IMPACT OF NEO-ADJUVANT CHEMOTHERAPY ON CARDIORESPIRATORY RESERVE, SARCOPENIA AND QUALITY OF LIFE IN OESOPHAGO-GASTRIC CARCINOMA

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Abstract

Background

The UK management of locally advanced oesophago-gastric (OG) adenocarcinoma includes three cycles of MAGIC protocol neoadjuvant chemotherapy (NAC). NAC may have a detrimental impact on fitness, quality of life and sarcopenia. Determination of the oxygen uptake at the anaerobic threshold (AT) by cardiopulmonary exercise testing (CPET) objectively measures cardiorespiratory reserve (fitness). AT can be used to predict perioperative risk. Sarcopenia is defined by decreased skeletal muscle mass and is a poor prognostic factor. Patients view their health by means of quality of life (QOL) rather than traditional clinical outcomes. This study was conducted to determine the impact of neoadjuvant chemotherapy on fitness, sarcopenia and quality of life following neoadjuvant chemotherapy.

Methods

Patients with locally advanced OG adenocarcinoma were recruited. CPET, sarcopenia and QOL were measured before and following NAC. AT and peak oxygen uptake (VO_2 Peak) were used to assess fitness before NAC, immediately after, and at two and four weeks interval post neoadjuvant chemotherapy. Computerised topography (CT) at staging and upon completion of NAC was used to measure sarcopenia (muscle mass and function). Quality of life was assessed at similar intervals to CPET, using European Organisation for Research and Treatment quality of life questionnaires: EORTC *QOL-Core 30* and *QLQ-Oesophagogastric 25*.

Results

Thirty one patients with a median age of 65 (41-81) were recruited, 27 patients completed all three cycles of NAC. The results of pre and post NAC measured parameters, represented in mean (+/-1 standard deviation) are as follow: Anaerobic Threshold (ml/kg/min) 15.3 (3.4) versus 11.9(2.5) *P<0.01,* Peak Oxygen Uptake (ml/kg/min) 21.7 (3.9) versus 17.5(3.0) *P<0.01,* Mean Muscle Index (cm^2/m^2) 53.3 versus 49.6(9.5) *P <0.001,* Grip Strength 39.4 (6.6) versus 36.5(6.5) *P<0.01* and Global Health Status (QoL) 72.2(20.5) versus 59.3(25.3) *p=0.043.*

Conclusion

NAC significantly impacts fitness, sarcopenia levels and QoL. Preventing this reduction through development of 'prehabilitation' strategies, or optimising timing of surgery after recovery of the observed decline, may decrease perioperative risk, reduce postoperative complications and improve quality life. This should be the focus of future studies.

Acknowledgements

The work presented in this thesis was undertaken when the author was a Clinical Research Fellow at the Northern Oesophago-Gastric Cancer Unit based at Royal Victoria Infirmary. The work is entirely that of the author although valuable assistance and support was received from others.

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I am indebted to all the study participants, some of whom have sadly passed away, their resilience, humanity and humour was a constant source of encouragement, strength and awe.

Declaration

I declare that the work presented in this thesis is original. I performed the literature searches and critically reviewed the literature on multimodality treatment of oesophago-gastric cancer, CPET in relation to Oesophago-gastric cancer, sarcopenia and quality of life parameters in order to develop the objectives of the study.

I wrote and revised the protocol for the study, the patient participation questionnaire, patient information sheet, GP letters and consent forms. I wrote and presented the study to the ethics committee to gain ethical approval.

I recruited the patients into the study, collected all the relevant clinical data prospectively, coordinated and conducted CPET tests at appropriate time intervals, performed Grip Strength and The Timed Get Up And Go tests as well as completed all the relevant quality of life questionnaires. I performed all the relevant processing of raw data apart from areas which have been mentioned in the acknowledgement section.

The write up of the thesis is entirely my own work. I have presented the work nationally and internationally (Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland and European Society for Diseases of the Esophagus). Finally, the primary end point of the thesis has been published in *British Journal of Surgery* and is included as Appendix 8.1.

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List of Abbreviations

ACA	Adenocarcinoma
ASA	American Society of Anaesthesiologist
AT	Anaerobic Threshold
ATP	Adenosine triphosphate
BMI	Body Mass Index
bpm	beat per minute
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Test
CT	Computersied Topography
DEXA	Dual-energy X-ray Absorptiometry
DNA	Deoxyribonucleic Acid
ECCG	Esophageal Complications Consensus Group
ECF	Epirubicin Cisplatin Fluorouracil
ECG	Electrocardiogram
ECX	Epirubicin Cisplatin Capecitabine
EORTC	European Organization for Research and Treatment
EWGSOP	European Group on Sarcopenia in Older People
FACT-G	Functional Assessment of Cancer Therapy Scale General Measure
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GI	Gastro Intestinal
Hb	Haemoglobin
HR	Heart Rate
LV	Left Ventricular
MDT	Multi Disciplinary Team
MRI	Magnetic Resonance Imaging
NAC	Neoadjuvant chemotherapy
NCRI	National Cancer Research Institute
OG	Oesophagogastric
OGJ	Oesophagogastric Junction
POSSUM	Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity
QoL	Quality of Life
RNA	Ribonucleic Acid
SCC	Squamous cell Carcinoma
SD	Standard Deviation
SV	Stroke Volume
TGUG	Timed get-up-and-go
TNM	Tumour Node Metastasis
UK	United Kingdom
VCO_2	Carbon Dioxide Consumption
VE	Expired Ventilation
VO_2	Oxygen Consumption/Uptake
VO_2 Max	Maximal Aerobic Capacity
VO_2 Peak	Peak Oxygen Uptake
WHO	World Health Organisation

1. Chapter 1 Introduction

1.1 Epidemiology of oesophago-gastric cancer

There are three main types of oesophageal and gastric cancer: squamous cell carcinoma (SCC), adenocarcinoma of the oesophagus and its junction (ACA) and gastric adenocarcinoma of either intestinal or diffuse type(1). Each presents a major health problem in different parts of the world. Carcinoma of the oesophagus is the eighth commonest cancer worldwide(2). Incidence varies across the world with SCC predominating in the less developed countries, reflecting poor socioeconomic status(1).

Adenocarcinoma of the oesophagus and its junction (OGJ) accounts for variable proportions of oesophageal cancer worldwide. ACA is the predominant form of oesophageal cancer in the UK with a male predominance in incidence(3). Furthermore, the overall incidence of ACA is on the rise in the UK(3).

Gastric cancer is the fourth most frequent cancer worldwide with the majority of cases occurring in the developing world(4). Intra-country variations are well known between the Far East and the West where a much lower incidence is noted(5). Interestingly, both in the Far East and the UK, wide inter-country variations are noted with northern provinces demonstrating a higher incidence of gastric cancer(4). There is male predominance in the incidence of both gastric and oesophageal cancer worldwide(5).

1.2 Surgical management of oesophago-gastric cancer

Surgical resection offers the best chance of cure for patients presenting with gastro-oesophageal cancer(6). Oesophagectomy or gastrectomy with curative intent, should only be carried out when an R0 (macroscopic and microscopic clearance) resection is deemed feasible. The operative choice for an oesophagectomy is varied. There are a number of potential operative approaches for oesophagectomy, each with their own advantages and disadvantages, with proponents of different techniques advocating advantages of their technique. However, four randomised control trials comparing the two main types of surgery (transhiatal and trans thoracic) have not demonstrated a difference between the two approaches in heterogeneous groups of patients(7-10). There is however, strong evidence that significantly more nodes are harvested through a transthoracic oesophagectomy in adenocarcinoma of the oesophagus(7, 11). The argument for a formal radical lymphadenectomy is that of optimal staging, improved loco-regional control, improved cure

rates and prognostic(11, 12). A recent meta-analysis of 26 studies demonstrated a significant improvement in overall and disease free survival in patients with an increased lymph node yield(13). This was replicated in patients treated with neoadjuvant therapy followed by resection(13). Therefore a two field, two phase oesophagectomy is the standard operation at our institution.

The same rationale regarding lymph node harvest and extent of lymphadenectomy can be extended to the treatment of adenocarcinoma of the stomach. The evidence in favour of extensive (D2) lymphadenectomy has gained further support by a randomised control trial, which finally demonstrated significantly fewer gastric cancer deaths after D2 dissection(14). D2 gastrectomy is now the recommended mode of lymphadenectomy by the European Society of Medical Oncology(15). This mode of lymphadenectomy is accompanied by either a total gastrectomy for proximal or a subtotal gastrectomy for distal adenocarcinoma of the stomach.

1.2.1 Complications associated with surgery

There is considerable morbidity associated with oesophagectomy and gastrectomy, with cardiopulmonary complications responsible for a substantial proportion of postoperative morbidity and mortality(16). Some of the more substantial and concerning complications include that of anastomotic leak, chest sepsis, acute respiratory distress syndrome, cardiac and thromboembolic compilations. The Esophageal Complications Consensus Group (ECCG) which consists of 24 worldwide high-volume oesophageal surgical centres, has developed a standardized prospective platform for recording complications and quality measures associated with esophagectomy(17).

The ECCG to which The Northern Oesophago-Gastric Cancer Unit in Newcastle, is a major contributor, has recently demonstrated that within two years, in its 24 participating centres, 1955 patients received neoadjuvant oncological therapy (75.6%). The overall incidence of complications was 59% with the most common individual complications reported as pneumonia (14.6%) followed by atrial dysrhythmia (14.5%). Anastomotic leak, conduit necrosis, chyle leaks, recurrent nerve injury occurred in 11.4%, 1.3%, 4.7%, and 4.2% of cases, respectively(17).

1.2.2 Grading of complications

The ECCG uses the Clavien-Dindo system(18) of reporting complications (table 1). ECCG reported that grade IIIb or greater complications occurred in 17.2% of patients. Readmissions occurred in 11.2% of cases and 30- and 90-day mortality was 2.4% and 4.5%, respectively.

Table 1. Clavien-Dindo Classification

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetic, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anaesthesia
- IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication requiring IC/ICU-management
- IVa	single organ dysfunction
- IVb	Multi organ dysfunction
Grade V	Death of a patient

Adapted from Classification of surgical complications(18).

At the Northern Oesophago-gastric Cancer Unit, an overall severe complication rate of 20% (grade III or above) and 90 day mortality of 2.2% has been reported(19). This is compares favourably to earlier published national data by National Oesophago-gastric Cancer Audit(20) and ECCG published data on complications and mortality(17).

1.2.3 Impact of complications

Complications have multiple consequences. Postoperative complications have been demonstrated to be an independent risk factor in reducing overall and disease free survival in patients post oesophageal and gastric resections (figure 1) due to early disease recurrence(21-24). This phenomenon maybe due to immunologic host factors which may dampen the host response's ability to deal with residual disease or enhance microscopic residual disease to develop more rapidly into clinically detectable recurrence(24, 25). Additionally, complications have an impact on patients reported quality of life post-surgery. Two Swedish studies have demonstrated statistically significant reduction in patients' quality of life parameters five years post-surgery(26, 27). These included dyspnoea, fatigue and eating restrictions in patients with at least one major postoperative complication(26, 27).

The results of these studies indicate that new perioperative strategies should aim to optimise technique and minimise post-operative complications, furthermore, patients who experience major postoperative complication should be actively screened for these symptoms and offered rehabilitation (24).

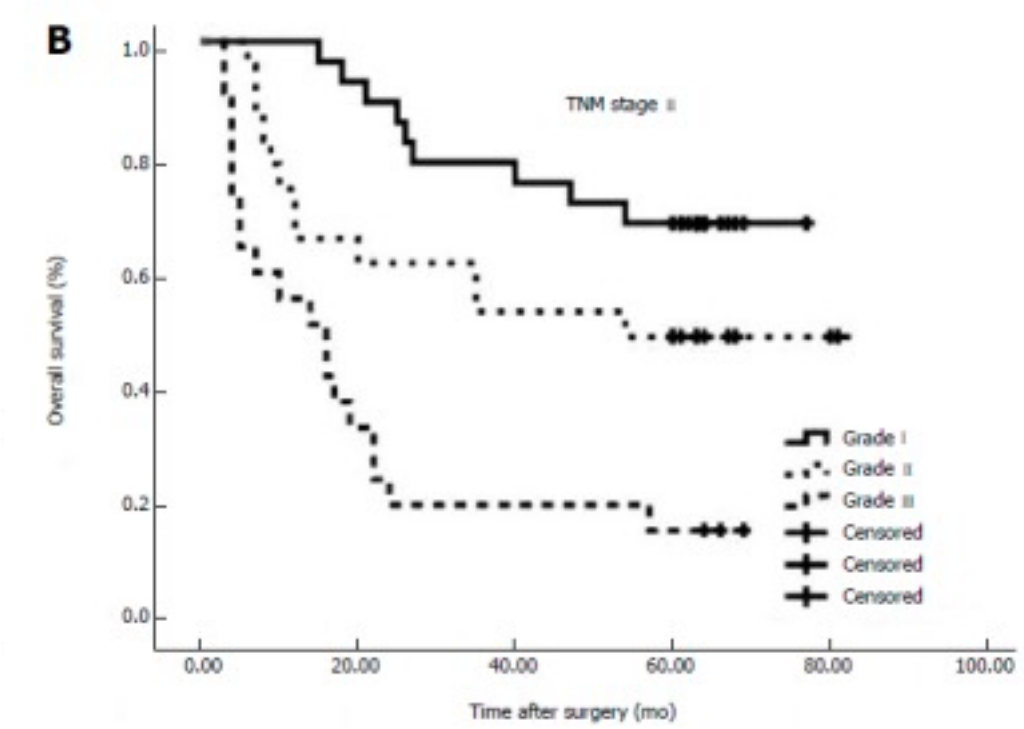

Figure 1. Overall survival curves in patients with different grades of complications (grades I to III) post gastrectomy for stage II cancer. Adapted from Jinag et. al. (25).

1.3 Multimodal treatment of oesophago-gastric cancer

The treatment of oesophagogastric cancer has become more complex; multimodality treatment has become the accepted form of therapy, with improved survival benefits over unimodality therapy. In addition to surgery, the role of neoadjuvant chemotherapy has become accepted practice over the last decade(28). The Medical research council (MRC) OE02 trial was the largest and arguably the most influential trial in this area. It demonstrated that two cycles of preoperative cisplatin and fluorouracil improve survival without additional serious adverse events in the treatment of patients with resectable oesophageal cancer(28). This was followed by the 503-patient United Kingdom National Cancer Research Institute (NCRI) Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC/STO2) Study(29). Although, initially recruiting patients with gastric adenocarcinomas, recruitment was extended to include lower oesophageal adenocarcinomas. The results showed that patients who received perioperative chemotherapy with ECF (epirubicin, cisplatin, and continuous infusion 5-fluorouracil, 5FU) demonstrated a 5- year

survival of 36%, compared with 23% in patients treated with surgery alone. Progression-free survival was also improved by perioperative chemotherapy(29). These results support the use of this treatment strategy as an option for patients with resectable gastro-oesophageal adenocarcinoma. The US Intergroup 0116 trial, INT 0116 demonstrated a survival benefit for patients with gastric adenocarcinomas receiving postoperative chemoradiotherapy as opposed to surgery alone(30).

A more recent trial (FLOT4-AIO) comparing MAGIC protocol perioperative chemotherapy with four pre-op and four post-op cycles of docetaxel, oxaliplatin and leucovorin, demonstrated superior survival outcomes(31). These three major trials demonstrate improved survival with addition of perioperative therapy in oesophagogastric cancer (Table 2).

Table 2. Selection of phase III clinical trials in oesophageal and gastric carcinoma. The first three studies compared surgery alone with perioperative oncological therapy and surgery. In FLOT4 trial, MAGIG protocol perioperative chemotherapy was compared to FLOT perioperative chemotherapy.

Trial	Tumour types (number of patients)	Treatment arms	Median survival (months)	5 year survival (%)	Hazard ratio (95% confidence interval)
OE02(28)	SCC (269) Adeno (533)	Surgery alone Neoadjuvant chemotherapy	13 17	17 23	HR=0.84(0.72-0.98)
MAGIC(29)	Adeno (503) Gastric and GOJ	Surgery alone Perioperative chemotherapy	20 24	23 36	HR=0.75(0.6-0.93)
CROSS(32)	SCC (96) Adeno (270)	Surgery alone Neoadjuvant chemoradiotherapy	24 49	33 47	HR = 0.67 (0.51-0.87)
FLOT4(31)	Adeno (716) Gastric and GOJ	ECX/ECF FLOT	35 50	Not yet published	HR 0.77 (0.63-0.94)

Whilst the relative merits of each approach can be debated, one certain conclusion is that, for all but early-stage tumours, surgery alone is no longer the standard of care. In the UK, based on the results of the MAGIC/ST02 trial, the standard management of patients with operable oesophagogastric adenocarcinoma would involve perioperative ECX (Epirubicin, Cisplatin and Capecitabine) chemotherapy followed by resection(33)(Figure2). This however, may soon alter, as FLOT4 perioperative chemotherapy regimen appears superior to ECX(31).

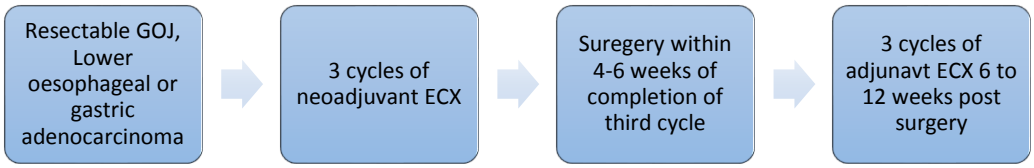

Figure 2. Current clinical UK pathway of patients with locally advanced oesophago-gastric adenocarcinoma, suitable for multimodality treatment.

1.4 Chemotherapy drugs

Chemotherapy is a type of anti-cancer therapy that uses one or more potent chemotherapeutic agent. This alone or in combination with surgery or radiotherapy, have improved survival, reduced recurrence rates and provided palliation to patient with a variety of cancers. Chemotherapy treatments have improved substantially over the recent years with much lower toxicity profiles.

1.4.1 Mechanism of action of Cisplatin

Cisplatin is a member of a class of platinum-containing anti-cancer drugs which is wildly used in a variety of cancers including testicular, ovarian, bladder, neck, cervical, mesothelioma and endometrial cancers. These platinum complexes react *in vivo*, binding to and causing crosslinking of DNA, which triggers apoptosis(34). Cisplatin's therapeutic impact is significantly improved by dose escalation. However, this is offset by increasing nephron and neuro toxicity (35)(figure 3). Cisplatin is transported into cells by a copper transporter, once inside cells, cisplatin binds cellular nucleotides in DNA, RNA and proteins. This consequently leads to apoptosis . Cisplatin induced apoptosis in renal cells as well as tumour cells has been widely reported in both animal and in cell culture systems(36, 37). Furthermore, it has been demonstrated that cisplatin targets mitochondrial pathways thus compromising the electron transporter chain which leads to reduction in cellular Adenosine triphosphate (ATP) levels, if dose of cisplatin is high, ATP depletion can be severe (34). This can result in rapid metabolic collapse and cell death in tumour cells but also in all body systems including cardiac, respiratory and GI systems(37).

The major side effect of cisplatin is that of its nephrotoxicity. The severity of this in early clinical trials led to introduction of hydration protocols, allowing dose escalation to therapeutic levels. However, even with careful hydration therapy almost 30% of patients suffer an elevated blood urea escalation or other evidence of kidney dysfunction days post treatment(35, 37). Tubular epithelial cell damage post cisplatin therapy is a major cause of renal injury. Oxidative stresses also significantly contribute to cisplatin-associated cytotoxicity. The renal micro-environmental changes following cisplatin treatment is a complex process including the initial cytotoxic events, inflammatory events and fibro-proliferative events, all contribute to its toxicity(37).

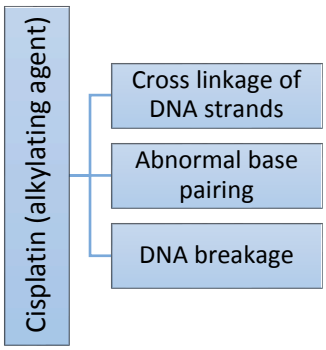

Figure 3. Cisplatin mechanism of action

1.4.2 Mechanism of action of Epirubicin

Epirubicin is an anthracycline drug that acts by intercalating DNA strands. Anthracyclins were introduced over 40 years ago and revolutionised the treatment of many cancers(38). Anthracyclines inhibit topoisomerase II, which is a consequence of anthracycline intercalation between adjacent DNA base pairs (39). This leads to production of hydroxyl free radicals which results in a variety of anti-tumour effects such as apoptosis and cell necrosis. Intercalation can lead to formation of complexes which in turn lead to inhibition in DNA and RNA synthesis as well as initiating DNA cleavage by topoisomerase II, resulting in mechanisms that lead to cell death(40) (Figure 4). Binding to cell membranes and plasma proteins may be involved in the compound's cytotoxic effects(41). Epirubicin also generates free radicals that cause cell and DNA damage(40). This process however causes toxicity to healthy tissues. Myocardial tissue is particularly susceptible to free radical damage. The dose-limiting adverse effects of anthracyclines include acute myelosuppression and cumulative dose-related cardiotoxicity(42). Anthracycline-induced cardiomyopathy is often irreversible and may lead to cardiac failure. Other toxicities of the anthracyclines, including stomatitis, nausea, vomiting, alopecia and ‘radiation recall’ reactions, are generally reversible(39, 42).

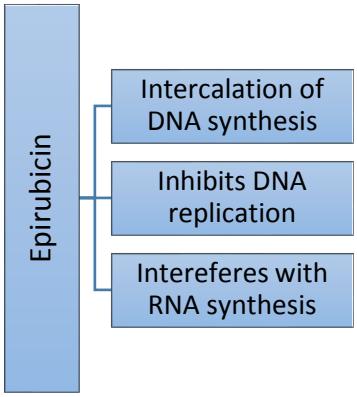

Figure 4. Mechanism of action of epirubicin

1.4.3 Mechanism of action of Capecitabine

Capecitabine is a prodrug that is administered orally and is enzymatically converted to 5-fluorouracil (5-FU) in vivo and works through irreversible inhibition of thymidylate synthase(43). Carboxylesterase and other enzymes convert capecitabine to 5-fluorouracil (5-FU) in normal and tumour cells. Ultimately 5-FU is metabolised to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury and death in two different ways(44). FdUMP and the folate co-factor, N^{5-10}-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex(43). This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division (Figure 5). Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis(44).

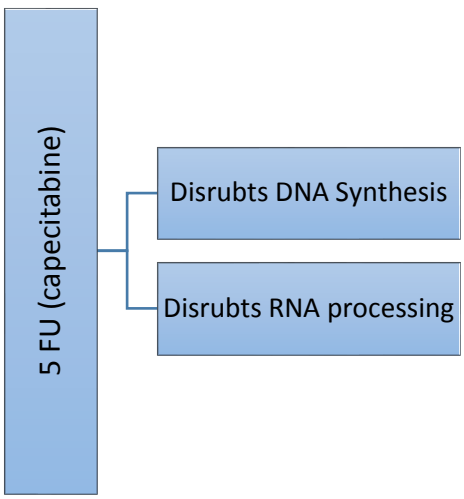

Figure 5. Capecitabine mechanism of action

1.4.4 Multi-system impact of chemotherapy

The mechanism by which the ECX therapy leads to cell apoptosis has been outlined above. However, these cellular changes lead to multiple systemic manifestations. The apoptotic pathways leading to growth deprivation and angiogenesis suppression not only impact the cancerous cells, but can also lead to myocardial cell death(45). Epirubicin induces mitochondrial damage and thereby impacts ATP production adversely leading to increased free radical production(46). This leads to myocardial membrane disruption. However, whether myocardial damage observed has any clinical implication remain controversial. A study of patients receiving high dose of anthracyclines demonstrated that 63% of these patients had left ventricular (LV) dysfunction 10 years after follow up. The prevalence of LV dysfunction was 18% in the lower dose patient group(42). ECX therapy, in particular cisplatin therapy can lead to platelet aggregation, thromboxane formation, endothelial disruption and thrombosis leading to ischaemia in all tissues particularly cardiac and cerebral(46). It has also been demonstrated that patients who received 5-flourouracil and cisplatin are more likely to suffer from dysrhythmias, this can be explained by prolongation of the QT interval(47). Furthermore, hypertension is a side effect of antiangiogenic chemotherapy via the inhibition of the NO-synthase activity and reduction of NO production as well as the cumulative impact of vasoconstriction(48).

1.4.5 Myelosuppression impact of chemotherapy

Myelosuppression is another by product of ECX therapy. It can manifest in a variety of clinical scenarios including neutropenia. Neutropenia increases the risk of infections. This is directly related to the severity and duration of the neutropenia[47]. Anaemia can also result from myelosuppression[47]. This can result in fatigue, tissue under perfusion and thrombocytopenia. Myelosuppression can be managed with a delay and/or a dose reduction in the next scheduled cycle of chemotherapy. This allows to hematopoietic activity to recover and lessens the clinical impacts mentioned earlier(49-52). However, modifications which result in chemotherapy regimen changes result in a lower relative dose intensity (the ratio of delivered dose intensity to planned dose intensity). Some studies, particularly in breast cancer, non-Hodgkin's lymphoma and ovarian cancer have demonstrated that survival may be compromised if the total dose or relative dose intensity falls below a threshold value. However, such studies have not been conducted in the field of oesophagogastric surgical oncology (49-52).

1.4.6 Anaemia

Anaemia is common in patients with oesophagogastric malignancy and its incidence has been

shown to be as high as 40% in some series (53). The incidence of severe anaemia (Hb <8 g/dl) in patients post ECX therapy has been reported to be around 10%(33). The aetiology of malignancy related anaemia is multifactorial with factors such as impaired iron absorption, marrow infiltration, nutritional deficiencies, haemolysis and chemotherapy induced myelosuppression contributing to its manifestation(53). Importantly, a low haemoglobin (Hb <10 g/dl) has been shown to be an independent prognostic factor in gastric cancer patients who underwent 5-fluorouracil-based chemotherapy. This study demonstrated lower response rates, higher rates of disease progression and death in anaemic patients(53). A further study has demonstrated that anaemic (Hb <9 g/dL) patients with gastric cancer who underwent curative treatment with surgery and chemotherapy had a lower 5 year survival rates of 10% than non-anaemic patients 29%. Furthermore, this study demonstrated that non-anaemic patients had much higher chemotherapy response rates. This study also demonstrated that anaemic patients who had received blood transfusion had the worst outcomes(54). The negative effect of anaemia and blood transfusion seems to extend to oesophageal cancer patients too. In a study of anaemic upper gastrointestinal cancer patients, oesophageal cancer patients whom had received blood transfusions demonstrated a shorter overall survival (univariate HR, 2.50; $P = 0.0006$) and disease-free survival (univariate HR, 1.71; $P = 0.016$) than anaemic patients without transfusion. Similar results were observed in gastric cancer patients in the same study(55).

Table 3. Grade 3/4 complication of adjuvant ECF therapy as reported by the MAGIC trial(29)

Grade ¾ Side effects of preoperative ECF therapy in MAGIC trial (29)	**Percentage of participant affected**
Leukopenia	11.5%
Haemoglobinopathy	4.7%
Lymphocytopenia	19.9%
Thrombocytopenia	1%
Nausea	15%
Vomiting	13%
Neurological Effect	9%
Skin effects	8%
Stomatitis	10%
Diarrhoea	6%

ECX regimen chemotherapy has many other reported and prevalent side effects; these include that of thrombocytopenia, neutropenia, diarrhoea, stomatitis, nausea/vomiting, lethargy, alopecia and thromboembolism (Table3) (33). Although, it is difficult to establish a causal link between these complications and fitness, they may impact many health factors, which may result in poorer fitness. Currently there are no published studies on their impact on cardiorespiratory fitness. Furthermore, their impact on patients' quality of life should not be

underestimated and where possible measures should be taken to control or prevent their occurrence(56).

1.5 Risk Stratification

Surgery places severe stresses on a patient's cardiopulmonary reserve, increasing oxygen demand by approximately 40%(57). The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) concluded that although the overall mortality rate post operatively is low 1.6%, patients with certain co-morbidities such as cirrhosis, cardiac failure, history of stroke or diabetes have much higher post-operative mortality rates(58). It is therefore imperative that risk stratification is carried out prior to any surgery and that is the current standard of care as outlined by NCEPOD. Fitness or physiological reserve can be defined as the ability of the patient's organ systems to appropriately and adequately respond the stresses of surgery. Complex surgery such as an oesophagectomy or a gastrectomy exerts a significant physiological impact on organ systems, especially that of cardiorespiratory system(57). Therefore, the ability of the cardiorespiratory system as well as other organ systems to cope with major surgery and its sequelae plays a vital role in determining postoperative outcomes. To that end, accurate assessment of physiological fitness plays a vital role in patient selection; individualised risk prediction and the consent process(59). It also plays a vital role in preoperative optimisation as well as perioperative management. There are many methods to assess fitness and risk stratify patients, including single or composite scores derived from physiological and biochemical variables.

The Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) is one of most used scores for risk-prediction in general surgery(60). POSSUM evaluates 12 preoperative physiological variables and six operative variables using a 4-grade scoring system. The POSSUM scoring system has been reported to overestimate mortality(61, 62). To rectify this, modifications of the POSSUM scoring system have been proposed, including Portsmouth-POSSUM (p-POSSUM)(63) and oesophagogastric-POSSUM (o-POSSUM)(64). Many studies have demonstrated that p-POSSUM is more accurate compared to POSSUM(63, 64). O-POSSUM was designed to predict only postoperative mortality in oesophagogastric patients(64).

The APACHE and the subsequent APACHE II scoring systems, evaluate disease severity by quantifying various physiological variables(65). The APACHE II scoring system is primarily used for monitoring response to therapy in intensive care, with some evidence to suggest that it can predict perioperative events in patients undergoing a variety of surgical procedures(65).

These scoring systems can be used to predict mortality rate to a certain degree, however, they were developed for broad applicability and therefore their ability to accurately predict mortality in a specific patient population limited(66).

1.6 Static versus dynamic testing

Most patients undergoing pre-operative assessment for major surgery such as an oesophagectomy or gastrectomy will undergo conventional tests of cardiac and respiratory function to assess performance at rest or one component of the cardiorespiratory system. These tests include; echocardiography, spirometry or a dobutamine stress test to assess cardiopulmonary performance. However, it is clear that while these screening tests may identify some high-risk patients, they do not provide accurate objective information or guide management to reduce postoperative morbidity and mortality(59). Moreover, none of these tests adequately measure the ability of the cardiopulmonary system to deliver oxygen to the tissues at times of increased demand(59). Furthermore, it can be argued that the traditional methods of assessing fitness has wide inter clinician variability. Therefore, an objective way of assessing fitness in a non-invasive and reproducible way is of great clinical importance

Patients with sub-clinical cardiopulmonary dysfunction or limitation cannot be identified on these tests alone. It is this group of patients who are most likely to be at greater risk of complications and who will most benefit from targeted prehabilitation.

Moreover, composite score such as o-POSSUM do not provide information on the ability of the patient to cope with physiological stress or on how their risk may be mitigated before surgery. A systematic review in prediction models for predicting mortality post oesophagectomy concluded that none of the models identified, including that of o-Possum, could be reliably used in clinical practice with any confidence. This was due to unreliable performance, poor discriminatory values and lack of large validation in the studies to-date(67).

Cardiopulmonary exercise testing overcomes the limitations described so far by providing a global assessment of the patient's oxygen delivery mechanisms at times of increased physiological demand.

1.7 Cardiopulmonary Exercise Test

1.7.1 Historic background

Hill and colleagues reported on adaptations made to an existing apparatus to allow measurement of oxygen consumption VO_2 and carbon dioxide production VCO2 during exercise in 1924(68). Their method involved running a subject connected to a large

bag which collected expired gases. Interestingly, the premise of their method remains unchanged to this date; to examine the response of the cardiopulmonary system to exercise. Such methods were to devise more practical methods suitable for medical use(69).

The application of these dynamic tests in surgical patients was reported by Starr and colleagues in the 1950s. They devised a test that attempted to assess respiratory function and oxygen utilisation in surgical patients peri-operatively(69). Their work suggested that a delayed return to baseline of heart rate, respiratory rate and oxygen utilisation after surgery, could potentially identify patients who are unfit or slow to recover.

Breath-by-breath analysis of gas exchange combined with concurrent electrocardiography during incremental exercise testing was devised by Wasserman. This is what we refer to as cardiopulmonary exercise testing in its current form (Figure 6). Furthermore, Wassermann and his team reported on the ventilatory response to exercise and how it may be used to identify cardiorespiratory disease in 1964(70). The concept of anaerobic threshold was also discovered by his team and applied to the assessment of patients with cardiac disease(70-73).

Presently, Cardiopulmonary Exercise Test (CPET) has become an important method of functional assessment. In its most frequent clinical applications, CPET is performed by deploying a gradually increasing intensity exercise (e.g. ergometer) until exhaustion or until the appearance of limiting symptoms or clinical signs that warrant termination of the exercise (74). Many methods exist for measurement of respiratory gas components during exercise, with the commonest method being that of breath-by-breath analysis. A non-rebreathing mask is used to prevent mixing of inspired and expired gas, respiratory volumes are measured in the process. Both cycle ergometers and treadmills have been used to measure CPET. However, it has become clear that cycle ergometry is the preferred choice with patients as it easier to use, requires less leg training and safer (75).

1.7.2 Parameters measured during CPET

The following parameters are measured during CPET: ventilation; oxygen consumption (VO_2); carbon dioxide production (VCO_2); and the other variables of conventional exercise testing such as pulse, blood pressure and continuous cardiac monitoring. In addition, in specific situations, flow-volume loops before, during and after exertion are measured. CPET provides an integrated method of assessment of all body systems including respiratory, cardiac, vascular, haematopoietic and musculoskeletal. Furthermore, it is non-invasive, dynamic and safe. It permits assessment of both maximal and submaximal peak exercise response to stress. It therefore allows the clinician to diagnose exercise intolerance and functional capacity. It is vital to emphasise that one of the major advantages of CPET is its

ability to be a dynamic test as resting respiratory and cardiac assessment of 'fitness' cannot reliably predict body's response to stresses. It is therefore now accepted that CPET provides a better predictive representation of overall health status(76).

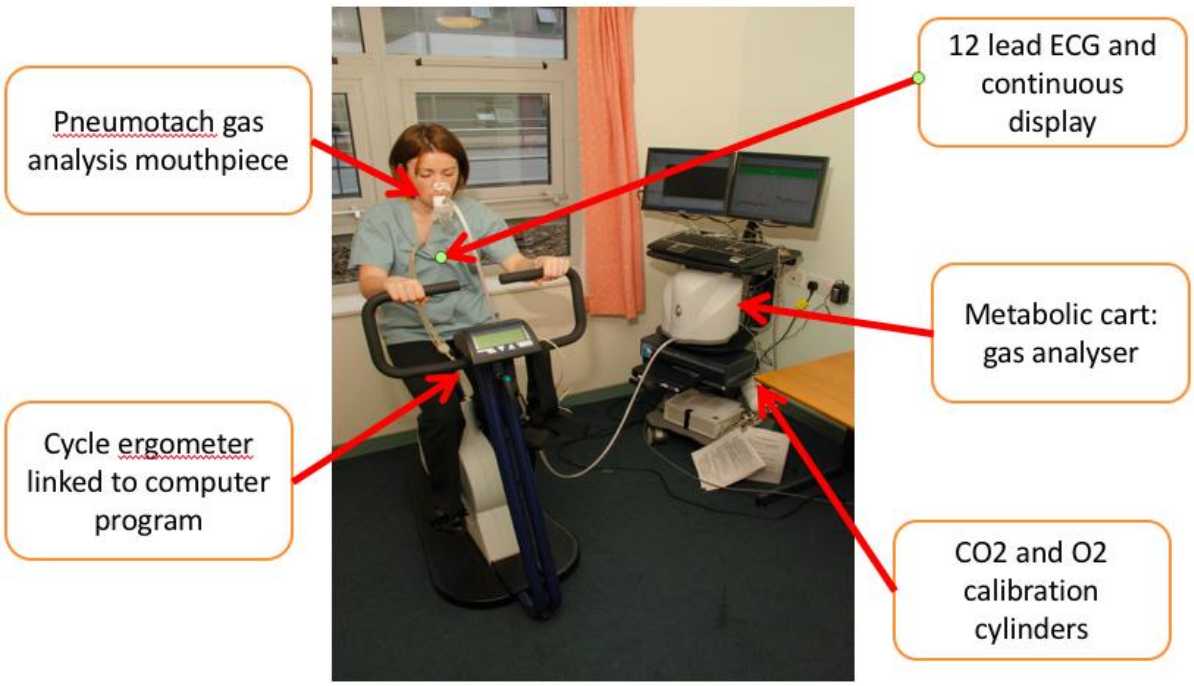

Figure 6. Cardiopulmonary Exercise Room with important attachments indicated in the photograph. With permission from Dr R Sinclair.

1.7.3 Physiology of CPET

CPET measures oxygen uptake at increasing levels of work and can measure cardiopulmonary performance objectively at rest and under stress, determining the patient's physiological capacity to cope with the demands of surgery(77).

Peak exercise capacity is defined as 'the maximum ability of the cardiovascular system to deliver O_2 to exercising skeletal muscle and of the skeletal muscle to extract O_2 from blood"(78). Peak exercise capacity is therefore derived by measuring the following factors: respiratory gas exchange; cardiac and vascular performance; and muscle metabolism.

In order to understand the physiological basis of CPET and exercise physiology, an appreciation of the Fick equation is vital. At rest, the Fick equation states that oxygen uptake (VO_2) equals cardiac output multiplied by arterial minus venous oxygen content (79).

$$VO_2 = (SV \times HR) \times (Cao_2 - Cvo_2)$$

Oxygen uptake is therefore adjusted for body weight and expressed in units of ml O_2/kg/min. Furthermore, it is vital to appreciate the maximal ability of an individual to inspire, transport and metabolise oxygen. This is expressed by the Fick equation at maximum exercise(80).

$$VO_2max = (SVmax \times HRmax) \times (Cao_2max - Cvo_2max)$$

VO_2max (maximal aerobic capacity) is one of the most important parameters in measurement of cardiorespiratory fitness and functional exercise(80).

In healthy individuals a VO_2 plateau that occurs at near maximal exercise and represents the point of maximum oxidative metabolism, has been regarded as the best point for calculating VO_2max. However, in clinical practice a patient may not achieve a demonstrable and clear plateau before cessation of exercise and therefore VO_2 Peak is used as estimate of VO_2max. VO_2 Peak is expressed in absolute values of (ml/min)(79). Resting VO_2 values can increase substantially by a factor of 15 to VO_2 Peak Values of up to 30-50 ml/kg/min in healthy individuals(80).

Many factors may impair an individual's VO_2max/VO_2 Peak. This will therefore result in an abnormally low Vo_2max which is defined as exercise intolerance or functional aerobic impairment. This occurs when one or more of the four variables in Fick equations are impaired. For instance, anaemia or disease of the respiratory system will have a profound impact on Vo_2max by affecting arterial or mixed venous content. Equally, cardiac failure will result in marked reduction in stroke volume in response to exercise. Importantly, interventional studies in anaemic patients with end stage renal failure and chronic heart failure have demonstrated significant improvement to exercise capacity with erythropoietin administration(81, 82). The only study to date, with the aim of establishing an improvement in an anaerobic threshold in adult anaemic patients post transfusion of packed red cells, was conducted in patients with haematological conditions in whom transfusions were required(83). No interventional studies have been conducted to establish whether correction of anaemia in oncological patients results in improved exercise capacity.

In a healthy individual many important changes occur in the four aforementioned parameters in the Fick equation as one proceeds from rest to maximal exercise and after sustained training. The VO_2max is linear at 10 ml/min/watt until a plateau is reached at near VO_2max. Exercise training will increase maximal work load and result in higherVO_2max over time. Training results in lower resting HR. However, the maximal heart rate does not change and is often calculated as 220 beats per minute (bpm) – age. Stroke volume is curvilinear, training increases resting stroke volume and stroke volume at each work load according to Frank-Starling law of cardiac contractility. The a-v O_2 content changes as the mixed venous O_2 content falls. However, O_2 content remains static in healthy individuals. Therefore, training will result in higher maximal a-v O_2 content(76, 78, 80).

It has been demonstrated that low VO_2max predicts higher peri-operative complication rates(84). However, VO_2max requires the patient to exercise to exhaustion and therefore produce a maximal effort. This can be inadvisable or unachievable in patients(85).

Oxygen pulse is a measure of oxygen consumed per heart beat and may provide adjunctive information about and individual cardiac function as it is a measure for stroke volume and peripheral oxygen extraction during exercise(86). Although it has been demonstrated that measuring oxygen pulse provides complementary information to AT and VO_2max about cardiorespiratory fitness and prognosis in patients with coronary heart disease (87), no such data is available in the setting of prognostication in oesophago-gastric surgery or to study the impact of neoadjuvant chemotherapy on oxygen pulse.

1.7.4 Anaerobic Threshold

The concept of an 'anaerobic threshold' (AT) which occurs at an exercise level below that of VO_2max has been proposed as a better index of 'fitness'. During the aerobic phase of CPET, expired ventilation (VE) and VO_2 increases in a linear fashion. This reflects aerobically produced CO_2 production in skeletal muscles[59,60]. Lactic acidosis is negligible during this period of exercise. However, as one continues exercising, anaerobic metabolism becomes dominant as oxygen supply to muscles becomes limited. At this point, there is a substantial increase in lactic acid levels. The oxygen uptake VO_2 at the initial phase of lactic acid production is regarded as AT this is usually seen at 60-70% of Vo_2max. There are invasive and non-invasive methods of measuring AT. Invasive methods are often carried out by direct blood sampling which is impractical in a clinical setting. The non-invasive methods, however, rely on the pattern of change in expired ventilation (VE) relative to Oxygen uptake (VO_2) during exercise. There are two main methods of determining AT non-invasively: the ventilatory equivalent which measures AT as VO_2 at which ventilatory equivalent for O_2 (VE/VO_2 ratio) and end tidal O_2 begin to increase without an immediate increase for Co_2; the V-slope model that defines AT as the Vo_2 at which the rate of increase in VCO_2 relative to VO_2 increases without the presence of hyperventilation. It has to be taken into account that there is inter and intra observer variability in determining AT using the above methods(75, 76, 80).

1.7.5 CPET in perioperative risk assessment in oesophagogastric surgery

There has been great interest in the role of cardiopulmonary exercise testing (CPET) in perioperative assessment of high-risk patients(57). CPET is a simple, non-invasive, cost-effective test that can be performed in either an inpatient or outpatient setting, providing the clinician with an integrated assessment of a patient's cardiovascular and pulmonary system in a short period of time(80). Older *et al* demonstrated that all postoperative cardiopulmonary deaths occurred in patients with an anaerobic threshold (AT) of <11ml/min/kg and/or with significant myocardial ischaemia on CPET(57). Nagamatsu and colleagues were the first group to try and risk stratify upper GI patients based on CPET parameters(88). They demonstated that a low VO_2 max is associated with much higher overall complications rates *p=0.001.* However, no difference was noted in AT levels between the two cohorts *p 0.12*. Forshaw and colleagues have also demonstrated that oesophagogastric patients whose anaerobic threshold was below that of 11ml/min/kg were possibly at higher risk of developing postoperative complications, this was more marked in those whose anaerobic threshold was

below that of 9ml/min/kg(89). However, an earlier study by the same author had demonstrated that an AT cut off of 11 mL/kg/min was a poor predictor of postoperative cardiopulmonary morbidity, this study did however, demonstrate that the level of VO2 peak was significantly lower in patients with postoperative cardiopulmonary morbidity(90).

Table 4. Summary of oesopago-gastric studies using CPET parameters to risk stratify patients.

	CPET parameters	**Complications Present**	**Complications Absent**	***P Value***
Nagamatsu 2001(88)	VO_2 Peak (ml/min)	789	966	*<0.001*
	AT (ml/min)	488	436	*0.12*
Forshaw 2008(90)	VO_2 Peak (ml/min/kg)	19.2	21.4	*0.04*
	AT (ml/min/kg)	13.2	14.4	*0.07*
Moyes 2013(89)	VO_2 Peak (ml/min/kg)	14.6	16.6	*0,07*
	AT (ml/min/kg)	9.9	11.2	*0.05*

These studies (Table 5) have their limitations. The study populations are often heterogeneous with patients undergoing gastrectomy and oesophagectomy which often requires a thoracotomy. Furthermore, these studies are retrospective studies with their inherent limitations. In addition, their results are contradictory. One systematic review in the role of CPET assessment in non-cardiopulmonary surgery has demonstrated that CPET derived variables are superior to other methods of fitness assessment. Furthermore, in 11 of 12 and 7 of 12 studies which were studied in this review, a significant association was noted between VO_2 at anaerobic threshold and VO_2 Peak and postoperative outcomes respectively(91). A recent study by Sinclair and colleagues demonstrated that by using multivariate analysis, any postoperative complication was associated with ventilatory equivalents for carbon dioxide, odds ratio (95%CI) 1.088 (1.02-1.17) p = 0.018 and not AT or VO_2 Peak(92).

CPET results have been increasingly used to stratify patients undergoing major surgery, to guide preoperative optimisation, to predict postoperative cardiac complications after abdominal surgery and, in some centres, to assess whether borderline patients should undergo resection(93). However, as outlined above the evidence in support of the use of exercise derived parameters in risk stratification of oesophago-gastric cancer patients is less well studied.

1.8 Sarcopenia

An obvious by product of ageing is that of a decline in muscle mass. In 1989 Irwin Rosenberg described age related loss of mass as 'sarcopenia'(94). Sarcopenia is not a single entity but rather a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength. The European Group on Sarcopenia in Older People (EWGSOP) has developed a practical clinical definition of sarcopenia which requires the use of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia(95). The reason that both criteria are used for diagnosis of sarcopenia lies in the fact that muscle strength does not only depend on muscle mass and that the relationship between mass and strength are not linear(96, 97).

1.8.1 Mechanism of sarcopenia

There are multiple mechanisms involved in initiation and progression and establishment of sarcopenia. These include protein synthesis and lysis, abnormal levels of circulating hormones such as corticosteroids and insulin, inadequate nutrition and malabsorption, muscle disuse, cachexia and finally age-related changes (apoptosis and mitochondrial dysfunction)(95). In patients with cancer many of these mechanisms are at work resulting in much higher rates of sarcopenia than the general population.

1.8.2 Frailty

Frailty has been demonstrated to impact postoperative complication rates and length of hospital stay. The frailty 'phenotype' can be defined by the presence of several components including unintended weight loss, weakness, poor endurance, slowness and low physical activity(95, 98). Sarcopenia is a major contributor to the above factors. It is vital to appreciate that weight loss is a commonly noticed phenomenon, which is easy to measure and assess in patients. WHO categories of body mass index (BMI) are the reference standard and most commonly used tool in stratification of human body weight: >40.0 morbid obesity, 35.0-39.9 class II obesity, >30 class I obesity, 25.0-29.9 overweight and <18.5 classed as underweight. However, this classification fails to recognise the actual composition of a unit of weight, specifically, proportions of fat and lean tissue such as skeletal muscle. There is wide variation of this and a more objective assessment tool is required.

1.8.3 Measurement of sarcopenia

As described before to measure sarcopenia, muscle volume and its function need to be measured. The possible measurable variables include that of mass, strength and physical performance. Muscle mass can be measure through a variety of measure. Clinical availability, tends to determine which methods is the preferred mechanism. EWGSOP has

produced a list of possible mechanisms by which muscle mass can be measured. Body imaging techniques such as CT, Magnetic Resonance Imaging(MRI) and Dual Energy X- ray Absorptiometry (DEXA) scans are routinely used. CT and MRI scans are the most precise method of measuring muscle mass are extensively used(95). In surgical oncology, as planning and staging scans are mostly carried out with the use of CT scans, muscle mass is mostly measured by computed tomography. Other methods of muscle mass measurements include that of bio-impedance analysis, total or partial body potassium per fat free soft tissue and anthropometric measures such as calf and mid upper arm-circumferance(99-101). The above methods are not as routinely used the use of cross sectional imaging and are therefore not validated in surgical oncology.

The vast majority of studies in surgical oncology only measure muscle mass as a surrogate for true 'sarcopenia'(102). However, it has become standard nomenclature to refer to low muscle mass as sarcopenia and henceforth, this term will be used for referral to low muscle volume since most discussed articles employ this terminology.

A muscle mass of over two standard deviations below that of a typical healthy adults is the commonest method of measuring sarcopenia in studies that have investigated the impact of cancer or chemotherapy on muscle mass (sarcopenia) (95). This is carried out by measurements and assessment of adipose and skeletal muscle surface area on transverse slides at the caudal level of third lumbar vertebra (L3) (Figure 7), where both transverse processes are visible.

Cross sectional muscle area measurements are corrected for patients' heights resulting in L3 muscle index (cm^2/m^2). The derived value is then compared to internationally recognised and accepted BMI and sex specific cut off values: 43 cm^2/m^2 for males with a BMI of < 25.0 and 53cm^2/m^2 for BMI> 25; in females a cut off of 41cm^2/m^2 has been set(103).

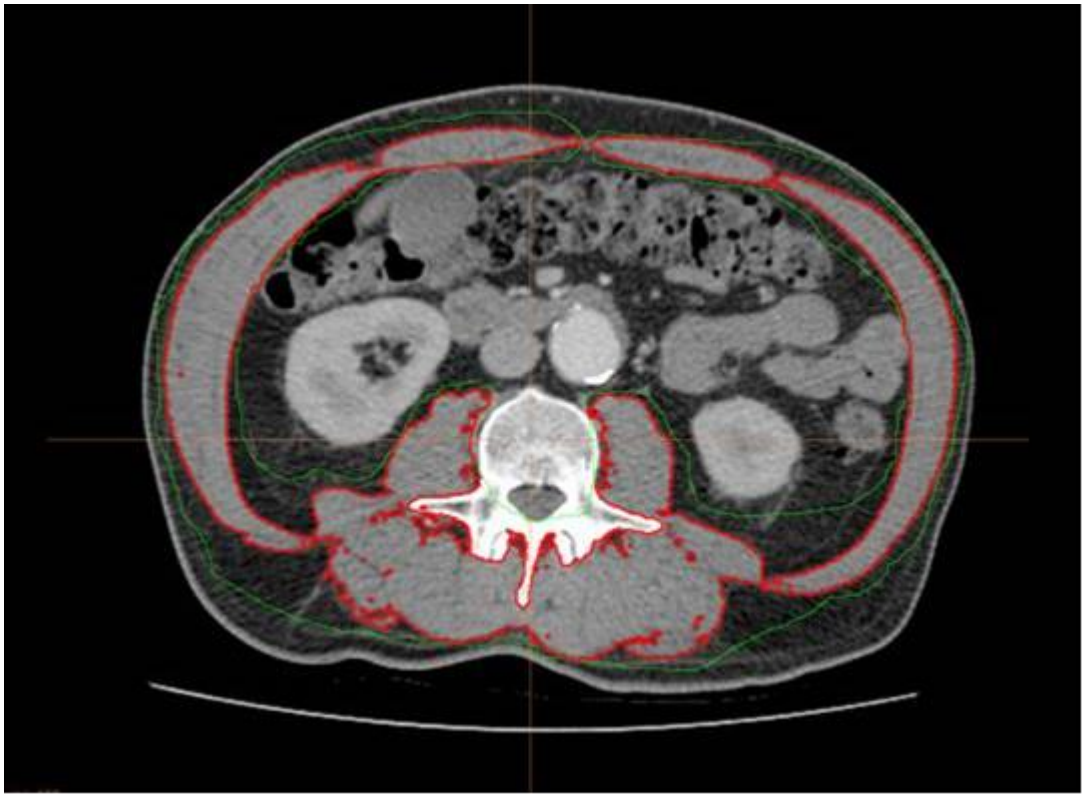

Figure 7. Cross sectional muscle area (red outline) at third lumbar vertebra from a patient recruited in this study.

1.8.4 Clinical implications of sarcopenia

Sarcopenia is associated with physical disability, higher rate of mortality and worse outcomes in patients with non-malignant conditions(104). In malignant conditions, sarcopenia has been associated with a variety of poorer outcomes(105). Sarcopenia has been demonstrated to be a common phenomenon among patients undergoing pancreaticoduodenectomy(106). The combination of visceral obesity and sarcopenia has been demonstrated to be a reliable predictor of postoperative death in this group of patients(106). Furthermore, sarcopenia has been demonstrated to be a predictor of survival following pancreatic surgery, with sarcopenic patients having a 63 % increased risk of death at 3 years. With sarcopenia deemed as an objective measure of patient frailty that is strongly associated with long-term outcome independent of tumour-specific factors(106). In colorectal surgery, sarcopenia has been associated with higher rates of postoperative sepsis, delayed recovery and increased length of stay (105, 107). This phenomenon has been further duplicated in patients with bladder cancer, in whom sarcopenia was associated with higher rates of post-operative complications(108).

1.8.5 Sarcopenia in oesophago-gastric surgery

Impact of sarcopenia on outcomes in oesophagogastric cancer reflects similar findings to the previously mentioned studies. The majority of oesophagogastric cancer patients present with

an element of dysphagia or weight loss which may have an impact on their ability to tolerate NAC followed by surgery. This may further impact on clinical outcomes. Sarcopenia was shown to be common (44.2%) and a significant predictor of pulmonary complications in a cohort of 138 Japanese patients. However, there was no association between other complications or mortality and sarcopenia(109). These results were further replicated in a study in 2016, which further identified sarcopenia as a common entity (75%) and a predictor of pulmonary complications (*p 0.026*) in 199 Japanese patients(110).

Another Japanese study whose focus was that of 325 patients with SCC of the oesophagus demonstrated that sarcopenia was not significantly associated with overall survival (*P 0.54*)(111). However, it did demonstrate that lymph node involvement significantly altered the relationship between sarcopenia and survival rate. In patients without lymph node involvement, sarcopenia significantly reduced overall survival (*P 0.035*), but was uncorrelated with overall survival in patients with lymph involvement (*P = 0.31*)(111). This study also demonstrated a significantly higher anastomosis leakage rate in the sarcopenia group than in the non-sarcopenia group (*P = 0.032*), but other surgical complications did not significantly differ between the two groups(111).

Data in relation to sarcopenia and gastric cancer is sparse with only two published studies. The only western study, was carried out by a Dutch group, who demonstrated that in 152 gastric cancer patient sarcopenia was present in 57.7% of patients. However, this was not a predictor for in-hospital mortality, severe complications, or short term mortality (6-months).(102) The only other study in this field, demonstrated the prevalence of sarcopenia to be lower than previously published data (12.5%)(112). This study however, did demonstrate that sarcopenia was associated with higher risk of complications, longer postoperative hospital stay and costs after gastrectomy. Interestingly this was the only published study in the field of oesophagogastric surgery that defined sarcopenia in accordance to EWGSOP criteria, taking into account both muscle mass (lumbar skeletal muscle index) and function hand grip strength and gait speed. This had allowed for a much more rigorous assessment of sarcopenia. In this study, a sizable number of patients (8.2%) with low muscle mass could not be diagnosed with sarcopenia in view of normal muscle function. There was no difference in clinical outcomes in patients with low muscle mass and those with normal muscle mass. This further demonstrates that combining low muscle mass with reduced muscle function is important in diagnosis of sarcopenia and could predict clinical outcomes more accurately.
It is important to note that recent studies have demonstrated that dose limiting toxicity was associated with sarcopenia in oesophagogastric cancer patients undergoing neoadjuvant chemotherapy(113). This study also demonstrated that the overall survival of sarcopenic

patients was almost half of those who were not sarcopenic – 569 days versus 1013 days *(p=0.04)(113).* Similar finding have been replicated in colorectal cancer patients receiving FOLFOX chemotherapy(114).

1.8.6 Assessment of function

Muscle strength can be measured in a variety of ways as part of assessment of sarcopenia. However, there are very few validated techniques to measure strength. One of the very few validated ways of measuring strength is that of hand grip strength. Hand grip strength is widely used as a surrogate of muscle strength. It is easy to use, replicate and cost effective. However, usefulness will depend on a patient's cognitive and motivational status. Isometric hand grip strength correlates extremely well with lower extremity muscle power and calf cross-sectional muscle area. It has been demonstrated that previously examined upper and lower extremity muscle strength and cross-sectional calf muscle area in the healthy elderly correlate well to sarcopenia. This study also found that hand grip strength was strongly related to knee extension torque and calf cross-sectional muscle area(115). Hand grip strength is measured in kg. Based on statistical analysis of over a thousand patients a cut of point of <30kg in men and <20kg in women denotes a low hand grip strength(115). A further study also reported that hand grip strength correlates well with the results of other muscle function tests (116). However, a large UK study looking at association between grip strength and cardiovascular, respiratory, and cancer outcomes has defined weak grip strength as grip strength of <26 kg in men and <16kg in women (117).

1.8.7 Hand grip strength

EWGSOP recommends that hand grip strength should be used as a measure of muscle strength when diagnosing sarcopenia(95). There are only a few published articles with a focus on hand grip strength and outcomes in the field of oesophagogastric surgical oncology. In a study of 61 patients with SCC of the oesophagus, it was demonstrated that low hand grip was associated with increased mortality (*p 0.016*) and morbidity (*P<0.0001*)(118). A further study in 293 gastric cancer patients, demonstrated that a low hand grip strength was associated with higher risk of post-operative complications especially pneumonia *(p 0.0005)(119).* However, a further study in patients with oesophageal cancer has demonstrated no correlation between functional status including that of hand grip strength and post-operative complications(120).

1.8.8 Timed get up and go as a surrogate for physical performance

Another component of measuring function is that of physical performance. A wide range of tests are available and are validated for this task. The EWGSOP recommends Timed get-up-

and-go test (TGUG) as one of the validated tests to assess lower extremity function, mobility and dynamic balance(95). It is simple and easy to reproduce with excellent inter and intra observer reliability. It uses the time that a person takes to rise from a chair unassisted, walk three metres at a comfortable pace turn around, walk back to the chair and sit down. During the test, the person is expected to wear their regular footwear and use any mobility aids that they would normally require. Normal mobility in large scale studies, have concluded that a cut-off point of 12 seconds to compete TGUG has a good discriminatory value to identify those with poor mobility(121). Furthermore, it has been shown that TGUG correlates well with other established measures of mobility including that of Gait Speed Scores on the Berg Balance Scale and the Barthel Index, however, these tests are much more complex.(122) To date, there are no publications in the field of oesophagogastric surgical oncology outcomes and TGUG.

1.9 Quality of life

There is no strict definition of the elements that contribute or specify the exact components to health related quality of life (QOL). It is globally accepted that physical, psychological and social aspects all contribute to health related QOL.(123) World Health Organization (WHO) defines quality of life (QOL) as an individual perception of life, values, objectives, standards, and interests in the framework of culture.(124) QOL is increasingly used as a primary outcome to measure effectiveness and impact of treatment on patients with a vast array of conditions. Patients, instead of measuring traditional clinical or biological parameters of a treatment or intervention outcomes such as complications, cancer response levels or biomarkers, view their health by means of QOL which estimates the effects on outcomes important to themselves and their daily life.(125)

Morbidity, mortality and long term survival data are widely available for all cancers including oesophagogastric surgery. However, the broader impact of cancer and its oncological and surgical treatment impact on health requires closer attention. QOL can be assessed with the use of variety of validated questionnaires such as Functional Assessment of Cancer Therapy Scale General Measure (FACT-G), Gastrointestinal Quality of Life Index (GIQLI) or the European Organisation for Research Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30).(123) These well-established questionnaires, have been specifically designed for patients with cancer. Some of these questionnaires have cancer specific modules to improve sensitivity, specificity and coverage of the core modules. For patients with upper gastrointestinal cancers, encompassing oesophageal, junctional and gastric cancers impact of specific of symptoms such as dysphagia is profound. Furthermore, to improve survival many

of these patients under-go extensive multi-modal therapy. These therapies impact a patient's a well-being and therefore require objective assessment. (123, 126)

1.9.1 European Organization for Research and Treatment of Cancer (EORTC) Quality of life questionnaires (QLQ)

European Organization for Research and Treatment of Cancer (EORTC) has created one of the most comprehensive Quality of life questionnaires (QLQ) for assessment of health related quality of life in generic cancer patients. This core questionnaire (QLQ-C30) is widely validated and has been used in over 2000 studies in variety of malignancies. EORTC originally developed two additional modules (QLQ-OES18) for oesophageal and (QLQ-STO22) for gastric to the core module (EORTC QLQ-C30) to assess the impact of these cancers on QOL.(123, 126)

They were developed after extensive interviews with patients, health care individuals and study of previously available QOL assessment tools. They were both subject to extensive prospective, international psychometric testing in large group of patients. These results confirmed their reliability and validity in assessing treatment benefit in patients with gastric and oesophageal cancer in conjunction with the core module. The QLQ-OES18 contains 18 items and incorporates four symptom scales measuring dysphagia, eating restrictions, reflux and pain and a further six single items measuring dry mouth, speaking difficulties, difficulties in swallowing saliva, choking and coughing. The QLQ-STO22, includes similar assessment scales for dysphagia eating restrictions, pain and reflux a swell as single item scales for dry mouth and taste. In addition, it has scales for addressing anxiety, body image and hair loss. (123, 126) As stated above, there are many overlaps between QLQ-OES18 and QLQ-STO22.

Therefore, a study on behalf of EORTC attempted to produce a single EORTC questionnaire module (QLQ-OG25) to assess quality of life in upper gastrointestinal cancer patients.(127) In a large, international and multi-centre prospective study the validity and reliability of QLQ-OG25 was established. The QLQ has six symptom scales containing dysphagia, reflux, odynophagia, eating restrictions, pain and discomfort as well as a single scale assessing anxiety. Furthermore, 10 other single items relevant to potentially curative treatment and follow up are included. It is therefore now accepted that EORTC QLQ-OG25 together with QLQ-C30 is a validated, accurate and simple way of measuring health related quality of life in patients with cancer of oesophagus, oesophago-gastric junction and stomach(127).

1.10 Changes in fitness after chemotherapy -- a local pilot study

At our institution, clinicians had noted a decline in fitness in patients treated with neoadjuvant chemotherapy followed by resection. The exact nature of this had not been investigated and there were no objective data to quantify this perceived loss of fitness. With the addition of CPET testing to the perioperative assessment of patients in 2012, an opportunity presented to review CPET data, pre and post ECX chemotherapy in 30 patients (Figure 8) (128).

1.10.1 Results of the local pilot study

This group underwent pre and post chemotherapy CPET testing. The mean AT pre and post neoadjuvant chemotherapy was compared. Mean VO2 at AT pre and post NAC was 13.9ml.kg-1.min-1 (SD 3.1) and 11.5ml.kg-1.min-1 (SD 2.0) respectively (Figure 8). The mean decrease was 2.4 ml.kg-1.min-1 (95%CI 1.2-3.6, p<0.001). Mean VO2 peak also decreased by 2.17 ml.kg-1.min-1 (95% CI 0.73-3.61, p<0.005) pre and post NAC. Ventilatory equivalents were unchanged(128). Please see *Appendix 8.2*.

A reduction in health and 'fitness' post chemotherapy was noticed after treatment with ECX chemotherapy. The cytotoxic effects of these agents and their systemic manifestations may explain this phenomenon as outlined previously(129, 130).

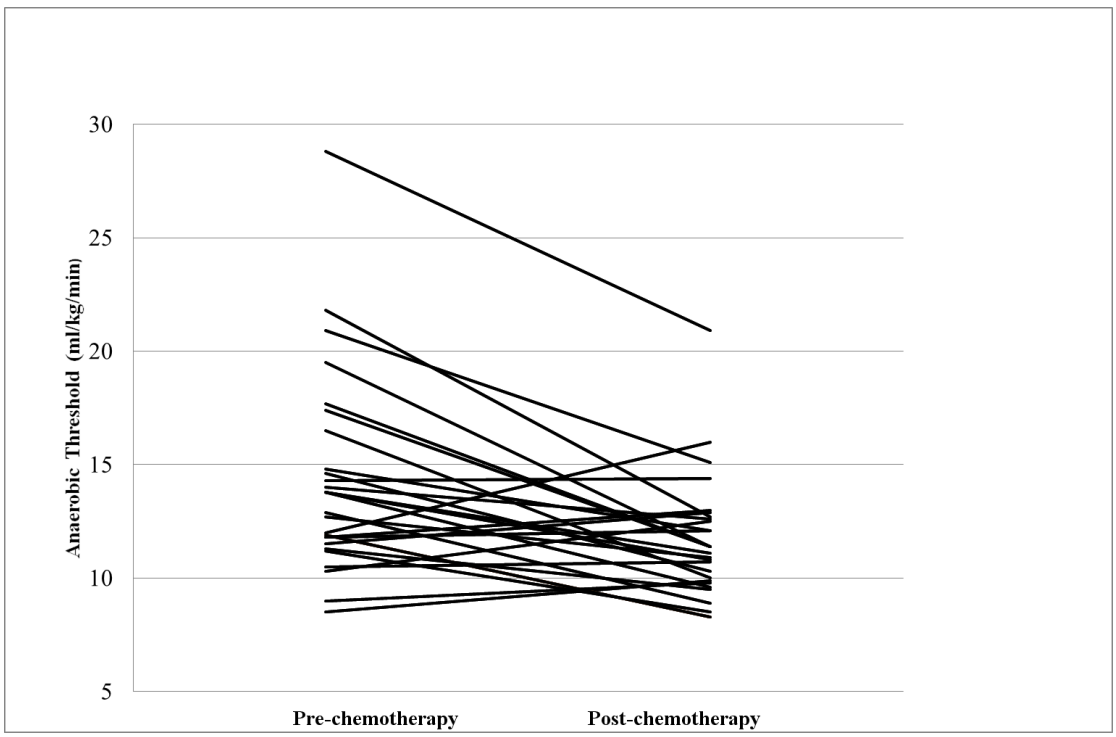

Figure 8. Ladder Plot comparing patients anaerobic threshold before and after neoadjuvant chemotherapy.

This study had a number of limitations. It was an observational retrospective study which looked at data collected in our unit over a period of time. CPET tests post NAC were

scattered over time and the timing of post chemotherapy CPET had a wide variation in its implementation.

1.11 Impact of chemotherapy on fitness before surgery and possible reversibility of its impact

Interventions to improve post-surgical recovery and by implication potentially reduce morbidity, have often focused on intra- and postoperative interventions which for high-risk populations maybe be too late. The preoperative period might be a better time to engage patients in enhancing physical fitness, that is, 'prehabilitation'. Therefore the following areas of research are of clinical significance and may alter practice:

- It is imperative to study the impact of NAC during the preoperative period to establish if the previously witnessed decline in fitness measured by CPET improves, worsens or remains static up to the point of surgical intervention?
- A better understanding of impact of NAC on fitness at the point of surgical intervention may impact the timing of surgery. This will be of huge importance as it may alter standard and currently accepted practice. If fitness remains poor at 4 to 6 weeks post completion of NAC, should surgical intervention be postponed?
- It is also vital to establish the impact of neoadjuvant chemotherapy on sarcopenia and quality of life, as these may play a crucial role on patients' overall fitness.

Once these areas of research have been adequately studied, it may be feasible for further studies to investigate the following clinical relevant area of research:

- The impact of pre-surgical exercise interventions (prehabilitation) on fitness, quality of life and sarcopenia.

Therefore, identifying the pattern of fitness post NAC in oesophagogastric cancer should be a priority and is the primary aim of this study.

2. Chapter 2. Rationale, Aim and Objective

The pilot study carried out at our institution(128), in conjunction with a further recently published study(129) supports the hypothesis that neoadjuvant chemotherapy (NAC) may lead to a measurable and potentially clinically significant reduction in exercise capacity after preoperative ECX chemotherapy. To date, the optimal timing of surgical procedures after neoadjuvant chemotherapy in oesophagogastric cancer is not well defined with no published study exploring this important clinical question. Data in rectal cancer suggest that a prolonged interval between treatment and operation may improve tumour pathologic response, R0 resection rate, and survival(131). One recent study which examined perioperative morbidity and mortality, demonstrated that there was no change to patients' postoperative outcomes when surgery was delayed after neoadjuvant chemoradiotherapy in oesophageal cancer(132). The rate of complete tumour response was higher in patients with a time interval of more than 40 days between neoadjuvant chemoradiotherapy and surgery. This however did not influence long-term survival or recurrence rates(132). Additionally, no study to date has established the oncological safety (survival) when time to surgery is prolonged following neoadjuvant chemotherapy. Conversely, some evidence on the impact on survival exists from a study(133) that demonstrated that the interval between neoadjuvant chemoradiotherapy and surgery may be prolonged with no effect on survival. However, a recent meta-analysis(134), performed to clarify the oncological safety in prolonging the period between completion of neoadjuvant chemoradiotherapy and surgery, demonstrated that an increased interval may have a negative impact on long-term overall survival.

Furthermore, no publication to date has studied the potential reversibility of reduction in fitness post neoadjuvant chemotherapy in oesophagogastric cancer. There are some encouraging data that suggests that a six week exercise programme reversed the effects of neoadjuvant chemo-radiotherapy in a group of rectal cancer patients. This study demonstrated a CPET measured reduction in AT after chemoradiotherapy that remained at six weeks in the control group, but was returned to normal pre-chemoradiotherapy baseline by exercise in the intervention group(135). In a randomised trial in patients with breast cancer undergoing chemotherapy, improvement in physical fitness, body composition, and chemotherapy completion rate was noted(136). A further study in patients undergoing lung resection demonstrated an increase in VO_2Peak of 2.4 (p *0.002*) following a structured exercise programme prior to surgery(137). These studies point to a potential possible benefit in pre-habiliatation prior to surgical intervention. However, the timing of this has yet to be determined.

Currently surgical resection is carried out at four to six weeks post completion of NAC in OG cancer. At our institution the median length of interval between the last capecitabine tablet and resection stands at 36 days, range (27-44). Based on these preliminary data, we therefore hypothesise that NAC will significantly reduce cardiorespiratory fitness, muscle mass and function as well as quality of life and therefore propose a pilot study to investigate the following primary and secondary end points:

2.1 Primary Outcome

Determination of the fitness level, including changes over time, measured objectively by CPET parameters post neoadjuvant chemotherapy and prior to curative intent surgery in oesophago-gastric cancer.

2.2 Secondary outcomes

Secondary end points which will be investigated throughout the course of this study will include:

- Impact of NAC on quality of life indices using The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) in combination with Oesophago-gastric Questionnaire (EORTC QLQ-OG25)
- Impact of NAC on sarcopenia
    - Muscle Mass – CT scans pre and post chemotherapy performed as part of routine clinical care
    - Muscle strength – Grip strength
    - Muscle Function – Timed Get up and Go test (TGUG)
- To explore clinical outcomes
    - Complications post-surgery
    - Survival

3. Chapter 3 Methodology

3.1 Patient Numbers

This pilot study aimed to recruit 30 patients over a 16-month period. This number was decided upon following analysis of the results of the pilot study(128). This was discussed with a university statistician who deemed 30 a suitable number for a pilot study and advised that no power calculations were needed.

3.2 Identification of Patients

Suitable patients were identified at the time of the multidisciplinary team meeting (MDT). This meeting is carried out on a weekly basis and all patients with a new diagnosis of oesophageal or gastric cancer are discussed. All patients who were deemed suitable for NAC followed by surgery were initially seen and informed of the MDT agreed management plan by the surgical team and then referred to the oncology team. At the point of first contact, patients were approached about inclusion in this study. At this point, a patient information leaflet was provided. Patients who were potentially suitable for recruitment in this study were approached during their initial meeting with the surgical team. A patient information leaflet outlining the study design was provided at this point. Patients were given at least 24 hours to consider this information and had the opportunity to ask further questions. Those who were willing to participate in this study were consented accordingly.

3.3 Consent Process and Ethics Approval

The consent process was according to trust policies and involved a written record of patient's agreement. A copy of this was displayed in patient's medical notes. A letter outlining the research was distributed to the participant's general practitioner. This pilot study was approved by the Research Ethics Committee (15/NE/0276) and sponsored by the Newcastle upon Tyne NHS Hospitals Trust (172690). The study was also registered on ISRCTN: 44343129.

3.4 Data Collection

This was a prospective study, which involved measurement of CPET prior to commencement of chemotherapy and at fortnightly intervals post completion of chemotherapy up until the currently accepted date for surgery at approximately four to six weeks post completion of chemotherapy. This was only done in patients with adenocarcinoma of the oesophagus or stomach. Data for secondary outcomes was collected prospectively and in a linear fashion to the above. Furthermore, all routine data, which formed part of the assessment of such patients,

was recorded contemporaneously. All data remained confidential and was secured on an encrypted database. Data specific to this study was not analysed at or communicated to the clinical team. This was to reduce bias. However, if clinical concerns were raised during a an encounter between the research team and the patient, the clinical team were informed with the patient's consent. This had no impact to the flow of routine, predetermined clinical care.

3.5 Inclusion Criteria

- Histological diagnosis of adenocarcinoma of the oesophagus or stomach
- Patients deemed suitable for neo-adjuvant chemotherapy prior to surgery with curative intent
- No absolute or relative contraindication in the patient's ability to perform serial CPETs (table 6)
- Written informed consent

3.6 Exclusion Criteria

- A pathological diagnosis other than adenocarcinoma
- Inability to consent or withdrawal of consent at any point during the research process
- Age of less than 18
- Emergency surgery
- Pregnancy
- Change of neoadjuvant chemotherapy to that of unimodality therapy or neoadjuvant chemoradiation

The exclusion criteria were predominantly designed to protect participants for whom CPET could potentially be harmful. From a practical point of view, and following preliminary patient consultations, patients who were referred from Carlisle, and who met the inclusion criteria were not recruited. This was due to the number of additional journeys (3) that the participants would have had to make and the long distances involved. Additionally, patients who had had their pre neoadjuvant chemotherapy CPET test performed at other institutions, were excluded from the study. This was to reduce potential bias and to maintain consistency within the study.

Table 5. Absolute and relative contraindication to CPET testing. Adapted from ATS/ACCP statement on CPET(138).

Absolute	Relative
Acute myocardial infarction (3–5 days)	Left main coronary stenosis or its equivalent
Unstable angina	Moderate stenotic valvular heart disease
Uncontrolled arrhythmias causing symptoms or haemodynamic compromise	Severe untreated arterial hypertension at rest or haemodynamic compromise (>200 mm Hg systolic, >120 mm Hg diastolic)
Syncope	Tachyarrhythmias or bradyarrhythmias
Active endocarditis	High-degree atrioventricular block
Acute myocarditis or pericarditis	Hypertrophic cardiomyopathy
Symptomatic severe aortic stenosis	Significant pulmonary hypertension
Uncontrolled heart failure	Advanced or complicated pregnancy
Acute pulmonary embolus or pulmonary infarction	Electrolyte abnormalities
Thrombosis of lower extremities	Orthopaedic impairment that compromises exercise performance
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary oedema	
Room air desaturation at rest 85%*	
Respiratory failure	
Acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (ie, infection, renal failure, thyrotoxicosis)	
Mental impairment leading to inability to cooperate	

3.7 Study outline

Following the consent process, suitable patients received three cycles of neoadjuvant chemotherapy. During this process, regular phone follow up was maintained with the patients to be prospectively informed of any changes – two phone calls during each cycle of chemotherapy. This allowed me to be informed of cessation of chemotherapy, dose reductions and chemotherapy complications, if changes were motioned this was recorded. This allowed

me to inform patients of the planned dates for their first post neoadjuvant chemotherapy study date. At this the first post NAC CPET, quality of life questionnaires, Grip Test and Time Get up and Go would be performed. This was carried out between day 0 and seven post completion of NAC. The second CPET test was then accordingly planned for 14 to 21 days post completion of NAC. The final set of data was collected at 28 to 35 days post completion of NAC. Please see figure 9. In some instances, patients were diagnosed with conditions that excluded them from any further CPETs such as thromboembolic events. In such scenarios, this was recorded and no further CPETs were conducted. However, every effort was made to complete the other aspects of the study at the predetermined time intervals.

3.8 Outline of Study Flow

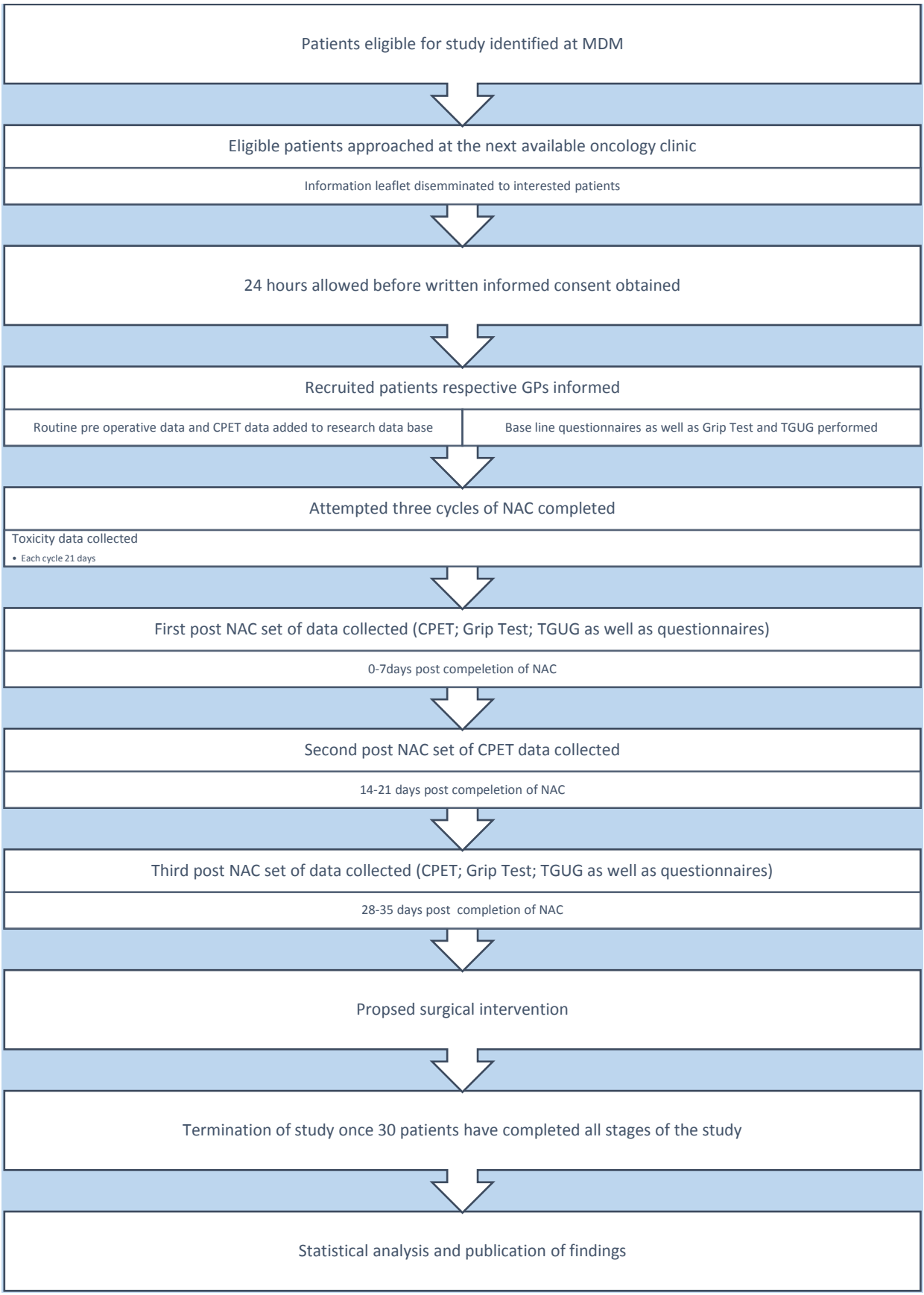

Figure 9. Study flow

3.9 Study Tests

3.9.1 Methodology of CPET

Initial baseline CPET (test 1) was carried out as part of the multidisciplinary meeting investigations before administration of neoadjuvant chemotherapy or staging laparoscopy when possible. The next CPET was performed immediately after completion of neoadjuvant chemotherapy (7-day window) (test 2); the third and fourth tests were completed a further 2 and 4 weeks after the completion of neoadjuvant chemotherapy.

CPET was performed in accordance with the American Thoracic Society/American College of Chest Physicians guidelines(139) for cardiopulmonary exercise testing in. All tests were supervised by trained investigators with full resuscitation facilities immediately available. No adverse event was witnessed during the study period.

3.9.1.1 Equipment and calibration

Flow and gas calibrations was performed before each test session. Calibrations of the preVent TM pneumotachograph was performed with a 3L syringe. The oxygen and carbon dioxide analysers were routinely calibrated with standard gases. Each test was conducted according to our standard protocol, based upon that described by Older (140). Metabolic gas analysis was performed via the metabolic cart (Ultima Series; MGC Diagnostics, Saint Paul, Minnesota, USA), and 12-lead ECG, heart rate and pulse oximetry (Welch Allyn, Skaneateles Falls, New York, USA) was recorded throughout the test.

3.9.1.2 Cardiopulmonary Exercise Test

A resting 12-lead ECG was obtained prior to formal exercise testing and 12-lead ECG monitoring with ST segment analysis was performed continuously. The criteria prompting termination of a test was patient distress or development of >2mm ST depression in any ECG lead. The test protocol was designed to exercise participants to their maximum tolerated aerobic capacity (VO_2 Peak)

Patients performed a symptom-limited continuous ramped test using a cycle ergometer (Ergoselect 200; Ergoline, Bitz, Germany). The subjects initially cycled for up to three-minutes with no resistance applied (un-ramped period). This un-ramped period allowed the participants to warm up and for them to become accustomed to breathing through the pneumotach mouthpiece. An increase in ramped-work-rate was calculated for each individual using age, sex and height to achieve a loaded test with duration of 6–10 min(141). A pedal rate of between 60–70 revolutions per minute was maintained using a visual pedal rate indicator. Each test was terminated when either the participant has reached their peak exercise ability (VO_2 peak), clinical indications to discontinue testing were met, the patient reached

volitional exhaustion (fatigue, pain, lightheaded) or the patient failed to maintain the appropriate pedal speed for 30 seconds despite encouragement(75).

Data analysis using the Breeze Suite™ software (Ultima Series; MGC Diagnostics) was used to determine the VO_2 peak (highest oxygen uptake in the last 30 s of exercise), oxygen uptake at AT using the V-slope method described by Beaver *et al.*(141), and the ventilatory equivalents for carbon dioxide at AT. Oxygen consumption during testing (VO_2) was used to calculate both in millilitres per min and indexed to bodyweight (ml per kg per min).

3.9.1.3 CPET data collected

The principle CPET parameters recorded in this study were those that are routinely recorded in clinical practice (please see figure 6) and included the two main parameters used to measure the primary end point of this study:

- Oxygen consumption at anaerobic threshold AT
- Oxygen consumption at volitional exhaustion (VO_2 Peak)

Other CPET parameters were measured

3.9.1.4 Peak Oxygen Consumption/uptake (VO_2 Peak)

This was measured as the maximum oxygen consumption recorded at volitional exhaustion during the ramped exercise stage of CPET. This is routinely measure by the Breeze Gas Analysis Software.

3.9.1.5 Anaerobic Threshold (AT)

The V-slope method was used to detect AT. This was achieved by 'analysing the behaviour of VCO_2 as a function of VO_2 during progressive exercise tests when exceeding the lactate threshold is accompanied by buffering lactic acid with a consequent increase in VCO_2. This results in a transition in the relationship between VCO_2 and VO_2.(141)'Practically, a change in the slope of the VCO_2 versus VO_2 graph is observed – VO_2 at this point is regarded as AT.

3.9.1.6 Performing and reporting of baseline Test (Test 1)

Test 1 was conducted by an experienced practitioner as per routine clinical care and according to parameters outlined in earlier chapters. This was then reported to the clinical team caring for a study participant through the normal route. It was reported by an anaesthetic consultant who is a member of the preoperative assessment team and then a written report detailing the test outcomes was written into the clinical notes and a full formal printout, including nine panel plot, was filed in the notes. This information was freely available for any clinician to access. A copy of this test result was kept on the CPET software hospital database, and the data required for the study was recorded on the study data collection form. Clinical

investigations that were required as a result of this test proceeded as normal and did not affect the continuation of the participant in the study

3.9.1.7 CPET measurements and reporting of tests 2,3 &4, accuracy and bias

The study CPET tests (tests 2,3 &4) were conducted by myself following a period of apprenticeship to ensure that all appropriate steps in conducting an appropriate ramped exercise test according to standards outlined before were adhered to. The results were not analysed at the time of the actual study as to reduce observer bias.

Two 'clinical experts' with vast experience in interpretation of CPET data (tests 2, 3 and 4) were analysed once the study was completed. Disagreements between the two assessors were resolved by a third assessor. Inter observer consistency was excellent: an interclass correlation coefficient of 0.964 (95 per cent c.i. 0.947 to 0.976) was noted. The primary measured outcome chosen for this study of AT (ml/kg/min) is an objective, reliable measurement of cardiopulmonary reserve that is not dependent upon effort. Studies have demonstrated this to be a reproducible parameter without a significant or clinically relevant variation in measurements across a number of repeated tests(142). V_{O_2} peak was also analysed in similar fashion. The principle sources of bias in this study were that of operator and observer bias.

As stated previously, AT is a reproducible, consistent measurement and is indeed independent of effort for a specific participant, this has been demonstrated in previous studies(142). This effectively excluded operator bias in this study. In order to diminish observer bias, CPETs were analysed once all tests were conducted, no patient identifiable data was evident, the sequence of tests as well as the timing of the tests were not available to the assessors. Furthermore, they were blinded to one another results.

3.9.1.8 Safety of repeated cardiopulmonary exercise tests

No data in literature was encountered to suggest that performing more than one CPET test would negatively impact study subjects. Furthermore, patient participation questionnaires have indicated that patients were willing to undertake the proposed extra tests. No adverse outcomes were encountered as result of extra CPETs.

3.10 EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires

3.10.1 Methodology

To measure quality of life, this study employed the validated, 30 item European Organisation Research and Treatment of Cancer-Quality of Life – C30 (EORTCQLQ-C30); version 3 questionnaire. This encompasses; a global quality of life subscale, five functional subscales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea &

vomiting, pain) and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). All the above scales range from 0 to 100. In the Global quality of life subscale as well as the five functional scales a higher value will indicate a higher quality of life and better level of function respectively. In the symptom scales as well as the single items, a higher score is indicative of more symptoms. Furthermore, the oesophageal and gastric cancer specific quality of life concerns are assessed using the validated 25-item oesophagogastric module (QLQ-OG25). This consists of six symptom scales (dysphagia, eating restrictions, reflux, odynophagia, pain, and anxiety). This is also scored from 1 to 100, with higher scores indicating more symptoms. A linear scale of 0-100 was achieved by converting all scales and item scores from QLQ-C30 and QLQ-OG25 according to the EORTC-C30 scoring manual (127).

3.10.1.1 Timing of questionnaires

These questionnaires were given to the study participants at the time of the consent (Test 1), immediately post neoadjuvant chemotherapy (Test 2), and at the final CPET test (Test 3). Participants were given time to fill the questionnaires before the conduct of CPET, hand grip or Get up and Go part of the assessment. The questionnaires were inspected by myself to ensure correct completion. When a participant failed to attend the scheduled hospital appointment to carry out the CPET, the questionnaires were posted at the appropriate time interval and collected at the time of the surgery.

3.10.1.2 Quality of life questionnaires accuracy and bias

All questionnaires were examined by myself at the time of completion to ensure completion as this ran into three pages and at times participants stopped at page two. Once a questionnaires was completed this was filed and not analysed. At consequent tests (tests 2 and 3) for the same participants, I and the participants deliberately did not have access to the previously completed tests to eliminate potential operator and observer bias. All questionnaires were only analysed by myself once the study was completed. I was blinded to patients' other tests results. Measurements were tabulated and all calculations were checked twice to ensure accuracy.

3.11 Sarcopenia Score, Grip strength and timed get up and go

3.11.1 Measurement of Sarcopenia

Sarcopenia is a syndrome characterised by progressive and generalised loss of skeletal muscle mass and function. Patients with sarcopenia have a higher incidence of chemotherapy-related toxicity and decreased survival (113). The European Working Group on Sarcopenia recommends using the presence of both low muscle mass and low muscle function (strength

or performance) for the diagnosis of sarcopenia(95).

To investigate this phenomenon, staging CT scans were performed as part of routine clinical care, pre and post neoadjuvant chemotherapy and were analysed to determine the sarcopenic effect of NAC. Skeletal muscle measurements were performed using an image manipulation software HERMES Software (Hermes Medical Solutions, AB Skeppsbron 44, 111 30 Stockholm, Sweden). Each radiologist was instructed to select an axial slice at mid L3 level using a sagittal image for reference. They then drew a region of interest to include all skeletal muscle in the chosen slice including; the psoas muscles, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, and rectus abdominus. Within this region of interest, voxels within the Hounsfield Unit range -29 to +150 were automatically selected. These threshold volumes were then manually adjusted to remove any non-muscle groups of voxels. The muscle area (cm^2) and slice position were recorded.

3.11.2 Accuracy of measured muscle area

Measurements for all patients was performed twice by each radiologist, with repeated measurements performed at least a week apart. The radiologists were be blinded to clinical data, other investigator measurements and their own previous measurements. In patients with discrepant identification of L3 between radiologists, the 'correct' level of L3 was agreed by consensus. Intra-observer comparisons were made between repeated measurements (Table 7) on the same patient by the same radiologist using Bland-Altman plots. Variability was calculated as 1.96*standard deviation of the differences, and the limits of agreement as the mean difference +/- variability. The mean of the absolute values of the differences between single and two slice analyses were 0.98 cm^2 and 0.95cm^2 with variability of 2.92 and 2.80 respectively. This demonstrated excellent intra-observer consistency. Inter-observer comparisons between radiologists demonstrated non-significant variation in measurements between radiologist.

Table 6. Inter observer differences between three radiologist in determining muscle area at L3

	Number of paired measurements	Mean Difference, cm^2 (95% Confidence Interval)	Variability (1.96*SD), cm^2	Mean Absolute Difference, cm^2
2 slice data				
Radiologist:				
A v B	58	-1.99 (-2.50, -1.47)	3.94	2.18
A v C	58	0.15 (-0.25, 0.55)	3.05	0.87
B v C	58	2.14 (1.60, 2.68)	4.09	2.42

Upon completion of the tests and once all muscle areas were calculated, the muscle mass area (cm^2) was converted to Muscle Mass Index (cm^2/m^2) using patients' heights and muscle mass

area. This allowed comparison to internationally published radiologically derived sarcopenia cut-off points of < 52.4 (cm^2/m^2) and <38.5 (cm^2/m^2)(143) in men and women respectively to arrive at a proportion of radiologically sarcopenic patients before and after neoadjuvant chemotherapy.

3.11.3 Methodology of Grip Strength

Furthermore, grip strength (kg) as a surrogate of muscle function, was measured pre and post neoadjuvant therapy and prior to surgery using a digital hand dynamometer (Table 8). This was carried out after the completion of quality of life questionnaires and before CPET testing. The hand dynamometer is the most widely used instrument with established test-retest, inter-rater and intra-rater reliability(144). The patient's dominant hand was used with the maximum score out of three attempts recorded. This was according to the Southampton protocol(144).

Table 7. Summary of steps measuring grip strength

Posture	Seated
Arm position	Rested on a pillow or arm of the chair
Wrist position	Neutral, thumb facing up
Lower extremity position	Feet on the floor
Verbal instructions	'*I want you to squeeze as hard as you can for as long as you can, till I say stop. Squeeze, squeeze, squeeze stop.'*
Number of attempts	Three trials with the dominant hand and best score recorded.

In order to reduce bias, patients were blinded to their previous scores. Furthermore, I was also blinded to the patients' previous effort so as to reduce observer bias. Results were not analysed until the completion of the study. At the time of the analysis results were processed in random without knowledge of the sequence of tests.

3.11.4 Methodology of Timed Get up and Go

Another component of measuring function is that of physical performance. As per The EWGSOP recommendation Timed Get-up-and-Go test (TGUG) as one of the validated tests to assess lower extremity function, mobility and dynamic balance, was used in this study(95). This test is simple and easy to reproduce with excellent inter and intra observer reliability. Patients were asked to rise from a chair unassisted, walk three metres at a comfortable pace turn around, walk back to the chair and sit down. The distance was marked and a stop clock was used. During the test, the person was expected to wear their regular footwear and use any mobility aids that they would normally require (this did not apply to the study cohort). Normal mobility in large scale studies, have concluded that a cut-off point of 12 seconds to compete TGUG has a good discriminatory value to identify those with poor mobility, this was used in this study(121). Furthermore, it has been shown that TGUG correlates well with other

established measures of mobility including that of Gait Speed Scores on the Berg Balance Scale and the Barthel Index, however, these tests are much more complex(122). As in previous sections, participants and assessor were blinded to previous results. Data was not analysed until the completion of the study to reduce bias. To date, there are no publications in the field of oesophagogastric surgical oncology outcomes and TGUG.

3.11.5 Methodology of METs Score

An estimated Metabolic Equivalents Score (METS Score) will be used to assess functional capacity. One METS is defined as the energy expenditure while at rest. Light intensity activities are classified as having a METS score of <3 (1=walking around the house; 2= eating and dressing; 3= walking 200 yards on the flat) moderate intensity activities are assigned a METs score of 3 to 6 (5= climbing a flight of stairs and 6+ brisk walking) and high intensity activities a METs score of 6 to 10(9= jogging and 10 = brisk swimming)(145). METS are assessed using a self-reported questionnaire and are an estimate, as such an over estimation of fitness may occur(146). Participants will be asked as what is a maximum equivalent activity to the above scale and a score will be assigned to them. This will be carried out as part of the preassessment process for every patient and is conducted by a trained nurse.

3.12 Data collected

Summary of all the data collected during the study outlined in the table below.

Table 8. Data collected during the study

CPET and physiological data
Predicted and achieved maximal heart rate (bpm); predicted and achieved AT (ml/kg/min); predicted and achieved VO_2 peak (ml/kg/min); VE/VCO_2 at AT; VE/VO_2 at AT; O_2/pulse at AT; $MMVVO_2$ at rest (pre-exercise); dates between chemotherapy and CPET tests; Dates of CPET tests (1,2,3,4). Resting blood pressure(mmHg); resting heart rate (bpm); baseline ECG report; baseline Pulmonary function tests (FVC, FEV1, FEV1/FVC ratio); physical examination (normal /abnormal)
Quality of life Quaternaries
EORTC QLQ-C30 and EORTC QLQ OG25
Muscle Mass and Function
CT L3 muscle area measurements before and after CPET. Grip strength (Kg). Timed get up and go measurements (S)
Chemotherapy Data
Chemo regimen; number of cycles; reason for stopping cycles; toxicity
Demographic information
Age (yrs); sex; weight (kg); height; (cm); BMI (kg/m^2); haemoglobin concentration (g/dl) before and after chemotherapy; ASA grade (1-4); proposed operation; METs score; list of co-morbidities (cardiac, respiratory, GI, endocrine, thromboembolic etc); smoking history, drug history; NYHA Heart Failure Class (1-4); TNM 7 classification for gastric and oesophageal tumours preoperatively; WHO performance status; nutritional assessment form; date of admission; date of discharge; proposed operation; actual operation; position of tumour; postoperative stage TNM 7 for oesophageal and gastric tumours; operation date; post-operative complications (infection; GI leak; cardiorespiratory complications, other post-operative complications); Accordion score (0-6); return to theatre; return to ITU; reason for return; in hospital death, 30 and 90 day mortality; cause of death. Date and location of recurrence at one year post surgery.

3.13 Statistical methods

All data were analysed by the author who had sought statistical advice to ensure that correct analysis were performed. A Shapiro-Wilk test was used to distinguish between normally and non-normally distributed data sets in all obtained data. When comparing normally distributed data only once, a paired *t* test was carried out to identify statistical significance. The Wilcoxon matched-pairs signed rank test was used for non-normally distributed data such as forced vital capacity.

When results from test 1 (baseline) were compared with results from tests 2, 3 and 4 (after neoadjuvant chemotherapy) an ANOVA with *post hoc* Tukey's honestly significant difference test was used. An ANOVA test was used instead of a paired t-test to reduce Type I error. This was an important consideration as by running two *t*-tests or more on the same data, a significant and unacceptable Type 1 error would have occurred. For instance, had CPET results between test 1 and test 2; test 1 and test 3; test 1 and test 4; and test 2 and 4, been compared using repeated paired *t* test, there would have been a strong possibility that the falsely significant *P* values may have been achieved. Using ANOVA tests controlled for these errors so that the Type I error remained at less than 5%, therefore, *p* values were archived with the confidence that statistically significant result detected were not due to multiple duplication of tests. A *P* value of < 0.050 was deemed statistically significant. Analysis was performed using SPSS® version 21.0 (IBM, Armonk, New York, USA) and Microsoft Office Excel version 2016 (USA).

Inter and intra observer variability when analysing CPET and muscle area measurement as well as questions of bias and measure to reduce these were addressed in previous relevant sections (3.10&3.11).

3.14 Ethical and Safety Considerations

3.14.1 Timing of surgery

No adverse events as a result of CPET tests were noted. The routine post NAC care pathway was followed irrespective of patient participation in this study. All patients involved in the study followed the established and routine pathway. The median time between completion of NAC and surgery stood at 31 (26-42) days. This time frame allowed for completion of all proposed sets of data collection, prior to surgery, with-out deviation from the currently accepted care pathway. One patient had to undergo surgery at an earlier date post NAC, at 26 days due to acute haemorrhage. Therefore, the participant could not undergo the final set of

tests (CPET test 4). No safety considerations were encountered during the conduct of this study.

3.14.2 Safety profile of repeated CPET tests

There is no data in literature to suggest that performing more than one CPET test will negatively impact study subjects. This was replicated in this study with no reported adverse outcomes secondary to CPET.

3.15 Patient involvement in design of study

The overall design of the study was put forward to a group of patients with treated oesophago-gastric cancer in the form of a presentation with a distributed questionnaire that was answered by individual patients separately. This was received positively with an overall 100% positive response to the design of questionnaires. Furthermore twenty post-operative patients were questioned regarding their overall experience with the CPET test and their willingness to participate in the proposed study. Ninety five per cent of patients rated their CPET experience as good or satisfactory, additionally, 90% of participants were willing to undergo further 3 CPETs post completion of NAC. Please see appendix 1. This indicated a high level of satisfaction with the study design amongst patients with oesophago-gastric cancer and their potential willingness to participate in such a study and to completion of all three sets of data collection.

4. Chapter 4. Results

The results of this study are discussed in this chapter. This chapter considers the descriptive results of the studied cohort and the CPET results. As well as the quality of life questionnaires and data in relation to muscle mass and function.

4.1 Patient Demographics

4.1.1 Participant selection and exclusion

A total of 38 patients were deemed suitable to participate in the study. Thirty-one patients consented to part take. Although, the study design had anticipated to recruit 30 patients only, as the last two patients were recruited at the same time it was decided to allow a total of thirty one recruited patients to remain within the study. Two patients subsequently had a change of management plan to that of neoadjuvant chemoradiotherapy and one patient decided not to take part post completion of the neoadjuvant chemotherapy. Pre neoadjuvant therapy, a total of 31 individuals completed CPET tests, thirty individuals completed all quality of life questionnaires, one set of questionnaires was not returned for analysis. All other pre neoadjuvant data sets were completed.

Post neoadjuvant chemotherapy, CPET tests 2,3,4 were completed by 23, 22 and 22 individuals respectively. Two individuals were excluded due to change of treatment plan, one patients did not wish to further take part, disease progression and thromboembolic events accounted for the remaining non-attenders for CPET tests 2, 3 and 4.

Post neoadjuvant chemotherapy, twenty five and twenty four individuals completed the quality of life questionnaires (test 2&3). Two individuals were excluded due to change of treatment plan, one patient did not wish to further take part, disease progression and thromboembolic events accounted for the remaining non responders.

All other parameters were completed pre and post neoadjuvant chemotherapy. All completed data sets were used in statistical analyses. The two individuals with a change of treatment option were excluded from further statistical analyses where cohorts were compared.

4.1.2 Data Quality Control

All data sets were scrutinised for accuracy and potential errors. All CPET tests were conducted by the author and reported independently by two experienced assessors, blinded to each other's assessments. Disagreements were resolved by a third assessor. Inter-observer consistency was excellent: interclass correlation coefficient 0.964 (95 per cent c.i. 0.947 to 0.976). (see previous sections).

All questionnaires, Grip strengths and Timed-Get-Up-And-Go tests were performed by the myself. I remained blinded to the results of all previously collected data points for all individuals at all time points during the study. Raw data were not analysed until the completion of the study.

Muscle mass measurements for all patients were performed twice by three radiologist, with repeated measurements performed at least a week apart. The radiologists were blinded to clinical data, other investigator measurements and their own previous measurements. In patients with discrepant identification of L3 between radiologists the 'correct' level of L3 was agreed by discussion and measurements repeated as necessary.

4.1.3 Patient Characteristics

The participants recruited in this study are outlines in the table below. They were recruited after MDM discussion and post pre-assessment clinic (Table 10).

Table 9. Patient characteristics

	No. of patients* (*n* = 31)
Patient characteristics	
Age (years)†*	65 (41–81)
Sex ratio (M : F)	27 : 4
ASA fitness grade†	2 (1-3)
BMI (kg/m^2)†	27.0 (19.4–37.7)
Smoking History	19
Tumour location	
Lower oesophagus	11
Gastro-oesophageal junction	12
Stomach	8
TNM7 Classification	T3/4a N0-3 M0

*Unless indicated otherwise; †values are median (range).

The participants were predominantly male. This reflects the gender distribution of adenocarcinoma of oesophagus and stomach. A median age of 65 (41-81) is in keeping within the previously published studies in OG cancer. American Society of Anaesthesiologists (ASA) score, was recorded for all patients routinely, ASA 1 represents patients with no comorbidity, ASA 2 denotes mild systemic disease and ASA 3 indicates systemic disease that impacts upon normal daily activities. Due to the wide variation between each subgroup, some studies have concluded that ASA grade is not a useful marker of disease status or surgical risk factor(147). However, despite its in inadequacies, multiple studies have confirmed ASA grade

as a useful predictor of morbidity and mortality(148, 149). A large retrospective study of over a 1000 oesophagogastric patients, has identified an ASA grade of III and IV as a predictor for post-operative mortality, higher anastomotic leak rates and higher pulmonary complication rates(150).

All patients had locally advanced tumours on preoperative staging: cT3–4a N0–3 (TNM7 classification(2)). No cT2 N+ tumours or cT4b tumours were noted. This again follows the usual practice of locally advanced tumours suitability for neoadjuvant chemotherapy followed by resection. The majority of tumours were either lower oesophageal N:23 or junctional N:8. Eight purely gastric tumours were noted. This reflects the higher incidence of oesophageal cancer in the UK.

Majority of recruited patients were overweight with a median BMI of 27 (19.4-37-7). This reflects the fact the North East of England is the most obese part of the UK. Multiple studies have confirmed that obesity is a risk factor for gastro-oesophageal reflux, and oesophageal adenocarcinoma(151). A high BMI is a risk factor for Oesophageal cancer and reflects the prevalence of obesity in the local population. Interestingly, despite the fact that the majority of the studied cohorts were overweight, the results from the mini nutritional assessment questionaries' indicates the majority of the recruited patients were at risk of malnutrition prior to commencement of NAC.

Majority of recruited patients had a positive smoking history or were active smokers at the time of the recruitment. This would have an impact on lung function tests as well as CPET parameters. This will be looked at more closely in subsequent sections.

4.1.4 Comorbidities

All comorbidities, drug history, Metabolic Equivalent Scores (METS) and WHO performance status assessments scores were documented pre neoadjuvant chemotherapy as part of a comprehensive preoperative evaluation programme. Eighteen patients were noted to have cardiovascular comorbidities, of these the commonest condition was that of hypertension (n=15) followed by stroke/transient ischaemic attach (n=3). Seven patients were noted to have respiratory comorbidities with Asthma/COPD accounting for all of these patients, all patients with a positive respiratory past medical history had a positive smoking history. Three patients suffered from diabetes and one patient with sclerosing cholangitis was noted to have cirrhosis (Child-Pugh 1). An estimated Metabolic Equivalents Score (METS Score) of 8.1 (4.8-9.9) was noted. One METS is defined as the energy expenditure while at rest. Light intensity activities are classified as having a METS score of <3; moderate intensity activities are assigned a METs score of 3 to 6 and high intensity activities a METs score of 6 to 10(145). METS are assessed using a self-reported questionnaire and are an estimate, as such

an over estimation of fitness may occur(146). Twenty patients had a performance status of 0 with the remaining participants demonstrating a performance status of 1. Given that the majority of patients had a performance status of 0 to 1 and a median estimated MET score of 8.1, indicate that the studied population were an active cohort of patients (Table 11).

Table 10. Documented comorbidities, performance status and METs score (median)

Cardiovascular comorbidities	Respiratory comorbidities	Liver Cirrhosis	Diabetes Mellitus	Performance status of 1	Performance status of 0	METs Score
18	7	1	3	11	20	8.1 (4.8-9.9)

4.2 Chemotherapy Results

All chemotherapy data was collected contemporaneously and complications were recorded prospectively. Twenty seven (87 per cent) of the 31 patients completed all three cycles of neoadjuvant chemotherapy. Two patients had a change of oncological treatment and received neoadjuvant chemoradiotherapy, these two patients were recruited into the neo-AEGIS Trial, consequently to recruitment to this study. Given the nature of this randomised controlled trial, and following discussion with the local recruiter to this study and formal discussions with the study coordinator, it was concluded that given the change of intended therapy from neoadjuvant chemotherapy to chemoradiotherapy, these two patients were to be excluded from further participations in this study.

One patient completed only one cycle (due to an acute tumour haemorrhage requiring an urgent operation), one patient completed two cycles before an embolic event requiring an embolectomy. Ten (35 per cent) of 29 patients had one or more cycles of adjuvant (post operative) chemotherapy.

During neoadjuvant chemotherapy, twelve patients reported grade 3/4 toxicity: two of 29 patients had febrile neutropenia, four had thromboembolic events, four had emesis, one had diarrhoea, three had fatigue and two had palmar plantar erythema. Chemotherapy toxicity was recorded and reported as per Common Terminology Criteria for Adverse Events guide lines (CTCAE V4.03)(152). Treatment for chemotherapy complications were according to local and national guidelines(153). Neoadjuvant chemotherapy was provided across three different hospital sites, although hospital notes could not be obtained from two hospital sites, prospective complication recording allowed for the capture of all grades of complications. This however, resulted in discrepancy in recording of treatment of Grade 1 &2 complications.

Table 11.Chemotherapy toxicity graded according to Common Terminology Criteria for Adverse Events Guide Lines Version 4.03(154).

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Nine patients had dose changes during their neoadjuvant chemotherapy. In patients with Palmer Palnter Erythema (PPE) or diarrhoea grade 3 or 4, capecitabine was stopped until toxicity had resolved, this was restarted with a 25% dose reduction in those patients *(n=3)*.

In patients with platelets 50 - 74 x 10^9/l or neutrophils 0.5 – 0.9 x 10^9/l, capecitabine, was stopped, epirubicin and cisplatin were restated upon recovery. Capecitabine was reinstated at full dose and epirubicin reduced by 25% upon subsequent cycles. In patients with platelets 25 – 49 x 10^9/l or neutrophils <0.5 x 10^9/l, capecitabine was stopped and epirubicin as well cisplatin delayed until recovery. Upon subsequent cycles capecitabine was reintroduced at full dose and epirubicin reduced by 50% on subsequent cycles. In patients with platelets <25 x 10^9/l or neutrophils <0.5 x 10^9/l, capecitabine was stopped, cisplatin was delayed until recovery and capecitabine restated at full dos at next cycle epirubicin was omitted from subsequent cycles *(n=5).*

In patients in whom a thromboembolic event was discovered during administration of neoadjuvant chemotherapy, no further chemotherapy was administered *(n=1).* It is important to note that there were other thromboembolic events which were only discovered upon post completion of neoadjuvant chemotherapy and restaging CT scans.

The median time from last oral chemotherapy tablet to first CPET after chemotherapy (test 2) was 3 (range 1–14) days. The timing of test 4 was at a median of 27 (24–37) days, and surgery was performed at 31 (26–42) days. There were no significant differences haemoglobin levels before and after neoadjuvant chemotherapy.

Table 12. Chemotherapy data including toxicity data

All three cycles of NAC *(n27)*	**93%**	
Any cycle of adjuvant chemotherapy *(n10)*	**35%**	
Grade 3-4 toxicities *(n12)*	**41%**	
	Febrile neutropenia	7 %
	Thromboembolic event	14 %
	Emesis	14%
	Diarrhoea	3%
	Fatigue	10%
	PPE	7%

Twelve patients were noted to be anaemic at pre assessment work up prior to commencement of neoadjuvant chemotherapy and therefore had iron replacement therapy commenced (Table 14). One patient suffered an acute upper GI bleed (tumour haemorrhage and necessitated a blood transfusion and an expedited operation during NAC).

Table 13. Comparison of haemoglobin levels before and after NAC

	Pre NAC	**Post NAC**	**P Value**
Haemoglobin Levels (g/L)	125.7 (108-148)	121.7 (109-144)	0.07

Unless indicated otherwise; †values are median (range)

4.3 CPET Results

Baseline measurements taken before chemotherapy (test 1) were compared with CPET results for tests 2, 3 and 4 after completion neoadjuvant chemotherapy. This is represented in Table 14. These data represent our population with respect to their 'fitness'. Cardiorespiratory reserve and the ability to deliver oxygen in the face of increasing demand. Results were compared between different tests to assess the impact of neoadjuvant chemotherapy on fitness and to delineate if a period of rest between test 2 and test 4 would allow for reversal of a presumed reduction in fitness. 31 Trial participants completed Test 1. Of these, 23 patients completed test 2. Detection of thromboembolic events (*n=4*), failure to attend *(n=1)* and ineligibility secondary to change of management from NAC to neoadjuvant chemoradiation (n=2) accounted for the reduction in number of study participants between the test 1 and 2. Disease progression in two patients accounted for two further losses between test 2 and 4.

Table 14. Comparison of CPET parameters before and after neoadjuvant chemotherapy

	Test 1 (baseline) (*n* = 31)	**Test 2 (week 0 after NAC) (*n* = 23)**	**Test 3 (week 2 after NAC) (*n* = 22)**	**Test 4 (week 4 after NAC) (*n* = 21)**
AT (ml per kg per min)	15.3(3.4)	11.9(2.5)†	12.1(2.7)†	12.6(2.7)†
VO_2 peak (ml per kg per min)	21.7(3.9)	17.5(3.0)†	18.6(2.9)†	19.3(3.6)†
Maximum HR	141.6(16.0)	135.9(18.9)	134.7(16.8)	139.1(17.8)
Peak Oxygen Pulse at VO_2 peak∗ ∗	12.7(2.6)	10.3(2.3)†	11.4(2.0)††	11.3(1.7)†††
FEV1 (litres)∗	3.0(0.7)	2.8(0.5)	2.7(0.6)	2.8(0.8)
FVC (litres)	4.0(0.8)	3.9(0.6)	4.0(0.6)	4.0(0.9)
VE/VCO_2 at AT	28.9(4.7)	31.0(4.5)	30.0(14.1)	30.0(13.9)
BMI (kg/m^2)∗	27.0 (19.4–37.4)	25.9 (18.3–38.6)	26.4 (18.4–38.2)	26.4 (24.2–29.7)

Values are mean (S.D.) unless indicated otherwise; *values are median (range). NAC, neoadjuvant chemotherapy; NAT, anaerobic threshold; VO_2, oxygen uptake; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity, VE, ventilation; VCO_2, carbon dioxide output, heart rate HR. †P < 0.010 versus test 1 (ANOVA with post hoc Tukey's honestly significant difference test). ∗∗millilitres per beat. †† p =0.06 ††† p=0.05

4.3.1 Target Maximum Heart Rate

Maximum heart rate does not alter irrespective of improving or deleterious factors and as such is an excellent surrogate to determine if an adequate CPET test was conducted. Traditionally this is defined as a test during which patients achieve their target maximum heart rate (220-age).

Our study population achieved a mean maximum heart rate of 141.6 (SD 16.0) at Test 1, 135.9 (SD 18.9) at Test 2, 134.7 (SD16.8) at Test 3 and 139.1 (SD 17.8) at Test 4. This represents a mean percentage of the target heart rate of 90% at Test 1, 88% at Test 2, 86% at Test 3 and 90% at Test 4 respectively. This indicates that our population was exercised to an

adequate and safe level yet allowed the examiner to stop the CPET test when study subjects indicated that they no longer could continue with the test. This represents a clinically accepted compromise between achieving an absolute maximum VO_2 and using a submaximal test to maintain safety.

4.3.2 Peak Oxygen Pulse

There was a substantial and statistically significant decline in the peak oxygen pulse between Test 1 and Test 2 (19%) (*P=0.001).* Although there was a trend towards improvement of peak oxygen pulse between Test 1 and Test 4, the difference between the two tests remained statistically significant at 12% *(p=0.05).* Importantly, when Test 2 was compared to test 4 a significant difference was noted indicating a statistically significant improvement in peak oxygen pulse between the end of completion of neoadjuvant chemotherapy and surgery *(p=0.04).*

4.3.3 Peak Oxygen Uptake

This was measured as the maximum oxygen consumption recorded at volitional exhaustion during the ramped exercise stage of CPET. This is routinely measure by the Breeze Gas Analysis Software (please see methodology section 3.9).

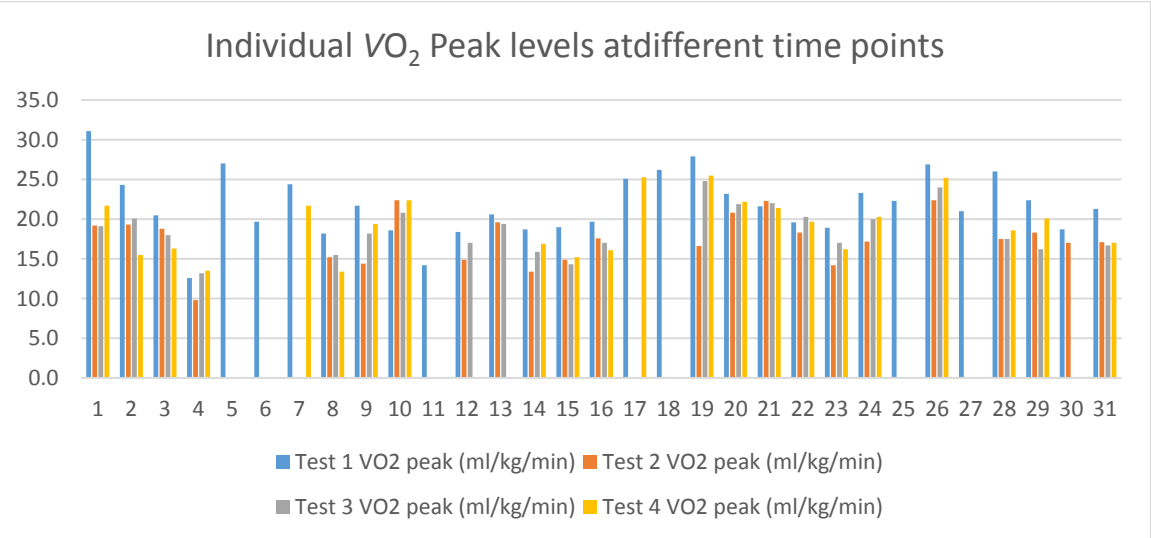

Figure 10. Individual VO_2 levels at test 1, 2, 3 and 4. Study participants numbers are demonstrated on the x axis

A reduction of VO_2 peak was noted before and after administration of NAC in all study participants except three as demonstrated in Table 15 and Figure 10. (Study ID numbers10, 22 & 23). In 13 participants, a slight improvement was noted between Tests 2 and 3 or 4. There was a statistically significant reduction in the mean VO_2 peak between test 1 (21.7 ml

per kg per min) and tests 2, 3 and 4 (17.5, 18.6 and 19.3 ml per kg per min respectively) ($P < 0.01$).

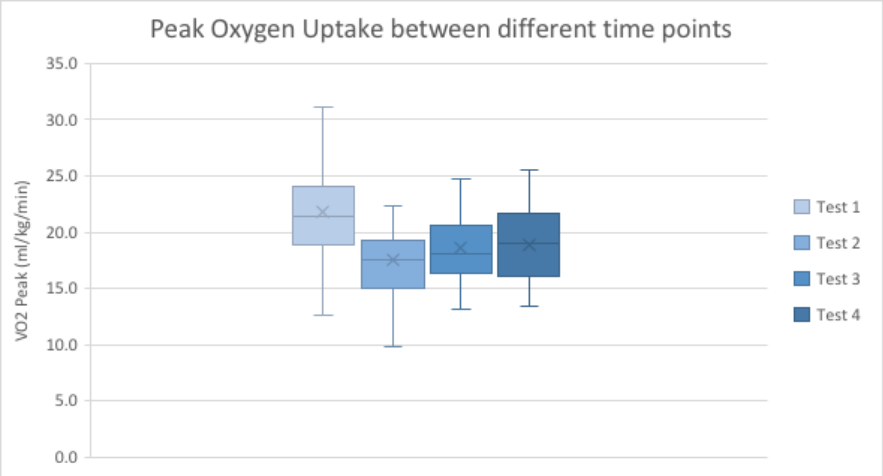

Figure 11. Box-and-Whisker Plot Peak Oxygen Uptake VO_2 Peak (ml/kg/min) over time; at baseline (test 1) and post neoadjuvant therapy at week 0 (test 2), week 2 (test 3) and week 4 (test 4). The first and third interquartile are represented by the bottom and top of the box. The median is presented by a band inside the box. The mean is presented by a cross inside the box. The ends of the whiskers represent the lowest and highest data points within 1.5 of the interquartile range (IQR). Any data not included between the whiskers is plotted as an outlier with a dot.

When the results of test 2 were compared with those of test 4, mean VO_2 peak were not statistically different ($P = 0.214$). The reduction VO_2 peak did not improve during the time between completion of neoadjuvant chemotherapy and surgery. This indicated that the accepted rest period between completion of NAC and surgery does not improve VO_2 peak.

4.3.4 Anaerobic Threshold

The V-slope method was used to detect AT. This was achieved by analysing the behaviour of VCO_2 as a function of VO_2 during progressive exercise tests when exceeding the lactate threshold is accompanied by buffering lactic acid with a consequent increase in VCO_2 (please see methodology section 3.9). A reduction in AT was noted before (Test 1) and after administration of NAC (Test 4) in all study participants except two (study ID numbers 14 and 21). This is demonstrated in figure 12. One participants demonstrated a higher AT at Test 4 compared to Test 1 (Study ID 17). Interestingly, there was no correlation between those individuals with higher VO_2 peak at test 2 and those individuals with higher AT at Test 2.

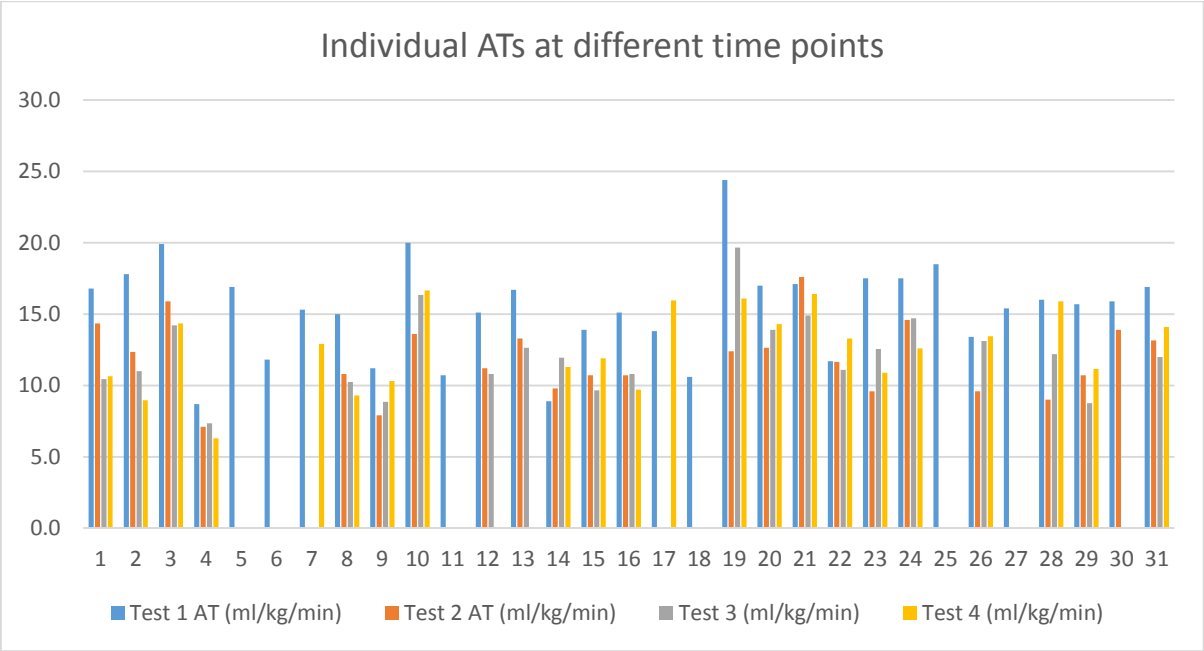

Figure 12. Individual AT levels at test 1, 2, 3 and 4. Study participants numbers are demonstrated on the x axis

There was a statistically significant reduction in the mean AT between test 1 (15.3 ml/kg/min), test 2 (11.9 ml/kg/min) (22% reduction), test 3 (12.1 ml per kg per min) (21% reduction) and test 4 (12.6 ml/kg/min) (21% reduction) ($P < 0.01$). When the results of test 2 were compared with those of test 4, mean AT were not statistically different ($P = 0.45$). The reduction in AT did not improve during the time between completion of neoadjuvant chemotherapy and surgery.

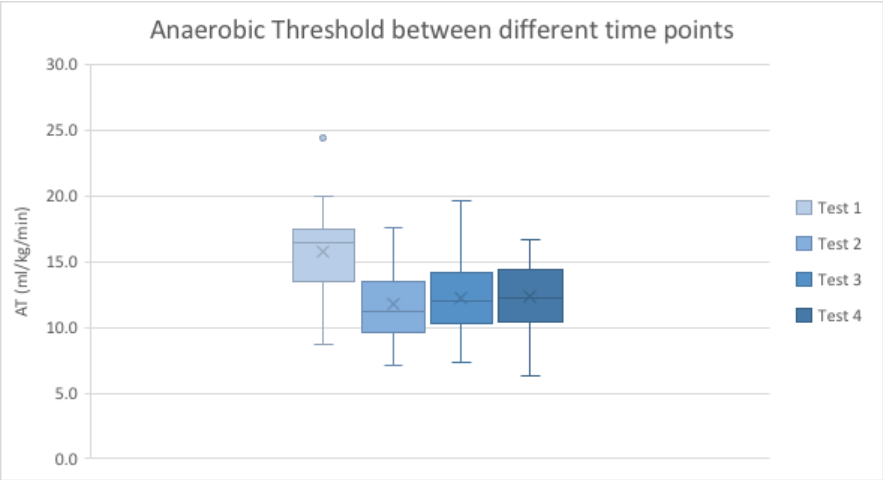

*Figure 13. Box-and-Whisker Plot Peak Oxygen Uptake VO_2 Peak (ml/kg/min) over time; at baseline (test 1) and post neoadjuvant therapy at week 0 (test 2), week 2 (test 3) and week 4 (test 4).*The first and third interquartile are represented by the bottom and top of the box. The median is presented by a band inside the box. The mean is presented by a cross inside the box. The ends of the whiskers represent the lowest and highest data points within 1.5 of the interquartile range (IQR). Any data not included between the whiskers is plotted as an outlier with a dot.

4.3.5 Other CPET parameters

Other CPET measurements (V_E/ VCO_2 at AT, forced expiratory volume in 1 second , forced vital capacity and BMI) were not significantly different between the four time points *($p > 0.05$).*

4.4 Quality of life results

Thirty patients completed (EORTCQLQ-C30) questionnaire as well (QLQ-OG25) questionnaire prior to NAC (test 1). One patients did not return the completed questionnaires. All patients who attended the post NAC CPET tests, completed both questionnaires (Test 2 *n=23* & Test 3 *n= 22*). Two patients who did not attend further CPET tests, completed both questionnaires and returned them at the appropriate time frames. Two patients were excluded as they had a change of treatment from NAC to neoadjuvant chemoradiation. Three patients did not complete Tests 2 and 3 due to disease progression. Comparison between quality of life between Test 1, Test 2 and Test 3 are illustrated in Table 15 and 16.

4.4.1 EORTC QLQ 30 results

The mean (SD) Global Health Status (QoL) scores substantially declined before and after neoadjuvant chemotherapy 72.22 (20.45) versus 59.33(25.33) ($p=0.04$). This decline however had reversed by the time of surgery 71.18 (24.32) ($p=0.87$). Across the five Functional Scale Questions; Physical functioning, Role functioning and Cognitive functioning, there was a statistically significant decline between the mean scores (SD) in Test 1 and 2 (*P <0.0, p<0.01 & P <0.05 respectively*). There was a statistically significant improvement in Emotional Functioning between Test 1 and Test 3 ($p=0.02$). No statistically significant changes were noted before and after NAC in Social Functioning ($p=0.08$) .

Across the symptom scales, a reduction in mean scores (SD) was noted in Fatigue and Dyspnoea before and immediately after NAC ($p<0.01$). No changes were noted in Nausea and Vomiting, Pain, Insomnia, Appetite Loss, Constipation, Diarrhoea and Financial Difficulties before and after NAC.

Across all parameters (QoL, Functional scales and Symptom Scales) either no change was noted between Test 1 and Test 2, or the decline at Test 2 was reversed by the time of surgery (Test 3). Only in Emotional Functioning, an improvement was noted between Tests 1 and 3.

4.4.2 EORTC QLQ-OG 25 results

The oesophageal and gastric cancer specific quality of life concerns were assessed using the validated 25-item oesophagogastric module (QLQ-OG25). A statistically significant decline was noted in the mean (SD) scores across the following parameters: Dry Mouth; Sense of Smell; Hair Loss ($p<0.01$) and Body Image ($p<0.05$) between Test 1 and 2. In all the other parameters: Dysphagia, Eating Restrictions; Reflux; Odynophagia; Pain and Discomfort; Anxiety; Eating with others; Saliva; Choking; Cough; Speech and Weight Loss no statistically significant difference was noted.

Table 15. Comparison of quality of life (EORTC QLQ-C30) before and after neoadjuvant chemotherapy

		Test 1 (*n 30*)		**Test 2 (*n 25*)**		**Test 3 (*n 24*)**		**Test 1 vs Test2**	**Test 1 vs Test 3**	**Test 2 vs Test 3**
EORTC QLQ-C30 V 3.0	Questions	mean	SD	mean	SD	mean	SD	*p*-value	*p*-value	*p*-value
Global Health Status (QoL)	29, 30	72.22	20.45	59.33	25.27	71.18	24.32	**0.04**	0.87	0.10
Functional Scales										
Physical Functioning (PF2)	1 to 5	92.67	13.71	79.73	17.69	87.01	11.46	**<0.01**	0.11	0.10
Role Functioning (RF2)	6, 7	90	22.99	67.07	28.7	78.19	23.49	**<0.01**	0.07	0.15
Emotional Functioning (EF)	21 to 24	72.5	19.35	75.33	14.93	84.03	19.35	0.63	**0.02**	0.14
Cognitive Functioning (CF)	20, 25	88.89	14.73	78.67	22.83	86.89	14.73	**0.05**	0.55	0.22
Social Functioning (SF)	26, 27	83.89	26.8	70	30.05	83.33	16.3	0.08	0.93	0.06
Symptom Scales										
Fatigue (FA)	10, 12, 18	20.91	24.73	41.28	28.91	20.91	24.73	**<0.01**	0.21	0.14
Nausea and Vomiting (NV)	14, 15	11.11	16.57	19.33	15.72	9.72	16.97	0.07	0.76	**0.05**
Pain (pain)	9, 19	17.22	22.95	12	21.26	11.11	15.28	0.39	0.27	0.87
Dyspnoea (DY)	8	7.78	16.8	26.67	23.57	18.06	21.93	**<0.01**	0.06	0.19
Insomnia (SL)	11	24.44	31.48	24	37.91	19.44	29.35	0.96	0.55	0.64
Appetite Loss (AP)	13	18.89	34.67	28	40.46	15.28	31.05	0.37	0.69	0.22
Constipation (CO)	16	17.78	20.96	20	27.22	11.11	21.23	0.73	0.25	0.21
Diarrhoea (DI)	17	5.56	12.63	9.33	15.28	4.417	11.26	0.32	0.68	0.19
Financial Difficulties (FI)	28	12.22	22.29	16	25.68	13.89	23.91	0.56	0.79	0.77

All the above scales range from 0 to 100. In the Global quality of life subscale as well as the five functional scales a higher value will indicate a higher quality of life and better level of function respectively. In the symptom scales as well as the single items, a higher score is indicative of more symptoms. Values are mean (S.D.) unless indicated otherwise. (ANOVA with post hoc Tukey's honestly significant difference test was used to determine significance).

Table 16. Quality of Life EORTC QLQ-OG25 before and after Neoadjuvant chemotherapy

		Test 1 (n 30)		***Test 2 (n 25)***		***Test 3 (n 24)***		***Test 1 vs Test2***	***Test 1 vs Test 3***	***Test 2 vs Test 3***
EORTC QLQ-OG25	Questions	mean	SD	mean	SD	mean	SD	*p*-value	*p*-value	*p*-value
Dysphagia (OGDYS)	31, 32, 33	18.11	24.55	13.55	24.12	8.33	16.78	0.49	0.10	0.39
Eating Restrictions (OGEAT)	34, 35, 36, 37	31.48	28.04	24.33	27.63	17.71	24.98	0.35	0.07	0.38
Reflux (OGRFX)	38, 39	12.78	21.30	12.67	21.67	9.72	24.04	0.99	0.62	0.65
Odynophagia (OGDYN)	40, 41	27.22	32.89	15.33	24.49	14.58	24.23	0.14	0.12	0.92
Pain and Discomfort (OGP & D)	42, 43	25.56	31.18	21.33	25.69	17.36	24.32	0.59	0.30	0.58
Anxiety (OGANX)	44, 45	66.67	33.33	54.00	33.43	50.69	25.76	0.17	0.06	0.70
Eating with others (OGEO)	46.00	16.67	31.26	16.00	25.68	10.42	22.95	0.93	0.42	0.70
Dry Mouth (OGDM)	47.00	18.89	27.24	48.00	33.44	33.33	35.44	**<0.01**	0.10	0.14
Sense of Taste (OGTA)	48.00	6.67	20.34	42.67	39.11	33.33	38.07	**<0.01**	**<0.01**	0.40
Body Image (OGBI)	49.00	15.56	28.68	32.00	31.15	20.83	29.18	**0.05**	0.20	0.51
Saliva (OGSV)	50.00	5.56	19.74	8.00	17.43	4.17	11.26	0.63	0.76	0.37
Choking (OGCH)	51.00	3.33	13.42	5.33	15.75	1.39	6.80	0.61	0.52	0.26
Cough (OGCO)	52.00	22.22	28.14	22.67	20.91	19.44	21.79	0.95	0.69	0.60
Speech (OGSP)	53.00	1.11	6.09	1.33	6.67	1.39	6.80	0.90	0.88	0.98
Weight Loss (OGWL)	54.00	18.89	25.80	30.67	28.74	11.11	16.05	0.12	0.20	**<0.01**
Hair Loss (OGHAIR)	55.00	0.00	0.00	26.67	25.46	16.67	17.03	**<0.01**	**<0.01**	0.11

All the above scales range from 0 to 100, a higher score is indicative of more symptoms. Values are mean (S.D.) unless indicated otherwise. (ANOVA with post hoc Tukey's honestly significant difference test was used to determine significance).

4.5 Sarcopenia Data

4.5.1 Muscle Mass

Muscle mass was measured twice by each radiologist, with repeated measurements performed at least a week apart. Upon completion of the tests and once all muscle areas were calculated, muscle mass area (cm^2) was converted to Muscle Mass Index (cm^2/m^2) using patients' heights and muscle mass area. This allowed comparison to internationally published radiological sarcopenia cut-off points of < 52.4 (cm^2/m^2) and <38.5 (cm^2/m^2)(143) in men and women respectively to arrive at a proportion of radiologically sarcopenic patients before and after neoadjuvant chemotherapy. Please see section *Sarcopenia Methodology Section* (3.11).

Patients with a change of treatment plan to neoadjuvant chemoradiotherapy were excluded from data analysis *(n=2).* Twenty nine patients' CT scans were analysed pre and post NAC to determine sarcopenia cut-off points. A mean (SD) muscle mass index of 53.3(cm^2/m^2) (9.5) was noted pre NAC. This was significantly higher than the post NAC value of 49.6 (cm^2/m^2) (9.5) (table 17). None of the four female participants were noted to be sarcopenic prior to, or post NAC, however, all four had a significant decline in muscle mass. Amongst men, radiological sarcopenia was prevalent in 12(41%) pre NAC, this increased to 16 (64%) post NAC. Given the small number of female patients and the different cut-off points for the diagnosis of radiological sarcopenia in females, female participants were excluded from the analysis below.

Table 17. Muscle Mass before and after neoadjuvant chemotherapy

	Pre NAC	**Post NAC**
Muscle Mass (cm^2)*	162.7 +/- 33.5	151.2+/-30.9**
Muscle Mass Index (cm^2/m^2)*	53.3 +/- 9.5	49.6 +/-9.5 **
Prevalence of radiological sarcopenia in men (n)	12 (41%)	16 (64%)

* Mean +/- 1 SD

** Compared to pre NAC $P < 0.001$

4.5.2 Differences between sarcopenia and fitness

The possibility of a connection/differences between loss of muscle mass index (radiological sarcopenia) and a decline in fitness was explored (table 18). Amongst radiologically sarcopenic patients a mean (SD) muscle mass index of 46.1(4.38) $cm^2/m^2$was noted. This was significantly lower than the mean (SD) of muscle mass index of 61.6(8.5) cm^2/m^2 in non-sarcopenic patients. Anaerobic thresholds between these two cohorts were compared. No significant decline in mean (SD) in AT (ml/kg/min) was noted in the radiologically sarcopenic group 15.1(3.1) versus the non-sarcopenic group 16.6 (3.0).

Table 18. Comparison of anaerobic threshold in sarcopenic versus non-sarcopenic patients

	Radiologically Sarcopenic	**Radiologically non-sarcopenic**	***P* Value**
Muscle Mass Index (cm^2/m^2)*	46.1+/-4.4	61.6+/-8.5	***<0.001***
Anaerobic Threshold (ml/kg/min) pre NAC*	15.9+/-3.1	16.6+/-3.0	*0.27*
Anaerobic Threshold (ml/kg/min) post NAC*	11.5+/-1.3	12.9+/-2.8	*0.16*
Forced Vital Capacity (l) pre NAC* *	4.3 (3.5-4.9)	3.9 (3.5-5.2)	*0.07*
Forced Vital Capacity (l) post NAC* *	4.2 (3.5-5.2)	3.8 (3.0 -5.1)	*0.06*

* Mean +/- 1 SD
* * Median (Range)

Furthermore, post NAC anaerobic thresholds were compared between the two cohorts. A decline of 3.6 (ml/kg/min) versus a decline of 3.5(ml/kg/min) was noted in the sarcopenic and non-sarcopenic cohorts respectively. This was statistically non-significant.

Forced vital capacity (l) pre and post NAC was compared between the sarcopenic and non-sarcopenic cohorts. Prior to and post NAC, no statistically significant difference was noted between the cohorts.

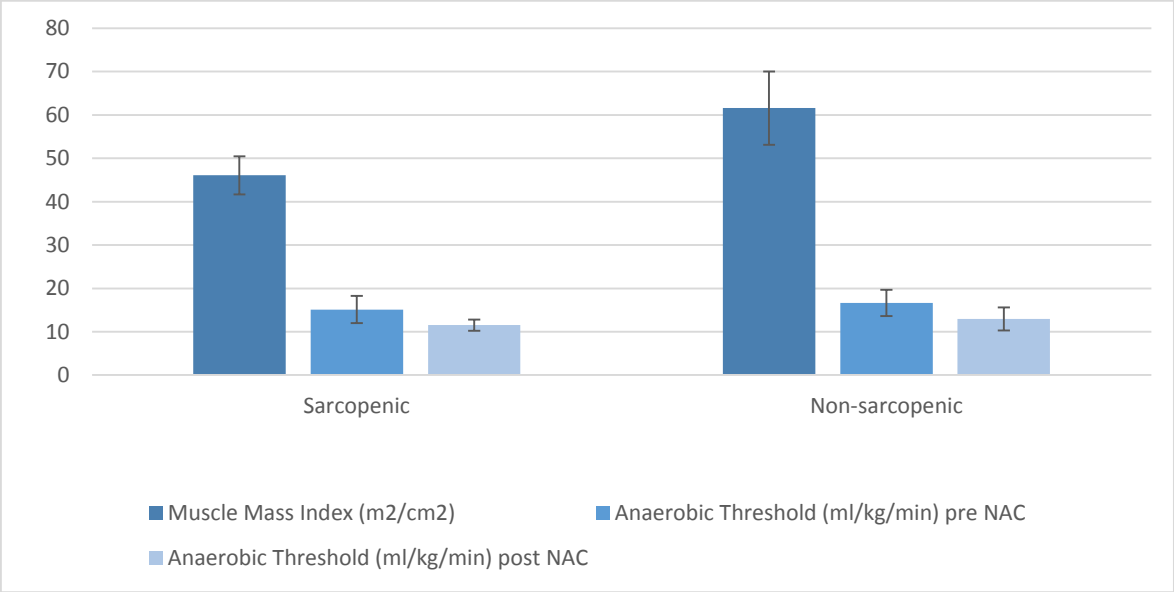

Figure 14. Comparison of mean +/- 1 SD of muscle mass index and anaerobic threshold before and after neoadjuvant chemotherapy in sarcopenic versus non-sarcopenic patients

The above data indicates that neoadjuvant chemotherapy has a deleterious impact on both muscle mass and fitness. However, the decline in fitness seems to be independent from the decline in muscle mass.

4.5.3 Muscle function

Muscle function was measured in patients before NAC (test1), immediately after NAC (test 2) and prior to surgical intervention (test 4). Grip Strength was measured using a hand

dynamometer as described in methodology, Timed Get and Go was measured using a three meter walking test. According to established cut-off points (115, 117), only one male patient had a 'weak grip strength' at all three time points. None of the female participants had a weak grip strength. There was a significant decline in mean (SD) in grip strength before and immediately after NAC and prior to surgical intervention ($p< 0.01$). There was no statistically significant reversal in this observed decline prior to surgery. A Timed-Get-Up And-Go of greater than 12 second was noted in one patient at only one time point. No statistically significant difference was noted between the mean (SD) at any time point ($p=0.5$). Given that only one patient had a weak grip strength or slow timed get and Go, no meaningful comparisons could be drawn between muscle function, muscle mass (sarcopenia) and fitness (anaerobic threshold).

Table 19. Muscle function before and after neoadjuvant chemotherapy

	Test 1 (pre NAC)	**Test 2**	**Test 4**
Grip Strength (kg)*	39.4 +/- 6.6	36.5 +/- 6.5**	37.8 +/- 6.2***
Timed-Get-Up-And-Go (s)*	10.43 +/- 1.7	10.6 +/- 1.7	10.3 +/- 1.4

* Mean +/- 1 SD
** Compared to pre NAC $P < 0.01$
*** Compared to pre NAC $p <0.04$

4.6 Perioperative Data

Three patients did not undergo resection due to disease progression. Additionally, one patient had an open-and-close laparotomy following discovery of liver metastases. The median length of hospital stay was 9 (7–14) days. No deaths at 90 days or as in-patient were noted. Of the 25 patients who had resection with curative intent after neoadjuvant chemotherapy, nine (36%) had complications: there were four wound infections, three lower respiratory tract infections, two duodenal stump leaks, three cases of atrial fibrillation, and two patients had postoperative delirium. No anastomotic leaks were observed. Given the small number of patients involved no meaningful comparisons could be made between different fitness (AT) levels and complication rates.

Of the 25 patients who underwent resection with curative intent, to-date, 8 (32%) have developed recurrent disease with an observed mortality of seven patients (28%). Amongst patients with recurrent disease, low muscle mass (sarcopenia) was observed in only one patient.

Table 20. Surgical outcomes

Operation		
Ivor Lewis oesophagectomy	13	
D2 total gastrectomy	9	
D2 subtotal gastrectomy	3	
Lymph node yield†*	37 (19–70)	
Blood loss†	350 (150-1300)	
Length of stay (days)	9 (7-14)	
90 day mortality	0	
Observed complications *(n=9)*	Wound infection	16%
	Pneumonia	12%
	AF	12%
	GI leak	8%
	Delirium	8%

*Unless indicated otherwise; †values are median (range).

5. Chapter 5. Discussion

This chapter sets out to explore the impact of neoadjuvant chemotherapy on fitness, muscle mass and function and quality of life. Each parameter is looked at separately and possible connections explored when indicated. Clinical implications of the demonstrated outcomes are exemplified and explored. Finally, the study's short comings as well as possible future studies which may further address some of the question raised by this study, are reviewed.

5.1 Impact of neoadjuvant chemotherapy on fitness

This study confirms that a significant reduction in CPET measured fitness (cardiorespiratory reserve) is seen after neoadjuvant chemotherapy in patients treated for oesophago-gastric cancer. The mean oxygen uptake at Anaerobic threshold and at peak exercise fell by 3.8 and 4.2 ml/kg/min respectively immediately after neoadjuvant chemotherapy (test1 vs test2). This is a clinically significant reduction in cardiorespiratory reserve. Importantly, this effect is seen immediately after neoadjuvant chemotherapy and sustained throughout the four week period after neoadjuvant chemotherapy and before surgery (AT Test 2 vs Test 4 $p=0.45$).

Fitness (AT) does not recover during this time and therefore patients proceed to surgical intervention with suppressed cardiopulmonary reserve. The two patients who did not complete all three cycles of neoadjuvant chemotherapy also demonstrated a reduction in fitness, despite receiving a smaller total dose of NAC. Two individuals demonstrated no decline in their fitness between different time points. In one individual a higher anaerobic threshold was noted at test 4 versus test 1, interestingly, the patient had started rowing between test 2 and 4.

This study complements a growing body of evidence that uses CPET to objectively confirm the deleterious effect of neoadjuvant oncological treatments upon cardiopulmonary reserve. Jack et. al. have published a comparable reduction in VO_2 at AT in oesophago-gastric patients completing preoperative chemotherapy(129). However, multiple chemotherapy regimens were used in that study and reversibility was not assessed. Similarly, the effect on cardiopulmonary reserve is demonstrated after neoadjuvant chemoradiotherapy for rectal adenocarcinoma and after neoadjuvant chemotherapy and adjuvant radiotherapy given for breast cancer(135, 155).

The observed sustained reduction in oxygen delivery may be attributed to several cancer and chemotherapy effects: poor nutritional intake and malabsorption secondary to diarrhoea, sarcopenia, anaemia, myelosuppression and sepsis, reduced oxygen delivery secondary to oxidative stress or as a direct consequence of chemotoxicity on cardiac or

respiratory systems(42, 46-48). However, in this study haemoglobin levels and BMI of the patients did not alter in a statistically significant manner between tests indicating that neither anaemia nor weight loss were responsible for reduced oxygen delivery in this cohort of patients.

One possible contributory factor to the observed decline in fitness maybe the cardiac toxicity associated with ECX neoadjuvant chemotherapy, in this study there was a significant and sustained decline in peak oxygen pulse between Test 1 and Test 2 *(p=0.001)* and test 1 and test 4 *(p= 0.05)*, indicating that oxygen pulse which can be regarded as a surrogate of stroke volume had declined as a result of NAC. Whereas VO_2 Peak indicates oxygen consumption per minute during exercise, oxygen pulse is primarily an indicator of oxygen consumption per heart beat, reflecting myocardial oxygen supply and cardiac functional reserve(87). This study therefore demonstrates that the decline in cardiac functional reserve as a result of NAC may be contributory factor in the witnessed decline in fitness. In this study no difference between length of stay *(p=0.7)* or overall complications rate *(p=0.08)* were noted between patients with a low oxygen pulse of less than 13(ml/beat) and those with peak oxygen pulse of equal or more than 13 (ml/beat). However, given the small number of patients further studies should explore these relationships further. Additionally in this cohort of patients, although sarcopenic patients had a slightly lower AT pre and post NAC when compared to non-sarcopenic patients, this was not statistically significant (*p=0.27* and *p=0.16* respectively).

CPET measures total oxygen delivery and utilization: this is the integrated effect of multiple homeostatic mechanisms. Thus, this test does not identify the pathophysiological mechanisms causing the decrease in VO_2 Peak and VO_2 at AT after neoadjuvant chemotherapy. Additionally, the aim of this study was not to account or identify factors that may contribute to this decline.

5.1.1 Clinical implications associated with decline in fitness

Neoadjuvant oncological therapy with surgery improves survival over surgical intervention alone for this patient group. Multiple randomised trials have reinforced the superiority of multimodal therapy over surgery alone(28-30, 32). Consequently, the proportion of patients who receive perioperative oncological therapy has increased(156). The decline in cardiorespiratory reserve demonstrated in this study has potential implications for clinical management of these patients. A patient with ‘borderline fitness’ may experience a reduction in cardiopulmonary reserve that places them into a higher operative risk category than may have been ascribed based solely on CPET testing before neoadjuvant chemotherapy. For

example, in this study, a patient with a starting AT of 11.2 (ml/kg/min) demonstrated a sustained reduction of 3.3 (ml/kg/min) post chemotherapy, resulting in a preoperative AT of 7.9 (ml/kg/min). An AT of 7.9ml/kg/min would be considered low and likely indicate that this patient is in a high risk group for potential post-operative complications(57, 89, 90). The implications of this in terms of individualised risk prediction remain unknown. There is significant morbidity associated with gastro-oesophagectomy, with cardiopulmonary complications responsible for a substantial proportion of postoperative morbidity and mortality(16). The ability to counteract the reduction in reserve seen after neoadjuvant therapy and improve a patient's condition before 'major' surgery is appealing. This will be further explored in the subsequent sections.

5.2 Impact of Neoadjuvant chemotherapy on muscle mass, strength and function

A high proportion of patients (41%) in this study had muscle mass measurements which placed them in the radiological sarcopenic category prior to start of NAC, this increased to 64% post NAC. The prevalence of low muscle mass (radiological sarcopenia) amongst healthy 60-70 year olds is reported as between 5% to 13%(104). This is a much lower prevalence than the incident of low muscle mass (radiological sarcopenia) amongst this cohort of patients. This study has also demonstrated a significant decline in muscle mass (radiological sarcopenia) pre and post NAC ($p<0.001$). Additionally, this study demonstrated a significant decline in the mean (SD) muscle strength as measured by hand grip strength (Kg) pre and post NAC from 39.4 (6.6) Kg to 36.5(6.5) Kg. However, this decline in muscle strength was not replicated in muscle function as measured by the Timed Get-Up-And-Go.

Sarcopenia is a syndrome characterised by loss of skeletal muscle as well as strength(95). The rationale to measure contributing parameters in defining sarcopenia in this study, was based on the fact that muscle strength/function does not only depend on muscle mass. Previous studies have demonstrated that muscle mass and strength are not linear(96). It is therefore important to use both mass and strength/function in diagnosis of sarcopenia. This study has confirmed a statistically significant decline in both muscle mass (radiological sarcopenia) and muscle strength pre and post NAC. However, when muscle mass and muscle strength were combined to define sarcopenia, no patients were sarcopenic based on this combined definition. There are several factors which may contribute to sarcopenia and its decline by chemotherapy agents. Protein synthesis, proteolysis and damage to mitochondrial integrity may all contribute to this phenomenon. Additionally, muscle disuse during a prolonged period of inactivity may exacerbate this phenomenon(95, 157).

The body composition of cancer patients vary widely. Severe muscle wasting 'cachexia', is a recognised consequence of the pro inflammatory state in malignancy. In this study muscle mass declined significantly pre and post NAC, however, no significant loss in median (range) BMI was noted pre and post NAC 27.0 (19.4-37.4) versus 25.9 (18.3-38.6). Body mass index is the metric conventionally used to evaluate patients' body habitus. However, this metric does not distinguish between the different components of body mass such as bone, fat and muscle(158). Patients with identical BMIs may have substantially different percentages of lean and fat tissues. Therefore, our results may be partly explained by sarcopenic obesity, a state during which muscle mass is lost whilst fat mass is preserved or even increased(158, 159). Furthermore, sarcopenic obesity in oesophago-gastric patients has been demonstrated to be a risk factor for dose limiting toxicity during neoadjuvant chemotherapy(160). Association between chemotherapy toxicity and sarcopenic obesity is explained by the hypothesis that in in sarcopenic obese patients a high absolute dose of chemotherapy agents is combined with a reduced volume of distribution. However, no studies exist to investigate the impact of sarcopenic obesity on pharmakokintetic distribution of chemotherapy drugs. In our study no obvious relationship between radiological sarcopenia and fitness was noted, however, given the small number of patients no obvious conclusions can be drawn on the presence of sarcopenic obesity and its impact on cardiopulmonary fitness. Further studies in this area are needed.

The use of Timed -Get-Up-And-Go as a possible measure of muscle function is advocated by The European Working Group on Sarcopenia(95). In this study no difference was noted in the times attained to complete Timed-Up-And-GO, pre and post NAC. This can be explained by the fact that the Timed-Get-And-Go is mainly used to assess frailty, lower extremity function and fall risk in geriatric population (121). In this study all patients had a performance status of either 0 or 1 and were fit enough to undergo multimodality therapy and therefore cannot be deemed frail. It has been demonstrated that timed get and go is of limited use in patients with relatively high function scores(121). This study further supports this finding. It is therefore important that other physical performance tests such as the *short physical performance battery* (95)are validated in oncological research. This study further supports that measurement of CPET parameters maybe a sufficient and far more comprehensive assessment of physical performance.

5.3 Impact of neoadjuvant chemotherapy on patient reported quality of life parameters

The symptoms associated with oesophageal and gastric cancer are mainly gastrointestinal in nature. Neoadjuvant oncological therapy, through a variety of possible mechanisms, may exacerbate some of these symptoms. Therefore, the assessment of the effect of oncological or surgical treatment on health-related quality of life pre and post therapy, is an important marker for patients and clinicians alike. This study therefore compared global health related quality of life pre and post neoadjuvant chemotherapy using the EORT QLQ30. EORTC QLQ-OG 25 validated questionnaires was used in oesophageal and gastric cancer specific quality of life concerns.

In this study a substantial difference in the mean (SD) Global Health Status (QoL) scores before and after neoadjuvant chemotherapy 72.22 (20.45) versus 59.33(25.33) ($p=0.04$) was noted. This decline however had reversed by the time of surgery 71.18 (24.32) ($p=0.87$). This pattern was duplicated across the five Functional Scale Questions; Physical functioning, Role functioning and Cognitive functioning as well as across two symptom scales (dyspnoea and fatigue). Similar findings were reported by Safieddine and colleagues who in the context of neoadjuvant chemoradiation and using a different questionnaire (FACT-E) demonstrated that a substantial decline in quality of life which was transient and had recovered by time of surgical intervention(161). A further study, has replicated these results in patients undergoing NAC and surgery, with a global decline in health related quality of life immediately after surgery which had recovered fully by six months post surgery(162).

However, it is important to note that in our study, no changes were noted in Nausea and Vomiting, Pain, Insomnia, Appetite Loss, Constipation, Diarrhoea and Financial Difficulties before and after NAC. Additionally, across all parameters (QoL, Functional scales and Symptom Scales) either no change was noted between Test 1 and Test 2, or the decline at Test 2 was reversed by the time of surgery (Test 3). Only in Emotional Functioning, an improvement was noted between Tests 1 and 3. The rapid recovery of the observed decline may be attributed to a response shift causing an inflated level of quality of life in subsequent tests. In other words, an adaptation mechanism of the health related quality of life may occur secondary to a change in standards and values. This may lead to a perception of a new normal which may explain the improvement in certain parameters(163).

In this study, in the oesophageal and gastric cancer specific quality of life questionnaires, a significant decline was noted across the following parameters: Dry Mouth; Sense of Smell; Hair Loss ($p<0.01$) and Body Image ($p<0.05$) between Test 1 and 2. In all the other parameters: Dysphagia, Eating Restrictions; Reflux; Odynophagia; Pain and

Discomfort; Anxiety; Eating with others; Saliva; Choking; Cough; Speech and Weight Loss no statistically significant difference was noted. Neoadjuvant chemotherapy has a downsizing impact on tumour volume in some patients. This may in part explain the lack of decline in GI symptoms such as dysphagia and odynophagia. Furthermore, the adaptation mechanisms may also play a part in normalisation of oesophago-gastric specific symptoms before and after NAC(163).

Oesophago-gastric cancer patients suffer from feelings of depression and anxiety(164). These psychological disorders require screening through adequate tools so that psychological intervention can augment anxiety, facilitate adaptation to their psychological health and disease status as well as improve self-efficacy(164, 165).

In this study a significant decline in fatigue and emotional scores were noted post NAC. This may adversely impact upon activity levels during neoadjuvant chemotherapy which has the potential to contribute to the decline noted in both fitness levels and in physical functioning score. Furthermore, oncological related physical impairment as demonstrated by the substantial and sustained decline in cardiorespiratory fitness in this study, may profoundly impact on one's ability to conduct or engage in functional activities such as walking which negatively impacts normal activities of daily living. Consequently, the decline in physical function can negatively impact on health related quality of life (HR-QOL)(166). Studies which use a variety of quality of life questionnaires have consistently reported a decline in physical function at various time points during oncological or surgical therapy of oesophageal or gastric cancer patients(167). However, all quality of life questionnaires are self-reported and subjective. Prior studies have demonstrated poor correlation between self-reported physical function and objectively measured exercise capacity(168). This observation was indeed replicated in our study where despite a significant and persistence decline in objectively measured CPET parameters prior to surgery, almost all domains of the self-reported quality of life questionaries' had returned to pre-treatment levels. Therefore, objective measures of fitness in conjunction with QOL assessments are required tools in any future studies that uses a multidisciplinary prehabilitation programme.

5.4 Possible interventions to minimise perioperative decline in fitness

Postoperative complications are independently associated with the reduced survival rates due to cancer recurrence(24). Patients with serious complications following surgery have diminished long term survival(22). It is therefore imperative that new perioperative strategies should aim to minimize postoperative complications. In patients with lower or borderline cardiopulmonary fitness, various strategies could be employed to attempt to negate the effects

of chemotherapy and minimize complications: surgery alone, chemotherapy with delayed surgery until fitness recovers, or 'prehabilitation'.

The possibility of improving a patient's fitness prior to surgery is attractive: if the effects of chemotherapy could be offset, then a 'fitter' group of patients would undergo surgery post neoadjuvant chemotherapy(22). The complications of surgery are likely to have a greater impact upon the 'unfit' patient with low cardiopulmonary reserve. Would a 'borderline' patient be better served by surgery or definitive oncological therapy alone? A recent preoperative nomogram has identified combination of neoadjuvant chemoradiotherapy and surgery had a clear 5 year over-all survival in low risk patients compared to high-risk patients(169). However, CPET parameters, sarcopenia and quality of life were not used as part of this risk stratifying nomogram. Addition of these parameters in future studies, will further clarify their relevance in clinical practice. This study has demonstrated a trend to towards improvement/recovery in many of its studied parameters between Test 2 and Test 4 (AT, VO_2 Peak, peak oxygen pulse and grip strength). Although these had not reached statistical significance, implementation of an exercise programme between Test 2 and Test 4, may significantly improve these parameters. Equally, it may be feasible to stop the decline all together by introducing an exercise programme with the induction of NAC.

The current accepted time frame post completion of NAC and surgical intervention is four to six weeks. It may be argued that prolongation of the period between neoadjuvant chemotherapy and surgery offers a reasonable strategy to combat the demonstrated reduction in fitness, however, this study has established that fitness does not recover during a 4 week period of rest. It is unclear if prolongation of the rest period without active prehabilitation, would lead to recovery of fitness. Additionally, to the authors' best knowledge, no study to-date has established the oncological safety (survival) by prolongation of time to surgery post neoadjuvant chemotherapy. This is unlike neoadjuvant chemoradiation where some evidence on impact of survival exists, a previous study had demonstrated that the interval between neoadjuvant chemoradiotherapy and surgery can be prolonged with no impact on survival(133). However, a recent meta-analysis to clarify the oncological safety in prolonging the period between completion of neoadjuvant chemoradiotherapy and surgery, has demonstrated that the increase in this interval, may have a negative impact on long term over-all survival(134). This topic should be the subject of future randomised trials.

Prehabilitation has been defined as '*the process of enhancing functional capacity of an individual to enable him/her to withstand the stressor of inactivity'(170).* In a study of patients undergoing thoracic operations, an increase of 2.4 ml/kg/min in VO_2 was noted in patients who were placed on an anaerobic exercise programme(137). It may also be possible

to maintain or improve fitness and muscle mass during oncological therapy. Resistance exercise in breast cancer patients receiving adjuvant chemotherapy resulted in higher chemotherapy completion rates(136). In our study less than half of the patients had adjuvant chemotherapy (similar rates to the Magic trial) (29). West and colleagues have also demonstrated similar declines in anaerobic threshold associated with neoadjuvant oncological therapy in colorectal patients to our study. However, they demonstrated an improved AT in the intervention arm, who had undergone a 6-week exercise programme(135). Conversely, other studies have not been able to reproduce these findings, with poor compliance sited as the most important factor for failure of prehabiltation(171, 172).

Maintaining or improving fitness and aerobic capacity may also impact the observed decline in muscle mass, function and quality of life. These improvements may increase the number of patients who complete all cycles of neoadjuvant/adjuvant therapy, and potentially alter survival. This should be the focus of further studies.

5.5 Limitations of the study

This is an observational, single unit study with some limitations. The number of recruited patients are modest and there is a male preponderance. The male preponderance is a well-established reflection of the much greater incidence of adenocarcinoma of the oesophagus and stomach in males. It is important to note that, unfit patients based on a comprehensive preassessment process including CPET data, were excluded from multimodality therapy (NAC plus surgery) and therefore, were not eligible for inclusion in this study. This reflects routine clinical practice. However, our methods of managing patients through the MDM reviews remained constant throughout the study, patients eligible for the study were approached with the designated time frame with no bias as in regards to their sex or fitness levels, once a decision was established that they were fit enough for multimodality therapy. Importantly, the clinical team was blinded to the results of serial CPETs, sarcopenia data as well as quality of life results. No special measures were undertaken in the study group and 93% of patients who had chemotherapy completed all 3 cycles of planned neoadjuvant chemotherapy.

Serial CPETs were performed in an experienced clinical unit and conducted by the author who was blinded to the results of CPET tests. The ‘raw’ CPET data, the sarcopenia measurements as well as quality of life questionnaires were analysed once the study was completed. The reporting clinicians, who have a vast experience in reporting CPET, were blinded to the sequence of tests, patient demographics as well as all other parameters which were investigated in this study. This pattern of reporting was also replicated in reporting of

muscle mass measurements to calculate radiological sarcopenia. The above processes were to ensure that bias is reduced to a minimum within the confines of an observational study.

In this study the two main parameters which were compared before and after NAC were AT(ml/kg/min) and VO_2Peak (ml/kg/min). Conventionally, these parameters have been reported as per weight ratios (ml/kg/min). This allows comparison between patients and between different studies which historically reported CPET parameters in (ml/kg/min). However, some studies have suggested that normalising AT and VO_2Peak using total body weight leads to spurious correlation errors(173, 174). In patients with BMI which are abnormally high, AT may not be due to poor cardiorespiratory fitness and may simply be secondary to scaling(173, 174). This may falsely penalise obese patients with lower values. This should be taken into account in future studies when CPET parameters are used. However, in his study *changes* at different time points in CPET parameters were measured. Additionally, no statistically difference in BMIs were noted between tests at different time points. This study observed changes in fitness rather than absolute values and therefore is not affected by the previously observed correlation errors.

In this study muscle mass index (radiological sarcopenia) was measured using CT scans pre and post NAC. Recent studies have demonstrated that additional information on muscle quantity and adiposity from clinically acquired CT scans provide significant prognostic information which are far superior to that of BMI measurements (158, 175). Such an assessment may have provided further useful insights into the relationship between radiological sarcopenia, sarcopenia in the presence of obesity and fitness. Both muscle mass and adiposity represent modifiable targets through prehabilitation and should form the basis for further studies.

In this study, 23 out of a recruited 31 patients completed Test 2. This was mainly due to a high incidence of thromboembolic events (14%) which was an absolute contraindication to repeat CPET testing. There is a well-established link between oesophago-gastric cancer, oncological therapy and thromboembolic events, however, thromboembolic rates were higher than we had anticipated based on results from previous studies(176). This is a significant attrition rate and one which should be taken into consideration in future studies. A recent review of available literature has indicated a thromboembolic risk of up to 19% in patients undergoing NAC for oesophageal and gastric cancer. This is reflected in our study(177). It is therefore imperative that interventions to minimise this risk should be considered prior to the start of neoadjuvant therapy. Safety of such interventions should form the basis of future studies.

Chemotherapy induced toxicity results from cellular damage and inflammation of healthy cells. Symptoms of toxicity include bone marrow suppression, GI symptoms such as nausea, vomiting and diarrhoea, loss of appetite, fatigue, nerve damage and cardiorespiratory damage(45). The aim or the scope of this study was not to exclude all or any of these contributory mechanisms as the reason for the noted decline in fitness, loss of muscle function/mass or quality of life. This study however, excluded certain possible contributory factors such an anaemia and loss of weight as the noted decline.

Finally, this study was not designed to look at the relationship between the studied parameters such as CPET, Sarcopenia and Quality of life as well as their impact on surgical or oncological complications and survival. Although, we have demonstrated a statistically significant decline in all parameters pre and post NAC, no concrete conclusions can be drawn between the potential interrelationship of one parameter on another and their impact on complications and survival. This should form the basis of future studies.

5.6 Conclusion

This study evaluated the impact of neoadjuvant chemotherapy on cardiorespiratory fitness, QOL, and sarcopenia. A number of key findings were observed. Neoadjuvant chemotherapy resulted in a significant and sustained reduction in fitness, this impact had not significantly reversed prior to surgery. This study further demonstrated a significant decline in muscle mass and function (sarcopenia) post neoadjuvant chemotherapy. Muscle function had not recovered by the time of surgery. Additionally, aspects of quality of life were also significantly impacted by neoadjuvant chemotherapy. These findings may aid decision making in patients with borderline fitness and or sarcopenia and should prompt further studies into the impact of ‘prehabilitation’ on above parameters, during oncological therapy and prior to surgery. This may aid in maintaining cardiorespiratory reserve, muscle function/mass as well as quality of life. These results represent a natural precursor to the introduction of ‘prehabilitation’ which may lead to a reduction in morbidity and improve survival.

6. References

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7. Chapter 8. Appendices

7.1 Appendix 3. Published article based on primary end points of this thesis

Original article

Cardiopulmonary fitness before and after neoadjuvant chemotherapy in patients with oesophagogastric cancer

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Background: Neoadjuvant chemotherapy may have a detrimental impact on cardiorespiratory reserve. Determination of oxygen uptake at the anaerobic threshold by cardiopulmonary exercise testing (CPET) provides an objective measure of cardiorespiratory reserve. Anaerobic threshold can be used to predict perioperative risk. A low anaerobic threshold is associated with increased morbidity after oesophagogastrectomy. The aim of this study was to establish whether neoadjuvant chemotherapy has an adverse effect on fitness, and whether there is recovery of fitness before surgery for oesophageal and gastric adenocarcinoma.

Methods: CPET was completed before, immediately after (week 0), and at 2 and 4 weeks after neoadjuvant chemotherapy. The ventilatory anaerobic threshold and peak oxygen uptake (V_{O_2} peak) were used as objective, reproducible measures of cardiorespiratory reserve. Anaerobic threshold and V_{O_2} peak were compared before and after neoadjuvant chemotherapy, and at the three time intervals.

Results: Some 31 patients were recruited. The mean anaerobic threshold was lower following neoadjuvant treatment: 15·3 ml per kg per min before chemotherapy *versus* 11·8, 12·1 and 12·6 ml per kg per min at week 0, 2 and 4 respectively ($P < 0·010$). Measurements were also significantly different at each time point ($P < 0·010$). The same pattern was noted for V_{O_2} peak between values before chemotherapy (21·7 ml per kg per min) and at weeks 0, 2 and 4 (17·5, 18·6 and 19·3 ml per kg per min respectively) ($P < 0·010$). The reduction in anaerobic threshold and V_{O_2} peak did not improve during the time between completion of neoadjuvant chemotherapy and surgery.

Conclusion: There was a decrease in cardiorespiratory reserve immediately after neoadjuvant chemotherapy that was sustained up to the point of surgery at 4 weeks after chemotherapy.

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Introduction

Surgical resection offers the best chance of cure for patients with oesophagogastric cancer[1]. However, over the past decade multimodality treatment involving perioperative oncological therapy has become the standard of care for potentially curable oesophagogastric cancer, demonstrating improved survival benefits over unimodality therapy alone[2–4]. Increasingly large proportions of patients are treated with neoadjuvant oncological therapy and surgery. However, these trials also report morbidity and toxicity associated with perioperative therapy, with a resultant reduction in the proportion of treated patients who successfully complete all prescribed cycles of oncological therapy[3,5].

The impact of chemotherapy, with or without toxicity, on surgical outcomes has not been reported widely. Although two previous studies[6,7] confirmed a deleterious effect on physical fitness following neoadjuvant oncological therapy, they did not report on the potential reversibility of this effect or on its change over time. If the reduction in cardiorespiratory reserve is sustained to the point of surgery, this could have a negative effect on postoperative recovery, overcoming complications, survival and the ability of the patient to complete the planned postoperative chemotherapy regimen.

Cardiopulmonary exercise testing (CPET) provides an objective assessment of cardiorespiratory function during physiological stress. CPET measurements of oxygen uptake at anaerobic threshold (AT), peak oxygen uptake ($V\dot{O}_2$ peak) and ventilatory equivalents for carbon dioxide ($V\dot{E}/V\dot{C}O_2$) are used in other surgical disciplines to provide individualized risk assessment, guide preoperative optimization and predict postoperative complications[8–10]. CPET could potentially provide vital information to enable multidisciplinary decision-making and to counsel patients. This may be of particular benefit to those with borderline fitness[11]. Low AT and low $V\dot{O}_2$ peak have been shown to be the best predictor of morbidity and outcomes in a variety of general surgical abdominal procedures[8–10,12,13], and superior to other predication tools[8,14]. Furthermore, there may be an association with outcomes after foregut surgery, although published studies assessing the value of CPET in oesophagectomy are limited and do not consider homogeneous populations[13,15,16].

This prospective study was designed to measure objectively the impact of a single neoadjuvant chemotherapy regimen on cardiorespiratory reserve immediately after chemotherapy and before surgery, and to establish whether a reduction in fitness recovers over time before surgery. CPET was used to quantify cardiopulmonary reserve using AT and $V\dot{O}_2$ peak.

Methods

This feasibility study was approved by the Research Ethics Committee (15/NE/0276) and sponsored by the Newcastle upon Tyne NHS Hospitals Trust (172690); registered as ISRCTN44343129. The study was conducted according to standards of good clinical practice.

Thirty-one consecutive eligible patients attending the Northern Oesophagogastric Cancer Unit at the Royal Victoria Infirmary, Newcastle upon Tyne, were recruited during a 6-month period in 2015–2016. The number of recruited patients was based on a previous study[6] and a minimum number of patients required to detect a statistically significant difference in AT. All patients were discussed at the multidisciplinary meeting, and appropriate staging investigations, which included endoscopy and biopsy, thoracoabdominal CT, PET(–CT) and endoscopic ultrasound examination, were carried out. An ultrasound scan of the neck and staging laparoscopy were performed if merited clinically. A health and fitness assessment, including CPET, was completed before recruitment to the study; this is the current standard of care at this institution. Following these investigations, patients were invited to enrol in the study and complete further exercise tests.

Patients with a diagnosis of operable locally advanced adenocarcinoma of the oesophagus, gastro-oesophageal junction or stomach in whom neoadjuvant chemotherapy was planned, and who had undergone CPET, were included. Neoadjuvant chemotherapy was administered to all patients with locally advanced disease (any T3/4 N+ M0) (TNM7)[17] with adequate renal (glomerular filtration rate above 60 ml/min) and cardiac function (no previous history of significant cardiac disease or echocardiogram/multigated acquisition scan with adequate left ventricular ejection fraction) and WHO performance status of 2 or above.

The chemotherapy regimen comprised epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 on day 1 (both intravenously) and capecitabine 652 mg/m^2 twice daily, orally, on days 1–21, every 3 weeks for a planned three preoperative and three postoperative cycles (ECX regimen)[3]. All patients had restaging investigations after neoadjuvant chemotherapy, and were discussed again at a multidisciplinary meeting to assess operability. All patients were encouraged to maintain a healthy lifestyle and to keep active during neoadjuvant chemotherapy and before surgery. However, no structured exercise programme was provided. Patients with a histology of squamous cell carcinoma, patients who received combined preoperative chemotherapy and radiotherapy, those who had surgery alone, and patients with a palliative treatment plan were excluded from the study.

Cardiopulmonary exercise testing protocol

Initial baseline CPET (test 1) was carried out as part of the multidisciplinary meeting investigations before administration of neoadjuvant chemotherapy or staging laparoscopy. The next CPET was performed immediately after completion of neoadjuvant chemotherapy (7-day window) (test 2); the third and fourth tests were completed a further 2 and 4 weeks after the completion of neoadjuvant chemotherapy. CPET was performed in accordance with the American Thoracic Society/American College of Chest Physicians guidelines[18] for cardiopulmonary exercise testing, and their stated exclusion criteria. Patients performed a symptom-limited continuous ramped test using a cycle ergometer (Ergoselect 200; Ergoline, Bitz, Germany). Metabolic gas analysis was performed via the metabolic cart (Ultima Series; MGC Diagnostics, Saint Paul, Minnesota, USA), and 12-lead ECG, heart rate and pulse oximetry (Welch Allyn, Skaneateles Falls, New York, USA) were recorded throughout the test.

Table 1 Study characteristics

	No. of patients* (*n* = 31)
Patient characteristics	
Age (years)†	65 (41–81)
Sex ratio (M:F)	27:4
ASA fitness grade†	2 (1-3)
BMI (kg/m^2)†	27·0 (19·4–37·7)
Tumour location	
Lower oesophagus	11
Gastro-oesophageal junction	12
Stomach	8
Operation	
Ivor Lewis oesophagectomy	13
D2 total gastrectomy	9
D2 subtotal gastrectomy	3
Lymph node yield†	37 (19–70)

*Unless indicated otherwise; †values are median (range).

Flow and gas calibrations were performed before each test session. Ramped work rate increase was calculated for each individual using age, sex and height to achieve a loaded test with duration of 6–10 min[19]. Tests were stopped when clinical indications to discontinue testing were met, the patient reached volitional exhaustion (fatigue, pain, lightheaded) or the patient failed to maintain the appropriate pedal speed for 30 s despite encouragement[20].

Data analysis using the Breeze Suite™ software (Ultima Series; MGC Diagnostics) allowed determination of $V\text{O}_2$ peak (highest oxygen uptake in the last 30 s of exercise), oxygen uptake at AT using the V-slope method described by Beaver *et al.*[19], and the ventilatory equivalents for carbon dioxide at AT. Oxygen consumption during testing ($V\text{O}_2$) was calculated both in millilitres per min and indexed to bodyweight (ml per kg per min). Tests were conducted by one author and reported independently by two experienced assessors, blinded to each other's assessments. Disagreements were resolved by a third assessor. Interobserver consistency was excellent: interclass correlation coefficient 0·964 (95 per cent c.i. 0·947 to 0·976). The primary measured outcome chosen for this study was AT (ml per kg per min); this is an objective, reliable measurement of cardiopulmonary reserve that is not dependent upon effort. $V\text{O}_2$ peak was also analysed.

Statistical analysis

Results from test 1 (baseline) were compared with results from tests 2, 3 and 4 (after neoadjuvant chemotherapy). Further comparison of results from test 2 was made with test 4 to investigate changes in cardiopulmonary reserve over time after completion of chemotherapy. A Shapiro–Wilk test confirmed that CPET parameters were normally distributed. ANOVA with *post hoc* Tukey's honestly significant difference test was used to compare CPET parameters. Paired *t* tests were used for normally distributed data, and the Wilcoxon matched-pairs signed rank test was used for non-normally distributed data. $P < 0{\cdot}050$ was deemed statistically significant. Analysis was performed using SPSS® version 21.0 (IBM, Armonk, New York, USA).

Results

Thirty-eight patients who met the inclusion criteria were reviewed at a regional multidisciplinary meeting; of these, 31 patients were recruited (*Table 1*). Seven patients did not consent, or had completed baseline CPET at a different institution. Three patients were later excluded: two had a change of management to chemoradiotherapy after enrolment and one patient later declined to take part further in the study.

All patients had locally advanced tumours on preoperative staging: cT3–4a N0–2 (TNM7 classification[17]). Three patients did not undergo resection owing to disease progression, and one patient had an open-and-close laparotomy following discovery of liver metastasis. The median

Table 2 Cardiopulmonary exercise test results before and after neoadjuvant chemotherapy

	Test 1 (baseline) (*n* = 31)	Test 2 (week 0 after NAC) (*n* = 23)	Test 3 (week 2 after NAC) (*n* = 22)	Test 4 (week 4 after NAC) (*n* = 21)
AT (ml per kg per min)*	15·3(3·4)	11·9(2·5)†	12·1(2·7)†	12·6(2·7)†
$V\text{O}_2$ peak (ml per kg per min)	21·7(3·9)	17·5(3·0)†	18·6(2·9)†	19·3(3·6)†
FEV1 (litres)*	3·0(0·7)	2·8(0·5)	2·7(0·6)	2·8(0·8)
FVC (litres)	4·0(0·8)	3·9(0·6)	4·0(0·6)	4·0(0·9)
$Vc/V\text{co}_2$ at AT	28·9(4·7)	31·0(4·5)	30·0(14·1)	30·0(13·9)
BMI (kg/m^2)*	27·0 (19·4–37·4)	25·9 (18·3–38·6)	26·4 (18·4–38·2)	26·4 (24·2–29·7)

Values are mean(s.d.) unless indicated otherwise; *values are median (range). NAC, neoadjuvant chemotherapy; AT, anaerobic threshold; $V\text{O}_2$, oxygen uptake; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity, $V\text{E}$, ventilation; $V\text{co}_2$, carbon dioxide output. †$P < 0{\cdot}010$ *versus* test 1 (ANOVA with *post hoc* Tukey's honestly significant difference test).

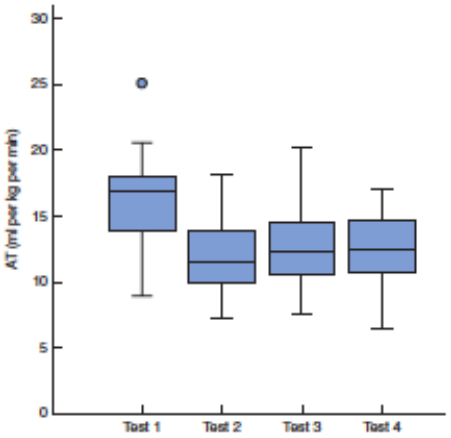

Fig. 1 Box-and-whisker plot comparing anaerobic threshold (AT) over time: at baseline (test 1) and after neoadjuvant therapy at week 0 (test 2), week 2 (test 3) and week 4 (test 4). Median values, interquartile ranges and ranges (excluding outlier) are denoted by horizontal bars, boxes and error bars respectively

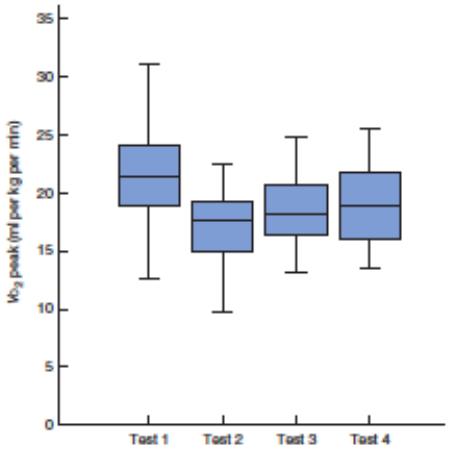

Fig. 2 Box-and-whisker plot comparing peak oxygen uptake (V_{O_2} peak) over time: at baseline (test 1) and after neoadjuvant therapy at week 0 (test 2), week 2 (test 3) and week 4 (test 4). Median values, interquartile ranges and ranges are denoted by horizontal bars, boxes and error bars respectively

length of hospital stay was 9 (7–14) days, and there were no deaths at 90 days. Of 25 patients who had resection with curative intent after neoadjuvant chemotherapy, nine (36 per cent) had complications: there were four wound infections, three lower respiratory tract infections, two duodenal stump leaks, three cases of atrial fibrillation, and two patients had postoperative delirium. No anastomotic leaks were observed.

Chemotherapy results

Twenty-seven (87 per cent) of the 31 patients completed all three cycles of neoadjuvant chemotherapy. Two patients had a change of oncological treatment and received neoadjuvant chemoradiotherapy. One patient completed only one cycle (due to an acute tumour haemorrhage requiring an urgent operation), and one patient completed two cycles before an embolic event requiring an embolectomy. Ten (34 per cent) of the 29 patients had one or more cycles of neoadjuvant chemotherapy.

During neoadjuvant chemotherapy, 12 patients reported grade 3/4 toxicity: two of 29 patients had febrile neutropenia, four had thromboembolic events, four had emesis, one had diarrhoea, three had fatigue and two had palmar planar erythema.

The median time from last oral chemotherapy tablet to first CPET after chemotherapy (test 2) was 3 (range 1–14) days. The timing of test 4 was at a median of 27 (24–37) days, and surgery was performed at 31 (26–42) days. There were no significant differences in inflammatory markers, albumin or haemoglobin levels before and after neoadjuvant chemotherapy.

Cardiopulmonary exercise test results

Baseline measurements taken before chemotherapy (test 1) were compared with CPET results for tests 2, 3 and 4 (*Table 2*). There was a statistically significant reduction in the mean AT between test 1 (15·3 ml per kg per min), test 2 (11·9 ml per kg per min), test 3 (12·1 ml per kg per min) and test 4 (12·6 ml per kg per min) ($P < 0·010$) (*Fig. 1*). The same pattern was found for V_{O_2} peak between test 1 (21·7 ml per kg per min) and tests 2, 3 and 4 (17·5, 18·6 and 19·3 ml per kg per min respectively) ($P < 0·010$) (*Fig. 2*).

When the results of test 2 were compared with those of test 4, mean AT and V_{O_2} peak were not statistically different ($P = 0·452$ and $P = 0·214$ respectively). The reduction in AT and V_{O_2} peak did not improve during the time between completion of neoadjuvant chemotherapy and surgery. Other CPET measurements (V_E/V_{CO_2} at AT, forced expiratory volume in 1 s, forced vital capacity and BMI) were not significantly different between the four time points (*Table 2*).

Discussion

This study confirms that a reduction in CPET-measured fitness (cardiorespiratory reserve) is seen after neoadjuvant chemotherapy in patients treated for oesophagogastric cancer. Immediately after neoadjuvant chemotherapy, mean oxygen uptake at AT and at $V'O_2$ peak fell by 3·4 and 4·2 ml per kg per min respectively (test 1 *versus* test 2). This is a clinically significant reduction in cardiorespiratory reserve. Importantly, this effect was seen immediately after neoadjuvant chemotherapy and was sustained throughout the 4-week period after neoadjuvant chemotherapy and before surgery (AT test 2 *versus* test 4: $P = 0{\cdot}452$). Thus, fitness (AT) does not recover during this time and patients proceed to surgery with suppressed cardiopulmonary reserve. The two patients who did not complete all three cycles of chemotherapy also demonstrated a reduction in fitness, despite receiving a smaller total dose of neoadjuvant chemotherapy.

The present results support the growing body of evidence from CPET studies that oncological treatments have a deleterious effect on cardiopulmonary reserve. Jack and colleagues[7] found a similar reduction in AT in patients with oesophagogastric cancer who completed preoperative chemotherapy. However, different chemotherapy regimens were used in that study and reversibility was not assessed. Similarly, an effect on cardiopulmonary reserve has been demonstrated following neoadjuvant chemoradiotherapy for rectal cancer[21], and after neoadjuvant chemotherapy and adjuvant radiotherapy for breast cancer[22].

The observed sustained reduction in oxygen delivery may be attributed to several cancer and chemotherapy effects: poor nutritional intake and malabsorption secondary to diarrhoea, sarcopenia, anaemia, myelosuppression and sepsis, reduced oxygen delivery secondary to oxidative stress or as a direct consequence of chemotoxicity on cardiac or respiratory systems[23–26]. In the present study, haemoglobin levels and BMI did not change significantly between tests, indicating that neither anaemia nor weight loss was responsible for the reduced oxygen delivery in this patient cohort.

CPET measures total oxygen delivery and utilization. This is the integrated effect of multiple homeostatic mechanisms. Thus, CPET does not identify the pathophysiological mechanisms causing the decrease in $V'O_2$ peak and AT after neoadjuvant chemotherapy.

Neoadjuvant oncological therapy with surgery improves survival compared with surgery alone in this patient group[2–4,27]. As a result of these trials, the proportion of patients receiving perioperative oncological therapy has increased[28]. The decline in cardiorespiratory reserve demonstrated in the present study has potential implications for the clinical management of these patients. A patient with borderline fitness may experience a reduction in cardiopulmonary reserve that places them in a higher operative risk category than may have been ascribed based solely on CPET before neoadjuvant chemotherapy. For example, in this study, a patient with a starting AT of 11·2 ml per kg per min demonstrated a sustained reduction of 3·3 ml per kg per min following chemotherapy, resulting in a preoperative AT of 7·9 ml per kg per min. An AT of 7·9 ml per kg per min would be considered low and likely indicate that this patient was in a high-risk group for postoperative complications[12,13,15]. The implications of this in terms of individualized risk prediction remain unknown. Gastro-oesophagectomy is associated with significant morbidity, and cardiopulmonary complications are responsible for a substantial proportion of the postoperative morbidity and mortality seen[29]. The ability to counteract the reduced fitness seen after neoadjuvant therapy and improve a patient's condition before major surgery is appealing.

Postoperative complications are also independently associated with early death from cancer recurrence[30]. Patients with serious complications following surgery have diminished long-term survival[31]. It is therefore imperative that new perioperative strategies should aim to minimize postoperative complications. In patients with lower or borderline cardiopulmonary fitness, various strategies could be employed in an attempt to negate the effects of chemotherapy and minimize complications: surgery alone, chemotherapy with delayed surgery until fitness recovers, or prehabilitation. The possibility of improving a patient's fitness before surgery is attractive; if the effects of chemotherapy could be offset, a fitter group of patients would undergo surgery after neoadjuvant chemotherapy[31]. The complications of surgery are likely to have a greater impact on an unfit patient with low cardiopulmonary reserve. Would a 'borderline fit' patient be better served by surgery alone? The current accepted time frame following completion of neoadjuvant chemotherapy and surgery is 4–6 weeks. It may be argued that prolongation of the period between neoadjuvant chemotherapy and surgery offers a reasonable strategy to combat the demonstrated reduction in fitness. However, this study has established that fitness does not recover during a 4-week period of rest. It is unclear whether prolongation of the rest period with no active prehabilitation would lead to recovery of fitness. Additionally, no study to date has established the oncological safety (survival) when time to surgery is prolonged following neoadjuvant chemotherapy. This is unlike the situation with neoadjuvant chemoradiotherapy, where some evidence of impact on survival exists from a study[32] that demonstrated the interval between neoadjuvant

chemoradiotherapy and surgery may be prolonged with no effect on survival. However, a recent meta-analysis[33], performed to clarify the oncological safety in prolonging the period between completion of neoadjuvant chemoradiotherapy and surgery, demonstrated that an increased interval may have a negative impact on long-term overall survival.

It may be possible to maintain or improve fitness during oncological therapy. Resistance exercise in patients with breast cancer who received adjuvant chemotherapy resulted in higher chemotherapy completion rates[34]. In that study, less than half of the patients had adjuvant chemotherapy (similar rates to those in the MAGIC trial[3]). Maintaining or improving fitness may increase the number of patients who complete all cycles of neoadjuvant/adjuvant therapy, and potentially alter survival. This should be the focus of further studies.

This is an observational single-unit study with some limitations. The number of recruited patients was modest and there was a preponderance of men. However, the method of managing patients through multidisciplinary meeting reviews remained constant and the clinical team was blinded to the results of serial CPETs. No special measures were undertaken in the study group; 27 (93 per cent) of the 29 patients who had chemotherapy completed all three cycles of planned neoadjuvant chemotherapy, and CPET was performed in an experienced clinical unit and was conducted by one member of the team who was blinded to the CPET results. The reporting clinicians, who were experienced in reporting CPET results, were blinded to the sequence of tests and to patient demographics.

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7.2 Preliminary published article on impact of neoadjuvant chemotherapy on fitness prior to commencement of thesis

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The impact of neoadjuvant chemotherapy on cardiopulmonary physical fitness in gastro-oesophageal adenocarcinoma

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ABSTRACT

INTRODUCTION Operable oesophagogastric adenocarcinoma management in the UK includes three cycles of neoadjuvant chemotherapy (NAC) followed by resection. Determination of oxygen uptake at the anaerobic threshold (AT) with cardiopulmonary exercise testing (CPET) is used to objectively measure cardiorespiratory reserve. Oxygen uptake at AT predicts perioperative risk, with low values associated with increased morbidity. Previous studies indicate NAC may have a detrimental impact on cardiorespiratory reserve.

METHODS CPET was completed by 30 patients before and after a standardised NAC protocol. The ventilatory AT was determined using the V-slope method, and the peak oxygen uptake and ventilatory equivalents for carbon dioxide measured. Median AT before and after chemotherapy was compared using a paired Student's *t*-test.

RESULTS Median oxygen uptake at AT pre- and post-NAC was 13.9±3.1 ml/kg/min and 11.5±2.0 ml/kg/min, respectively. The mean decrease was 2.4 ml/kg/min (95% confidence interval [CI] 1.3–3.85; p<0.001). Median peak oxygen delivery also decreased by 2.17 ml/kg/min (95% CI 1.02–3.84; p=0.001) after NAC. Ventilatory equivalents were unchanged.

CONCLUSIONS This reduction in AT objectively quantifies a decrease in cardiorespiratory reserve after NAC. Patients with lower cardiorespiratory reserve have increased postoperative morbidity and mortality. Preventing this decrease in cardiorespiratory reserve during chemotherapy, or optimising the timing of surgical resection after recovery of AT, may allow perioperative risk-reduction.

KEYWORDS
Exercise test – Neoadjuvant chemotherapy – gastrointestinal neoplasms – Oesophagectomy – Preoperative care

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Based on the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial,[1] the current management in the UK of advanced but resectable oesophagogastric adenocarcinoma combines surgical resection and perioperative chemotherapy. Perioperative chemotherapy improves survival over surgery alone by 15%, but it is not without potential toxicity; in the MAGIC trial, only 41% of patients completed all six planned cycles of chemotherapy.[1,2] In our centre, 86% of patients complete the preoperative component of MAGIC chemotherapy and 45% complete all six cycles. Twenty-six per cent of patients who complete preoperative chemotherapy do not commence postoperative treatment (unpublished audit data). Among the side effects of chemotherapy, fatigue is almost universally reported.

Cardiorespiratory reserve is important to patients undergoing major surgery. The metabolic stress incurred during major surgery and in the perioperative period requires a protracted increase in oxygen delivery.[3] The cardiopulmonary exercise test (CPET), alongside estimation of the lactate threshold/anaerobic threshold (AT), is employed during preoperative assessment before major surgery. The AT provides an objective measure of physical fitness and is associated with postoperative survival and morbidity for a variety of populations undergoing major non-cardiac and cancer surgery.[4–6] Older *et al* originally described the association between a low AT (<11 ml/kg/min) and surviving cardiopulmonary and surgical complications after non-cardiac surgery.[6] More recently, AT has been shown to be an independent predictor of complications and length of stay in other major surgeries,[4] and to predict mortality and length of stay after hepatobiliary surgery.[7] Wilson *et al* demonstrated that AT and ventilatory equivalent for carbon dioxide ($VeVCO_2$) was associated with all-cause mortality after

elective intra-abdominal surgery and could be used to identify high-risk patients.[5]

The evidence base for CPET before oesophagogastric cancer resection is limited and does not yet show a strong correlation between CPET measurement and postoperative complications.[8,9] The most recent UK publication exploring the ability of CPET to predict postoperative cardiopulmonary complications in these patients showed a trend towards patients with a lower AT developing more cardiopulmonary complications.[9] However, this was a small, single-centre study of a heterogeneous group, and many patients with existing cardiorespiratory comorbidities were deemed unfit for surgery and managed nonoperatively. Patients with comorbidities had a significantly lower mean AT than the resected group, at 8.6 versus 10.8 ml/kg/min.[9]

The Northern Oesophagogastric Cancer Unit, based at The Royal Victoria Infirmary, Newcastle-upon-Tyne, UK, is a large tertiary referral unit that received 659 new patient referrals and performed 159 surgical resections for malignant disease in 2015. Coordinated multidisciplinary team (MDT) management is essential to the success of the unit. Patients deemed to have potentially curable disease at initial presentation are seen in a staging clinic and complete tumour staging is carried out in accordance with national guidelines. This includes endoscopic ultrasound examination, computed tomography/positron emission tomography, staging laparoscopy and ultrasound scanning of the neck. A health and fitness assessment, including CPET, is also performed. This informs the MDT discussion and treatment planning.

As part of a service evaluation project, we performed CPET at two time points within our MDT pathway to appropriately design and optimise the timing of CPET for our patients. We analysed the data as part of a service evaluation and improvement project within our unit. Hypothesising that perioperative chemotherapy may have a deleterious effect on physical fitness and cardiorespiratory reserve, we compared the results from CPET at baseline and after neoadjuvant chemotherapy (NAC).

Methods

Between November 2012 and April 2014, all patients with oesophagogastric adenocarcinomas deemed by the MDT suitable for perioperative chemotherapy and surgical resection were included in this retrospective analysis. All patients had undergone paired CPET testing at baseline as part of their fitness assessment and after the preoperative component of chemotherapy as part of our service evaluation. There was no randomisation; selection for a second CPET test was based on the availability of patients and CPET slots. The decision to perform a second CPET test was not related to poor performance or any perceived deterioration in health post-NAC.

Staging and surgical data were obtained retrospectively from the prospectively collected Northern Oesophagogastric Unit database. Preoperative chemotherapy data was retrospectively obtained from patient notes. CPET measurements for each patient were derived from the CPET database.

Chemotherapy

Patients with T3 and/or N1 resectable oesophagogastric adenocarcinoma were considered for perioperative ECX chemotherapy. This consisted of three preoperative and three postoperative cycles of intravenous epirubicin 50 mg/m^2 body-surface area and cisplatin 60 mg/m^2 on day 1, and a continuous intravenous infusion of fluorouracil 200 mg/m^2/day for 21 days, as per the MAGIC Trial.[1] To be suitable for chemotherapy, all patients had World Health Organization Performance status 0 or 1, and adequate renal, haematological and cardiac function. All patients had a restaging computed tomography scan post-chemotherapy and were rediscussed in the MDT to assess operability.

Cardiopulmonary exercise testing

CPET was performed in accordance with the American Thoracic Society/American College of Chest Physicians guidelines for cardiopulmonary exercise testing.[10] Patients performed a symptom-limited continuous ramped test using a cycle ergometer (Lode, Groningen, the Netherlands), while metabolic gas analysis was performed using a metabolic cart (Scott Medical, Plumsteadville, PA, USA). In addition, 12-lead electrocardiography, heart rate monitoring and pulse oximetry were recorded throughout the test (Welch Allyn, Skaneateles Falls, NY, USA). Each test was conducted using an individualised ramp protocol.[10] Tests were performed at baseline as part of standard cancer staging and after completion of preoperative chemotherapy.

The data derived from the CPET was recorded by the clinician responsible for their interpretation. The amount of oxygen extracted from the gases (VO_2) was calculated as ml/min and indexed to body weight as ml/kg/min. This was measured both at peak exercise (VO_2peak) and at the ventilatory anaerobic threshold (VAT). Ventilatory equivalents for carbon dioxide (VCO_2) were measured at VAT. Ventilatory AT was derived from the V-Slope breakpoint between VO_2 and VCO_2,[11] and by confirming the increase in Ve/VO_2 and the plateau of Ve/VCO_2. The same investigator interpreted all tests and all data were analysed using BreezeSuite version 6.2 (MGC Diagnostics Corporation, Saint Paul, MN, USA).

The primary measured outcome was VO_2 at AT (ml/kg/min) before and after preoperative chemotherapy. We also considered the VO_2peak and VE/VCO_2 before and after chemotherapy.

Statistical analysis

Median values for the baseline tests were compared to those for our whole patient population using a paired Student's *t*-test to exclude inclusion bias. CPET results before and after neoadjuvant chemotherapy were compared on a paired Student's *t*-test. All analyses were carried out using SPSS Statistics version 21 (IBM, Armonk, NY, USA). P values <0.05 were deemed significant and 95% confidence intervals (CIs) were determined.

Results

Between November 2012 and April 2014, 30 patients with operable oesophagogastric adenocarcinomas underwent

preoperative ECX chemotherapy, at a median of three cycles, and had paired CPET at baseline and post-chemotherapy. The median patients age was 67.8 years, and 24 were male. Ten patients stopped treatment early, all as a result of toxicity. The most commonly observed grade 3/4 toxicity was neutropenia, in 17% of patients, followed by diarrhoea in 13%, fatigue in 10%, neutropenic sepsis in 10%, thromboembolism in 7% (one axillary vein thrombus and one ulnar artery embolus) and emesis in 5%. The median time (range) from the final oral chemotherapy tablet to postchemotherapy CPET was 50 (6–78) days.

Baseline CPET measurements were compared with those of our entire oesophagogastric population over the same time period, with no significant differences found between the groups (Table 1). The two groups were managed identically with NAC and surgery, and had comparable baseline descriptive characteristics. The CPET data were normally distributed.

There was a significant change in VO_2 measured at AT and at peak exercise between baseline and post-chemotherapy CPET (see Table 2). VAT decreased from 13.8 ml/kg/min to 11.3 ml/kg/min (95% CI 1.30–3.85; p<0.001). VO_2peak decreased from 16.8 to 14.7 ml/kg/min (95% CI 1.02–3.84; p=0.001) (see Figure 1).

Discussion

Our results support the hypothesis that, alongside the known toxic effects of chemotherapy, there is a measurable reduction in cardiorespiratory reserve (fitness), quantified here by CPET. These results are consistent with the only other published data in patients receiving preoperative chemotherapy for oesophagogastric cancers.[12]

Table 1 Baseline characteristics of our study population (before NAC) and the reference population. All patients were managed with the same perioperative chemotherapy regimen and surgery for operable oesophagogastric cancer. The reference population had CPET prior to NAC. The study group had CPET pre- and post-chemotherapy CPET.

	Reference population (n=140)	Study group (n=31)
Age (years)	66 (10.1)	67.8 (7.9)
BMI (kg/m2)	25.9	27.8
VO_2 at AT (ml/kg/min)	13.0 (3.8)	13.8 (4.3)
VO_2 at AT (ml/min)	1002 (389)	819 (340)
VO_2peak (ml/kg/min)	18.0 (4.8)	16.8 (5.1)
VO_2peak (ml/min)	1341 (509)	1186 (331)
Median Ve/VCO_2 at AT	30	30

All values median (SD) unless otherwise stated
BMI, body mass index; VO_2 at AT, oxygen uptake measured at ventilatory anaerobic threshold; VO_2peak, peak oxygen uptake during testing; Ve/VCO_2 at AT, ventilatory equivalents for carbon dioxide measured at ventilatory anaerobic threshold

Table 2 CPET at baseline and post-NAC

	Baseline	Post-NAC	P value	95% CI
Median VO_2 at AT (ml/kg/min)	13.8	11.3	<0.001	1.30 to 3.85
Median VO_2 at AT (ml/min)	902	768	0.012	32.0 to 235.3
Median VO_2peak (ml/kg/min)	16.8	14.7	0.001	1.02 to 3.84
Median VO_2peak (ml/min)	1186	1026	0.001	71.0 to 248.7
Median Ve/VCO_2 at AT	30	31	0.33	-2.70 to -0.21
Median Hb (g/L)	136.5	120.5	0.72	-1.25 to 27.5

Hb, haemoglobin concentration; VO_2 at AT, oxygen uptake measured at ventilatory anaerobic threshold; VO_2peak, peak oxygen uptake during testing; Ve/VCO_2 at AT, ventilatory equivalents for carbon dioxide measured at ventilatory anaerobic threshold

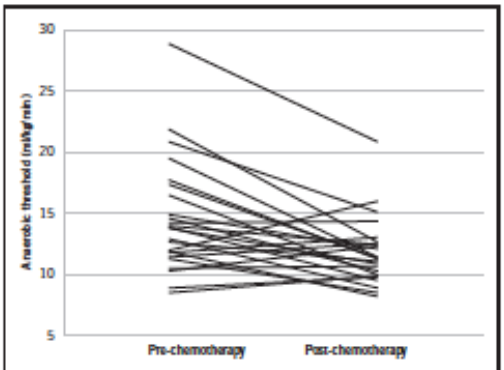

Figure 1 Ladder plot showing individual pairs of anaerobic thresholds at baseline and post-NAC

Jack *et al* conducted a prospective study between 2007 and 2009 in 59 patients with resectable oesophagogastric cancers. They reported a mean reduction in the measured VO_2 at lactate threshold of 2.19 ml/kg/min (95% CI 1.47–2.91) 4 weeks after neoadjuvant chemotherapy. VO_2peak was also significantly reduced after neoadjuvant chemotherapy (2.5 ml/kg/min (95% CI 0.44–4.07). Kaplan-Meier analysis suggested that a lower level of fitness (VO_2 at AT) was associated with decreased 1-year survival in patients who completed both full preoperative chemotherapy and surgery.[12] The authors postulated whether higher baseline fitness was required to offset effectively the dual insult of chemotherapy and surgery. It was also observed that the 50

patients who did not complete all their cycles of preoperative chemotherapy had a lower baseline VAT and VO_2peak than those who did complete chemotherapy. However, there was no association between baseline VO_2 at AT and 1-year survival in this group.

A similar study investigating the effects on fitness of neoadjuvant chemoradiotherapy before rectal cancer resection demonstrated a reduction in VO_2 at AT and VO_2peak of 1.5 and 1.4 ml/kg/min, respectively ($p<0.001$).[15]

CPET measurements have also been published in women with treated breast cancer.[14] In a study of 222 patients, VO_2peak was lower in matched groups who had completed surgery and a course of either neoadjuvant or adjuvant chemotherapy compared with those tested in the first 2 weeks of their adjuvant chemotherapy. The group who had surgery alone had a lower VO_2peak than those managed with surgery and adjuvant chemotherapy. VO_2 at AT was not significantly different across the groups ($p=0.21$). VO_2peak and VO_2 at AT were lowest following surgery and postoperative adjuvant chemotherapy.[14]

Dual modality treatment with perioperative chemotherapy and surgery for operable oesophagogastric adenocarcinomas offers the best chance of cure. However, it results in substantial morbidity, as evidenced by only 40% of patients completing all planned treatment. Our data demonstrates that preoperative chemotherapy resulted in a decline in fitness, as measured by AT. The interpretation of these preliminary results should not, on the basis of this study, be extrapolated beyond this statement; however, potentially important clinical implications arise from our findings. Reduced fitness (cardiorespiratory reserve) may alter the ability of an individual to respond appropriately of the perioperative and postoperative physiological insults. In other major surgeries, a low AT is predictive of increased morbidity.[4,6,15] A reduction in AT and cardiopulmonary reserve below the pre-chemotherapy baseline may move patients into a higher perioperative risk category. This may also be the case for those undergoing surgery for oesophagogastric cancers, and we may therefore be able to identify a group of patients who could benefit from prehabilitation to maintain or improve fitness during chemotherapy. Perhaps we should adjust the timing of surgery to allow recovery of baseline fitness. Moreover, intervention to maintain fitness during treatment may increase the number of patients able to complete the entire planned chemotherapy and surgery programme and, in turn, improve survival. This would be a useful focus for future studies.

As demonstrated in Figure 1, not all patients experienced a decline in fitness; however, the group effect was a reduction in median VAT and VO_2peak, despite a measured increase in fitness in six patients. This increase in fitness may partially be explained by improved nutrition following commencement of NAC, alongside improvements in dysphagia and/or the insertion of adjuncts such as feeding jejunostomies prior to NAC. As no dysphagia scores were maintained, this is, however, only a hypothesis and further studies comparing quantitative measurements of nutritional status and fitness measures are required. Although there was a reduction in haemoglobin concentration between the pre- and post-NAC measurements, this did not reach statistical significance.

CPET is an integrated test of all the homeostatic mechanisms involved in oxygen delivery, including respiratory, cardiovascular and circulatory systems, as well as muscle oxygen extraction and oxygen utilisation at the cellular level. As such, any attempt to elicit the mechanisms that might alter oxygen homeostasis and result in the earlier use of anaerobic metabolism (AT) after chemotherapy is outside the scope of this investigation. However, it should be noted that analysis of patient comorbidities, via clinical histories, in our group confirmed that these did not alter during testing. Similarly, there was no significant cancer disease progression that would confound the CPET results. Analysis of haemoglobin concentrations before and after neoadjuvant chemotherapy showed a reduction in haemoglobin measurement between the two time points that did not reach statistical significance. There is little evidence to illuminate the clinical effect of decreased haemoglobin in this context. Published work from our institution suggests that each g/dl increase in haemoglobin in patients with chronic haematological disorders receiving blood transfusions results in a mean increase in VO_2 of 0.39 ml/kg/min.[16]

Our study has a number of limitations. It is observational and retrospectively examines data on a small proportion of the patients treated in our unit. Chemotherapy data has been collected retrospectively and is therefore reliant on the accurate recording of clinical information. In contrast, CPET data, the principle outcome measure, was derived from the original test data and is thus robust. True randomisation of testing was not observed and yet our cohort have the same characteristics as our local operable population. Despite the limitations, our results concur with other recently published data.[12] Furthermore, our management of patients via MDT meeting reviews remained consistent throughout the study and all patients were treated by the same oncology and surgical teams using a consistent chemotherapy regimen and surgical approach. CPET was performed in a single testing clinic using standardised protocols and equipment.

We have not included postoperative data in this analysis, since this is beyond the power of this small, retrospective, observational sample, and we do not believe that further conclusions can be drawn from this data. We hypothesise that the observed reduction in fitness was caused by a multi-system effect of chemotherapy, including bone marrow suppression. However, we acknowledge that there are many factors involved that cannot be elucidated with our data.

Conclusions

In conclusion, this study objectively demonstrates a significant reduction in fitness following preoperative chemotherapy for oesophagogastric cancer when using a robust objective measurement. Prospective evaluation of 'prehabilitation' or 'fitness maintenance' exercise training before and during preoperative chemotherapy may help to

maintain cardiorespiratory reserve and have an impact upon survival, and is therefore worthy of prospective evaluation in further studies.

Acknowledgement

Our thanks are extended to the data managers of the Northern Oesophagogastric Cancer Unit database and to our preassessment clinic for facilitating this work.

Contributions to the writing of this paper were as follows: RCFS, study design, data collection, analysis and interpretation, writing all drafts, decision to submit; MN, data collection, analysis and interpretation, report writing; SMG, writing report final drafts, decision to submit; and KS, study design, data collection, analysis and interpretation, report writing all drafts, decision to submit.

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7.3 Appendix 1. Patient Involvement and Participation Questionnaires

Overall, do you feel that this project answers questions, which are important to patients who suffer from gullet or stomach cancer?

Yes No

16 (100%) patients answered positively.

1. Would you be prepared to carry out three extra bike tests at fortnightly intervals after completion of your chemotherapy?

Yes No

16 (100%) patients answered positively.

2. Would you be willing to under go the Grip Test and the Get Up and Go test prior to chemotherapy, and at fortnightly intervals on three more occasions, after your chemotherapy?

Yes No

16 (100%) patients answered positively.

3. Do you feel that the Mini Nutritional Assessment and the Quality of Life questionnaires address issues that are important to patients with this type of cancer?

Yes (16) No (0)

16 (100%) patients answered positively.

4. Would you be willing to answer these questionnaires once before and on three occasions after chemotherapy at fortnightly intervals?

Yes (16) No (0)

16 (100%) patients answered positively.

Is there anything that you would alter about the design of this project?

Yes (0) No (16)

16 (100%) indicated that they would not change the design of the study.

In addition to the above questionnaire, twenty post operative patients were questioned regarding their overall experience with the CPET test and their willingness to participate in the proposed study. The following questions and responses were obtained.

1. Overall, how would you rate your bike test experience?
   Bad (1) 5% Satisfactory (3) 15% Good (16) 80%

2. Would you be prepared to do this test three times post chemotherapy, at fortnightly intervals, as part of a research project?

   Yes (18) 90% (no) 10%

7.4 PATIENT INFORMATION SHEET

(Version 3, August 2015.)

IMPACT OF NEO-ADJUVANT CHEMOTHERAPY ON CARDIORESPIRATORY RESERVE IN OESOPHO-GASTRIC CARCINOMA

You are being invited to take part in a research study.

Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

Thank you for reading this information sheet.

What is the purpose of the study?

We now know that chemotherapy before surgery improves the chances of you living longer and without cancer compared to surgery alone. We also know that chemotherapy can negatively impact on your fitness levels and well-being. What we do not know, is when your health returns to normal or near normal, after chemotherapy. This is a very important question that can help us work out the best time for an operation when your body has recovered from the negative effects of chemotherapy.

During your visit to the pre-assessment clinic we used an exercise bike to measure how fit you were and how your heart and lungs worked.

In order to find out when your health returns to near normal after chemotherapy, we would like to ask you to perform the bike test that you did before the start of chemotherapy, on three more occasions after the completion of chemotherapy. This would be at fortnightly intervals. We will also ask you to kindly complete a grip test and a timed get up and go test which measures your muscle strength and function.

Both are very easy to do. We also ask you to complete two questionnaires about your diet and general well-being.
This research will give us some very important answers on your over all fitness and health. Once the data has been analysed this may help us to change the time of surgery and or introduce measures in the future that may stop or slow the decline in health and well-being during chemotherapy.
Without this research we will not be able to answer these questions.

Why have I been chosen?

You have been chosen because you are suitable to have chemotherapy prior to surgery. We have also not found any reasons why you can not perform or complete the bike test.

Do I have to take part?

It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show that you have agreed to take part. You are free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part?

1) The bicycle test for fitness assessment

You will have already undergone this test as part of your routine assessment to measure your fitness and suitability of chemotherapy and surgery. We will ask you to do this test on three more occasions.

First we connect you to heart, blood pressure and breathing monitors. Then we ask you to pedal an exercise bike very slowly while you breathe in and out through a tube which is connected to a machine which monitors your breathing. The effort needed to cycle is very gentle and is gradually increased until the test is complete. The whole test takes 20 to 30 minutes, and a doctor will carefully monitor your condition throughout the test. If you feel at any time that the test is too much or you wish to

stop we will do so. As we said earlier, we will ask you to repeat this test on three occasions, at two weekly intervals, following the completion of chemotherapy and before your date for surgery.

2) The Grip Test, Timed Get Up and Go and muscle mass assessment

The Grip Test is a small test that we would like you to do before you get on the bike. It involves you squeezing a handle (dynamometer) with your right hand three times. The highest reading will be recorded. We will also ask you to get up from a seated position, walk three metres, turn around, walk back to the chair, and sit down. This will be timed. Both of these tests are completely risk free and should not cause you any pain, but if for any reason you decided that you did not want to participate, you can still participate in the other sections of the study. As part of the same study we would like your permission to analyse your scans that you normally have as part of your treatment plan, so that we can analyse your muscle mass. This does not involve any more tests for you. This test will not impact your treatment in any shape or form.

3) Nutritional and fatigue questionnaires

Whilst you wait for your bike test we would like you to answer a couple of questionnaires about your diet and well being. These are very simple questions. It would take you less than five minutes to complete both. This test will not impact your treatment in any shape or form.

What do I have to do?

If you agree to take part, we will ask you to do three extra bike tests at two weekly intervals after you have finished your chemotherapy. We will also ask you to complete the grip test, the get up and go test as well as answer the two questionnaires before you get on the bike before and after the start of your chemotherapy and at the time of your last bike test.
You are free to withdraw at any stage and your future care will not be affected.

What is the procedure that is being tested?

We are assessing your level of fitness after you have finished your chemotherapy. This will give us some very important answers into the way patients' bodies respond to chemotherapy. We aim to determine the best time for surgery when patients' fitness has returned to normal.

What are the possible risks of taking part?

The risks are very small but if you need help at any time, one of the study doctors or research nurse will be available. The exercise bike test is not designed to be strenuous; most of our patients have no problems completing these tests. Fully trained staff are always available in the hospital in case you need urgent medical help. The fitness assessments are supervised by a nurse and doctor at all times. The questioners are simply designed and easy to understand. We are at hand to help you with any questions about them. The grip test and get up and go test are safe and do not expose you to any risks or pain.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research study will be strictly confidential and only shared between members of the research team. Your name and address will not be disclosed outside the hospital. Your own GP, and any other doctor who is currently treating you, will be informed that you are taking part in the study. Furthermore, if during one of your bike tests, we discover something about your health that we feel is important for your GP and the team who is looking after you to be aware of, we will inform them of this.

What will happen to the results of the research study?

When we have collected the results we will compare the results of your bike test; grip test; get up and go test and questionnaires before and after chemotherapy. Once we have completed the study we will write up the results of the study to let other doctors know about the effects of chemotherapy on fitness and when the best time for performing the surgery might be. We expect to publish the results in a medical journal. We will not publish any information or details, which could identify any of our patients. We will keep hold of your results for 12 months. Furthermore, long-term

data related to survival and complications, related to your condition will be recorded and kept safe by the team looking after you for five years. This is routine for all patients.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact information below). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital, or local PALS team.

Contact for Further Information

Please feel free to discuss the study with a member of the research team listed below,

Dr Maziar Navidi	Surgical Research Registrar
Dr Kate Sumpter	Consultant Oncologist
Dr Rhona Sinclair	Consultant Anaesthetist

All members of the research team can be contacted via Royal Victoria Infirmary Switch Board 0191 233 6161.

Thank you for taking the trouble to read this. If you agree to take part you will be given a copy of this information sheet and the consent form to keep.

7.5 **GP Information Letter**

Version number *1.0*, version date *16 March 2015*

IMPACT OF NEO-ADJUVANT CHEMOTHERAPY ON CARDIORESPIRATORY RESERVE IN OESOPHAGO-GASTRIC CARCINOMA

Dear Dr .....

Patient's Name:

Address:

Hospital/NHS No:

DOB:

Treatment plan: Neoadjuvant chemotherapy followed by surgery

I am writing to inform you that the above named patient who is registered under your care has recently been diagnosed with cancer of oesophagus or stomach. Following a discussion at MDT it was deemed that the best course of therapy for the above patient is that of neo-adjuvant chemotherapy followed by surgical resection. It has been the clinical team's decision that they are suitable to participate in the above study. This is a prospective observational study that is investigator initiated and led. This study has no active interventional component and does not alter the course of treatment for patients enrolled in this study. The study is carried out by Northern Oesophago Gastric Cancer Unit based at royal Victoria Infirmary in Newcastle upon Tyne. Your patient has consented to take part in this study.

The primary out come of this study is to investigate the effect of neoadjuvant chemotherapy on cardiorespiratory fitness in patients with oesophagogastric adenocarcinoma.

Secondary end points that will be investigated throughout the course of this study will include:

- Impact of neoadjuvant therapy on quality of life indices using The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) in combination with Oesophago-gastric Questionnaire (EORTC QLQ-OG25)

- Impact of neoadjuvant therapy on performance status
- Impact of neoadjuvant therapy on nutritional status using Mini Nutritional Assessment questionnaire (MNA)
- Impact of neoadjuvant therapy on sarcopenia
    - Muscle Mass – CT scans pre and post chemotherapy performed as part of routine clinical care
    - Muscle strength – Grip strength
    - Muscle Function – Timed Get up and Go test (TGUG)

Your patient has been provided with a Patient Information Sheet for the study (copy enclosed). This explains why they have been approached to take part in the study, the study schedule and that their participation is entirely voluntary. The information sheet also explains what participation in the study will involve, the risks and benefits of taking part, and emphasises that your patient is free to withdraw from the study at any time without the need for justification and without prejudicing their future medical care.

If you have any queries or require any further information about this research, please do not hesitate to contact your patient's research team using the contact details below.

Yours sincerely .....

On behalf of Prof S M Griffin, Dr R Sinclair, Dr K Sumpter and Dr M Navidi

Contact for Further Information

Please feel free to discuss the study with a member of the research team listed below,

Dr Maziar Navidi	Surgical Research Registrar
Dr Kate Sumpter	Consultant Oncologist
Dr Rhona Sinclair	Consultant Anaesthetist

All members of the research team can be contacted via Royal Victoria Infirmary Switch Board 0191 233 6161

7.6 Consent Form

Trial ID Number:

CONSENT FORM Version 1 March 2015

Title of Project:

IMPACT OF NEO-ADJUVANT CHEMOTHERAPY ON CARDIORESPIRATORY RESERVE IN OESOPHO-GASTRIC CARCINOMA

Name of Researcher(s)

Dr R Sinclair	Consultant Anaesthetist
Dr K Sumpter	Consultant Oncologist
Dr M Navidi	Surgical Research Fellow

Please initial box

1. I confirm that I have read and understand the information sheet dated August 2015 (Version 3) 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. ☐

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. ☐

   I agree to take part in the above study. ☐

4. I understand that my general practitioner (GP) will be informed of my participation in the study. ☐

----------	----------	----------
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

7.7 Appendix 2. Quality of Life questionnaires

7.7.1 Questionnaires QLQ-C30 and QLQ-OG25

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

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

	Scale name	Number of items	Item range	QLQ-OG25 item numbers
Functional scales				
Body image	OGBI	1	3	19
Symptom scales				
Dysphagia	OGDYS	3	3	1 – 3
Eating	OGEAT	4	3	4 – 7
Reflux	OGRFX	2	3	8,9
Odynophagia	OGODYN	2	3	10,11
Pain and discomfort	OGPD	2	3	12,13
Anxiety	OGANX	2	3	14,15
Eating with others	OGEO	1	3	16
Dry mouth	OGDM	1	3	17
Trouble with taste	OGTA	1	3	18
Trouble swallowing saliva	OGSV	1	3	20
Choked when swallowing	OGCH	1	3	21
Trouble with coughing	OGCO	1	3	22
Trouble talking	OGSP	1	3	23
Weight loss	OGWL	1	3	24
Hair loss	OGHL	1	3	25