**Cardiopulmonary Exercise Testing has Greater Prognostic Value than Sarcopenia in Oesophago-gastric Cancer patients undergoing Neoadjuvant Therapy and Surgical Resection**

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**Synopsis**

With advancements in prehabilitation, oncological and surgical interventions for oesophago-gastric cancer, it has become increasingly important to establish methods of risk-stratification based on post-operative outcomes. We describe a multicentre, observational study investigating the impact and relationship of neoadjuvant therapy on fitness and body composition. Our findings demonstrate that fitness, and not body composition parameters, has a significant effect on short-term post-operative survival.

**Abstract**

**Background**

Sarcopenia (low skeletal muscle mass), myosteatosis (low skeletal muscle radiation-attenuation) and fitness are independently associated with post-operative outcomes in oesophago-gastric cancer. This study aimed to investigate 1) the effect of neoadjuvant therapy (NAT) on body composition and fitness, 2) the relationship between sarcopenia, myosteatosis and cardiopulmonary exercise testing (CPET) and 3) their association with post-operative morbidity and survival.

**Methods**

Body composition was analysed using single slice Computed Tomography (CT) images from chest (superior to aortic arch) and abdominal CT scans (third lumbar vertebrae). Oxygen uptake at anaerobic threshold (O2 at AT) and at peak exercise (O2 Peak) were measured using CPET. Measurements were performed before and after NAT and an adjusted regression model assessed their association.

**Results**

Of the 184 patients recruited, 100 underwent surgical resection. Following NAT, skeletal muscle and fitness reduced significantly (p<0.001). When adjusted for age, sex and BMI, only pectoralis muscle mass was associated with O2 Peak (p=0.001). O2 at AT and Peak were associated with 1-year survival, while neither sarcopenia nor myosteatosis were associated with morbidity or survival.

**Conclusion**

Skeletal muscle and fitness reduced following NAT and were positively associated with each other. Cardiorespiratory function significantly contributes to short-term survival after oesophago-gastric cancer surgery.

**Keywords:**

Body composition, Physical Fitness, Sarcopenia, Myosteatosis, Oxygen Uptake, Neoadjuvant Therapy

**Introduction**

The standard of care for patients with locally advanced oesophago-gastric (OG) cancer is multimodal therapy incorporating neoadjuvant therapy (NAT; neoadjuvant chemotherapy/chemoradiotherapy) followed by surgical resection, which offers modestly improved overall survival (OS) compared to surgery alone [1,2]. This treatment pathway presents an increased risk of morbidity and mortality [3,4]. Despite improvements in surgical and oncological interventions, accurate methods of identifying patients at risk of poor post-operative outcomes are needed urgently. Identifying high-risk patients early in the pathway would inform shared decision making, direct peri-operative management and interventions, such as multimodal prehabilitation, in an attempt to improve outcomes.

Objectively measured fitness using cardiopulmonary exercise testing (CPET) is an objective measure of physical function and resilience (characterised by oxygen uptake (O2) at anaerobic threshold (AT) or O2 Peak). Despite a relative paucity of data in OG cancer surgery, preliminary data suggest selected CPET variables may be associated with survival and length of hospital stay [5]. NAT before OG cancer surgery results in a clinically important reduction in fitness (O2 at AT and O2 Peak) [6–9]. Although CPET is used widely in the UK, it is a relatively expensive, specialised test, adding additional hospital visits to an already complex cancer pathway.

Body composition (BC) analysis provides an objective structural measure that could be a useful risk-stratification alternative. Computed Tomography (CT) is the most widely recognised tool for measuring BC and a single-slice at the third lumbar vertebrae (L3) is a commonly used anatomical site in clinical research [10]. Other axial anatomical sites, such as a single-slice immediately superior to the aortic arch from chest CT scans, are being increasingly used in pulmonary pathologies [11,12]. This site has not been used in OG cancer patients despite NAT and surgery having a direct impact on the chest wall. Moreover, the majority of complications secondary to surgical resection are respiratory-related [13].

During NAT, a reduction in skeletal muscle mass is observed, leading to an increase in the rate of sarcopenia [14–18]. Sarcopenia in OG cancer has been associated with increased dose-limiting chemotherapy toxicity [14,19], increased circumferential resection margin positivity [18] and increased mortality [15,20]. Poor skeletal muscle quality due to triglyceride invasion (myosteatosis), is seen as low skeletal muscle radiation attenuation (SM-RA) and is also associated with poor outcomes in several cancer types [21–23]. ﻿We hypothesized that sarcopenia and myosteatosis result in diminished muscle function, phenotypically expressed as poor objectively measured fitness, resulting in worse post-operative outcomes.

The functional and structural changes following NAT reported to date have only been investigated independently, with their association and relationships to post-operative morbidity and mortality currently unexplored. In this study, our primary aim was to assess the impact of NAT on chest wall and abdominal skeletal muscle quantity and quality and its effect on physical fitness in an OG cancer cohort. Our secondary aim was to interrogate the association between CPET-derived measures of physical fitness (O2 at AT and O2 Peak) and skeletal muscle quantity and quality, before and after NAT. Exploratory analyses investigated the relationship of these metrics with post-operative in-hospital morbidity and overall survival at 1 and 2-years.

# Materials and Methods

## Subjects and Data collection

Between September 2011 to May 2017, patients with OG cancer were recruited from four UK hospitals into a prospective, observational cohort study. This was carried out as part of a study funded by the National Institute for Health Research (NIHR) for Patient Benefit Programme (PB-PG-0609-18262). The initial research protocol was registered with clinicaltrials.gov (NCT01325883) and published elsewhere [24]. This study was reviewed and approved by the South East Scotland Research Ethics Committee (16/SS/0188) and is registered with clinicaltrials.gov (NCT03641118). Inclusion criteria included adult patients with a WHO performance status 0-2 and with a histologically confirmed and potentially curable (able to undergo NAT followed by surgery), locally advanced (at least cT2 and/or cN1+) adenocarcinoma, squamous cell carcinoma, or mucinous/undifferentiated carcinoma of the oesophagus, oesophagogastric junction (tumours involving both the cardia and the oesophagus) or stomach. Eligible patients underwent routine CPET and CT scans before and after completing NAT. The trial excluded patients who had benign or non-resectable disease, a diagnosis of a gastro-intestinal stromal tumour, were unable to perform CPET, had poor quality CT scans or who declined NAT. CT scans were excluded based on the presence of artefacts which invalidated either skeletal muscle and/or adipose tissue values. All patients were followed-up prospectively (by staff blinded to CPET and BC results) for in-hospital morbidity and overall survival (OS) at 1 and 2-years. Morbidity was defined according to the Clavien-Dindo-Demartines complications score [25] with any-morbidity scoring 1-5 and major morbidity 3a-5. Resection margin positivity was defined as per the Royal College of Pathologists guidelines with circumferential resection margin being positive if tumour is present at or within 1mm of the margin.

Neoadjuvant Chemotherapy and Chemoradiotherapy

As this was a pragmatic observational study, no attempt was made to standardise NAT regimes. Chemotherapy regimens included: epirubicin, oxaliplatin, capecitabine (EOX); epirubicin, cisplatin, capecitabine (ECX) [26]; epirubicin, cisplatin, 5-fluorouracil (ECF) [1], chemotherapy as part of the STO3 trial – ECX or ECX + bevacizumab [27], chemotherapy as part of the OEO5 trial – ECX or cisplatin and 5-fluorouracil [28]; chemoradiotherapy as part of the CROSS trial – carboplatin, paclitaxel with concurrent radiotherapy [29]; chemoradiotherapy as part of the NEOSCOPE trial – oxaliplatin and capecitabine or carboplatin and paclitaxel with concurrent radiotherapy and induction oxaliplatin and capecitabine chemotherapy [30]; trastuzumab, cisplatin and capecitabine; capecitabine alone; and cisplatin alone. Radiotherapy in the CROSS study was administered at a total radiation dose of 41.4Gy given in 23 fractions of 1.8Gy each, with 5 fractions administered per week, starting on the first date of the first chemotherapy cycle. Radiotherapy in the NEOSCOPE study was administered at a total radiation dose of 45Gy given in 25 fractions of 1.8Gy each, with 5 fractions administered per week, starting on the first date of the first chemotherapy cycle.

## Cardiopulmonary Exercise Testing

CPET was conducted according to standardized methodology published by the Perioperative Exercise Testing and Training Society [31]. All patients were planned to undergo CPET immediately before and approximately 4 weeks following completion of NAT. All cancer multi-disciplinary team members including surgeons, anaesthetists, oncologists and peri-operative teams were blind to CPET data. CPET was independently reported by two independent experienced observers blinded to CPET timepoint and clinical outcomes, with a third adjudicator if >5% variance in O2 at AT was observed.

## Computer Tomography-derived Body Composition Analyses

The pre-NAT and post-NAT CT scans were performed as close as possible to the date of commencing NAT and surgery, respectively. CT image parameters included: contrast enhanced, 1.5 to 5mm slice thickness and tube voltage of 100-120 kVp. BC was performed by two assessors who were trained to isolate lumbar vertebrae, aortic arch anatomy and quantify tissues at these regions using s*liceOmatic*® [TomoVision, Magog, Canada) version 5.0 [32]. The pre-defined Hounsfield Unit (HU) threshold ranges used for distinguishing adiposity and muscle were: -29 to +150 HU for skeletal muscle, -150 to -50 HU for visceral adipose tissue and -190 to -30 HU for subcutaneous and intramuscular adipose tissue. The cross-sectional area of skeletal muscle was normalised for stature to produce skeletal muscle index (SMI). Radiation attenuation was reported as the mean HU across all muscle groups at L3 (SM-RA). Sarcopenia and myosteatosis were defined from BMI and sex-specific cut-offs, as described by Martin et al [33] (*Supplementary Table 1*).

For chest CT scans, a single slice was exported from the first image immediately superior to the aortic arch, as previously reported [11,12]. Measurements from this site included major and minor pectoralis muscle area (PMA) which were normalised to height to produce pectoralis muscle index (PMI) and pectoralis muscle radiation attenuation (PM-RA).

## Statistical Analysis

Intra- and inter-observer reliability was assessed using the intraclass correlation coefficient (ICC) [34], while significant differences were measured by paired samples t-test and Wilcoxon-signed rank test for nonparametric data. BC and CPET data were dichotomised between sexes. Wilcoxon-signed rank and McNemar tests were used to calculate significant changes between these parameters from pre- to post-NAT. Linear regression was performed to understand the relationship between SMI, SM-RA, PMI, PM-RA and O2 at AT/O2 Peak. Magnitude of effect of BC variables were assessed both individually and adjusted for age, gender and BMI. For correlations, the degree of association was calculated using Spearman’s rank correlation coefficient. Survival and morbidity analyses were conducted using logistic regression. Survival was recorded from the date of operation to the time of death or last recorded follow-up and was complete to a minimum of two years. A p-value < 0.05 was considered statistically significant and data analyses were performed with SPSS® v.24 (SPSS Inc, Chicago, IL) and R 3.5.3.

**Results**

Population

A study enrolment diagram is outlined in *Figure 1*. One-hundred and eighty-one patients underwent a pre-NAT CPET, 142 patients underwent NAT and 136 patients had paired pre-NAT CPET and BC data. The median time between both scans, for those with two suitable CTs was 113 days (IQR 72-154). Patient characteristics, surgical and post-operative outcome data are shown in *Table 1.* The majority of the eligible population were males (72%) with a median BMI of 26.9 kg.m-2 (IQR 22.0-31.8) and median age of 67 years (IQR 55-79). Most patients underwent chemotherapy alone (75%) with doublet or triplet chemotherapy regimens (the majority, 57 patients (42%) underwent epirubicin, cisplatin, capecitabine (ECX) and 25% of patients underwent combined chemoradiotherapy). NAT completion rates were high with 84% of patients completing all cycles of planned chemo and/or chemoradiotherapy.

 One hundred patients underwent curative resection, of which Ivor-Lewis oesophagectomy (76%) was the most common procedure and was mainly performed laparoscopically (53%). A gastrectomy was undertaken in twenty-four patients which again, was predominantly laparoscopic (79%).

## Intra- and inter-observer agreement

There was very high intra- and inter-observer agreement for the first 10 paired scans (ICC>0.941, ICC>0.806 respectively). There was no significant difference in landmark selection at L3 or superior to aortic arch (*Supplementary Figures 1.1-1.3*).

Changes in Computer Tomography-derived Body Composition

All skeletal muscle measurements from abdominal and chest CT slices significantly reduced after NAT in both males and females, with the exception of SM-RA in males (-1.3 HU, 95% CI -2.76 to + 0.13, p=0.059) (*Table 2)*. This was reflected by an increase in the total number of patients classified as sarcopenic after NAT (from 47 to 67 (+20; p<0.0001)), but not those classified as having myosteatosis (36 to 43 (+7; p=0.310)). Significant reductions in adiposity were observed and are displayed in *Supplementary Table 2.* Exploratory analysis investigated changes between neoadjuvant chemotherapy and chemoradiotherapy (*Supplementary table 3).* Both regimes showed significant decline in skeletal muscle mass (SMI, PMI), however, the reduction in SM-RA was only present in neoadjuvant chemotherapy (-4.0HU 95%CI -5.8 to -2.23, p<0.001). Nevertheless, this is unlikely to be of clinical significance given such a small mean reduction and no significant change in the number of patients with myosteatosis.

Changes in Physical Fitness

All 136 patients underwent a baseline CPET of whom one patient did not attain O2 at AT. Ninety-four patients underwent a post-NAT CPET, of which another patient did not reach O2 at AT. There were no adverse events during CPET. Sex-specific changes in CPET data following NAT are presented in *Table 3.* In the whole cohort, we observed significantly lower weight adjusted O2 at AT and O2 Peak after NAT (both p<0.001). In females separately, the decline in O2 at AT did not reach statistical significance (non-weight adjusted, p=0.241; and weight adjusted, p=0.989). When dichotomised between neoadjuvant chemotherapy and chemoradiotherapy, both therapies showed significant decline in all CPET variables (*Supplementary table 4*).

Relationship between CT-derived Body Composition and CPET variables

In univariate analysis, fitness (O2 at AT and O2 Peak) had a significant positive association with: male sex, SMI, SM-RA, PMI, PM-RA, while a negative association with increasing age and BMI (*Table 4)*. When adjusted for age, sex and BMI, only PMI showed a significant positive association withO2 Peak (B=0.36 (95%CI: 0.14 to 0.57) p=0.001, R2=0.11), but not O2 at AT. Post-NAT, only pectoralis musculature was significant in univariate analysis, with both PMI and PM-RA being positively associated withO2 at AT and O2 Peak (*Supplementary Table 5).* When adjusted for age, sex and BMI, post-NAT PMI remained significantly associated with O2 at AT (B=0.24; (95%CI: 0.06 to 0.43); p=0.012) and O2 Peak (B=0.58; (95%CI: 0.26 to 0.9); p=0.001). The absolute change in abdominal and chest wall musculature from pre- to post-NAT did not significantly correlate with the change in CPET variables.

Associations with Patient-level Outcomes

In the one hundred patients undergoing potentially curative surgery, 46% sustained a post-operative complication and 15% suffered from a major complication (Clavien-Dindo 3a-5). Pre-NAT CPET and BC variables were not significantly associated with post-operative complications or major postoperative complications either overall or for patients undergoing oesophagectomy alone (*Supplementary Table 6, 8*). OS for the whole cohort was 85% at 1-year and 68% at 2-year. We used logistic regression to assess the magnitude of effect of BC and fitness on OS. When adjusted for age, pathological stage, type of operation (gastrectomy/oesophagectomy) and resection margin status, O2 at AT and at Peak conferred a significant association for 1 year overall-survival (*Supplementary Table 7)*. However, this did not extend to 2 years or for OS (*Figure 2*). Similar results are seen when analysing patients undergoing oesophagectomy alone.

We also analysed the effect of post-NAT body composition and CPET variables (supplementary tables 10-11). In contrast to the pre-NAT data, we found that post-NAT pectoralis muscle index (PMI) was associated with morbidity (but not major morbidity). This difference persisted when adjusted for age, gender, BMI and type of surgery (OR 0.6, 95%CI 0.41-0.87, p=0.008). No other post-NAT CPET or body composition variables were associated with morbidity or mortality. BC parameters were not associated with survival at 1 year or 2 years. Resection margin status (R1), pathological T-stage and N-stage were associated with both 1-year and 2-year OS.

**Discussion**

We have reported novel concomitant, deleterious changes in physical fitness (O2 at AT and O2 Peak) and CT-derived BC (at L3 and superior to the aortic arch) following NAT. Pre-NAT physical fitness was positively associated with abdominal and chest wall skeletal muscle mass and quality. Only physical fitness variables were associated with 1-year survival which did not extend to 2-years.

Cancer of the oesophagus and stomach effects two main body cavities: thoracic and abdominal. Curative oesophagectomy and gastrectomy relies on operating in both compartments, with a direct insult to the soft tissue, muscle and viscera in these areas. The impact OG cancer has on BC has only been investigated using abdominal CT images [35,36]. Chest wall BC analyses has been limited to cohorts with respiratory and cardiovascular pathology, where low pectoralis muscle mass has been associated with raised systemic inflammatory markers, pulmonary complications, worse progression-free and OS [12,37–39]. Interestingly, we observed a stronger relationship between physical fitness and PMI than traditional SMI variables. *Teigen et al.* [39]considers assessing chest wall BC to have two distinct advantages. Firstly, this anatomical site could be a more indicative sign of fraility, since spinal muscles at L3 are involved in maintaining up-right posture until late illness. *Mendis et al.* [40]found that following prolonged periods of bed rest there were no signficant changes in the cross sectional area of psoas major or illiacus at the abdomen. Therefore, assessing these muscle groups for predictors of physiological resilience may not provide the most accurate generalisable results. Secondly, measurements of SM-RA made from the abdomen could be affected by the accumulation of oedema that does not significantly affect chest wall musculature. Low SM-RA reflects either the invasion of triglycerides (myosteatosis) or fluid (muscle oedema) into the muscle [21]. Accumulating fluid is a common feature in this region and could impact the quantification of myosteatosis [41,42]. Despite observing a statistically significant reduction in SM-RA and PM-RA, this is unlikely to be clinically significant as there was no significant increase in myosteatosis. In agreement with previous studies, our findings suggest that low pectoralis muscle mass could be an indicator of frailty and a surrogate marker for poor cardiorespiratory reserve.

We found a high proportion of our population present as sarcopenic at baseline (47%), which increased significantly with NAT (67%) [18,43]. Recently, multimodality (nutrition and exercise) prehabilitation interventions prior to OG cancer surgery have improved fitness and postoperative outcomes [44]. These mechanisms are however unclear, especially because BC in our cohort has not been found to be related to morbidity or mortality. However, this might be a symptom of our small sample size. This highlights the need for research into risk stratification measures (like BC and CPET) and their relationship with morbidity and mortality in OG cancer patients.

Consistent with other studies, the effects of chemotherapy significantly reduced objectively measured physical fitness [6–9,45]. The exact mechanism of this is unknown. Mitochondrial dysfunction and reduced muscle mass are attributed to toxicity from neoadjuvant platinum-based compounds. Platinum damage of mitochondrial DNA [46], cell cycle arrest [47], impaired Akt phosphorylation, sustained activation of degradative proteasome and autophagy systems [48], altered NF-kB signaling [49] and increased intramuscular protein levels of β-dystroglycan in OG patients link cancer cachexia, toxicity and poor survival [50]. Ultimately, these changes increase mitochondrial reactive species production, induce mitochondrial and cellular protein damage, leading to autologous mitochondrial destruction [46] – mytophagy and muscle wasting phenotypically expressed in the present study as a reduction in muscle quality, muscle mass, oxygen utilization and power output at AT and Peak exercise. Our group has previously reported significant reductions in physical fitness associated with dysfunction in mitochondrial oxidative phosphorylation in a rectal cancer cohort receiving neoadjuvant chemoradiotherapy [51], rescued with exercise prehabilitation [52].

Although in univariable analysis low SMI at L3 was inversely associated with O2 at AT and Peak, it had no relationship with worse OS. This is at odds with recently published meta-analyses that show that preoperative sarcopenia is an independent unfavorable prognostic factor for oesophageal and gastric cancer patients after oesophagectomy and gastrectomy [53,54]. The prognostic value of CPET in OG cancer patients is uncertain, with most studies only identifying a significant relationship with cardiopulmonary complications [5,9,55]. Our group has established that along with other key markers of pathological progression, such as staging and resection margin, cardiorespiratory resilience appears to play an important role in short-term survival. However, beyond 1-year, tumour stage and resection margin status seem to be the main determinant of OS. With regards to morbidity, neither BC nor CPET variables were associated with all-cause morbidity. This again is at odds with current literature as SMI at L3 was frequently found to be predictive of post-operative complications [53,54].

We acknowledge some limitations that were unfortunately difficult to control. From a relatively large cohort size of 181 patients undergoing pre-NAT CPET, many patients were excluded due to the lack of appropriate imaging for BC analysis and non-progression to NAT. Patients underwent NAT according to local clinical guidelines (non-standardised), as this heterogeneous cohort provided a pragmatic snapshot capture of the OG patient population reflecting tertiary UK OG cancer practices, this lends itself easily to external validation in other patient cohorts. Furthermore, nutritional status and concomitant disorders were not recorded during this study and would have been useful risk-factors for modelling morbidity status relative to body composition and physical fitness.

In conclusion, NAT has a significant detrimental impact on abdominal and chest wall BC and physical fitness prior to OG cancer surgery. Interestingly, skeletal muscle quantity and quality were not predictive of mortality, whereas physical fitness (function) predicted 1-year survival. Histopathology predicted both 1- and 2-year survival, suggesting tumour phenotype is more important than physical fitness in determining longer term outcomes. Understanding the underlying mechanisms resulting in these phenotypic changes in order to develop effective targeted interventions is urgently needed.

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**Conflict of Interest**

All authors declare no conflict of interest

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**Data Availability Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Figure Legends**

**Figure 1** Consort Flow Diagram of the inclusion pathway

For twenty-nine patients, their post-NAT CT scan was unavailable due to: death during NAT (n=3), disease progression (n=2), unsuitable CT scan quality (n=3) and scan inaccessibility (n=21), therefore a total of 107 patients had paired pre- and post-NAT body composition data.

Forty-two patients did not undergo a post-NAT CPET due to: disease progression (n=7), complications (sepsis, bowel perforation, stroke, acute dysphagia) (n=4), declining 2nd CPET (n=2), death following NAT (n=4) and surgical resection being brought forward before 2nd CPET (n=25).

NAT, Neoadjuvant therapy; CPET, Cardiopulmonary Exercise Test; BCA, Body Composition Analysis; GIST, Gastrointestinal Stromal Tumour; OG, Oesophago-gastric

**Figure 2** Overall Survival of patients undergoing surgery stratified by (A)O2 at AT dichotomised at median and (B)O2 at Peak dichotomised at median

Survival groups were dichotomised at the median of the whole CPET cohort: O2 at AT 11ml.kg-1.min-1, O2 at Peak. 19.75ml.kg-1.min-1. All 100 patients undergoing NAT and curative resection are included.O2 at AT, Oxygen uptake at anaerobic threshold; O2 at Peak, Oxygen uptake at peak exercise