Exercise prehabilitation during neoadjuvant chemotherapy may enhance tumour regression in oesophageal cancer: results from a prospective non-randomised trial

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ABSTRACT

Background There is increasing evidence for the use of exercise in cancer patients and data supporting enhanced tumour volume reduction following chemotherapy in animal models. To date, there is no reported histopathological evidence of a similar oncological benefit in oesophageal cancer.

Methods A prospective non-randomised trial compared a structured prehabilitation exercise intervention during neoadjuvant chemotherapy and surgery versus conventional best-practice for oesophageal cancer patients. Biochemical and body composition analyses were performed at multiple time points. Outcome measures included radiological and pathological markers of disease regression. Logistic regression calculated ORs with 95% CI for the likelihood of pathological response adjusting for chemotherapy regimen and chemotherapy delivery.

Results Comparison of the Intervention (n=21) and Control (n=19) groups indicated the Intervention group had higher rates of tumour regression (Mandard TRG 1–3 Intervention n=15/20 (75%) vs Control n=7/19 (36.8%) p=0.025) including adjusted analyses (OR 6.57; 95% CI 1.52 to 28.30). Combined tumour and node downstaging (Intervention n=9 (42.9%) vs Control n=3 (15.8%) p=0.089) and Fat Free Mass index were also improved (Intervention 17.8 vs 18.7 kg/m²; Control 16.3 vs 14.7 kg/m²; p=0.026). Differences in markers of immunity (CD-3 and CD-8) and inflammation (IL-6, VEGF, INF-γ, TNFα, MCP-1 and EGF) were observed.

Conclusion The results suggest improved tumour regression and downstaging in the exercise intervention group and should prompt larger studies on this topic.

Trial registration number NCT03626610.

INTRODUCTION

Neoadjuvant chemotherapy (NAC), while potentially beneficial in tumour downstaging before surgery and improving survival in oesophageal adenocarcinoma, has a deconditioning effect on patient fitness. An increased incidence of sarcopenia is common following NAC which in combination with visceral obesity has been associated with cancer progression and poor chemotherapy response. While not currently prescribed as part of standard care, there is burgeoning evidence of the benefits of exercise in the treatment of cancer. One study reported on the molecular basis for linking exercise to improved cancer outcomes while also suggesting a role in the prevention of cancer development and the regulation of cancer progression. A recent systematic review of 27 relevant observational studies found evidence of reduced cancer-specific mortality associated with physical exercise. Furthermore, moderate intensity exercise has been linked to a reduction in both recurrence and the development of new primary tumours in patients with breast cancer.

Recent studies, conducted using animal models, have reported a positive impact of exercise on tumour volume shrinkage following chemotherapy. One study described a reduction of tumour volumes, improved perfusion and reduced tumour hypoxia in exercising mice. However, there is to our knowledge, no evidence in human participants of the histopathological benefits of exercise in patients undergoing NAC for oesophageal cancer.

The purpose of the trial was to evaluate the clinical impact of a structured exercise intervention in patients with operable oesophageal cancer during NAC compared with those on a standard treatment pathway. This study specifically assessed the impact of exercise on measures of chemotherapy response.

METHODS

Study design
Following patient and public involvement consultation, support was received from the Oesophageal Patients Association to undertake the study.

Patients underwent a standard pathway of staging investigations including oesophagogastroduodenoscopy and tissue biopsy, CT imaging (CT), positron emission tomography imaging and endoscopic ultrasound. Staging laparoscopy was used selectively. All patients were discussed in a specialist upper gastrointestinal multidisciplinary meeting (UGI MDM).

After completion of staging investigations, the final clinical cancer tumour node metastasis (TNM) stage was agreed by the UGI MDM and consensus
achieved on patients’ treatment pathways.11 Patients were reviewed by the clinical team in the out-patient department and assessed for eligibility to participate in the trial, ‘Prehabilitation of patients with oEsophageal Malignancy undergoing Peri-operative Treatment’ (Pre-EMPT)—a non-randomised, interventional study comparing the effects of a structured exercise programme, or ‘prehabilitation’ (Intervention), versus conventional best practice (Control) in patients undergoing NAC following a diagnosis of operable adenocarcinoma of the lower oesophagus or gastro-oesophageal junction. Inclusion criteria are described in online supplemental information.

Guy’s and St Thomas National Health Service (NHS) Foundation Trust is a high volume, tertiary specialist centre for oesophago-gastric cancer receiving referrals from a large geographical area divided into two similar-sized cancer networks. All patients being considered for oesophagectomy are assessed at the surgical centre. Patients received advice from specialist nurses, dietitians and physiotherapists as to how best to prepare for the proposed treatment. This multi-disciplinary input was considered to be best current practice and included nutritional, physical activity and smoking cessation advice.

Eligible patients were offered participation in the study, either the Intervention or Control arms, depending on their region of origin. Historical data reported no differences in clinical outcomes in patients from either region. Randomisation into treatment arms was considered at the outset however the exercise intervention was delivered by a collaborating institution within a single geographical area. As a result, the time and financial constraints for patients regularly travelling from the other region to receive the intervention was considered excessive. Clinical commissioning constraints also mandated a minimisation of travel to the centre from patients within this region. All surgery was performed at St Thomas’ Hospital, London.

Following informed and written consent to participation in the trial, patients undertook relevant baseline study procedures as per study protocol (figure 1). Instruction on physical activity during NAC was provided by a registered specialist Physiotherapist to all patients attending a regular surgical-oncology clinic at St Thomas’ Hospital, London. In addition, a structured exercise training programme was given to the Intervention group, by a specialist Exercise Physiologist, at the Centre for Health and Human Performance (CHHP) in London. The exercise intervention or ‘prehab’ programme undertaken during NAC, was based on a ‘moderate intensity’ programme in line with WHO, UK Chief Medical Officer Physical Activity and Macmillan ‘Recommended levels of physical activity for adults aged 18–64 years, ‘also relevant to healthy adults aged 65 and above’, unless contraindicated’ guidelines, incorporating combined aerobic and strength training.12 13 ‘Moderate intensity’ was prescribed using a modified Rating of Perceived Exertion of 4–5 (the modified scale has a range from 0 to 10, with 0 being no exertion and 10 being maximum effort). Prescribing exercise intensity in this way enables the patient to self-monitor intensity when exercising at home. Patients received training sessions at each monitoring point and were encouraged to attend additional sessions at CHHP. They were also provided with written and diagrammatic instructions on how to continue the exercise programme at home. Patients were not withdrawn from the Intervention arm if they failed to comply with the exercise programme. Similarly, no restrictions on physical activity were imposed on the Control group.

According to protocol, baseline trial measures were repeated within 1 week of completion of NAC. Patients were then reviewed in the UGI MDM for suitability for surgery. A third set of trial evaluations were carried out within a week preceding surgery.

**Oncological and surgical treatment**

Oncological practices within the two regions were very similar. At the commencement of the study, perioperative treatment with epirubicin, cisplatin and five fluorouracil (ECF)
or epirubicin, oxaliplatin and capecitabine (ECX) were considered to be the first choice regimens. Both incorporated three cycles of chemotherapy before and after surgery. With the publication of the FLOT trial, oncological practice in both regions changed simultaneously to four cycles of preoperative and postoperative fluorouracil plus leucovorin, oxaliplatin and docetaxel (FLOT). The study protocol accommodated this change in practice. Dose reductions were recorded prospectively. Oesophagectomy included transthoracic and transthoracic resections at the discretion of the individual surgeon, taking into account both patient and tumour characteristics.

**Outcome measures**

Trial end-points such as clinical outcomes, cardiovascular fitness parameters and health-related quality of life will be reported elsewhere. This study focused on the relationship between exercise and measures of chemotherapy response.

**Pathological analysis**

Pathological outcomes were recorded using the Royal College of Pathologists guidelines. All postoperative histopathology was undertaken by a group of specialist UGI Pathology Consultants at Guy’s and St Thomas’ NHS Foundation Trust. Histological regression utilised a categorical scoring system based on the proportion of fibrosis to residual tumour as originally described by Mandard (Mandard Tumour Regression Grade, MTRG). This measure of tumour regression following chemotherapy has been shown to be prognostic in oesophageal cancer patients and is recommended as part of standard histopathological reporting in the UK. Lymph node regression scoring (LNRS) similarly categorised each lymph node by allocating a score based on fibrosis and viable tumour with the best score per patient being recorded. For both primary tumour and lymph node regression, a score of 1–3 was classified as a responder (score 1 no residual tumour, score 3 more than 50% fibrosis) whereas a score of 4–5 was deemed a non-responder (score 4 more than 50% viable tumour, score 5 viable tumour with no evidence of response). Alternative classifications have been proposed in the literature (eg, MTRG 1–2 vs 3–5) and these were also analysed.

**Tumour downstaging**

Downstaging was defined as a patient in whom the pathological TNM stage (ypTNM) was less advanced than the clinical TNM staging (cTNM) at diagnosis, subdivided into T, N and combined categories.

**Body composition**

CT scans of the thorax and abdomen were performed routinely on all patients at Baseline and following NAC. Axial images from these staging scans were processed to assess changes in body composition (fat and muscle). In each participant, axial images equivalent to a 10 mm z-axis stack were sampled at the level of the third Lumbar vertebra. Following Hounsfield unit thresholding and automated segmentation of subcutaneous and visceral fat and muscle (FATS software, King’s College London) parameters including Fat-to-Muscle Ratio (FMR), Fat Free Mass Index (FFMi) and FMi were assessed. Immunity and inflammatory markers were assessed for changes and compared between the two cohorts. T lymphocyte subsets, CD3, CD4 and CD8, were measured using flow cytometry on a Beckman Coulter AQUIOS flow cytometer. Groups of cytokines—lymphokines, interferons, haemopoietic and non-haemopoietic growth factors, measured on a RANDOX Evidence Investigator, were analysed using Competitive and Sandwich antibody, chemiluminescent, biochip immunoassays.

Due to the impact of COVID-19 on laboratory facilities during the latter part of the study period, data on body composition and inflammatory markers was only available for 27 patients. (Intervention n=13; Control n=14). Similarly LNRS availability was limited (Intervention n=12; Control n=13).

**Statistical analysis**

Study sample size calculations were based on clinical outcome measures including a reduction in postoperative complications and hospital length of stay. χ² and Fisher’s exact tests were used to analyse categorical data, the latter being used when the frequency of variables was low. The Mann-Whitney U test was used for comparison of non-normally distributed continuous data. Logistic regression analysis provided ORs with 95% CIs (crude and adjusted) for the likelihood of responder status (primary outcome), according to the study exposure (exercise Intervention vs Control). Following causal directed acyclic graph assessment (figure 2), analyses adjusted for chemotherapy regimen (ECF/ECX vs FLOT) and chemotherapy delivery (full vs dose reduction). Other factors, such as age, sex, tumour stage and functional status, that would be considered confounders in models assessing survival were not included as there was no evidence that they would directly affect chemotherapy response.

**RESULTS**

**Patient demographics**

This analysis included 21 patients in the Interventional group and 19 patients in the Control group who had completed the perioperative treatment pathway and were in follow-up. One patient in each group was unsuitable for surgery after NAC and results for these patients included baseline and post-NAC parameters but no postoperative outcomes. All patients completed the prescribed chemotherapy with four patients in...
the Invention arm and two patients in the Control arm having dose reductions or a delay during treatment. At diagnosis, there were comparable baseline demographics of age, sex and tumour characteristics between the two groups (table 1).

**Primary tumour regression**

MTRG of the primary tumour was significantly improved in the exercise group using both definitions of responders vs non-responders (MTRG 1–3 Intervention n=15/20 (75%), Control n=7/19 (36.8%), p=0.025 and MTRG 1–2 Intervention n=7/20 (35%), Control n=1/19 (5.3%), p=0.044) (table 2). Similarly, crude MTRG 1–3 (Intervention OR 6.50; 95% CI 1.60 to 26.40); MTRG 1–2 (Intervention OR 12.00; 95% CI 1.32 to 108.67) and adjusted logistic regression analysis MTRG 1–3 (Intervention OR 6.57; 95% CI 1.52 to 28.30); MTRG 1–2 (Intervention OR 17.90; 95% CI 1.73 to 185.40) demonstrated significantly improved tumour regression in the exercise group (tables 2 and 3).

### Table 1  Patient demographics

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<th>%</th>
<th>Control group</th>
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BMI, body mass index; COPD, chronic obstructive pulmonary disease; NOGCA, National Oesophago-Gastric Cancer Audit; TNM, tumour node metastasis.
Four patients in the Intervention group and five patients in the Control group had negative lymph nodes with no evidence of prior tumour involvement. Of the remaining patients, those in the Intervention group had a non-statistically significant higher rate of lymph node regression using both definitions of responders versus non-responders (LNRS 1–3 vs 4–5 Intervention n=4/8 (50%) vs Control n=2/8 (25%) p=0.608; LNRS 1–2 vs 3–5 Intervention n=4/8 (50%) vs Control n=1/8 (12.5%) p=0.282). Using an alternative classification (worst response per patient) as proposed prior to commencement of the study, showed an improvement in lymph node regression in the Intervention group (Intervention n=4/8 (50%) vs Control n=0/8 (0%) p=0.077). (table 2)

**Lymph node regression score**

Downstaging

The patients in the Intervention group had evidence of improved CT-based downstaging for T Stage (downstaged Intervention n=14 (66.7%) vs Control n=6 (31.6%), p=0.056; OR 4.33...
Body composition

Patients in the exercise Intervention group had an improved median FMR of $-7.15\%$ after prehabilitation, with increases in skeletal muscle and decreases in visceral and subcutaneous fat areas compared with baseline scans, while remaining weight stable. The Control group, who were already in the overweight category at diagnosis, increased FMR by $+12.4\%$ with overall weight gain, associated with increased visceral and skeletal fat, and reduced muscle mass.

FFMi and FMI, normalised for patient height and weight, also improved in the Intervention group (median FFMi improvement of $+2.3\%$ vs $-1.9\%$ Control, $p=0.03$). There was a corresponding reduction in overall fat mass in the Intervention group, especially visceral fat (median FMI improvement of $-3.8\%$ Intervention vs $+0.7\%$ Control, $p=0.689$) (figure 3).

Inflammatory and immunity markers

Online supplemental tables 5 and 6 summarise the changes in inflammatory and immune markers after NAC. The Intervention group exhibited significantly higher median T lymphocyte counts post-NAC compared with the Control group (CD-3: 1681.2 vs 981.08, $p=0.03$; CD-8: 29.41 vs 0.98, $p=0.03$).

Following NAC, IL-6 levels increased in both groups (Intervention 27.9% vs Control 126.4%; $p=0.04$). TNFa levels reduced in the Intervention group compared with an increase in the Control group (Intervention $-2.4\%$ vs Control $+28.3\%$, $p=0.25$). IFN-γ increased in both groups (Intervention $15.3\%$ vs Control $27.24\%$, $p=0.36$). MCP-1 increased more in the Control group (Intervention $+52.1\%$ vs Control $+169.7\%$, $p=0.09$) (figure 4).

DISCUSSION

The results from this prospective trial suggest there may be novel and important clinical benefits of a structured exercise programme during NAC for oesophageal adenocarcinoma. Prehabilitation in this patient group appears to be able to respect the limitations imposed on patients by chemotherapy schedules. Perhaps most importantly there is some evidence, although in a small group of patients, of improved pathological, radiological and immunological responses to chemotherapy in the exercise Intervention group.

Some methodological issues merit consideration. This study, while prospective, was not formally randomised for the reasons outlined above, which introduces the risk of confounding. However, the geographical regions were similarly sized with comparable oncological practices. Many aspects of patient care were consistent, such as MDM decision making, the location of surgery and pathological analysis, all of which occurred at one central site. As patients were all deemed to be oncologically suitable and physically fit enough to tolerate NAC and surgery prior to inclusion in the study, heterogeneity between the groups was reduced. Therefore, as expected, demographics and staging at diagnosis were very similar, although some non-significant differences in the groups were observed, such as a higher body mass index in the Control group. Some changes in practice occurred following commencement of the study such as the adoption of the ‘FLOT’ regimen as first choice chemotherapy. Numerous other prospective trials have also adapted to this by adjusting their protocols. While the proportions of patients receiving FLOT differed slightly between the groups, this was adjusted for in the analysis. However, the possibility of unmeasured confounding remains in studies of this kind. The study numbers were relatively small, lacking statistical power, and therefore susceptible to sparse-data bias. Nonetheless, some statistically significant differences in the groups were observed particularly with regards to pathological tumour regression, immunological markers and body composition. While these findings are certainly of clinical interest, they need to be interpreted with some caution pending validation in larger studies.
Tumour downstaging and response to chemotherapy are arguably the most important prognostic factors in oesophageal cancer. A high proportion of patients undergoing oesophagectomy have evidence of micrometastases at the time of surgery and the introduction of NAC has been associated with improvements in survival, cancer recurrence and systemic control. Nonetheless, a significant proportion of patients do not respond to chemotherapy and these patients have poorer outcomes. Oesophageal cancer, because of its neoadjuvant treatment strategy and established pathological methods of quantifying tumour regression, is an ideal tumour group on which to examine hypotheses of exercise-related chemotherapy response. That structured exercise programmes might contribute to improved cancer regression, possibly through enhanced immunological and/or inflammatory modulation, is potentially clinically significant. The results from this analysis, showing improvements in pathological regression in the primary tumour and clinical downstaging are hypothesis generating and the first to be demonstrated in a clinical trial in oesophageal cancer. The results also concur with an increasing body of evidence supporting exercise in animal cancer models.

Differences in some of the other study outcome measures may provide some potential mechanisms for the observed improvements in chemotherapy response. However, these interactions are likely to be complex and must be considered theoretical at this stage. The Intervention group exhibited significantly higher median T lymphocyte counts (CD-3 and CD-8) than the Control group suggesting improved adaptive immune function and tumour-cell destruction capability, despite immunosuppressive chemotherapy. Following NAC, IL-6 levels increased significantly more in the Intervention group than the Control group, which has been proposed to have a tumour-suppressive role, increased in both groups but significantly more so in the Intervention group. MCP-1 increased more in the Control group and is believed to regulate the tumour cell and macrophage cell cycles, potentially having a role in promoting tumour progression. Patients undertaking a structured exercise programme during NAC improved muscle mass compared with the Control group. This might be particularly relevant in an age-associated condition, such as oesophageal adenocarcinoma, in which sarcopenia is prevalent. Sarcopenia, obesity and sarcopenic obesity, are associated with cancer development and progression in general. NAC for oesophageal adenocarcinoma is frequently associated with sarcopenia. In this trial, a reversal of sarcopenia and sarcopenic obesity was observed in patients undertaking the exercise intervention. Analysis of body composition demonstrated that these patients experienced reduced overall Fat Mass—both subcutaneous and visceral—and reduced FMR, while largely maintaining body mass. Conversely, there was an increase in overall Fat Mass, but particularly visceral fat in the Control group, which has been associated with inflammation and immunosuppression in patients with cancer.

Patient fitness is an important component of clinical decision-making in oesophageal cancer. Patients undergoing multimodality treatment experience the cumulative physiological insults of chemotherapy and major surgery. Patients who are deemed unable to tolerate such deconditioning treatment may be offered a less radical therapeutic approach. While not directly related to the outcome measures of this study, results from this trial suggest that a structured exercise intervention ameliorates some of this treatment-related deconditioning and improves body composition. This potentially increases the choices for radical treatment in a greater number of patients with cancer.
CONCLUSION
In conclusion, the initial results of this prospective clinical trial are the first to suggest a possible association between a structured exercise programme (prehabilitation) and improved chemotherapy response in oesophageal cancer. Numerous biochemical and CT-based parameters differed between the Intervention and Control groups, suggesting reduced inflammation, improved immune function and improved body composition in the Intervention group. These may represent some of the potential mechanisms by which the chemotherapy response may have been enhanced. While the limitations in patient numbers and non-randomised design mandate caution, the impact for patients is potentially significant. Further work to confirm or refute these findings is urgently required including whether or not improvements in chemotherapy response may translate into a survival advantage. Pending this, the present results further strengthen the rationale for exercise to be prescribed as standard care in patients undergoing treatment for cancer.

What are the findings?
- First reported pathological evidence in humans with oesophageal cancer that exercise may enhance tumour regression during chemotherapy.
- Exercise prehabilitation during neoadjuvant chemotherapy appears beneficial to pathophysiological, immunity and inflammatory markers.
- Reversal of sarcopenia and sarcopenic obesity in patients undertaking exercise intervention during chemotherapy.

How might it impact on clinical practice in the future?
- Studies assessing the potential benefits of prehabilitation should now include measures of chemotherapy response in their study protocols.
- Strengthens the argument for prehabilitation being the standard of care for all patients undergoing cancer treatment, not just those on a surgical pathway.
- The translational mechanistic relationships between exercise and chemotherapy response need to be interrogated further.

Drafted or revised the manuscript. 3. Approved the final version. 4. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JZ, GPW, KB, JP, ASO, LG-A, NM, JW, JT, JL, MG, MK, CB, MVH, VG, JG, MB, AD contributed to 1, 2, 3, 4 above. 5. Guarantor, AD. Further contributors are listed under Acknowledgements.

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Competing interests
None declared.

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Data are available on reasonable request. Data reported may be requested by contacting the corresponding author.

Supplemental material
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