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The relationship between computed tomography-derived sarcopenia, cardiopulmonary exercise testing performance, systemic inflammation, and survival in good performance status patients with oesophago-gastric cancer undergoing neoadjuvant treatment

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Abstract

Background Thought to capture the nutritional and functional reserve of the cancer patient, whether the computed tomography (CT)-derived sarcopenia score (CT-SS) has complimentary prognostic value to commonly utilized pre-treatment host assessments in patients with oesophago-gastric (OG) cancer is unknown. The aim of the present study was to examine if the CT-SS can stratify survival in OG cancer patients with good performance status [Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0/1]. Furthermore, if the CT-SS had complimentary prognostic value to cardiopulmonary exercise testing (CPET) performance and systemic inflammation.

Methods Consecutive patients with confirmed OG cancer and good performance status, who received neoadjuvant chemotherapy (NAC) with a view to surgical resection with curative intent, between 1 January 2010 and 31 December 2015, within NHS Greater Glasgow and Clyde (NHSGGC) and NHS Forth Valley (NHSFV), were identified from a prospectively maintained database. CT-SSs were grouped as 0/1/2. CPET variables recorded included VO_2 anaerobic threshold (AT) and peak. Systemic inflammatory response was determined by modified Glasgow prognostic score (mGPS) and neutrophil/lymphocyte ratio (NLR). Associations between categorical variables were examined using χ^2 test and binary logistics regression analysis.

Results A total of 232 patients met the inclusion criteria. 75% ($n = 174$) of patients were male, 54% ($n = 126$) were 65 years or older, and 60% ($n = 139$) were overweight [body mass index (BMI) ≥25 kg/m^2]; 33% ($n = 77$) of patients had CT-SS ≥ 1, 36% ($n = 83$) had a low VO_2 AT (≤11 ml/kg/min), and 57% ($n = 132$) had a low VO_2 peak (≤19 ml/kg/min). Of the 200 patients who had pre-NAC bloods facilitating calculation of the mGPS, 28% ($n = 55$) had mGPS ≥ 1. Of the 211 patients who had pre-NAC bloods facilitating calculation of NLR, 38% ($n = 80$) had an NLR ≥ 3; 82% ($n = 190$) and 53% ($n = 122$) were alive at 1 and 3 years post-NAC, respectively. On univariate analysis, CT-SS was significantly associated with sex ($P < 0.05$), histological cell type ($P < 0.05$), low VO_2 AT ($P < 0.05$), low VO_2 peak ($P < 0.05$), BMI ($P < 0.05$), mGPS ($P < 0.05$), and 3-year survival ($P < 0.05$). On multivariate analysis, tumour, node, and metastasis (TNM) stage ($P < 0.05$) and CT-SS ($P < 0.05$) remained significantly associated with 3-year survival. CT-SS was significantly associated with 3-year survival in patients who had mGPS 0 ($P < 0.05$), but not low VO_2 AT ($P = 0.066$) or peak ($P = 0.065$).

Conclusion The CT-SS would appear to capture the nutritional and functional reserve of the patient and is a useful objective measure for stratifying long-term survival in patients with good performance status undergoing potentially curative treatment for OG cancer.

Keywords Clinical outcomes; CPET; ECOG-PS; mGPS; Sarcopenia

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Introduction

Despite a fall in incidence rates, the 5-year survival of patients with oesophageal and gastric cancer in the United Kingdom remains poor.[1,2] Neoadjuvant chemotherapy (NAC), in combination with surgical resection, is the gold-standard radical treatment for oesophago-gastric (OG) cancer.[3] However, studies have demonstrated the adverse effects of chemotherapy on quality of life,[4] as well as the negative impact that post-operative complications have on long-term oncological outcomes.[5] Therefore, in the age of precision medicine, it is imperative that the right treatment will be given to the right patient, at the right time.

In elderly, cachectic, and co-morbid cancer patients, deciding on whether to embark on radical, but potentially curative treatment is difficult. Despite being subject to limitations, the physician-determined Eastern Cooperative Oncology Group Performance Status (ECOG-PS) remains a cornerstone.[6] Therefore, there is continued interest in identifying objective pre-treatment host assessments that can further stratify the prognostic value of ECOG-PS to clinical outcomes in patients with cancer. One such example is systemic inflammation, with the modified Glasgow prognostic score (mGPS) shown to stratify survival across performance status in patients with cancer.[6,7]

Computed tomography (CT)-derived muscle measurements—skeletal muscle index (SMI) and density (SMD)—have recently been combined to form the CT-derived sarcopenia score (CT-SS). Similar to ECOG-PS, this objective host assessment may be considered to capture the nutritional and functional reserve of the cancer patient.[8] However, although CT-derived muscle measurements have been shown to have prognostic value in OG cancer,[9,10] whether the CT-SS score can stratify survival in patients with OG cancer is not known, specifically, in patients with good performance status (ECOG-PS 0/1). Furthermore, it has yet to be examined whether the CT-derived sarcopenia has complimentary prognostic value to cardiopulmonary exercise testing (CPET) performance or systemic inflammation, shown to be prognostic factors in patients with OG cancer.[11–13] Therefore, the aims of this study were two-fold: firstly, to examine whether the CT-SS can stratify survival in patients with OG cancer and good performance status (ECOG-PS 0/1), who underwent NAC with a view to potentially curative resection, and, secondly, to examine whether CT-derived sarcopenia had complimentary prognostic value to CPET performance or systemic inflammation.

Methods

Patients

Consecutive patients with confirmed OG cancer, who received NAC with a view to surgical resection with curative intent, between 1 January 2010 and 31 December 2015, within NHS Greater Glasgow and Clyde (NHSGGC) and NHS Forth Valley (NHSFV), were identified from a prospectively maintained database. Patients with a documented pre-NAC ECOG-PS 0/1, recorded height and weight, and CT imaging for body composition analysis and who underwent pre-NAC CPET were assessed for inclusion. Exclusion criteria were as follows: patients who did not have satisfactory pre-operative CT imaging for body composition analysis, did not have recorded height and weight prior to NAC, did not undergo pre-NAC CPET, did not have a recorded ECOG-PS or had ECOG-PS $>$ 1, received radical chemoradiation without plans for surgery, were initially diagnosed with metastatic disease, and received palliative treatment only.

Neoadjuvant chemotherapy regimens included a combination of epirubicin, cisplatin, and either fluorouracil or capecitabine. Selected patients had a combination of cisplatin and fluorouracil alone. A median period of 8 weeks was left between the end of treatment and commencing surgery, during which re-staging occurred. Patients who proceeded to surgery were operated on at Glasgow Royal Infirmary, a single tertiary referral teaching hospital. Patients with oesophageal cancer underwent transhiatal, Ivor Lewis, left thoraco-abdominal, or three-stage oesophagectomy depending on tumour site and surgeon preference. Patients with gastric cancer received either sub-total or total gastrectomy. Prophylactic antibiotics were administered at the induction of anaesthesia. As per unit policy, subcutaneous low-molecular-weight heparin and pneumatic compression stockings were given to patients as venous thromboprophylaxis.

The primary endpoints were progression to surgery and overall survival at 1 and 3 years post-NAC. The cause and date

of death were confirmed with the Registrar General (Scotland). Death records were complete until 1 March 2019 that served as the censor date. Informed consent was obtained from patients prior to surgery. This study was approved with the need for individual patient consent waived by the Oxford B Research Ethics Committee due to the nature of the study (19/SC/0653).

Methods

Routine demographic details included age, sex, and body mass index (BMI). Age categories were grouped into <64, 65–74, and >74 years. BMI was categorized as <20, 20–24.9, 25–29.9, and ≥30 kg/m^2. Tumour site and histological subtype were identified from pre-operative endoscopy and pathology reports. Tumour site was categorized as oesophageal, junctional, and gastric. Histological subtype was categorized as adenocarcinoma and squamous cell carcinoma. All tumours were retrospectively staged using the eighth edition of the tumour, node, and metastasis (TNM) classification and categorized into clinical American Joint Committee on Cancer (AJCC) stage groupings.[14]

Pre-treatment assessment of physical fitness was determined using the ECOG-PS, a 6-point score, determined by healthcare professionals, used to assess pre-treatment fitness.[15] This was assessed by a clinician prior to commencement of NAC. The systemic inflammatory status was retrospectively assessed by calculating the neutrophil/lymphocyte ratio (NLR) and mGPS for each patient, using pre-NAC blood results, as previously described.[16,17] mGPS was categorized as 0/1/2. NLR was categorized as <3/3–5/>5. An autoanalyser was used to measure serum CRP (mg/L) and albumin (g/L) concentrations (ARCHITECT; Abbott Diagnostics, Maidenhead, UK).

Computed tomography imaging for body composition analysis

Region of interest (ROI) measurements were made of subcutaneous fat (SFA), visceral fat (VFA), and skeletal muscle area (SMA) (cm^2) using standard Hounsfield unit (HU) ranges (adipose tissue −190 to −30 and skeletal muscle −29 to +150), as previously described.[18] These were then normalized for height^2 to create indices, subcutaneous fat index (SFI, cm^2/m^2), and SMI (cm^2/m^2). Skeletal muscle radiodensity (SMD, HU) was measured from the same ROI used to calculate SMI, as its mean HU.

A high SFI was defined as ≥50.0 cm^2/m^2 in males and ≥42.0 cm^2/m^2 in females.[19] Visceral obesity was defined as VFA > 160 cm^2 for male patients and >80 cm^2 for female patients.[20] A low SMI was defined as an SMI < 43 cm^2/m^2 if BMI < 25 kg/m^2 and SMI < 53 cm^2/m^2 if BMI > 25 kg/m^2 in male patients and SMI < 41 cm^2/m^2 in female patients.[21] A low SMD was defined as an SMD < 41 HU in patients with BMI < 25 kg/m^2 and <33 HU in patients with BMI > 25 kg/m^2.[21] CT-derived sarcopenia was quantified in the form of a score by combining the assessment of SMI and SMD as follows: a normal/high SMI and normal/high SMD = 0, low SMI and normal/high SMD = 1, and low SMI and low SMD = 2.

Cardiopulmonary exercise testing

CPET was performed in a single respiratory function laboratory using a ZAN 600 (nSpire Health, Hertford, UK) and Ergoselect bicycle ergometer (Ergoline, Bitz, Germany), with a doctor and resuscitation equipment, as previously described.[22] Several variables were recorded including electrocardiography, blood pressure, oxygen uptake, and carbon dioxide output from analysis of inspiratory and expiratory gases. Patients were exposed to an incremental physical exercise protocol to their maximally tolerated level, which was determined by exhaustion, symptomatic breathlessness, or pain. The measured variables along with the exercise protocol allowed VO_2 at AT and peak exercise to be quantified. For analysis, thresholds for an AT were defined as ≤11 and >11 ml/kg/min, and peak ≤19 and >19 ml/kg/min, as used in previous studies.[23]

Statistical analysis

Survival curves were constructed using the Kaplan–Meier technique, and log-rank test was used to compare survival between groups of patients. Demographic data, clinicopathological variables, CT-derived sarcopenia, VO_2 AT and peak, CT-derived adipose measurements, mGPS, NLR, progression to surgery, and 1- and 3-year survival were presented as categorical variables. Categorical variables were analysed using χ^2 test for linear-by-linear association. Relationships between demographic data, clinicopathological variables, CT-derived sarcopenia, VO_2 AT and peak, mGPS, NLR, and 3-year survival were examined using univariate and multivariate binary logistic regression, to calculate odds ratios and 95% confidence intervals. Clinicopathological factors that had a P value <0.1 were taken into a multivariate model using a backward conditional model to identify independently significant factors. The relationships between CT-SS and VO_2 AT, VO_2 peak, mGPS, and 3-year survival in patients with OG cancer and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially curative surgical resection were also analysed using the χ^2 test for linear-by-linear association.

Missing data were excluded from analysis on a variable-by-variable basis. Two-tailed P values <0.05 were considered

statistically significant. Statistical analysis was performed using SPSS software Version 27.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient inclusion

Of the 335 patients with OG cancer, who had ECOG-PS 0/1 and underwent NAC with a view to potentially curative resection, during the study time frame, 103 did not meet the inclusion criteria. Of the 223 patients, who had ECOG-PS 0/1 and underwent pre-NAC CPET and had CT imaging for body composition analysis, 9% (*n* = 23) did not proceed to surgery (15 patients had disease progression while undergoing NAC, and five patients had significantly impaired performance status post-NAC; see *Figure 1*).

The clinicopathological characteristics of the included patients are shown in *Table 1*; 75% (*n* = 174) were male, 54% (*n* = 126) were 65 years or older, and 60% (*n* = 139) were overweight (BMI $\geq$ 25 kg/m^2); 33% (*n* = 77) of patients had oesophageal tumours, 58% (*n* = 135) had junctional tumours, and 9% (*n* = 20) had gastric tumours; 93% (*n* = 215) of patients had an adenocarcinoma and 7% (*n* = 17) had squamous cell carcinoma; and 9% (*n* = 21) had Stage I disease, 26% (*n* = 61) Stage II, 60% (*n* = 137) Stage III, and 5% (*n* = 11) Stage IV.

Sixty-seven per cent (*n* = 155) of patients had CT-SS of 0, 9% (*n* = 21) CT-SS 1, and 24% (*n* = 56) CT-SS 2; 67% (*n* = 156) of patients had a high SFI and 66% (*n* = 152) a high VFA. The median VO_2 AT value on CPET was 11.6 ml/kg/min (10.0–13.1), with 36% (*n* = 83) of patients having a VO_2 AT $\leq$ 11 ml/kg/min. The median VO_2 peak value on CPET was 19.2 ml/kg/min (16.9–22.4), with 57% (*n* = 132) of patients having a VO_2 peak $\leq$19 ml/kg/min. Of the 200 patients who had pre-NAC bloods facilitating calculation of the mGPS, 28% (*n* = 55) had mGPS $\geq$ 1. Of the 211 patients who had pre-NAC bloods facilitating calculation of NLR, 38% (*n* = 80) had an NLR $\geq$ 3; 82% (*n* = 190) and 53% (*n* = 122) were alive at 1 and 3 years post-NAC, respectively.

The relationship between the clinicopathological variables, CT-SS, CT-derived obesity measurements, systemic inflammation, and survival in patients with OG cancer and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially curative resection is shown in *Table 1*. On univariate analysis, CT-SS was significantly associated with sex ($P < 0.05$), histological cell type ($P < 0.05$), low VO_2 AT ($P < 0.05$), low VO_2 peak ($P < 0.05$), BMI ($P < 0.05$), mGPS ($P < 0.05$), and 3-year survival ($P < 0.05$). On univariate analysis, CT-SS was not associated with age ($P = 0.261$), tumour site ($P = 0.417$), clinical TNM stage ($P = 0.932$), high SFI ($P = 0.084$), high VFA ($P = 0.504$), NLR ($P = 0.134$), progression to surgery ($P = 0.333$), and 1-year survival ($P = 0.075$).

The Kaplan–Meier curve in *Figure 2* shows the relationship between the CT-SS and 3-year survival in patients with OG

Figure 1 Patients included in study. *Fifteen patients had disease progression while undergoing neoadjuvant chemotherapy (NAC), and five patients had significantly impaired performance status post-NAC. CPET, cardiopulmonary exercise testing; CT, computed tomography; CT-BC, computed tomography imaging for body composition analysis; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; OG, oesophago-gastric

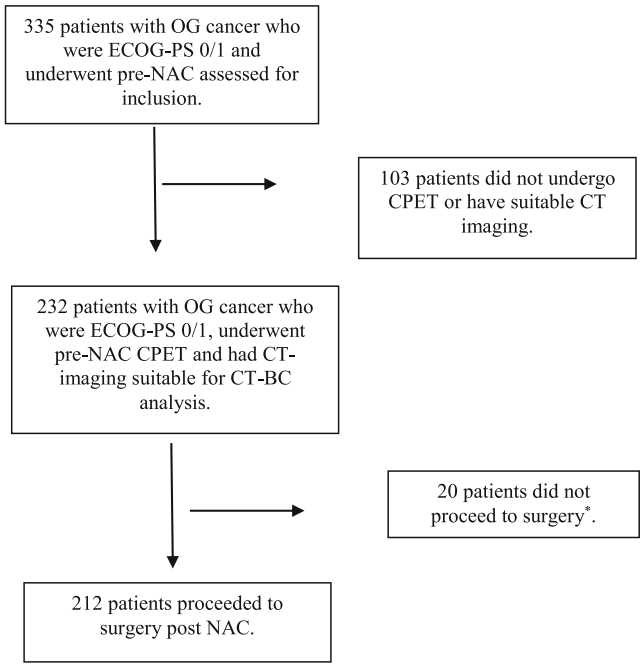

Table 1 The relationship between clinicopathological characteristic, CT-SS, CPET performance, systemic inflammation, and clinical outcomes in patients with OG cancer and good performance status (ECOG-PS 0/1) undergoing NAC with a view to curative resection, stratified by CT-SS (n = 232)

	CT-SS 0 (n = 155)	CT-SS 1 (n = 21)	CT-SS 2 (n = 56)	P value[a]
Age				0.261
<65	70 (45%)	16 (76%)	20 (36%)	
65–74	60 (39%)	4 (19%)	22 (39%)	
>74	25 (16%)	1 (5%)	14 (25%)	
Sex				0.024
Female	32 (21%)	6 (29%)	20 (36%)	
Male	123 (79%)	15 (71%)	36 (64%)	
Tumour site				0.417
Oesophageal	47 (30%)	10 (48%)	20 (36%)	
Junctional	94 (61%)	10 (48%)	31 (55%)	
Gastric	14 (9%)	1 (4%)	5 (9%)	
Histological subtype				0.015
Adenocarcinoma	149 (96%)	17 (81%)	49 (87%)	
Squamous cell carcinoma	6 (4%)	4 (19%)	7 (13%)	
Clinical TNM stage				0.932
I	15 (10%)	2 (9%)	4 (7%)	
II	39 (25%)	6 (29%)	16 (29%)	
III	90 (59%)	13 (62%)	34 (61%)	
IV	9 (6%)	0 (0%)	2 (3%)	
Low VO_2 AT (≤11 ml/kg/min)				0.001
No	104 (67%)	14 (67%)	23 (41%)	
Yes	51 (33%)	7 (33%)	33 (59%)	
Low VO_2 peak (≤19 ml/kg/min)				0.002
No	85 (55%)	10 (48%)	17 (30%)	
Yes	70 (45%)	11 (52%)	39 (70%)	
BMI				0.034
<20	4 (3%)	5 (24%)	6 (11%)	
20–24.9	56 (36%)	3 (14%)	19 (34%)	
25–29.9	56 (36%)	12 (57%)	23 (41%)	
≥30	39 (25%)	1 (5%)	8 (14%)	
High SFI				0.084
No	55 (36%)	9 (43%)	12 (21%)	
Yes	100 (64%)	12 (57%)	44 (79%)	
High VFA				0.504
No	49 (32%)	12 (57%)	19 (34%)	
Yes	106 (68%)	9 (43%)	37 (66%)	
mGPS[b]				0.008
0	103 (76%)	14 (74%)	28 (61%)	
1	23 (17%)	1 (5%)	8 (17%)	
2	9 (7%)	4 (21%)	10 (22%)	
NLR[c]				0.134
<3	94 (66%)	11 (61%)	26 (52%)	
3–5	32 (22%)	5 (28%)	16 (32%)	
>5	17 (12%)	2 (11%)	8 (16%)	
Proceeded to surgery				0.333
Yes	144 (93%)	18 (86%)	50 (89%)	
No	11 (7%)	3 (14%)	6 (11%)	
1-year survival				0.075
Yes	130 (84%)	20 (95%)	40 (71%)	
No	25 (16%)	1 (5%)	16 (29%)	
3-year survival				0.009
Yes	89 (57%)	13 (62%)	20 (36%)	
No	66 (43%)	8 (38%)	36 (64%)	

Abbreviations: AT, anaerobic threshold; BMI, body mass index; CPET, cardiopulmonary exercise testing; CT-SS, computed tomography-derived sarcopenia score; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; mGPS, modified Glasgow prognostic score; NAC, neoadjuvant chemotherapy; NLR, neutrophil/lymphocyte ratio; OG, oesophago-gastric; SFI, subcutaneous fat index; TNM, tumour, node, and metastasis; VFA, visceral fat.

[a]P value is from χ^2 analysis.

[b]Thirty-two patients did not have pre-NAC bloods for calculation of mGPS.

[c]Twenty-one patients did not have pre-NAC bloods for calculation of NLR.

cancer and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially curative surgical resection (log-rank P = 0.036).

The relationship between demographic data, clinicopathological variables, CT-derived sarcopenia, VO_2 AT, VO_2 peak, mGPS, NLR, and 3-year survival in patients with OG cancer

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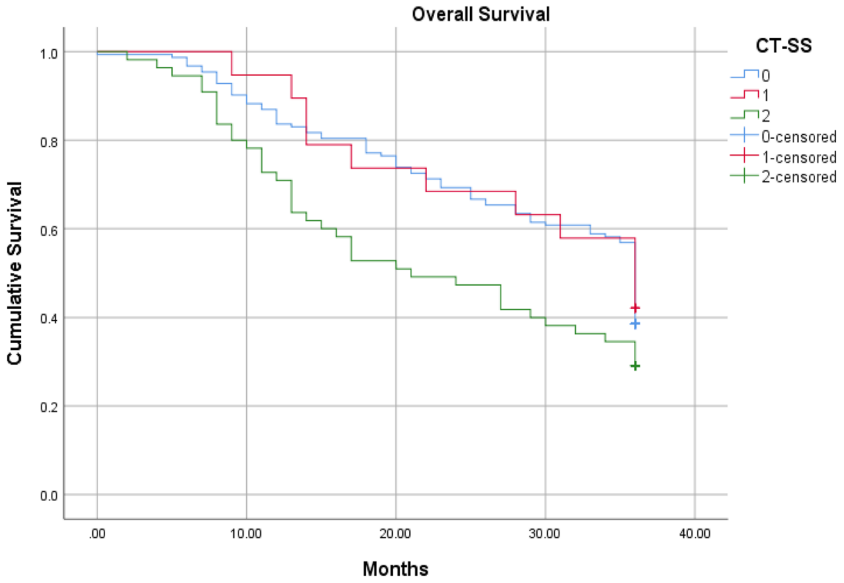
Figure 2 Kaplan–Meier curve of the relationship between computed tomography-derived sarcopenia score (CT-SS) and overall survival in patients with oesophago-gastric (OG) cancer and good performance status [Eastern Cooperative Oncology Group Performance Status (ECOG-PS 0/1)] who underwent neoadjuvant chemotherapy (NAC) with a view to potentially curative resection (n = 232)



(log rank $P = 0.036$)

Table 2 The relationship between clinicopathological characteristic, CT-SS, CPET performance, systemic inflammation, and 3-year survival in patients with OG cancer and good performance status (ECOG-PS 0/1) undergoing NAC with a view to curative resection (n = 232)

	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Age (<65/65–74/>74)	1.18 (0.83–1.68)	0.348	—	—
Sex (male/female)	1.38 (0.76–2.53)	0.289	—	—
Tumour site (oesophageal/junctional/gastric)	0.91 (0.59–1.40)	0.664	—	—
Histological subtype (adenocarcinoma/SCC)	0.76 (0.28–2.07)	0.594	—	—
Clinical TNM stage (I/II/III/IV)	1.46 (1.01–2.12)	0.046	1.73 (1.14–2.64)	0.011
BMI (<20/20–24.9/25–29.9/≥30)	0.78 (0.57–1.06)	0.107	—	—
CT-SS (0/1/2)	1.50 (1.10–2.05)	0.010	1.42 (1.01–2.00)	0.047
Low VO_2 AT (yes/no)	1.32 (0.78–2.24)	0.300	—	—
Low VO_2 peak (yes/no)	1.43 (0.85–2.39)	0.180	—	—
mGPS (0/1/2)	1.12 (0.75–1.68)	0.590	—	—
NLR (<3/3–5/>5)	1.50 (1.00–2.26)	0.052	—	0.128

Abbreviations: AT, anaerobic threshold; BMI, body mass index; CI, confidence interval; CPET, cardiopulmonary exercise testing; CT-SS, computed tomography-derived sarcopenia score; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; mGPS, modified Glasgow prognostic score; NAC, neoadjuvant chemotherapy; NLR, neutrophil/lymphocyte ratio; OG, oesophago-gastric; OR, odds ratio; SCC, squamous cell carcinoma; TNM, tumour, node, and metastasis.

and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially curative resection is shown in *Table 2*. On univariate analysis, clinical TNM stage ($P < 0.05$) and CT-SS ($P < 0.05$) were significantly associated with 3-year survival. Age (P = 0.348), sex (P = 0.289), tumour site (P = 0.664), histological subtype (P = 0.594), BMI (P = 0.107), low VO_2 AT (P = 0.300), low VO_2 peak (P = 0.180), mGPS (P = 0.590), or NLR (P = 0.052) were significantly associated with 3-year survival. On multivariate analysis, clinical TNM stage ($P < 0.05$) and CT-SS remained significantly associated with ($P < 0.05$) with 3-year survival.

The relationship between CT-SS, VO_2 AT, and 3-year survival in patients with OG cancer and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially curative surgical resection is shown in *Table 3*. On univariate analysis, CT-SS was not significantly associated with 3-year survival in patients who did not have a low VO_2 AT (P = 0.066). A low VO_2 AT was not significantly associated with 3-year survival in patients who had CT-SS 0 (P = 0.922).

The relationship between CT-SS, VO_2 peak, and 3-year survival in patients with OG cancer and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially

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Table 3 The relationship between CT-SS, VO_2 AT, and 3-year survival in patients with OG cancer and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially curative surgical resection (n = 232)

	VO_2 AT > 11 ml/kg/min (n = 91)	VO_2 AT ≤ 11 ml/kg/min (n = 141)	P value[a]
CT-SS 0 (n = 155)	60 (66%)	29 (21%)	0.922
CT-SS 1 (n = 21)	10 (11%)	3	0.204
CT-SS 2 (n = 56)	8 (9%)	12 (9%)	0.903
P value[a]	0.066	0.108	

Note: Each cell, n (%). Abbreviations: AT, anaerobic threshold; CT-SS, computed tomography-derived sarcopenia score; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; NAC, neoadjuvant chemotherapy; OG, oesophago-gastric.
[a]P value is from χ^2 analysis.

Table 4 The relationship between CT-SS, VO_2 peak, and 3-year survival in patients with OG cancer and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially curative surgical resection (n = 232)

	VO_2 peak > 19 ml/kg/min (n = 91)	VO_2 AT ≤ 19 ml/kg/min (n = 141)	P value[a]
CT-SS 0 (n = 155)	52 (57%)	37 (26%)	0.297
CT-SS 1 (n = 21)	6	7 (5%)	0.864
CT-SS 2 (n = 56)	14 (15%)	6	0.965
P value[a]	0.065	0.112	

Note: Each cell, n (%). Abbreviations: AT, anaerobic threshold; CT-SS, computed tomography-derived sarcopenia score; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; NAC, neoadjuvant chemotherapy; OG, oesophago-gastric.
[a]P value is from χ^2 analysis.

curative surgical resection is shown in *Table 4*. On univariate analysis, CT-SS was not significantly associated with 3-year survival in patients who did not have a low VO_2 peak (P = 0.065). A low VO_2 peak was not significantly associated with 3-year survival in patients who had CT-SS 0 (P = 0.297).

The relationship between CT-SS, mGPS, and 3-year survival in patients with OG cancer and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially curative surgical resection is shown in *Table 5*. On univariate analysis, CT-SS was significantly associated with 3-year survival in patients who had mGPS 0 ($P < 0.05$). mGPS was not significantly associated with 3-year survival in patients who had CT-SS 0 (P = 0.732).

Table 5 The relationship between CT-SS, mGPS, and 3-year survival in patients with OG cancer and good performance status (ECOG-PS 0/1) who underwent NAC with a view to potentially curative surgical resection (n = 200)

	mGPS 0 (n = 145)	mGPS 1 (n = 32)	mGPS 2 (n = 23)	P value[a]
CT-SS 0 (n = 135)	57 (39%)	11 (34%)	5	0.732
CT-SS 1 (n = 19)	9 (6%)	0	2	0.504
CT-SS 2 (n = 46)	8 (6%)	3	4	0.478
P value[a]	0.026	0.560	0.506	

Note: Each cell, n (%). Abbreviations: CT-SS, computed tomography-derived sarcopenia score; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; mGPS, modified Glasgow prognostic score; NAC, neoadjuvant chemotherapy; OG, oesophago-gastric.
[a]P value is from χ^2 analysis.

Discussion

The results of the present study show that the combination of pre-treatment CT-derived muscle measurements in the form of CT-SS was associated with CPET performance, systemic inflammation, and survival in patients with good performance status (ECOG-PS 0/1) undergoing potentially curative treatment for OG cancer. Although the CT-SS did not add to the prognostic value of CPET performance or systemic inflammation, it was found to be an important determinant of survival. The CT-SS would appear to not only capture the nutritional and functional reserve of patients' undergoing potentially curative treatment for OG cancer but also provide a useful, objective measure for stratifying long-term survival.

In the present study, a combination of CT-derived muscle measurements (CT-SS) was significantly associated with both a low VO_2 AT and peak. These observations are consistent with recent work of West et al., who reported that CT-derived muscle measurements were associated with CPET performance in patients with OG[24] and hepatopancreatobiliary cancer.[25] Therefore, the CT-SS provides an objective measure that reflects, in part, cardiopulmonary fitness and therefore a useful measure in those patients where CPET is contraindicated.[26] Furthermore, confirms the importance of sarcopenia assessment in these patients. Further research is therefore merited into the utility of the CT-SS as an objective assessment of pre-treatment fitness in patients with malignant and non-malignant disease.

The results of the present study are consistent with previous observations that measures of muscle mass and density are correlated with the systemic inflammatory response, in particular the mGPS.[27] More recently, Hacker et al. reported that CT-derived muscle measurements were correlated with the mGPS in a cohort of 509 patients with advanced gastric and oesophago-gastric junctional cancers.[13] Therefore, it was of interest that they observed that the prognostic value of CT-derived muscle measures was not retained when adjusted for systemic inflammation.[13] Therefore, although it is clear that there is an close relationship between skeletal muscle measures and the systemic inflammatory response, and their effect on clinical outcome, it remains to be determined which is the optimal therapeutic target in these patients.[28]

There are several limitations to the present study. Firstly, this is a single-centre, retrospective cohort study with a relatively small sample size and has limitations seen with this study design. However, a low VO_2 at AT and peak were prevalent in the present cohort, even though the patients were of good performance status and so mitigated the relatively small sample size. The present study also highlights the need for population-specific thresholds for CPET, specifically in malnourished, inflamed, and de-conditioned patients with cancer.[29] Lastly, although the CT-SS has been shown to be prognostic in the present study and across other cancer subtypes,[8] the use of CT-derived body composition is currently limited to research purposes. This is in part due to the training requirements and time-consuming nature of scan analysis. The emergence of fully automated, artificial intelligence-based segmentation and quantification tools may readily facilitate the use of measures such as the CT-SS in routine clinical practice.[30]

In conclusion, the CT-SS would appear to capture the nutritional and functional reserve of patients undergoing potentially curative treatment for OG cancer. Furthermore, the CT-SS stratified survival in patients who were not inflamed and had good performance status.

Author contributions

JM, JD, and DCM wrote the manuscript and analysed the data. MJF, GM, ABC, DM, BJL, PGH, STM, and RDD were involved in the conceptualization and reviewing of the manuscript. STM and RDD had the primary responsibility for the final content.

Ethics approval and consent to participate

This study was approved with the need for individual patient consent waived by the Oxford B Research Ethics Committee due to the nature of the study (19/SC/0653). The study was conducted in accordance with the Declaration of Helsinki and conformed to the STROBE guidelines for cohort studies. All authors have read and approved the final manuscript.

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Conflicts of interest

None declared.

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