Routine pre- and post-neoadjuvant chemotherapy fitness testing is not indicated for oesophagogastric cancer surgery

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ABSTRACT

INTRODUCTION There is a known correlation between anaerobic threshold (AT) during cardiopulmonary exercise testing and development of cardiopulmonary complications in high-risk patients undergoing oesophagogastric cancer surgery. This study aimed to assess the value of routine retesting following neoadjuvant chemotherapy.

METHODS Patients undergoing neoadjuvant chemotherapy with subsequent oesophagogastric cancer surgery with pre- and post-neoadjuvant chemotherapy cardiopulmonary exercise data were identified from a prospectively maintained database. Measured cardiopulmonary exercise variables included AT and maximum oxygen uptake at peak exercise (VO₂ peak). Anaerobic threshold values within 1 ml/kg/minute were considered static. Patients were grouped into AT ranges of less than 9 ml/kg/minute, 9–11 ml/kg/minute and greater than 11 ml/kg/minute. Outcome measures were unplanned intensive care stay, postoperative cardiovascular morbidity and mortality.

RESULTS Between May 2008 and August 2017, 42 patients from 675 total resections were identified, with a mean age of 65 years (range 49–84 years). Mean pre-neoadjuvant chemotherapy AT was 11.07 ml/kg/minute (standard deviation, SD, 3.24 ml/kg/minute, range 4.6–19.3 ml/kg/minute) while post-neoadjuvant chemotherapy AT was 11.19 ml/kg/minute (SD 3.05 ml/kg/minute, range 5.2–18.1 ml/kg/minute). Mean pre-neoadjuvant chemotherapy VO₂ peak was 17.13 ml/kg/minute, while post-chemotherapy this mean fell to 16.59 ml/kg/minute. Some 44.4% of patients with a pre-chemotherapy AT less than 9 ml/kg/minute developed cardiorespiratory complications compared with 42.2% of those whose AT was greater than 9 ml/kg/minute ($P = 0.914$); 63.6% of patients in the post-neoadjuvant chemotherapy group with an AT less than 9 ml/kg/minute developed cardiorespiratory complications. There was no correlation between direction of change in AT and outcome.

CONCLUSION In our patient population, neoadjuvant chemotherapy does not appear to result in a significant mean reduction in cardiorespiratory fitness. Routine pre- and post-neoadjuvant chemotherapy cardiopulmonary exercise testing is currently not indicated; however, larger studies are required to demonstrate this conclusively.

KEYWORDS

Oesophagectomy – Gastrectomy – Exercise testing – Chemotherapy

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Introduction

In patients with oesophageal or gastric cancer, the best chance of cure remains surgical resection. Despite evolutions in surgical approaches and postoperative care pathways,¹ there remains a significant morbidity associated with the surgery.^{2,3} Cardiopulmonary complications are responsible for a substantial proportion of this postoperative morbidity and mortality.⁴ The 2016 National Oesophagogastric Cancer Audit in England and Wales revealed that 16.2% of patients undergoing oesophagectomy admitted to critical care required advanced cardiovascular support and 29.6% of patients required advanced respiratory support.⁵

Cardiopulmonary exercise testing is a non-invasive, cost-effective dynamic test of a patient's cardiovascular and respiratory reserve.⁶ It allows the measurement of a patient's maximum oxygen uptake (VO_{2max}) and the point at which anaerobic metabolism exceeds aerobic metabolism (AT). It has been demonstrated that a low AT is associated with increased cardiorespiratory complications in patients undergoing non-cardiac surgery.⁷ Preoperative AT has been shown to be an independent predictor of complications and length of stay in both major elective surgery including aortic aneurysm repair, aortobifemoral grafting, liver resection and large sarcoma surgery,⁸ as well as hepatobiliary surgery.⁹ We have previously demonstrated a correlation between AT during cardiopulmonary exercise

testing and the development of cardiopulmonary complications in high-risk patients undergoing oesophagogastric cancer surgery.¹⁰

As a result of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial,¹¹ current gold standard management for patients with resectable oesophagogastric cancer in the UK usually includes three cycles of preoperative or neoadjuvant chemotherapy. General malaise and fatigue are frequently reported during chemotherapy regimens.¹² There is concern that this may be reflected in a general decline in patients' exercise tolerance and therefore lead to a potential increase in perioperative risk. Within a colorectal cancer population, chemoradiotherapy had been shown to result in significant decrease in AT.¹³ Evidence in the literature has suggested a significant decrease in both AT as well as peak oxygen uptake (VO₂ peak) following neoadjuvant chemotherapy in patients with oesophagogastric cancer.¹⁴ However, it remains unclear as to the relevance of this change with respect to the patient's perioperative risk.

This study aimed to assess the value of routine cardiopulmonary exercise retesting following neoadjuvant chemotherapy and its relationship to clinical outcome.

Methods

Selection

All patients with oesophagogastric adenocarcinoma being considered for resectional surgery within our regional unit undergo routine cardiopulmonary exercise testing as part of their initial standard fitness assessment alongside staging investigations including upper gastrointestinal endoscopy, computed tomography (CT), positron emission tomography-CT, endoscopic ultrasound and laparoscopy. This is usually performed prior to attendance for neoadjuvant chemotherapy and helps to inform discussions with patients and relatives about perioperative risk. Following chemotherapy, patients are reviewed prior to surgery and any patient with fitness concerns, as perceived by the surgeon because of chemotherapy toxicity, undergo repeat cardiopulmonary exercise testing. To ensure that our population was representative, baseline AT was compared with the entire resectional population over the same time period.

Chemotherapy

Following multidisciplinary team discussion and full staging, patients with oesophagogastric cancer considered suitable for resection underwent standard chemotherapy regime of three cycles of combination epirubicin, cisplatin and either 5-fluorouracil (ECF) or capecitabine (ECX) prior to surgery. Prior to referral for chemotherapy, it was ensured that all patients had adequate renal, cardiac and haematological function. Following completion of chemotherapy, all patients were re-discussed at the multidisciplinary team with repeat staging performed prior to final decision to proceed to resectional surgery.

Surgery

Patients received standard care under the responsible consultant surgeon with administration of prophylactic

antibiotics and thromboembolic prophylaxis. The type of operation performed depended on tumour site, size, American Society of Anesthesiologists grading and surgeon preference. Patients were nursed in a high dependency unit postoperatively. A radiological swallow test was performed on day seven after oesophagectomy and total gastrectomy to assess anastomotic healing.

Cardiopulmonary exercise testing

As per the protocol from our previous study,¹⁰ cardiopulmonary exercise testing was performed in a respiratory function laboratory with a doctor and full resuscitation equipment present. The ZAN® 600 and the Ergoselect bicycle ergometer were used for the tests. During the test, patients were exposed to incremental physical exercise on a bicycle ergometer to their maximally tolerated level, which was determined by either exhaustion or, more often, the development of symptoms (pain or breathlessness). Several variables were recorded throughout the procedure including blood pressure, cardiac activity via electrocardiography, and inspiratory and expiratory gases (to calculate oxygen uptake and carbon dioxide output).

Two key measurements were determined from the accrued data, oxygen uptake at peak exercise and AT, indicating the point at which anaerobic metabolism is inadequate to maintain high-energy phosphate production in exercising muscles, forcing anaerobic metabolism to make up the deficit.¹⁵ All patients were tested at baseline prior to undergoing chemotherapy with subsequent post-chemotherapy being conducted within four weeks of their final cycle.

Outcome measures

Measured cardiopulmonary exercise variables including AT and VO₂ peak were recorded prospectively. For the purpose of analysis, values within 1 ml/kg/minute were considered static. Patients were grouped for analysis based on our previous AT ranges of less than 9 ml/kg/minute, 9–11 ml/kg/minute and greater than 11 ml/kg/minute. Outcome measures of unplanned intensive care unit admission, postoperative cardiorespiratory morbidity and mortality (Clavien–Dindo Grade II and above) were obtained from the unit database.

Data collection

All patient data were collected prospectively to a unit database (using Microsoft Excel) recording demographic details, cardiopulmonary exercise values, operation performed and postoperative morbidity and mortality.

Statistical analysis

Variables were grouped using standard thresholds. Categorical data was compared using chi-squared tests. Continuous data was analysed using Student's *t*-test and Mann–Whitney *U* test where appropriate. *P*-values of less than 0.05 were considered to be statistically significant. All analysis was performed using SPSS version 22.

Results

Between May 2008 and August 2017, a total of 42 patients were identified with a mean age of 65 years (range 49–84

Table 1 Operative procedures	
Procedure	Number
Ivor-Lewis oesophagectomy	12
Transhiatal oesophagectomy	11
Thoraco-abdominal oesophagectomy	2
Three-stage oesophagectomy	5
Total gastrectomy	4
Subtotal/distal gastrectomy	5
Inoperable during procedure	3

years). Patients were predominantly male (37 males vs 5 females). The majority of cancers were oesophageal (33 oesophageal vs 9 gastric). A breakdown of procedures performed is outlined in Table 1.

To ensure the validity of the selected population, baseline AT was compared to that of our entire oesophagogastric resection population ($n = 675$) over the same time period. There was no statistical difference in age (mean 64.8 years vs 64.5 years, $P = 0.549$). Our study population demonstrated a slightly higher male preponderance (male 88.1% vs 71.6%, $P = 0.02$) and lower baseline AT (mean 11.07 vs 12.0, $P = 0.076$).

In our study population, mean pre-neoadjuvant chemotherapy AT was 11.07 (SD 3.24 ml/kg/minute, range 4.6–19.3 ml/kg/minute) while post-neoadjuvant chemotherapy AT was 11.19 (SD 3.05 ml/kg/minute, range 5.2–18.1 ml/kg/minute). There was no significant change in AT before or after chemotherapy (Table 2). Some 35.3% of patients experienced a decrease in AT following chemotherapy compared with 38.1% whose AT increased following chemotherapy; 28.6% experienced no significant change (Fig 1). Patients with a baseline AT greater than 11 ml/kg/minute were more likely to experience a decrease in AT following neoadjuvant chemotherapy ($P = 0.02$).

Similarly, VO_2 peak was unchanged following neoadjuvant chemotherapy (17.13 ml/kg/minute vs 16.59 ml/kg/minute, $P = 0.367$).

As per our previous study,¹⁰ patients were grouped based on AT of less than 9, 9–11 and greater than 11 ml/kg/minute. Complications within these stratified groups are presented in Table 3. Some 44.4% of patients with pre-neoadjuvant chemotherapy AT less than 9 ml/kg/minute developed cardiorespiratory complications compared with 42.2%

Table 2 Change in cardiopulmonary exercise data			
	Baseline	Post-NAC	P-value
Anaerobic threshold (ml/kg/minute)	11.07	11.19	0.756
VO_{2peak} (ml/kg/minute)	17.13	16.59	0.367
NAC, neoadjuvant chemotherapy; VO_2 , oxygen uptake.

Figure 1 Ladder plot of pre- and post-neoadjuvant chemotherapy anaerobic threshold

of those with AT greater than 9 ml/kg/minute ($P = 0.914$). In contrast, 65.6% of patients in the post-neoadjuvant chemotherapy group with AT less than 9 ml/kg/minute developed cardiorespiratory complications compared with 35.5% of those with AT greater than 9 ml/kg/minute ($P = 0.113$).

There was no statistically demonstrable correlation between direction of change in AT value and outcome however a trend could be observed towards increased cardiorespiratory complications in those with decreased AT following neoadjuvant chemotherapy compared with those whose AT increased (Table 4). When stratified by AT group, 62.5% of patients who dropped from a group to a lower stratification developed cardiorespiratory complications compared with 42.3% of those remaining in the same stratification and 25% of patients who improved to a 'higher' AT stratification ($P = 0.197$; Table 5).

Discussion

In contrast to previous publications,^{14,16} in our patient population, neoadjuvant chemotherapy does not appear to result in a significant mean reduction in cardiorespiratory fitness. As described above, one-third of our patients do demonstrate a decrease in their observed AT; however, 29.7% of our patient cohort appeared to improve their fitness following chemotherapy. We postulate that this may be due to familiarity with the test or indeed a desire to perform well in a circumstance where the patient is concerned that the progression to resection may be under threat following perceived cardiorespiratory decline.

Our study is limited by a degree of selection bias in that included patients have had a concern raised either by themselves or a managing clinician regarding their fitness and this may limit the application of these results to the general population despite the relative homogeneity

Table 3 Complications by group

Group	Number	Complications		
		Unplanned intensive care <i>n</i> (%)	Cardiorespiratory complications <i>n</i> (%)	Mortality <i>n</i> (%)
All patients (<i>n</i> = 37)	42	14 (33.3)	18 (42.9)	1 (2.4)
Pre-NAC:				
< 9 ml/kg/minute	9	4 (44.4)	4 (44.4)	0 (0)
9–11 ml/kg/minute	15	6 (40.0)	7 (46.7)	0 (0)
> 11 ml/kg/minute	18	4 (22.2)	7 (38.9)	1 (5.6)
Post-NAC:				
< 9 ml/kg/minute	11	5 (45.5)	7 (63.6)	0 (0)
9–11 ml/kg/minute	13	5 (38.5)	5 (38.5)	0 (0)
> 11 ml/kg/minute	18	4 (22.2)	6 (33.3)	1 (5.6)

NAC, neoadjuvant chemotherapy.

Table 4 Change in anaerobic threshold and complications

Change in anaerobic threshold	Number	Unplanned intensive care <i>n</i> (%)	Cardiorespiratory complications <i>n</i> (%)	Mortality <i>n</i> (%)
Increased	16	9 (56.3)	6 (37.5)	1 (6.3)
Static	12	3 (25)	5 (41.7)	9 (0)
Decreased	14	4 (28.6)	7 (50)	0 (0)

Table 5 Stratification Change and Complications

Change in stratification	Number	Unplanned intensive care <i>n</i> (%)	Cardiorespiratory complications <i>n</i> (%)	Mortality <i>n</i> (%)
Increased	8	2 (25)	2 (25)	0 (0)
Static	26	9 (34.6)	11 (42.3)	1 (3.8)
Decreased	8	3 (37.5)	5 (62.6)	0 (0)

between this study population and our greater resectional population. We also recognise that we are limited by relatively small numbers within this study, resulting in trends as opposed to outright statistical significance.

Previous studies have suggested that, in patients completing neoadjuvant chemotherapy, pretreatment cardiopulmonary exercise testing correlates with mortality and survival as well as demonstrating a significant reduction in cardiopulmonary exercise variables with neoadjuvant chemotherapy.⁶ Of note, our population has a lower mean pre-neoadjuvant chemotherapy AT in comparison with both published cohorts and therefore appears to demonstrate overall stasis with regards to fitness testing.^{14,16} This may be more representative of the general fitness of our

population compared with the other cohorts as it is recognised that patients with a lower socioeconomic status are more likely to have significantly lower peak oxygen consumption and heart rate reserve.¹⁷ We have demonstrated that patients with a baseline AT greater than 11 ml/kg/minute were more likely to experience a decrease in AT following chemotherapy. Thus, it may be that the effects of neoadjuvant chemotherapy are more evident within a generally healthier population who essentially have ‘more to lose’.

Other published studies do not appear to show whether the decrease in AT itself is of importance or whether post-neoadjuvant chemotherapy retesting informs morbidity or mortality. We believe that we have demonstrated that,

within a population of concern following neoadjuvant chemotherapy, repeated AT testing is not currently warranted. Further study is required to assess whether pre- or post-neoadjuvant chemotherapy cardiorespiratory testing is more indicative of perioperative morbidity; however, as pre-chemotherapy fitness testing often informs the decision whether to proceed down a curative versus palliative pathway at present, it is unlikely that the majority of patients would be managed solely with post-neoadjuvant chemotherapy AT testing. With further study in larger numbers, it may become evident that post-neoadjuvant chemotherapy testing may be more informative with respect to informing patients regarding their cardiorespiratory risk prior to embarking on resectional surgery however doing this routinely at present without specific concern does not appear to be warranted.

In conclusion, we have demonstrated that in a select group there was no change between pre- and post-neoadjuvant chemotherapy cardiopulmonary exercise testing and any change does not appear to be predictive of clinical outcomes. However, larger studies are required to demonstrate this conclusively. Further large-scale studies should also demonstrate the effect on both perioperative morbidity and mortality, as well as long-term survival in these patients to identify patients that may have significant decrease in fitness with neoadjuvant chemotherapy necessitating a more patient-specific approach in some situations.

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