I have conducted the following PPI activity during the design process of the ChemoFit study.

2.2.1 PPI activity 1

A group of oesophago-gastric cancer survivors were approached at the local Northern Oesophago-gastric Cancer support group session held at the Maggie's Centre which is a branch of a national cancer charity. Results of previous work performed at NOGU looking at the impact of neoadjuvant chemotherapy on cardiopulmonary fitness were presented.

The ChemoFit study was also discussed with these patients. A presentation of the proposed study was given, and this was followed by discussion. Questionnaires were circulated. Patients were asked to reflect on their experience during chemotherapy and focused mainly on topics like fitness and exercise. Ideas and comments about this study were sought.

All the patients (14 out of 14 answering this question) felt that the proposed research is patient centred and (14 out of 14 answering this question) said that they supported this as an important area of work. All the patients (12 out of 12 answering this question) agreed that if they had been in the position of awaiting surgery again, they would have liked to participate in such a study. Additional time required attending extra tests, sessions and the time needed to spend complying with the study protocol was found to be acceptable by all responders (14 out of 14 answering

this question). The majority of patients (13 out of 14 answering this question) suggested that the best exercise activity to be employed was walking. A number of other activities were suggested, and it was agreed that these could be substituted into the regimen if so desired. The majority (8 out of 11 answering this question) of survivors stated that the prescribed amount of exercise intervention is realistic and achievable.

2.2.2 PPI activity 2

Multiple patients recovering from resectional surgery for oesophago-gastric cancer were approached on a postoperative surgical ward at the RVI, Newcastle upon Tyne. The idea of prehabilitation and the study was introduced to them and they were asked about their fitness levels prior to diagnosis, during neoadjuvant chemotherapy and after this, but prior to surgery. Their opinion was sought regarding the feasibility of this study and about their willingness to participate if they had the opportunity to choose this programme prior to their surgery. Again, all patients confirmed that neoadjuvant chemotherapy had a detrimental effect on their activity levels, and they would have considered this programme in order to be a fitter. All patients confirmed that they would be happy to wear pedometers every day and attend hospital for an extra CPET and education session. Some of the patients regretted that this research had not been proposed to them.

2.3 Health research authority (HRA), Research ethical committee (REC) approval, study funding

The Principal investigator of the ChemoFit study together with myself completed the Integrated research application system (IRAS) application form in order to obtain research and ethical approvals to conduct the study. The Trust agreed to act as a study sponsor after the review of the ChemoFit study design and appropriate documentation. The IRAS application form was submitted and shortly after that I attended a REC meeting via a teleconference in December 2018. Minor changes to the documentation were suggested by the ethical committee panel members. These were addressed satisfactorily and in January 2019 HRA approval to the ChemoFit study was granted. This was again reviewed by study research sponsor and on 28th February 2019 the ChemoFit study was opened for recruitment. Funding for the study was obtained via successful grant application to Jon P Moulton Charitable Foundation. The finance of £111,031.26 was obtained on 29th January 2019.

Chapter 3. Methods

3.1 Study design

The ChemoFit study was a prospective, single group, single centre study which investigated the feasibility of a home-based exercise intervention during the oncological treatment of patients presenting with operable advanced adenocarcinoma of the oesophagus, oesophago-gastric junction and stomach. Patients were invited to participate in the study which involved provision of a home-based exercise intervention before, during and after neoadjuvant chemotherapy, in the weeks leading up to surgical resection of the cancer.

3.2 Sample size

A sample size of 40 participants was selected in accordance with previously published recommendations for feasibility studies [194, 195]. Further, this was thought to be an achievable number of patients to recruit within the 12 months. Approximately 130 patients undergo oesophago-gastric resections each year for cancer at the NOGU. It was estimated that 70% would be eligible to take part in the study (i.e. will receive preoperative chemotherapy for adenocarcinoma). A sample size of 40 realistically represented the number of patients that were expected to be recruited in a year.

3.3 Inclusion criteria

- Operable adenocarcinoma of the oesophagus, oesophago-gastric junction and stomach (locally advanced adenocarcinoma with planned preoperative chemotherapy, T3+, T1/2 N+)
- Planned preoperative chemotherapy with ECX, ECX variant or FLOT chemotherapy
- Age >18
- Ability to complete CPET
- Ability to consent to study and carry out the planned intervention

3.4 Exclusion criteria

- Standard contraindications to CPET testing as defined by American Thoracic Society guidance [196]
- Orthopaedic limitations to CPET and / or daily exercise, for example, amputation, severe knee or hip disease
- Inoperable cancer at initial screening multidisciplinary team meeting (MDT)
- Planned non-surgical treatment with either radiotherapy or combined chemoradiotherapy
- Patients who are not for chemotherapy and are straight to surgical operation

3.5 Screening of the patients and consent process

Patients were identified during the MDT and cancer staging process at the NOGU. Suitable patients, who met the eligibility criteria, were provided with a patient information sheet (PIS) explaining the study. They were consented for the study after the finalised oncological treatment plan has been agreed by the MDT and discussed with the patient. By providing a PIS early in the staging process patients had sufficient time to consider their participation in the study and ask questions. All eligible patients were approached, and their participation was completely voluntary: they were able to withdraw consent at any point during the study. Patients who had not agreed to take part in the study by the time they started their first chemotherapy session were not be eligible to participate.

During the first study enrolment meeting, informed, written consent was obtained prior to any study procedures. This was conducted in line with the Trust Research and Development policy and standard operating procedures and in line with Good Clinical Practice. Each patient was asked to complete baseline QLQ-C30 and QLQ-OG25 quality of life questionnaires (see later). The handgrip strength of their dominant hand was measured using grip strength dynamometer (T.K.K. 5101 GRIP-D, Takei scientific instruments Co., Ltd., Japan). Participants were provided with a simple, easy to use pedometer (Walking style One 2.1, Omron Healthcare UK Ltd., UK), resistance band (BodyMax resistance tube, BodyMax Ltd., UK) and exercise diaries. Participants were given an option to choose between two strengths of resistance tubes, medium or easy resistance. This allowed greater individualisation of the strengthening exercises according to patient needs. They received information about what the exercise intervention

involves and were taught how to use the pedometer, resistance band and exercise diaries. The Borg scale was explained to them. Those patients who declined to participate were asked if they were happy to provide the reason for their decision, and if so what the reason(s) were.

Figure 5 Pedometer used by the ChemoFit study participants.

3.6 Primary outcomes

The primary outcomes for this study examined feasibility:

1. Recruitment rate, defined as the proportion of all patients approached that agreed to enter the study.

2. Completion rate, defined as the proportion of all patients who entered the study that remained participants at the end of the defined study period.

3. Individual compliance with the intervention, defined as the percentage of intervention days when the patients were wearing their pedometer, whether they were contactable every week, and whether they were recording their daily step count.

3.7 Secondary outcomes

Secondary outcomes are listed in the table 4.

CPET measurements	Change in VO_2peak (defined as max VO2 during last 30 seconds load exercise at CPET) Change in VO_2 at AT (defined as VO_2 at respiratory AT using V slope method)
Sarcopenia	Change in amount of L3 level skeletal muscle area determined on CT scan by methodology described by Perthen et al. [197] Change in fat composition and volume measured by CT scan Change in grip strength
Exercise intervention	Change in daily step count from pedometer each day
Health related quality of life	Quality of life using QLQ-C30 and QLQ-OG25 questionnaires

Table 4 Secondary outcome measures of the ChemoFit study.

3.8 Intervention

3.8.1 Baseline measurement

Once enrolled in the study, participants entered a six- or seven-days period (depending on the day of the week when consent was obtained) of monitoring using a simple pedometer to monitor their habitual daily step count. This initial period was used to establish the baseline activity and to calculate each individual's median daily step count. This is referred to as the baseline daily step count.

3.8.2 The exercise intervention

The exercise intervention started immediately after the end of the baseline observation week had been completed. The exercise continued during neoadjuvant chemotherapy but also after completing neoadjuvant chemotherapy until surgery was undertaken or change of treatment plan was established.

The intervention was individualised to every single patient based on their baseline level of activity (as recorded by a pedometer during the first week of observation), age, general health, motivation and social circumstances in order to achieve greatest improvement in their cardiopulmonary fitness.

The intervention initially involved a prescription of target daily step count which was 2000 steps above the median baseline daily step count. This increase in step count was meant to be

achieved by walking or jogging at moderate intensity for a target of 30 minutes per day, each day. Patients were instructed in how to achieve moderate intensity activity using the modified Borg rating of perceived exertion (RPE) scale aiming for achieving the levels between 3-4, moderate to somewhat strong (copy of modified Borg scale in Appendix 7.6). This was to ensure that the intensity at which these 30 minutes bouts were prescribed was maintained throughout the exercise period.

Participants were instructed that pedometers should be worn all the time during the day. These were usually attached to the waist of study participants if possible. Patients were allowed to remove them when sleeping or when showering/bathing. Each participant was asked to record their daily step count every day before they go to sleep and write this down in an exercise diary. The pedometers stored a 7-day record of the daily step count achieved.

After the first week of the exercise intervention patients were contacted by me or by research occupation therapist. Their exercise data were collected. They were supported and given an option to maintain or to increase their step count further if they felt that they had managed to achieve the prescribed number of steps. The same approach was used after each week of the intervention. The outline of this is described in the figure 4.

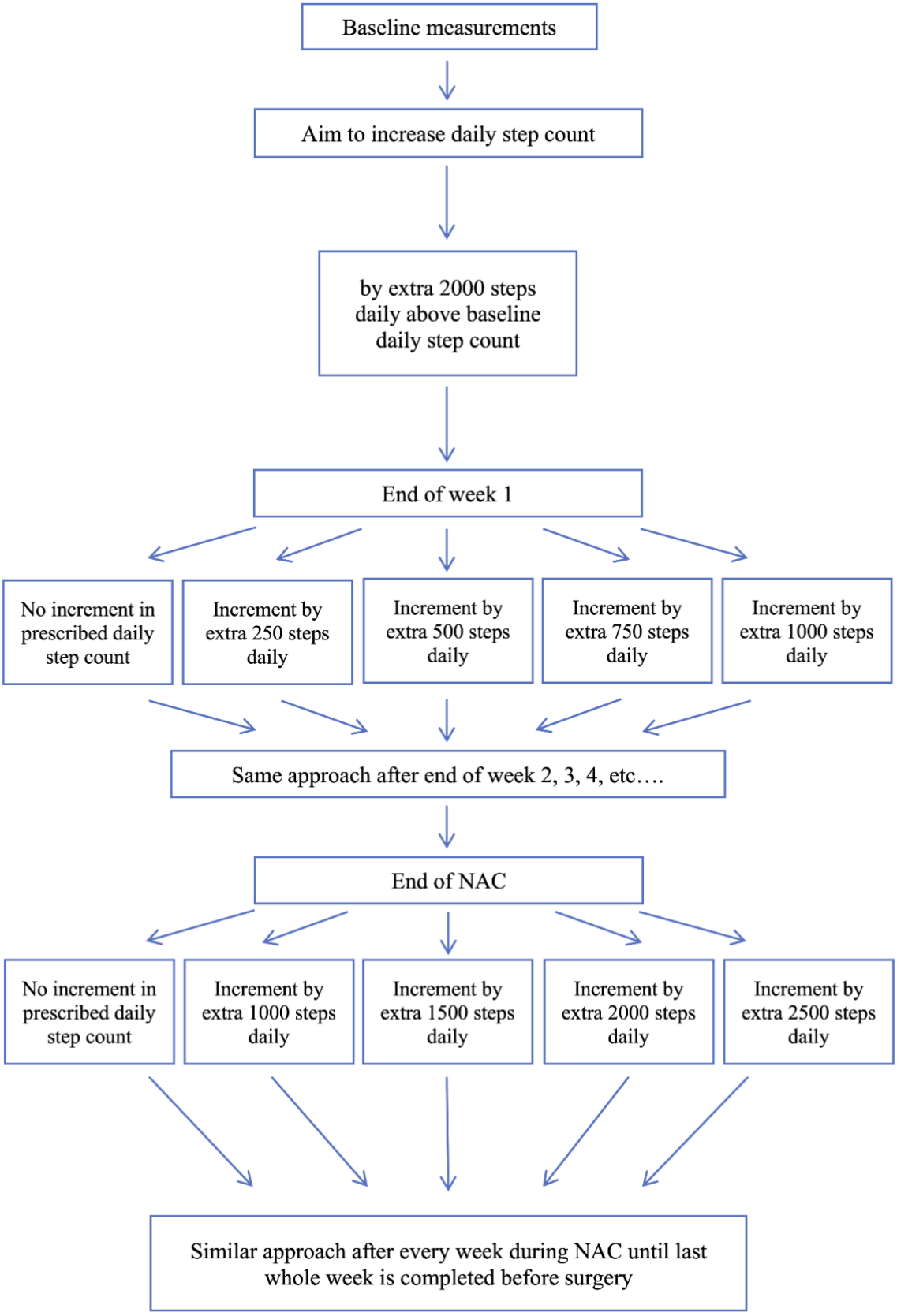


Figure 6 Flow diagram of the ChemoFit step count prescription.
NAC, neoadjuvant chemotherapy.

Participants were also encouraged to perform other physical activities such as jogging, swimming, cycling or group activities if they wished and were able to.

Patients' progress was monitored in diaries using a daily log. Diaries were given to patients upon enrolment. Participants were asked to record the prescribed step count for each week, daily step count at the end of the day, whether a 30-minute bout of walking/jogging activity had been performed and whether this was performed at the prescribed modified Borg rate (3-4), any other exercise activities performed that day and whether the prescribed strengthening exercises (7 times a week) were completed that day or not (example of the diary can be seen in Appendix 7.4).

After completion of neoadjuvant chemotherapy, seven days after the last oral chemotherapy tablet (ECX or ECX variant regimen) or seven days after last infusion (FLOT regimen), a further enhanced increase in the daily step count target above the current step count target was implemented if the participant agreed to this. The amount was based on current progress and again this was individualised. This increment period lasted until the surgery or until the change of treatment plan was established. This period usually lasted 4 to 6 weeks and on each of these weeks there was again an option to further increase the step count target (see flow chart).

3.8.3 Interim analysis

Once the first ten participants had completed the first week of the exercise regimen during neoadjuvant chemotherapy an interim analysis of their achieved daily step count was performed. Based on conditions previously described in the study protocol, the initial increment was lowered from 2000 steps to 1000 steps above the baseline daily step count for all participants recruited after the interim analysis. For more details about the interim analysis, see the results chapter. This strategy was chosen to 'fine adjust' the initial step increment after the first observation week as it was difficult to predict how demanding this increment was going to be for patients, especially in the context of starting chemotherapy treatment.

3.8.4 Strengthening exercises

Strengthening exercises formed a further part of the exercise intervention. Strengthening exercises were prescribed to be performed every day, 7 days a week, and started after the end of the baseline observation week had been completed. Patients were supplied with resistance

bands with handles. They were educated on how to perform two repetitions of five simple exercises, each for one-minute duration. This equates to 10 minutes of strengthening exercise in total each day. Each exercise was prescribed at two levels of difficulty in order to tailor them to individual fitness. Patients recorded whether the full session was performed in their daily diaries (see Appendix 7.4).

3.8.5 Sit to stand/wall squat

Patients were instructed to perform two bouts of this exercise, each lasting for one minute. They were asked to repeatedly stand from a chair and then slowly sit back down. If possible, the exercise was meant to be completed without using their arms to push up from the chair. A more difficult level of this exercise was to perform a wall squat with their back against a wall for stability. This should be held for one minute and repeated twice (see pictures in Appendix 7.7).

3.8.6 Biceps curls

Patients were instructed to perform this exercise for a duration of one minute using both arms for two bouts. Patients performed the biceps curls while sitting or standing. The easiest level of difficulty was to perform this with a light resistance band. The most difficult level was to perform this using a medium resistance band. The band was secured under the patient's feet using their body weight to hold it whilst performing the exercise and the biceps curls were performed as slowly as possible keeping tension on the band throughout the movement (see pictures in Appendix 7.7).

3.8.7 Upright row

Patients were instructed to perform two bouts of this exercise, each lasting for one minute while standing. Again, this exercise was performed using two levels of difficulties, as with the other exercises (with a light resistance band or with a medium resistance band). See pictures in Appendix 7.7. The upright row was performed as slowly as possible keeping tension on the band throughout the movement.

3.8.8 Leg abduction

Patients were instructed to perform this exercise for one minute on each leg. This exercise was performed using two levels of difficulties: with a resistance band or without it (see pictures in

Appendix 7.7). The leg abduction was performed as slowly as possible keeping tension on the band throughout the movement.

3.8.9 Wall press

Patients were instructed to perform two bouts of this exercise, each lasting for one minute. The patient placed their hands on the wall in front of them and then slowly lowered their upper body to the wall then used their arms to push back into an upright position. To increase the difficulty the patient was instructed to move their feet further away from the wall. See pictures in Appendix 7.7.

3.8.10 Reporting, reinforcement and encouragement

Once a week a member of a research team (my research colleague or myself) contacted each study participant in order to support the patient, reinforce the programme, monitor activities and exercises and collect previous week's data.

Participants were encouraged to reflect upon the previous week's achievements and discuss any problems or factors which inhibited progress. This was recorded. Patients were given the opportunity to increase their daily target for the next week if they felt that this was achievable or appropriate.

3.8.11 Completion of study

Participants were asked to attend the CPET laboratory 1-14 days prior to their scheduled operation. During this time CPET was performed. Participants also completed an end of study questionnaire and quality of life questionnaires. Their handgrip strength on the dominant hand was measured and the end of study blood sample was obtained. If the surgery was rescheduled at a short notice and participant has already completed end of study testing, these tests were not repeated again.

Patients continued with their exercise programme until the end of the last full week prior to their scheduled surgery. Patients whose treatment plan was changed based on the MDT decision or patients' choices and did not proceed to surgery stopped their participation in the study. This came into effect when MDT decision was conveyed to patient.

Patients who withdrew their consent during the study stopped their participation with immediate effect when the research team member was notified.

After the surgery, when fully recovered, participants were invited to share their ideas and thoughts related to the study during the Focus group session. Attendance was voluntary. Timing of this session was chosen to make this suitable for multiple study participants at one time.

3.9 Outline of the study

The study schedule is outlined in figure 5.

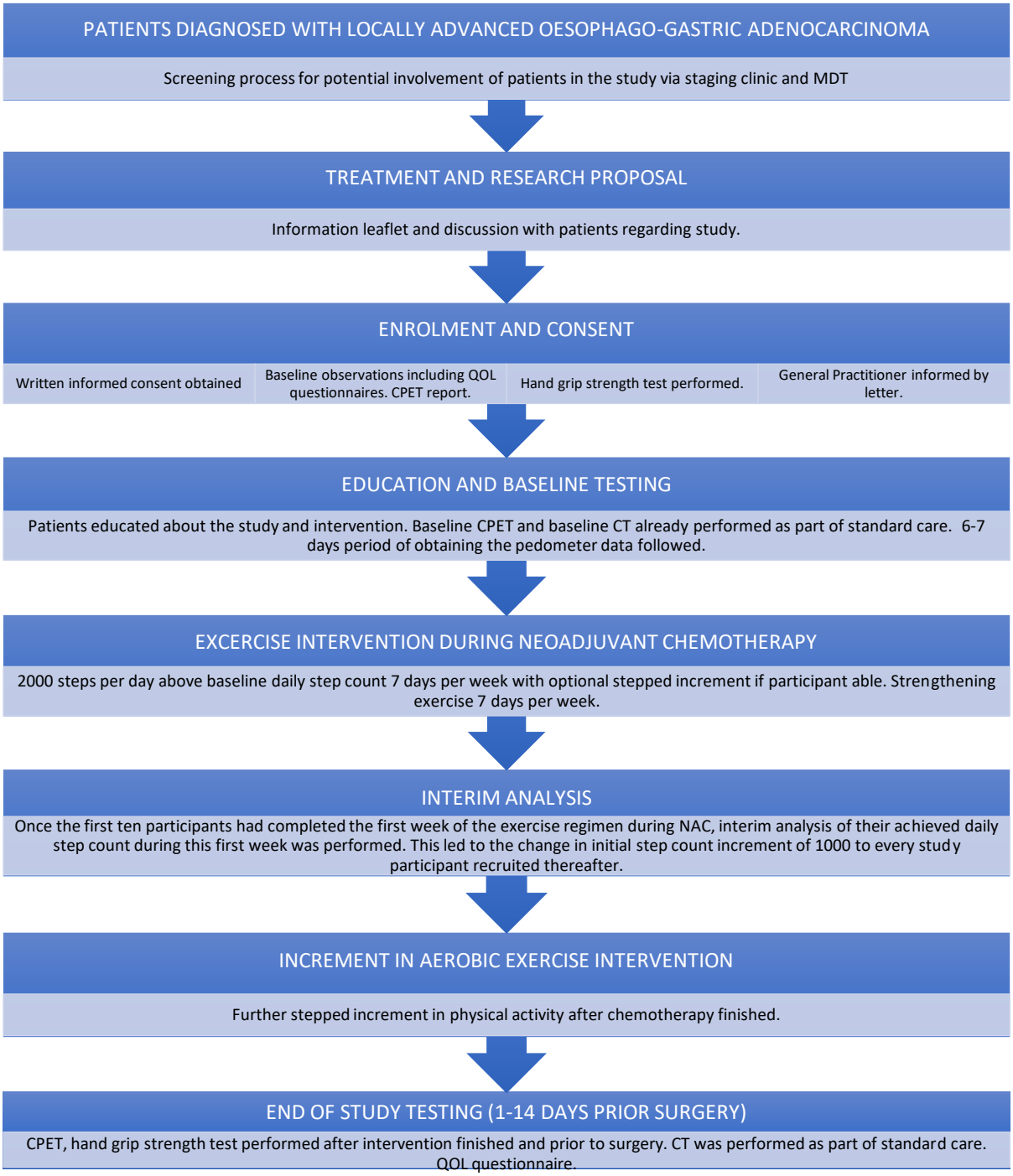


Figure 7 Outline of the ChemoFit study.
MDT, multidisciplinary team. QOL, quality of life. CPET, cardiopulmonary exercise testing. NAC, neoadjuvant chemotherapy.

3.10 Collected data

Data collected during the study are mentioned in table 5.

Category of collected data	
Demographic data	Age, sex, distance between home address and NOGU, weight, height, BMI, list of co-morbidities, smoking status, site of the tumour, clinical stage of the disease according to TNM classification of malignant tumours, 8th edition [28, 29]
Screening data	Date of consent, reason for non-enrolment, withdrawal date, withdrawal reason
Exercise intervention	Duration of exercise intervention, engagement with weekly phone call, daily step count, aerobic 30min bout completion, Borg target achieved/not achieved, strengthening exercise session completion, other physical activities performed
Chemotherapy data	Chemotherapy regimen, number of cycles, start date of chemotherapy, completion chemotherapy date
Physiological data	Resting heart rate, baseline pulmonary function tests (FVC, FEV1, FEV1/FVC ratio)
CPET data	Achieved AT (ml/kg/min), achieved VO_2peak (ml/kg/min), VE/VCO2 at AT, CPET date
Sarcopenia	Date of staging CT scan, date of re-staging CT scan, skeletal muscle index, lean body mass, grip strength, total subcutaneous fat area
Health related quality of life	EORTC QLQ-C30 and QLQ-OG25 questionnaires

Table 5 Data collected during the ChemoFit study.

3.11 Measurement of the exercise intervention: primary outcomes

3.11.1 Measurement of recruitment

Patients who were suitable for this study and passed all the inclusion criteria were invited to participate. If they declined participation because of personal, psychological, sociological, geographical or any other reasons, this was recorded. Recruitment rate was therefore defined as: (total number of patients included in the study) divided by (total number of patients deemed suitable for neoadjuvant chemotherapy followed by surgery by MDT who met the inclusion criteria of the study and who were asked to consider participating).

3.11.2 Measurement of compliance

At the end of the study the compliance of each patient was calculated based on contemporaneously collected data from participants' diaries. Individual compliance was defined as the percentage of intervention days when the participant wore their pedometer, was contactable (every week) and was recorded their daily step count.

3.11.3 Measurement of completion

At the end of the study the completion rate was calculated as the proportion of all patients that entered the study that remained participants at the end of the defined study period.

3.11.4 Measurement of step count

Step count during the period when patient was receiving chemotherapy was compared with the period after the chemotherapy but before the end of patient's participation in the study. Comparison was also made between the achieved step count and prescribed step count.

3.12 Measurement of cardiopulmonary fitness and lung function

CPET is a non-invasive stress test that allows determination of individual oxygen uptake (VO_2). It can be used to objectively quantify fitness through the determination of a reproducible, achievable measurement – AT. Research CPETs were all performed by myself after I had completed training in how to conduct this test. I was trained by an experienced CPET practitioner who routinely conduct exercise testing in the Trust before I started to conduct research testing.

3.12.1 Timing of CPET

Patients had their first CPET performed during the staging process and this was part of normal clinical care. The second CPET was performed as a research test 1-14 days prior to surgery except for the following cases. Patients who received FLOT chemotherapy had their second test performed close to their surgery date as this was part of normal clinical care. Some patients who received ECX or an ECX variant chemotherapy had their second test performed as a part of routine clinical care if this was decided by a consultant anaesthetist. In these cases, another research CPET was not performed again. One patient who received FLOT chemotherapy underwent post neoadjuvant chemotherapy CPET and as the results of this test were unsatisfactory for the patient to safely proceed to surgery, it was decided that surgery should be postponed by 4 weeks. As per the protocol he continued on his programme until he completed the last whole exercise week prior to surgery. A repeat CPET was planned as part of his routine clinical care (see Results section for more details).

3.12.2 Equipment and calibration

Analysis of gas exchange during the CPET was performed using metabolic cart Ultima CPX™ metabolic stress testing system (Ultima Series; MGC Diagnostics, Saint Paul, Minnesota, USA).The participants cycled on the Ergoselect 200 cycle ergometer (Ergoline GmbH, Germany). Calibrations of the preVent TM pneumotachograph was performed with a 3L syringe before each testing session. The oxygen and carbon dioxide analysers were routinely calibrated with standard gases. Each test was conducted according to unit's standard protocol, based upon that described by Older [71].

3.12.3 Cardiac monitoring and spirometry

Prior to the test, a resting 12-lead ECG was obtained. During the exercise test 12-lead ECG monitoring with ST segment analysis was performed continuously as well as pulse oximetry (Welch Allyn, Skaneateles Falls, New York, USA). Following this, participants performed three spirometry attempts of maximum inspiration followed by maximum expiration. This was performed to obtain baseline pulmonary function.

3.12.4 Ramped exercise protocol

Resistance in terms of work rate increase per minute on the cycle ergometer after an initial three minutes of un-ramped pedalling was chosen, so as to be the same as during the first clinical CPET. Values ranged between 15-30 watts per minute. Participants were instructed to maintain a cadence of 55-65 revolutions per minute throughout the test. Each test was terminated when the participant had either reached their peak exercise ability (VO_2peak), reached exhaustion (such as due to breathlessness), fatigue, pain or if a clinical indication to discontinue testing was met.

3.12.5 Data analysis

Breeze SuiteTM software (Ultima Series; MGC Diagnostics) was used to obtain the VO_2peak, AT and VE/VCO_2 and total oxygen consumption values. AT was analysed using the V-slope method [198]. These tests were not analysed until the end of the study. Tests were interpreted by two experienced consultant anaesthetists who routinely interpret these tests for clinical use. The first staging CPET of all participants which had already been reported for clinical use was re-analysed. Both anaesthetists were blinded to participants' identifiable data and whether this was the pre- or post-intervention test. This was to reduce observation bias.

3.13 Measurement of sarcopenia

3.13.1 CT assessment of sarcopenia

CT scans which were part of routine clinical care for participants in the study were used to assess and quantify muscle mass and therefore sarcopenia changes prior to and after the intervention. The first CT scan used was that from the initial staging process. If there were multiple CT scans performed during staging process, then CT scan performed closer to the consent data was chosen for analysis. The second CT scan used was the restaging CT scan after neoadjuvant chemotherapy had finished. Sarcopenia analysis was performed by myself after being trained by a radiologist with expertise in this analysis. Image manipulation research software package under development by HERMES (Hermes Medical Solutions AB, Sweden) was used for this analysis. An axial slice at the mid-level of the third lumbar (L3) vertebra using a sagittal image for reference was selected. The region of interest was then drawn to include all skeletal muscles in the chosen slice. Voxels in the Hounsfield Unit range -29 to +150 were automatically selected in this drawn region of interest [197]. The volumes within these thresholds were then manually adjusted to remove any non-muscle groups of voxels. The muscle area (cm^2) and slice position was then recorded. This value formed the lean tissue area at the L3 level (LTA). Skeletal muscle index (SMI) was calculated as LTA (cm^2) / height (m^2). Sarcopenia was defined as SMI less than 52.4 $cm^2.m^{-2}$ for male gender and 38.5 $cm^2.m^{-2}$ for female gender in accordance with the published sarcopenia cut off points [199, 200]. LTA was also used to calculate lean body mass (LBM) in kg as per previously published formula ($LBM = 0.3 \times LTA\ at\ L3 + 6.06$) which was developed and validated against bone density scans (DXA) as standard [199, 200].

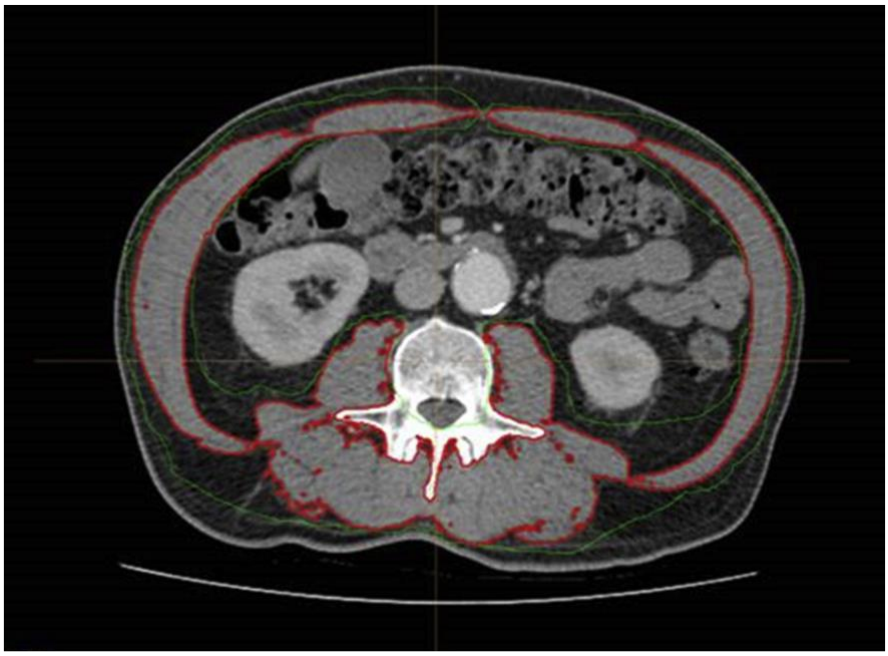


Figure 8 CT assessment of sarcopenia at the level of third lumbar vertebra. Adapted from Perthen et al. [197]. Skeletal muscle area is encircled by red colour.

3.13.2 CT assessment of the amount of subcutaneous fat

In order to assess sarcopenic obesity, assessment of the amount of subcutaneous fat at the L3 level was performed. This was performed on the same CT scans as the measurement of muscle mass using identical software. The same axial slice at the mid-level of L3 which was used for muscle mass was used to calculate subcutaneous fat mass. The region of interest was then drawn to include subcutaneous area in the chosen slice. Within this region of interest, voxels within the Hounsfield Unit range -190 to -30 were automatically selected [201]. The volumes within these thresholds were then manually adjusted to remove any non-fat groups of voxels. The fat area (cm^2) and slice position was then recorded. This value formed total fat area at L3 level.

3.14 Measurement of grip strength test

This test was used to measure loss of muscle function as a part of sarcopenia assessment. Patients were tested at baseline and then again 1-14 days prior to surgery. The patient's dominant hand was used for this test and which was performed using a hand dynamometer. The Southampton protocol was used to conduct this test [202]. Three attempts were performed and the maximum score out of these three attempts was recorded and used for analysis. Patients sat in the chair with an opportunity to rest their dominant arm at the elbow. Their wrist was kept in a neutral position (pronation/supination) with the thumb facing upwards. They were given these

verbal instructions: ‘I want you to squeeze as hard as you can for as long as you can, until I say stop. Squeeze, squeeze, squeeze stop.’ During the end of study testing I was blinded to the results from the baseline testing. Participants were never informed about their results. Results were analysed after the study had been completed in order to reduce observer bias.

3.15 Measurement of quality of life

EORTC QLQ-C30 and EORTC QLQ-OG25 quality of life questionnaires which were created by the EORTC are in combination validated to be used to describe quality of life of this group of patients. These questionnaires can be found in Appendix 7.8 and 7.9. These were given to patients to fill at the baseline timepoint and then again 1-14 days prior to their surgery. Completeness of the filled in questionnaires were checked immediately so participants could be asked to address any uncompleted portion.

EORTC QLQ-C30 consists of five functional scales and nine symptom scales. There are one to five questions per each scale. In addition to this there are two questions assessing global health status forming together another scale. Answers and therefore scores from each of this scale were linearly transformed into the final 0-100 score which was then compared before and after the intervention. Higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms. Methods describing this linear transformation are present in EORTC scoring manual [203].

Similarly, EORTC QLQ-OG25 consisting of one functional scale and fifteen symptom scales was scored and linearly transformed into 0-100 score which was compared prior and post intervention.

3.16 Statistical analysis

All statistical analyses were performed solely by me. This was performed using IBM® SPSS® Statistics version 26 (IBM, Armonk, USA). Data were collected and organised in Microsoft® Excel version 16 (Microsoft, Redmond, USA). Charts and graphs presented were constructed using either Microsoft® Excel version 16 (Microsoft, Redmond, USA) or GraphPad Prism version 9 (GraphPad Software, San Diego, USA). Patient clinical characteristics and primary

outcomes of the study are recorded descriptively. Normally distributed data are presented as a mean and standard deviations (SD) or standard error of mean (SEM). Non-normally distributed data are presented as a median and interquartile range (IQR). The Shapiro-Wilk test was used to test the assumption of normality of the data. The differences between step counts at three time points ('Step count related results') were tested using the Friedman test. The agreement between two anaesthetist who reported CPET is expressed as intraclass correlation coefficient (ICC) and 95% confidence intervals (95% CI). A paired t test was used to compare normally distributed data. The Wilcoxon matched pairs signed rank test was used for non-normally distributed data. A p value of <0.05 was deemed statistically significant throughout.

Chapter 4. Results

4.1 Recruitment process

The ChemoFit study started recruitment on 28th February 2019 with the last two patients recruited on 18th March 2020. During this time period there were 60 patients who met the inclusion criteria. There were 42 patients who were successfully recruited to the study. Three of these 42 participants had to discontinue their participation as during the initial weeks of participation they no longer met the inclusion criteria for the recruitment. In all cases this was due to the fact that subsequent investigation carried out by oncological team revealed that these three participants were not fit enough to receive neoadjuvant chemotherapy and their management plan was changed. As neoadjuvant treatment is vital component of this study, participation for these three patients was discontinued. A further three patients withdrew consent (two participants during the baseline week and one participant during the fourth exercise week). This led to 36 patients completing the study.

On 20th March 2020 a decision was made by the investigating ream that the Chemofit study should cease recruitment due to the global COVID-19 pandemic that was starting to have a significant impact on NHS treatment and medical studies in the UK. A local policy that withdrew the use of CPET in the pre-surgery evaluation of patients was made. This meant that the study failed with its initial ambition of recruiting 40 patients to the study.

4.2 Patient demographics

Of the 39 participants recruited to the study, the majority of them were male (33 participants, 84.6%) with a median age of 68 years (range 51-81, IQR 63-73). They were overweight with median BMI of 27.3 $kg.m^{-2}$ (range 19.7-41.3, IQR 25.28-31.18). The most common comorbidity was that of asthma/chronic obstructive pulmonary disease (COPD) (eight participants) followed by diabetes mellitus (five participants). The majority of participants had oesophageal or junctional tumours (32 participants, 82.1%) compared to seven participants who had a gastric adenocarcinoma. Chemotherapy using the FLOT regimen was administered to 27 participants compared to the ECX/ECF chemotherapy regimen which was administered to 12

participants. Participant demographics can be seen in table 3. The stage of their disease is presented in the tables 6-8.

	39 participants
Age, years, median (range)	68 (51-81)
Gender, male	33
BMI, kg.m^{-2}, median (range)	27.3 (19.7-41.3)
Smoking status	
Never	9
Ex-smoker >1 year	24
Current smoker	6
Comorbidities	
Asthma/COPD	8
Diabetes mellitus	5
Ischaemic heart disease	1
Atrial fibrillation	2
Heart failure	0
Cerebrovascular disease	1
Tumour location	
Middle oesophagus	2
Lower oesophagus	15
Oesophago-gastric junction	15
Gastric	7
Neoadjuvant chemotherapy regimen	
ECX/ECF	12
FLOT	27

Table 6 Characteristics of the ChemoFit study participants including participants who later withdrew consent.
BMI, body mass index. COPD, chronic obstructive pulmonary disease.

	Stage	Number of patients
T2 N1 M0	III	2
T3 N0 M0	III	5
T3 N1 M0	III	7
T3 N2 M0	IVA	5
T3 N3 M0	IVA	1
T4a N1 M0	III	3
T4a N2 M0	IVA	7
T4a N3 M0	IVA	2

Table 7 Disease stage of participants with oesophageal or junctional adenocarcinoma.

	Stage	Number of patients
T1b N1 M0	IIA	1
T3 N0 M0	IIB	1
T3 N1 M0	III	1
T4a N1 M0	III	1
T4a N2 M0	III	3

Table 8 Disease stage of participants with gastric adenocarcinoma.

4.3 Primary outcomes results

4.3.1 Recruitment rate

This was defined as the proportion of all patients approached that agreed to enter the study. There were 60 patients initially screened and thought to potentially meet the eligibility criteria. Two patients were missed and not recruited. Sixteen patients declined participation. Recruitment rate therefore reached 72.4% (42/58). Nine patients declined their participation due to distance reasons (not willing to travel for consent and education session). Of those, six patients were residents in Cumbria, the region most distant to the unit. Seven patients quoted other reasons for not taking the part in the study. Comparison of distance between patients' home and the unit demonstrated that the median (IQR) distance of those who declined participation was 41.1miles (9.9-82.6) versus 10.1miles (4.8-22.8) of those who agreed to participate and signed the consent form ($p<0.001$). Flow diagram of the study can be seen in figure 6. Reasons for not taking the part are summarised in figure 7.

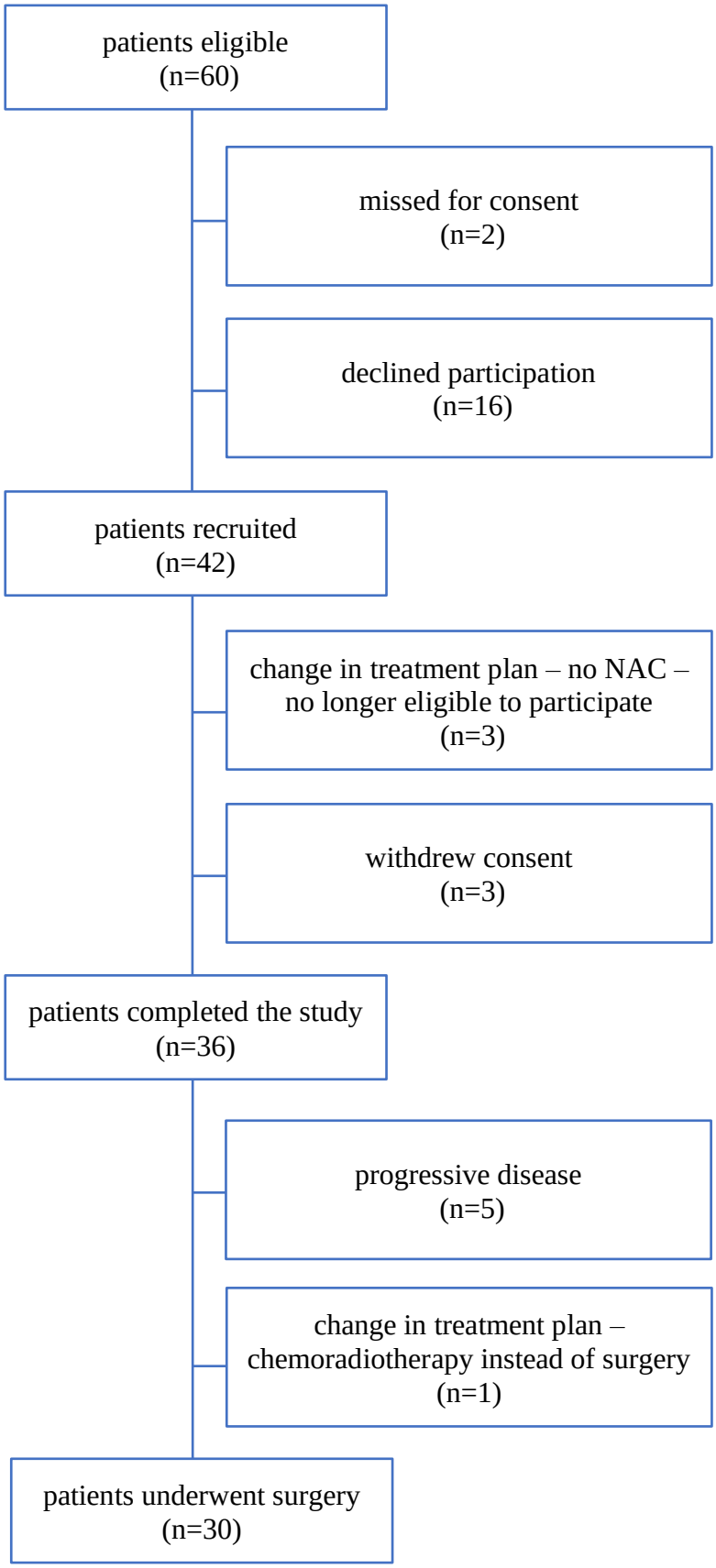


Figure 9 Flow diagram of the ChemoFit study participants.
NAC, neoadjuvant chemotherapy.

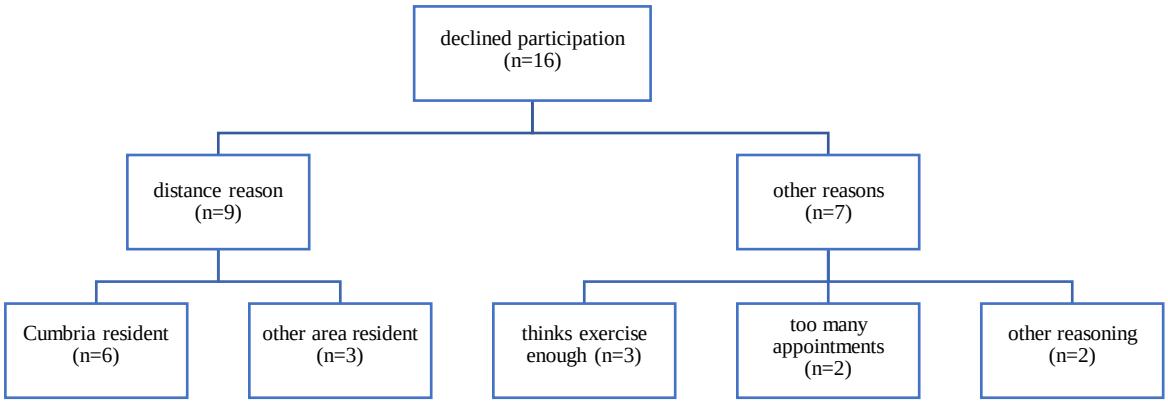


Figure 10 Reasoning for declined consent in the ChemoFit study by eligible patients.

4.3.2 Completion rate

This was defined as the proportion of all patients who entered the study and remained participants at the end of the defined study period. The completion rate was 92.3% (=36/39).

4.3.3 Individual compliance

The median (IQR) duration of the exercise intervention was 91 days (84-105). Data was acquired which permitted compliance to be recorded from 37 participants. Three participants who were initially recruited but had their treatment plan changed so that it did not include neoadjuvant chemotherapy were not included for analysis. Three patients withdrew their consent during the study. Of these two patients decided to do so during or after the baseline week and therefore no intervention data were collected, and one patient withdrew consent at later time. This patient's data is included in the compliance section.

As per the methods, individual compliance was calculated by evaluating the overall participation rate of the 37 patients included. A median (IQR) compliance of wearing the pedometer and recording the daily step count was found to be 97.8% (93.2-100). Similarly, the patients' engagement with weekly telephone calls was found to be a median (IQR) of 100% (93.1-100). A median (IQR) compliance with daily 30-minutes aerobic session and a median (IQR) compliance with daily strengthening exercise session reached 70.2% (53.1-88.9) and 69.4% (52.1-84.3) respectively. Individual compliance with Borg 3-4 level was observed to be a median (IQR) of 96.7% (85.4-99.4). Results are summarised in table 9.

	Median (IQR)
Compliance - wearing pedometer + recording data	97.8% (93.2-100.0)
Engagement telephone contact	100.0% (93.1-100.0)
Compliance - aerobic 30min session	70.2% (53.1-88.9)
Compliance with intensity (during aerobic session)	96.7% (85.4-99.4)
Compliance - strengthening session	69.4% (52.1-84.3)

Table 9 Individual compliance with the ChemoFit intervention.
IQR, interquartile range.

4.3.4 Change in compliance during the study

Compliance with aerobic and strengthening sessions and also compliance with intensity during aerobic sessions (only if aerobic session was performed) was compared between the time period during administration of neoadjuvant chemotherapy and the time period after completion of neoadjuvant chemotherapy but prior to surgery. Compliance with aerobic exercise and compliance with intensity during aerobic sessions improved during the time after neoadjuvant chemotherapy was completed. Compliance with strengthening sessions decreased over the time. These changes were however statistically significant for compliance with intensity during aerobic sessions only (p 0.028). The results of this comparison are demonstrated in table 10.

	Median (IQR) during NAC	Median (IQR) after NAC	p value
Compliance - aerobic 30min session	68.4% (54.8-84.1)	71.8% (47.9-95.1)	0.574
Compliance with intensity (during aerobic session)	97.6% (80.0-100.0)	100.0% (100.0-100.0)	0.028
Compliance - strengthening session	69.7% (43.6-84.1)	68.6% (54.3-87.2)	0.074

Table 10 Individual compliance with the ChemoFit intervention during and after neoadjuvant chemotherapy.
IQR, interquartile range. NAC, neoadjuvant chemotherapy.

4.4 Step count related results

The mean daily step count was compared between three time intervals – at baseline, during neoadjuvant chemotherapy and post- neoadjuvant chemotherapy. Only participants who supplied step count data during all three time periods were included in the analysis (35 patients). Three participants did not undergo neoadjuvant chemotherapy, and three participants withdrew their consent during the study. One patient was not compliant with telephone consultations and only provided baseline readings so that an initial number of steps could be prescribed after the

first cycle of chemotherapy. Unfortunately, this participant did not complete neoadjuvant chemotherapy as they became clinically unwell and disease progression was confirmed which meant that they had to withdraw. This participant was excluded from the final analysis as there was insufficient data obtained.

The mean ± SEM daily step count during the baseline period was 5529 ± 656 steps, which decreased during neoadjuvant chemotherapy to 5121 ± 519 steps and increased during post-neoadjuvant chemotherapy to 5792 ± 609 steps. The differences between step counts during these intervals were not statistically significant (p 0.091). Participants failed to increase their step count to the prescribed target of 1000 additional steps above baseline. However, they were able to maintain baseline daily step count throughout the study period. This is demonstrated in figure 8.

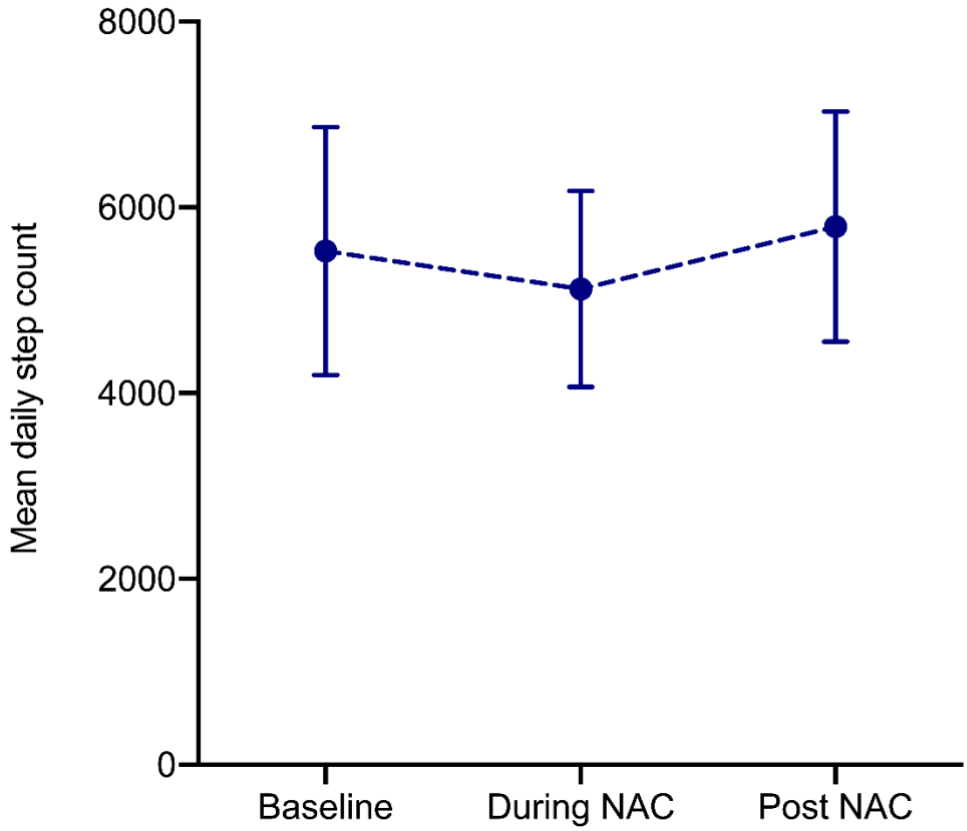


Figure 11 Differences in mean (95% CI) daily step count during the study. NAC, neoadjuvant chemotherapy.

4.5 CPET results

The first CPET was performed during the staging process as a part of normal clinical care. The second test was performed one to 14 days prior to surgery as described in the study protocol.

All patients underwent the first CPET. Only 19 patients underwent both tests. Three patients did not undergo neoadjuvant chemotherapy, three patients withdrew their consent during the study, five patients experienced disease progression and became palliative. One patient attended for a repeat CPET session however due to equipment failure the test was not carried out. An additional 11 patients did not undergo CPET due to the COVID-19 pandemic. Both tests were analysed by two consultant anaesthetists. Readings by two anaesthetists of both AT and VE/VCO_2 demonstrated excellent intraclass correlation coefficient (ICC) [204] as demonstrated in table 11.

	Mean difference, (95 % CI)	SD	95% LOA	ICC (95% CI)
VO_2 at AT (first CPET) $ml.min^{-1}.kg^{-1}$	-0.19 (-0.54, 0.15)	0.73	1.42	0.987 (0.966, 0.995)
VO_2 at AT (second CPET) $ml.min^{-1}.kg^{-1}$	-0.05 (-0.39, 0.28)	0.70	1.37	0.985 (0.962, 0.994)
VE/VCO_2 (first CPET)	-0.37 (-0.80, 0.06)	0.90	1.75	0.985 (0.959, 0.994)
VE/VCO_2 (second CPET)	0.00 (-0.48, 0.48)	1.00	1.96	0.987 (0.967, 0.995)

Table 11 VO_2 at AT and VE/VCO_2 inter-observer variability.
AT, anaerobic threshold. VE/VCO_2, Ventilatory equivalents for carbon dioxide. CI, confidence intervals. SD, standard deviation. LOA, limit of agreement (1.96 x SD). ICC, Intraclass correlation coefficient.

4.5.1 Anaerobic threshold

Ten participants demonstrated reduction of AT between the two CPETs compared to nine participants who demonstrated an improvement of the AT between two tests. In these participants oxygen uptake at AT was not statistically different over the study period. (mean difference -0.5 $ml.kg^{-1}.min^{-1}$, 95% CI -1.6 to +0.6, p 0.387).

4.5.2 Peak oxygen uptake

Very similar findings were observed for the peak oxygen uptake (VO_2peak). Ten participants improved their VO_2peak and nine decreased this variable however some participants who improved their AT decreased their VO_2peak and vice versa. There was no statistically different change in VO_2peak (mean difference -0.1 $ml.kg^{-1}.min^{-1}$, 95% CI -1.6 to +1.4, p 0.952). Peak oxygen uptake was preserved during the study period. CPET parameters achieved by study participants during the first and second test and their comparison can be seen in table 12 and figure 9.

	first CPET, mean (SD)	second CPET, mean (SD)	p value
VO_2 at AT ($ml.min^{-1}.kg^{-1}$)	14.33 (3.19)	13.86 (2.83)	0.387
VO_2peak ($ml.min^{-1}.kg^{-1}$)	19.35 (4.24)	19.26 (4.20)	0.952
VE/VCO_2	30.55 (3.83)	31.47 (4.30)	0.087
FEV1 (l)	2.57 (0.77)	2.55 (0.73)	0.820
FVC (l)	3.61 (0.86)	3.64 (0.89)	0.672

Table 12 Comparison of CPET parameters before and after intervention.
AT, anaerobic threshold. VE/VCO_2, Ventilatory equivalents for carbon dioxide. FEV1, forced expiratory volume in 1s. FVC, forced vital capacity. SD, standard deviation.

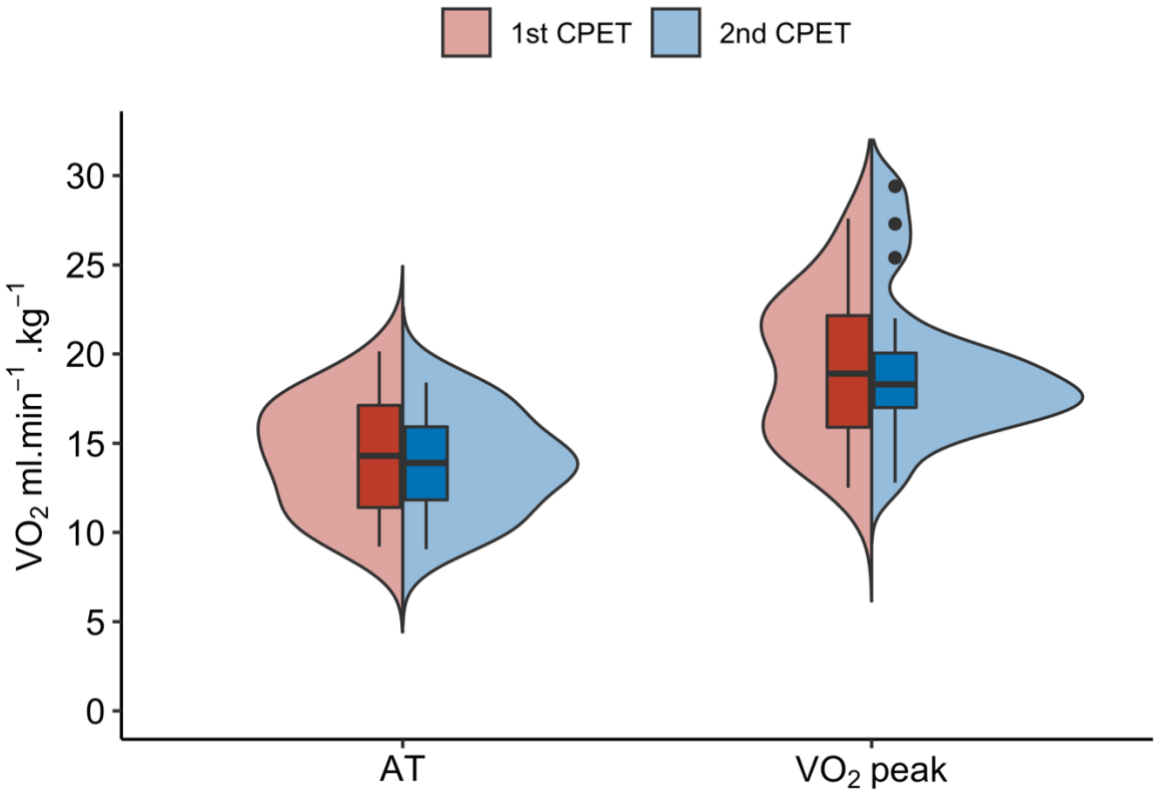


Figure 12 Violin plot – changes in AT and VO_2peak between the two CPETs.
The first and third quartile are represented by the bottom and top of the box. The median is presented by a band inside the box. The lines stretched from the bar represent the lowest and the highest data points within 1.5 of the interquartile range. Any data not included between the lines is plotted as an outlier with a dot. AT, anaerobic threshold. VO_2peak, peak oxygen consumption. CPET, cardiopulmonary exercise testing.

4.5.3 Other variables

Ventilatory equivalents for carbon dioxide (VE/VCO_2) increased during the study period from 30.6 to 31.5 however this change was not statistically significant (p 0.087). There was no statistical difference in the change of forced expiratory volume in 1s (FEV1) and forced vital capacity (FVC).

4.5.4 Sub analysis according to chemotherapy regimen

Eight patients underwent ECX compared to 11 patients who received the FLOT neoadjuvant regimen.

Participants who received ECX/ECF chemotherapy improved their AT by 0.7 $ml.min^{-1}.kg^{-1}$ (95% CI -1.3 to +2.7, p 0.459) and the VO_2peak by 1.5 $ml.min^{-1}.kg^{-1}$ (95% CI -0.2 to +3.1, p 0.080). This is also seen in figure 10. Participants who underwent FLOT chemotherapy maintained both their VO_2 at AT (mean difference -1.3 $ml.min^{-1}.kg^{-1}$, 95% CI -2.6 to +0.0, p 0.050) and VO_2peak (mean difference -1.2 $ml.min^{-1}.kg^{-1}$, 95% CI -3.4 to +1.0, p 0.253) respectively. Results of this sub analysis are demonstrated in table 13 and figure 10 and 11.

	first CPET, mean (SD)	second CPET, mean (SD)	p value
ECX (8 participants)			
VO_2 at AT ($ml.min^{-1}.kg^{-1}$)	13.41 (3.66)	14.08 (3.09)	0.459
VO_2peak ($ml.min^{-1}.kg^{-1}$)	17.64 (4.70)	19.09 (4.61)	0.080
FLOT (11 participants)			
VO_2 at AT ($ml.min^{-1}.kg^{-1}$)	15.00 (2.78)	13.71 (2.76)	0.050
VO_2peak ($ml.min^{-1}.kg^{-1}$)	20.59 (3.57)	19.39 (4.11)	0.253

Table 13 Comparison of CPET parameters before and after intervention for participants who received ECX and participants who received FLOT.
AT, anaerobic threshold. SD, standard deviation. Bold indicates significant findings.

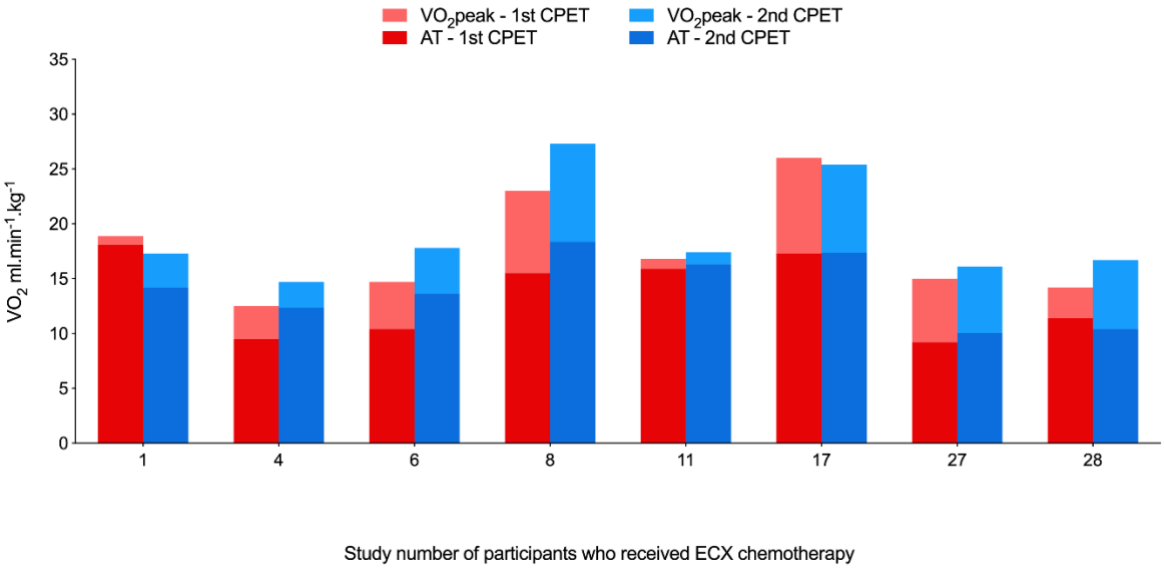


Figure 13 Comparison of AT and VO_2peak between two CPET of participants who received ECX chemotherapy.
AT is demonstrated as a proportion of VO_2peak, which is represented by full bar (both shades of colour). AT, anaerobic threshold. VO_2peak, peak oxygen uptake.

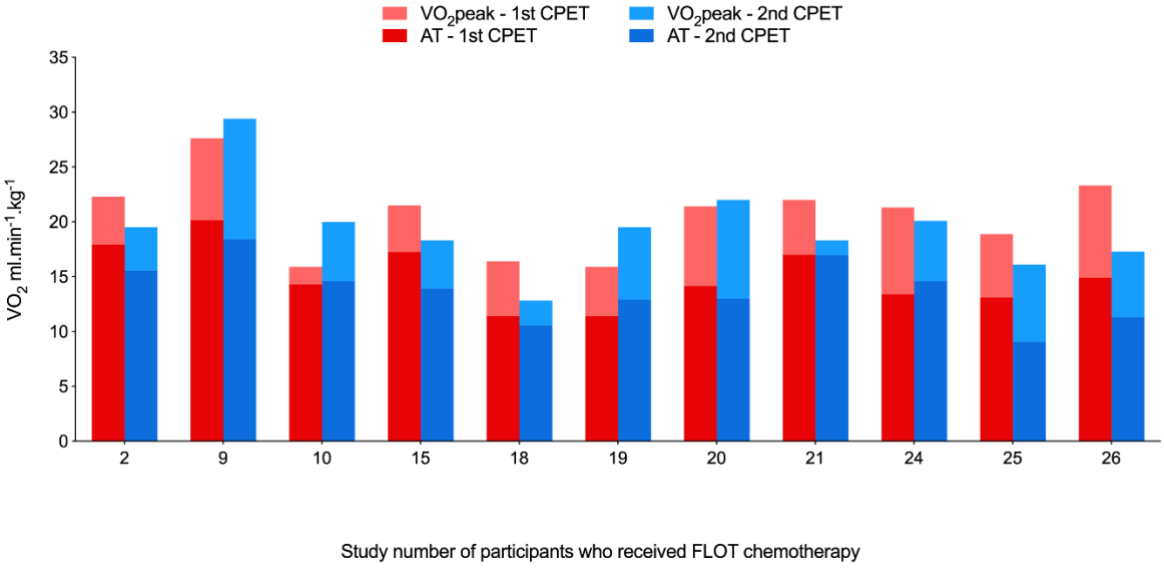


Figure 14 Comparison of AT and VO_2peak between two CPET of participants who received FLOT chemotherapy.
AT is demonstrated as a proportion of VO_2peak, which is represented by full bar (both shades of colour). AT, anaerobic threshold. VO_2peak, peak oxygen uptake.

4.6 Sarcopenia results

4.6.1 Muscle mass

Muscle mass area at the level of third lumbar vertebra on CT scans was calculated. This area was compared on CT scans from 36 participants prior and post intervention. The mean (SD)

and median (IQR) time between the staging CT scan and the consent to enter the study was 35.7 days (16.8) and 38.0 days (27.5-46.8) respectively. Based on skeletal muscle index (SMI), there were 17 participants (47.2%) sarcopenic prior to exercise intervention. This increased to 26 participants (72.2%) after intervention. The change was found to be statistically significant ($p<0.001$). The mean (SD) lean body mass (LBM) decreased from 52.3kg (9.8) to 49.1kg (9.4), which was statistically significant ($p<0.001$). These results are demonstrated in table 14.

	first test	second test	p value
Sarcopenic, yes (%)	17 (47.2%)	26 (72.2%)	<0.001
Mean LBM, kg (SD)	52.3 (9.8)	49.1 (9.4)	<0.001

Table 14 Comparison of sarcopenia results between two tests.
SD, standard deviation. LBM, lean body mass.

Subgroup analysis was performed on 30 participants who proceeded to surgery. In this group 13 participants (43.3%) were sarcopenic based on the staging CT scan compared to 21 participants (70.0%) based on the re-staging CT scan (p 0.002). The mean (SD) LBM has decreased from 52.6kg (10.4) to 49.7kg (9.8), ($p<0.001$).

4.6.2 Muscle function

Muscle function was measured using a hand-grip strength test. Thirty participants underwent two tests, before and after the intervention. Three patients did not undergo neoadjuvant chemotherapy, three patients withdrew their consent during the study, and five patients experienced disease progression and became palliative, their repeat grip strength test was not performed. One patient did not have a second test performed due to the change in the date of surgery. Results are demonstrated in table 15.

	first test, mean (SD)	second test, mean (SD)	p value
Grip strength (kg)	34.38 (8.77)	33.61 (8.96)	0.386

Table 15 Comparison of hand-grip strength test results between two tests.
SD, standard deviation.

The change between the two tests was small and did not reach statistical significance (p 0.386). Muscle function measured by hand-grip strength test was preserved during the neoadjuvant chemotherapy and time leading to surgery.

4.6.3 Total subcutaneous fat area

Total subcutaneous fat area was measured for the same number of participants on the same CT scans as muscle mass. The median (IQR) subcutaneous area at the level of third lumbar vertebra indexed by participants' height was 56.80 $cm^2.m^{-2}$ (38.07-88.15) on the staging CT scan. This decreased to a median (IQR) of 55.23 $cm^2.m^{-2}$ (33.63-82.16) on the restaging CT scan. This change was statistically significant (p 0.002). There was no correlation found between change in total subcutaneous fat area indexed by height and LBM between two the CT scans (Spearman's *r* 0.201, p 0.241).

4.7 Quality of life results

Quality of life was measured using the validated EORTC QLQ-C30 version 3.0 questionnaire and validated EORTC QLQ-OG25 questionnaire. Thirty-one participants completed questionnaires at both time points: at the beginning and at the end of the study period. Eleven participants did not complete questionnaires at the end of the study period. Three patients did not undergo neoadjuvant chemotherapy, three patients withdrew their consent during the study, four patients experienced disease progression and became palliative. One patient did not complete the questionnaires at the end of the study due to the change in the date of surgery. One patient whose disease progressed during the study period completed questionnaires at both time points and their data is included in the analysis.

4.7.1 EORTC QLQ-C30

Global quality of life significantly improved during the study time period ($p<0.001$). In functional scales, physical functioning improved significantly (p 0.020). No significant changes were noted in other functional scales. Symptoms of fatigue, nausea and loss of appetite improved significantly during the study period as demonstrated in relevant symptom scales (p 0.039, p 0.005, p 0.025, respectively). There were non-significant changes in other symptom scales such as pain, dyspnoea, insomnia, constipation, diarrhoea and financial difficulties during the study period. The results are summarised in the table 16. Figure 12 and 13 demonstrate these findings on radar plots.

	first test, mean score (SD)	first test, median score (IQR)	second test, mean score (SD)	second test, median score (IQR)	p value
Global health status / QoL					
Global health status (QL2)	65.32 (17.76)	66.67 (16.67)	78.23 (21.16)	83.33 (33.33)	**<0.001**
Functional scales					
Physical functioning (PF2)	85.59 (18.39)	93.33 (20.00)	91.40 (15.98)	100.00 (6.67)	**0.020**
Role functioning (RF2)	84.41 (26.85)	100.00 (33.33)	86.02 (24.76)	100.00 (16.67)	0.546
Emotional functioning (EF)	74.73 (23.12)	83.33 (41.67)	79.03 (23.06)	83.33 (33.33)	0.394
Cognitive functioning (CF)	89.78 (19.09)	100.00 (16.67)	91.40 (15.44)	100.00 (16.67)	0.638
Social functioning (SF)	79.57 (28.45)	100.00 (33.33)	82.80 (23.76)	100.00 (33.33)	0.373
Symptom scales / items					
Fatigue (FA)	28.49 (24.20)	33.33 (22.22)	21.86 (20.79)	22.22 (0.00)	**0.039**
Nausea (NV)	15.59 (18.73)	16.67 (33.33)	5.38 (10.88)	0.00 (16.67)	**0.005**
Pain (PA)	14.52 (19.60)	16.67 (16.67)	13.44 (24.50)	0.00 (33.33)	0.460
Dyspnoea (DY)	17.20 (20.85)	0.00 (33.33)	15.05 (22.51)	0.00 (66.67)	0.366
Insomnia (SL)	38.89 (31.66)	33.33 (41.67)	32.26 (34.94)	33.33 (66.67)	0.630
Appetite loss (AP)	38.89 (34.00)	33.33 (66.67)	22.58 (36.91)	0.00 (33.33)	**0.025**
Constipation (CO)	13.98 (25.49)	0.00 (33.33)	18.28 (27.00)	0.00 (33.33)	0.486
Diarrhoea (DI)	9.68 (23.08)	0.00 (0.00)	6.45 (15.91)	0.00 (0.00)	0.582
Financial difficulties (FI)	18.28 (30.84)	0.00 (33.33)	15.05 (27.00)	0.00 (33.33)	0.590

Table 16 Comparison of quality of life using EORTC QLQ-C30 questionnaire before and after intervention.

In the global health status subscale as well as in the functional subscales a higher value will indicate a higher quality of life and better level of functioning. In the symptom scales a higher score is indicative of more symptoms. QoL, quality of life. SD, standard deviation. IQR, interquartile range. Bold indicates significant findings.

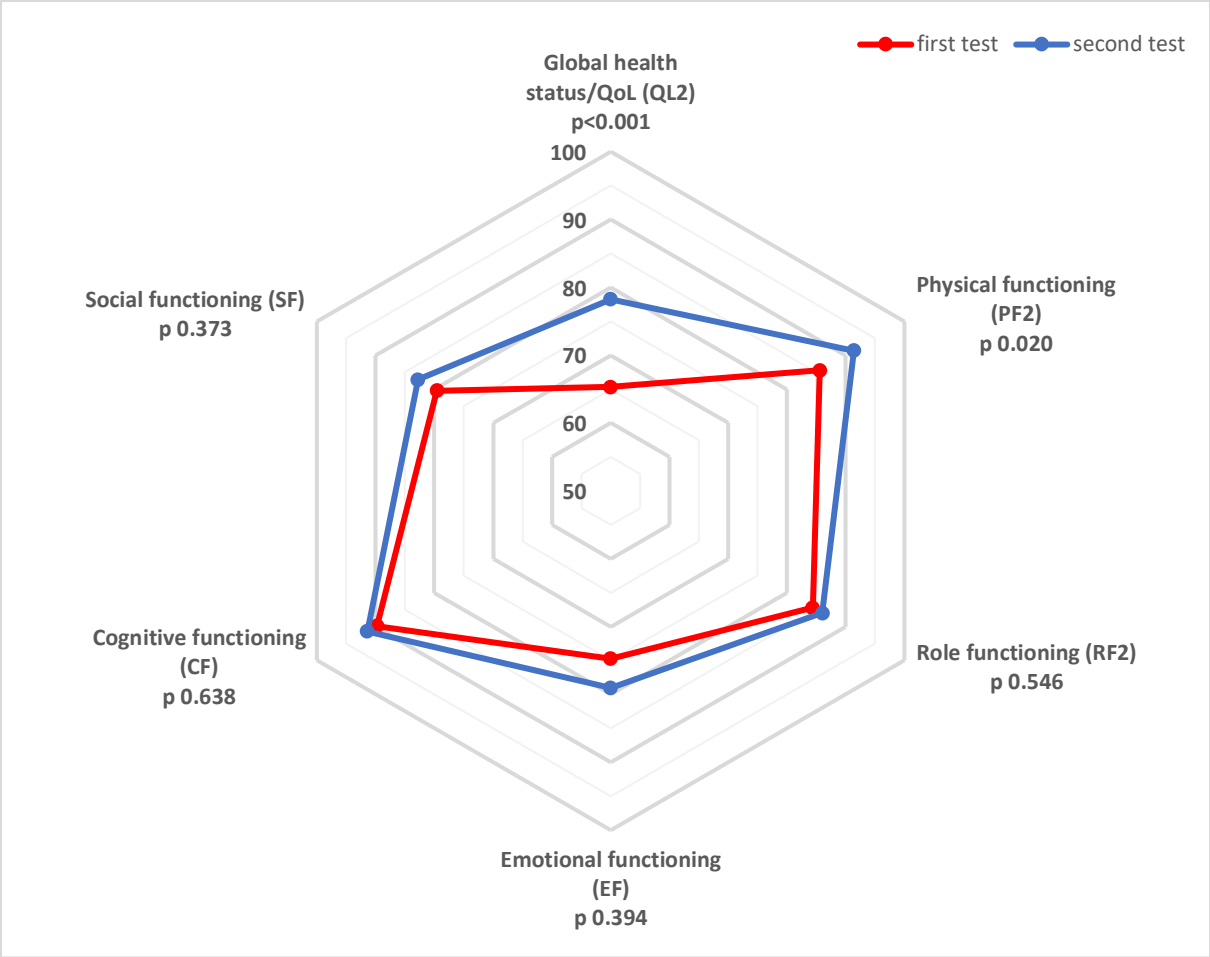


Figure 15 Radar plot comparing global health status and functional scales as a part of EORTC QLQ-C30 quality of life questionnaire before and after intervention.

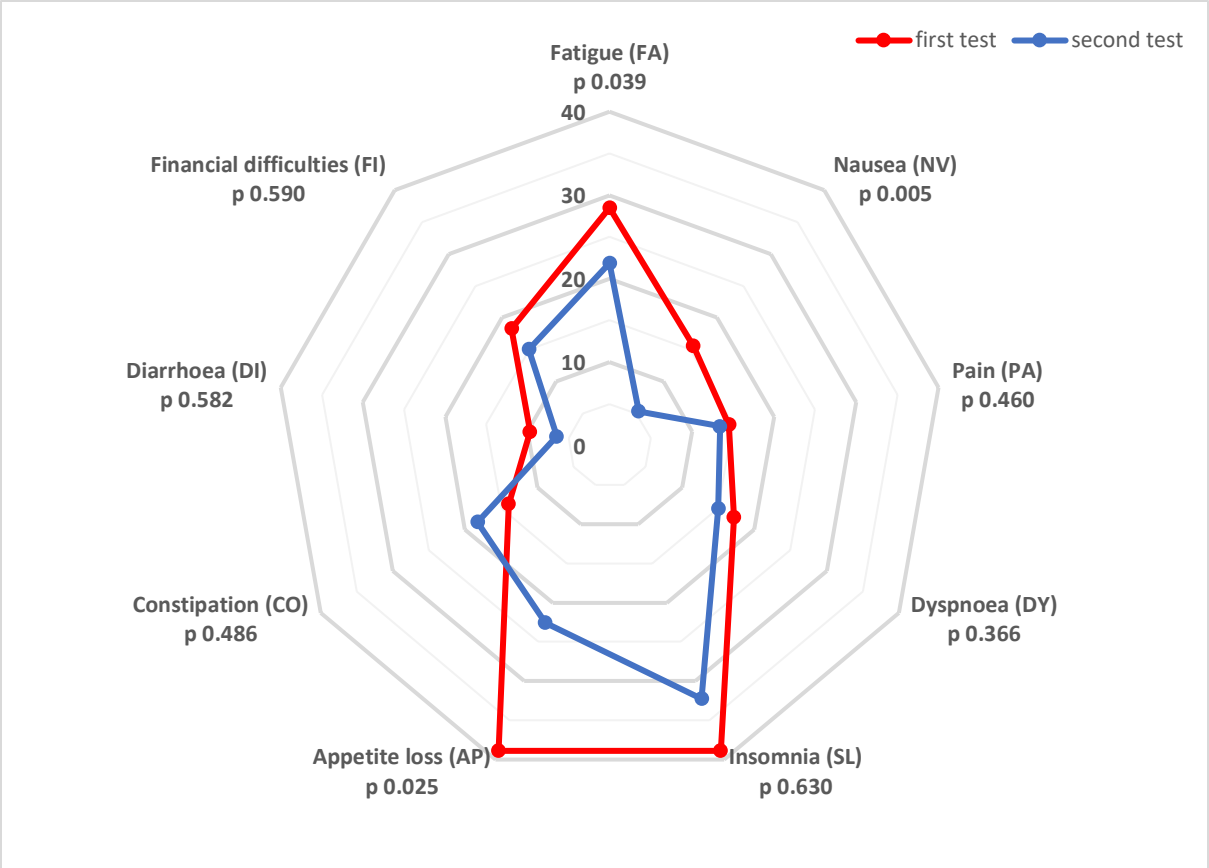


Figure 16 Radar plot comparing symptom scales as a part of EORTC QLQ-C30 quality of life questionnaire before and after intervention.

4.7.2 EORTC QLQ-OG25

Symptoms of dysphagia, eating restriction, odynophagia, pain and discomfort, eating with others and cough have significantly improved during the study period (p 0.020, p 0.015, p 0.004, p 0.022, p 0.004, p 0.025 respectively). Symptoms of trouble with taste significantly worsened during the study period (p 0.007). From the functional scale, body image worsened significantly (p 0.007). Questions related to participants' hair loss was not analysed. This question is only answered by participants if they lose hair. The results of EORTC QLQ-OG25 questionnaire are summarised in table 1.

	first test, mean score (SD)	first test, median score (IQR)	second test, mean score (SD)	second test, median score (IQR)	p value
Functional scale					
Body image (OGBI)	7.53 (14.17)	0.00 (0.00)	23.65 (31.26)	0.00 (33.33)	**0.007**
Symptom scales					
Dysphagia (OGDYS)	26.88 (29.22)	11.11 (44.44)	15.77 (25.62)	11.11 (22.22)	**0.020**
Eating (OGEAT)	40.86 (33.50)	25.00 (58.33)	27.69 (32.09)	16.67 (50.00)	**0.015**
Reflux (OGRFX)	11.29 (19.43)	0.00 (16.67)	13.98 (28.90)	0.00 (16.67)	0.471
Odynophagia (OGDYN)	28.89 (32.14)	16.67 (54.17)	13.98 (22.81)	0.00 (33.33)	**0.004**
Pain and discomfort (OGP & D)	23.66 (28.47)	16.67 (33.33)	12.37 (26.16)	0.00 (16.67)	**0.022**
Anxiety (OGANX)	60.22 (27.45)	66.67 (50.00)	51.07 (30.41)	33.33 (33.34)	0.078
Eating with others (OGEO)	23.66 (33.55)	0.00 (33.33)	8.89 (26.16)	0.00 (0.00)	**0.004**
Dry mouth (OGDM)	27.96 (27.35)	33.33 (33.33)	32.26 (33.87)	33.33 (33.33)	0.355
Trouble with taste (OGTA)	13.98 (24.00)	0.00 (33.33)	35.48 (39.38)	33.33 (66.67)	**0.007**
Trable swallowing saliva (OGSV)	7.53 (20.56)	0.00 (0.00)	6.45 (21.81)	0.00 (0.00)	0.916
Choked when swallowing (OGCH)	6.45 (18.09)	0.00 (0.00)	5.38 (15.15)	0.00 (0.00)	0.655
Trouble with coughing (OGCO)	31.18 (22.67)	33.33 (33.33)	22.58 (18.03)	33.33 (33.33)	**0.025**
Trouble talking (OGSP)	0.00 (0.00)	0.00 (0.00)	2.15 (8.32)	0.00 (0.00)	0.157
Weight loss (OGWL)	21.50 (27.95)	0.00 (33.33)	19.35 (30.76)	0.00 (33.33)	0.484
Hair loss (OGHAIR)	N/A	N/A	N/A	N/A	N/A

Table 17 Comparison of quality of life using EORTC QLQ-OG25 questionnaire before and after intervention.

A higher score is indicative of more symptoms. SD, standard deviation. IQR, interquartile range. N/A, not applicable. Bold indicates significant findings.

Chapter 5. Discussion

5.1 Summary of findings

- These results demonstrate the successful implementation of a home-based prehabilitation programme for oesophago-gastric cancer patients who receive neoadjuvant treatment. Of those recruited 92.3% completed the programme at overall recruitment rate of 72.4%.

- Further, the overall compliance with each component of the regimen was very good in those that enrolled in the study. This was particularly true for compliance with wearing pedometer and recording data (median 97.8%), engagement with telephone contact (median 100%) and compliance with intensity during aerobic session (median 96.7%). The compliance with aerobic sessions (median 70.2%) and strengthening sessions (median 69.4%) was not so good.

- The mean daily step count during the baseline period was 5529 steps, which decreased during neoadjuvant chemotherapy to 5121 steps and increased during post- neoadjuvant chemotherapy to 5792 steps. These differences were not statistically significant.

- There was no statistically different change in AT or VO_2peak during the study period. Both AT and peak oxygen uptake were preserved.

- The number of patients being sarcopenic increased from 47.2% in the beginning of the study to 72.2% towards the end of the study. This change was statistically significant.

- The mean LBM decreased from 52.3kg to 49.1kg, which was statistically significant.

- The change in muscle function measured by hand-grip strength test during the study period was small and not statistically significant.

- Global quality of life significantly improved during the study period. This was also found for change in physical functioning. Symptoms of fatigue, nausea and loss of

appetite, dysphagia, eating restriction, odynophagia, pain and discomfort, eating with others and cough have significantly improved during the study period.

5.2 Clinicopathological characteristics of participants

Participants of the ChemoFit study represent the typical UK population of patients with oesophago-gastric adenocarcinoma. This is predominantly male disease with male to female ratio of oesophageal adenocarcinoma and gastric adenocarcinoma of 5.1 and 2.3 respectively in the UK [205, 206]. In this study males were slightly more represented. A median age of 68 years and BMI of 27.3 $kg.m^{-2}$ is similar to other published UK or European studies in oesophago-gastric field [207, 208] and it is also comparable with the historical data from this unit [209]. The majority of the participants had very advanced disease (stage III in 56% and stage IVA in 38%). This was influenced mainly by the inclusion criteria. The location of the tumours of these participants corresponds with its incidence in the UK [206, 210]. Smoking is a risk factor for both oesophageal and gastric adenocarcinomas [16]. Only nine participants (23%) never smoked.

The chemotherapy regimen used indicates shift from the ECX regimen of chemotherapy as originally presented in the MAGIC study [37], to the more recently advocated FLOT regimen based on the results of the recent phase III FLOT4-AIO trial [40]. This trial included patients with gastric and junctional cancer and did not include pure oesophageal tumours. It can be however expected that similar survival benefit of FLOT regimen could be possibly achieved in oesophageal adenocarcinoma. This led to recent tendency amongst local oncologists to administer FLOT chemotherapy more commonly to patients with adenocarcinoma in oesophagus proper. There were 11 participants out of 17 with oesophageal adenocarcinoma who received FLOT chemotherapy in the ChemoFit study.

5.3 Feasibility outcomes

Oesophago-gastric cancer patients at NOGU were highly motivated to participate in a previous study which investigated the impact of neoadjuvant chemotherapy on patients' fitness [179]. Similar results in terms of recruitment rate was observed in the ChemoFit study. Nine participants declined participation due to geographical reasons which had negative impact on recruitment rate. The majority of these patients live in the western region of the catchment area

and thus patients frequently have the treatment decisions discussed with them by the team located in Carlisle. This saves patients from travelling long distances for another appointment. These patients would have needed to travel a long distance for consent to be obtained should they wanted to participate. However, this geographical distance would not be expected to preclude patients from access to this programme if it existed as part of routine care, rather than as part of a clinical study.

The high completion rate also indicates good patient engagement, which may highlight the determination of the patients involved and the appropriateness of the intervention. Together with an appropriate regimen, telephone support and realistic targets, this could have kept participants motivated throughout the study period. Compliance with monitoring and communication aspects (wearing a pedometer, engagement with telephone calls) of the programme was higher than compliance with the actual "activity" components (aerobic and strengthening sessions). The former is likely to reflect determination and willingness of participants to 'succeed' whereas the latter is probably a reflection of actual achievability of a demanding training prescription. It appears that the weekly telephone contact involving feedback and positive reinforcement was sufficient to keep the vast majority of patients engaged and compliant with the programme. Barriers which were possibly contributing to lower compliance with "activity" components could have been tiredness and fatigue with the chemotherapy but also bad weather. This reasoning was commonly mentioned to researchers during regular telephone contacts. However, the only statistically significant difference in compliance during the time period when neoadjuvant chemotherapy was being administered and time period after neoadjuvant chemotherapy but prior to surgery was observed for compliance with intensity during aerobic session (p 0.028).

It is difficult to compare compliance from this study to other prehabilitation studies, given differences in the population and the exercise regimens used, and also the heterogeneity in defining compliance. Compliance is sometimes defined based on exercise frequency [190, 211-213], exercise volume [159] or exercise frequency, duration and intensity combined [214]. The definition of compliance as a proportion of participants being 100% compliant with the intervention has also been used [160, 166, 180]. Compliance with prehabilitation regimens for cancer patients has been reported as low as 16% [159] but also as high as 98% [190]. Future rehabilitation studies should clearly define compliance and if possible, report various type of compliance.

Another important finding of this work is related to the coronavirus pandemic which impacted on the study. The ChemoFit programme was feasible during this time period and although the recruitment had to stop, the programme continued. Follow up of the patients via weekly telephone calls remained unchanged. Participants continued to exercise unlike in many other prehabilitation studies being conducted at that time which had to stop due to being mainly hospital-based or gym-based and involving first-person supervision [215].

5.4 Step count related outcomes

Participants failed to increase their daily step count to achieve prescribed step targets. This target was initially 2000 steps above the median baseline daily step count. However, after the planned interim analysis, this was revised to 1000 steps. The mean daily step count has decreased during neoadjuvant chemotherapy and then increased in the period after. The differences between the mean baseline step count, the mean daily step count during neoadjuvant chemotherapy and the mean daily step count after neoadjuvant chemotherapy were however not statistically significant. This indicates that patients had difficulties even to maintain their daily step count from baseline period when they were undergoing chemotherapy treatment. The explanation for this again might be in chemotherapy induced fatigue. It can be speculated that the prehabilitation regimen prevented further decline in daily step count during neoadjuvant chemotherapy and helped to improve this in the period thereafter.

West et al. conducted a prehabilitation study on a group of patients undergoing neoadjuvant chemoradiotherapy for rectal cancer [180]. This study administered intervention in the time period after the neoadjuvant chemoradiotherapy and before surgery only. The intervention used in this study was supervised hospital-based cycle ergometer training. The authors observed a similar decline and then resumption in the mean daily step count in both exercise group and non-exercise comparison group during neoadjuvant chemoradiotherapy and after. They hypothesised that physical activity expressed as step count improves naturally after neoadjuvant chemoradiotherapy as a resumption of the activities of daily living. This change did not correspond with a change in cardiopulmonary fitness. They concluded that improving physical activity is not enough to improve physical fitness. Naturally this led to the premise that improving step count cannot lead to changes in fitness. Nonetheless, increased step count should be part of the structured exercise intervention, not just part of improving physical activity if changes in fitness are expected.

5.5 Impact of the ChemoFit prehabilitation regimen on the cardiopulmonary fitness

This study demonstrates that cardiopulmonary fitness of participants during the study period was maintained. The AT and the VO_2peak of participants remained unchanged. Sub analysis according to chemotherapy treatment received showed the maintenance of cardiopulmonary fitness as well. Eight participants who received ECX chemotherapy started treatment with lower cardiopulmonary fitness as demonstrated by lower values of AT and VO_2peak, compared to 11 participants who received FLOT chemotherapy. Whilst the group of participants with ECX treatment improved their CPET variables, the group of participants with FLOT chemotherapy observed some decline in the same variables. None of these changes however reached statistical significance.

A previously conducted study at NOGU investigated the impact of the ECX regimen on cardiorespiratory reserve [179]. This study confirmed that ECX has a detrimental effect on fitness and in the period after chemotherapy prior to surgery, this effect is sustained. The effect of FLOT chemotherapy has however never been evaluated. It has been suggested that the FLOT regimen may have a more deleterious physiological impact than ECX as observed in the FLOT4-AIO trial [40]. In this trial patients who received FLOT chemotherapy had significantly higher rates of chemotherapy-related grade 3 and 4 infections and neutropenia. This trend of FLOT being more physiologically demanding is also seen in the present study. Locally, there has been some feeling by oncologists that FLOT may have a larger physiological impact on patients which could consequently lead to such deconditioning that they would be denied surgery. Thus FLOT, particularly with its early integration, was reserved for those deemed fitter. This is reflected in the difference in baseline CPET outputs obtained from the groups which demonstrated better AT and better VO_2peak in the cohort that underwent FLOT. Interestingly, second CPET values were broadly similar between the groups and this is likely to represent a maintenance of fitness in the ECX group, which would ordinarily have had a fall as previously demonstrated [179]. It is difficult to know what degree of deterioration of fitness the FLOT cohort would have, but it could be speculated that these patients would have been at an even poorer level of fitness had they not engaged in the ChemoFit programme.

The evidence demonstrating impact of prehabilitation on fitness of patients is already mentioned in the first chapter of this thesis. There are however a limited number of studies

where prehabilitation was administered either during or after neoadjuvant chemotherapy. The study conducted by West et al. administered an exercise programme to patients post neoadjuvant chemoradiotherapy for rectal cancer [180]. The programme lasted six weeks and demonstrated improvement in cardiopulmonary fitness measured by CPET during the time of exercise intervention. Authors also conducted one CPET before the neoadjuvant therapy was started (at baseline). Although they did not present results of statistical tests comparing CPET before neoadjuvant treatment with CPET after intervention, it seems to be that after an initial decline in fitness during neoadjuvant therapy, fitness improved to almost the same levels as those at baseline. The control group demonstrated a decline in cardiopulmonary fitness during the study. These groups were selected without randomisation and when comparison with the intervention group was made, participants in the intervention group were significantly younger and their ASA grade was lower.

Argudo et al. recently conducted a similar study on patients with locally advanced oesophago-gastric cancer [216]. The prehabilitation regimen was started after patients finished neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy treatment and lasted five weeks. This exercise intervention resulted in the significant improvement of cardiopulmonary fitness measured by CPET before and after exercise intervention. Similarly, to West et al. this study also assessed fitness before neoadjuvant therapy (at baseline). Again, the authors did not present the results of statistical tests comparing CPET at baseline with CPET after intervention. From the CPET values presented, it can be expected that a similar pattern of initial decline during neoadjuvant therapy and improvement afterwards, effectively leading to maintenance of fitness was experienced. This study did not have any control group for comparison.

Results from these two studies might lead to a conclusion that the fitness improvement is achieved after the neoadjuvant treatment is finished. It is difficult to appreciate during which part of the ChemoFit study the intervention had the biggest impact on fitness. There were only two CPETs performed and therefore it is unknown whether the maintenance of the cardiopulmonary fitness was mainly achieved during the neoadjuvant chemotherapy, after the neoadjuvant chemotherapy or during both time periods. The study by West et al. [180] and study by Argudo et al. [216] were conducted as hospital-based high intensity regimens. Less intense home-based regimen implemented during the ChemoFit study might require a longer period to achieve similar effect on fitness. It is also possible that implementing the exercise intervention for this group of patients as early as possible is advantageous. It is likely that establishing and

learning new habits by patients may take some time and therefore starting the prehabilitation intervention early might be beneficial.

There are three other studies which investigated the effect of home-based prehabilitation on the cardiopulmonary fitness for oesophago-gastric cancer patients. An RCT by Minnella et al. compared a home-based exercise intervention consisting of 30-minute aerobic workout three times a week and once weekly 30-minute strengthening exercise with routine care [175]. Improvement in fitness measured by 6MWT in the intervention group was observed whereas the control group demonstrated a decline in 6MWT results. Only 77% of participants in the prehabilitation arm received neoadjuvant treatment limiting comparison with the ChemoFit study. Sub analysis of this group was not performed. There was no difference in postoperative outcomes between the groups.

Another RCT conducted by Xu et al. administered a home-based prehabilitation regimen in the intervention group to patients with neoadjuvant chemoradiotherapy or radiotherapy for only four to five weeks [173]. Walking capacity was assessed by 6MWT. Results indicated that the intervention group demonstrated less decline in walking distance than the control group. Generalization to the UK population is limited as the majority of patients had an SCC. Both RCTs by Minella et al. and by Xu et al. decided to use 6MWT as their main outcome. This test has its limitations including being effort dependent and requiring some repetition by performing subject to achieve results which represent fitness levels. CPET also in contrary has got better established associations with many of the postoperative outcomes.

The study by Halliday et al. demonstrated the maintenance of fitness of patients undergoing neoadjuvant chemotherapy for oesophago-gastric cancer [191]. The interpretation of the results of this study are however limited by estimation of VO_2peak by the Chester step test rather than using CPET as an objective method of assessing cardiopulmonary fitness. This study did not have any control group.

There is emerging evidence that HIIT is the most effective way how to improve the fitness especially in a short period of time [63]. This leads to the current trend in prehabilitation where the majority of studies and prehabilitation exercise regimens are designed as HIIT programmes. The exercise regimen in the ChemoFit study was designed very pragmatically. The aim was to develop a programme that can be implemented into clinical practice with ease without large

personal and financial investment. There was also the intention for this regimen to be available to a large number of patients at any one time. Despite the fact that cost-effectiveness analysis of the ChemoFit regimen has not been performed, it can be expected that the cost to implement and operate a similar regimen in routine clinical practice will be low.

5.6 Impact of the ChemoFit prehabilitation regimen on sarcopenia

The present work demonstrates that the ChemoFit study participants preserved their muscle function during the study period measured by the hand-grip strength test. Muscle mass measured by CT scans assessment prior and post intervention significantly declined during the study period. The prevalence of sarcopenia amongst study participants during the study significantly increased. Further analysis excluding participants with progressive disease (as the effect of cancer in this subgroup on muscle mass might be more pronounced) demonstrated similar results, sarcopenia has increased during the study. Assessment of subcutaneous fat did not demonstrate a move to sarcopenia obesity body type as there was a significant decline in the amount of subcutaneous fat measured.

The consensual definition of sarcopenia by the European working group on sarcopenia in older people is based on both low muscle mass and low muscle strength [98]. Muscle weakness, in other words low muscle strength, was observed only in one male and one female participant at the beginning of the study and in a different male and the same female participant at the end of the study.

Should this definition be applied strictly, only one of the ChemoFit study participants would therefore be sarcopenic prior to intervention and none after it. Numerous studies however have studied sarcopenia based only on cut-off values for radiologically established skeletal muscle index [217-220]. There has been a demonstrated association with sarcopenia defined radiologically with outcomes after oesophago-gastric surgery [110]. The results of the present study are concerning when assessing sarcopenia based on radiological assessment of muscle mass. Prevalence of radiological sarcopenia increased from 43% at the beginning of the study to 70% at the end of the study amongst participants who progressed to surgery (p 0.002). Similar results were observed in the previous study at NOGU which investigated the effect of the ECX regimen on muscle mass (Navidi, unpublished, thesis only). Thus, it seems that prehabilitation does not

have any impact on sarcopenia, neither preventing it nor reversing it where it exists. These results are alarming given the fact that post neoadjuvant chemotherapy sarcopenia has been demonstrated to be independently predictive of length of stay after surgery and various postoperative complications in multivariable analyses [218].

Sarcopenia is more prevalent in cancer patients [221]. This can be explained by the catabolic and proinflammatory effect of cancer. Low muscle mass likely leads to systemic inflammation, altered protein status, mitochondrial dysfunction, altered insulin-dependent glucose handling but also altered pharmacokinetics of chemotherapy agents [222]. All these factors can then contribute to worse clinical outcomes including the increased risk of postoperative complications. Altered pharmacokinetics leading to further chemotherapy toxicity is probably a contributing factor to the additional increase in sarcopenia after chemotherapy [222] which was also observed in this study. The overdosage hypothesis suggests that dosing chemotherapy agents based on body surface area leads to a relative overdose on patients with low muscle mass due to volume distribution [223]. To counteract this, dosing based on lean body mass has been suggested [224]. Currently, both ECX and FLOT chemotherapy dosing in patients with oesophago-gastric adenocarcinoma is based on body surface area. However, relationships which play a role in sarcopenia are complex and there is likely to be interplay between the cancer itself and chemotherapy as well as interactions between the pathophysiological mechanisms mentioned [222].

It has been postulated that a combined prehabilitation intervention involving exercise and nutritional support is the ideal way of improving sarcopenia [225]. Whilst there is some evidence of the role of prehabilitation in improving muscle function, there is a paucity of evidence the utility of prehabilitation to maintain or improve muscle mass in cancer patients. An RCT by Moug et al. investigated the role of a home-based walking exercise intervention during neoadjuvant chemoradiotherapy for rectal cancer patients [226]. The majority of patients in the prehabilitation group increased their muscle mass compared to the majority of patients in the control group who experienced a decline in the amount of muscle mass.

Yamamoto et al. conducted the prospective study on sarcopenic patients aged 65 years and older with gastric adenocarcinoma who were enrolled onto an exercise and nutritional programme lasting a median duration of 16 days prior to their surgery [174]. Four patients became non sarcopenic at the end of the programme and the authors concluded that this programme has

a potential to reduce sarcopenia. However, it is worth noting that the authors do not mention whether patients received chemotherapy. In addition, the majority of patients also had early disease.

The ChemoFit programme did not contain any nutritional aspects as this already forms part of the routine care that patients at NOGU are provided with: patients receive dietitian input from the time point they are referred to the Unit. It is not known whether loss of subcutaneous fat can be attributed to higher energy expenditure due to the exercise intervention or due to cancer or the chemotherapy treatment itself. Nevertheless, these findings highlight the need for a more structured and focused approach of nutritional assessment and intervention for this group of patients. It is also important to comment that the ChemoFit strengthening exercises focused on improvement of different set of muscle groups to those assessed using CT to evaluate muscle mass. This may explain the discrepancy between preserved muscle function assessed by hand-grip strength test and the decline in muscle mass assessed by imaging.

The protective effect of endurance exercise against chemotherapy toxicity and muscle wasting has been demonstrated in experiments on mice [227, 228]. Further research should focus on whether this is could be achieved on oncological patients and if this is possible, what type of exercise regimen might be the most beneficial.

5.7 Impact of the ChemoFit prehabilitation regimen on quality of life

This work demonstrates that multiple aspects of the quality-of-life assessment of the ChemoFit study participants significantly improved during the intervention period. Global health status assessed using the EORTC QLQ-C30 questionnaire significantly improved ($p<0.001$) during the study period. Scores in all functional scales of EORTC QLQ-C30 improved but this was statistically significant in physical functioning only (p 0.02). Similarly, all symptoms assessed in the same questionnaire, apart from constipation, improved, this was statistically significant in symptoms of fatigue, nausea and vomiting and appetite loss (p 0.039, p 0.005, p 0.025 respectively). Multiple scores in the oesophago-gastric specific questionnaire EORTC QLQ-OG25 improved too.

It is possible that effect of some of the scores might be ascribed to neoadjuvant chemotherapy rather than the structured exercise intervention. This could be particularly the case in symptom

scales, namely nausea and vomiting, appetite loss, dysphagia, odynophagia, eating and trouble with coughing which improved and trouble with taste which worsened. Furthermore, it could be argued that patients in the study completing subjective assessment of their health might be more prone to reporting bias. A previous study at NOGU by Navidi et al. which investigated the impact of ECX chemotherapy on quality of life without exercise intervention using identical questionnaires however showed different results (Navidi, unpublished, thesis only). Global health status score declined after neoadjuvant chemotherapy and then recovered prior to surgery. Only emotional functioning and symptoms of nausea and vomiting significantly improved during the study. The other scores either demonstrated no change or significant decline. It is possible that reporting bias did not play significant role in the ChemoFit study and some of the symptom improvement could have been credited to the intervention. However, a randomised controlled trial is required to try and answer this question.

The evidence to support the effect of prehabilitation on quality-of-life improvement is lacking. Dunne et al. conducted an RCT of prehabilitation prior to liver resection [166]. Quality of life was assessed using SF-36 questionnaire and resulted in a significant increase in the score of the prehabilitation group. There is no reported prehabilitation influenced improvement of quality-of-life assessed by EORTC questionnaires.

Quality of life measures are important outcomes of the treatment and despite their subjective nature, these should accompany other outcomes when the treatment effects of oesophago-gastric surgery are assessed. A structured home-based exercise regimen with weekly telephone reinforcement may lead to improvement of quality-of-life measures.

5.8 Next steps

The results of the current work demonstrate safety and feasibility of the ChemoFit home-based prehabilitation regimen. It shows that the regimen may potentially enable patients with oesophago-gastric adenocarcinoma and undergoing neoadjuvant chemotherapy, to maintain or even improve their functional capacity and quality of life. Although even with the comparatively small numbers included in this study it was evident that patients receiving ECX did not experience an objectively measured fall in fitness, which has been historically demonstrated [97, 179]. An RCT would be desirable to assess this effect. It is likely that to achieve

enough power to demonstrate the effect of the intervention on these outcomes, a multicentre trial will be needed. This trial should also focus and explore whether improvement in preoperative cardiopulmonary fitness translates into better postoperative outcomes such as decreased length of stay, decreased morbidity and mortality.

More work is needed to identify whether physical exercise can mitigate the negative effect of neoadjuvant chemotherapy on sarcopenia. It is possible that different chemotherapy dosing strategies or future chemotherapy agents might not pose so much myotoxic effect on patients' muscle mass. Multimodal prehabilitation interventions seems to be more effective than unimodality exercise interventions [160]. Specifically, nutritional assessment and thorough nutritional follow up is needed given the nature of the disease but also increasing energy demands associated with the exercise. Psychological support is another modality which is being increasingly used nowadays [160, 161]. Although these modalities are rarely assessed separately, delivered together they seem to be effective [161].

Another potential exercise intervention which could have impact on postoperative outcomes of oesophago-gastric surgery appears to be IMT in the preoperative period. This intervention has been shown to have some effect on the rate of postoperative pneumonia in cardiac surgery [229, 230]. IMT together with intense aerobic exercise seems to be effective in reduction of pneumonia in oesophageal surgery. Valkenet et al. have conducted a multicentre RCT to investigate the impact of this intervention [177]. They randomized 241 patients either to an IMT group or to a control group without intervention. Although inspiratory muscle function increased in intervention group, this effect has not been translated into a decreased rate of postoperative pneumonia. This study however is limited by heterogeneity of operations performed and by low rates of compliance. Future researchers should consider including this modality into their prehabilitation programmes. This intervention can easily be performed at home without direct supervision.

The ChemoFit study has shown that a home-based approach is feasible and potentially effective despite the fact that the intervention did not include high-intensity exercises. This approach is promising given its apparent acceptability to patients. The cost-effectiveness of this model should be also the focus of further research.

5.9 Limitations of the study

There are several limitations of this work which should be acknowledged. A lack of control group does not allow direct conclusion about the effectiveness of this intervention to be determined. However, the ChemoFit programme was not designed for this purpose, but rather as a feasibility study in order to test whether it is possible to recruit to this type of study and whether it is possible and safe to run a programme with this intervention. It was also aimed to obtain preliminary data which could then be used to inform about the sample size of future studies. Selection bias was limited by inviting all eligible patients to participate in the study. Only two patients were missed for recruitment. It can be argued however that only motivated patients with a better prospect of maintaining/improving the fitness agreed to participate in the ChemoFit study. Those who declined, not due to distance reasons, might have achieved poorer outcomes with regards to compliance but also in their CPET parameters. This forms another limitation of the study.

The Covid-19 pandemic had significant impact on the study. This prevented carrying out CPET on more participants such that only 19 patients had an evaluation of the fitness by CPET both prior and after intervention. This unfortunate situation also limits the interpretation of the impact of the intervention on cardiopulmonary fitness. Further, there were two chemotherapy regimens used for the study participants. The impact of ECX/ECF chemotherapy on fitness is known, but there is still a lack of knowledge on how FLOT impacts on a patients' physiology and well-being as it has not been previously studied. It has been suggested anecdotally that FLOT chemotherapy may have a more profound physiological impact than the ECX regimen. Data from this work confirm that FLOT appears to have been administered to more fit patients and the trend of FLOT regimen being more detrimental towards patients' fitness is being observed in the ChemoFit study too. Finally, the measurement of the exercises and physical activity performed, and the measurement of step count was self-reported by patients into the exercise diaries. This was then collected by the research team over the telephone. This might pose a concern about the validity and veracity of this data. Future studies may consider using devices which can upload participants exercise data online in real time to avoid this form of bias.

5.10 Conclusion

It can be concluded that the ChemoFit home-based prehabilitation regimen is a safe and feasible programme for patients with locally advanced oesophago-gastric adenocarcinoma. Patients were compliant and engaged in the programme. The novelty of this research lies in that it is a home-based exercise approach. It permitted a potential maintenance of the objectively measured cardiopulmonary fitness and a potential improvement of the quality of life during and after neoadjuvant chemotherapy, prior to surgery. Another important finding of this study is that this regimen has not been effective at decreasing the prevalence of sarcopenia during the study period. There is a need to find different exercise interventions or other strategies, to battle this common problem in the field of oesophago-gastric surgical oncology. A randomised controlled trial is needed to investigate the impact of this regimen not only on cardiopulmonary fitness but also on postoperative outcomes. Cost-effectiveness of this regimen needs to be explored.

References

1. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut. 2015;64(3):381-387.
2. Khazaei S, Rezaeian S, Soheylizad M, Biderafsh A. Global Incidence and Mortality Rates of Stomach Cancer and the Human Development Index: an Ecological Study. Asian Pac J Cancer Prev. 2016;17(4):1701-1704.
3. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? Cancer Epidemiol Biomarkers Prev. 2010;19(6):1468-1470.
4. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. Semin Radiat Oncol. 2013;23(1):3-9.
5. Abnet CC, Arnold M, Wei WQ. Epidemiology of Esophageal Squamous Cell Carcinoma. Gastroenterology. 2018;154(2):360-373.
6. Thrift AP, Whiteman DC. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. Ann Oncol. 2012;23(12):3155-3162.
7. Thrift AP. The epidemic of oesophageal carcinoma: Where are we now? Cancer Epidemiol. 2016;41:88-95.
8. Kong CY, Nattinger KJ, Hayeck TJ, et al. The Impact of Obesity on the Rise in Esophageal Adenocarcinoma Incidence: Estimates from a Disease Simulation Model. Cancer Epidemiology Biomarkers & Prevention. 2011;20(11):2450-2456.
9. Zhu AL, Sonnenberg A. Is gastric cancer again rising? J Clin Gastroenterol. 2012;46(9):804-806.
10. Fitzsimmons D, Osmond C, George S, Johnson CD. Trends in stomach and pancreatic cancer incidence and mortality in England and Wales, 1951-2000. Br J Surg. 2007;94(9):1162-1171.
11. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. Best Pract Res Clin Gastroenterol. 2006;20(4):633-649.
12. La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Electric refrigerator use and gastric cancer risk. Br J Cancer. 1990;62(1):136-137.
13. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.

14. Ajiki W, Tsukuma H, Oshima A. Cancer incidence and incidence rates in Japan in 1999: estimates based on data from 11 population-based cancer registries. Jpn J Clin Oncol. 2004;34(6):352-356.
15. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. Br J Cancer. 1990;62(3):440-443.
16. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003;95(18):1404-1413.
17. Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther. 2010;32(10):1222-1227.
18. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381(9864):400-412.
19. Cook MB, Kamangar F, Whiteman DC, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2010;102(17):1344-1353.
20. Thrift AP, Shaheen NJ, Gammon MD, et al. Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. J Natl Cancer Inst. 2014;106(11).
21. Xie FJ, Zhang YP, Zheng QQ, et al. Helicobacter pylori infection and esophageal cancer risk: an updated meta-analysis. World J Gastroenterol. 2013;19(36):6098-6107.
22. Eslick GD, Lim LL, Byles JE, Xia HH, Talley NJ. Association of Helicobacter pylori infection with gastric carcinoma: a meta-analysis. Am J Gastroenterol. 1999;94(9):2373-2379.
23. Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, Graham DY. Association Between Helicobacter pylori Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis. Gastroenterology. 2016;150(5):1113-1124.e1115.
24. Yang P, Zhou Y, Chen B, Wan HW, Jia GQ, Bai HL, Wu XT. Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. Eur J Cancer. 2009;45(16):2867-2873.
25. Genta RM. Acid suppression and gastric atrophy: sifting fact from fiction. Gut. 1998;43 Suppl 1(Suppl 1):S35-38.
26. Joossens JV, Hill MJ, Elliott P, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. Int J Epidemiol. 1996;25(3):494-504.

27. Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, Lunet N. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control. 2008;19(7):689-701.

28. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours: John Wiley & Sons; 2017.

29. Amin MB, Edge SB, Greene FL, et al. AJCC cancer staging manual: Springer; 2017.

30. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v38-v49.

31. Krill T, Baliss M, Roark R, et al. Accuracy of endoscopic ultrasound in esophageal cancer staging. Journal of thoracic disease. 2019;11(Suppl 12):S1602.

32. Case-mix adjusted percentage of cancers diagnosed at stages 1 and 2 by CCG in England, 2019: NHS Digital; 2021 [updated 16.12.2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/case-mix-adjusted-percentage-cancers-diagnosed-at-stages-1-and-2-by-ccg-in-england/2019.

33. National Oesophago-Gastric Cancer Audit 2020 2020 [Available from: https://www.nogca.org.uk/content/uploads/2021/02/REF217_NOGCA_2020-Annual-Report-FINAL-V2.0.pdf.

34. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v50-v57.

35. Markar SR, Gronnier C, Pasquer A, et al. Role of neoadjuvant treatment in clinical T2N0M0 oesophageal cancer: results from a retrospective multi-center European study. Eur J Cancer. 2016;56:59-68.

36. Gabriel E, Attwood K, Narayanan S, Brady M, Nurkin S, Hochwald S, Kukar M. Does neoadjuvant/perioperative chemotherapy improve overall survival for T2N0 gastric adenocarcinoma? J Surg Oncol. 2018;117(4):659-670.

37. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.

38. Medical Research Council Oesophageal Cancer Working Party. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359(9319):1727-1733.

39. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-2084.

40. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393(10184):1948-1957.
41. Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. Lancet Oncol. 2017;18(9):1249-1260.
42. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393(10184):1948-1957.
43. Siddik ZH. Cisplatin: mode of cytotoxic action and molecular basis of resistance. Oncogene. 2003;22(47):7265-7279.
44. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev. 2004;56(2):185-229.
45. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3(5):330-338.
46. Herbst RS, Khuri FR. Mode of action of docetaxel - a basis for combination with novel anticancer agents. Cancer Treat Rev. 2003;29(5):407-415.
47. Al-Batran SE, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol. 2008;19(11):1882-1887.
48. Kamarajah SK, Phillips AW, Hanna GB, Low D, Markar SR. Definitive Chemoradiotherapy Compared to Neoadjuvant Chemoradiotherapy With Esophagectomy for Locoregional Esophageal Cancer: National Population-Based Cohort Study. Ann Surg. 2020.
49. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005;23(10):2310-2317.
50. Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol. 2007;25(10):1160-1168.

51. Siewert JR, Hölscher AH, Becker K, Gössner W. [Cardia cancer: attempt at a therapeutically relevant classification]. Chirurg. 1987;58(1):25-32.
52. Haverkamp L, Seesing MF, Ruurda JP, Boone J, R VH. Worldwide trends in surgical techniques in the treatment of esophageal and gastroesophageal junction cancer. Dis Esophagus. 2017;30(1):1-7.
53. Oesophagogastric Surgery. Lamb SMGP, editor: Elsevier; 2018.
54. Jamieson GG, Lamb PJ, Thompson SK. The role of lymphadenectomy in esophageal cancer. Ann Surg. 2009;250(2):206-209.
55. Lerut T, Nafteux P, Moons J, et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg. 2004;240(6):962-972; discussion 972-964.
56. Li B, Chen H, Xiang J, Zhang Y, Li C, Hu H, Zhang Y. Pattern of lymphatic spread in thoracic esophageal squamous cell carcinoma: A single-institution experience. J Thorac Cardiovasc Surg. 2012;144(4):778-785; discussion 785-776.
57. Peyre CG, Hagen JA, DeMeester SR, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549-556.
58. Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S, Wisnivesky JP. Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. Cancer. 2008;112(6):1239-1246.
59. Dresner SM, Griffin SM. Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy. Br J Surg. 2000;87(10):1426-1433.
60. Mocellin S, McCulloch P, Kazi H, Gama-Rodrigues JJ, Yuan Y, Nitti D. Extent of lymph node dissection for adenocarcinoma of the stomach. Cochrane Database Syst Rev. 2015;2015(8):Cd001964.
61. Oesophagogastric Surgery: Elsevier; 2018 30.4.2018. 368 p.
62. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-131.
63. Weston M, Weston KL, Prentis JM, Snowden CP. High-intensity interval training (HIT) for effective and time-efficient pre-surgical exercise interventions. Perioper Med (Lond). 2016;5:2.

64. Mann TN, Lamberts RP, Lambert MI. High responders and low responders: factors associated with individual variation in response to standardized training. Sports Med. 2014;44(8):1113-1124.
65. Wilson MG, Ellison GM, Cable NT. Basic science behind the cardiovascular benefits of exercise. Br J Sports Med. 2016;50(2):93-99.
66. Balady GJ, Larson MG, Vasan RS, Leip EP, O'Donnell CJ, Levy D. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. Circulation. 2004;110(14):1920-1925.
67. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. N Engl J Med. 1993;328(8):533-537.
68. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346(11):793-801.
69. Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. Jama. 1995;273(14):1093-1098.
70. Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. Bmj. 2012;344:e70.
71. Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. Chest. 1993;104(3):701-704.
72. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth. 2016;116(2):177-191.
73. Barakat HM, Shahin Y, McCollum PT, Chetter IC. Prediction of organ-specific complications following abdominal aortic aneurysm repair using cardiopulmonary exercise testing. Anaesthesia. 2015;70(6):679-685.
74. Lai CW, Minto G, Challand CP, Hosie KB, Sneyd JR, Creanor S, Struthers RA. Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery. Br J Anaesth. 2013;111(4):607-611.
75. West MA, Lythgoe D, Barben CP, Noble L, Kemp GJ, Jack S, Grocott MP. Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. Br J Anaesth. 2014;112(4):665-671.

76. Kaibori M, Ishizaki M, Matsui K, et al. Assessment of preoperative exercise capacity in hepatocellular carcinoma patients with chronic liver injury undergoing hepatectomy. BMC Gastroenterol. 2013;13:119.

77. Prentis JM, Manas DM, Trenell MI, Hudson M, Jones DJ, Snowden CP. Submaximal cardiopulmonary exercise testing predicts 90-day survival after liver transplantation. Liver Transpl. 2012;18(2):152-159.

78. West MA, Asher R, Browning M, et al. Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. Br J Surg. 2016;103(6):744-752.

79. Hartley RA, Pichel AC, Grant SW, et al. Preoperative cardiopulmonary exercise testing and risk of early mortality following abdominal aortic aneurysm repair. Br J Surg. 2012;99(11):1539-1546.

80. Myers J, Voodi L, Umann T, Froelicher VF. A survey of exercise testing: methods, utilization, interpretation, and safety in the VAHCS. J Cardiopulm Rehabil. 2000;20(4):251-258.

81. Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for healthcare professionals from the American Heart Association. Writing Group. Circulation. 1995;91(2):580-615.

82. Levett DZH, Jack S, Swart M, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. Br J Anaesth. 2018;120(3):484-500.

83. Coyle EF. Improved muscular efficiency displayed as Tour de France champion matures. J Appl Physiol (1985). 2005;98(6):2191-2196.

84. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. Heart. 2007;93(10):1285-1292.

85. 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.

86. Whipp BJ, Ward SA, Wasserman K. Respiratory markers of the anaerobic threshold. Adv Cardiol. 1986;35:47-64.

87. Wilson RJT, Yates DRA, Walkington JP, Davies SJ. Ventilatory inefficiency adversely affects outcomes and longer-term survival after planned colorectal cancer surgery. Br J Anaesth. 2019;123(2):238-245.

88. Benington S, Bryan A, Milne O, Alkhaffaf B. CPET and cardioesophagectomy: A single centre 10-year experience. Eur J Surg Oncol. 2019;45(12):2451-2456.

89. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-213.

90. Patel N, Powell AG, Wheat JR, et al. Cardiopulmonary fitness predicts postoperative major morbidity after esophagectomy for patients with cancer. Physiol Rep. 2019;7(14):e14174.

91. Forshaw MJ, Strauss DC, Davies AR, et al. Is cardiopulmonary exercise testing a useful test before esophagectomy? Ann Thorac Surg. 2008;85(1):294-299.

92. Moyes LH, McCaffer CJ, Carter RC, Fullarton GM, Mackay CK, Forshaw MJ. Cardiopulmonary exercise testing as a predictor of complications in oesophagogastric cancer surgery. Ann R Coll Surg Engl. 2013;95(2):125-130.

93. Lam S, Alexandre L, Hardwick G, Hart AR. The association between preoperative cardiopulmonary exercise-test variables and short-term morbidity after esophagectomy: A hospital-based cohort study. Surgery. 2019;166(1):28-33.

94. Drummond RJ, Vass D, Wadhawan H, Craig CF, MacKay CK, Fullarton GM, Forshaw MJ. Routine pre- and post-neoadjuvant chemotherapy fitness testing is not indicated for oesophagogastric cancer surgery. Ann R Coll Surg Engl. 2018;100(7):515-519.

95. Thomson IG, Wallen MP, Hall A, et al. Neoadjuvant therapy reduces cardiopulmunary function in patients undegoing oesophagectomy. Int J Surg. 2018;53:86-92.

96. Whibley J, Peters CJ, Halliday LJ, Chaudry AM, Allum WH. Poor performance in incremental shuttle walk and cardiopulmonary exercise testing predicts poor overall survival for patients undergoing esophago-gastric resection. Eur J Surg Oncol. 2018;44(5):594-599.

97. Jack S, West MA, Raw D, et al. The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery. Eur J Surg Oncol. 2014;40(10):1313-1320.

98. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-423.

99. Janssen I. Influence of sarcopenia on the development of physical disability: the Cardiovascular Health Study. J Am Geriatr Soc. 2006;54(1):56-62.

100. Shafiee G, Keshtkar A, Soltani A, Ahadi Z, Larijani B, Heshmat R. Prevalence of sarcopenia in the world: a systematic review and meta- analysis of general population studies. J Diabetes Metab Disord. 2017;16:21.

101. Thomas DR. Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia. Clin Nutr. 2007;26(4):389-399.

102. Bauer JM, Sieber CC. Sarcopenia and frailty: a clinician's controversial point of view. Exp Gerontol. 2008;43(7):674-678.

103. Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol (1985). 2003;95(5):1851-1860.

104. Giampaoli S, Ferrucci L, Cecchi F, et al. Hand-grip strength predicts incident disability in non-disabled older men. Age Ageing. 1999;28(3):283-288.

105. Al Snih S, Markides KS, Ottenbacher KJ, Raji MA. Hand grip strength and incident ADL disability in elderly Mexican Americans over a seven-year period. Aging Clin Exp Res. 2004;16(6):481-486.

106. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-1547.

107. Reisinger KW, van Vugt JL, Tegels JJ, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg. 2015;261(2):345-352.

108. Ida S, Watanabe M, Yoshida N, et al. Sarcopenia is a Predictor of Postoperative Respiratory Complications in Patients with Esophageal Cancer. Ann Surg Oncol. 2015;22(13):4432-4437.

109. Nishigori T, Okabe H, Tanaka E, Tsunoda S, Hisamori S, Sakai Y. Sarcopenia as a predictor of pulmonary complications after esophagectomy for thoracic esophageal cancer. J Surg Oncol. 2016;113(6):678-684.

110. Papaconstantinou D, Vretakakou K, Paspala A, et al. The impact of preoperative sarcopenia on postoperative complications following esophagectomy for esophageal neoplasia: a systematic review and meta-analysis. Dis Esophagus. 2020.

111. 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. Dis Esophagus. 2018;31(8).

112. Kamarajah SK, Bundred J, Tan BHL. Body composition assessment and sarcopenia in patients with gastric cancer: a systematic review and meta-analysis. Gastric Cancer. 2019;22(1):10-22.
113. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013;381(9868):752-762.
114. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-156.
115. Hallet J, Look Hong NJ, Zuk V, et al. Economic impacts of care by high-volume providers for non-curative esophagogastric cancer: a population-based analysis. Gastric Cancer. 2020;23(3):373-381.
116. Tramontano AC, Chen Y, Watson TR, Eckel A, Hur C, Kong CY. Esophageal cancer treatment costs by phase of care and treatment modality, 2000-2013. Cancer Med. 2019;8(11):5158-5172.
117. Thein HH, Jembere N, Thavorn K, et al. Estimates and predictors of health care costs of esophageal adenocarcinoma: a population-based cohort study. BMC Cancer. 2018;18(1):694.
118. Oesophago-gastric cancer, Assessment and management in adults, Appendix L, NICE Guideline NG83, Cost-effectiveness analyses
2018. Available from: https://www.nice.org.uk/guidance/ng83/evidence/appendix-l-pdf-170036297751.
119. Russell IT, Edwards RT, Gliddon AE, et al. Cancer of Oesophagus or Gastricus - New Assessment of Technology of Endosonography (COGNATE): report of pragmatic randomised trial. Health Technol Assess. 2013;17(39):1-170.
120. Hisashige A, Sasako M, Nakajima T. Cost-effectiveness of adjuvant chemotherapy for curatively resected gastric cancer with S-1. BMC Cancer. 2013;13:443.
121. Wang SJ, Fuller CD, Choi M, Thomas CR. A cost-effectiveness analysis of adjuvant chemoradiotherapy for resected gastric cancer. Gastrointest Cancer Res. 2008;2(2):57-63.
122. Lee L, Sudarshan M, Li C, et al. Cost-effectiveness of minimally invasive versus open esophagectomy for esophageal cancer. Ann Surg Oncol. 2013;20(12):3732-3739.
123. Derogar M, Lagergren P. Health-related quality of life among 5-year survivors of esophageal cancer surgery: a prospective population-based study. J Clin Oncol. 2012;30(4):413-418.

124. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-376.
125. Lagergren P, Fayers P, Conroy T, et al. Clinical and psychometric validation of a questionnaire module, the EORTC QLQ-OG25, to assess health-related quality of life in patients with cancer of the oesophagus, the oesophago-gastric junction and the stomach. Eur J Cancer. 2007;43(14):2066-2073.
126. Blazeby JM, Farndon JR, Donovan J, Alderson D. A prospective longitudinal study examining the quality of life of patients with esophageal carcinoma. Cancer. 2000;88(8):1781-1787.
127. Djärv T, Lagergren P. Six-month postoperative quality of life predicts long-term survival after oesophageal cancer surgery. Eur J Cancer. 2011;47(4):530-535.
128. Noordman BJ, Verdam MGE, Onstenk B, et al. Quality of Life During and After Completion of Neoadjuvant Chemoradiotherapy for Esophageal and Junctional Cancer. Ann Surg Oncol. 2019;26(13):4765-4772.
129. Developing NICE guidelines: the manual2014 31.10.2014.
130. Darling GE. Quality of life in patients with esophageal cancer. Thorac Surg Clin. 2013;23(4):569-575.
131. Gielen S, Schuler G, Adams V. Cardiovascular effects of exercise training: molecular mechanisms. Circulation. 2010;122(12):1221-1238.
132. Coffey VG, Hawley JA. The molecular bases of training adaptation. Sports Med. 2007;37(9):737-763.
133. Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. J Appl Physiol Respir Environ Exerc Physiol. 1984;56(4):831-838.
134. Davis JA, Vodak P, Wilmore JH, Vodak J, Kurtz P. Anaerobic threshold and maximal aerobic power for three modes of exercise. J Appl Physiol. 1976;41(4):544-550.
135. Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet. 2016;388(10051):1302-1310.
136. Edinger JD, Morey MC, Sullivan RJ, Higginbotham MB, Marsh GR, Dailey DS, McCall WV. Aerobic fitness, acute exercise and sleep in older men. Sleep. 1993;16(4):351-359.

137. Petruzzello SJ, Landers DM, Hatfield BD, Kubitz KA, Salazar W. A meta-analysis on the anxiety-reducing effects of acute and chronic exercise. Outcomes and mechanisms. Sports Med. 1991;11(3):143-182.
138. Wolin KY, Yan Y, Colditz GA, Lee IM. Physical activity and colon cancer prevention: a meta-analysis. Br J Cancer. 2009;100(4):611-616.
139. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(20):1548-1561.
140. Moore SC, Lee IM, Weiderpass E, et al. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. JAMA Intern Med. 2016;176(6):816-825.
141. Rezende LFM, Sá TH, Markozannes G, et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. Br J Sports Med. 2018;52(13):826-833.
142. Lynch BM, Dunstan DW, Vallance JK, Owen N. Don't take cancer sitting down: a new survivorship research agenda. Cancer. 2013;119(11):1928-1935.
143. Li T, Wei S, Shi Y, et al. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. Br J Sports Med. 2016;50(6):339-345.
144. Ulrich CM, Himbert C, Holowatyj AN, Hursting SD. Energy balance and gastrointestinal cancer: risk, interventions, outcomes and mechanisms. Nat Rev Gastroenterol Hepatol. 2018.
145. Strasser B, Steindorf K, Wiskemann J, Ulrich CM. Impact of resistance training in cancer survivors: a meta-analysis. Med Sci Sports Exerc. 2013;45(11):2080-2090.
146. Betof AS, Lascola CD, Weitzel D, et al. Modulation of murine breast tumor vascularity, hypoxia and chemotherapeutic response by exercise. J Natl Cancer Inst. 2015;107(5).
147. UK Chief Medical Officers' Physical Activity Guidelines. 2019.
148. Murphy MH, Lahart I, Carlin A, Murtagh E. The Effects of Continuous Compared to Accumulated Exercise on Health: A Meta-Analytic Review. Sports Med. 2019;49(10):1585-1607.
149. Townsend N WK, Williams J, Bhatnagar P, Rayner M. Physical Activity Statistics 2015. 2015.
150. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining

cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334-1359.

151. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol. 1990;13(8):555-565.

152. Jones LW, Eves ND, Peppercorn J. Pre-exercise screening and prescription guidelines for cancer patients. Lancet Oncol. 2010;11(10):914-916.

153. Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. Ann Med Exp Biol Fenn. 1957;35(3):307-315.

154. Gonzaga LA, Vanderlei LCM, Gomes RL, Valenti VE. Caffeine affects autonomic control of heart rate and blood pressure recovery after aerobic exercise in young adults: a crossover study. Sci Rep. 2017;7(1):14091.

155. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-381.

156. Jakobsen MD, Sundstrup E, Persson R, Andersen CH, Andersen LL. Is Borg's perceived exertion scale a useful indicator of muscular and cardiovascular load in blue-collar workers with lifting tasks? A cross-sectional workplace study. Eur J Appl Physiol. 2014;114(2):425-434.

157. Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. Lancet. 1995;345(8952):763-764.

158. Findlay JM, Gillies RS, Millo J, Sgromo B, Marshall RE, Maynard ND. Enhanced recovery for esophagectomy: a systematic review and evidence-based guidelines. Ann Surg. 2014;259(3):413-431.

159. Carli F, Charlebois P, Stein B, et al. Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg. 2010;97(8):1187-1197.

160. Li C, Carli F, Lee L, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. Surg Endosc. 2013;27(4):1072-1082.

161. Barberan-Garcia A, Ubré M, Roca J, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. Ann Surg. 2018;267(1):50-56.

162. Katsura M, Kuriyama A, Takeshima T, Fukuhara S, Furukawa TA. Preoperative inspiratory muscle training for postoperative pulmonary complications in adults undergoing cardiac and major abdominal surgery. Cochrane Database Syst Rev. 2015(10):Cd010356.

163. Durrand J, Singh SJ, Danjoux G. Prehabilitation. Clin Med (Lond). 2019;19(6):458-464.

164. Stefanelli F, Meoli I, Cobuccio R, et al. High-intensity training and cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease and non-small-cell lung cancer undergoing lobectomy. Eur J Cardiothorac Surg. 2013;44(4):e260-265.

165. Barakat HM, Shahin Y, Barnes R, et al. Supervised exercise program improves aerobic fitness in patients awaiting abdominal aortic aneurysm repair. Ann Vasc Surg. 2014;28(1):74-79.

166. Dunne DF, Jack S, Jones RP, et al. Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg. 2016;103(5):504-512.

167. Jones LW, Peddle CJ, Eves ND, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. Cancer. 2007;110(3):590-598.

168. Timmerman H, de Groot JF, Hulzebos HJ, de Knikker R, Kerkkamp HE, van Meeteren NL. Feasibility and preliminary effectiveness of preoperative therapeutic exercise in patients with cancer: a pragmatic study. Physiother Theory Pract. 2011;27(2):117-124.

169. Barakat HM, Shahin Y, Khan JA, McCollum PT, Chetter IC. Preoperative Supervised Exercise Improves Outcomes After Elective Abdominal Aortic Aneurysm Repair: A Randomized Controlled Trial. Ann Surg. 2016;264(1):47-53.

170. 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 J Surg. 2019;43(7):1661-1668.

171. Vermillion SA, James A, Dorrell RD, Brubaker P, Mihalko SL, Hill AR, Clark CJ. Preoperative exercise therapy for gastrointestinal cancer patients: a systematic review. Syst Rev. 2018;7(1):103.

172. Cho H, Yoshikawa T, Oba MS, et al. Matched pair analysis to examine the effects of a planned preoperative exercise program in early gastric cancer patients with metabolic syndrome to reduce operative risk: the Adjuvant Exercise for General Elective Surgery (AEGES) study group. Ann Surg Oncol. 2014;21(6):2044-2050.

173. Xu YJ, Cheng JC, Lee JM, Huang PM, Huang GH, Chen CC. A Walk-and-Eat Intervention Improves Outcomes for Patients With Esophageal Cancer Undergoing Neoadjuvant Chemoradiotherapy. Oncologist. 2015;20(10):1216-1222.

174. Yamamoto K, Nagatsuma Y, Fukuda Y, et al. Effectiveness of a preoperative exercise and nutritional support program for elderly sarcopenic patients with gastric cancer. Gastric Cancer. 2017;20(5):913-918.
175. Minnella EM, Awasthi R, Loiselle SE, Agnihotram RV, Ferri LE, Carli F. Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial. JAMA Surg. 2018;153(12):1081-1089.
176. Dettling DS, van der Schaaf M, Blom RL, Nollet F, Busch OR, van Berge Henegouwen MI. Feasibility and effectiveness of pre-operative inspiratory muscle training in patients undergoing oesophagectomy: a pilot study. Physiother Res Int. 2013;18(1):16-26.
177. Valkenet K, Trappenburg JCA, Ruurda JP, et al. Multicentre randomized clinical trial of inspiratory muscle training versus usual care before surgery for oesophageal cancer. Br J Surg. 2018;105(5):502-511.
178. West MA, Loughney L, Barben CP, Sripadam R, Kemp GJ, Grocott MP, Jack S. The effects of neoadjuvant chemoradiotherapy on physical fitness and morbidity in rectal cancer surgery patients. Eur J Surg Oncol. 2014;40(11):1421-1428.
179. Navidi M, Phillips AW, Griffin SM, Duffield KE, Greystoke A, Sumpter K, Sinclair RCF. Cardiopulmonary fitness before and after neoadjuvant chemotherapy in patients with oesophagogastric cancer. Br J Surg. 2018;105(7):900-906.
180. West MA, Loughney L, Lythgoe D, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. Br J Anaesth. 2015;114(2):244-251.
181. Bhatia C, Kayser B. Preoperative high-intensity interval training is effective and safe in deconditioned patients with lung cancer: A randomized clinical trial. J Rehabil Med. 2019;51(9):712-718.
182. McBride CM, Ostroff JS. Teachable moments for promoting smoking cessation: the context of cancer care and survivorship. Cancer Control. 2003;10(4):325-333.
183. Carli F, Silver JK, Feldman LS, et al. Surgical Prehabilitation in Patients with Cancer: State-of-the-Science and Recommendations for Future Research from a Panel of Subject Matter Experts. Phys Med Rehabil Clin N Am. 2017;28(1):49-64.
184. Weston M, Taylor KL, Batterham AM, Hopkins WG. Effects of low-volume high-intensity interval training (HIT) on fitness in adults: a meta-analysis of controlled and non-controlled trials. Sports Med. 2014;44(7):1005-1017.

185. Milanovic Z, Sporis G, Weston M. Effectiveness of High-Intensity Interval Training (HIT) and Continuous Endurance Training for VO2max Improvements: A Systematic Review and Meta-Analysis of Controlled Trials. Sports Med. 2015;45(10):1469-1481.
186. Liou K, Ho S, Fildes J, Ooi SY. High Intensity Interval versus Moderate Intensity Continuous Training in Patients with Coronary Artery Disease: A Meta-analysis of Physiological and Clinical Parameters. Heart Lung Circ. 2016;25(2):166-174.
187. Biddle SJ, Batterham AM. High-intensity interval exercise training for public health: a big HIT or shall we HIT it on the head? Int J Behav Nutr Phys Act. 2015;12:95.
188. Ferreira V, Agnihotram RV, Bergdahl A, van Rooijen SJ, Awasthi R, Carli F, Scheede-Bergdahl C. Maximizing patient adherence to prehabilitation: what do the patients say? Support Care Cancer. 2018;26(8):2717-2723.
189. Tew GA, Ayyash R, Durrand J, Danjoux GR. Clinical guideline and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery. Anaesthesia. 2018;73(6):750-768.
190. Bousquet-Dion G, Awasthi R, Loiselle S, et al. Evaluation of supervised multimodal prehabilitation programme in cancer patients undergoing colorectal resection: a randomized control trial. Acta Oncol. 2018;57(6):849-859.
191. 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. J Gastrointest Surg. 2020.
192. Grimmett C, Bradbury K, Dalton SO, Fecher-Jones I, Hoedjes M, Varkonyi-Sepp J, Short CE. The Role of Behavioral Science in Personalized Multimodal Prehabilitation in Cancer. Frontiers in Psychology. 2021;12.
193. Okwose NC, Avery L, O'Brien N, et al. Acceptability, Feasibility and Preliminary Evaluation of a Novel, Personalised, Home-Based Physical Activity Intervention for Chronic Heart Failure (Active-at-Home-HF): a Pilot Study. Sports Med Open. 2019;5(1):45.
194. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract. 2004;10(2):307-312.
195. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. J Clin Epidemiol. 2012;65(3):301-308.
196. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211-277.
197. Perthen JE, Ali T, McCulloch D, et al. Intra- and interobserver variability in skeletal muscle measurements using computed tomography images. Eur J Radiol. 2018;109:142-146.

198. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol (1985). 1986;60(6):2020-2027.
199. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-635.
200. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.
201. Yoshizumi T, Nakamura T, Yamane M, et al. Abdominal fat: standardized technique for measurement at CT. Radiology. 1999;211(1):283-286.
202. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, Sayer AA. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing. 2011;40(4):423-429.
203. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.
204. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15(2):155-163.
205. Wong MCS, Hamilton W, Whiteman DC, et al. Global Incidence and mortality of oesophageal cancer and their correlation with socioeconomic indicators temporal patterns and trends in 41 countries. Sci Rep. 2018;8(1):4522.
206. Cancer Research UK, Stomach cancer incidence statistics 2020 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/incidence.
207. Saunders JH, Yanni F, Dorrington MS, Bowman CR, Vohra RS, Parsons SL, Trent Oesophago Gastric U. Impact of postoperative complications on disease recurrence and long-term survival following oesophagogastric cancer resection. Br J Surg. 2020;107(1):103-112.
208. Elliott JA, Docherty NG, Murphy CF, et al. Changes in gut hormones, glycaemic response and symptoms after oesophagectomy. Br J Surg. 2019;106(6):735-746.
209. Griffin SM, Jones R, Kamarajah SK, et al. Evolution of Esophagectomy for Cancer Over 30 Years: Changes in Presentation, Management and Outcomes. Ann Surg Oncol. 2020.
210. Cancer Research UK, Oesophageal cancer incidence by anatomical site. 2015.

211. Kim DJ, Mayo NE, Carli F, Montgomery DL, Zavorsky GS. Responsive measures to prehabilitation in patients undergoing bowel resection surgery. Tohoku J Exp Med. 2009;217(2):109-115.

212. Dronkers JJ, Lamberts H, Reutelingsperger IM, Naber RH, Dronkers-Landman CM, Veldman A, van Meeteren NL. Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. Clin Rehabil. 2010;24(7):614-622.

213. Valkenet K, Trappenburg JC, Schippers CC, Wanders L, Lemmens L, Backx FJ, van Hillegersberg R. Feasibility of Exercise Training in Cancer Patients Scheduled for Elective Gastrointestinal Surgery. Dig Surg. 2016;33(5):439-447.

214. Gillis C, Li C, Lee L, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology. 2014;121(5):937-947.

215. NHS England and NHS Improvement South East - News and Events [Available from: https://www.england.nhs.uk/south-east/cancer-alliances/wessex/news-and-events/.

216. Argudo N, Rodó-Pin A, Martínez-Llorens J, et al. Feasibility, tolerability, and effects of exercise-based prehabilitation after neoadjuvant therapy in esophagogastric cancer patients undergoing surgery: an interventional pilot study. Dis Esophagus. 2020.

217. Grotenhuis BA, Shapiro J, van Adrichem S, de Vries M, Koek M, Wijnhoven BP, van Lanschot JJ. Sarcopenia/Muscle Mass is not a Prognostic Factor for Short- and Long-Term Outcome After Esophagectomy for Cancer. World J Surg. 2016;40(11):2698-2704.

218. Elliott JA, Doyle SL, Murphy CF, et al. Sarcopenia: Prevalence, and Impact on Operative and Oncologic Outcomes in the Multimodal Management of Locally Advanced Esophageal Cancer. Ann Surg. 2017;266(5):822-830.

219. Järvinen T, Ilonen I, Kauppi J, Salo J, Räsänen J. Loss of skeletal muscle mass during neoadjuvant treatments correlates with worse prognosis in esophageal cancer: a retrospective cohort study. World J Surg Oncol. 2018;16(1):27.

220. Nakashima Y, Saeki H, Nakanishi R, Sugiyama M, Kurashige J, Oki E, Maehara Y. Assessment of Sarcopenia as a Predictor of Poor Outcomes After Esophagectomy in Elderly Patients With Esophageal Cancer. Ann Surg. 2018;267(6):1100-1104.

221. Pacifico J, Geerlings MAJ, Reijnierse EM, Phassouliotis C, Lim WK, Maier AB. Prevalence of sarcopenia as a comorbid disease: A systematic review and meta-analysis. Exp Gerontol. 2020;131:110801.

222. Looijaard S, Te Lintel Hekkert ML, Wüst RCI, Otten RHJ, Meskers CGM, Maier AB. Pathophysiological mechanisms explaining poor clinical outcome of older cancer patients with low skeletal muscle mass. Acta Physiol (Oxf). 2021;231(1):e13516.
223. Prado CM, Baracos VE, McCargar LJ, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res. 2007;13(11):3264-3268.
224. Hilmi M, Jouinot A, Burns R, et al. Body composition and sarcopenia: The next-generation of personalized oncology and pharmacology? Pharmacol Ther. 2019;196:135-159.
225. Koh FH, Chua JM, Tan JL, et al. Paradigm shift in gastrointestinal surgery - combating sarcopenia with prehabilitation: Multimodal review of clinical and scientific data. World J Gastrointest Surg. 2021;13(8):734-755.
226. Moug SJ, Barry SJE, Maguire S, et al. Does prehabilitation modify muscle mass in patients with rectal cancer undergoing neoadjuvant therapy? A subanalysis from the REx randomised controlled trial. Tech Coloproctol. 2020;24(9):959-964.
227. Kwon I. Protective effects of endurance exercise on skeletal muscle remodeling against doxorubicin-induced myotoxicity in mice. Phys Act Nutr. 2020;24(2):11-21.
228. Hojman P, Fjelbye J, Zerahn B, et al. Voluntary exercise prevents cisplatin-induced muscle wasting during chemotherapy in mice. PLoS One. 2014;9(9):e109030.
229. Hulzebos EH, Helders PJ, Favié NJ, De Bie RA, Brutel de la Riviere A, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. Jama. 2006;296(15):1851-1857.
230. Mans CM, Reeve JC, Elkins MR. Postoperative outcomes following preoperative inspiratory muscle training in patients undergoing cardiothoracic or upper abdominal surgery: a systematic review and meta analysis. Clin Rehabil. 2015;29(5):426-438.

Appendices

7.1 Participant information sheet

Version 2, date 1.1.2019 IRAS ID 254553

ChemoFit study

We would like to invite you to participate in our research study which aims to maintain or improve patients' fitness during the time when patients are undergoing chemotherapy prior to their surgery for cancer of the gullet or stomach. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through this information sheet with you and answer any questions you have. This should take about 10 minutes. Part 1 of this information sheet tells you the purpose of the study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Please ask us if anything is not clear.

PART 1

What is the purpose of this study?

We are carrying out this study to maintain or improve patients' fitness during the time when they are having chemotherapy treatment before surgery for their gullet or stomach cancer. We will do this by asking patients to perform exercises on daily basis. The majority of the exercise will be done by walking and the aim will be to increase the amount of steps that you walk each day. There will also be some strengthening exercises to do each day.
We believe that there are benefits to be gained by encouraging patients to exercise and increase the amount of steps they do before major operations. We would like to know whether our exercise programme is manageable. This study will help us to understand how we might improve our programme in the future so patients can maintain or improve their fitness before their surgery. We will measure the number of steps that patients do each day by asking them to wear a pedometer. This is a small device designed to count patient's steps which is worn at the waist level.

Why have I been invited?

The clinical team looking after you have identified you as a potential participant in this study. We are inviting patients who have been diagnosed with stomach or gullet cancer and have a treatment plan involving taking chemotherapy before the surgery to remove the cancer.

Do I have to take part?

It is up to you to decide whether you join this study. We will describe the study and go through this information sheet. If you agree to take part, we will ask you to sign a consent form. You are free to withdraw at any time without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part we will explain to you how to follow our exercise programme. Initially you will be given a pedometer which will monitor the amount of steps you do on a daily basis. You will be required to wear it for the most of the day. We will ask you to record the amount of steps you do each day.

In the beginning of the study we will ask you to fill two questionnaires, we will obtain a sample of your blood and we will perform handgrip strength test with you (simple test to check strength in your hand). All of these will not take more than 15 minutes to do.

After one week we will contact you and ask you to increase your daily step count by 2000 steps. You will do this by walking or jogging at moderate intensity for about 30 minutes a day. We will also provide you with elastic resistance bands so you can perform strengthening exercises we have designed. We will teach you how to perform them.

You will be provided with an exercise logbook where we will ask you to record the exercises you do each day and the number of steps you have achieved on each day.

After this we will be in regular weekly contact with you in order to support you with your exercises and monitor your progress. When you feel that you can do more steps each day we will increase the daily step target.

When you feel that you are not able to reach your step goal for the day, you will record this in your diary. This is important information for us. We do not want our patient to be pushed to their limits at all cost especially when they are not feeling well.

This exercise programme will last throughout the entire time that you are receiving chemotherapy, and also in the time after chemotherapy leading up to your surgery. When we know the date of your operation we will ask you to come into the hospital to perform another

fitness test on our bike (the same as the one you did at the beginning). This will measure how has your fitness changed compared to at the beginning of this exercise programme. During this time we will ask you again to fill same questionnaires like you have done in the beginning and also one more questionnaire where you will be asked to provide some feedback about the study. We will once more ask you to perform the handgrip strength test and we will obtain a blood sample from you.

In order to get your views and ideas about the exercise programme, you will be invited to attend our patient feedback group sessions. This will allow us to discuss patients' experience with the programme, and is very important to us, so that we know how you felt about it. We expect that your involvement in the study will take between 13 to 16 weeks.

What happened to my blood samples?

The blood samples that we collect at the beginning and end of the study will be stored in a biobank in Newcastle University. This means that the samples are frozen and kept there for analysis in the future. The samples will be anonymised and stored under your study number. We anticipate completing the tests on these to look at markers of inflammation and cancer in the blood cells within the next few years. We will not be doing any genetic analysis on these samples. If you decide that you do not want us to store your samples then you can ask us to remove these at any point during, or after, the study.

What will I have to do?

If you would like to take part in the study you will need to read this information sheet carefully and take time to consider if you would like to take part. We will then ask you to sign a consent form and you will attend teaching session where we will explain to you how our exercise programme works. After this you can start to follow this programme and we will stay in regular contact with you, each week, to support you and help you to follow this programme.

What are the possible advantages and disadvantages of taking part?

We believe that improving fitness during cancer treatment gets you in better health for having a major operation. This exercise regimen may help to get you fitter for your operation. There are also some pieces of work published that suggest that doing exercise during chemotherapy can make this treatment more effective.

However, the information gained from the study will not alter your treatment, which will be exactly the same as for patients not participating in the study. It is hoped that the study will allow us to help future patients stay fit for surgery.

What happens when the research study stops?

After you have completed the bike test and questionnaires and we have taken blood samples from you before your surgery you will be invited to our voluntary patients' group feedback session. These may take place before or after your surgery, depending upon the timing of the session. After this you will not need to have any further active involvement with the study. The study will not interfere with the normal pathway of care before or after your

operation. We will display the results of the study in our clinic after we have completed this so that you can see these results in the future when returning to clinic.

Will my taking part in the trial be kept confidential?

Yes, we will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

What will happen if I do not want to carry on with the study?

It is completely up to you should you decide to withdraw from the study. You do not need to give a reason if you want to withdraw. If you do decide to withdraw from the study it will not affect the care you may receive in the future. If you do withdraw we will ask you whether we can use the data we have already collected.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the study team who will do their best to answer your questions, Dr Rhona Sinclair or Dr Jakub Chmelo. If you remain unhappy and wish to complain formally, you can do this using the NHS Complaints Procedure.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation from the NHS. You may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study remain confidential?

Newcastle upon Tyne Hospitals NHS trust is the sponsor for this study based in the UK. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. NUTH will keep identifiable information about you for 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information is http://www.newcastle-hospitals.org.uk/about-us/freedom-of-information_how-we-use-information.aspx.

Newcastle upon Tyne Hospitals NHS trust (NUTH) will collect information from you and your medical records for this research study.

NUTH will use your name, MRN number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your

care, and to oversee the quality of the study. Individuals from NUTH and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The research team will pass these details to NUTH along with the information collected from you and your medical records. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

Will my GP be informed I am participating in a study?

We will inform your GP of your participation in the study with a short letter: it will not alter the treatment you will receive.

Who is organising the research?

The research will be organised by Newcastle upon Tyne Hospitals NHS Trust.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee; this is to protect your interests. This study has been reviewed by an ethics committee.

Should you require further information about either:

a) *General information about research contact Newcastle Hospitals NHS Foundation Trust Research and Development department on 0191 282 0059.*
b) *This study or further advice about whether you should participate, please contact the main researchers, Dr Rhona Sinclair (Consultant Anaesthetist) via the Newcastle Hospitals switchboard (0191 2336161). Alternatively you can email Dr Sinclair using Rhona.Sinclair@nuth.nhs.uk.*

If you prefer to raise your concerns with someone not involved in your care, you can contact the Patient Advise and Liaison Service (PALS). This service is confidential and can be contacted on Freephone: 0800 032 0202

Alternatively, if you wish to make a formal complaint you can contact the Patient Relations Department through any of the details below:
Telephone: 0191 223 1382 or 0191 223 1454
Email: patient.relations@nuth.nhs.uk
Address: Patient Relations Department
The Newcastle upon Tyne Hospitals NHS Foundation Trust
The Freeman Hospital
Newcastle upon Tyne
NE7 7DN

7.2 Consent form

Version 2, date 1.1.2019 IRAS ID 254553

Trial ID Number:

Title of Project: ChemoFit study

Name of Researcher(s)

Dr R Sinclair	Consultant Anaesthetist, Royal Victoria Infirmary
Dr J Chmelo	MD student, Newcastle University

Please initial box

1. I confirm that I have read and understand the information sheet dated 1.1.2019 (Version 2) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I understand that if there are changes to the study I will be informed of these. ☐
3. I understand that sections of any of my medical notes will be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐
5. I understand that my general practitioner (GP) will be informed of my participation in the study. ☐
6. I agree to donate blood samples, which will be taken during this study to tissue bank for further research. ☐

----------	----------	----------
Name of Patient	Date	Signature
----------	----------	----------
Name of Person taking consent (if different from researcher)	Date	Signature
----------	----------	----------
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes.

7.3 Letter to general practitioner

Headed paper.
Date:

Dear Dr

(Insert patient details)

ChemoFit study.

Your patient has kindly agreed to take part in this study which is trying to test feasibility of the exercise programme during neo-adjuvant chemotherapy for gastric and oesophageal cancer.
The patient has agreed to perform aerobic and strengthening exercises daily at home. The patient will wear a pedometer to monitor step count as the one aim of the programme is to increase step count performed daily. The patient will also complete an exercise diary and we will be in regular contact with the patient to monitor progress. We expect that involvement of the patient in the study will take between 13-19 weeks. Their involvement in this study will not change their clinical management in any way.
If you have any questions please contact Dr Rhona Sinclair (Consultant Anaesthetist) through the Newcastle Hospitals switch board (0191 233 6161).

Yours Sincerely

Dr R Sinclair
Consultant Anaesthetist, Preoperative Assessment, RVI

7.4 Exercise diary – participant version

EXERCISE DIARY

ChemoFit study – 'get fitter before your surgery'

Version 1, date 25.10.2018 IRAS ID 254553

Name of study participant:

Exercise week number:

Chemotherapy week number:

Target step count for this week	

Date (DD/MM/YY)	Day of the week	Achieved step count today (steps)	30 min aerobic session? (Y/N)	Were you at Borg 3-4? (Y/N)	Strengthening exercise session? (Y/N)	Other physical activities today and their length

7.5 Exercise diary – researcher version

EXERCISE DIARY – RESEARCHER VERSION *ChemoFit study – 'get fitter before your surgery'*

Version 1, date 25.10.2018 IRAS ID 254553

Name of study participant:

Exercise week number:

Chemotherapy week number:

Chemotherapy side effects or toxicity:

Chemotherapy dose reduction:

Target step count for this week	

Date (DD/MM/YY)	Achieved step count today (steps)	30 min aerobic session? (Y/N)	Were you at Borg 3-4? (Y/N)	Strengthening session? (Y/N)	Comments / problems / reasons why step count not achieved	Other physical activities today and their length

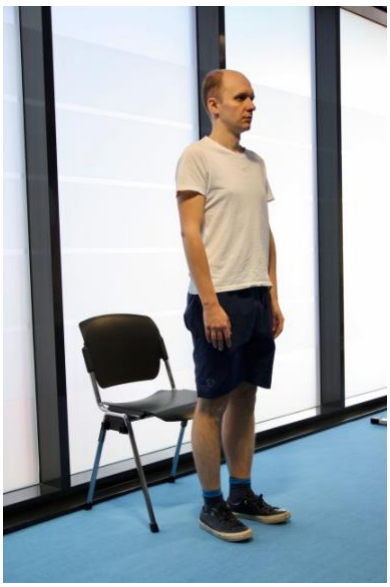
7.6 Borg scale

We want you to achieve the step increment at the levels 3-4 (moderate to somewhat strong) on this scale.

0	Nothing at all
0.5	Extremely weak (just noticeable)
1	Very weak
2	Weak (light)
3	**Moderate**
4	**Somewhat strong**
5	Strong (heavy)
6	
7	Very strong
8	
9	
10	Extremely strong (almost max)
□	Maximal

7.7 Instructional images of strengthening exercises

Exercise 1a - Sit to stand, position 1



Exercise 1a - Sit to stand, position 2

Perform two bouts of this exercise, each lasting for one minute

Repeatedly stand from a chair and then slowly sit back down

If you are able, try not to use your arms to push up from the chair

This exercise can be made more difficult (see exercise two 'wall squat')

Exercise 1b - Wall squat

Perform two bouts of this exercise, each lasting for one minute

Repeatedly lower into a seated position, then back up to standing using the wall to support

Exercise 2 - Biceps curl - Position 1

Exercise 2 - Biceps curl - Position 2

Perform this exercise for a duration of one minute using both arms for two bouts

You can do this exercise in sitting or standing using your resistance band

Secure the band under your feet, using your body weight to hold it in place

Use the band as slowly as possible

Exercise 3 - Upright row - Position 1

Exercise 3 - Upright row - Position 2

Perform two bouts of this exercise, each lasting for one minute in standing

Secure the band under your feet using your body weight to hold it in place

Use the band as slowly as possible

Perform two bouts of this exercise, each lasting for one minute in standing

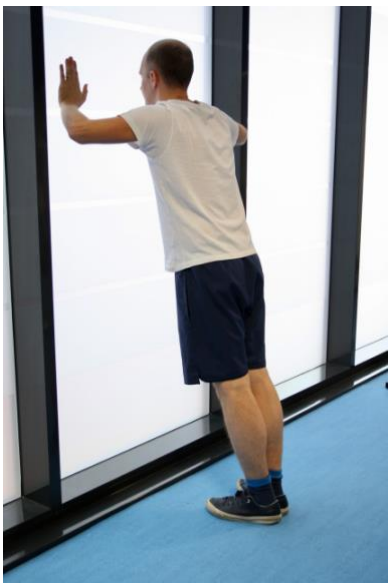
Secure the band under your feet using your body weight to hold it in place

Use the band as slowly as possible

Exercise 4 - Leg abduction - Position 1

Exercise 4 - Leg abduction - Position 2

Exercise 5 - Wall press - Position 1



Exercise 5 - Wall press - Position 2

Perform two bouts of this exercise, each lasting for one minute

Place your hands on the wall in front of you and slowly lower your upper body to the wall

Use your arms to push back into an upright position

This exercise can be made for difficult by moving your feet further away from the wall

7.8 EORTC QLQ-C30 questionnaire

Version 1, date 25.10.2018 IRAS ID 254553

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

7.9 EORTC QLQ-OG25 questionnaire

Version 1, date 25.10.2018 IRAS ID 254553

ENGLISH

EORTC QLQ – OG25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had trouble enjoying your meals?	1	2	3	4
35. Have you felt full up too quickly after beginning to eat?	1	2	3	4
36. Has it taken you a long time to complete your meals?	1	2	3	4
37. Have you had difficulty eating?	1	2	3	4
38. Have you had acid indigestion or heartburn?	1	2	3	4
39. Has acid or bile coming into your mouth been a problem?	1	2	3	4
40. Have you had discomfort when eating?	1	2	3	4
41. Have you had pain when you eat?	1	2	3	4
42. Have you had pain in your stomach area?	1	2	3	4
43. Have you had discomfort in your stomach area?	1	2	3	4
44. Have you been thinking about your illness?	1	2	3	4
45. Have you worried about your health in the future?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you had a dry mouth?	1	2	3	4
48. Have you had problems with your sense of taste?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
50. Have you had difficulty swallowing your saliva?	1	2	3	4
51. Have you choked when swallowing?	1	2	3	4
52. Have you coughed?	1	2	3	4
53. Have you had difficulty talking?	1	2	3	4
54. Have you worried about your weight being too low?	1	2	3	4
55. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4