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Original Research Article

ORIGINAL RESEARCH ARTICLE

Cardiopulmonary exercise variables and their association with postoperative morbidity and mortality after major oesophagogastric cancer surgery—a multicentre observational study

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Abstract

Background: Outcomes after oesophagogastric cancer surgery remain poor. Cardiopulmonary exercise testing (CPET) used for risk stratification before oesophagogastric cancer surgery is based on conflicting evidence. This study explores the relationship between CPET and postoperative outcomes, specifically for patients undergoing neoadjuvant treatment.
Methods: Patients undergoing oesophagogastric cancer resection and CPET (pre- or post-neoadjuvant treatment, or both) were retrospectively enrolled into a multicentre pooled cohort study. Oxygen uptake at peak exercise (VO_2 peak) was compared with 1-yr postoperative survival. Secondary analyses explored relationships between patient characteristics, tumour pathology characteristics, CPET variables (absolute, relative to weight, ideal body weight, and body surface area),

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and postoperative outcomes (morbidity, 1-yr and 3-yr survival) were assessed using logistic regression analyses.
Results: Seven UK centres recruited 611 patients completing a 3-yr postoperative follow-up period. Oesophagectomy was undertaken in 475 patients (78%). Major complications occurred in 25%, with 18% 1-yr and 43% 3-yr mortality. No association between VO_2 peak or other selected CPET variables and 1-yr survival was observed in the overall cohort. In the overall cohort, the anaerobic threshold relative to ideal body weight was associated with 3-yr survival (P=0.013). Tumour characteristics (ypT/ypN/tumour regression/lymphovascular invasion/resection margin; P<0.001) and Clavien–Dindo ≥3a (P<0.001) were associated with 1-yr and 3-yr survival. On subgroup analyses, pre-neoadjuvant treatment CPET; anaerobic threshold (absolute; P=0.024, relative to ideal body weight; P=0.001, body surface area; P=0.009) and V_E/VCO_2 at anaerobic threshold (P=0.026) were associated with 3-yr survival. No other CPET variables (pre- or post-neoadjuvant treatment) were associated with survival.
Conclusions: VO_2 peak was not associated with 1-yr survival after oesophagogastric cancer resection. Tumour characteristics and major complications were associated with survival; however, only some selected pre-neoadjuvant treatment CPET variables were associated with 3-yr survival. CPET in this cohort of patients demonstrates limited outcome predictive precision.
Clinical trial registration: NCT03637647.

Keywords: cardiopulmonary exercise testing; fitness; mortality; morbidity; neoadjuvant cancer treatments; oesophagogastric cancer; tumour outcomes

Oesophagogastric cancer is increasingly prevalent.[1] Surgery, often combined with neoadjuvant chemotherapy or chemoradiotherapy, gives the best chance of cure but is associated with a high degree of morbidity. Mortality after oesophagectomy has decreased but complications remain high,[2] often leading to a protracted recovery.[3] Furthermore, life-prolonging neoadjuvant cancer treatments are completed in fewer than 50% of patients, with adjuvant cancer treatments given to fewer than 10%.[4,5]

Accurate identification of patients at risk of poor postoperative outcomes is urgently needed. Various risk scores have been implemented, but few have predicted outcomes in oesophagogastric cancer.[6] The evidence for cardiopulmonary exercise testing (CPET) as a risk prediction tool before major intra-abdominal surgery has rapidly expanded.[7,8] CPET allows detailed preoperative risk assessment with interrogation of the physiological causes of exercise intolerance, with the opportunity for optimising fitness with prehabilitation interventions.[9] Accurate risk prediction before neoadjuvant treatment and surgery might also allow for better patient selection, enhance shared decision-making, and improve neoadjuvant treatment completion rates and consequently improve outcomes.[10] Specific CPET-derived variables including maximal oxygen consumption at peak exercise (VO_2 peak), the anaerobic threshold (AT), the ventilatory equivalent for carbon dioxide at the anaerobic threshold (V_E/VCO_2 at AT) have demonstrated good discrimination for both short- and long-term outcomes in oesophagogastric surgery patients.[7,11]

In oesophagogastric surgery, the evidence for CPET is based on relatively small single-centre observational studies (n=78–273).[12–19] These studies have yielded inconsistent associations between CPET (VO_2 at peak,[12] AT,[13,19] both VO_2 at peak and AT,[15] and V_E/VCO_2[14]) and surgical outcomes. A meta-analysis[20] demonstrated associations between VO_2 at peak, cardiopulmonary complications and 1-yr survival, however the effect size was small and its risk discrimination poor. CPET variables were not associated with non-cardiopulmonary complications. Recently, a retrospective pooled analyses from six centres[21] showed that the discriminatory ability of CPET for determining risk of morbidity and mortality after oesophagogastric cancer surgery was poor. Given the early data reporting that preoperative CPET predicts postoperative outcomes,[12–19] these findings are surprising, however the single-centre nature of these studies, combined with relatively small cohort sizes may contribute. The reasons for the limited predictive utility of CPET and outcomes published recently in oesophagogastric surgery patients in comparison to other surgical settings remains unclear. Moreover, the effect of neoadjuvant treatment on fitness and outcomes has not been thoroughly evaluated. Neoadjuvant treatment is now common practice, being given to 72% of patients before oesophagogastric surgery.[22] Neoadjuvant treatment results in a clinically meaningful reduction in fitness, with some studies showing significant associations with baseline fitness, complications, and 1-yr survival.[17,23–26]

The retrospective pooling of patient-level data[21] needs further confirmation by physiological and long-term outcome data, derived from a purposefully conducted multicentre pooled cohort study. We aimed to retrospectively evaluate the utility of selected CPET variables to predict survival and in-hospital morbidity, with specific analysis of patients undergoing neoadjuvant treatment in a pragmatic oesophagogastric cancer patient cohort.

Methods

Consecutive patients treated between June 2012 and March 2019 at seven high-volume oesophagogastric surgery units in England (Southampton, Royal Surrey, Plymouth, Aintree, Leicester, Oxford, and Salford) were included. Inclusion criteria were patients 18 yr and over, considered suitable for major curative oesophagogastric surgery, with no absolute contraindications to CPET.[27] Patients were excluded if they changed to a palliative treatment pathway before surgery, surgery was abandoned without resection, if they did not undergo a CPET at any stage, or if complication data were missing. Data were collected from prospectively maintained clinical perioperative databases at each contributing site with documentation of CPET data, characteristics, treatment pathways, and in-hospital morbidity from 2012 onwards. The study was initiated as a national quality improvement project

by the Perioperative Exercise Training and Testing Society (POETTS) in 2012 where the study was presented and a CPET protocol, statistical analyses, and data management plan was drawn up and shared amongst collaborating centres. A core outcome dataset of routine clinical data was shared with collaborators so that all centres would collect the same data in a similar standard format. This study was approved by the South Central and Oxford research ethics committee (17/SC/0331) in 2017 with the same full protocol and database generated in 2012 as collaborators were keen to publish their findings. The study protocol was registered with clinicaltrials.gov (NCT03637647) in January 2018. All data were then analysed retrospectively; hence the study is a retrospective multicentre pooled cohort study. Survival follow-up was undertaken centrally (in Southampton) for all patients up to 3 yr after surgery using NHS Digital Summary Care Records.

Cardiopulmonary exercise testing

CPET at all centres followed a predefined protocol based upon the American Thoracic Society recommendations[28] and subsequently the UK POETTS Society guidance.[27] CPET was conducted on a cycle ergometer, comprising 3 min resting, 3 min freewheel pedalling, a ramped incremental protocol until volitional termination, and up to 5-min recovery. Spirometry was carried out before the resting phase. Ventilation and gas exchange were measured using a metabolic cart. Heart rate, 12-lead ECG, blood pressure, and pulse oximetry were monitored throughout. The ramp gradient was set to 10–25 W min^{-1} calculated using predicted freewheel oxygen uptake (VO_2), predicted VO_2 peak, height, and age[27] to produce 8–12 min of exercise.

Resting spirometry, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), gas exchange variables (VO_2, ventilatory equivalents for oxygen and carbon dioxide [V_E/VO_2 and V_E/VCO_2] and oxygen pulse [VO_2/heart rate]), at the AT and at peak exercise were derived according to national guidance.[27] The AT was estimated using the modified V-slope.[27] VO_2 peak was averaged over the last 30 s of exercise. Workload at AT and at peak (W), including peak power indexed to weight per kilogram (W kg^{-1}) were reported.[29] The V_E/VCO_2 slope is a ratio of minute ventilation (V_E) to CO_2 output (VCO_2); a measure of 'ventilatory efficiency'. All CPETs were reported by experienced clinicians at each centre. AT and VO_2 peak were reported as absolute data (ml min^{-1}), relative to weight (ml kg^{-1} min^{-1}), ideal body weight (IBW) (ml kg^{-1} min^{-1}), and body surface area (BSA) (ml min^{-1} m^{-2}) as a result of cancer cachexia being highly prevalent in this population.

For patients who underwent neoadjuvant treatment, CPET was performed either at diagnosis (CPET-pre) or after neoadjuvant treatment, immediately before surgery (CPET-post) at the discretion of the treating centre. Ramp gradient was kept constant between both tests. If tested twice, the CPET with the highest AT was taken for final analyses (CPET Both). Treating clinicians were not blinded to CPET results. All patients were enrolled into an enhanced recovery programme according to international guidance.[30]

Patient characteristics, treatments, and outcome measures

Patient characteristics included: age, sex, height, weight, IBW {men=50+(0.91×[height in centimetres−152.4]) and women=45.5+(0.91×[height in centimetres−152.4])},[31] BSA computed using the Du Bois equation,[32] body mass index (BMI), operation type, and radiological tumour, node, metastasis (TNM) stage.

Staging and surgical approach were decided according to surgeons' preference, with prior multidisciplinary oesophagogastric cancer discussion. Histopathological staging was based on TNM v7, with tumour regression described using the Mandard Tumour Regression Grade. Circumferential resection margin involvement was defined as <1 mm. As this was a pragmatic observational study, no attempt was made to standardise neoadjuvant treatment regimens.

In-hospital surgical morbidity was recorded using the Clavien–Dindo–Demartines classification,[33] with major morbidity defined as ≥3a. Total duration of critical care and in-hospital length of stay, along with 30-day readmission were recorded. The 90-day, 1-yr, and 3-yr mortalities were recorded centrally.

The primary aim of this study was to establish a relationship between VO_2 peak (absolute; ml min^{-1}, relative to weight; ml kg^{-1} min^{-1}, IBW; ml kg^{-1} min^{-1}, and BSA; ml min^{-1} m^{-2}) and 1-yr survival from date of surgery. Secondary aims will explore:

(1) relationships between selected patient characteristics (sex, age, operation type, cancer treatment received, ASA, and WHO performance status), tumour pathology characteristics (pT/ypT, pN/ypN, Mandard Tumour Regression Grade, lymphovascular invasion, resection margin status), selected CPET variables of interest (AT and VO_2 peak (absolute; ml min^{-1}, relative to weight; ml kg^{-1} min^{-1}, relative to IBW; ml kg^{-1} min^{-1}, and relative to BSA; ml min^{-1} m^{-2}), V_E/VCO_2 slope, V_E/VCO_2 at AT, work rate (AT [W], peak [W]), peak power output (W kg^{-1}), FEV1/FVC (%), and postoperative morbidity (overall and major complications), and overall survival (1-yr and 3-yr);
(2) relationships between selected CPET variables and postoperative overall survival (1-yr and 3-yr) for patients undergoing CPET pre-neoadjuvant treatment alone, CPET post-neoadjuvant treatment alone, and change in CPET with neoadjuvant treatment. An *a priori* subanalysis with separate oesophagectomy and gastrectomy patient groups was performed;
(3) relationships between selected CPET variables and postoperative surgical complications presented as separate oesophagectomy and gastrectomy patient groups;
(4) change in physical fitness with neoadjuvant treatment.

Statistical analysis

A sample size calculation was conducted based on a hypothesised anticipated overall mortality of 33.5% in 1 yr after surgery. We assumed that the death event rate would increase in the unfit (control) patient group up to 50%, while the fit group would average 33.5%, a difference of 16.5% based on previous data.[18] We consider this effect size clinically relevant. Assuming 5% (two-sided) significance and 90% power, 150 events are needed to detect this size of difference in a log-rank survival comparison between the two groups. This requires 372 patients in total in the analysis. Allowing for 20% loss to follow-up, 446 patients, with complete CPET and outcome data, were required.

We used the Shapiro–Wilk test to assess the data for normality. Continuous data were presented as median (interquartile range [IQR]). The relationship between CPET variables and outcome was quantified using the Mann–Whitney *U*-test and logistic regression. Univariable logistic regression with

robust standard errors (accounting for centre clustering) was used to investigate the association between baseline characteristics, CPET, survival, and postoperative complications. The Wilcoxon signed rank test was used to evaluate differences between pre- and post-neoadjuvant treatment CPET. Receiver operating characteristic (ROC) curves were constructed for CPET variables associated with 1-yr or 3-yr survival and postoperative complications to assess their predictive precision. Optimal discriminatory cut points were determined by maximising the Youden index (sensitivity + specificity −1) across 100 bootstrap resamples. A variable was considered discriminative if the area under ROC and its 95% confidence interval were both >0.7.

Multivariable logistic regression models for major complications and 1-yr survival with robust standard errors, considering centre clustering, were fitted to the data. CPET variables for the overall cohort were dichotomised around their optimum ROC cut-off point, with $P<0.25$ in the univariable analysis for 1-yr survival used as candidates for the final model, in addition to age at operation, and operation type. The ability of the final model to discriminate between patients with, and without postoperative complications and patients dead or alive at 1 yr was investigated using ROC analysis. Data for calculating the V_E/VCO_2 slope were missing for some patients, who were excluded by pairwise deletion.

Additionally, the importance of individual CPET variables on outcome adjusted for relevant variables was then calculated using logistic regression. Specifically, 90-day mortality, 1-yr mortality, 3-yr mortality, and major complications were used sequentially as outcome variables and gender, age, operative approach, type of operation, neoadjuvant treatments, and ASA as adjustment variables. We also included year of operation as a further adjustment variable to account for any potential changing treatment practice or patient characteristics during the study. Each CPET variable was then included as a single further variable in turn to calculate adjusted odds ratios for each.

All analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria). A value of $P<0.05$ was considered statistically significant.

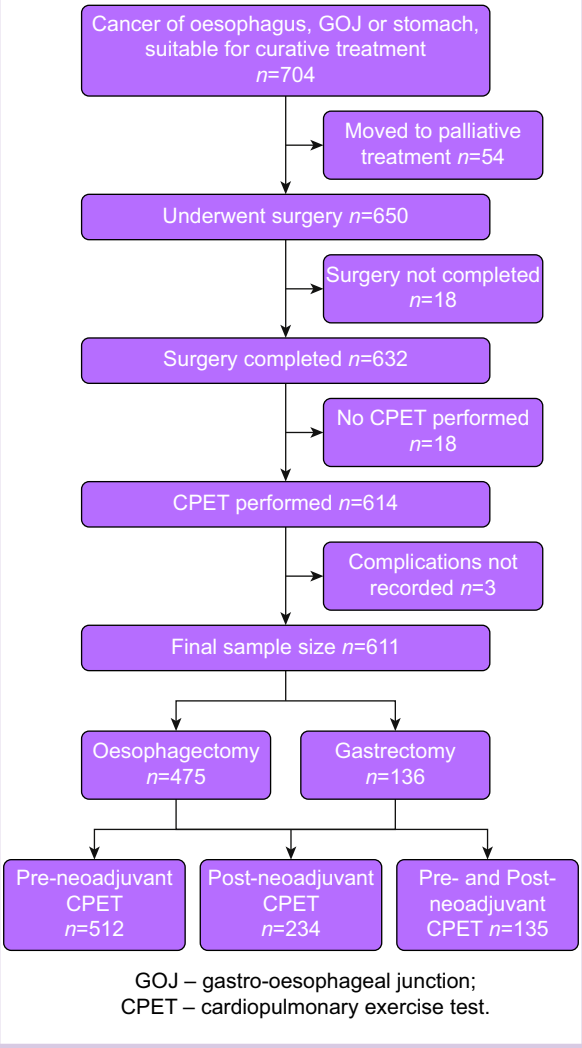

Fig 1. Study flow diagram detailing inclusions and exclusions to reach final sample size. CPET, cardiopulmonary exercise test; GOJ, gastro-oesophageal junction.

Results

Complete outcome data (complications and 3-yr survival) were available for 611 patients who underwent at least one CPET (pre-neoadjuvant treatment, post-neoadjuvant treatment or both) followed by elective surgery (Fig. 1).

Three (Salford, Aintree, and Southampton) of the seven centres recruited 58% of all patients. None of the patients recruited have been included in any other published study. Oesophagectomy was undertaken in 475 patients (77.7%), the majority being two-phase Ivor Lewis procedures (427/475, 89.9%) with comparatively few left thoraco-abdominal (28, 5.9%) and three phase (16, 3.4%) procedures. Gastric procedures were predominantly total/extended total gastrectomies (88, 64.7%). A fully minimally invasive operation was completed in 122 (20%) patients, whereas 171 (28%) patients had an open thoracic phase and a minimally invasive abdominal phase, with the remainder having an open procedure or a conversion to open.

Patient characteristics, with 77.9% males and a median age of 69, were typical for oesophagogastric cancer (Table 1). Neoadjuvant treatment before surgery was given in seven of 10 cases. Complications occurred in 408 patients (66.8%), with major complications (Clavien–Dindo ≥3a) occurring in 150 patients (24.5%). The mortality at 90 days, 1 yr, and 3 yr was 3.8%, 18.3%, and 42.7%, respectively. The median length of hospital stay was 12 days (IQR 9–18 days) and the median duration of critical care (Level 1/2) was 4 days (IQR 2–7 days). Eighty-six (14%) patients were readmitted within 30 days. Pre-neoadjuvant treatment CPET was conducted in 512 patients (83.8%), post-neoadjuvant treatment in 234 (38.3%), and both pre- and post-neoadjuvant treatment in 135 patients (22.1%).

Safety

No major adverse events occurred during CPET at any site. Ten patients developed supraventricular tachycardia at peak exercise, which resolved spontaneously during recovery; after review by a cardiologist, surgery proceeded as normal. Two patients developed CPET signs suggestive of severe myocardial ischaemia during early exercise, were subsequently diagnosed with flow-limiting left mainstem coronary artery stenosis, and

Table 1 Pretreatment patient characteristics, tumour pathology characteristics, and outcomes. Mean and standard deviation (SD) or median and inter-quartile ranges (IQR) presented. ASA, American Society of Anesthesiology score; BMI, body mass index; CD, Clavien–Dindo; CPET, cardiopulmonary exercise test; CPET-both, patients who underwent a CPET pre- and post-neoadjuvant cancer treatment with the highest oxygen uptake (VO_2) at anaerobic threshold (AT) CPET reported here; CPET-post, CPET after neoadjuvant cancer treatment; CPET-pre, CPET before neoadjuvant cancer treatment; NACRT, neoadjuvant chemoradiotherapy; NACT, neoadjuvant chemotherapy; pN/ypN, pathological lymph node stage/post-neoadjuvant cancer treatment lymph node stage; pT/ypT, pathological tumour stage/post-neoadjuvant cancer treatment tumour stage; R, resection margin.

	Overall	CPET-pre	CPET-post	CPET-both
n	***N*=611**	***N*=512**	***N*=234**	***N*=135**
Male sex (%)	476 (77.9)	395 (77.1)	184 (78.6)	103 (76.3)
Age (IQR)	69.0 (62.0–74.0)	69.0 (62.0–75.0)	66.0 (60.0–71.0)	65.0 (60.0–69.0)
BMI (IQR)	26.8 (23.6–30.0)	26.7 (23.6–30.1)	27.1 (23.9–29.8)	27.04 (23.8–30.0)
Procedure: gastrectomy (%)	136 (22.3)	126 (24.6)	29 (12.4)	19 (14.1)
Neoadjuvant treatment (%)				
Yes	425 (69.6)	332 (64.8)	234 (100.0)	135 (100.0)
No	179 (29.3)	173 (33.8)	0 (0.0)	0 (0.0)
Missing (%)	7 (1.1)	7 (1.4)	0 (0.0)	0 (0.0)
Neoadjuvant regime (%)				
NACRT	77 (12.6)	63 (12.3)	34 (14.5)	20 (14.8)
NACT	241 (39.4)	172 (33.6)	178 (76.1)	109 (80.7)
None	179 (29.3)	173 (33.8)	0 (0.0)	0 (0.0)
Missing	114 (18.7)	104 (20.3)	22 (9.4)	4 (3.0)
ASA (%)				
1	39 (6.4)	34 (6.6)	26 (11.1)	21 (15.6)
2	289 (47.3)	248 (48.4)	113 (48.3)	72 (53.3)
3	181 (29.6)	151 (29.5)	55 (23.5)	25 (18.5)
4	3 (0.5)	3 (0.6)	1 (0.4)	1 (0.7)
Missing	99 (16.2)	76 (14.8)	39 (16.7)	16 (11.9)
WHO performance status (%)				
0	280 (45.8)	209 (40.8)	116 (49.6)	45 (33.3)
1	188 (30.8)	173 (33.8)	63 (26.9)	48 (35.6)
2	47 (7.7)	46 (9.0)	4 (1.7)	3 (2.2)
3	4 (0.7)	4 (0.8)	0 (0.0)	0 (0.0)
Missing	92 (15.1)	80 (15.6)	51 (21.8)	39 (28.9)
pT/ypT (%)				
0	54 (8.8)	49 (9.6)	23 (9.8)	18 (13.3)
1	123 (20.1)	109 (21.3)	34 (14.5)	20 (14.8)
2	86 (14.1)	72 (14.1)	33 (14.1)	19 (14.1)
3	289 (47.3)	232 (45.3)	124 (53.0)	67 (49.6)
4	47 (7.7)	41 (8.0)	14 (6.0)	8 (5.9)
Missing	12 (2.0)	9 (1.8)	6 (2.6)	3 (2.2)
pN/ypN (%)				
0	287 (47.0)	247 (48.2)	105 (44.9)	65 (48.1)
1	134 (21.9)	108 (21.1)	55 (23.5)	29 (21.5)
2	93 (15.2)	79 (15.4)	35 (15.0)	21 (15.6)
3	85 (13.9)	69 (13.5)	33 (14.1)	17 (12.6)
Missing	12 (2.0)	9 (1.8)	6 (2.6)	3 (2.2)
Mandard tumour regression (%)				
1	41 (6.7)	36 (7.0)	16 (6.8)	11 (8.1)
2	34 (5.6)	27 (5.3)	13 (5.6)	6 (4.4)
3	82 (13.4)	60 (11.7)	31 (13.2)	9 (6.7)
4	106 (17.3)	80 (15.6)	53 (22.6)	27 (20.0)
5	77 (12.6)	52 (10.2)	40 (17.1)	15 (11.1)
Missing	271 (44.4)	257 (50.2)	81 (34.6)	67 (49.6)
Lymphovascular invasion (%)				
Yes	173 (28.3)	146 (28.5)	56 (23.9)	29 (21.5)
No	293 (48.0)	251 (49.0)	110 (47.0)	68 (50.4)
Missing	145 (23.7)	115 (22.5)	68 (29.1)	38 (28.1)
Resection margin (%)				
R0	373 (61.0)	322 (62.9)	134 (57.3)	83 (61.5)
R1	92 (15.1)	73 (14.3)	33 (14.1)	14 (10.4)
R2	3 (0.5)	3 (0.6)	0 (0.0)	0 (0.0)
Missing	143 (23.4)	114 (22.3)	67 (28.6)	38 (28.1)
Alive at 90 days after surgery (%)	588 (96.2)	491 (95.9)	229 (97.9)	132 (97.8)
Alive at 1 yr after surgery (%)	499 (81.7)	418 (81.6)	193 (82.5)	112 (83.0)
Alive at 3 yr after surgery (%)	350 (57.3)	218 (57.4)	138 (59.0)	82 (60.7)
All complications (%)	408 (66.8)	338 (66.0)	154 (65.8)	84 (62.2)
Major complication (CD ≥3a) (%)	150 (24.5)	121 (23.6)	47 (20.1)	18 (13.3)

underwent coronary revascularisation before returning for surgery 2 months later.

Relationship between VO_2 peak and 1-yr survival

AT was achieved in 606 cases (99.2%) with median AT and VO_2 peak of 11.5 ml kg^{-1} min^{-1} (IQR 10.1–13.5 ml kg^{-1} min^{-1}) and 18.1 ml kg^{-1} min^{-1} (15.4–21.4 ml kg^{-1} min^{-1}), respectively. Selected CPET variables are shown in Table 2. The distribution of AT and VO_2 peak values for the entire cohort can be seen in Supplementary Figure 1.

No association was observed between VO_2 peak (absolute, relative to weight, relative to IBW, and relative to BSA) and 1-yr survival (Supplementary Table S1). When cases were dichotomised at median VO_2 peak, there was no difference in overall survival (median 55.9 months ≥18.1 ml kg^{-1} min^{-1}, 64.5 months <18.1 ml kg^{-1} min^{-1}, P=0.771, Fig. 2a). When cases were dichotomised at median AT, there was also no difference in overall survival (median 55.9 months ≥11.5 ml kg^{-1} min^{-1} 64.5 months <11.5 ml kg^{-1} min^{-1}, P=0.794, Fig. 2b).

Relationships between patient characteristics, tumour characteristics, CPET variables, morbidity, and survival in the overall cohort

There were 499 patients (81.7%) alive at 1 yr and 350 (57.3%) at 3 yr after surgery (Supplementary Table S1). Tumour characteristics (ypT, ypN, Mandard tumour regression, lymphovascular invasion, and resection margin status) were significantly associated with both 1-yr and 3-yr survival. No association with survival was found for any other patient or cancer treatment variable. Major postoperative complications were significantly associated with both 1-yr and 3-yr survival (P<0.001). None of the overall cohort CPET variables were associated with 1-yr survival. The AT indexed to IBW (P=0.013) was the only CPET variable associated with 3-yr survival. The area under the ROC curve for AT indexed to IBW was 55.8% suggesting limited predictive precision (Supplementary Table S2).

The type of operation (gastrectomy) (P=0.001 and P=0.002) and ASA score (P=0.003 and P=0.013) were significantly associated with both overall and major complications. Tumour characteristics (lymphovascular invasion [P=0.001] and resection margin status [P<0.001]), were significantly associated with major complications. The absolute VO_2 peak (P=0.013), VO_2 peak indexed to BSA (P=0.034), and work rate at peak (P=0.023) were associated with all complications (Table 3). The area under the ROC curve suggested limited predictive precision for absolute VO_2 peak (56.1%), VO_2 peak indexed to BSA (55.3%) and work rate at peak (55.6%) (Supplementary Table S2).

Relationship between CPET variables, morbidity and survival analysed according to CPET time point and surgical procedure

Data were analysed by CPET timepoint, conducted pre-neoadjuvant treatment (n=512), CPET post-neoadjuvant treatment (n=234) and, change in CPET with neoadjuvant treatment (n=135), and their relationship with all complications, major

Table 2 Cardiopulmonary exercise testing variables. Median and inter-quartile ranges (IQR) presented. CPET, cardiopulmonary exercise test; CPET-pre, CPET before neoadjuvant cancer treatment; CPET-post, CPET after neoadjuvant cancer treatment; CPET-both; patients who underwent a CPET pre- and post-neoadjuvant cancer treatment with the highest oxygen uptake at anaerobic threshold (AT). AT (ml kg^{-1} min^{-1}, ml min^{-1}, ml min^{-1} m^2); oxygen uptake at the AT absolute, relative to weight, ideal body weight (IBW) and body surface area (BSA), VO_2 peak (ml kg^{-1} min^{-1}, ml min^{-1}, ml min^{-1} m^2); oxygen uptake at peak exercise absolute, relative to weight, IBW and BSA; FEV1/FVC, ratio of forced expiratory volume in the first 1 s to the forced vital lung capacity expressed as a percentage; V_E/VCO_2 at AT, ventilatory equivalent for carbon dioxide at the anaerobic threshold; V_E/VCO_2 slope, ventilatory efficiency slope; W, watts. *As not all patients underwent standard spirometry, sample size for overall n=487, CPET-pre; n=399, CPET-post; n=192, CPET-both; n=104. †V_E/VCO_2 slope unavailable for one centre, sample size for overall n=529, CPET-pre; n=474, CPET-post; n=155, CPET-both; n=100.

	Overall	CPET-pre	CPET-post	CPET-both
n	**N=611**	**N=512**	**N=234**	**N=135**
AT indexed to weight (ml kg^{-1} min^{-1})	11.5 (10.1–13.5)	11.4 (10.0–13.3)	11.1 (9.8–12.8)	12.1 (10.9–14.1)
AT absolute (ml min^{-1})	894 (740.0–1080.0)	897.0 (740.0–1069.8)	865.5 (726.3–1019.8)	970.0 (825.0–1175.0)
AT indexed to IBW (ml kg^{-1} min^{-1})	13.7 (11.6–16.2)	13.7 (11.6–16.1)	12.9 (11.0–14.7)	14.6 (12.9–16.7)
AT indexed to BSA (ml min^{-1} m^{-2})	472.3 (409.7–547.4)	472.7 (408.6–539.7)	453.1 (397.6–511.3)	497.7 (447.7–572.8)
VO_2 peak indexed to weight (ml kg^{-1} min^{-1})	18.1 (15.4–21.4)	18.0 (15.2–21.1)	17.8 (15.3–20.3)	20.1 (16.5–22.6)
VO_2 peak absolute (ml min^{-1})	1428 (1161.5–1711.5)	1406.0 (1144.0–1704.5)	1389.5 (1160.0–1647.5)	1570.0 (1355.0–1840.0)
VO_2 peak indexed to IBW (ml kg^{-1} min^{-1})	21.9 (18.1–25.4)	21.5 (17.9–25.3)	21.4 (18.0–24.0)	23.7 (20.5–26.6)
VO_2 peak indexed to BSA (ml min^{-1} m^{-2})	748.4 (628.9–879.7)	742.3 (624.2–872.3)	724.9 (622.7–833.5)	814.7 (717.3–935.3)
V_E/VCO_2 at AT	32.0 (28.7–35.8)	31.9 (28.2–35.3)	31.6 (28.4–34.7)	32.7 (29.8–35.9)
V_E/VCO_2 slope†	30.0 (27.0–33.4)	30.2 (27.0–33.5)	29.9 (27.0–33.0)	30.4 (27.4–33.0)
Work rate at AT (W)	64.0 (50.0–80.0)	64.0 (49.0–80.0)	63.0 (51.0–78.0)	76.0 (62.0–92.0)
Work rate at peak (W)	113.0 (87.0–140.0)	110.0 (86.0–140.0)	118.0 (92.0–138.0)	138.0 (112.5–164.0)
Peak power output (W kg^{-1})	1.45 (1.1–1.8)	1.44 (1.1–1.8)	1.5 (1.2–1.8)	1.7 (1.4–2.1)
FEV1/FVC*	75.8 (69.0–80.0)	75.0 (69.0–80.0)	76.6 (72.0–81.0)	78.0 (74.8–83.0)

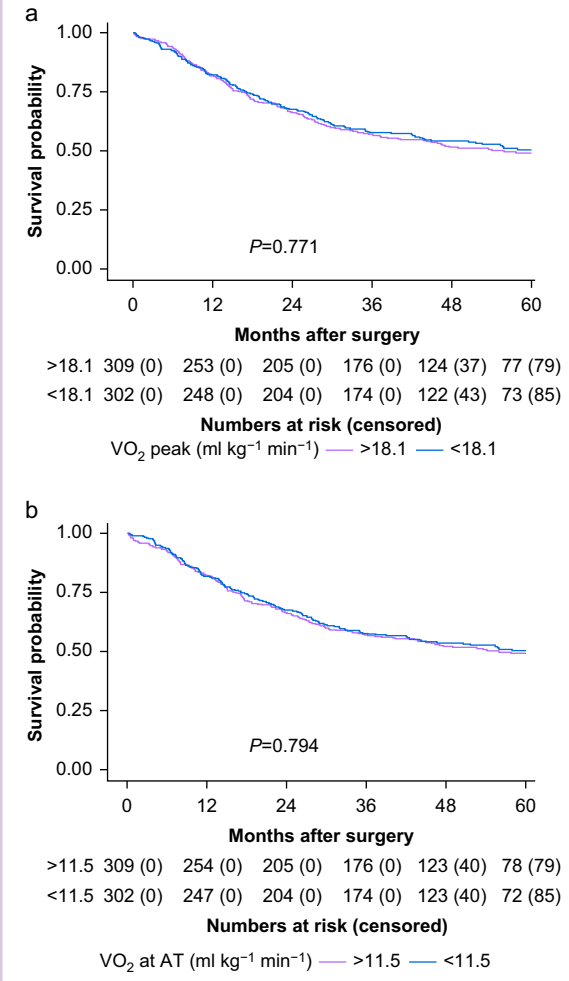

Fig 2. Kaplan–Meier curve showing the overall survival after surgery stratified at median (a) oxygen uptake at peak (VO_2 peak [ml kg^{-1} min^{-1}]) and (b) oxygen uptake at anaerobic threshold (AT [ml kg^{-1} min^{-1}]) for the whole cohort. No survival difference was found when patients were dichotomised around median VO_2 peak (P=0.771) or AT (P=0.794).

complications, 1-yr and 3-yr survival outcomes was interrogated. The pre-neoadjuvant treatment absolute VO_2 peak (P=0.031) and work rate at peak (P=0.044) were associated with all complications, while FEV1/FVC was associated with both all (P=0.019) and major complications (P=0.027). The pre-neoadjuvant treatment AT (absolute [P=0.024], relative to IBW (P=0.001) and BSA (P=0.009)), and V_E/VCO_2 at AT (P=0.026) showed significant associations with 3-yr survival (Supplementary Table S3). CPET variables post-neoadjuvant treatment did not show any associations with outcomes (Supplementary Table S4). No relationship was observed between change in CPET variables with neoadjuvant treatment and all complications, major complications or 1-yr mortality (Supplementary Table S5). Interestingly, reduced AT with neoadjuvant treatment (relative to weight [P=0.045], IBW [P=0.010], and BSA [P=0.012]) was associated with 3-yr survival.

In the oesophagectomy-only cohort (Supplementary Table S6), AT absolute (P=0.028), VO_2 peak (absolute [P=0.001], relative to IBW [P=0.024], and relative to BSA [P=0.003]), work rate at AT(P=0.043) and work rate at peak (P<0.001) showed a significant relationship to all complications. The AT relative to IBW was the only variable associated with 3-yr survival (P=0.019).

In the gastrectomy-only cohort (Supplementary Table S7) V_E/VCO_2 at AT (P=0.040) and V_E/VCO_2 slope (P=0.039) showed a significant relationship to major complications. No other CPET variables were associated with morbidity or mortality.

A multivariable logistic regression model for major complications retained operation type alone. Gastrectomy (odds ratio 0.38 [0.22–0.66]; P=<0.001) was significantly associated with a reduced odds of major complications. This model poorly discriminates between patients with and without major complications (AUC 0.56). In a multivariable logistic regression model for 1-yr mortality, no CPET variables were retained.

Patient characteristics were also split into year of surgery to interrogate any changes over time (Supplementary Table S8). Changes in baseline characteristics and cancer treatments over time were found; for example, there was increased use of neoadjuvant treatment (P<0.001), increased ASA score (P<0.001), and increased tumour regression score (P<0.001). After adjustment for year of operation, which accounts for changes in practice over time or patient characteristics, none of the CPET variables retained statistical significance for their relationship with 90-day mortality, 1-yr mortality, 3-yr mortality or major complications.

Changes in physical fitness with neoadjuvant treatment

Among patients who underwent CPET both before and after neoadjuvant treatment (n=135), AT, VO_2 peak, AT relative to IBW and BSA, VO_2 peak relative to IBW and BSA, work rate at AT and peak (all P<0.001), and peak power output (P=0.035), all significantly declined with neoadjuvant treatment (Table 4).

Discussion

This multicentre study pragmatically demonstrates the relationships of selected CPET variables, patient and tumour characteristics, with in-hospital morbidity and survival, in patients undergoing oesophagogastric cancer surgery. We report on CPETs carried out pre-neoadjuvant treatment, post-neoadjuvant treatment, and changes with neoadjuvant treatment, including independent reporting of separate oesophagectomy and gastrectomy cohorts. This is the largest single cohort of patients undergoing CPET, with more than twice as many patients as the largest previously reported study.[14]

Based on our findings, CPET can be safely performed, before neoadjuvant treatment, after neoadjuvant treatment, or both as we report no major adverse clinical events. VO_2 peak was not associated with 1-yr survival. Tumour characteristics and major complications alone were significantly associated with both 1-yr and 3-yr survival, whereas tumour characteristics were significantly associated with both overall and major complications. None of the selected CPET variables was associated with 1-yr survival. Selected pre-neoadjuvant treatment CPET variables, especially in the oesophagectomy-only groups were associated with all complications, major complications, and 3-yr survival; however, their predictive precision was poor.

Our findings are in line with other studies reporting weak associations between CPET and postoperative outcomes after oesophagogastric surgery.[20,21] Chmelo and colleagues[34]

Table 3 Univariate associations between selected patient characteristics, tumour pathological characteristics, cardiopulmonary exercise testing variables (overall cohort), and post-operative overall complications and major complications (CD ≥3a). CPET data presented are for the overall cohort (i.e. patients who had one CPET either before or after NAT and for patients who underwent a CPET pre- and post-NAT) the highest oxygen uptake at anaerobic threshold (AT) CPET was reported here. AT, oxygen uptake at the anaerobic threshold absolute (ml min^{-1}), relative to weight (ml kg^{-1} min^{-1}), relative to ideal body weight (ml kg^{-1} min^{-1}), and relative to body surface area (ml min^{-1} m^2); VO_2 peak, oxygen uptake at peak exercise absolute (ml min^{-1}), relative to weight (ml kg^{-1} min^{-1}), relative to ideal body weight (ml kg^{-1} min^{-1}) and relative to body surface area (ml min^{-1} m^2); V_E/VCO_2 at AT, ventilatory equivalent for carbon dioxide at the anaerobic threshold; V_E/VCO_2 slope, ventilatory efficiency slope; FEV1/FVC (%), ratio of forced expiratory volume in the first 1 s to the forced vital lung capacity expressed as a percentage. BSA, body surface area; CD, Clavien–Dindo; CPET, cardiopulmonary exercise test; IBW, ideal body weight; IQR, inter-quartile range; NACT, neo-adjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy; NAT, neoadjuvant cancer treatments; W, Watts. *Mann–Whitney *U*-test. †V_E/VCO_2 slope unavailable for 1 unit, sample size overall *n*=529. ‡N=487. Bold values are significant values *P*<0.05.

	All complications			Major complications (CD ≥3a)		
	Yes (*n*=408)	No (*n*=203)	*P*-value*	Yes (*n*=150)	No (*n*=461)	*P*-value*
Male sex (%)	311 (76.2)	165 (81.3)	0.188	118 (78.7)	358 (77.7)	0.884
Age (IQR)	69.0 (61.0–75.0)	69.0 (62.0–73.8)	0.999	68.1 (61.50–75.0)	69.0 (62.0–74.0)	0.868
Procedure: gastrectomy (%)	74 (18.1)	62 (30.5)	**0.001**	19 (12.7)	117 (25.4)	**0.002**
Neoadjuvant treatment (%)			0.817			0.393
Yes	286 (70.1)	139 (68.5)		99 (66.0)	326 (70.7)	
No	118 (28.9)	61 (30.0)		50 (33.3)	129 (28.0)	
Missing	4 (1.0)	3 (1.5)		1 (0.7)	6 (1.3)	
Neoadjuvant regime (%)			0.106			0.465
NACRT	55 (13.5)	22 (10.8)		19 (12.7)	58 (12.6)	
NACT	149 (36.5)	92 (45.3)		53 (35.3)	188 (40.8)	
None	204 (50.0)	89 (43.8)		78 (52.0)	215 (46.6)	
ASA (%)			**0.003**			**0.013**
1	26 (6.4)	13 (6.4)		7 (4.7)	32 (6.9)	
2	172 (42.2)	117 (57.6)		56 (37.3)	233 (50.5)	
3	140 (34.3)	41 (20.2)		51 (34.0)	130 (28.2)	
4	2 (0.5)	1 (0.5)		1 (0.7)	2 (0.4)	
Missing	68 (16.7)	31 (15.3)		35 (23.3)	64 (13.9)	
WHO performance status (%)			0.37			0.563
0	194 (47.5)	86 (42.4)		73 (48.7)	207 (44.9)	
1	121 (29.7)	67 (33.0)		42 (28.0)	146 (31.7)	
2	32 (7.8)	15 (7.4)		8 (5.3)	39 (8.5)	
3	4 (1.0)	0 (0.0)		1 (0.7)	3 (0.7)	
Missing	57 (14.0)	35 (17.2)		26 (17.3)	66 (14.3)	
pT/ypT (%)			0.208			0.783
0	35 (8.5)	19 (9.4)		12 (8.0)	42 (9.1)	
1	88 (21.6)	35 (17.2)		32 (21.3)	91 (19.7)	
2	58 (14.2)	28 (13.8)		16 (10.7)	70 (15.2)	
3	197 (48.3)	92 (45.3)		76 (50.7)	213 (46.2)	
4	24 (5.9)	23 (11.3)		10 (6.7)	37 (8.0)	
Missing	6 (1.5)	6 (3.0)		4 (2.7)	8 (1.7)	
pN/ypN (%)			0.097			0.927
0	207 (50.7)	80 (39.4)		67 (44.7)	220 (47.7)	
1	83 (20.3)	51 (25.1)		33 (22.0)	101 (21.9)	
2	59 (14.5)	34 (16.7)		24 (16.0)	69 (15.0)	
3	53 (13.0)	32 (15.8)		22 (14.7)	63 (13.7)	
Missing	6 (1.5)	6 (3.0)		4 (2.7)	8 (1.7)	
Mandard tumour regression (%)			0.952			0.852
1	27 (6.6)	14 (6.9)		9 (6.0)	32 (6.9)	

Continued

Table 3 Continued

	All complications			Major complications (CD ≥3a)		
	Yes (n=408)	No (n=203)	P-value*	Yes (n=150)	No (n=461)	P-value*
2	25 (6.1)	9 (4.4)		11 (7.3)	23 (5.0)	
3	55 (13.5)	27 (13.3)		18 (12.0)	64 (13.9)	
4	71 (17.4)	35 (17.2)		28 (18.7)	78 (16.9)	
5	53 (13.0)	24 (11.8)		20 (13.3)	57 (12.4)	
Missing	177 (43.4)	94 (46.3)		64 (42.7)	207 (44.9)	
Lymphovascular invasion (%)			0.729			**0.001**
Yes	116 (28.4)	57 (28.1)		39 (26.0)	134 (29.1)	
No	199 (48.8)	94 (46.3)		59 (39.3)	234 (50.8)	
Missing	93 (22.8)	52 (25.6)		52 (34.7)	93 (20.2)	
Resection margin (%)			0.296			**<0.001**
R0	247 (60.5)	126 (62.1)		71 (47.3)	302 (65.5)	
R1	67 (16.4)	25 (12.3)		27 (18.0)	65 (14.1)	
R2	3 (0.7)	0 (0.0)		0 (0.0)	3 (0.7)	
Missing	91 (22.3)	52 (25.6)		52 (34.7)	91 (19.7)	
Alive at 1 yr (%)	326 (79.9)	173 (85.2)	0.136	104 (69.3)	395 (85.7)	**<0.001**
Alive at 3 yr (%)	181 (44.4)	80 (39.4)	0.281	84 (56.0)	177 (38.4)	**<0.001**
AT indexed to weight (IQR) (ml kg^{-1} min^{-1})	11.4 (10.0–13.5)	11.9 (10.2–13.4)	0.438	11.7 (10.3–13.6)	11.4 (10.1–13.3)	0.363
AT absolute (IQR) (ml min^{-1})	890.0 (740.0–1070.0)	900.0 (740.0–1119.0)	0.286	896.5 (724.3–1070.0)	893.0 (740.0–1080.0)	0.581
AT indexed to IBW (IQR) (ml kg^{-1} min^{-1})	13.7 (11.6–16.3)	13.8 (11.7–16.0)	0.908	13.8 (11.5–16.2)	13.7 (11.7–16.1)	0.745
AT indexed to BSA (IQR) (ml min^{-1} m^{-2})	471.9 (409.6–542.6)	472.7 (412.3–551.3)	0.606	477.7 (410.4–551.3)	470.2 (409.6–543.8)	0.896
VO_2 peak indexed to weight (IQR) (ml kg^{-1} min^{-1})	18.0 (15.38–21.02)	18.2 (15.5–21.8)	0.346	18.0 (15.4–21.4)	18.2 (15.4–21.4)	0.946
VO_2 peak absolute (IQR) (ml min^{-1})	1406.0 (1144.8–1669.3)	1480.0 (1190.0–1840.0)	**0.013**	1406.0 (1168.5–1689.3)	1450.0 (1160.0–1720.0)	0.533
VO_2 peak indexed to IBW (IQR) (ml kg^{-1} min^{-1})	21.5 (18.0–24.9)	22.2 (18.6–26.3)	0.116	21.4 (18.4–24.7)	22.0 (18.0–25.6)	0.642
VO_2 peak indexed to BSA (IQR) (ml min^{-1} m^{-2})	740.0 (620.4–848.6)	768.1 (643.0–911.7)	**0.034**	723.6 (632.1–847.4)	752.3 (628.4–882.4)	0.474
V_E/VCO_2 at AT (IQR)	32.0 (28.7–35.8)	32.0 (28.8–35.3)	0.599	32.9 (29.0–36.3)	32.0 (28.0–35.5)	0.087
V_E/VCO_2 slope† (IQR)	29.9 (27.0–33.1)	30.1 (27.1–33.6)	0.581	30.2 (27.4–33.4)	30.0 (27.0–33.4)	0.376
Work rate at AT (IQR) (W)	64.0 (50.0–79.0)	66.0 (49.5–82.0)	0.643	63.0 (48.0–78.0)	64.0 (50.0–80.0)	0.334
Work rate at peak (IQR) (W)	109.0 (85.8–136.0)	119.0 (91.5–147.0)	**0.023**	109.0 (85.3–134.0)	114.0 (88.0–140.0)	0.334
Peak power output (IQR) (W kg^{-1})	1.44 [1.1–1.8)	1.47 (1.2–1.8)	0.151	1.4 (1.1–1.8)	1.5 (1.1–1.8)	0.456
FEV1/FVC‡ (IQR)	75.0 (69.0–80.0)	76.6 (71.0–81.0)	0.06	74.0 (65.6–79.8)	76.0 (70.0–80.0)	0.082

Table 4 Cardiopulmonary exercise testing variables for patients tested before and after neoadjuvant cancer treatments (NAT). Results presented as median and inter-quartile range (IQR). AT (ml kg^{-1} min^{-1}, ml min^{-1}, ml min^{-1} m^2), oxygen uptake at the anaerobic threshold absolute, relative to weight, ideal body weight, and body surface area, VO_2 peak (ml kg^{-1} min^{-1}, ml min^{-1}, ml min^{-1} m^2), oxygen uptake at peak exercise absolute, relative to weight, ideal body weight and body surface area; V_E/VCO_2 at AT, ventilatory equivalent for carbon dioxide at the anaerobic threshold; V_E/VCO_2 slope, ventilatory efficiency slope; FEV1/FVC (%), ratio of forced expiratory volume in the first 1 s to the forced vital lung capacity expressed as a percentage. BSA, body surface area; CPET; cardiopulmonary exercise test; IBW, ideal body weight; W, Watts. *Mann–Whitney *U*-test. †V_E/VCO_2 slope unavailable for one centre, CPET-pre *n*=100, CPET-post *n*=100. Bold describes significant *P*-values.

	CPET-pre N=135	CPET-post N=135	*P*-value*
AT indexed to weight (IQR) (ml kg^{-1} min^{-1})	11.8 (10.5–13.9)	10.7 (9.6–12.5)	**<0.001**
AT absolute (IQR) (ml min^{-1})	76 (62.0–92.0)	64.0 (52.0–80.5)	**<0.001**
AT indexed to IBW (IQR) (ml kg^{-1} min^{-1})	14.21 (12.15–15.95)	12.61 (10.99–14.51)	**<0.001**
AT indexed to BSA (IQR) (ml min^{-1} m^{-2})	487.88 (428.74–545.73)	443.62 (382.14–498.04)	**0.001**
VO_2 peak indexed to weight (IQR) (ml kg^{-1} min^{-1})	19.55 (16.30–22.37)	17.20 (14.90–19.90)	**<0.001**
VO_2 peak absolute (IQR) (ml min^{-1})	138.0 (103.5–160.5)	122.0 (99.0–150.0)	**<0.001**
VO_2 peak indexed to IBW (IQR) (ml kg^{-1} min^{-1})	23.53 (19.75–25.79)	20.79 (17.96–23.29)	**<0.001**
VO_2 peak indexed to BSA (IQR) (ml min^{-1} m^{-2})	786.54 (684.44–903.07)	718.49 (616.55–820.51)	**<0.001**
V_E/VCO_2 at AT (IQR)	30.70 (28.75–33.05)	31.90 (28.90–34.70)	0.076
V_E/VCO_2 slope (IQR)†	28.15 (26.30–31.05)	28.70 (25.85–32.15)	0.478
Work rate at AT (IQR) (W)	935.0 (792.5–1100.0)	860.0 (710.0–1000.0)	**<0.001**
Work rate at peak (IQR) (W)	1500.0 (1280.0,1795.0)	1350.0 (1141.0–1635.0)	**<0.001**
Peak power output (IQR) (W kg^{-1})	1.68 (1.37–2.05)	1.54 (1.25–1.89)	**0.035**
FEV1/FVC* (IQR)	77.00 (73.05–82.40)	77.00 (72.00–82.00)	0.594

showed that an elevated V_E/VCO_2 at AT was the only CPET variable significantly related to 3-yr survival (hazard ratio 1.05) post-esophagectomy. In this study, pre-neoadjuvant treatment V_E/VCO_2 at AT was associated with 3-yr survival in the whole cohort. Ventilatory inefficiency (high V_E/VCO_2 at AT and elevated V_E/VCO_2 slopes) is sparsely documented in the perioperative setting, however when reported it shows an association with poor outcomes.[35,36] In oesophagogastric surgery, the utility of CPET for discriminating risk is poor.[20,21] It is not clear why CPET is non-discriminatory in this setting in comparison to others.[7] The underlying pathophysiology that results in cardiopulmonary complications from multicompartment surgical trauma differs from other abdominal surgical procedures (e.g. one lung ventilation, thoracic/high abdominal incisions). Furthermore, the incidence of surgery-specific complications (e.g. anastomotic leak in the thoracic cavity, pneumonia, atrial fibrillation), and tumour characteristics makes these factors, and their sequalae, more prognostic than physical fitness.

A significant decline in fitness with neoadjuvant treatment was observed in this cohort, consistent with previous observations.[17,23,24,26] Neoadjuvant treatment has become increasingly prevalent,[22] however, neither post-neoadjuvant treatment fitness, nor the change in fitness with neoadjuvant treatment were associated with outcomes, as previously reported by our group.[17,18] Although overall survival has moderately improved for oesophagogastric surgery patients as a result of the improvement in tumour regression grading with neoadjuvant treatment, the reduction in perioperative fitness and increased postoperative mortality needs to be acknowledged during shared decision-making.[37] In some unfit patients, preoperative treatment might have no meaningful survival benefit and may even cause harm.[38] Baseline fitness, especially in the oesophagectomy cohort, might have a role in selecting patients for neoadjuvant treatments, as further patient deconditioning may result in an iatrogenic survival reduction. The impact of changing fitness on postoperative outcomes is of interest, as prehabilitation can improve fitness and reduce complications.[39] Minnella and colleagues[40] have demonstrated increased fitness with prehabilitation persisting into the postoperative period, however no difference in complications or survival.

This observational study has limitations. Firstly, the temporality of the data may impact external validity and relevance to contemporary practices. To undertake such a large multicentre study, patients recruited between 2012 and 2019 were enrolled. We acknowledge that lead-time bias for earlier patients may exist, but upper gastrointestinal surgical practices did not radically change in these centres, especially with regards to CPET assessments and methodology, enrolment in enhanced recovery programmes after surgery, surgical technical preferences, and recording of complications and survival. Further, there was no clinician blinding to CPET measurements, so confounding by indication may have occurred and it is likely that some patients who were

subjectively unfit (theoretically at most risk of poorer outcomes) did not undergo surgery and never underwent CPET. However, almost 25% of operated patients had an AT of <10.0 ml kg^{-1} min^{-1} and 12.5% had an AT of <9.0 ml kg^{-1} min^{-1}, which should adequately represent the higher risk, less fit population. CPET was not analysed in either a blinded or a dual reported fashion, as the authors felt that this study should mimic real-life clinical practice. This study does not provide a distinction between cardiopulmonary and non-cardiopulmonary complications, measuring instead complications requiring intervention (Clavien-Dindo >3) and long-term survival. This has ensured uniformity of reporting across sites, avoiding challenges in complication definitions (only recently defined[2]), but reduces the study's ability to detect differences in specific complications. Previous studies have similarly not identified differences in either AT or VO_2 peak in patients who suffered non-cardiopulmonary complications.[14–16,21] Finally, this was a mixed cohort of patients diagnosed with squamous cell carcinoma and adenocarcinoma, which might have influenced mortality.

In summary, this large, multicentre study of patients undergoing major oesophagogastric cancer surgery found some associations between selected CPET variables and adverse outcomes, but these are not considered to be reliable or offer adequate discrimination to predict outcomes in this patient group. These findings, unfortunately, echo similar results from other published studies. The utility of CPET alone, as a risk stratification tool before oesophagogastric cancer surgery, is now challenged because of its poor discriminatory ability and poor predictive power found in this study and across other studies in the literature. This finding is in marked contrast to other surgical groups. The lack of standardisation around CPET timings in relation to neoadjuvant treatment, the unblinded nature of CPET, and the lack of certainty around the unfit, untested patient not being offered surgery are still key unaddressed considerations. Avoiding such confounding by indication by conducting a prospective, fully blinded study, where CPET will not be used in treatment decisions, will be very challenging to undertake because of the widespread use of CPET in the UK. Beyond CPET, further work to delineate means of anticipating, preventing, and mitigating surgical complications utilising comprehensive perioperative risk stratification tools, remains a priority.

Authors' contributions

Study design: MAW, SJ, MPWG, DZHL
Data collection and analyses: MAW, SR
Writing of first draft: MAW, SR, SJ
Data interpretation and finalising of manuscript: MAW, SJ, MPWG, DZHL

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Declarations of interest

DZHL, MPWG, and SJ are on the steering committee for iPOETTS and CPX International. All other authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2024.100289.

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