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Neoadjuvant therapy reduces cardiopulmunary function in patients undegoing oesophagectomy

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TITLE PAGE:

Title:

NEOADJUVANT THERAPY REDUCES CARDIOPULMUNARY FUNCTION IN PATIENTS UNDEGOING OESOPHAGECTOMY

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Short Title / Running head:

Reduced fitness after neoadjuvant therapy

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Abstract

Neoadjuvant therapy (NAT) for oesophageal cancer may reduce cardiopulmonary function, assessed by cardiopulmonary exercise testing (CPEX). Impaired cardiopulmonary function is associated with mortality following esophagectomy. We sought to assess the impact of NAT on cardiopulmonary function using CPEX and assessing the clinical relevance of any change in particular if changes were associated with post-operative morbidity.

This was a prospective, cohort study of 40 patients in whom CPEX was performed before and after NAT. Thirty-eight patients underwent surgery and follow-up with perioperative outcomes measured. The primary variables derived from CPEX were the anaerobic threshold (AT) and peak oxygen uptake ($\dot{V}O_2$peak).

There were significant reductions in the AT (pre-NAT: 12.4 ± 3.0 vs. post-NAT 10.6 ± 2.0 mL.kg^{-1}.min^{-1}; p=0.001). This reduction was also evident for $\dot{V}O_2$peak (pre-NAT: 16.6 ± 3.6 vs. post-NAT 14.9 ± 3.7 mL.kg^{-1}.min^{-1}; p=0.004). The relative reduction in $\dot{V}O_2$peak was greater in chemotherapy patients who developed any peri-operative morbidity (p=0.04). For patients who underwent chemoradiotherapy, there was a significantly greater relative reduction in AT (p=0.03) for those who encountered a respiratory complication.

Cardiopulmonary function significantly declined as a result of NAT prior to oesophagectomy. The reduction in AT and $\dot{V}O_2$peak was similar in both the chemotherapy and chemoradiotherapy groups.

Keywords

Oesophagectomy, neoadjuvant therapy, Cardiopulmonary exercise test, morbidity.

Highlights

- Neoadjuvant therapy reduces a patient's anaerobic threshold by 14.5%

- Neoadjuvant therapy reduces a patient's peak oxygen uptake by 10.2%

- The reduction in cardiopulmonary function is similar with neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy

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1. Introduction

Oesophageal cancer is a significant cause of cancer related mortality(1). Surgical resection remains an integral component of curative treatment. Advances in perioperative care, surgical technique and patient selection have seen mortality rates from specialised centres fall to rates of 1-2% (2, 3). Morbidity remains a significant issue for patients recovering from oesophagectomy, with rates of significant morbidity reported to be 30-40%(4). In patients who present with resectable disease, there is a survival benefit with the addition neo-adjuvant treatment being chemotherapy or chemoradiotherapy (5). There is conflicting data as to whether NAT increases the risk of perioperative morbidity. A meta-analysis by Kumagai et al. examining morbidity and mortality associated with NAT and oesophageal cancer found no overall increase risk from NAT, however here was a higher risk of postoperative mortality from neoadjuvant chemoradiotherapy in patients with oesophageal squamous cell carcinoma (SCC) (6). Other studies have found an increase in cardiopulmonary morbidity in patients receiving chemoradiotherapy (7, 8). With regard to cardiopulmonary reserve there is limited data on whether there is an objective decline in cardiopulmonary reserve in patients with oesophageal cancer who receive NAT.

There is mounting evidence that a limited cardiopulmonary reserve is associated with increased risk of poor postoperative outcomes(9, 10). Assessment of perioperative risk has historically been conducted with a variety of tools. Cardiopulmonary exercise testing (CPEX) provides an objective assessment of a patient's ability to tolerate the increased metabolic

demands and increase in oxygen consumption associated with surgery (11). There is evidence that CPEX derived variables provide insight into assessing patient risk (12). Peak oxygen uptake ($\dot{V}O_2$peak) and the anaerobic threshold (AT) are two measurements derived from CPEX. Both markers have demonstrated prognostic significance and may significantly impact the post-operative course (12). Jack and colleagues (2014) demonstrated a reduction in CPEX defined variables with preoperative chemotherapy (13). It remains unclear whether these changes were associated with increased perioperative morbidity following oesophagectomy. The impact of CRT, as measured by CPEX, on patients undergoing oesophagectomy has been presented in abstract form and to our knowledge, not previously been published.(14)

The aim of this study was to measure CPEX derived variables in patients scheduled for an oesophagectomy before and after NAT. The primary objective was to assess for significant changes in the CPEX derived variables, anaerobic threshold (AT) and peak oxygen uptake ($\dot{V}O_2$peak). We also sought to assess if changes in these variables were associated with any difference in short-term surgical outcomes, in particular perioperative cardiorespiratory morbidity.

2. Materials and methods

2.1 Patients

This study was a single centre, prospective, cohort study. Hospital Ethics approval and individual patient consent was obtained, (HREC/11/QPAH/332) and the study was registered on the Research Registry. This study has been

reported in line with the STROCSS criteria (15). Patients scheduled to undergo NAT prior to oesophagectomy between January 2011 and July 2015 were invited to participate in the study. The inclusion criteria were the diagnosis of oesophageal cancer being treated with NAT followed by oesophagectomy and the completion of CPEX prior to and post NAT. The decision to offer NAT followed by oesophagectomy was made at the multidisciplinary team (MDT) meeting of the upper gastrointestinal unit. Patients were excluded from participation if they had a non-resectable tumor, chemotherapy and/or radiotherapy in the 30-days prior to screening, or unable to complete CPEX.

All patients were staged with endoscopy and FDG - positron emission tomography with computed tomography. Endoscopic ultrasound and staging laparoscopy were used selectively. Patients were restaged following NAT, with endoscopy and computed tomography scan of the chest and abdomen. NAT consisted of either neo-adjuvant chemotherapy or neo-adjuvant chemoradiotherapy. The standard choice of NAT during this period was enrollment in the DOCTOR trial (Appendix 1) which was a randomized phase II trial. Neoadjuvant treatment consisted of cisplatin, 5 fluorouracil alone, or combined with docetaxel. Treatment for Siewert III lesions requiring oesophagectomy was enrollment in the TOPGEAR trial. This is a randomized phase III trial comparing 3 cycles of epirubicin, cisplatin and 5-fluorouracil (MAGIC protocol) (16) with and without concurrent radiation (Appendix 1). The standard radiotherapy regimen was 45 Gy radiation in 25 fractions (Appendix 1). Outside of the trials the decision for preoperative NAT was

made in the MDT based on the individual patient information. Generally, NAT with radiation is preferred for squamous pathology or bulky disease. This is a MDT decision based on both diameter and length of the tumour or concerns that circumferential margin clearance may be difficult. NAT without radiation preferred for less bulky node negative disease. Oesophagectomy was scheduled for 4-6 weeks after completion of NAT. The surgery was performed at a single institution by one of four surgeons in the upper gastrointestinal surgical unit either as a thoracoscopic assisted 3-stage oesophagectomy or as an Ivor-Lewis oesophagectomy based on tumour location and surgeon preference. The techniques have been described in detail previously (17, 18). Briefly, a thoracoscopic assisted oesophagectomy involves a thoracoscopic chest dissection followed by an open abdominal dissection and cervical anastomosis. Some cases will have had a laparoscopic abdominal dissection rather than open based on surgeon preference. The Ivor-Lewis oesophagectomy is an open abdominal dissection and thoracotomy in the majority. Recently the unit has performed some cases with a laparoscopic and thoracoscopic Ivor-Lewis approach. The decision on approach relates to the site of the primary cancer with the thoracoscopic three field approach our preferred and the Ivor-Lewis approach performed for carcinomas that involved a significant length of the gastric cardia.

2.2 Study procedures

Patients completed a CPEX at the hospital's CPEX laboratory before NAT and was scheduled four weeks after the completion of the treatment. Patient demographic information, co-morbidity, surgical, perioperative outcomes

including postoperative morbidity and mortality were collected prospectively. The complications were graded using the Clavien-Dindo classification(19) and were defined based on Esophagectomy Complication Consensus Group definitions (20). Anastomotic leaks were classified using these definitions. Prior to 2014 all patients had routine contrast swallows on postoperative day 5-7. Since then clinical concerns are investigated with a combination of contrast swallow, CT scan with oral contrast and or endoscopy. Radiologic evidence of a leak was recorded and graded(20).

2.3 Cardiopulmonary exercise test

CPEX was conducted according to the guidelines published in the American Heart Association 2010 Scientific Statement (21). CPEX was performed on an upright cycle ergometer (Lode, Gronigen, NED). Following 1-minute of seated rest, participants maintained a constant cadence during a continuous incremental ramping protocol until volitional exhaustion. Gas exchange (VO_2 and VCO_2) and ventilatory (V_E) variables were measured using a breath-by-breath metabolic system (Ultima Cardio O2, MCG Diagnostics, St. Paul, MN). Heart rate, oxygen saturation, non-invasive blood pressure and 12-lead electrocardiography were monitored throughout the test.

The primary variables derived from CPEX were the AT and $\dot{V}O_2$peak; these were expressed in relative ($mL.kg^{-1}.min^{-1}$) terms. These were chosen as primary measures as they have been previously demonstrated to be associated with postoperative outcomes(12). The workload achieved at AT and $\dot{V}O_2$peak was recorded in watts (W). Ventilatory equivalents for oxygen

($V_E/\dot{V}O_2$) was used as a measure of ventilation required for metabolic demand at anaerobic threshold. The $VE/\dot{V}CO_2$ slope and oxygen uptake efficiency slope (OUES) were used as measures of the efficiency of ventilation with respect to carbon dioxide removal and oxygen uptake throughout the test.

2.4 Statistical Analysis

All continuous variables were assessed for normality using a Shapiro-Wilk test and are presented as mean ± standard deviation or median (Interquartile range). For categorical variables, the data was expressed as a count and percentage. Independent- t-tests and Mann-Whitney U-tests compared all variables between patients who received chemotherapy or chemoradiotherapy. Categorical variables were compared using Chi-square tests. Paired t-tests were also used to determine the change in variables derived from CPEX as a result of NAT. All statistical analyses were performed in a software package (SPSS, Version 22, IBM, New York, USA). Statistical significance was assumed if $p<0.05$. The sample size was calculated for paired statistics comparing the change in relative AT. Published data has previously demonstrated NAT is associated with a reduction in relative AT of 2.2 $mL.kg^{-1}.min^{-1}$, for this study, a standard deviation of 3.8 $mL.kg^{-1}.min^{-1}$ was used (13). Therefore, in order to obtain statistical power of 0.9 with statistical significance set at 0.05, a sample size of 34 was required.

3. Results

3.1 Patient demographics

During the study period 387 patients with oesophageal cancer were managed with curative intent following presentation at the MDT. The management is outlined in figure 1. Within this group 97 patients (25%) received neoadjuvant chemotherapy and 84 (22%) patients received neoadjuvant chemoradiotherapy. Within this group of patients 40 patients consented to participate in the study and completed CPEX testing before and after NAT. Two patients who received neo-adjuvant chemoradiotherapy did not progress to surgical resection; one due to disease progression and the other due to general performance status deterioration and an associated reduction in anaerobic threshold (pre NAT: 9.7 $mL.kg^{-1}.min^{-1}$; post NAT: 6.9 $mL.kg^{-1}.min^{-1}$) so that surgery was not considered appropriate. From the 38 patients who proceeded to oesophagectomy; 15 patients underwent an Ivor-Lewis resection, 12 with open abdomen and thoracotomy and 3 patients had a laparoscopic and thoracoscopic approach. The remaining 23 patients had a thoracoscopic assisted 3-stage oesophagectomy, 2 of these had laparoscopic abdominal dissection and one case was converted to a trans-hiatal approach due to severe pleural adhesions (Table 1). The majority were male with a median age of 66. Sixteen (42%) patients were treated with neo-adjuvant chemoradiotherapy and the remaining 22 (58%) received neo-adjuvant chemotherapy. The median follow-up of all patients was 31 months (range 7-69 months). (Table 1).

3.2 Neo-adjuvant treatment

Of the 22 (58%) patients receiving neo-adjuvant chemotherapy, 13 (33%) received 2 cycles of cisplatin and 5-fluorouracil (CF), 7 (18%) received 3

cycles of CF with docetaxel added to the second & third cycle as per the DOCTOR protocol, and 2 (5%) received 3 cycles of epirubicin and CF (ECF). Of the 16 undergoing neo-adjuvant chemoradiotherapy 13 (81%) were treated with 2 cycles of CF and 45 Gy in 25 fractions. The remaining three patients (7.5%) had different regimens: One patient received 3 cycles CF with docetaxel added to the second & third cycles and 45 Gy in 25 fractions (DOCTOR protocol), one patient received 5 cycles carboplatin & paclitaxel with 41.4 Gy in 23 fractions (CROSS protocol), one patient received 3 cycles ECF with 45 Gy in 25 fractions (TOPGEAR protocol). Four patients in the neo-adjuvant chemotherapy group had grade 3 complications during chemotherapy. Three required a dose reduction of docetaxel and the fourth patient developed a pulmonary embolus. There were no grade 3 or 4 complications in the neoadjuvant chemoradiotherapy group.

3.3 Effect of neo-adjuvant treatment on CPEX variables

The impact of NAT on variables derived from CPEX is presented in Table 2. There was a significant reduction of 14.5% in relative AT (pre-NAT: 12.4 ± 3.0 $mL.kg^{-1}.min^{-1}$; post-NAT: 10.6 ± 2.0 $mL.kg^{-1}.min^{-1}$; p=0.001) and 10.2% in $\dot{V}O_2$peak (pre-NAT: 16.6 ± 3.6 $mL.kg^{-1}.min^{-1}$; post-NAT: 14.9 ± 3.7 $mL.kg^{-1}.min^{-1}$; p=0.004). This significant decrease was also seen in the absolute value for AT and $\dot{V}O_2$peak. There was also a significant 24.2% reduction in the work rate required to achieve AT (pre-NAT: 69.3 ± 30.3 W; post-NAT: 52.5 ± 20.9 W; p=0.002) and 8.9% at $\dot{V}O_2$peak (pre-NAT: 101.6 ± 32.9 W; post-NAT: 92.6 ± 31.4 W; p=0.03).

A separate analysis was also performed to determine the changes in CPEX variables based on treatment modality. In patients receiving chemotherapy there was a 14.6% reduction in AT (pre NAT: 12.3 ± 3.3 mL.kg^{-1}.min^{-1}; post NAT: 10.5 ± 2.0 mL.kg^{-1}.min^{-1}; p=0.01) and 12% reduction in $\dot{V}O_2$peak (pre NAT: 16.6 ± 3.5 mL.kg^{-1}.min^{-1}; post NAT: 14.6 ± 3.1 mL.kg^{-1}.min^{-1}; p=0.02). Patients who received chemoradiotherapy also experienced a 14.4% reduction in AT (pre NAT: 12.5 ± 2.7 mL.kg^{-1}.min^{-1}; post NAT: 10.7 ± 2.0 mL.kg^{-1}.min^{-1}; p=0.04). Although there was a 7.3% decrease in $\dot{V}O_2$peak (pre NAT: 16.5 ± 3.7 mL.kg^{-1}.min^{-1}; post NAT: 15.3 ± 3.3 mL.kg^{-1}.min^{-1}; p=0.12). There was no significant between-group decrease in AT and $\dot{V}O_2$peak based on therapy type. However, there was a significant between-group increase in the VE/$\dot{V}CO_2$ slope for patients who underwent chemoradiotherapy (pre NAT: 26.5; post NAT: 30.0; p=0.01), compared to those who received chemotherapy alone (pre NAT: 26.5; post NAT: 26.0; p=0.62) [F(1,37) = 6.96, p=0.01, partial η^2 = 0.16]. No other CPEX variables were significantly different based on the type of treatment used.

3.4 Perioperative outcomes & morbidity

There was no in hospital or 30-day mortality. The median length of stay was 13 days. One patient died on postoperative day 77, due to disease progression (Table 2). Morbidity was seen in 28 patients (74%), respiratory morbidity was most common with 14 patients (37%) having 18 events. There were 7 patients (18%) with Clavien-Dindo grade 3/4 morbidity. One (3%) returned to theatre for drainage of an anastomotic leak and one (3%) returned

to theatre and ICU for treatment of empyema secondary arising from pneumonia. Two patients (5%), required re-intubation due to ARDS while in ICU. Three patients required radiologic insertion of chest drains for pleural effusions. The cardiac morbidity, seen in 13 (34%) patients, were Clavien-Dindo grade 2 arrhythmias. There were 5 (13%) patients with anastomotic leak of which, 4 (11%) were grade 1, managed with dietary modification (Table 3).

3.5 Relationship of CPEX variables and morbidity

Analysis of the entire cohort demonstrated no statistical difference in the relative change in CPEX variables following NAT between those who did or did not develop peri-operative complications. However, analyzing patients who received preoperative chemotherapy, there was a significant relative reduction in $\dot{V}O_2$peak for patients who developed peri-operative complications (-23.2 ± 22.98%) compared to those who did not (2.2 ± 25.4%)(p=0.04)(Figure 3).

For those patients who underwent chemoradiotherapy, there was no significant difference in CPEX variables for patients who did or did not develop peri-operative complications. However, those patients who developed a respiratory complication had a significantly greater relative reduction in AT (-20.5 ± 15.9%) compared to patients without any respiratory complications (2.55 ± 19.8%)(Figure 4).

4. Discussion

This study aimed to assess the change in CPEX derived variables in patients undergoing NAT prior to oesophagectomy. The results presented demonstrate that NAT significantly reduces the measures of cardiopulmonary function derived from CPEX. We observed a 14.5% and 10.2% decline in relative AT and $\dot{V}O_2$peak, respectively. For patients who received neo-adjuvant chemotherapy, the decline in $\dot{V}O_2$peak was associated with peri-operative complications and anastomotic leaks. For patients who received neo-adjuvant chemoradiotherapy the decline in AT was associated with respiratory complications.

There is evidence demonstrating a survival benefit from the use of NAT in oesophageal cancer (5). However, the ideal combinations of chemotherapy and radiation are still examined and debated. There remains a significant incidence of morbidity following oesophagectomy (4). It is postulated that NAT has a direct influence on the type and severity of perioperative morbidity. Until recently, the impact of these treatments on a patient's physical fitness remained unclear. Jack and colleagues demonstrated a reduction in physical fitness in 39 patients undergoing neo-adjuvant chemotherapy with a 15% reduction in AT (mean difference 2.2 $mL.kg^{-1}.min^{-1}$) and a 12% reduction in $\dot{V}O_2$peak (mean difference 2.5 $mL.kg^{-1}.min^{-1}$) (13). Similarly, a recent investigation also demonstrated a 17.3% reduction in AT (mean difference 2.4 $mL.kg^{-1}.min^{-1}$) in 30 patients receiving neo-adjuvant chemotherapy (22). These reductions were similar compared to the findings presented here, with reductions in AT of 9.1% (mean difference 1.9 $mL.kg^{-1}.min^{-1}$) and at peak

exercise of 16.3% (mean difference 2.0 $mL.kg^{-1}.min^{-1}$) for our cohort of patients who received chemotherapy.

The only study assessing the impact of neoadjuvant chemoradiotherapy reported a 10.5 % reduction in AT in 17 patients receiving neo-adjuvant chemoradiotherapy, which is similar to the 11.4% (mean difference 1.8 $mL.kg^{-1}.min^{-1}$) reduction in AT seen in our cohort of patients who received chemoradiotherapy (14). The impact of CRT in a cohort of patients who had rectal cancer as measured by CPEX reported a similar effect on the CPEX variables in 25 patients, demonstrating a mean reduction in AT and peak exercise of 1.5 and 1.4 $mL.kg^{-1}.min^{-1}$, respectively (23). Our data and all of these studies demonstrate a consistent and similar negative impact of NAT on patient cardiopulmonary reserve (AT ranging from 9.1%-17.3%; $\dot{V}O_2$peak ranging from 12%-16.3%)

There are concerns that neoadjuvant chemoradiotherapy may increase perioperative complications(7, 8), and recent results demonstrating increased mortality in the first 12 months(24). Few studies have examined the change in CPEX variables and the association with morbidity after CRT. We have demonstrated both neo-adjuvant chemotherapy and chemoradiotherapy have a similar impact on CPEX variables. The only significant between-group difference was the increase in the $VE/\dot{V}CO_2$ slope for patients who were treated with chemoradiotherapy. Patients receiving chemoradiotherapy experienced a 15% increase in the $VE/\dot{V}CO_2$ slope, in comparison to a -0.5% decrease for those who underwent chemotherapy. An elevated $VE/\dot{V}CO_2$

reflects ventilation-perfusion mismatching and is associated with unfavorable cardiopulmonary complications, (23, 24) the radiation dose to surrounding lung may be an explanation for this change and has been demonstrated to be related to respiratory complications(25). However, this was not predictive of post-operative morbidity or mortality. The decline in AT in those receiving neoadjuvant chemoradiotherapy was not associated with a significant increase risk of overall complications or mortality. The decline in AT in those receiving neoadjuvant chemoradiotherapy however was associated with respiratory complications.

The majority of patients considered to be suitable for oesophagectomy and NAT using a traditional medical assessment are likely to have an acceptable CPEX result pretreatment. The information obtained from CPEX related to a patient's potential cardiopulmonary reserve and provides additional quantification of post-operative risk, which is more likely to be relevant to those clinically borderline patients. The exact measurement or value that provides the best information in this select population is not clear (26). Jack and colleagues determined an optimal cutoff value of the AT to be ≥ 13.9 $mL.kg^{-1}.min^{-1}$ for post-oesophagectomy survival following NAT (13). Data from non oesophagectomy series suggests that an AT<11 $mL.kg^{-1}.min^{-1}$ is associated with increased perioperative risk (10). Our median AT post NAT was 10.6 $mL.kg^{-1}.min^{-1}$ leaving 50% of our patients "not fit" or at least at increased risk if they had an oesophagectomy. There is likely no absolute cutoff point or 'magic number'; rather the information derived from CPEX needs to be integrated into the comprehensive peri-operative assessment in

selected patients. The demonstrated reduction in cardiorespiratory fitness seen with NAT may have significant implications for patients bordering the 'high-risk' stratification during assessment. Knowledge of the potential risk for developing complications in the post-operative phase may then outweigh the potential benefits seen with NAT.

The role of exercise training or 'prehabilitation' is an expanding area of research. Improving outcomes with an intervention such as exercise training has a strong appeal and CPEX provides an ideal method for quantifying changes. Patients who are undergoing NAT for esophageal cancer are commonly scheduled for surgery 4-6 weeks following the completion of NAT. This scheduling provides an opportunity to improve cardiorespiratory fitness, and potentially reduce morbidity and improve recovery from surgery. There is uncertainty as to whether such an intervention will result in improved clinical outcomes. A systematic review of exercise training in elective abdominal and cardiothoracic surgery examined 10 randomized-controlled trials (27). The authors concluded that exercise training is safe, feasible and improves several health-related physical fitness outcomes in this population (27). The improvement in clinical outcomes was less clear with one cardiac surgery study showing a reduced ICU and hospital stay with the exercise program.

The anastomotic leak rate in this study was 13% overall which may at first appear high, however the clinically more relevant grade 3 anastomotic leak rate was 2.6%. The overall rate reflects accurate reporting with accepted definitions and a majority of patients with a cervical anastomosis. The leak

rate reported in this series is comparable to those from large single centre MIE series reporting a 5% grade 3 leak rate (28), and an overall rate of 12% in a large series with cervical anastomosis(29). It compares favourably with reported rates in recent randomized trials investigating NAT in esophageal cancer of 9 - 30%(24, 30)

A limitation of this study is the small sample size which makes difficult the comparison of the CPEX variables following NAT with clinical outcomes, however our primary objective was to quantify the reduction in CPEX variables for which the study is adequately powered. Minor variations in the neo-adjuvant treatments used in our study reflect current practice and our involvement in ongoing clinical trials. The variation in surgical technique in the study is another source of bias which may have an impact on the short term clinical outcomes. Minimally invasive techniques were applied in 25 (68%) of resected patients, this may be a confounder particularly with regard to respiratory complications. We feel these differences are unlikely to have a significant impact on the primary outcome measures. Another limitation is the fact that only 40 of 181 possible patients were recruited over the study period. We have analysed the group who did not participate and there were no major differences with regard to comorbidities or postoperative outcomes compared to the study population (data not shown). Within this group 15 patients underwent a CPEX prior to NAT, with a median AT of 11.3mL.kg^{-1}.min^{-1} which would suggest those patients in the study had similar cardiorespiratory fitness to those not included. A strength of our study is the use of internationally recognized definitions of complications and a grading system which will be

allow accurate comparison of our findings with other research in this population (20).

The current study demonstrates significant reduction in objective measures of cardiopulmonary reserve associated with NAT prior to oesophagectomy. This impact is demonstrated for both neo-adjuvant chemotherapy and neo-adjuvant chemoradiotherapy. The adverse effect on clinical outcomes is uncertain and more investigation is required. The negative effect of NAT should be considered in the perioperative management of those patients who have a reduced cardiopulmonary reserve. Additionally, the role of exercise training to improve or restore cardiopulmonary reserve prior to surgery should be investigated.

Competing Interests

There are no external funding or competing interests to declare.

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Figure 1. Patient recruitment

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Figure 2. Neoadjuvant treatment outline

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Table 1. Patient demographics and clinical characteristics.

Variables [a]	Chemotherapy (n=22)	Chemoradiotherapy (n=16)	Overall (n=38)
Age	65 (15.3)	67.5 (7.3)	66 (10.5)
Sex: male (n, %)	19 (86.4%)	12 (75%)	31 (81.60%)
Body mass index (kg/m^2)	29.56 ± 4.22	28.56 ± 3.38	29.17 ± 3.87
Clinical T Stage (n, %)			
T2	5 (22.7%)	9 (56.3%)	14 (36.8%)
T3	17 (77.3%)	7 (43.8%)	24 (63.2%)
Clinical N Stage (n, %)			
N0	16 (72.7%)	8 (50%)	24 (63.2%)
N1	6 (27.3%)	8 (50%)	14 (36.8%)
ASA (n, %)			
1	3 (13.6%)	0	3 (7.9%)
2	10 (45.5%)	11 (68.8%)	21 (55.3%)
3	9 (40.9%)	5 (31.3%)	14 (36.8%)
Surgical resection (n, %)			
Ivor Lewis	8 (36.4%)	7 (43.8%)	15 (39.5%)
Thoracoscopic 3 stage	14 (63.6%)	9 (56.3%)	23 (60.5%)
Days from post CPEX to surgery	15.0 (14.0)	16.8 (8.7)	22 (11.3)
Follow up (months)	33.5 (7-69))	30.5 (8-65)	31 (7-69)

[a] Continuous variables as mean ± SD or median (interquartile range). Categorical data as number (%).

ASA = American Society of Anesthesiologists; CPEX = cardiopulmonary exercise test

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Table 2. Differences in cardiopulmonary exercise testing variables before and after neoadjuvant therapy.

Variables [a]	Before therapy (n=40)	After therapy (n=40)	Mean difference (95% CI)	P-value
Outcomes at anaerobic threshold				
Work rate (W)	69.3 ± 30.3	52.5 ± 20.9	16.8 (6.8 to 26.7)	0.002
$\dot{V}O_2$ (mL.kg^{-1}.min^{-1})	12.4 ± 3.0	10.6 ± 2.0	1.9 (0.8 to 2.9)	0.001
$\dot{V}O_2$ (mL.min^{-1})	1053.6 ± 330.1	858.9 ± 207.6	194.7 (105.2 to 284.2)	<0.001
Outcomes at peak exercise				
Work rate (W)	101.6 ± 32.9	92.6 ± 31.4	9.15 (0.9 to 17.4)	0.030
$\dot{V}O_2$ (mL.kg^{-1}.min^{-1})	16.6 ± 3.6	14.9 ± 3.7	1.6 (0.5 to 2.7)	0.004
$\dot{V}O_2$ (mL.min^{-1})	1402.5 ± 397.1	1224.0 ± 357.6	178.5 (84.7 to 272.2)	<0.001
VE/$\dot{V}CO_2$ slope	26.5 ± 3.6	27.7 ± 5.1	-1.2 (-2.9 to 0.5)	0.170
OUES	2.0 ± 0.5	1.7 ± 0.4	0.3 (0.1 to 0.4)	<0.001

[a] Continuous variables as mean ± SD.

$\dot{V}O_2$ = oxygen uptake; VE/$\dot{V}CO_2$ = ventilatory equivalents for carbon dioxide; OUES = oxygen uptake efficiency slope

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Table 3. Patient surgical and perioperative outcomes.

Variables [a]	Chemotherapy (n=22)	Chemoradiotherapy (n=16)	Overall (n=38)
30-day in-hospital mortality (n, %)	0	0	0
90-day mortality (n, %)	1 (4.5%)	0	1 (2.6%)
All peri-operative morbidity (n, %)	16 (72.7%)	12 (75%)	28 (73.7%)
Clavien-Dindo ≥ Grade 3	3 (13.6%)	4 (25%)	7(18.4%)
Return to operating theatre or ICU (n, %)	1 (4.5%)	1 (6.2%)	2 (5.3%)
Anastomotic leak (n %)	5 (22.7%)	0	5 (13.2%)
Grade 1 (n %)	4 (18.2%)	0	4 (10.5%)
Grade 2 (n %)	0	0	0
Grade 3 (n %)	1 (4.5%)	0	1 (2.6%)
Respiratory morbidity [b]	7 (31.8%)	7 (43.8%)	14 (36.8%)
Pneumonia (n)	6 (27.3%)	7 (43.8%)	13 (34.2%)
Effusion (n)	0	3 (18.8%)	3 (7.9%)
Respiratory failure/ARDS (n)	2 (9.1%)	0	2 (5.3%)
Cardiac morbidity (n %)	7 (31.8%)	6 (37.5%)	13 (34.2%)
Myocardial ischemia (n %)	0	0	0
Arrhythmia (n %)	7 (31.8%)	6 (37.5%)	13 (34.2%)

[a] Continuous variables as median (interquartile range). Categorical data as number (%).

[b] There were 14 patients with respiratory morbidity, with a total of 18 complications.

ARDS = acute respiratory distress syndrome

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Figure 3. Change in relative $\dot{V}O_2$ at peak exercise ($mL.kg^{-1}.min^{-1}$) before and after chemotherapy, divided into patients who did (Yes) or did not (No) develop one or more peri-operative complications.

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Figure 4. Change in $\dot{V}O_2$ at AT ($mL.kg^{-1}.min^{-1}$) before and after chemoradiotherapy, divided into patients who did (Yes) or did not (No) develop a respiratory complication following surgery.

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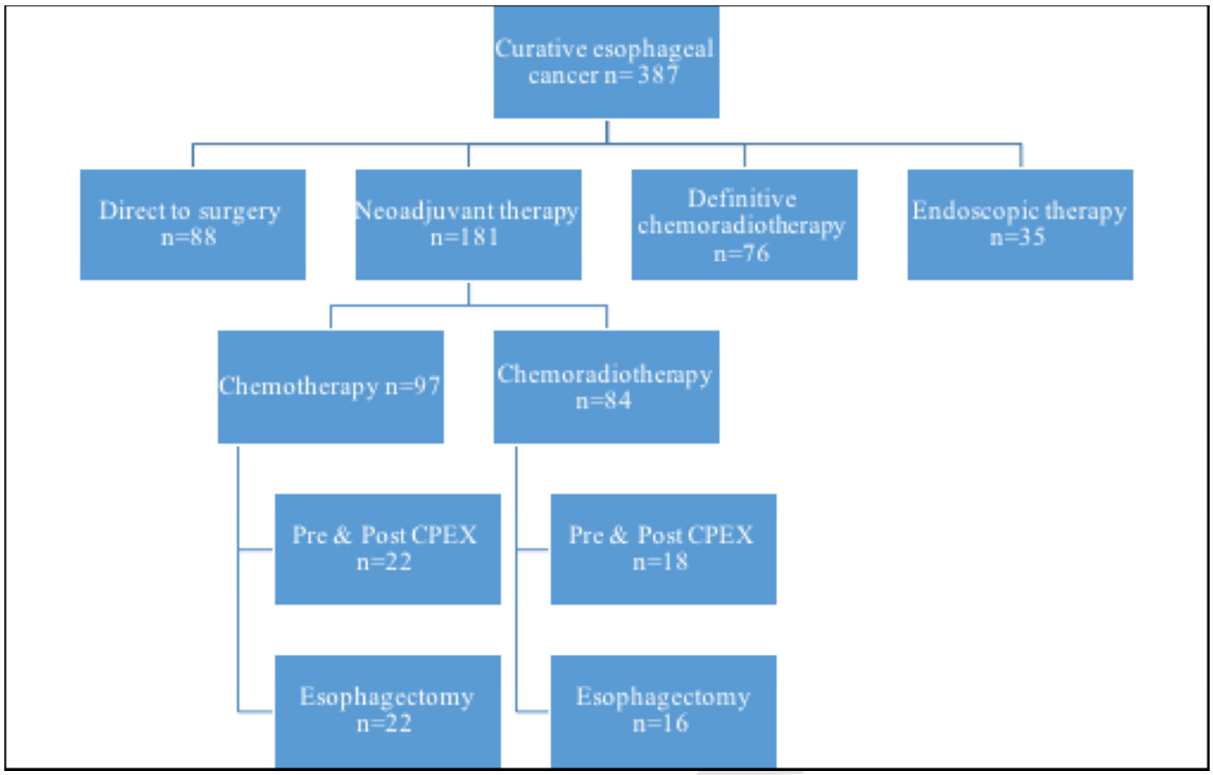

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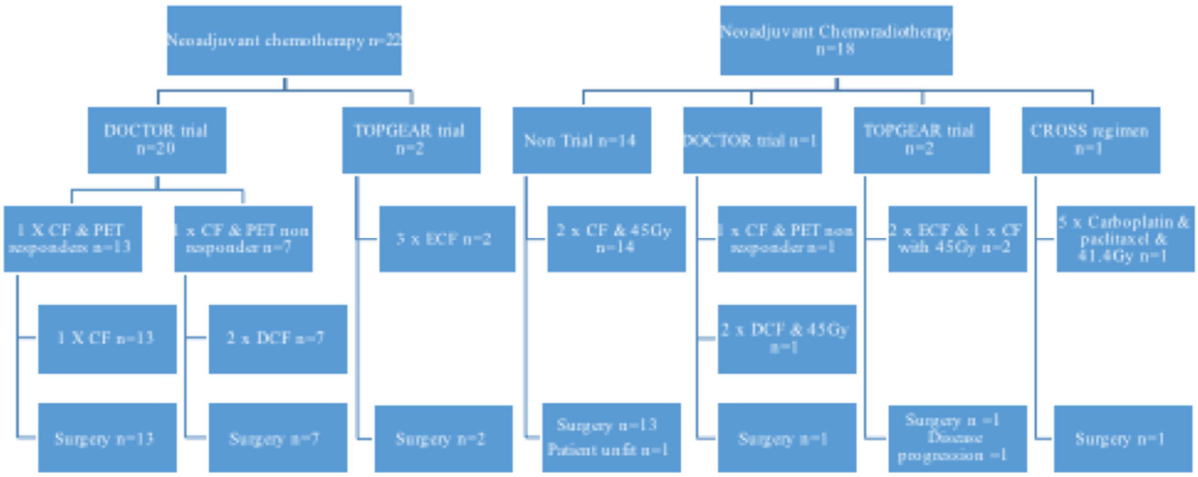

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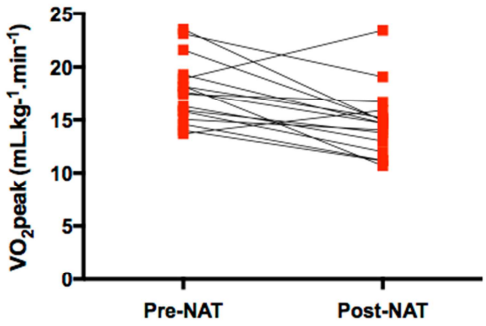

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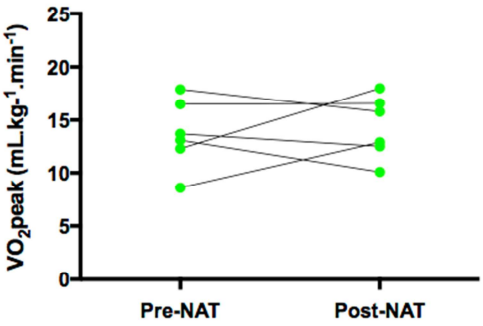

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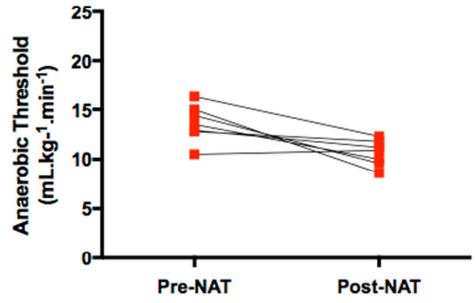

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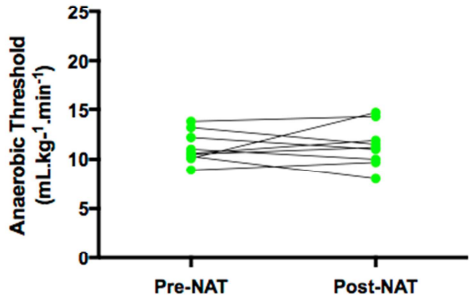

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Highlights

- Neoadjuvant therapy reduces a patient's anaerobic threshold (AT) by 14.5%

- Neoadjuvant therapy reduces a patient's peak oxygen uptake ($\dot{V}O_2$peak) by 10.2%

- The reduction in cardiopulmonary function is similar with neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy

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