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Feasibility, tolerability, and effects of exercise-based prehabilitation after neoadjuvant therapy in esophagogastric cancer patients undergoing surgery: an interventional pilot study

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ABSTRACT

Patients requiring surgery for locally advanced esophagogastric cancer often require neoadjuvant therapy (NAT), which may have a detrimental impact on cardiorespiratory reserve. The aims of this study were to investigate the feasibility and tolerability of a 5-week preoperative high-intensity interval training program after NAT, and to assess the potential effects of the training protocol on exercise capacity, muscle function, and health-related quality of life (HRQL). We prospectively studied consecutive patients with resectable locally advanced esophageal and gastric cancer in whom NAT was planned (chemo- or chemoradiotherapy). Feasibility was assessed with the TELOS (Technological, Economics, Legal, Operational, and Scheduling) components, and data on exercise tolerability (attendance and occurrence of adverse or unexpected events). Exercise capacity was assessed with peak oxygen uptake (VO_{2peak}) in a cardiopulmonary exercise test at baseline, post-NAT, and following completion of a high-intensity interval exercise training (25 sessions). Changes in muscle strength and health-related quality of life (HRQL) were also assessed. Of 33 recruited subjects (mean age 65 years), 17 received chemoradiotherapy and 16 chemotherapy. All the TELOS components were addressed before starting the intervention; from a total of 17 questions considered as relevant for a successful implementation, seven required specific actions to prevent potential concerns. Patients attended a mean of 19.4 (6.4) exercise sessions. The predefined level of attendance ($\geq$15 sessions of scheduled sessions) was achieved in 27 out of 33 (81.8%) patients. Workload progression was adequate in 24 patients (72.7%). No major adverse events occurred. VO_{2peak} decreased significantly between baseline and post-NAT (19.3 vs. 15.5 mL/Kg/min, $p<0.05$). Exercise led to a significant improvement of VO_{2peak} (15.5 vs. 19.6 mL/kg/min, $p<0.05$). Exercise training was associated with clinically relevant improvements in some domains of HRQL, with the social and role function increasing by

10.5 and 11.6 points, respectively and appetite loss and fatigue declining by 16 and 10.5, respectively. We conclude that a structured exercise training intervention is feasible and safe following NAT in patients with esophagogastric cancer, and it has positive effects to restore exercise capacity to baseline levels within 5 weeks with some improvements in HRQL.

Word count: 340

KEYWORDS: Feasibility; tolerability; prehabilitation; esophagogastric cancer; neoadjuvant therapy; high intensity interval training

INTRODUCTION

Multimodality treatment involving combined chemoradiation or perioperative chemotherapy has become the standard of care for resectable locally advanced esophagogastric cancer.[1] Potentially curative surgical resection for esophageal and gastric cancer is associated with significant morbidity and mortality.[2] Malnutrition, sarcopenia and anemia, commonly present in patients with esophagogastric cancer at diagnosis, as well as the deleterious effects of the neoadjuvant treatment (NAT) may impair physical fitness and negatively influence on surgical outcomes.[3]

Cardiopulmonary exercise testing (CPET) provides an objective assessment of the patients´ ability to tolerate the increased metabolic demands and oxygen consumption associated with surgery.[4] Peak oxygen uptake (VO_{2peak}) and oxygen uptake at anaerobic threshold (AT) are two measurements derived from CPET that have been used for risk stratification prior to major elective surgery.[5] Previous studies have shown a reduction in exercise capacity following either chemotherapy[6,7] or chemoradiotherapy[8] in patients undergoing esophagogastric cancer surgery. Data from Navidi *et al.*[7] suggest that the observed reduction in AT and VO_{2peak} following chemotherapy does not improve spontaneously during the 4 weeks between completing the NAT and surgical intervention.

The role of adding an exercise training intervention to improve or restore cardiopulmonary reserve preoperatively has been proposed in order to potentially reduce the incidence of postoperative complications.[9] There is, however, limited data on the effect of exercise training programs (prehabilitation) to counteract the detrimental effects of neoadjuvant therapy while the patient is awaiting surgical resection.[10-12] West *et al.*[11] reported that cardiopulmonary fitness could be improved rapidly within the first 3 weeks after starting a 6-week (three sessions per week) high-intensity interval training (HIIT)

program in rectal cancer patients receiving chemoradiotherapy. Nowadays there is lack of information on the feasibility and potential benefit of a preoperative HIIT program to reverse the deleterious effects of NAT on cardiopulmonary fitness in patients with esophageal and gastric cancer.[13] In addition, the impact of these programs on health-related quality of life (HRQL) in this group of patients is unknown.

The main objectives of this prospective pilot study were firstly to assess feasibility and tolerability of implementing a 5-week exercise intervention aimed to return fitness levels to those pre-NAT in patients with locally advanced esophagogastric cancer before surgery, and secondly to explore its effects on exercise capacity, muscle function, and HRQL.

MATERIAL AND METHODS

Patients and study design

This was a prospective pilot interventional study conducted according to standards of good clinical practice and approved by the local Ethics Committee (REC approval: 2013/50497/I) of a university tertiary hospital in Barcelona (Spain). Written informed consent was obtained from all patients. Between September 2016 and December 2018, we recruited all consecutive patients referred to the Upper Gastrointestinal Cancer Multi-Disciplinary Team, with resectable locally advanced cancer of the esophagus, gastroesophageal junction (GEJ) and stomach (cT3-4 regardless N status),[14] in whom NAT was planned. Exclusion criteria were musculoskeletal disorders precluding CPET or bicycle exercise, and evidence of disease progression after completion of NAT. At entry to the study, baseline characteristics (age, sex, smoking history, tumor characteristics, comorbidities, performance status and nutritional status) were collected. Comorbidities and performance status were assessed with Charlson index and the Eastern Cooperative Oncology Group (ECOG) performance score, respectively. All patients were staged with endoscopy and biopsy, computed tomography (CT) of the chest and abdomen, endoscopic ultrasound examination and positron emission tomography (PET-CT). Staging laparoscopy was used selectively for GEJ and gastric cancer.

NAT consisted of either chemoradiotherapy or perioperative chemotherapy. The standard choice of NAT for esophageal and GEJ cancer was chemoradiotherapy based on the CROSS regimen.[1] Perioperative chemotherapy regimens for gastric cancer comprised three different schemes during the study period: MAGIC protocol (3 preoperative cycles of epirubicin, cisplatin and 5-fluorouracil), FNCLCC protocol (3 preoperative cycles of cisplatin and 5-fluorouracil) and more recently, the FLOT scheme (5-fluorouracil,

oxaliplatin and docetaxel).[1,15,16] NAT-associated toxicity events were graded according to the National Cancer Institute Common Terminology Criteria (version 4.0), and acute radiation-induced skin toxicity using the Radiation Therapy Oncology Group scoring system.[17,18] All patients were restaged following NAT with endoscopy and CT. Esophagectomy or gastrectomy was scheduled 6-8 weeks after completion of NAT.

All patients were screened for malnutrition at baseline and preoperative. The evaluation of nutritional status included: body mass index, unintentional weight loss and the Subjective Global Assessment (SGA).[19] Nutritional therapy was individualized and initiated based on the nutritional status and the ability to meet caloric-protein requirements (CPR). All patients received nutritional counselling by a trained dietitian and in accordance with the current recommendations.[20] Patients covering ≥75% of their CPR received dietary advice; those covering 50-75% of their CPR were prescribed oral nutritional supplements (ONS); if intake was <50% of their CPR, enteral tube feeding (surgical jejunostomy) was initiated. Those who presented with malnutrition at diagnosis (BMI <18.5kg/m^2, weight loss >5% over 3 months or >10% over 6 months or SGA Grade B-C) received medical nutrition therapy (ONS or enteral nutrition -EN-) regardless of their ability to meet CPR.

Exercise intervention

The exercise intervention was scheduled during the window period between completion of NAT and surgery and was conducted in the Rehabilitation Department. The Template for Intervention Description and Replication (TIDieR) checklist was used to describe the exercise intervention.[21] Planned strategies to improve attendance to the intervention protocol consisted of: comprehensive information on the benefits of exercise was provided by the surgeon, and reinforced by the physical therapist during the training

sessions; moreover, patients who missed one session, the case manager contacted with them to detect and resolve eventual barriers to the exercise program. The exercise protocol consisted of a combination of two exercise modalities: interval training and respiratory muscle training (25 one-hour sessions, 5 times per week, 5 weeks). High-intensity interval training (HIIT) was performed on an ergometric bicycle and consisted of a warm-up period [5 min of cycling at 30% workload peak (W_{peak})] and exercise period (40 min of cycling, combining 1 min at high work rate, 80%W_{peak}, with 2 min at 40%W_{peak}), followed by a cool-down period (5 min of cycling at 30% W_{peak}). The rate of pedaling during the sessions was kept at 55-65 rpm. All sessions were supervised by an expert physiotherapist with continuous heart rate and pulse oximetry monitoring. The progression of the workload during the sessions was adjusted according to the patient's tolerance (Borg perceived effort scale).[22] Inspiratory and expiratory muscle training (IEMT) consisted of 5 sets of 10 repetitions followed by 1-2 min of unloaded recovering breathing (off the device), twice a day, 5 days per week, for 5 weeks, using a respiratory muscle trainer (Orygen Dual®, Forumed, Spain).[23] Respiratory training loads were adjusted weekly to the inspiratory and expiratory pressures which allowed patients to perform 10 consecutive maximal repetitions (10RM).[24,25] The IEMT sessions were performed 2 times per day (one after the interval training at the hospital, and the other unsupervised at home).

Measurements

Feasibility

Feasibility of the procedure was assessed with the technological, economic, legal, operation, and scheduling (TELOS) components, adapted from previous studies.[24,25] For the purpose of this intervention, the research team agreed which specific points should be considered for each TELOS component; 17 yes-no questions with their expected answers

were agreed. The procedure was considered feasible if all the answers were those expected, and otherwise, actions were taking to resolve these eventual problems.

Tolerability

In addition to the conventional exercise-related tolerability variables (lost to follow-up defined as the number of patients not completing the follow-up assessments), and attendance (number of attended sessions), other tolerability variables adapted from oncology drug trials[26] were registered: permanent discontinuation of aerobic training prior to week 24, treatment interruption (missing ≥3 consecutive sessions), exercise dose modification (number of patients requiring dose modification), number of sessions requiring early termination, and rescheduling of missed sessions. Attendance was categorized in patients who attended at least 15 of the 25 scheduled sessions and those who did not. Safety was evaluated by the frequency of major and minor events occurring during any supervised HIIT session (patient discomfort during the procedure, and occurrence of adverse or unexpected events).

Exercise capacity

Exercise capacity was measured by standardized incremental CPET.[27] CPET data were reported blind by one experienced investigator. Pulmonary gas exchange and ventilatory measurements were obtained from calibrated signals derived from rapid response gas analyzers and a mass flow sensor. Oxygen uptake (VO_2), pulmonary carbon dioxide output, minute ventilation, and respiratory exchange ratio were also registered during each respiration. Heart rate (HR) was determined using 10-lead online electrocardiogram and oxygen saturation by pulse oximetry (SpO_2). After 2 min of breathing at rest, subjects pedaled in an electrically braked cycloergometer (Ergoline Ergometrix 900, Uberprüfung, Germany). An integrated computer recorded cardiorespiratory variables during the test (Ultima, MedGraphics Corporation, St. Paul, MN, USA). Patients were encouraged to

continue until they could no longer sustain the target pedaling frequency. Exercise capacity was also estimated with the 6-min walk test (6MWT) according to the American Thoracic Society (ATS) recommendations.[28] Briefly, participants were asked to walk in a flat, straight, 25 m walking course supervised by a physiotherapist. HR and SpO_2 were measured using a pulse oximeter. A modified Borg scale was used to quantify the levels of dyspnea and legs discomfort.[22]

Pulmonary and muscle function

Forced spirometry, static lung volumes and diffusion capacity for carbon monoxide (DL_{CO}) adjusted for hemoglobin (EasyOne, ndd Medical Technologies, Zurich, Switzerland and MasterScreen; Jaeger, Würzburg, Germany) were measured; spirometric reference values from a Spanish population were used.[29]

Respiratory muscle strength, defined as the ability to develop a brief maximal respiratory effort, was assessed through maximal inspiratory and expiratory pressures (PI_{max} and PE_{max}, respectively). The PI_{max} was measured at the mouth during a maximum effort from residual volume against an occluded airway. To determine the PE_{max}, patients performed a maximum expiratory effort from total lung capacity in the face of the occluded airway. The mouthpiece used in the maneuvers was connected to a pressure transducer. The higher value of three reproducible maneuvers (<10% variability between values) was used for analysis. Predicted values from the reference population were calculated.[30]

Function of peripheral muscles was estimated with maximum voluntary contractions of hand flexor (handgrip) and quadriceps muscles. Handgrip strength was assessed using a handheld dynamometer (JAMAR®). The maximum voluntary contraction of the flexor muscles of both dominant and non-dominant hands was assessed, and the highest value of three reproducible (<10% variability between values) maneuvers was used in the

analysis. Function of the quadriceps muscle was evaluated by muscle strength of the dominant leg during specific single leg exercises. Specifically, muscle strength was assessed through quadriceps isometric maximum voluntary contraction (QMVC) of the dominant and non-dominant lower limb following the standard operating procedure of the ATS/European Respiratory Society (ERS) statement,[31] in which participants sit with knees and hips at 90º flexion, with both arms crossed in front of the chest The highest value from three brief (3 s) reproducible QMVC maneuvers (<5% variability between values) was included in the analysis. Strength was quantified by an isometric dynamometer (Biopac Systems) connected to a digital polygraph (Biopac Systems).

Health-related quality of life

Health-related quality of life (HRQL) was assessed with the European Organization of Research and Treatment of Cancer (EORTC) questionnaire (QLQ-C30), which is a 30-item questionnaire composed of multi-item scale and single items that reflects the multidimensionality of the quality of life in patients with cancer.[32] All responses were linearly transformed into scores from 0 to 100 to standardize the raw score. In the functional scales, high scores represent better quality of life (better function), whereas high scores in symptoms scales and items represent worse problems with symptoms. Mean scores and 95% confidence intervals (CIs) for HRQL were calculated at baseline, following the completion of NAT and after training. Changes of 10 or more points on a 0 to 100 scale were considered clinically relevant.[33]

All outcome variables related to exercise capacity, pulmonary and muscle function and HRQL were assessed three times throughout the study: baseline, post-NAT and post-training.

Sample size calculation

The change in VO_{2peak} before and after training was the outcome variable used to estimate the sample size. Based on a previous study with 16 patients in which the training program resulted in a 19% increase of VO_{2peak},[34] and accepting a significance level of 0.05 and a power of 90% to detect variations pre-to-post of 20%, the estimated sample size was 26 patients (method of approximation of the arc sine, GraphPad StatMate v. 2.0, CA, USA). Anticipating 30% of losses, the final sample size was estimated to be 40 patients.

Statistical analysis

The normality of continuous variables was assessed by the Kolmogorov-Smirnoff test. Variables not following the normal distribution were reported as median and interquartile range (IQR) whereas the normally distributed were reported as mean and standard deviation (SD). Categorical variables were reported as absolute numbers and frequency (%). Paired double tailed Student t-test or Wilcoxon test were used as appropriate to determine the change in variables as a result of NAT or training. All results were considered statistically significant at the 5% critical level. All statistical tests were performed using SPSS version 20.0 (Chicago, IL, USA).

RESULTS

Participant characteristics

During the study period, from 40 consecutive patients, 7 were excluded because of evidence of disease progression during NAT (n= 4), complications of the primary tumor during NAT requiring urgent surgery (n= 2), and musculoskeletal problems limiting the use of the cycle ergometer (n= 1). Baseline data of the 33 patients included in the study are shown in **Table 1**. After baseline nutritional assessment, 15 patients (45.5%) were given dietetic counseling, 6 patients (18.2%) received ONS and 12 patients (36.4%) required EN through the jejunostomy tube. The number of patients classified as mildly to

moderately malnourished (SGA B) or severely malnourished (SGA C) decreased from 18 (54.5%) at baseline to 4 (12%) at the end of the exercise training.

Feasibility

The **TELOS components** were assessed before baseline assessments started. From the 17 questions considered as relevant, 7 answers were unexpected or unknown, and their contents were specifically approached. The required equipment to conduct all the assessments and the intervention were available in the Respiratory Diseases, Endocrinology, and Rehabilitation departments. Professionals from these fields were invited and accepted to participate in the study. The implementation of the project did not require infrastructure investment, but three assessments per patient were highly time-consuming, especially for CPET. Operational needs required to extend the team composition of the Upper Gastrointestinal Cancer Multi-Disciplinary Team and reorganize the clinical pathway of patients with resectable locally advanced cancer. The project was perceived as an opportunity to improve outcomes in these patients, and none of the involved professionals expressed resistance to change. The main concerns were related to the TELOS Scheduling component. A case manager was appointed for complying with the established timeframe, which resulted in constant communication between all the involved parts. **Table 2** summarizes the 17 yes-no questions included in the TELOS components with their expected and real responses, as well as the actions conducted to anticipate eventual barriers in the implementation process.

Tolerability

Exercise-related tolerability variables are described in **Table 3.** Patients attended a mean of 19.4 (SD 6.4) of the 25 scheduled supervised exercise sessions, and 27 out of 33 (81.8%) patients achieved the predefined level of attendance (a minimum of 15 of the 25

scheduled sessions). After two weeks of training, two patients voluntarily stopped the exercise program; reasons for missing sessions of the rest were related to organizational issues (transportation issues and outpatient appointments). Workload progression was adequate in 24 patients (72.7%). No major adverse events were observed, but minor events such as excessive fatigue (n= 4), lower limbs pain (n=1), nausea (n=2), anxiety (n=1) and exercise-associated hypotension (n=1) were reported in 9 patients. Modifications of the exercise intervention during the study were not required.

Effect of NAT on exercise capacity and pulmonary function

The median duration of NAT was 36 days (IQR 31-53 days). Some degree of NAT related toxicity was observed in all patients, with nine of them requiring dose reduction but completing 75% of the treatment course. Eight patients (24.2%) developed grade 3/4 toxicity with neutropenia being the most common in 6 patients. The median time from the final of NAT to post-NAT CPET was 9 days (IQR 5-33 days). There was a significant decline in all CPET derived variables between baseline and post-NAT CPET (**Table 4**). A separate analysis was also performed to determine the changes in CPET variables based on the development of NAT-related toxicity and treatment modality (chemoradiotherapy *versus* chemotherapy). Baseline CPET variables, specifically workload and VO_{2peak}, were significantly lower in patients presented with grade 3/4 neoadjuvant therapy toxicity compared with patients with low toxicity (grades 1/2). These statistically significant differences were also observed at the post-NAT and post-training periods (**Figure 1**). There were no significant differences in workload and VO_2 at peak between the two main NAT groups (chemoradiotherapy vs. chemotherapy) (data not shown). A significant drop in corrected DL_{CO} from 80.3% to 74% ($p< 0.05$) was observed after NAT. No significant changes however were observed for FEV_1 and FVC during the study.

Effect of physical training on exercise capacity and muscle function

Table 4 shows the study outcomes at baseline, post-NAT and post-exercise intervention periods. At study completion, patients had restored (or even improved) exercise capacity in terms of VO_{2peak} and workload, as well as of distance improvement in the 6MWT when compared with baseline and post-NAT values. A significant improvement in inspiratory and expiratory muscle strength, but no significant differences in peripheral muscle strength were detected.

Changes in quality of life

Changes in the HRQL measures after NAT and following the HIIT are summarized in **Table 5**. Following NAT, patients reported a decrease in social function (-9.3) and experienced a clinically significant increase in fatigue (+10.1) and concern about their financial situation (+11.9). After completing the exercise program patients reported significant improvements in the social and role functions (+10.5 and +11.6, respectively). There was also a significant reduction of appetite loss (-16) and fatigue (-10.5).

DISCUSSION

This study shows the feasibility of implementing exercise-based prehabilitation to reverse the deleterious effects of NAT on cardiorespiratory fitness in patients with esophagogastric cancer before undergoing surgery. The intervention was well tolerated and lead to significant improvements in exercise capacity in patients with both low and high-grade neoadjuvant toxicity.

Medical evidence indicates that neoadjuvant treatments can lead to reduced cardiorespiratory fitness due to their effects on both cardiovascular and respiratory systems, treatment-associated anemia, cellular and mitochondrial metabolism leading to further oxidative stress, treatment-related fatigue and reduced physical activity levels.[35] Results of previous studies in patients with esophagogastric cancer have shown that neoadjuvant therapy is associated with marked reductions in exercise capacity as measured by CPET.[3,6-8] Our data support previous findings and identify a significant reduction in CPET-derived variables following NAT. Both neoadjuvant chemotherapy and chemoradiation have a similar negative impact on CPET variables. Similarly, Thomson *et al.*[8] identified 14.6% and 14.4% reduction in oxygen uptake at anaerobic threshold in patients with esophageal cancer receiving chemotherapy and chemoradiation, respectively.

Two previous studies suggested that the decline in exercise capacity did not reverse throughout the period following NAT and before surgery.[7,11] Only a limited number of studies have evaluated the effect of exercise training interventions using CPET in patients with gastrointestinal cancer receiving NAT to restore physical fitness.[10,11] West *et al.*[11] demonstrated that a 6-week (18 sessions) responsive exercise training program improves objectively measured physical fitness (a 2.65 mL/kg/min recovery of maximal oxygen

consumption) in patients undergoing rectal cancer surgery after neoadjuvant chemoradiation. The present study shows that a HIIT was effective, regardless of the presence of high-grade neoadjuvant toxicity. This regain in cardiopulmonary fitness has clinical implications, since it may change postoperative risk.[4]

The design of our supervised HIIT program originally considered 5 sessions per week over a 5-week period assuming that due to unplanned organizational problems (outpatient appointments), some patients would miss some sessions but completing at least more than 15 training sessions. Indeed, attendance was fairly good with 19.4 sessions before surgery (81.8% completing ≥15 sessions), which exceeds the minimum number of sessions recommended in the literature.[35] The inclusion of respiratory muscle training as an add-on exercise intervention to interval training was based on medical evidence: a systematic review and meta-analysis of randomized or quasi-randomized controlled trials including 295 patients conclude that preoperative inspiratory muscle training significantly improves respiratory muscle function in the early postoperative period and reduces the risk of postoperative respiratory complications following cardiothoracic and upper-abdominal surgery.[37] A recent study conducted by our group concluded that aerobic exercise combined with IEMT lead to improvements on exercise capacity and respiratory muscle strength.[23] West *et al.*[34] showed that only 3-week (9 sessions) preoperative HIIT are enough to significantly increased cardiorespiratory capacity.

The importance of the nutritional support should not be underestimated. The prehabilitation strategy in this study was bimodal combining exercise training and nutritional counselling and optimization as needed. Indeed, the nutritional status of the patients improved significantly over the study period. Research work investigating combined exercise training and nutritional interventions in patients with gastroesophageal cancer receiving NAT is ongoing.[38] Two randomized controlled trials have recently

investigated the efficacy of a prehabilitation program (home-based exercise training and nutritional intervention) during NAT in patients with esophageal cancer (77% and 100% with NAT, respectively) where physical function was assessed by 6MWT.[12,39] Both studies reported improved functional capacity and lesser weight loss in the prehabilitation group.

One aspect that has not been fully evaluated is the effect of exercise interventions and prehabilitation programs on HRQL. We demonstrated improvements in some domains such as the role and social, as well as a decrease in fatigue and inappetence. Burke *et al*.[40] found that patients with rectal cancer undergoing an exercise program before surgery experience increased vitality, a positive attitude, social connections and a strong sense of purpose.

The training program was feasible and safe. The absence of clinically relevant adverse events supports the safety and applicability of the program in this group of patients who stand out for their fragility and functional deterioration. However, to assess the possible inclusion of a physical exercise training program of this magnitude in routine practice, it is necessary to carefully consider aspects such as the patient's baseline physical status and their motivation, easy access to facilities, the availability of adequate infrastructure and personnel to carry out a program of this type and health care costs. Future studies will clarify which subgroups of patients are most likely to obtain the greatest benefits from supervised HIIT interventions.

This study has some limitations especially regarding the secondary aim. Firstly, the small number of recruited patients and the absence of a control group make difficult to quantify how much of the improvement is due to the intervention. In this respect, some might think that patient´s physical fitness restores back to baseline even without an exercise

intervention. However, Navidi *et al.*[7] reported that reduced exercise capacity following chemotherapy does not reverse during the window period between after completing the NAT and prior to surgical intervention. Secondly, the variability of the NAT with two different schemes of treatment (chemotherapy and chemoradiation) although this point may be compensated using the patient's own data as a baseline. However, strengths include its prospective design, the systematic use of CPET, the rigorous exercise intervention, and the assessment of quality of life. Moreover, differences observed between pre- and post-intervention could serve as a basis to perform a power calculation for a multicenter randomized clinical trial (RCT). According to our results and assuming similar differences in $VO_{2peak,}$ the estimated population for this RCT would be 82 patients per branch in a 1:1 distribution.

In conclusion, NAT before esophagogastric cancer surgery has a negative impact on exercise tolerance. A structured HIIT program is a feasible and well-tolerated intervention following NAT to be implemented in clinical practice. The findings of this pilot study suggest that HIIT could restore exercise capacity to baseline levels within 5 weeks, and results in some improvements in muscle function, nutritional status and HRQL.

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LEGENDS

Figure 1

Line diagram showing means and SD for (**A**) maximum workload (w) and (**B**) VO_2 at peak (ml/Kg/min) at baseline, post-NAT and post-training program for patients presenting with high toxicity (grades 3/4) and low toxicity (grades 1/2) during NAT (* $p<0.05$ vs. low toxicity group).

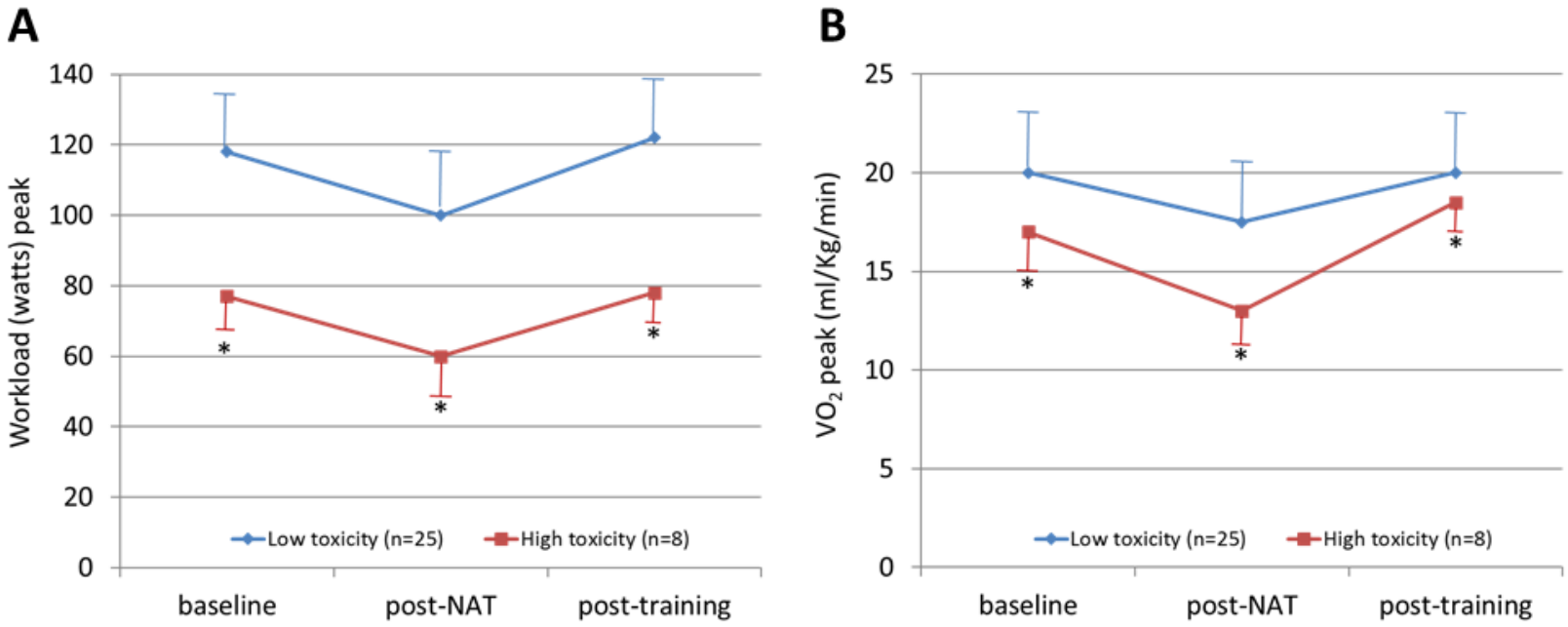

Table 1. Characteristics of the participants included in the study (n=33).

Age, years	65 (SD 12)
Gender	
- Men	26 (79%)
Smoking history	
- Active	3 (9%)
- Ever	16 (49%)
ECOG performance status	
- 0	14 (42%)
- 1	15 (46%)
- 2	4 (12%)
Charlson comorbidity index	
- 0	2 (6%)
- 1-2	10 (30%)
- ≥3	21 (64%)
ASA classification	
- I-II	18 (55%)
- III	15 (45%)
Body mass index, kg/m^2	25.9 (SD 4.2)
Weight loss ≥ 10%	13 (39%)
Subjective Global Assessment	
- A	15 (46%)
- B	13 (39%)
- C	5 (15%)
Site of tumor	
- Esophagus	8 (24%)
- Gastroesophageal junction	12 (36%)
- Stomach	13 (40%)
Neoadjuvant treatment regimens	
- Chemoradiotherapy (CROSS regimen)	17 (52%)
- Perioperative chemotherapy	16 (48%)

(*) ECOG, Eastern Cooperative Oncology Group; **ASA,** American Society of Anesthesiology; **CROSS**, ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study.

(*) Categorical variables are expressed with absolute number and percentages, and quantitative variables with mean and standard deviation (SD).

Table 2. Description of the technological, economic, legal, operation, and scheduling (TELOS) components and expected answers supporting the feasibility of the procedure.

Components	Questions to be considered	Expected answer	Real answer	Actions to anticipate eventual barriers in the implementation process
Technology	Is the required equipment available in the institution?	Yes	Yes	Not required
	Will we need third parties' dependencies?	No	**Yes**	To involve professionals from other fields (Respiratory Diseases, Rehabilitation, Endocrinology)
	Is staff properly trained to implement the intervention or will need to get skills in?	Yes	Yes	Not required
Economics	Are all the costs well-defined?	Yes	Yes	Not required
	Is the intervention expensive?	No	No	Not required
	Is an acceptable cost in terms of time?	Yes	**Unknown**	Three CPET assessments were planned in this pilot study; this point might be subject to change
Legal requirements	Does the new intervention conflict with legal requirements?'	No	No	Not required
	Have we ensured that we are following all the standards of good clinical practice?	Yes	Yes	Not required
Operational needs	Are all of the tasks properly defined?	Yes	Yes	Not required
	Are the involved third parties willing to participate?	Yes	Yes	Not required
	Do new teams have to be established?	No	**Yes**	To extend the multidisciplinary team
	Do we need to reorganize the processes?	No	**Yes**	To design a new clinical pathway prior to surgery
	Will there be staff resistance to the change?	No	**Unknown**	To discuss the views and wishes of all the parties involved
	Will there be costs in training?	No	No	Not required
Scheduling	Given our current experience, is the intervention realistic?	Yes	Yes	Not required
	Are there any timescale pressures to be met?	No	**Yes**	To designate a case manager to ensure compliance of the established timeframe
	Will the intervention be performed to led benefits for patients?	Yes	**Unknown**	To include a study subproject to assess potential benefits of the intervention

Table 3. Exercise-related tolerability and safety outcomes.

Outcome variables	**Sample (n= 33)**
Tolerability variables:	
- Lost to follow-up	0
- Attendance (mean attended sessions)	19.4 (SD 6.4)
- Number of patients who performed ≥15 sessions	27 (81.8%)
- Permanent discontinuation of aerobic training	2 (6.1%)
- Treatment interruption (missing ≥3 consecutive sessions)	0
- Exercise dose modification (number of patients requiring modification of exercise intensity)	9 (17.3%)
- Number of patients requiring early termination	0
- Re-scheduling of missed sessions	3 (9.1%)
Safety variables:	
- Major adverse events occurring during any sessions	0
- Minor adverse events occurring during any sessions	9 (17.3%)

Table 4. Differences in exercise capacity and muscle function at the three time points of the study protocol (n=33).

	Baseline	**Post-NAT**	**Post- training**
Exercise capacity:			
Workload (Wpeak)	106.4 (44.4)	88.8 (37.8) *	111.7 (42.8) #
VO_2 peak (ml/kg/min)	19.3 (4.7)	15.5 (4.2) *	19.6 (5) #
VCO_2 (L/min)	1.8 (0.7)	1.5 (0.6) *	1.8 (0.6) #
RQ	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)
VE peak (L/min)	56.2 (20.2)	50.5 (19.3) *	57.9 (20.3) #
HRpeak (b/min)	138.2 (18.4)	139 (16.3)	138.2 (18.1)
VO_2/HR (ml/b/min)	9.8 (2.9)	8.2 (2.1) *	10.1 (3) #
VO_2 at AT (ml/kg/min)	11.2 (2.3)	9.2 (2.6) *	10.8 (3) #
VE/VCO_2 at AT	31.2 (4.6)	33.2 (3.8) *	32.5 (5)
6MWD (meters)	500.9 (91.6)	485.1 (107.8)	515.5 (92.4) #
Muscle function:			
PImax (% predicted)	75.5 (27.2)	74.8 (21)	94.4 (27) #
PEmax (% predicted)	77.3 (22.5)	80 (21)	90.3 (27.3) #
Handgrip strength (kg)	33.7 (11.7)	31.4 (11.6) *	31.7 (11.6)
Quadriceps strength (kg)	43.1 (15.2)	38.6 (15.3)	41.3 (15)

Abbreviations: CPET, cardiopulmonary exercise testing; **NAT,** neoadjuvant treatment; **VO_2,** oxygen uptake; **VE/VCO_2**, ventilatory equivalent for carbon dioxide; **RQ,** respiratory quotient; **VE,** minute ventilation; **HR,** heart rate; **AT,** anaerobic threshold; **6WMD,** 6-minute walking distance; **PImax**, maximal inspiratory pressure; **PEmax,** maximal expiratory pressure.

Results are expressed with means and standard deviations (SD). P <0.05 post-NAT vs baseline [paired t- test, except for VE/VCO2 (Wilcoxon)]; # p <0.05 Post-training vs Post-NAT (paired t-test).

Table 5. Health-related quality of life (EORTC QLQ-C30) at baseline, post-NAT and post-exercise training.

	Baseline	**Post-NAT**		**Post-training**	
	Mean (95% CI)	**Mean (95% CI)**	**MSD[#]**	**Mean (95% CI)**	**MSD[#]**
Functional scales*					
Global health status	68.1 (58.6 to 77.5)	64.6 (58.4 to 70.8)	-3.5	68.3 (59.8 to 76.8)	+3.7
Physical function	88.2 (81.1 to 95.3)	83.9 (77.9 to 90.1)	- 4.3	89.1 (83.8 to 94.5)	+ 5.2
Emotional function	74.2 (66.8 to 81.5)	77.3 (69.4 to 85.3)	+3.1	79.1 (72.6 to 85.7)	+ 1.8
Social function	82.7 (74.4 to 91-2)	73.4 (65 to 81.9)	- 9.3	83.9 (75.8 to 92)	**+ 10.5**
Role function	79.4 (68.6 to 90.2)	74.5 (64.3 to 84.6)	- 4.9	86.1 (77.8 to 94.5)	**+ 11.6**
Cognitive function	89.4 (80.8 to 98)	89.1 (82.5 to 95.6)	-0.3	91.7 (86.1 to 97.3)	+ 2.6
Symptom scales**					
Fatigue	21.5 (11.9 to 31.1)	31.6 (24.6 to 38.6)	**+10.1**	21.1 (12.9 to 29.3)	**-10.5**
Nausea	9.4 (3.4 to 15.5)	10.4 (4.8 to 16.1)	+1	4.4 (-0.7 to 9.6)	-6
Pain	11.1 (5.6 to 16.6)	15.1 (9.1 to 21.1)	+4	13.9 (5.7 to 22.1)	-1.2
Dyspnea	1.1 (-1.1 to 3.4)	2.1 (-1 to 5)	+1	4.4 (-1.9 to 10.8)	+2.3
Insomnia	25.6 (13.9 to 37.2)	19.8 (8.8 to 30.7)	-5.8	18.9 (7.7 to 30.1)	-0.9
Appetite loss	30 (16 to 44)	26 (13.6 to 38.5)	-4	10 (0.1 to 19.9)	**-16**
Diarrhea	8.3 (0.5 to 16.1)	6.2 (-0.9 to 13.4)	-2.1	4.4 (0.1 to 8.7)	-1.8
Constipation	22.8 (12.4 to 33.2)	24 (13.3 to 34.6)	+1.2	24.1 (1.4 to 46.8)	+0.1
Financial difficulties	10 (1.3 to 18.7)	21.9 (10.6 to 33.1)	**+11.9**	17.8 (7.1 to 28.5)	-4.1

[#]**MSD**: Mean score difference; * Higher score represents better function;

[**] Higher score represents more symptoms. **NAT**: neoadjuvant treatment.