



The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery

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Abstract

Background: Neoadjuvant chemotherapy (NAC) followed by surgery for resectable oesophageal or gastric cancer improves outcome when compared with surgery alone. However NAC has adverse effects. We assess here whether NAC adversely affects physical fitness and whether such an effect is associated with impaired survival following surgery.

Methods: We prospectively studied 116 patients with oesophageal or gastric cancer to assess the effect of NAC on physical fitness, of whom 89 underwent cardiopulmonary exercise testing (CPET) before NAC and proceeded to surgery. 39 patients were tested after all cycles of NAC but prior to surgery. Physical fitness was assessed by measuring oxygen uptake (\dot{V}_{O_2} in $\text{ml kg}^{-1} \text{min}^{-1}$) at the estimated lactate threshold ($\hat{\theta}_L$) and at peak exercise (\dot{V}_{O_2} peak in $\text{ml kg}^{-1} \text{min}^{-1}$).

Results: \dot{V}_{O_2} at $\hat{\theta}_L$ and at peak were significantly lower after NAC compared to pre-NAC values: \dot{V}_{O_2} at $\hat{\theta}_L$ 14.5 ± 3.8 (baseline) vs. 12.3 ± 3.0 (post-NAC) $\text{ml kg}^{-1} \text{min}^{-1}$; $p \leq 0.001$; \dot{V}_{O_2} peak 20.8 ± 6.0 vs. 18.3 ± 5.1 $\text{ml kg}^{-1} \text{min}^{-1}$; $p \leq 0.001$; absolute \dot{V}_{O_2} (ml min^{-1}) at $\hat{\theta}_L$ and peak were also lower post-NAC; $p \leq 0.001$. Decreased baseline \dot{V}_{O_2} at $\hat{\theta}_L$ and peak were associated with increased one year mortality in patients who completed a full course of NAC and had surgery; $p = 0.014$.

Conclusion: NAC before cancer surgery significantly reduced physical fitness in the overall cohort. Lower baseline fitness was associated with reduced one-year-survival in patients completing NAC and surgery, but not in patients who did not complete NAC. It is possible that in some patients the harms of NAC may outweigh the benefits.

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Introduction

Worldwide, oesophageal cancer is the eighth most common cancer and the sixth most common cause of cancer-death, while gastric cancer is the fifth most common cancer and third most common cause of cancer-death.¹ In England and Wales, approximately 11,500 patients were diagnosed in 2013, of which 35% underwent planned curative resection.² Although potentially curative, surgical resection has a significant morbidity and mortality^{3,4}; recent national audit data report 90-day mortality for oesophagectomy and gastrectomy as 3.2% and 2.8% respectively, with 1-year survival rates between 76.1% and 78.0% depending on the site of the primary tumour.²

A recent meta-analysis provides evidence that for operable, early stage disease neoadjuvant chemotherapy improves survival over surgery alone⁵ and in the UK the MAGIC trial has resulted in practice change in favour of NAC.⁶ However treatment with NAC carries the risk of toxicity and in clinical practice this may be associated with an increased risk of surgical morbidity.⁵ Physiological toxicity includes down-regulated muscle proteasome dependent proteolysis leading to skeletal muscle wasting,⁷ oxidative stress⁸ and mitochondrial death.⁹ Although not statistically significant, sub-group analysis from the MAGIC study⁶ demonstrated efficacy of NAC before upper gastrointestinal (UGI) surgery and suggests that less fit patients benefit less from NAC than fitter patients.

Traditionally ‘fitness’ has been measured using crude tools (Eastern Cooperative Oncology Group Performance Status), the assessment of which often varies significantly between clinicians.¹⁰ An objective measure of physical fitness is therefore of significant clinical interest, provided the assessment can be undertaken non-invasively and reproducibly.

Oxygen consumption increases after major surgery and a greater physiological reserve may allow patients to better tolerate this metabolic stress.¹¹ Cardiopulmonary exercise testing (CPET) provides an objective assessment of cardio-respiratory function under the stress of exercise. Lower levels of physical fitness, as defined by oxygen uptake (\dot{V}_{O_2}) at estimated lactate threshold ($\hat{\theta}_L$) and at peak exercise (peak) assessed by CPET, are associated with worse outcome following general^{8–11} and UGI surgery.^{11–15} A systematic review¹⁴ concluded that CPET derived variables outperform alternative methods of preoperative risk stratification: 11 of 12 studies reported a significant association between \dot{V}_{O_2} at $\hat{\theta}_L$ and postoperative outcome and 7/12 studies for \dot{V}_{O_2} at peak.

In this study we set out to quantify CPET derived physiological parameters with the aim of assessing, whether the change of these variables over the course of NAC can be used to identify patients whose outcome is adversely affected by NAC.

Patients and methods

Methods and materials

We conducted a single-centre, prospective, observational cohort study to test the hypothesis that NAC prior to UGI cancer surgery has a harmful effect on physical fitness. We used \dot{V}_{O_2} at $\hat{\theta}_L$, assessed using CPET as a tool to measure physiological fitness. The ultimate aim was to assess whether changes in \dot{V}_{O_2} at $\hat{\theta}_L$ have an effect on overall survival. Research Ethics Committee approval (08/H1001/137; 08/H1001/139) and written informed consent were obtained. This study is registered with ClinicalTrials.gov (NCT01335555).

Patients and setting

The study was conducted in a National Health Service (NHS) tertiary upper gastrointestinal cancer service situated in an 800-bed University Hospital. We approached consecutive eligible patients presenting for surgery between August 2007 and February 2009 to be recruited into the study. We recruited patients ≥ 18 years of age with resectable oesophageal or gastric cancer who were considered suitable for NAC. Criteria for suitability for NAC were: patients ≤ 75 years; WHO performance status < 2 ; tumour, node, metastasis (TNM) classification of $\geq T2/N1$. We excluded patients with tumours considered surgically non-resectable, patients unable to perform CPET due to other coexisting illness or conditions (e.g. lower limb dysfunction), patients declining surgery or chemotherapy and patients unable to give informed consent. Tumour staging involved endoscopic ultrasound, computer aided tomography, and positron emission tomography prior to chemotherapy. Recruited patients who remained candidates for resection surgery underwent NAC: Oesophageal cancer patients received treatment as per the interventional arm of OEO2, whilst junctional and gastric cancer patients as per the interventional arm of the MAGIC trial ([Appendix 1](#)).^{6,16} Postoperative pathological staging was compared with initial radiological staging to assess disease progression. Patients who underwent surgery following NAC

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