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Is a prehabilitation program feasible and acceptable in patients with gastric adenocarcinoma undergoing FLOT neoadjuvant chemotherapy?

Lícia Beatriz Alves Araújo

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

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Dissertação de candidatura ao grau de **Mestre em Oncologia – Especialização em Oncologia Clínica –** submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

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“Science is more than a body of knowledge. It’s a way of thinking, a way of skeptically interrogating the universe.”

Carl Sagan

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In the end of this journey, I look to all the challenges this pathway posed, as a way of growing as a person and professional, and I am proud of myself for all the patience and persistence. At the same time, I recognize nothing is possible without other persons, we walk along with others, and we do science for the people.

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In the memory of those who were gone, my uncle Manuel, grandfathers José and Manoel, my friends Teresa and Guidinha, that will forever stay in my heart.

ABSTRACT

Gastric cancer is one of the most incident and deadly cancers. For locally advanced gastric cancer, the multimodal standard of care is gastrectomy and perioperative chemotherapy. Since 2019, the European Society for Medical Oncology recommends the FLOT regimen as the gold standard perioperative chemotherapy. This standard regimen has a toxicity profile more aggressive than others, impacting further physical fitness and the tolerance to chemotherapy. As it is a recent regimen, no prehabilitation studies exist where patients are exclusively under this treatment. To bring some clarify to these issues, this study aimed to assess if a prehabilitation program with structured exercise (Protocol 2) vs non-structured (Protocol 1, in the pre-operative period for patients undergoing FLOT treatment for locally advanced gastric adenocarcinoma, is feasible and acceptable. Furthermore, aimed to assess the impact of the program on the physical fitness and tolerance to chemotherapy.

The feasibility was determined by recruitment rate, retention rate and adherence to exercise. The acceptability by a structured questionnaire after the end of the chemotherapy neoadjuvant. Physical fitness by functional capacity with the six-minute walking test, lower body muscle strength with the 30 seconds sit-to-stand test and upper body muscle strength with handgrip strength, collected at the baseline and at the end of chemotherapy. Tolerance to chemotherapy by the number of adverse events and their grades evaluated by Common Terminology Criteria for Adverse Events, chemotherapy completion, delays, and dose adjustments.

There was a 55.7% of recruitment rate and 100% of retention rate, showing that is a feasible study, but with a lower adherence to strength (50%) and inspiratory muscle training (37.5%) compared to aerobic volume (87.5%) for protocol 2. The protocol 1 had a high adherence to aerobic volume (50%), but significantly lower strength frequency (0%; p=0.033). A structured home-based exercise programs seems to increase the adherence to strength compared to a non-structured. The study is acceptable, in most items participants “agree” or “strongly agree” and were “satisfied” to “very satisfied”. The physical fitness had no differences from baseline to the end of chemotherapy, it seems that both programs can preserve physical fitness. The non-structured exercise group had more severe leucopenia (55.6% vs 0%; p=0.029) and neutropenia (88.9% vs 22.2%; p=0.015), what seems that a structured exercise program may increase the tolerance to chemotherapy.

In conclusion, our study suggests that prehabilitation is feasible, acceptable and provides benefits to gastric cancer patients.

Keywords: Gastric cancer, Prehabilitation, Structured Exercise, Neodjuvant FLOT, Feasibility, Acceptability, Physical Fitness, Tolerance to chemotherapy

RESUMO

O cancro gástrico é dos cancros mais incidentes e mortais. Para o cancro gástrico localmente avançado, o padrão multimodal de tratamento é a gastrectomia e quimioterapia peri-operatória. Desde 2019, a Sociedade Europeia de Oncologia Médica recomenda como quimioterapia peri-operatória padrão-ouro o regime FLOT. Tem um perfil de toxicidade mais agressivo, impactando na aptidão física e na tolerância à quimioterapia. Por ser um regime recente, não existem estudos de pré-habilitação onde os pacientes estejam exclusivamente sob este tratamento. Para trazer alguns esclarecimentos a essas questões, este estudo teve como objetivo avaliar se um programa de pré-habilitação com exercício estruturado (Protocolo 2) vs. não estruturado (Protocolo 1), no pré-operatório com tratamento FLOT para adenocarcinoma gástrico localmente avançado, é exequível e aceitável. Além disso, tem como objetivo avaliar o impacto do programa na aptidão física e na tolerância à quimioterapia.

A exequibilidade foi determinada pela taxa de recrutamento, de retenção e adesão ao exercício. A aceitabilidade por um questionário estruturado aplicado após o término da quimioterapia neoadjuvante. Aptidão física pela capacidade funcional com o teste de caminhada de seis minutos, força muscular de membros inferiores com o de sentar e levantar em 30 segundos e força muscular de membros superiores com força de preensão manual, recolhidos antes e no final da quimioterapia. A tolerância à quimioterapia pelo número de eventos adversos e o respetivo grau, avaliados pelos Critérios de Terminologia Comum para Eventos Adversos, se completaram a quimioterapia, tiveram atrasos e ajustes de dose.

A taxa de recrutamento foi de 55,7% e a de retenção de 100%, o estudo é exequível. Há menor adesão no protocolo 2, ao treino de força (50%) e muscular inspiratório (37,5%) em relação ao aeróbio (87,5%). O protocolo 1 apresentou alta adesão ao volume aeróbio (50%) e significativamente menor adesão aos treinos de força (0%; p=0,033). Um programa estruturado parece aumentar a adesão à força em comparação com um não estruturado. O estudo é aceitável, na maioria dos itens os participantes responderam “concordo” ou “concordo totalmente”, “satisfeitos” a “muito satisfeitos”. A aptidão física não apresentou diferenças do início com o final da quimioterapia, parece que ambos os programas conseguem preservar a aptidão física. O grupo de exercício não estruturado apresentou mais leucopenia (55,6% vs. 0%; p=0,029) e neutropenia (88,9% vs. 22,2%; p=0,015) severa, parece que um programa de exercício estruturado pode aumentar a tolerância à quimioterapia. Em conclusão, o nosso estudo sugere que a pré-habilitação é segura, aceitável e beneficia os doentes com cancro gástrico.

Palavras-chave: Cancro gástrico, Pré-habilitação, Exercício estruturado, FLOT neoadjuvante, Exequibilidade, Aceitabilidade, Aptidão Física, Tolerância à quimioterapia

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LIST OF ABREVIATIONS

6MWT – six-minute walk test

30CST – 30 seconds sit-to-stand

AEs – Adverse events

CDH1 - Hereditary diffuse gastric cancer

CF – Cisplatin with fluoropyrimidine

CPET – Cardiopulmonary exercise testing

CRP – C reactive protein

CT – Contrast-enhanced computed tomography

CTC – Common toxicity criteria

CTCAE – Common Terminology Criteria for Adverse Events

CTX – Chemotherapy

CTX-RT – Chemoradiotherapy

DFS – Disease-free survival

ECF – Epirubicin, cisplatin and a fluoropyrimidine

ECX/ECF – Epirubicin, cisplatin, capecitabine/5-fluorouracil

EGC – Esophagogastric cancer

EGD – Esophagogastroduodenoscopy

EOX – Epirubicin, capecitabine and oxaliplatin)

ERAS – Enhanced Recovery After Surgery

EUS – Endoscopy with ultrasound

FCT – Fundação para a Ciência e Tecnologia

FITT – Exercise frequency, intensity, time and type

FLOT - 5-FU, leucovorin, oxaliplatin, and docetaxel

Fox – Oxaliplatin-fluoropyrimidine

GC - Gastric cancer

G-CSF – Granulocyte colony-stimulating factor

GOJ - Gastroesophageal junction

HGS – Handgrip strength

HITT – High-intensity interval training

HRQoL – Health-related quality of life

IARC – International Agency for Research on Cancer

IL – Interleukins

LBM – Lean Body Mass

LBMS – Lower body muscle strength

LOS – Length of hospital stay

N – Nodes

NAT – Neoadjuvant therapy

NACT – Neoadjuvant chemotherapy

NACRT – Neoadjuvant chemoradiotherapy

NCCN – National Comprehensive Cancer Network

M – Metastases

MRI – Magnetic resonance imagining

OS – Overall Survival

PCT – Perioperative chemotherapy

POCs – Post-operative complications

PPCs – Post-operative pulmonary complications

R0 – Microscopically margin-negative resection

RCT – Randomized controlled trial

RDI – Relative dose intensity

T – Tumor

TNF-α –Tumor necrosis factor alfa

UBMS – Upper body muscle strength

WHO - World Health Organization

CHAPTER I
INTRODUCTION

1. Gastric cancer

1.1 Epidemiology and Risk Factors

Cancer ranks are increasing as life expectancy raises, being a leading cause of death and disability. It is a present and future concern; the global cancer burden is estimated to be 28.4 million cases in 2040. Gastric cancer (GC) is one of the most incident and deadly cancers. According to Globocan 2020 data, approximately one million (5.6%) new cases of GC were diagnosed globally, which places GC as the fifth most frequent diagnosed cancer in the world (Figure1.A). Concerning the number of deaths of all malignancies (Figure 1.B), GC is responsible for 769 thousand deaths each year (7.7%), making it the fourth most deadly cancer. Both incidence and prevalence are higher among males (Sung et al. 2021).

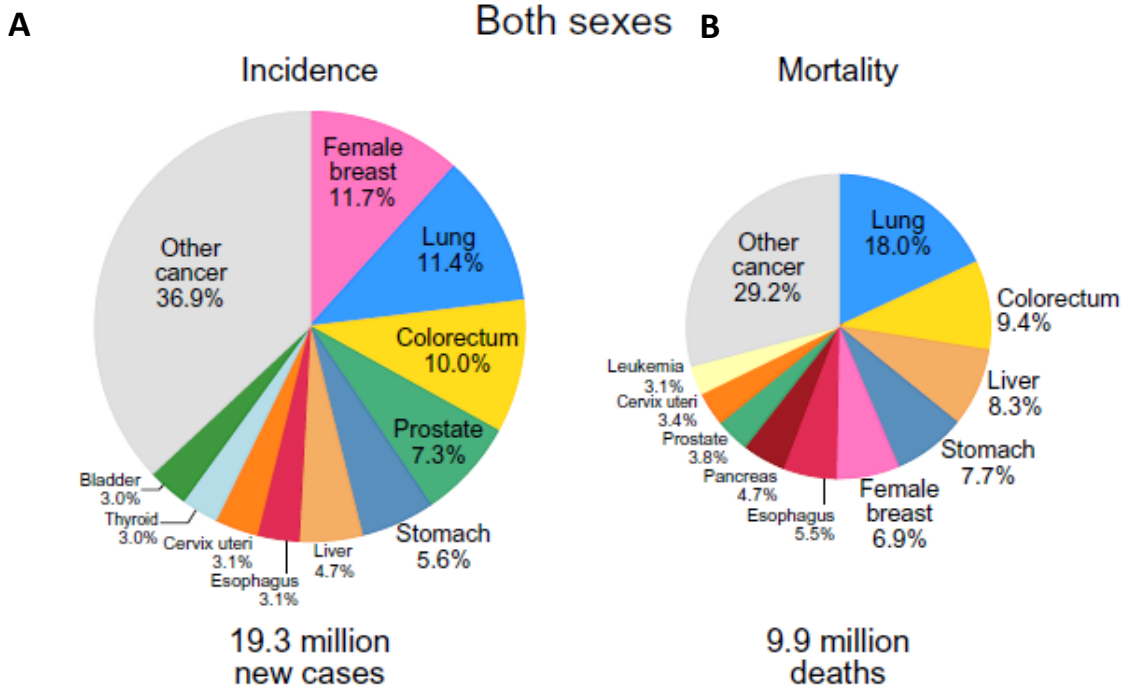

Figure 1 - **Statistics of cancer worldwide**: Incidence (A) and mortality (B) distribution of the most common types of cancer in 2020 for both sexes and all ages. Adapted from Sung et al., 2021.

Trends of GC incidence and mortality have been improving worldwide since the last decades, particularly in North America and Western Europe. The former seems to result from changes in major risk factors (e.g. improvements in food preservation, greater availability of fresh fruits and vegetables, reduction of H. pylori infection) and the latter from earlier detection and better treatment options (Prashanth and Adam 2019). However, when considering the absolute number of GC, the numbers remained stable or increased because of demographic changes (e.g., increase of global population and increased life-expectancy).

Most GC cases are sporadic while family aggregation represents approximately 10% of the cases, being the hereditary diffuse gastric cancer (CDH1) syndrome the most associated (80%) inherited syndrome with GC (Yusefi et al. 2018). Adenocarcinomas represent 95% of all GC and, according to their anatomic site, can be further divided as cardia and non-cardia. Gastric cardia tumors are located in the region adjoining the gastroesophageal junction (GOJ), including the fundus of the stomach, whereas non-cardia tumors (more common) originate in the lower portion of the stomach, below the cardia and the fundus (Prashanth and Adam 2019). According to its histological features, GC can also be classified in the following three major subtypes (Lauren Classification system): well differentiated (non-cardia/intestinal), poorly differentiated (cardia/diffuse), and mixed disease (Y. C. Chen et al. 2016). There is another major classification system that is also widely used, the World Health Organization (WHO) system, which elaborates further on the Lauren criteria and includes the following subtypes: papillary, tubular, signet ring, and mucinous. Due to its relative simplicity and long-term establishment within the medical community, the Lauren classification is the most used toll in the diagnostic of GC (Sexton et al. 2020).

In terms of etiology, longstanding mucosal inflammation is the main promotor of the oncogenetic cascade leading to sporadic GC. The most frequent cause of mucosal inflammation is the pathogenic infection by Helicobacter pylori, which was shown to be required (though not sufficient) to cause non-cardia GC. Other conditions include Epstein-Barr virus infection, autoimmune gastritis, Ménétrier's disease, and alkaline reflux disease (Sung et al. 2021)(Prashanth and Adam 2019). Moreover, observational data supports a positive association between the ingestion of salt-cured foods (fish, meat, vegetables) and GC, which is stronger in patients with H. pylori infection (Tsugane 2005). A causal relation between smoking and GC is also supported by observational data (Buckland et al. 2015). Regarding to the role of alcohol consumption, while the evidence for the association between GC and moderate alcohol drinking is lacking, there is a positive association with heavy alcohol drinking (Tramacere et al. 2012). Among non-modifiable risk factors, age and sex play a major role, with men have twice more risk than women to develop GC (Sitarz 2018).

Risk factors associated exclusively with cardia GC include obesity and gastroesophageal reflux disease, while H. pylori infection, low socioeconomic status, and dietary factors are risk factors exclusive for non-cardia GC (Sung et al. 2021)(Smyth et al. 2016). In addition, occupational exposure to dust, X and gamma-radiation, high-temperature particles and chromium VI are considered environmental factors that can conduce to chronic gastritis leading to non-cardia cancer (Sung et al. 2021)((IARC) and (WHO) 2021)(Prashanth and Adam 2019) (Yusefi et al. 2018) (Sitarz 2018)(Oo and

Ahmed 2019). On its turn, healthy lifestyle index (i.e., no smoking, limited alcohol consumption, and Mediterranean diet) was shown to be associated with a lower risk of non-cardia GC (Buckland et al. 2015).

1.2 Diagnosis, Staging and Treatment of Locally Advanced gastric adenocarcinoma

1.2.1 Diagnosis and staging

Patients with GC are asymptomatic in the early stages, which is the reason why most patients are diagnosed in advanced stages of the disease (Sitarz 2018). The numbers of patients with late diagnosis are anticipated to become worse due to the impact of COVID-19 pandemic management measures. Indeed, there was an abrupt decline in GC diagnosis per week by 54%, with screening and diagnostic tests being canceled or postponed because of the lack of medical services (e.g. endoscopy) and concerns about risk of infection (Hesary and Salehiniya 2021).

Patients reporting symptoms or signs of GC (e.g. dysphagia, dyspepsia, reflux, weight loss, emesis, recurrent aspiration, early satiety, iron deficiency anemia, gastrointestinal bleeding, recurrent aspiration), should be indicated for visual examination of the gastric mucosa through upper esophagogastroduodenoscopy (EGD) (Lordick et al. 2016) (Smyth et al. 2016). In the presence of suspected diagnostic of GC, this approach enables determining the precise location of the tumor and to obtain a surgical biopsy for histologic evaluation (Smyth et al. 2016) (Joshi and Badgwell 2021) (Chevallay et al. 2018).

The initial staging and risk assessment should include physical examination, full blood count, hepatic and renal function, endoscopy, and contrast-enhanced computed tomography (CT) scan of the thorax, abdomen, and pelvis. In candidates with potentially resectable GOJ and GC, endoscopy with ultrasound (EUS) provides additional measurement of the extent of the tumor, helping to define the T and the N clinical stage, with more accuracy of lymph node involvement than CT scan (Smyth et al. 2016) (Gwendolyn, Thomas Muhammad et al. 2019). Laparoscopy with peritoneal washings is recommended to exclude radiologically occult metastatic disease, this procedure increases staging accuracy and informs further treatment decisions (Smyth et al. 2016) (Lordick et al. 2016)(Narayan and Poultsides 2021).

1.2.2 Treatment

For patients with localized GC, resection represents the best chance for long-term survival, particularly in combination with adjuvant or perioperative chemotherapy (PCT) or chemoradiotherapy. However, as mentioned above, the identification of patients at a time when they are potentially curable is a major challenge. For locally advanced GC the multimodal standard of care is gastrectomy and PCT with or without radiotherapy (Chevallay et al. 2018) (Narayan and Poultsides 2021) (Oo and Ahmed 2019). The surgical management will depend on the tumor epicenter, extension, histological subtype and genomic etiology (Narayan and Poultsides 2021). The PCT can help achieve higher pathologic response, better R0 resection and significant improvement in overall survival (Ronellenfitsch et al. 2013)(S. Zhang et al. 2020). Since 2019, the European Society for Medical Oncology (ESMO) recommends the FLOT regimen (5-fluorouracil, leucovorin, oxaliplatin and docetaxel) as the gold standard PCT, as it was shown to results in higher complete pathological response rate (20%) and 1-year (79,3%) and 3-year (57%) survival rate (Schulz et al. 2015)(Koch et al. 2019) (Rinninella et al. 2021).

1.3 Impact of PCT with FLOT regimen

1.3.1 FLOT regimen

The FLOT regimen compared to surgery-only and other perioperative chemotherapies (CTXs) regimens was shown to provide greater outcomes (Stüben et al. 2022) (Moussa et al. 2022). However, almost 30% of the patients experience serious adverse events (AEs) what can lead to treatment delays, dosage reduction or discontinuation of CTX and thus not benefit from the potential therapeutic effects of FLOT (Stüben et al. 2022). The most common severe (AEs) reported in patients under the FLOT protocol (according to the Common Terminology Criteria for Adverse Events (CTCAE) are mainly hematologic and gastrointestinal toxicity (Table 1) (S. Zhang et al. 2020) (Sah et al. 2020)(Al-Batran et al. 2019) (Hofh et al. 2016)(Schulz et al. 2015). The FLOT regimen compared to other CTX regimens such as ECF (epirubicin, cisplatin and a fluoropyrimidine), CF (cisplatin with fluoropyrimidine), Fox (oxaliplatin-fluoropyrimidine) show minor increase in grade 3-4 AEs (neutropenia and leukopenia) and higher incidence of 1-2 AEs (gastrointestinal toxicity, stomatitis, fatigue, diarrhea and neuropathy) (Ende et al. 2019). FLOT regimen seems to present more potential impact to cardiopulmonary reserve compared ECX/ECF (Epirubicin, cisplatin, capecitabine/5-fluorouracil CTX) (Chmelo 2021). The profile of toxicity of FLOT is manageable but since

it is more aggressive, it is usually the preferred regimen for more fit patients (Ende et al. 2019).

Table 1- **Adverse events**: The most common severe AEs during FLOT regimen Adapted from (S. Zhang et al. 2020) (Sah et al. 2020) (Al-Batran et al. 2019) (Hofh et al. 2016) (Schulz et al. 2015). Legends: Yellow represents the most common and gray data those not presented by the cited the article. Only AE reported on at least two articles were summarized in the table.

	(S. Zhang et al. 2020)	(Al-Batran et al. 2019)	(Sah et al. 2020)	(Hofh et al. 2016)	(Schulz et al. 2015)
Adverse Event	**% grade 3/4**				
Hematologic					
Leucopenia	17.4%	27%	3.2%	28%	29.3%
Neutropenia	30.4%	51%	6.5%	52%	24.1%
Anaemia	13%	3%	12.9%	1%	1.7%
Trombocytopenia	0%	2%	3.2%	1%	1.7%
Febrile neutropenia			0%	5%	1.7%
Gastrointestinal					
Nausea	17.4%	7%	3.2%	9%	3.4%
Vomiting	8.7%	2%	3.2%	3%	3.4%
Diarrhea	4.3%	10%	0%	7%	12.1%
Constipation	8.7%	1%			0%
Stomatistis or Mucosistis		1%	0%	2%	6.9%
Metabolism and nutrition disorders					
Anorexia	13%		3.2%		0%
Laboratory					
Serum AST	0%	1%			0%
Serum ALT	0%	2%			1.7%
General disorders					
Fatigue	0%		0%		0%
Tromboembolic		3%		3%	
Nervous system disorders					
Peripherical neuropathy	0%	7%	0%		5.2%

Due to these AEs, GC patients often present significant reductions of physical function after the neoadjuvant chemotherapy (NACT) (O'Neill et al. 2018). The reduced physical function associated with NACT is a prognostic factor for development of post-operative complications (POCs). Due to systemic effects and AEs, patients reduce their physical activity levels and have impaired nutritional status. Patients with lower fitness levels were shown to have reduced CTX completion rates and a greater risk of developing the POCs, while those with lower baseline fitness were shown to have greater 1-year mortality. The incidence and severity of chemotherapeutic toxicity is associated with weight loss, being sarcopenic, an important prognostic factor for CTX tolerance and survival (O'Neill et al. 2018) (Koch et al. 2019). The mechanisms underlying are unclear, a prospective study with a total of 90 colorectal and GC patients suggested an association of CTX-induced sarcopenia with inflammatory markers C reactive protein (CRP), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α) (Oflazoglu et al. 2020). Of note, the impact of FLOT regimen on physical activity levels and physical fitness remains to be characterized.

1.3.2 Gastrectomy

The surgical stress response develops through immunologic, metabolic, and hormonal processes derived by direct and indirect injuries inflicted by surgery. The direct effects result from surgical manipulation of the tissues, while the indirect effects are secondary due to hypoperfusion, due to hypotension, blood loss and microvascular changes. Both will lead to activation of cellular injury cascade response with the up regulation of proinflammatory cytokines (TNF-α), and interleukins (IL-1, IL-6, IL-8) and synthesis of acute phase proteins (CRP, albumin, ferritin, transferrin, and fibrinogen). Along, the hormonal stress response is also triggered, with an elevation in counter-regulatory hormones (cortisol, growth hormone, glucagon, and catecholamines). The combination of the cytokines (TNF-α and IL-6) with glucostat hormones can lead to insulin resistance, which is further exacerbated in open abdominal surgery. Metabolically, major surgery is a burdensome, increasing serum glucose concentrations leading to hyperglycemia. Metabolic changes also include an increase in protein catabolism, with patient often presenting significant changes in terms of body composition, mainly due to loss of skeletal muscle mass, being those losses catastrophic for malnourished or in patients who are in a catabolic state (e.g. increased levels of pro-inflammatory cytokines) (Helander et al. 2019). These catabolic changes in response to surgery can exert even more dramatic effects in patients with poor nutritional status since baseline. Indeed, is has been reported that 79% to 83% of GC patients present with loss of weight at time of diagnosis (M. Ferreira et al. 2021). This poor nutritional status at

baseline is thought to be due to GC-related inflammatory mechanisms (promoting fat-free mass breakdown, insulin resistance) and due to the reduced calorie intake at diagnosis (Rinninella et al. 2021) (Oflazoglu et al. 2020). The pre-surgical catabolic state can explain the relationship between sarcopenic and POCs (van Kooten et al. 2021). A prevalence of 40.7% of sarcopenia has been reported in surgical GC patients, and was associated with post-operative complications, higher overall and disease-specific mortality. Finally, Ferreira et al analyzed the weight and muscle mass 12 months postoperatively of 39 patients undergoing gastrectomy and found that 82.1% of the patients lost weight and 76.9% lost muscle mass (lower L3 muscle index). The muscle mass loss was significantly associated with advanced GC and total gastrectomy (when compared with subtotal) (M. Ferreira et al. 2021).

Gastrectomy is associated with a high risk of postoperative complications (up to 40%), with pulmonary complications, anastomotic leakage, and wound complications as the most frequent (Gertsen et al. 2020). These complications will increase the risk if negative postoperative outcomes, such as mortality, length of hospital stay, number of reoperations, readmissions, and significant increase in healthcare costs (Gertsen et al. 2020). The appropriate surgical strategy depends on the epicenter and extent of the GC and the chosen strategy will have impact on the surgical risks. Patients undergoing proximal gastrectomy present more cases of reflux esophagitis and anastomotic structure compared to total gastrectomy. Total gastrectomy can lower those rates, but is associated with greater weight losses and anemia (Narayan and Poultsides 2021). Other risk factors that are independently associated to major complications after gastrointestinal cancer surgery are age, frailty, comorbidities such as heart failure, hypertension and renal insufficiency, history of alcohol and smoking (van Kooten et al. 2021). Some of those risk factors presented are modifiable, such as the management of acquired comorbidities and lifestyle habits (Grocott et al. 2019).

1.3.3 The “dual-hit” treatment

The therapeutic approach to locally advanced gastric adenocarcinoma is a “dual-hit” stressor for the body. PCT is linked to decreased physical fitness levels, cardiopulmonary fitness and increased toxicity, which is associated with lower tolerance to surgery, higher risk of postoperative morbidity and mortality and impossibility of performing postoperative chemotherapy (CTX) (Jack et al. 2014) (Loughney et al. 2016; Steffens et al. 2019). Because of the concerns associated with the PCT and the surgery, patients with poor baseline physical fitness (e.g. older, frail, sarcopenic, sedentary) are often directed to less effective therapeutic approaches. Thus, it is of huge importance to

invest on strategies capable to improve physical reserve or prevent its decline during pre-operative period targeting modifiable patient risk factors, which can potentially be achieved by prehabilitation.

2. Prehabilitation - making patients fit for cancer surgery

2.1 Prehabilitation

The term “prehabilitation” was first introduced in the scientific context in 1946 by the British Army to prepare the soldiers for the battle in the World War II (PREHABILITATION, rehabilitation, and revocation in the Army 1946). The concept has been evolving, and currently there is evidence about its utility in a wide range of surgical conditions, including orthopedic (Van Melick et al. 2016)(Moyer et al. 2017), cardiac (Hulzebos et al. 2012)(Snowdon, Haines, and Skinner 2014) (Marmelo, Rocha, and Gonçalves 2018) and major abdominal surgery (Hughes et al. 2019)(Barberan-Garcia et al. 2018). The rationale behind prehabilitation is to increase functional capacity before the surgery, leading to a higher functional capacity reserve (in terms of physical, mental, nutritional and metabolic status), representing the safety margin needed to meet the increased demands for surgery (F. Carli and Bousquet-Dion 2018). Consequently, postoperative losses in functional capacity are hypothesized to be less and recover is faster (**Figure 2**), in comparison to patients who don’t go through preparation during the preoperative period (Lundberg et al. 2019).

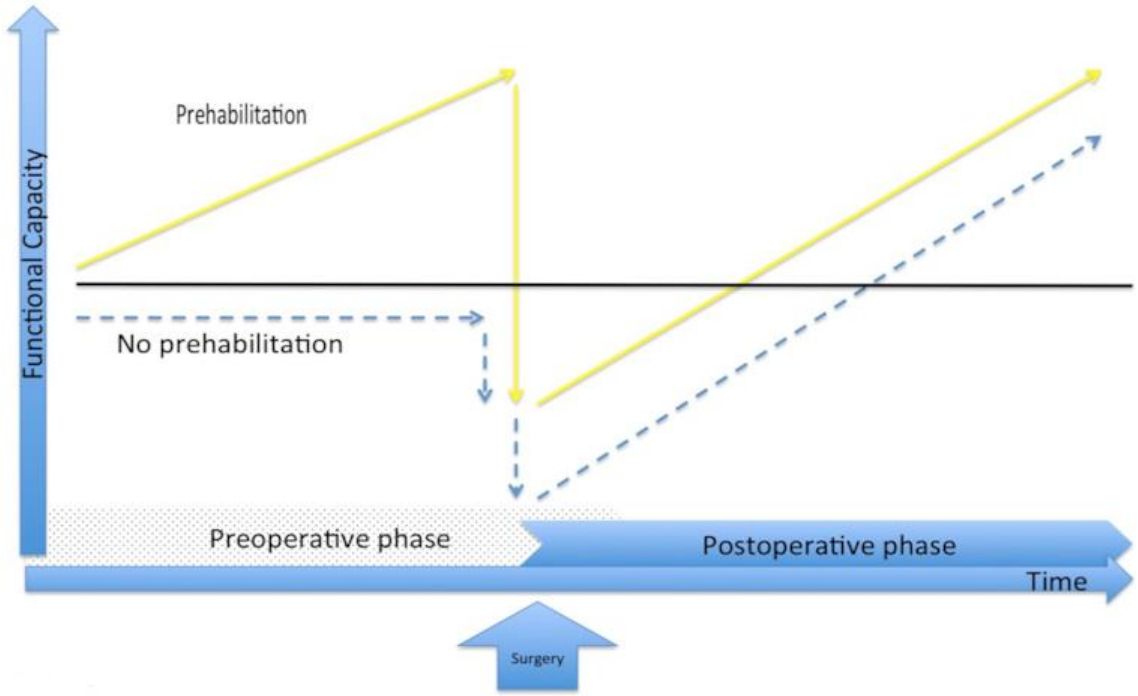

Figure 2-Theoretical model of prehabilitation: Adapted from (Lundberg et al. 2019) Legends: The yellow line represents the trajectory of patients receiving prehabilitation and the blue line the patients who receive the usual care. The black line represents the baseline functional capacity threshold.

Prehabilitation in the oncology setting starts from the diagnostic of the tumor to the moment of the primary treatment, including evaluations to identify possible alterations and targeted interventions, in order to increase their physiological reserve to deal with a forthcoming stressor. Similarly, as an athlete would prepare for the stressors of an upcoming competition**,** the patient with cancer should prepare to prevent and reduce the incidence and severity of cancer therapy related-complications and a faster recovery (Francesco Carli and Scheede-Bergdahl 2015)(Santa Mina et al. 2021). In this context, Dr. Francesco Carli (McGill University) is a pioneer and booster of the investigation, to a large extent, in colorectal surgery. On its first published randomized controlled trial (RCT) on the topic, 112 patients undergoing colorectal surgery were randomized to receive a home-based program with high-intensity training both aerobic and resistance exercise (experimental group) or recommended to walk daily and perform breathing exercises (control group). Unexpectedly, the control group performed better in functional walking capacity and the intervention group had a low compliance. The results supported that unimodal prehabilitation including exercise is not sufficient to enhance functional capacity (F. Carli et al. 2010). In the view of these findings, further research was conducted with multimodal prehabilitation programs. A trimodal prehabilitation program with nutritional counselling, protein supplementation and anxiety reduction added to moderate exercise had a better postoperative functional walking capacity, a faster recovery (Li et al. 2013). In addition to the Enhanced Recovery After Surgery (ERAS)

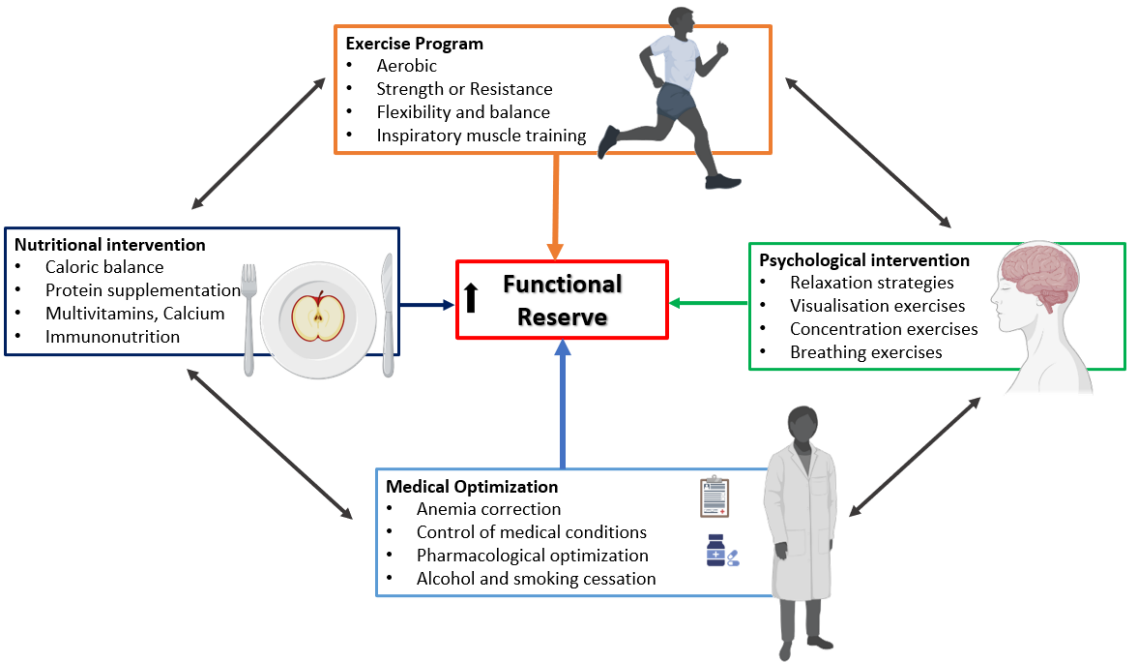

Figure 3-Components of a prehabilitation program and examples of each intervention. Adapted from (F. Carli and Bousquet-Dion 2018) and (van Kooten et al. 2021).

perioperative care guidelines, a multidisciplinary protocol had higher compliance, consequently, functional exercise capacity increased and returned faster to baseline values compared with patients who did only rehabilitation after surgery (Gillis et al. 2015). The authors also concluded that the postoperative period may not be opportune to make significant changes on physical, mental and nutrition status, when patients have postoperative symptoms and are concerned about healing process. The preoperative period is a time period opportunity for prehabilitation interventions that confers additional benefit to complement ERAS interventions, enhancing the patients to withstand the treatments stress response, thus improving postoperative outcomes (Francesco Carli, Gillis, and Scheede-Bergdahl 2017)(Rooijen et al. 2019)(Gillis et al. 2019). In conclusion, prehabilitation may include a multidisciplinary team and approach to induce a synergistic effect between the interventions: medical optimization, psychological intervention, nutritional intervention and an exercise training program (Molenaar et al. 2019).

2.2 Medical optimization

The introduction of the ERAS protocol to target the perioperative period has been associated with a reduction in postoperative complications and faster recovery. However, a significant proportion of patients still have complications, significant morbidity and longer recoveries, evidencing the need of a wider approach (Scheede-Bergdahl, Minnella, and Carli 2019)(Minnella, Drummond, and Carli 2021).

The medical optimization is an essential pillar on prehabilitation, addressing modifiable risk factors or acquired chronic conditions during the pre-operative time frame. The acquired conditions can be part fixed and part modifiable, for example, anemia and diabetes are part modifiable (Grocott et al. 2019). The control of preoperative anemia has shown to be associated with fewer postoperative complications, increase of overall (OS) and disease-free survival (DFS) and suggested to increase adherence to prehabilitation (Molenaar et al. 2019). Also an adequate preoperative glycemic control leads to less postoperative hyperglycemia, which is associated with fewer postoperative infectious complications (van Kooten et al. 2021). Pharmacological optimization of medical conditions is also taken in account, for example, hypertension, arthritis, for coronary heart disease and metabolic disorders (Li et al. 2013).

The risks linked to patient's lifestyle may be substantially modifiable, such as inactivity and alcohol and smoking consumption (Grocott et al. 2019). Data from three RTC's, with moderate to good quality, showed that perioperative alcohol cessation for more than four weeks including pharmacological strategies, reduced the number of patients with postoperative complications (Egholm et al. 2018). Smoke cessation, even

shortly before an operation, will reduce the detrimental effect of the consequences of smoking. At least four weeks of abstinence before the surgery were shown to reduce respiratory complications, and at least three weeks were shown to reduce wound healing complications. The higher the time of abstinence before the surgery, the greater the risk reduction of respiratory complications (Wong et al. 2012).

2.3 Psychological wellbeing

The stressful pre-operative period represent an emotionally difficult period for the patients since it is a time of uncertainty, impacting psychological, physiological and immunological outcomes (Li et al. 2013) (Hanalis-Miller et al. 2022). The presence of psychologically distress is very common, associated with anxiety and depression (Tsimopoulou et al. 2015). The goal of psychology during prehabilitation is to identify the patients that need psychological intervention and provide personalized strategies to help them cope with distress. The psychological distress in this population has been associated with a negative impact in postoperative comorbidities, mortality, and non-compliance with medical treatment (Francesco Carli, Gillis, and Scheede-Bergdahl 2017)(Scheede-Bergdahl, Minnella, and Carli 2019). Psychological preparation may be beneficial for postoperative pain and length of stay, but this research concerns caution of analysis since there is low quality (Powell et al. 2016). Nonetheless, the National Comprehensive Cancer Network (NCCN) has recognized the importance of this intervention before surgery (Gradishar et al. 2018). A most recent review demonstrated that psychological interventions have impact on short term-outcomes, but there is not enough evidence regarding long-term benefits. The authors concluded that this intervention alone may lack capacity to mitigate the stress and inflammatory responses, that additional interventions, such medical optimization, could influence the long-term outcomes (Hanalis-Miller et al. 2022). Also, the psychological intervention can have impact on the adherence to other interventions during prehabilitation, positive mental status will enforce the motivation for exercise training and eating (Molenaar et al. 2019).

2.4 Nutrition status optimization

The post-surgical period is characterized by an elevation in protein turnover, resulting in a negative net whole body protein balance and the wasting of lean tissues. The ERAS protocol is not enough to protect patients against post-surgical losses of lean body mass (LBM) (Gillis et al. 2019). The protein requirements are elevated in surgical cancer patients, and malnutrition and unintentional weight loss, which is a common

feature in GC patients, will increase patient's susceptibility to postoperative morbidity, mortality, longer recovery, and reduced efficacy of the treatments. Considering the consequences, it is important to start early nutritional interventions to enhance the adequate nutrition support and oppose depletion of physiologic reserves (Minnella, Drummond, and Carli 2021).

Perioperative nutrition for GC with nutrition supplementation, including protein supplementation, carbohydrate loading, and immunonutrition before and after gastrointestinal cancer surgery according to the requirements needed was associated with a lower risk of POCs and length of hospital stay (LOS) (B. Zhang et al. 2019).

Nutritional optimization will impact the adherence and the response to the physical training stimulus, an adequate protein substrate allow for successful muscle gain (Li et al. 2013) (Scheede-Bergdahl, Minnella, and Carli 2019).

2.5 Preoperative exercise training

Historically, patients diagnosed with cancer were recommended to rest, but this dogma has markedly changed over the last 20 years, as exercise interventions studies revealed benefits to help address the issues faced by oncological patients (J. Christensen, Simonsen, and Hojman 2019). Bed rest has bad effects on lean body mass (LBM), physical functional, strength, aerobic capacity and insulin sensitivity (Francesco Carli, Gillis, and Scheede-Bergdahl 2017). Cancer patients with low or none exercise behaviors have more risk of cancer-specific mortality, all-cause mortality, cancer recurrence and severe AEs than patients with greater levels of exercise (Cormie et al. 2017). Poor cardiopulmonary fitness assessed by cardiopulmonary exercise testing (CPET) before elective surgery is predictive of mortality and length of hospital stay, reflecting the implications of a reduced physiological reserve after a major surgery procedure (Snowden et al. 2013).

Currently, WHO recommends for adults with cancer to undertake regular physical activity, at least, 150 to 300 minutes of moderate-intensity aerobic physical activity and two days a week of muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups ((WHO) 2020). Physical activity differs from an exercise program. Physical activity is any body movement that results in measurable energy expenditure, while physical exercise is a physical activity that is planned and structured to achieve a specific goal of improving fitness, for example, enhancing aerobic capacity to improve cardiovascular fitness, muscle strength to preserve LBM. (Katsura et al. 2013) (F. Carli and Bousquet-Dion 2018)(Scheede-Bergdahl, Minnella, and Carli 2019). In this

case, the exercise program should specify the exercise frequency, intensity, time and type (FITT) and consider the overload principle (Francesco Carli, Gillis, and Scheede-Bergdahl 2017)(F. Carli and Bousquet-Dion 2018).

Evidence with good to moderate level supports that prehabilitation with exercise therapy for cancer patients undergoing surgery is safe, acceptable, feasible and improves functional capacity, as measured by the six-minute walk test (6MWT), pre- and postoperatively (Michael et al. 2021) and reduces hospital LOS (Waterland et al. 2021). Prehabilitation with high-intensity interval training (HIIT) was also shown to be safe and feasible in cancer patients, with improvements on cardiopulmonary capacity (Palma et al. 2021). At least four-weeks of prehabilitation seem to be required to increase patients physical levels, resulting in improved physical function before (B. P. Chen et al. 2017) and after surgery (Gillis et al. 2015). Even high-risk candidates for major abdominal surgery that are prone to more perioperative complications, were shown to develop reduced number of complications after prehabilitation with high-intensity endurance exercise training (Barberan-Garcia et al., 2018). Regarding patients with GOJ and stomach cancer awaiting surgery, preoperative exercise seems to improve exercise capacity, muscle strength, respiratory muscle function, Health-Related quality of life (HRQoL), PPCs and LOS. However, the results should be interpreted with caution because of the questionable methodological quality and limited number of RCTs. The optimal preoperative exercise program prescription in terms of frequency, intensity, time, and type remains to be established because of the heterogeneity of the exercises protocol and lack of details from the studies (Piraux et al. 2021).

The focus of prehabilitation is nearly exclusively between diagnosis and surgery, while cancer has multiple treatments and may be needed to prepare the patient for the subsequent cancer treatments and help tolerate their adverse effects during it, as for NACT (J. Christensen, Simonsen, and Hojman 2019) (Santa Mina et al. 2021).

3. Prehabilitation during neoadjuvant chemotherapy

3.1 Exercise training during chemotherapy

The period between the diagnosis and the NACT would be ideal to start a program, but it is often short to be practical for routine initiation. Also, recover between the end of NACT to the time of surgery is limited to mitigate the effects of the therapy, so the start of training should be as early as possible after treatment decision (Santa Mina et al. 2021). A systematic review with studies of breast cancer and locally advanced rectal cancer patients, showed that exercise training intervention during NAT or following

completion of NACRT was safe, feasible, acceptable (66-96%) and improved physical fitness when supervised, in-hospital (Loughney et al. 2016). In another study, patients from the intervention group were able to recover their cardiorespiratory fitness to their pre- surgical levels, while the control presented lower levels (M. West et al. 2015). On breast cancer patients undergoing adjuvant CTX, supervised programs with low-intensity or moderate-to high-intensity, resistance training (RT) and aerobic exercise (ArE) showed a beneficial impact on cardiorespiratory fitness, physical function, symptom burden such as nausea, vomiting and pain, faster return to work and lower percentage of dose adjustment compared to usual care (Van Waart et al. 2015). For outcomes such as muscle strength and physical fatigue, the higher intensity program seems to more effective (Van Waart et al. 2015). The volume of one hour for week of moderate-intensity exercise seems to be enough to maintain fitness capacity and improve HRQoL, but did not changed AEs, treatment delays and pathological complete response in breast cancer patients undergoing NAT (Sturgeon et al. 2022). In a pooled analysis of two multicenter trials, early stage breast cancer patients with higher baseline cardiovascular fitness and muscular strength pre-CTX were more likely to complete CTX with ≥ 85% average relative dose intensity (RDI) of the originally planned regimen, leading to conclusions that maybe prior ArE and RT have potential to improve tolerance to CTX (An et al. 2021). An unimodal preoperative exercise program in patients with gastro-oesophageal junction (GOJ) adenocarcinoma was shown feasible and safe during NAT. Also, it improved peak oxygen consumption, muscle strength and was suggested to be associated with lower risk of registered Common toxicity criteria (CTC), treatment failure and preoperative hospital admission during NAT. This has important implications on receiving the full dose of NAT and on the delay or preclude of the surgery. However, this study was not a RCT, and it fails to show the information on the evolution of exercise capacity and muscle strength of the standard-care control group (J. F. Christensen et al. 2019). Regarding multimodal prehabilitation programs, one study with nutritional and exercise interventions showed significant improvements in functional capacity (6MWT) (Minnella et al. 2018). Another, using psychological and exercise interventions showed attenuated decline of cardiopulmonary fitness (peak VO2), muscle loss, HRQoL, and dose adjustments (Allen et al. 2022). Further trials, with less variability in the neoadjuvant regimen, should confirm these promising findings and the effect on outcomes underexplored such as tolerance to CTX.

In addition, preclinical research provide evidence suggesting a potential positive effect of exercise during CTX on tumor biology (Yang et al. 2021). Exercise training was shown to remodel tumor vascularity, accelerate regression, reduce tumor growth and improve CTX efficacy on solid tumors (Betof et al. 2015)(Florez Bedoya et al. 2019).

Clinical trials also provide preliminary evidence of changes in tumor biology with exercise prehabilitation. Studies with rectal and esophageal cancer patients undergoing exercise prehabilitation programs during NAT or during and after neoadjuvant chemoradiotherapy (NACRT) showed a greater pathological tumor regression before surgery (M. A. West et al. 2019)(Morielli et al. 2021)(Zylstra et al. 2022). However, these studies were non-randomized.

At the moment, there are no prehabilitation studies where patients are exclusively under treatment with the FLOT regimen, as it is a recent regimen. The studies of prehabilitation on the GC population often have variations in the duration and type of NACT (e.g. they incorporate FLOT or others CTX regimen, such as ECF and ECX and epirubicin, capecitabine and oxaliplatin (EOX) or chemoradiotherapy (CTX-RT)) (Allen et al. 2022) (J. F. Christensen et al. 2019)(Minnella et al. 2018).

4. Conclusions

The benefit of prehabilitation in GC patients may be particularly important because of the 1) growing incidence of this cancer, diagnosed at more advanced stages and in more deconditioned patients due to the impact of COVID-19 pandemic; 2) these patients often have key potentially modifiable factors such lower physical fitness and nutritional status, 3) the PCT negatively affects physiological reserve that may lead to delays in surgery to allow for recovery, 4) the standard treatment of FLOT regimen has a toxicity profile more aggressive compared to other regimens and 5) surgery after NAT in these poorly optimized patients is associated with poor surgical outcomes.

Exercise before surgery and during NAT seems feasible and acceptable, but most programs are from populations of breast, lung, and colorectal cancer. The literature of prehabilitation in patients with GC is preliminary and show some benefits of those programs, but with questionable methodology quality, few RCTs and variability of the CTX regimens. To bring some clarity to these issues, we will perform a feasibility and acceptability study, to inform for a randomized control trial.

CHAPTER II
AIMS OF STUDY

1.Aims

1.1 Primary aims

To assess the feasibility and acceptability of a prehabilitation program in the pre-operative period for patients undergoing FLOT treatment for locally advanced gastric adenocarcinoma.

1.2 Secondary aims

(a) To assess the impact of the prehabilitation program on physical fitness, throughout the treatment journey.

(b) To assess the impact of the prehabilitation program on tolerance to FLOT therapy.

CHAPTER III
MATHERIALS AND METHODS

This thesis project was developed under the framework of the project PTDC/SAU-DES/7945/2020 - Prehabilitation to enhance cancer treatment in patients with adenocarcinoma of the gastroesophageal junction and the stomach - funded by Fundação para a Ciência e Tecnologia (FCT).

1.Trial design

This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)(Chan et al. 2013). We conducted an exploratory pilot randomized controlled trial, parallel two-arm group, with an equal allocation ratio (1:1).

2.Study setting

Oncology Center — Portuguese Institute of Oncology Francisco Gentil, district of Porto, Portugal.

3. Participants

Patients with locally advanced adenocarcinoma of the stomach, potentially resectable, and planned for perioperative FLOT regimen were invited to participate in the study, if they fulfill the following criteria: i) Participants >18 years of age older; ii) without any contraindication for physical exercise (Fletcher et al. 2013); iii) returning signed informed consent (Appendix I).

Patients treated for another cancer within 5 years (except basal skin carcinoma or carcinoma in situ of the cervix), with legal incapacity (person deprived of liberty or under guardianship), cognitive or severe psychiatric disorders, who are breastfeeding, pregnant (or planning to become pregnant), or participating in any other experimental study or clinical trial were excluded.

4. Intervention

The intervention comprises a multimodal preoperative program with four components, of which the first three are already part of the usual care — medical and pharmacological, psychological, and nutritional optimization — and was added an exercise component — general recommendations of physical activity (Protocol 1 – Control) or a structured exercise program (Protocol 2 - Prehab).

Medical and pharmacological optimization is followed by the doctors and nurses, with the aims to adjust patients' medication, control risk factors (for example, smoking, drinking alcohol, anemia, or hyperglycemia) and manage all conditions related to their health that may interfere with the treatment. The research team evaluated the need for psychological care with the NCCN Distress Thermometer and Problem List (DTPL)

(Version 2.2020). Those reporting a level of distress (score > 4) were referred to a psychiatrist to a personalized intervention. A clinical nutritionist evaluates the need for nutritional care through the Patient Generated Subjective Global Assessment (PG-SGA), where a score ≥9 indicate need for nutrition intervention. An individualized plan is then offered to the patients, which may include suggestions of meals and a list of foods to consume and avoid, to help achieve the recommended amount of protein intake (1.2-1.5 g/kg/day).

One week after the laparoscopy, the participants are evaluated by a physiatrist to confirm if they are eligible to exercise. Afterwards, they are randomized into the Protocol 1 or 2. Both groups receive a preoperative education session with a physiotherapist. Also, they learn about the benefits of prehabilitation (Banugo and Amoako 2017); be instructed on how to exercise at a level of perceived exertion between 4 (moderate) and 5 (somewhat strong exertion) using the modified Borg rating of perceived exertion (RPE) scale (0-10); learn what warning signs should pay attention to; and received a SmartBand with the goal of recording the levels of physical activity.

The participants at the Protocol 1 received the recommendations of the World Health Organization 2020 guidelines on physical activity and sedentary behavior for adults and older adults with chronic diseases((WHO) 2020), which ask them to increase their levels of physical activity and diminish the time they spent in sedentary behavior. This type of counselling is considered a non-structured exercise intervention.

The participants at the Protocol 2 were offered with a structured exercise program, with the goals of preserve or increase their cardiorespiratory capacity, muscle strength, muscle mass and strength of the inspiratory muscles. This program consisted of combined exercise training (aerobic exercise and strength exercise) and inspiratory muscle training. Participants were invited to perform, as tolerated, 3 sessions per week of combined exercise. For aerobic exercise, participants could opt for an aerobic activity of their interest, for example, walking, jogging, running, swimming, or cycling, at least 30 minutes uninterrupted (or fragmented throughout the day, if very deconditioned). For muscle-strengthening, participants were taught strength exercises. The exercise level was tailored according to each individual fitness level and function, as well as the intensity (resistance band, complexity of exercises and velocity of execution) and the volume (repetitions and sets). The Level 1 consists of the following exercises: i) wall press; ii) chair squats; iii) seated arm extension with resistance bands; iv) standing hip abduction; v) seated arm abduction with resistance bands; vi) abdominal crunches; vii) seated row with resistance bands; viii) standing leg curl. Before starting the strength training sessions, participants performed mobility exercises for warm up and, at the end, stretch exercises for cool down. Additionally, the days between the combined exercise

should be used for inspiratory muscle training with a Power Breathe device, set at 30% of the maximal inspiratory pressure (at least 3 times per week, 3 times per day), for a minimum of 2 cycles of 2 minutes and 1 minute of break between cycles. Distribution of the time of the exercise sessions was performed according to participant preferences. All participants received a diary to record what they have accomplished. At the days of CTX and the day after, they are advised to not perform the program. The progressions were adjusted during visits to CTX sessions.

5. Outcome measurements

The outcomes were assessed at different moments of evaluation, namely at baseline, during CTX and after CTX/before surgery. All the data method collection and timeline of assessments are summarized at the Appendix II.

5.1 Population characteristics

We recorded sociodemographic characteristics (age, age category (<65 or ≥65), gender, marital status, education level and occupation status), health condition (BMI (kg/m^2), presence of pathologies, cancer staging (TNM), alcohol consumption and smoking status, ECOG performance status, frailty, and sarcopenia). Frailty was evaluated in accordance to the Fried Phenotype (Fried et al. 2001) and sarcopenia with Sarcopenia European consensus (Cruz-Jentoft et al. 2019).

5.2 Primary outcome measures

5.2.1 Feasibility

Feasibility was determined by measuring:

(i) **Recruitment rate** — the percentage of all approached patients who meet the eligibility criteria and agree to participate in the trial.

(ii) **Retention rate** — the percentage of patients enrolled who remains at the end of the defined study period.

(iii) **Adherence to exercise** — assessed by adherence rate (done/expected*100) of aerobic volume (frequency*time), strength frequency, strength volume (frequency*series*repetitions) and IMT volume (frequency*cycles*times) and number of interruptions. The patients were defined as exercise adherents if they did at least two thirds (67%) of the prescribed, based in a RCT that study exercise adherence in cancer patients (Shang et al. 2012). Training interruption was considered as the frequency of periods of 7 days or more that the patients were without a training session.

The main reasons for lack of adherence were also pointed out. Those metrics were assessed at preoperative CTX during CTX sessions and through calls.

5.2.2 Acceptability

Acceptability of the exercise program was assessed after finishing NACT sessions, using a structured questionnaire that was developed for that purpose (Appendix III). The semi-structured questionnaire contains 14 (control group) and 16 (intervention group) questions divided into two parts, that the participants use a 5-point Likert Scale to answer. At the first part, the participants express how much they agree or disagree with each statement about the components of the prehabilitation program related with exercise and physical activity. At the second part, they express the satisfaction with the follow-up and the program in general. In addition, to seek further feedback about the preoperative program, there is an open-ended question asking for critics and suggestions.

5.3 Secondary outcome measures

5.3.1 Physical fitness

Functional capacity was assessed through the distance covered with the six-minute walking test (6MWT), in accordance with the American Thoracic Society Guidelines (ATS 2002) (Fig.4).

Figure 4- Functional capacity assessed with 6MWT.

Lower body muscle strength (UBMS) was evaluated by the 30 seconds sit-to-stand test (30CST). For both tests, the cut-offs were defined according to the functional fitness standards of Portuguese older adults (Marques et al. 2014).

Figure 5-Lower body muscle strength assessed with 30 seconds sit-to-stand test.

Upper body muscle strength (UBMS) was assessed by handgrip, using a dynamometer (SMEDLEY III T-19D) (Fig.6). The cut-off values were based on the Handgrip strength (HGS) values of Portuguese older people (Mendes et al. 2017).

Figure 6-Upper body muscle strength assessed with dynamometer.

For patients younger than 65 years, 6MWT cut-off was based on healthy subjects reference standards from seven countries (Casanova et al. 2011), for the UBMS, the New Normative Values for Handgrip Strength of the UK Biobank (Spruit et al. 2013) and LBMS based on the article Health-Related Physical Fitness Measures: Reference Values and Reference Equations for Use in Clinical Practice (Tveter et al. 2014).

5.3.2 Tolerance to chemotherapy

Tolerance to CTX was assessed through the number of adverse events during NACT and their corresponding grade, according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. (collected during CTX visits, calls and by consultation of clinical records). Also, it was assessed the number of patients who completed (or not) all prescribed cycles, had delays (frequency) and if they needed treatment dose adjustment.

6. Sample size

Since this is a feasibility and acceptability trial with the goal to inform the main randomized controlled trial, no sample size calculation was performed. The data was collected from October 2021 to June of 2022.

7. Recruitment

At the first hospital consultation or at the multidisciplinary oncology meeting, potential participants were identified. In the first clinic visit to discuss the therapeutic plan, a surgeon, medical oncologist, or anesthesiologist asked the patient to consider participating in the study. Patients received a handout detailing the rationale of the study, what participation implicate, obligations and possible risks. After 24 hours, a team member contacted patients by phone to clarify any issue related to the study and to schedule the first research visit to complete the enrollment for those willing to voluntarily participate. During the first research visit, participants were screened for eligibility and sign the consent form. Only consenting patients proceeded to further evaluations. Participants also were informed that they could discontinue and/or withdrawal the study at any time without compromising its standard care. The research medical team may discontinue a participant from the study due to the following reasons, but not limited to: i) withdrawal of consent; ii) not compliant with study arm and/or procedures; iii) development of a new medical illness limiting the participation in physical exercise; v) adverse events considered incompatible with the safe continuation in the study; vi) the research and/or the medical team decide it is for the best interest of the patient. The reasons for the participant's withdrawal and/or discontinuation from the study were recorded.

8. Allocation

Eligible patients were allocated in a 1:1 ratio to either Protocol 1 or Protocol 2 group and randomized using computer-generated blocks of 4, with an online tool (Sealed Envelope Ltd. 2019. Create a blocked randomization list. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists).

9. Blinding

This an unblinded study. Due to the nature of the intervention, it was not possible to blind the participants and the research team. Also, the researcher of this study was not blinded, since was also responsible for the intervention, data collection and analyzing it.

10. Data collection, management, and monitoring

Patients were informed and explicitly authorizes the collection, storage, and use of data for the research purpose in the signed consent form. Data was collected from clinical records and database systems at the hospital or assessed with the patients (e.g., questionnaires and physical fitness). All documents were stored securely in confidential conditions where only the principal investigator had access. In all other project-specific documents (including any database), other than the signed consent, the participant was referred by the study participant number and subject number (if applicable), not the name. For security and privacy, we also followed the instructions from The European Union General Data Protection Regulation (approved by the European Parliament in 14/4/2016; Enforcement date: 25/5/2018).

11. Statistical methods

Analysis was conducted with SPSS, version 27 (IBM Corp., USA). Normality of data was determined by using the Shapiro-Wilk test (if $n < 30$). The rates and the categorical variables are presented as frequencies and percentages. The continuous variables are presented as median and range (minimum and maximum) or mean and standard deviation, depending on the normal distribution of the population.

For categorical variables, comparison between groups were determined by using the chi-square test or Fisher's exact test, depending on the expected value for each cell. For continuous variables, comparison between groups was determined by using the independent samples t-test or Mann-Whitney's and comparison between pre- and post-intervention was analyzed using Paired Sample t-test or Wilcoxon test. For all analysis, p-value of less or equal than 0.05 was considered to indicate statistical significance.

12. Ethics

All procedures performed at this project and the informed consent were approved by the Ethical Authorities of IPO-Porto on 14 January 2021 (CES 145/020 — Appendix IV). The project was conducted in accordance with Declaration of Helsinki and National Legislation. Team members are committed to work according to the Good Clinical Practices, in agreement with the Declaration of Helsinki and respecting patients' confidentiality.

CHAPTER IV
RESULTS

1. Primary endpoints

1.1 Feasibility

1.1.1 Recruitment and retention rate

Recruitment started in October and closed in June of 2022, with 52 potential candidates. Of those, 29 fulfilled the eligibility criteria (55.7% of recruitment rate) and all stayed during the period of study defined (100% of retention rate). Therefore, all those patients were evaluated at the baseline and were allocated, 14 (48.3%) in the Protocol 2 and 15 (51.7%) in the Protocol 2. From those groups, a total of 18 participants (62%) completed the evaluation after the CTX and were analyzed on the period of study defined (Fig.7).

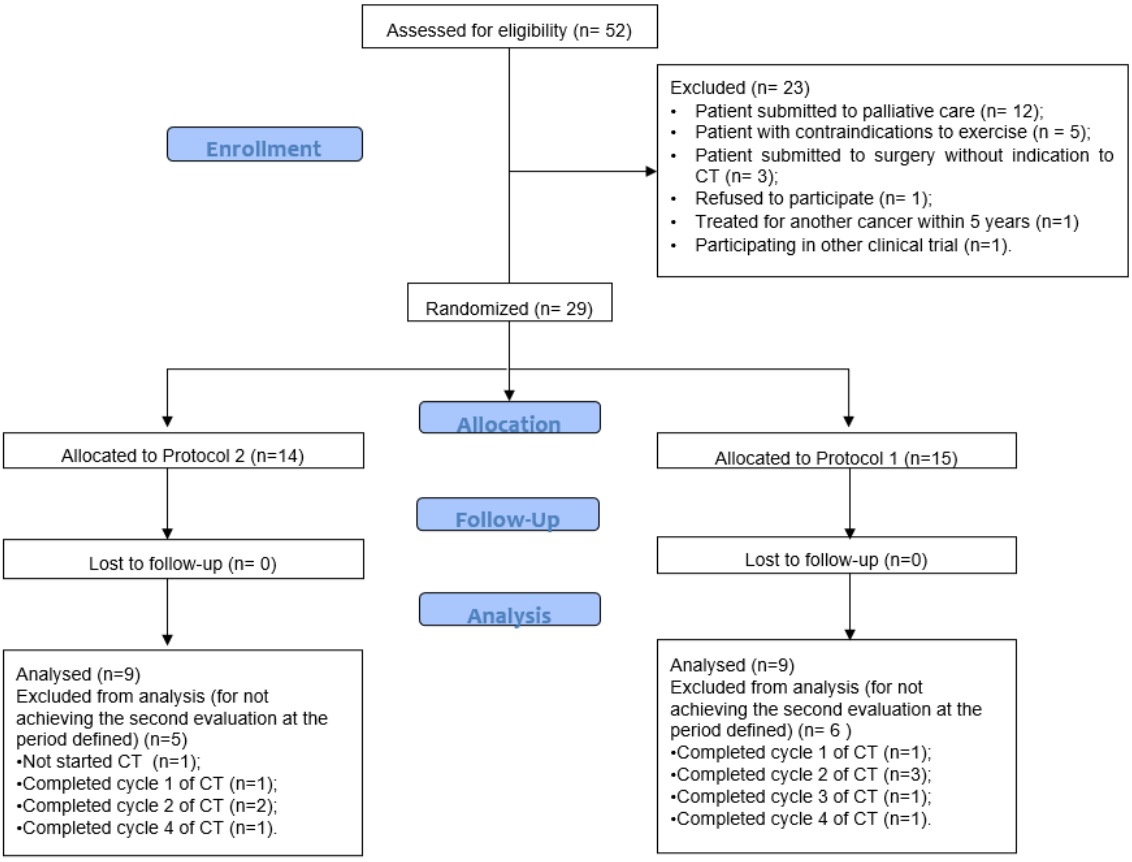

Figure 7-Consort Flow diagram of the study.

The characteristics of the 18 participants are presented in Table 2. Participants were mainly males (66.7%; n=8/9 in the Protocol 1 and n=4/9 in Protocol 2 group), with a mean age of 60.6±8.8 (n=10 (55.6%) younger than 65 years). The majority were married, had low educational level (88.9%) and are still active (50%) or retired (33.3%). Mean BMI was 26.3 kg/m^2±2.8 and the most frequent underlying comorbidities were classified as metabolic (72.2%) and musculoskeletal (50%). Regarding to clinic TNM stage, most patients were at T3 (44.4%) and has positive lymph nodes (94.4%). Most

patients are current smokers (22.2%) or used to smoke (33.3%) and have frequent alcohol intake (72.2%). A higher proportion is fully active, able to carry on all pre-disease performance without restriction (ECOG 0= 83.3%), pre-frail (83.3%) and non-sarcopenic (83.3%). No significant differences were found between groups.

Table 2- Participant characteristics

	Total (n= 18)	**Protocol 1 (n=9)**	**Protocol 2 (n=9)**	***p***
Age (years) - mean±SD	60.6±8.8	61.2 ±9.6	60 ±8.4	0.778
Age category – n (%)				0.637
< 65	10 (55.6%)	4 (44.4%)	6 (66.7%)	
≥65	8 (44.4%)	5 (55.6%)	3 (33.3%)	
Gender ratio – n (%)				0.131
Male	12 (66.7%)	8 (88.9%)	4 (44.4%)	
BMI (kg/m^2) - mean±SD	26.3±2.8	25.0 ± 2.3	27.5±2.8	0.057
Marietal status – n (%)				0.368
Married	16 (88.9%)	8 (88.9%)	8 (88.9%)	
Divorced	1 (5.6%)	1 (11.1%)	0 (0%)	
Widower	1 (5.6%)	0 (0%)	1 (11.1%)	
Educational level – n (%)				0.368
Low	16 (88.9%)	8 (88.9%)	8 (88.9%)	
Intermediate	1 (5.6%)	0 (0%)	1 (11.1%)	
High	1 (5.6%)	1 (11.1%)	0 (0%)	
Occupation status – n (%)				0.151
Working	9 (50%)	4 (44.4%)	5 (55.6%)	
Low from work	3 (16.7%)	3 (33.3%)	0 (0%)	
Retired	6 (33.3%)	2 (22.2%)	4 (44.4%)	
Pathologies – n (%)				
Musculoskeletal	9 (50%)	4 (44.4%)	5 (55.6%)	1.000
Metabolic	13 (72.2%)	5 (38.5%)	8 (61.5%)	0.294
Cardiovascular	7 (38.9%)	3 (33.3%)	4 (57.1%)	1.000
Mental	7 (38.9%)	3 (33.3%)	4 (57.1%)	1.000
Hepatic	3 (16.7%)	3 (33.3%)	0 (0%)	0.206
Respiratory	5 (27.8%)	2 (22.2%)	3 (33.3%)	1.000
cTNM stage				
T – n (%)				0.525
1	2 (11.1%)	1 (11.1%)	1 (11.1%)	
2	1 (5.6%)	0 (0 %)	1 (11.1%)	
3	8 (44.4%)	4 (44.4%)	4 (44.4%)	
4	2 (11.1%)	2 (22.2%)	0 (0%)	
Unknown	5 (27.8%)	2 (22.2%)	3 (33.3%)	
N – n (%)				1.000
Positive	17 (94.4%)	8 (88.9%)	9 (100%)	
Smoking status – n (%)				1.000
Current	4 (22.2%)	2 (22.2%)	2 (22.2%)	
Ex-smoker	6 (33.3%)	3 (33.3%)	3 (33.3%)	
Never	8 (44.4%)	4 (44.4%)	4 (44.4%)	

Alcohol consumption status				
Current	13 (72.2%)	7 (77.8%)	6 (66.7%)	0.815
Previous	3 (16.7%)	1 (11.1%)	2 (22.2%)	
Never	2 (11.1%)	1 (11.1%)	1 (11.1%)	
ECOG Perfomance Status – n (%)				1
0	15 (83.3%)	8 (88.9%)	7 (77.8%)	
1	3 (16.7%)	1 (11.1%)	2 (22.2%)	
Frailty – n (%)				0.513
Non-Frail	4 (22.2%)	1 (11.1%)	3 (33.3%)	
Pre-Frail	12 (66.7%)	7 (77.8 %)	5 (55.6%)	
Frail	2 (11.1%)	1 (11.1%)	1 (11.1%)	
Sarcopenia – n (%)				0.206
Sarcopenia probable	3 (16.7%)	3 (33.3%)	0 (0%)	
Non-sarcopenia	15 (83.3%)	6 (66.7%)	9 (100%)	

Abbreviations: SD, standard deviation, BMI – Body Mass Index; T – Primary tumor size and extension; N – Regional lymph nodes involvement; ECOG – Eastern Cooperative Oncology Group; ECOG 0 – fully active, able to carry on all pre-disease performance without restriction; ECOG 1 – Strenuous physical activity restricted; fully ambulatory and able to carry out light work; Statistical significance p≤0.05.

1.1.2 Adherence

Patients from Protocol 2 performed a higher (not statistically significant) mean weekly volume of aerobic exercise (152.5 (0 – 633.7) vs 113.3 min (30 – 310.6); p=0.753) (Table 3). The distribution of the volume is quite different within the groups, and while more participants in the Protocol 2 group performed higher volumes (median is above 150 min/week), some participants in Protocol 1 reported performing higher volumes. The median number of strength total training sessions in Protocol 2 was 13.5 (0 – 41) (vs 0 (0 – 8) in Protocol 1; p=0.05) (Table 3).

Adherence was assessed in 16 (2 were not evaluated with the most recent form; Appendix VII). The recommendations for the aerobic exercise/physical activity were the most followed of all the components (62.5% of participants did 100% or more of the prescribed) (Table 4). Four patients from Protocol 1 (50%) and 7 patients from Protocol 2 (75%) were classified as adherents (performed $\geq$ 67% of prescribed aerobic exercise sessions) and the remining as non-adherents.

Regarding adherence to frequency of strength training, only 4 patients were classified as adherents (25.1% of total sample) and all belonged to Protocol 2 (50%). Adherence to strength training volume was calculated for Protocol 2, with 50% being classified as adherents.

Finally, 37.5% of participants from Protocol 2 were classified as adherent to IMT.

Table 3-Adherence comparison

	Total (n= 16)	Protocol 1 (n=8)	Protocol 2 (n=8)	*p*
Weekly volume of aerobic exercise – median (minimum and maximum)	152.5 (0 – 633.7)	113.3 (0 – 633.7)	152.5 (30 – 310.6)	0.753
Frequency of strength sessions - median (minium and maximum)	0.5 (0 – 41)	0 (0 – 8)	13.5 (0 – 41)	**0.050**

Abbreviations: SD: Standard deviation; Statistical significance p≤0.05.

Table 4-Adherence rate

	Total (n= 16)	Protocol 1 (n=8)	Protocol 2 (n=8)	p
Adherence of the aerobic volume – n (%)				
0%	1 (6.3%)	1 (12.5%)	0 (0%)	
<33%	2 (25%)	2 (25%)	0 (0%)	0.355
≥33%	2 (12.5%)	1 (12.5%)	1 (12.5%)	
≥67%	1 (6.3%)	0 (0%)	1 (12.5%)	
≥100%	10(62.5%)	4 (50%)	6 (75%)	
Adherence of strength frequency – n (%)				
0%	8 (50%)	7 (87.5%)	1 (12.5%)	
<33%	2 (12.5%)	0 (0%)	2 (25%)	**0.033**
≥33%	2 (12.5%)	1 (12.5%)	1 (12.5%)	
≥67%	3 (18.8%)	0 (0%)	3 (37.5%)	
≥100%	1 (6.3%)	0 (0%)	1 (12.5%)	
Adherence of strength volume – n (%)				
0%			1 (12.5%)	
<33%			3 (37.5%)	
≥67%			3 (37.5%)	
≥100%			1 (12.5%)	
Adherence of IMT volume – n (%)				
0%			1 (12.5%)	
<33%			1 (12.5%)	
≥33%			2 (25%)	
≥50%			1 (12.5%)	
≥67%			2 (25%)	
≥100%			1 (12.5%)	

Abbreviations: IMT – Inspiratory muscle training; Statistical significance p≤0.05.

A total of five (31.3%) had at least one training interruption (n=4 from Protocol 1 and n=1 from Protocol 2). Overall, the main reasons for not following completely during the week with the recommendations were the chemotherapy effects (n=9; 56.3%), lack of will (n=8; 50%) and their physical condition (n=8; 50%) (Table 5). The top 3 reasons pointed by participants from Protocol 1 were climate change (50%), lack of will (50%) and chemotherapy effects (50%). Participants from Protocol 2 pointed more frequently for chemotherapy effects (62.5%), physical condition (62.5%), lack of will (50%) and social life (50%).

Table 5-Training interruptions and reasons for not following recommendations

	Total (n= 16)	**Protocol 1 (n=8)**	**Protocol 2 (n=8)**	***p***
Training interruptions – n (%)				
Yes	5 (31.3%)	4 (50%)	1 (12.5%)	0.282
Reasons for not following the recommendations of exercise/physical activity – n (%)				
Climate change	5 (31.3%)	4 (50%)	1 (12.5%)	0.282
Lack of will	8 (50%)	4 (50%)	4 (50%)	1.000
Chemotherapy effects	9 (56.3%)	4 (50%)	5 (62.5%)	1.000
Social life	5 (31.3%)	1 (12.5%)	4 (50%)	0.282
Lack of time	5 (31.3%)	2 (25%)	3 (37.5%)	1.000
Physical condition	8 (50%)	3 (37.5%)	5 (62.5%)	0.619
Psychological condition	5 (31.3%)	3 (37.5%)	2 (25%)	1.000
Forgetness	3 (18.8%)	0 (0%)	3 (37.5%)	0.200
Afraid to do alone	1 (6.3%)	0 (0%)	1 (12.5%)	1.000
Don’t like theraband	---	-----	1 (12.5%)	-----
Work in the field	2 (12.5%)	0 (0%)	2 (25%)	0.467

Statistical significance p≤0.05.

1.2 Acceptability

The responses of the semi-structured questionnaire about the acceptability are presented in Table 6. Most participants agreed they had no problems with the physical assessments (66.7% strongly agree) or performing the questionnaires (50% strongly agree). About the materials to support the intervention, most patients agreed the physical activity monitor (fit band) (72.2%) and the theraband (55.6% strongly agree) was easy to use. Regarding the inspiratory muscle training device, 55.6% of the users referred they strongly agree it was easy to use, while 44.4% disagreed. Furthermore, half of the participants considered the booklet helpful (50% strongly agree) and the material motivated them to be active (50% strongly agree). Related to the physical activity and exercise recommendations, most patients found it easy to perform (61.1% strongly agree), the intensity of exercise was considered appropriate (50% strongly agree and 38.9% agree), the amount of exercise/physical activity was adequate (55.6% strongly agree and 16.7% agree). Most participants also pointed that the time required to perform

the physical activity/exercise was adequate (50% strongly agree). The majority (56.7%) of participants also recognized that the supporting materials motivated them to be more active (50% strongly agree and 16.7% agree) and that the program help them to understand the role of physical exercise in preparing them for surgery (55.6% strongly agree and 33.3% agree). The teaching session was enough to made them autonomous to execute the exercise (33.3% strongly agree and 50% agree) and the program made them understand the importance of physical exercise in their preparation for the surgery (55.6% strongly agree and 33.3% agree). Overall, participants were very satisfied (66.7%) with the follow-up through phone calls and during the CTX sessions (61.1%). When asked about the overall experience with the program, 50% of the participants reported they felt very satisfied and 50% reported they felt satisfied.

Table 6-Acceptability of the preoperative program

Variables	**Total (n=18)**	**Protocol 1 (n=9)**	**Protocol 2 (n=9)**	***p***
1. The physical assessments did not bother me. **Strongly agree** **Agree** **Neutral**	 12 (66.7%) 4 (22.2%) 2 (11.1%)	 7 (77.8%) 2 (22.2%) 0 (0%)	 5 (55.6%) 2 (22.2%) 2 (22.2%)	0.311
2. Completing the questionnaires did not bother me. **Strongly agree** **Agree**	 9 (50%) 9 (50%)	 4 (44.4%) 5 (55.6%)	 5 (55.6%) 4 (44.4%)	1.000
3. The watch was easy to use. **Strongly agree** **Agree** **Disagree**	 13 (72.2%) 3 (16.7%) 2 (11.1%)	 7 (77.8%) 1 (11.1%) 1 (11.1%)	 6 (66.7%) 2 (22.2%) 1 (11.1%)	0.815
4. The elastic band/theraband was easy to use. **Strongly agree** **Agree** **Neutral**			 5 (55.6%) 1 (11.1%) 3 (33.3%)	
5. The inspiratory muscle training device was easy to use. **Strongly agree** **Disagree**			 5 (55.6%) 4 (44.4%)	
6. The booklet was helpful in helping me stay active. **Strongly agree** **Agree** **Neutral** **Disagree**	 9 (50%) 2 (11.1%) 6 (33.3%) 1 (5.6%)	 3 (16.7%) 1 (5.6%) 4 (22.2%) 1 (5.6%)	 6 (33.3%) 1 (5.6%) 2 (11.1%) 0 (0%)	0.446
7. It was easy to perform the proposed physical activity/exercise program recommended. **Strongly agree** **Agree** **Neutral** **Disagree**	 11 (61.1%) 3 (16.7%) 3 (16.7%) 1 (5.6%)	 6 (33.3%) 1 (5.6%) 1 (5.6%) 1 (5.6%)	 5 (27.8%) 2 (11.1%) 2 (11.1%) 0 (0%)	0.624
8. The intensity of physical activity/exercise was right for me.				**0.037**

Strongly agree **Agree** **Neutral**	9 (50%) 7 (38.9%) 2 (11.1%)	6 (33.3%) 1 (5.6%) 2 (11.1%)	3 (16.7%) 6 (33.3%) 0 (0%)	
9. The amount of physical activity/exercise was adequate for me. **Strongly agree** **Agree** **Neutral** **Disagree**	10 (55.6%) 3 (16.7%) 3 (16.7%) 2 (11.1%)	7 (38.9%) 0 (0%) 2 (11.1%) 0 (0%)	3 (16.7%) 3 (16.7%) 1 (5.6%) 2 (11.1%)	0.074
10. The time I spent on physical activity/exercise was adequate. **Strongly agree** **Agree** **Neutral** **Disagree**	9 (50%) 4 (22.2%) 4 (22.2%) 1 (5.6%)	5 (27.8%) 0 (0%) 3 (16.7%) 1 (5.6%)	4 (22.2%) 4 (22.2%) 1 (5.6%) 0 (0%)	0.106
11. The material delivered motivated me to be more active. **Strongly agree** **Agree** **Neutral** **Disagree**	9 (50%) 3 (16.7%) 4 (22.2%) 2 (11.1%)	5 (27.8%) 1 (5.6%) 1 (5.6%) 2 (11.1%)	4 (22.2%) 2 (11.1%) 3 (16.7%) 0 (0%)	0.328
12. The teaching session on the execution of the physical activity/ exercise was enough to become autonomous. **Strongly agree** **Agree** **Disagree**	6 (33.3%) 9 (50%) 3 (16.7%)	4 (22.2%) 4 (22.2%) 1 (5.6%)	2 (11.1%) 5 (27.8%) 2 (11.1%)	0.574
13. The program made me understand the importance of physical activity/exercise in my preparation for surgery. **Strongly agree** **Agree** **Neutral**	10 (55.6%) 6 (33.3%) 2 (11.1%)	6 (33.3%) 2 (11.1%) 1 (5.6%)	4 (22.2%) 4 (22.2%) 1 (5.6%)	0.587
14. Overall, with the follow-up I received through phone calls to keep active I feel **Very Satisfied** **Satisfied** **Neutral**	12 (66.7%) 5 (27.8%) 1 (5.6%)	7 (38.9%) 1 (5.6%) 1 (5.6%)	5 (27.8%) 4 (22.2%) 0 (0%)	0.209
15. Overall, with the follow-up I received during chemothrapy session to keep active I feel **Very Satisfied** **Satisfied**	11 (61.1%) 7 (38.9%)	7 (38.9%) 2 (11.1%)	4 (22.2%) 5 (27.8%)	0.335
16. Overall, with the program I feel… **Very Satisfied** **Satisfied**	9 (50%) 9 (50%)	7 (38.9%) 2 (11.1%)	2 (11.1%) 7 (38.9%)	0.057

Statistical significance p≤0.05.

Ten participants gave further feedback in the last open question (n=4 from Protocol 1 and n=6 from Protocol 2). The most frequent comments were related to the psychological and physical effect of the program (n=4), the support (n=3) and related to the exercise program and physical activity recommendations (n=3).

Table 7-Feedback related to the program

Theme	n	Group	Quotes
Support	**3**	**Protocol 1**	“With me everything went well, in the right proportion, once a week calls.” “It was great!”
		Protocol 2	“More couldn't be done, I feel good.”
Material	**2**	**Protocol 1**	“I don’t remember any booklet.”
		Protocol 2	“I ended up not realizing how the watch works, it's difficult without looking because I need reading glasses.”
Psychological and physic changes	**4**	**Protocol 1**	“I feel more energy and strength. The program encouraged me to exercise.”
		Protocol 2	“An asset to keep your head busy and your body strong.” “I feel so much better with the exercise, it was good to minimize the effects of chemotherapy, which I didn't feel was as difficult as they said going through all this. I was more relaxed after the walks.” “I feel stronger and less tired.”
Recommendation to other patients	**1**	**Protocol 2**	“It was worth it, and I recommend it to everyone.”
Related to the exercise or physical activity program	**3**	**Protocol 1**	“I didn't adhere to the recommendations because I don't like walking.”
		Protocol 2	“Inspiratory muscle training is boring. I get dizzy, my eyes bright.” “I think there were a lot of exercises for me that I already do a lot of things in my day to day, I don't have time.” “I suggest continuing the program with other people, but with a physical space to do the exercises in the hospital.” “I lacked the willingness to join, I was never into individualized sports. I like team sports and if there was, I would be more motivated to do it.”
Teaching session	**1**	**Protocol 2**	“The teaching with only 30 minutes was little time to see the exercises, I needed more. Gradually I tried and managed to do it right in front of the mirror.”

2. Secondary endpoint

2.1 Physical fitness

2.1.1 Functional capacity - 6MWT

Functional capacity was assessed at baseline (before starting NACT) and before surgery (after finishing NACT). No significant changes were observed between groups for these time points, nor in the difference or within groups, that is the comparison of the difference between the same group in two different time points (Table 8). When we compared the results of this assessment with normative values for the Portuguese population (Marques et al. 2014) and the reference standards from seven countries (Casanova et al. 2011), we noted that most of the participants presented a low level of functional capacity at baseline, and this pattern was maintained after NACT (77.8% at T0 and 72.2% at T1) (Table 9 and Figure 8). No significant changes were observed between Protocol 1 and 2.

Table 8-Mean Values at Baseline (T0) and End of Chemotherapy (T1), Between-Group and Within-group Differences for Functional capacity

Values	**Between-group difference at Baseline (T0)**		**Between-group difference at end of Neoadjuvant chemotherapy (T1)**		**Difference T1-T0**	**Within-group difference at T0-T1**
	Median (minimum and maximum)	*p-value*	Median (minmium and maximum)	*p-value*	Median (minimum and maximum)	*p-value*
6MWT, m		1.000		0.546		
Total (n=18)	449.2 (276–675)		444.5 (0-607)		-2.3 (-568 – 79.1)	0.678
Protocol 1 (n=9)	450.0(391–675)		450 (304.10-607)		0.5 (-145.9 – 79.06)	
Protocol 2 (n=9)	448.0(276–569)		439 (0-548)		-5 (-568 – 52.8)	0.594

Abbreviations; 6MWT, 6-minute walking-test; Statistical significance p≤0.05.

Table 9-Cutt-offs levels between groups at T0 and T1 for Functional capacity

	Between-group difference at Baseline (**T0**)				Between-group difference at end of Neoadjuvant chemotherapy (**T1**)			
	Total (n=18)	**Protocol 1 (n=9)**	**Protocol 2 (n=9)**	***p***	**Total (n=18)**	**Protocol 1 (n=9)**	**Protocol 2 (n=9)**	***p***
6MWT Level – n (%)				0.513				1.000
Low	14 (77.8%)	7 (77.8%)	7 (77.8%)		13 (72.2%)	6 (66.7%)	7 (77.8%)	
Normal	3 (16.7%)	1 (5.6%)	2 (11.1%)		5 (27.8%)	3 (38.9%)	2 (22.2%)	
High	1 (5.6%)	1 (5.6%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	

Abbreviations; 6MWT, 6-minute walking-test; Statistical significance p≤0.05.

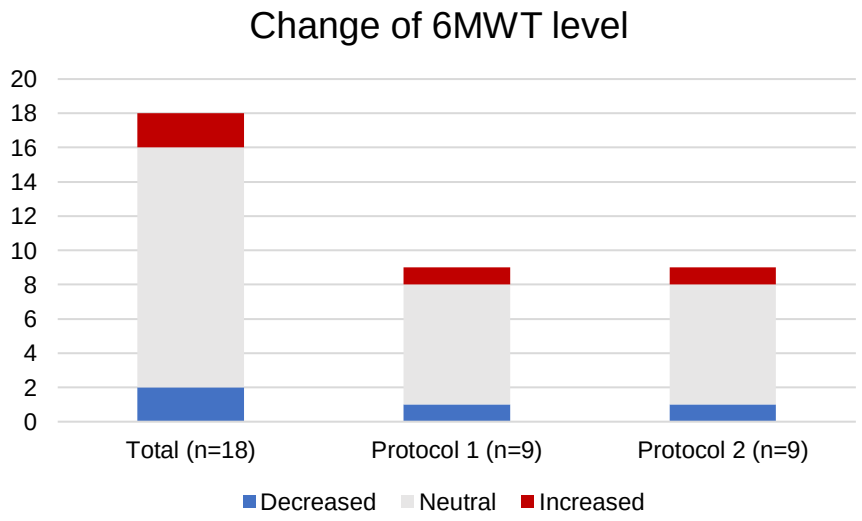

Figure 8-Level change of functional capacity

2.1.2 Lower body muscle strength - 30CST

We assessed lower limbs muscle strength throughout the 30 seconds chair stand test, at baseline (before starting NACT) and before surgery (after finishing NACT). No significant changes were observed between groups for these time points, nor in the difference or within groups (Table 10). When we compared the results of this assessment with normative values for the Portuguese population (Marques et al. 2014) and reference Values and Reference Equations for Use in Clinical Practice (Tveter et al. 2014) , we noted that most of the participants presented a low level of muscle strength in lower limbs at baseline, and this pattern was maintained after NACT (72.2% at T0 and 66.2% at T1) (Table 11 and Figure 9). Two patients from Protocol 2 improved from low to normal levels of muscle strength. No significant changes were observed between Protocol 1 and 2.

Table 10-Mean Values at Baseline (T0) and End of Chemotherapy (T1), Between-Group and Within-group Differences for Lower body muscle strength

Values	**Between-group difference at Baseline (T0)**		**Between-group difference at end of Neoadjuvant chemotherapy (T1)**		**Difference T1-T0**	**Within-group difference at T0-T1**
	Mean±SD	*p-value*	Mean±SD	p-value	Mean±SD	*p-value*
30CST, n		0.772		0.475		
Total (n=18)	15.3±3.1		15.0±3.2		-0.3±2.9	
Protocol 1 (n=9)	15.1±2.7		14.4±3.2		-0.7±3.2	0.554
Protocol 2 (n=9)	15.6±3.6		15.6±3.2		0.0±2.6	1.000

Abbreviations: SD, standard deviation, 30CST, 30-second sit-to-stand test; Statistical significance p≤0.05.

Table 11-Cutt-offs levels between groups at T0 and T1 for Lower body muscle strength

	Between-group difference at Baseline (**T0**)				Between-group difference at end of Neoadjuvant chemotherapy (**T1**)			
	Total (n=18)	**Protocol 1 (n=9)**	**Protocol 2 (n=9)**	***p***	**Total (n=18)**	**Protocol 1 (n=9)**	**Protocol 2 (n=9)**	***p***
30 CST Level -n (%)				0.584				0.620
Low	13 (72.2%)	6 (66.7%)	7 (77.8%)		12 (66.2%)	7 (77.8%)	5 (55.6%)	
Normal	4 (22.2%)	2 (22.2%)	2 (22.2%)		6 (33.3%)	2 (22.2%)	4 (44.4%)	
High	1 (5.6%)	1 (11.1%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	

Abbreviations: 30CST, 30-second sit-to-stand test; Statistical significance p≤0.05.

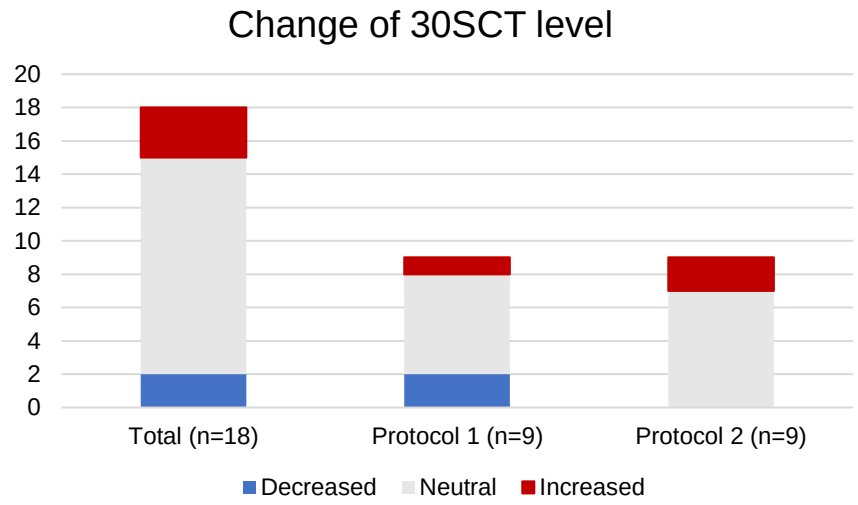

Figure 9-Level change of lower body muscle strength.

2.1.3 Upper body muscle strength - Grip strength

We assessed upper limb muscle strength through the HGS test, at baseline (before starting NACT) and before surgery (after finishing NACT). No significant changes were observed between groups for these time points, nor in the difference or within groups (Table 12). When we compared the results of this assessment with normative values for the Portuguese population (Marques et al. 2014) and the normative values from UK Biobank (Spruit et al. 2013), we noted that most of the participants presented a normal (50%) or high (16.7%) level of muscle strength in upper limbs at baseline, and this pattern was maintained after NACT (44.4% normal and 16.7% high) (Table 13 and Figure 10). One patient from Protocol 2 shifted from normal level to low level after CTX. No significant changes were observed between Protocol 1 and 2.

Table 12-Mean Values at Baseline (T0) and End of Chemotherapy (T1), Between-Group and Within-group Differences for Upper body muscle strength

Values	**Between-group difference at Baseline (T0)**		**Between-group difference at end of Neoadjuvant chemotherapy (T1)**		**Difference T1-T0**	**Within-group difference at T0-T1**
	Mean±SD	*p-value*	Mean±SD	*p-value*	Mean±SD	*p-value*
Grip strength, kg		0.831		0.749		
Total (n=18)	29.5±7.6		28.1±7.3		-1.5±2.5	0.159
Control (n=9)	29.9±8.2		28.6±8.2		-1.3±2.5	0.110
Prehab (n=9)	29.1±7.5		27.5±6.8		-1.6±2.7	

Abbreviations; SD, standard deviation; Statistical significance p≤0.05.

Table 13-Cutt-offs levels between groups at T0 and T1 for Lower body muscle strength

	Between-group difference at Baseline (**T0**)				Between-group difference at end of Neoadjuvant chemotherapy (**T1**)			
	Total (n=18)	**Control (n=9)**	**Prehab (n=9)**	***p***	**Total (n=18)**	**Control (n=9)**	**Prehab (n=9)**	***p***
Grip strength Level – n (%)				0.151				0.162
Low	6 (33.3%)	4 (44.4%)	2 (22.2%)		7 (38.9%)	4 (44.4%)	3 (33.3%)	
Normal	9 (50%)	5 (55.6%)	4 (44.4%)		8 (44.4%)	5 (55.6%)	3 (33.3%)	
High	3 (16.7%)	0 (0%)	3 (16.7%)		3 (16.7%)	0 (0%)	3 (33.3%)	

Abbreviations: SD, standard deviation; Statistical significance p≤0.05.

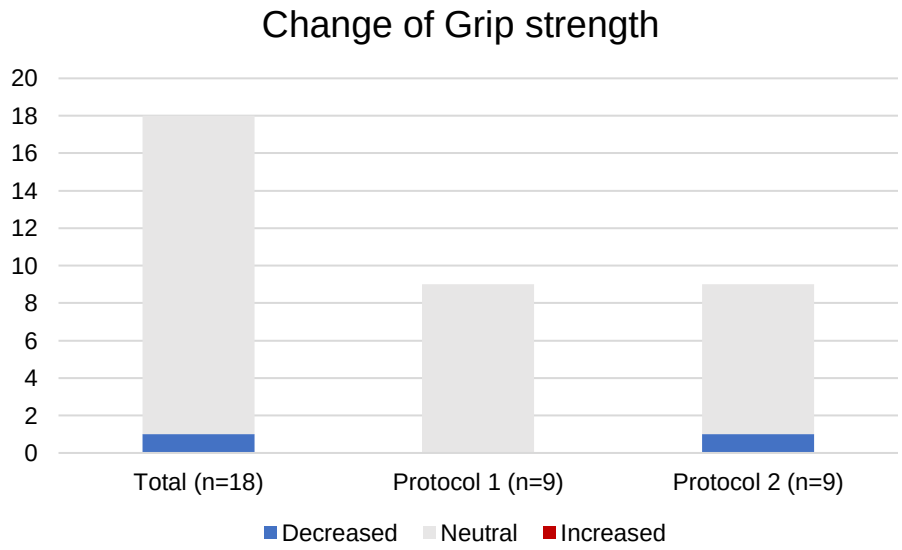

Figure 10-Level change of upper body muscle strength

2.2 Tolerance to chemotherapy

From the 18 participants, 2 did not complete all prescribed cycles. One was from Protocol 1 (failed 1 cycle due to serious hematologic toxicity) and 1 was from Protocol 2 (failed 1 cycle due to delays of CTX for leucopenia plus neutropenia and covid, and was not able to reach the last cycle before the useful time of surgery, so stopped after the third cycle).

Regarding to cycle delays, the median frequency was 1 cycle for both groups and the main reasons were because patients missed their premedication (33.3%) and leucopenia plus neutropenia (27.8%). These 2 events were more frequent in patients from Protocol 1, but no significant differences were detected between groups.

Three patients required dose adjustments (2 from Protocol 1 and 1 from Protocol 2). Two participants (1 from each group) had dose adjustment of 50% for the 5-FU because of *Dihydropyrimidine Dehydrogenase* (DPYD) deficiency, due genetic polymorphism at the variant c.2846A>T. A third patient (from Protocol 1) had an adjustment of 25% of oxaplatin and docetaxel doses, after the first cycle because of hematologic toxicity (severe leucopenia and neutropenia that delayed second cycle).

Table 14-Chemotherapy completion, delays, and dose adjusments

	Total (n=18)	**Protocol 1 (n=9)**	**Protocol 2 (n=9)**	**p**
Completed all cycle – n (%)				1.000
No	2 (11.1%)	1 (11.1%)	1 (11.1%)	
Reasons for no completion – n (%)				0.368
Cyle in time of the surgery	1 (5.6%)	0 (0%)	1 (11.1%)	
Serious hematologic toxicity	1 (5.6%)	1 (11.1%)	0 (0%)	
Frequency of delays – median (minimum and maximum)	1 (0 – 3)	1 (0 – 3)	1 (0 – 2)	0.489
Reason for delay – n (%)				
Premedication	6 (33.3%)	4 (44.4%)	2 (22.2%)	0.620
Leucopenia	1 (5.6%)	1 (11.1%)	0 (0%)	1.000
Neutropenia	3 (16.7%)	1 (11.1%)	2 (22.2%)	1.000
Leucopenia and Neutropenia	5 (27.8%)	4 (44.4%)	1 (11.1%)	0.294
COVID	1 (5.6%)	1 (5.6%)	0 (0%)	1.000
Hospitalized for tracheobronchitis	1 (5.6%)	0 (0%)	1 (11.1%)	1.000
Dose adjustment – n (%)				1.000
Yes	3 (16.7%)	2 (22.2%)	1 (11.1%)	
Percentage of adjustment – n (%)				0.587
25%	1 (5.6%)	1 (11.1%)	0 (0%)	
50%	2 (11.1%)	1 (11.1%)	1 (11.1%)	
Reason for dose adjustment – n (%)				1.000
Hematologic toxicity	1 (5.6%)	1 (11.1%)	0 (0%)	
c.2846A>T Variant	2 (11.1%)	1 (11.1%)	1 (11.1%)	

Statistical significance p≤0.05.

The AEs and corresponding severity occurring during NACT are summarized in table 15. The most common AEs with grades 1 or 2 were peripheral neuropathy (100%), fatigue (94.4%), nausea (77.8%), diarrhea (66.7%) and weight loss (61.1%), with no significant differences between groups. The most common grade 3 -4 AEs were neutropenia (55.6%) and leucopenia (27.8%) (Table 15 and Figure 12). Severe hematologic toxicity was mostly observed in patients from Protocol 1, with 5 patients accounting for 100% of the severe leucopenia cases (p =0.029 vs. Protocol 2), and 8 patients accounting for 80% of all neutropenia cases (p=0.015 vs. Protocol 2).

Table 15-Adverse events and severity during neoadjuvant chemotherapy

	Total (n= 18)	Protocol 1 (n = 9)	Protocol 2 (n = 9)	p	Total (n=18)	Protocol 1 (n=9)	Protocol 2 (n=9)	p
Adverse event	**% grade 1/2**				**% grade 3/4**			
Hematologic								
Leucopenia	7 (38.9%)	3 (33.3%)	4 (44.4%)	1.000	5 (27.8%)	5 (55.6%)	0 (0%)	**0.029**
Neutropenia	7 (38.9%)	4 (44.4%)	3 (33.3%)	1.000	10 (55.6%)	8 (88.9%)	2 (22.2%)	**0.015**
Trombocytopenia	1 (5.6%)	1 (11.1%)	0 (0%)	1.000	0 (0%)	0 (0%)	0 (0%)	**.**
Anemia	1 (5.6%)	0 (0%)	1 (11.1%)	1.000	0 (0%)	0 (0%)	0 (0%)	**.**
Febril neutropenia					1 (5.6%)	1 (11.1%)	0 (0%)	1.000
Gastrointestinal								
Nausea	14 (77.8%)	8 (88.9%)	6 (66.7%)	0.576	0 (0%)	0 (0%)	0 (0%)	**.**
Vomiting	8 (44.4%)	5(55.6%)	3 (33.3%)	0.637	0 (0%)	0 (0%)	0 (0%)	**.**
Diarrhea	12 (66.7%)	6 (66.7%)	6 (66.7%)	1.000	0 (0%)	0 (0%)	0 (0%)	**.**
Constipation	6 (33.3%)	5 (55.6%)	1 (11.1%)	0.131	0 (0%)	0 (0%)	0 (0%)	**.**
Mucosistis	8 (44.4%)	3 (33.3%)	5 (55.6%)	0.637	0 (0%)	0 (0%)	0 (0%)	**.**
Metabolism and nutrition disorders								
Anorexia	5 (27.8%)	2 (22.2%)	3 (33.3%)	1.000	2 (11.1%)	1 (11.1%)	1 (11.1%)	1.000
Weigth loss	11 (61.1%)	5 (55.6%)	6 (66.7%)	1.000	0 (0%)	0 (0%)	0 (0%)	.
Laboratory								
Serum AST	0 (0%)	0 (0%)	0 (0%)	**.**	0 (0%)	0 (0%)	0 (0%)	**.**
Serum ALT	0 (0%)	0 (0%)	0 (0%)	**.**	0 (0%)	0 (0%)	0 (0%)	**.**
General disorders								
Fatigue	17 (94.4%)	8 (88.9%)	9 (100%)	1.000	0 (0%)	0 (0%)	0 (0%)	**.**
Nervous system disorders								
Peripherical neuropathy	18 (100%)	9 (100%)	9 (100%)	.	0 (0%)	0 (0%)	0 (0%)	**.**

Abbreviations: SD, standard deviation; AST - aspartate aminotransferase; ALT - alanine aminotransferase; Statistical significance p≤0.05. **. [a] –** The statistic of p isn't present since both groups didn't have any case. Statistical significance p≤0.05.

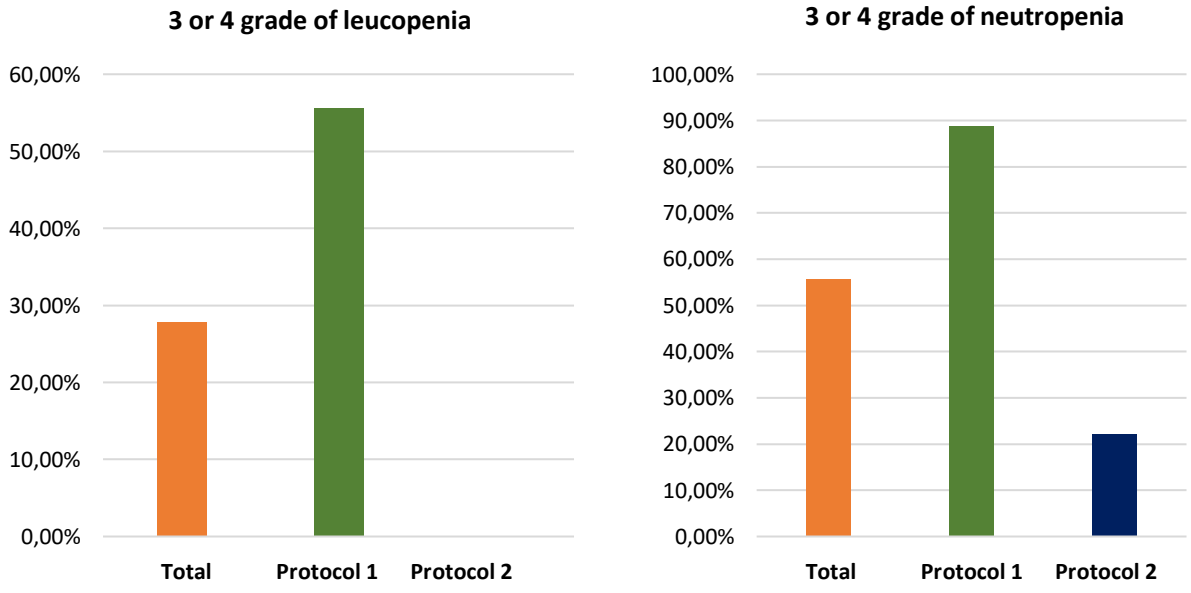

Figure 11-Percentage of patients who experienced at least 1 episode of severe leucopenia (left) and neutropenia (right) during neoadjuvant chemotherapy.

CHAPTER V
DISCUSSION

1. Feasibility and acceptability

This study aimed to assess if a structured vs. non-structured home-based prehabilitation program was feasible and acceptable among patients with adenocarcinoma of the stomach undergoing NACT. Our results reflect that is a feasible and acceptable study, with a higher adherence for the aerobic exercise volume component than strength and IMT. Also, that a structured program increases the adherence to strength frequency.

The recruitment rate was 55.7%, a higher rate compared to other studies in prehabilitation of GC, 31% (Minnella et al. 2018) and 23% (Allen et al. 2022). In these studies, the lower recruitment rate was mostly explained by patients declining to participate in the study or had barriers living far away to do exercise and/or the assessments. All the possible candidates on our study were recruited, which means we were capable to identify and screen all GC patients with locally advanced adenocarcinoma. However, 45.4% did meet the exclusion criteria, mostly by advanced disease. Indeed, 23% of identified patients were found to have peritoneal carcinomatosis at laparoscopy staging and were excluded. Previous data from literature reported a prevalence of 15% carcinomatosis in locally advanced GC patients (Lordick et al. 2016). The greater prevalence that we found in our study could be explained, at least in part, to the impact of COVID-19 pandemic on the access to health care services, favoring tumor progression, with a greater proportion of GC patients being diagnosed at more advanced stages (Hesary and Salehiniya 2021). Our retention rate was of 100%, which is superior to previous studies (Waterland et al. 2022)(Mawson et al. 2021)(Moug et al. 2019). We attribute this high retention to the constant support given by the research team during the participation in the study (face-to-face interaction every other week during chemotherapy sessions, and phone calls in between).

The adherence rate for aerobic volume has higher on the structured program than the non-structured (50% of the protocol 1 and 87.5% of the protocol 2), but with no significant differences. It is not possible to compare this data with other prehabilitation studies as the adherence is reported in various ways (e.g., adherence to the number or predicted sessions, volume, contents of the sessions). For instance, when adherence rate is reported by the number of weekly sessions completed, it does not provide much information about the volume of exercise (Minnella et al. 2018) (Allen et al. 2022) (V. Ferreira et al. 2018).

The adherence rate to the strength volume was 50% in protocol 2. The adherence rate for the strength frequency has 25% (50% adherents in the protocol 2 and 0% in the protocol 1). The lower adherence in Protocol 1 is explained, at least in part, by the difficulty of patients to recognize and introduce daily muscle-strengthening activities, as recommended. We rationalized that adherence in strength frequency has lower for the protocol 2 compared to other prehabilitation studies, as they included both aerobic and strength components frequency in the same session for the adherence rate. For example, 63% for home based exercise training (Minnella et al. 2018), home exercises 65±27% and supervised exercise sessions had 76%±2 (Allen et al. 2022), 77% for unsupervised tele-prehabilitation (Piraux et al. 2020) and 93% for a mix of home- and facility-based programming (V. Ferreira et al. 2018). It seems that a mix of home- and supervised sessions has a higher compliance, what can be a solution to increase the adherence to this component.

The adherence rate for IMT volume was 36.5%. The same lack of details in reporting training adherence happens for IMT compliance, most reported by the weekly sessions done. The feedback during CTX sessions and the acceptability questionnaire (Table 6 and 7), made us realize that it is difficult for the participants to use the inspiratory muscle trainer alone (44.6%), either they considered it boring, or with impact on dizziness. Suggestions to incorporate the IMT power breath in dynamic exercises can possibly decrease the boring aspect. In order to decrease the difficulty and increase adherence, incorporate instruction videos of the appropriate use of the device illustrated step by step, follow-up appointment to repeat the face-to-face instruction (Valkenet et al. 2018) or automatic internet-based feedback on the next IMT threshold level (Sørensen and Svenningsen 2018).

From the three components of the exercise, the aerobic volume had the highest volume adherence comparing to strength and IMT volume, in the Protocol 2. This could have happened, because from patient's perspective, the aerobic training is more enjoyable, while the strength is the most challenging (V. Ferreira et al. 2018). Also, walking is a core feature that can be easily performed (Jayedi, Gohari, and Shab-Bidar 2022). Several patients reported they could easily incorporate walking in their daily lives, but the same was not true for strength exercises.

Another important aspect that could have limited a greater adherence to prehabilitation (both protocol 1 and 2) was the impact of neoadjuvant treatment, which is often reported as a period where patients are less prone to exercise, for instance due to fatigue (OR: 0.45; 95% CI: 0.23–0.86) (Avancini et al. 2020). In fact, CTX side effects was the most frequent reason reported by patients (56.3%) to miss any component or session (Table 5). This was also a main barrier emphasized in an exploratory study that

focused on barriers and facilitators for upper gastrointestinal prehabilitation service (Chapman et al. 2022).

Participant acceptability in the program was similar with other previous prehabilitation studies (Piraux et al. 2020)(Waller et al. 2021)(Steffens et al. 2021), and most participants selected the items “agree” or “strongly agree” and were “satisfied” to “very satisfied”. The qualitative exploration of acceptability shows some positive perception of the effects of the program in the body and the support given and some negative feedback related to the material, the exercise program and teaching session. The feedback reinforces the importance of prehabilitation fitting the patients’ preferences and everyday lives, besides their physical condition, to increase adherence (Beck et al. 2021). Likewise, in other studies patient refer the importance of peer support with group sessions (V. Ferreira et al. 2018) (Chapman et al. 2022), which is considered by patients as an opportunity to share experiences and support each other. However, group sessions imply transportation and costs, which is viewed by others as a barrier (Chapman et al. 2022), as home-based is more easy to fit everyday lives (Beck et al. 2021). The adherence is higher (98%) when associated with facility-based (supervised programs) prehabilitation, as ought by one patient, compared to unsupervised programs/home-based (70%) (Gwendolyn, Thomas Muhammad et al. 2019). In spite of that, the method preferred for the exercise program delivery is home-based (37%) with one supervised session per week (37%) (V. Ferreira et al. 2018).

2. Physical fitness and Tolerance to chemotherapy

GC patients have significant reductions of physical capacity after the NACT (O’Neill et al. 2018). FLOT has shown to decrease the cardiopulmonary reserve compared to ECX/ECF (Chmelo 2021) and to decrease the tolerance to CTX, with a higher incidence of 1-2 AEs and a minor increase of hematologic 3-4 AEs compared to ECF, CF and Fox regimens (Ende et al. 2019). Almost 30% of the patients experience serious AEs what can lead to CTX discontinuation, delays before surgery, dosage adjustments or symptom burden (Stüben et al. 2022). Our results shown that both programs were effective on preserving the physical fitness and that a structured program probably may have more impact on preserving the tolerance to CTX in severe hematologic AEs than a non-structured program.

Physical fitness was divided in functional capacity (6MWT), UBMS (handgrip strength test) and LBMS (30CTS). The 6MWT is a validated measure for the cancer population (Schmidt et al. 2013) and has already demonstrated to be improved with an exercise and nutrition prehabilitation program (mean [SD] 6MWD change, 36.9 [51.4] vs

−22.8 [52.5] m; *P* < .001) before EGC surgery, from which 77% participants did during neoadjuvant FLOT regimen (Minnella et al. 2018). The differences in our study from the presented before is that the control group did not receive specific exercise recommendations before surgery. At ours, the control group received the OMS recommendations and 50% adhere to 100% of the aerobic volume recommendations. The high adherence in Protocol 1 possibly influenced the presence of no significant differences of functional capacity between groups (intervention -5 (-568 – 52.78)) vs control 0.5 (-145.9 – 79.1) (p=0.513) (Table 7) and the same number of increases and decreases of physical fitness level (Table 8).

Beside the significant differences of adherence of strength frequency, a structured home-based program does not seem enough to differentiate the muscle strength gains of the Protocol 2 compared to Protocol 1. The 30CTS performance and the HGS before surgery had near values from the baseline at both groups and with little differences of values and of levels (Table 10, 11,12 and 13). A study of EGC patients that compared a usual care group that received encouragement to remain active by undertaking regular aerobic exercise to a multimodal prehabilitation with twice-weekly supervised exercises (aerobic, resistance and flexibility) and a home exercise program for 1 hour, thrice weekly. Prehabilitation group exceeded the usual care in the HGS at cycle three of neoadjuvant therapy and on the preoperative day, while the control never regained the baseline levels (Allen et al. 2022).

The percentage of CTX completion was near the same presented in literature of FLOT groups with no intervention (88.9% vs 90%) (Al-Batran et al. 2019) (Giommoni et al. 2021). Two persons discontinued CTX after third cycle, one of them because of serious hematologic toxicity, who already had a dose adjustment at second cycle. This patient was non-adherent to the recommendations, belonged to the Protocol 1, and had low physical fitness at baseline and after CTX. In patients undergoing neoadjuvant CTX prior to EGC resection, the ones with a lower baseline physical fitness were less able to complete all the cycles (Jack et al. 2014). The current evidence of exercise in early breast cancer patients, the most type of cancer studied during CTX, shows that higher levels of cardiovascular fitness and muscular strength were associated with higher CTX completion (An et al. 2021). Those that have lower baseline levels of physical fitness, when going through a moderate-to-high intensity exercise training during CTX can improve their treatment completion (Groen et al. 2022). Patients from Protocol 1 had more delays because of leucopenia and neutropenia (44% Protocol 1 vs 11.1% Protocol 2; 27.8% Total) and small difference of higher dose adjustments (22% Protocol 1 vs 11% Protocol 2; 16.7% Total). The dose reduction in our study was lower than in observational prospective FLOT trials, of 43.1% (Schulz et al. 2015) and 39.8% (Giommoni et al. 2021).

A higher full dose (75% vs controls (46%); p=0.036) and less dose adjustments or delays (43% intervention and 16% control) p=0.041) can have a possible indirectly influence of the QOL improvement, associated to increasing patient's resilience allowing them to complete more of their prescribed course (Allen et al. 2022).

The most common AEs with grades 1 or 2 were peripheral neuropathy (100%), fatigue (94.4%), nausea (77.8%), diarrhea (66.7%) and weight loss (61.1%) (Table). Previous studies with FLOT treatment but no prehabilitation reported anaemia (80%) (Al-Batran et al. 2019); febril neutropenia, peripherical neuropathy, fatigue, diarrhea, oral mucositis (100%) (Sah et al. 2020); nausea (43%) (S. Zhang et al. 2020); anaemia (85%) (Hofh et al. 2016). In our study, most common grade 3 or 4 AEs were neutropenia (55.6%, (100%) Protocol 1; p =0.015) and leucopenia (27.8%; (88.9% Protocol 2; p =0.029) (Table 14). Severe hematological AEs were also frequent on other studies, neutropenia (51%) (Al-Batran et al. 2019); anemia (12.9%)(Sah et al. 2020); neutropenia (30.4%), leucopenia (17.4%) (S. Zhang et al. 2020); neutropenia (52%), leucopenia (28%), (Hofh et al. 2016); 29.3% leucopenia, 24.1% neutropenia (Schulz et al. 2015).

Few clinical studies of exercise have reported the tolerance as an endpoint, with the CTC toxicity evaluation, and none presented with the detail of ours. High-intensity aerobic and resistance exercise during neoadjuvant treatment of EGC has shown to decrease the risk of presenting CTC grade 1-4 toxicity (15% in the exercise group and 31% in the control group) (J. F. Christensen et al. 2019). Fewer step count (p=0.012) and higher baseline anxiety (p=0.03) were associated with higher number of CTX related symptoms rates "severe/very severe" (Nyrop et al. 2018). Furthermore, it is necessary to take into consideration the changes of protocols between institutions, related to premedication, medication control, prescribed of prophylactic granulocyte colony-stimulating factor (G-CSF), G-CSF regardless severity or concerned by it (Sah et al. 2020). Our findings of significant differences between groups in severe leucopenia and neutropenia may have clinical implications, there is a need for further research with a bigger sample to investigate the relationship between tolerance with adherence, baseline and after CTX levels of physical fitness, skeletal muscle mass, QOL, distress and step count.

3. Strengths and Limitations

This pilot trial presents some strengths. Notably, this study is the first randomized controlled trial of prehabilitation in patients awaiting GC resection including all the components of intervention, and with focus on a specific population and regimen of CTX,

decreasing the variability of type of cancer, surgery, regimen, and time of treatment. The definition of adherence rate including percentage of volumes gives more information, than the presented in most studies, of the number of attended sessions. Also, the evaluation of the endpoint tolerance by the CTC toxicity evaluation gives further details. The allocation method is considered a strength because of the blinding randomization, and each participant had the same chance of being assigned to control or intervention. At the same time, it was a limitation and could have posed the gender as a cofounding variable, as the control group had the double of men compared to the intervention. The blinding should be noted as well as other limitation, due to the nature of the intervention, it was not possible to blind participants and the data collector and analyst needed to know the assigned arm. It has a small sample size, and it is a single-center study, which may limit the generalizability of the results. It was not possible to see the total potential of the structured exercise program, as not all the participants of the intervention group were adherents to all the components. The adherence was self-reported and thus subject to recall bias. Also, the control group was aware of the importance of exercise during the preoperative period and half adherent to the aerobic component at 100%, which could have underestimated the comparative benefit of the prehabilitation with a structured exercise program.

CHAPTER VI
CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, this pilot study has shown that prehabilitation for GC cancer patients undergoing neoadjuvant FLOT regimen, is feasible and acceptable. Both a structured exercise program and non-structured can lead to high percentages of adherence to the aerobic volume. A structured exercise program can lead to higher percentage of adherence to strength frequency. The real benefit of the structured exercise program was not noticeable due to a low adherence to the strength and IMT exercise components. Thus, there are changes needed to be implemented to increase adherence on the full-scale trial, according to literature, a mix of home-based and supervised sessions should be considered. The groups did not present differences in physical fitness, but both programs seem able to preserve their baseline physical fitness. The structured program seems better at increasing the tolerance to chemotherapy, since the unstructured program had more significant severe hematologic adverse events. In the future, further work is needed to confirm these results on a bigger sample and to explore the reason behind them.

CHAPTER VII
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CHAPTER VIII

Appendices

Appendix I – Patient informed consent

DECLARAÇÃO DE CONSENTIMENTO LIVRE E ESCLARECIDO A ASSINAR PELO PARTICIPANTE

Considerando a "Declaração de Helsínquia", da Associação Médica Mundial

(Helsínquia 1964; Tóquio 1975; Veneza 1983; Hong Kong 1989; Somerset West 1996; Edimburgo 2000; Washington 2002, Tóquio 2004, Seoul, 2008 e Fortaleza 2013)

FORTALECER EM CASA/ FORTALECER EM CASA: uma plataforma interativa suportada pela internet para oferecer pré habilitação multimodal com o intuito de mitigar os efeitos do confinamento domiciliário e reduzir a carga pós-operatória em pacientes com cancro.

Eu, abaixo-assinado (nome <u>completo</u> do participante em LETRA MAIÚSCULA)

_____

Recebi o texto de *<u>Informação ao Participante</u>* relativo ao presente estudo e em que concordei participar. Compreendi a explicação que me foi fornecida pelo investigador que assina este documento. Foi-me ainda dada oportunidade de fazer as perguntas que julguei necessárias, e a todas obtive resposta satisfatória. Tomei conhecimento de que, de acordo com as recomendações da Declaração de Helsínquia, a informação ou explicação que me foi prestada versou os objetivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto que a participação neste estudo possa implicar. Além disso, foi-me afirmado que tenho o direito de anular a todo o tempo a minha participação no estudo, sem que isso possa ter como efeito qualquer prejuízo na assistência que me é prestada.

Por isso, consinto que me seja aplicada <u>a intervenção</u> FORTALECER EM CASA, proposta pelo investigador.

Adicionalmente, autorizo que os investigadores envolvidos (Tabela 1) procedam à recolha e consulta das avaliações realizadas ao longo do estudo, bem como o armazenamento temporário dessa informação, com o único propósito de auxiliar a minha monitorização e ajustar a intervenção, conforme necessário.

Assinatura do participante: _____ **Data: ___/___/202_**

Nome do Investigador responsável (EM LETRA MAIÚSCULA):

_____

Assinatura do Investigador responsável: _____ **Data: ___/___/202_**

<u>Anulação do Consentimento Informado</u>

Declaro que recebi a *<u>Informação ao Participante</u>* relativo ao estudo/projeto de investigação em questão, que me foi proposto pelo investigador que assina este documento e **<u>pretendo anular</u>** o consentimento dado na data ____/____/202___.

Assinatura do participante: _____ **Data: ___/___/202_**

Assinatura do Investigador responsável: _____ **Data: ___/___/202_**

Nota: Fornecimento <u>obrigatório</u> de cópia ao participante

Appendix II – Table of data collection method and timeline of assessment

Outcome	Assessment tool	Evaluation time			Evaluator	Source
		Baseline	During Chemotherapy	After Chemotherapy/ Before surgery		
Sociodemographic						
Gender	Questionnaire (Appendix VI)	X			Research Team	In Person
Age	Questionnaire (Appendix VI)	X			Research Team	In Person
Marietal Status	Questionnaire (Appendix VI)	X			Research Team	In Person
Educational level	Questionnaire (Appendix VI) - ISCED	X			Research Team	In Person
Occupation status	Questionnaire (Appendix VI)	X			Research Team	In Person
Health condition						
BMI (kg/m2)	Bioimpedance and Stadiometer	X		X	Research team	In Person
Pathologies		X			Surgical oncologist Research team	In Person Clinical records
Cancer staging	TNM system	X			Surgical oncologist Oncologist	Clinical records
Alcohol consumption		X			Nutritionist	In Person
Smoking status		X			Nutritionist	In Person
ECOG perfomance status	ECOG	X			Oncologist Nutritionist Internal medicine physicians	Clinical records
Frailty	Weight loss (kg), CESD-D, calories per week (IPAQ), gait speed (5-meter walk) and hand grip strength	X			Research team	In Person
Sarcopenia	Grip strength, Appendicular Skeletal Muscle Mass, and Gait-speed	X			Research team	In Person

Feasibility						
Recruitment rate	Registry of the patients who were eligible and consent to participate	X			Researcher	Study records
Retention rate	Registry of patients who remains on the study		X	X	Researcher	Study records
Adherence rate	Questions about adherence to exercise (Appendix VII)		X	X	Research team	In Person
Acceptability						
	Structured questionnaire (Appendix III)			X	Researcher	In Person
Physical Fitness						
Functional capacity/Aerobic endurance (m)	6-min walking test (Appendix VI)	X		X	Research team	In Person
Upper body strength (kg)	Grip Strength – Dynamometry (Appendix VI)	X		X	Research team	In Person
Lower body strength (n)	30-second chair stand test (Appendix VI)	X		X	Research team	In Person
Tolerance to chemotherapy						
	Common Terminology Criteria for Adverse Events (Appendix VII)		X		Medical oncologist Nurse Researcher	Clinical records In Person Calls

Appendix III - Acceptability of the prehabilitation program questionnaire

Questionário da Aceitabilidade - Protocolo 1

ID do Ensaio: _____

Data de Avaliação: ___/___/___

Avaliador: _____

Item	Concordo totalmente	Concordo	Não concordo, nem discordo	Discordo	Discordo totalmente
1. As avaliações físicas não me incomodaram.					
2. O preenchimento dos questionários não me incomodou.					
3. O relógio foi de fácil utilização.					
4. O manual de apoio foi útil para me ajudar a manter ativo.					
5. Foi fácil realizar a atividade física proposta.					
6. A intensidade da atividade física foi a adequada para mim.					
7. A quantidade de atividade física foi adequada para mim.					
8. O tempo que despendi para realizar atividade física foi adequado.					
9. O material entregue motivou-me a ser mais ativo.					
10. A sessão de ensino foi suficiente para eu perceber como me manter ativo.					
11. O programa fez-me compreender a importância da atividade física na minha preparação para a cirurgia.					
Item	Muito satisfeito	Satisfeito	Nem satisfeito nem insatisfeito	Insatisfeito	Muito insatisfeito
12. No geral, com o acompanhamento que recebi através dos telefonemas, para me manter ativo, sinto-me…					
13. No geral, com o acompanhamento que recebi durante as sessões de quimioterapia, para me manter ativo, sinto-me…					
14. No geral, com o programa, sinto-me…					

A sua opinião é muito importante para que possamos melhorar o programa e ir ao encontro das necessidades de todos os utentes. Por favor, indique-nos as suas sugestões:

Questionário da Aceitabilidade - Protocolo 2

ID do Ensaio: _____

Data de Avaliação: ___/___/___

Avaliador: _____

Item	Concordo totalmente	Concordo	Não concordo, nem discordo	Discordo	Discordo totalmente
1. As avaliações físicas não me incomodaram.					
2. O preenchimento dos questionários não me incomodou.					
3. O relógio foi de fácil utilização.					
4. A banda elástica/theraband foi de fácil utilização.					
5. O aparelho de treino dos músculos inspiratórios foi de fácil utilização.					
6. O manual de apoio foi útil para me ajudar a realizar os exercícios em casa de forma autónoma.					
7. Os exercícios propostos foram fáceis de realizar em casa.					
8. A intensidade dos exercícios foi a adequada para mim.					
9. A quantidade de exercícios recomendada foi adequada.					
10. O tempo que despendi para realizar todos os exercícios foi adequada.					
11. O material entregue motivou-me a ser mais ativo.					
12. A sessão de ensino sobre a execução dos exercícios foi suficiente para eu ficar autónomo.					
13. O programa fez-me compreender a importância do exercício físico na minha preparação para a cirurgia.					
Item	Muito satisfeito	Satisfeito	Nem satisfeito, nem insatisfeito	Insatisfeito	Muito insatisfeito
14.No geral, com o acompanhamento que recebi através dos telefonemas, para me manter ativo, sinto-me…					
15.No geral, com o acompanhamento que recebi durante as sessões de quimioterapia, para me manter ativo, sinto-me…					
16.No geral, com o programa, sinto-me…					

A sua opinião é muito importante para que possamos melhorar o programa e ir ao encontro das necessidades de todos os utentes. Por favor, indique-nos as suas sugestões:

Appendix IV – Ethical Authorities Approval

IPOPORTO
INSTITUTO PORTUGUÊS DE ONCOLOGIA DO PORTO FG, EPE

Parecer CES IPO: 145A/020

Assunto: Adenda ao pedido de realização de Projeto de Investigação intitulado ***"Stay Home but Stay Strong"***.

Investigador Principal: **Prof. Doutor Lúcio Lara Santos**

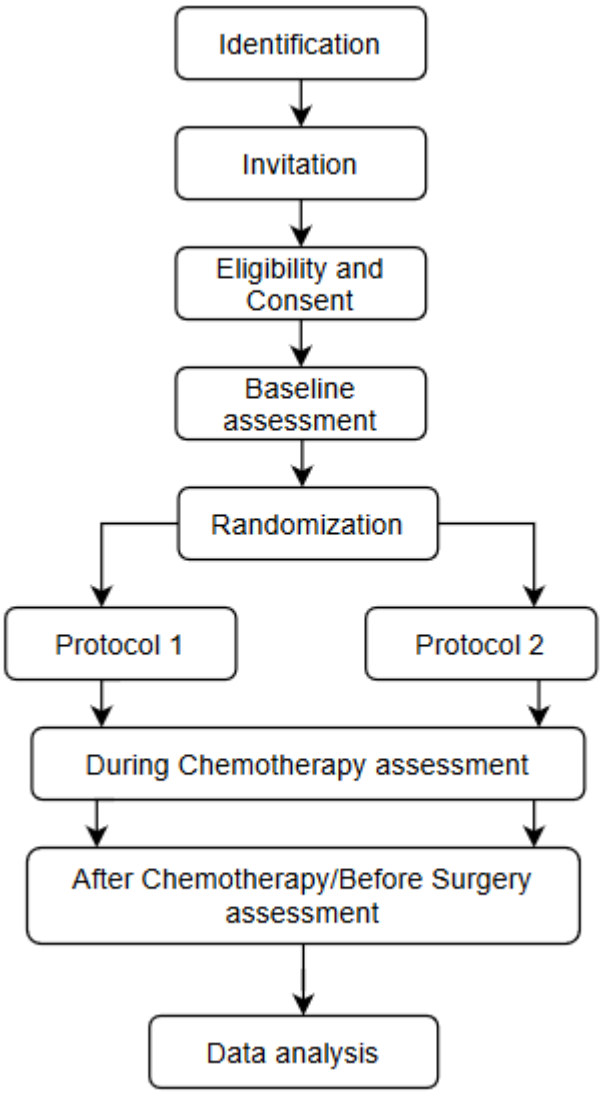
Data: 14 de janeiro de 2021

PARECER

É parecer desta CES, não existir impedimento de natureza ética ao desenvolvimento do referido estudo de Investigação (Adenda FCT: PTDC/SAU-DES/7945/2020).

Enf. José Carlos Pimentel
Vice-Presidente da CES – IPO Porto EPE

Appendix V – Consort diagram of the study



Appendix VI – Evaluation of Socio-demographic, body composition and physical fitness outcomes

Nº ID DO ENSAIO:_____

DADOS SOCIODEMOGRÁFICOS

Idade:_____ **Sexo:** M☐ F☐ **Estado Civil:** Solteiro☐ Casado☐ Divorciado☐ Viúvo ☐

Nível de Escolaridade:☐ Analfabeto ☐ Ensino Básico/ 1.º Ciclo (1.º, 2.º. 3.º e 4.º anos)

☐ Ensino Básico/ 2.º Ciclo (5.º e 6. anos) ☐ Ensino Básico/ 3.º Ciclo (7.º, 8.º e 9.º anos)

☐ Ensino Secundário (10.º, 11.º e 12.º anos) ☐ Ensino Superior (licenciatura, mestrado e doutoramento) ☐ Curso técnico

Trabalha? Sim☐ Não☐ Reformado☐ Baixa☐
Qual a sua atividade profissional? _____

Qual das seguintes situações se aplica a si?

- Tem acesso à internet através do meu: Computador ☐ Telemóvel ☐ Ambos ☐

- Tem acesso através de outras pessoas (familiares): Computador☐ Telemóvel☐ Ambos☐

AVALIAÇÕES FÍSICAS / FUNCIONAIS / ANTROPOMÉTRICAS

Mão dominante: DIREITA ☐ ESQUERDA ☐ AMBIDESTRO ☐

Perdeu peso de forma não intencional no último ano? SIM ☐ NÃO☐

Se sim, quantos quilos?_____.

	BASAL Data: ___ / ___/ _____			APÓS QT Data: ___ / ___/ _____			APÓS-CIRURGIA Data: ___ / ___/ _____		
	Dir.	Esq.		Dir.	Esq.		Dir.	Esq.	
Perímetro do Braço (cm)									
Perímetro do Gêmeo (cm)									
Estatura (cm)									
Peso Corporal (kg)									
% de Gordura									
% de Água Corporal									
Dinamómetro manual	1ª	2ª	3ª	1ª	2ª	3ª	1ª	2ª	3ª
Levantar e sentar 30'' (nºrep)									
Velocidade de marcha 5 m (s)	1ª	2ª	3ª	1ª	2ª	3ª	1ª	2ª	3ª
Agilidade (sentado, caminhar 2,44 m e voltar a sentar) (s)	1ª	2ª	Melhor	1ª	2ª	Melhor	1ª	2ª	Melhor
	Usou o apoio das mãos para levantar?			Usou o apoio das mãos para levantar?			Usou o apoio das mãos para levantar?		
	Sim	Não		Sim	Não		Sim	Não	

TESTE 6 MINUTOS DE MARCHA			**BASAL** Data:__ / __ / ____		**APÓS QT** Data:__ / __ / ____		**APÓS CIRURGIA** Data:__ / __ / ____	
Nº de voltas completas								
Distância adicional (m)								
Distância total percorrida (m)								
Necessitou de auxiliar de marcha (ex: bengala)?			Sim	Não	Sim	Não	Sim	Não
Necessitou parar?			Sim	Não	Sim	Não	Sim	Não
• Se "SIM"	Quantas vezes?							
	Quanto tempo (total)?							
• Se parou antes dos 6 minutos, perguntar: *"o que o/a impediu de continuar o teste?"*								
Presença de sinais e sintomas*			**Sim**	**Não**	**Sim**	**Não**	**Sim**	**Não**
• Dor, desconforto (ou outro equivalente anginoso) no peito, pescoço, mandíbula, membros superiores		Antes						
		Durante						
		Depois						
• Dispneia intolerável		Antes						
		Durante						
		Depois						
• Câibras nos membros inferiores		Antes						
		Durante						
		Depois						
• Marcha cambaleante		Antes						
		Durante						
		Depois						
• Diaforese e palidez ou aparência acinzentada		Antes						
• Tonturas		Durante						
		Depois						
Teve dor articular durante a locomoção?		Lombar						
		Coxo-femoral						
		Joelhos						
		Tornozelo-pé						
		Outra						
Recolha de parâmetros em REPOUSO **								
Pressão arterial (braço esquerdo)								
Frequência cardíaca de pulso (bpm)								
Saturação O2 (%)								
BORG (1 a 10)								
Recolha de parâmetros IMEDIATAMENTE APÓS O TESTE								
Pressão arterial (braço esquerdo)								
Frequência cardíaca de pulso (bpm)								
Saturação O2 (%)								
BORG (1 a 10)								
Recolha de parâmetros 1 MIN APÓS O TESTE								
Pressão arterial (braço esquerdo)								
Frequência cardíaca de pulso (bpm)								

Appendix VII – Evaluation of Symptoms and Adverse Events and Adherence to exercise

Protocolo 2 ID do Ensaio: _____	ETIQUETA	Momento: _____ ☐ Presencial ☐ Telefónica ___/___/___	Momento: _____ ☐ Presencial ☐ Telefónica ___/___/___	Momento: _____ ☐ Presencial ☐ Telefónica ___/___/___	Momento: _____ ☐ Presencial ☐ Telefónica ___/___/___	Momento: _____ ☐ Presencial ☐ Telefónica ___/___/___
AVALIAÇÃO DE SINTOMAS E EFEITOS ADVERSOS		Avaliador:__	Avaliador:__	Avaliador:__	Avaliador:__	Avaliador:__
Esta semana, sentiu algum dos seguintes sintomas (de novo)? *escrever qual(ais) o(s) sintoma(s) na caixa em branco						
• Dor, artralgias/dor óssea, dor abdominal? • Desconforto (ou outro equivalente anginoso) no peito, pescoço, mandibula, membros superiores? • Dispneia em repouso ou esforços/exercício ligeiro? • Ortopneia ou dispneia paroxística noturna? • Taquicardia, palpitações, arritmias? • Claudicação intermitente? • Edema dos membros inferiores? • Sudorese fria ou palidez? • Tonturas, desequilíbrio ou lipotimia? • Confusão/delirium? • Letargia/fraqueza muscular? • **Náuseas? Vómitos?** • **Problemas de memória**? (Leve, moderada ou grave) Interferem com as atividades habituais (instrumentais) ou diárias (autocuidado)? • **Febre?** (se sim, quanto e durante quanto tempo?) • **Fadiga?** (alivia com repouso? Se não alivia, interfere nas suas atividades habituais ou autocuidado? • **Parestesias nas extremidades?*** (Leve, moderada ou grave) Interfere com as atividades habituais ou autocuidado? • **Boca seca/Saliva espessa?** Interfere com a sua alimentação? • **Mucosite oral/Feridas ou dor na boca/garganta?** (pouca/moderada/muita?) Interfere com a sua alimentação?						
• **Diarreia**? Frequência em relação ao normal (< 4; 4-6; ≥7) • **Obstipação?** Ocasional ou regular? Interferiu nas suas atividades habituais (instrumentais) ou diárias (autocuidado)? • **Alopecia/Queda de cabelo?** Caiu menos (< 50%) ou mais (≥ 50%) de metade o que tinha antes?						
Necessitou de tomar alguma medicação para resolução de algum dos sintomas acima? Se sim, qual? E com que frequência?						
AVALIAÇÃO DA NUTRIÇÃO						
Teve dificuldades em se alimentar?						
Sentiu diminuição do apetite?						
Alterou a quantidade de comida?						
Perdeu peso? Se sim, indicar quanto?						
AVALIAÇÃO DA ADESÃO AO PROGRAMA DE EXERCÍCIO FÍSICO						
Esta semana, conseguiu cumprir o que lhe foi recomendado? (Sim, Não ou em parte)						
Se **NÃO** ou **EM PARTE**, quais os motivos?						
Se **SIM**:						
Exercício Aeróbico	Com que frequência? (vezes/ semana)					
	Qual a duração? (horas/minutos)					
	Qual a perceção do seu esforço? (0 a 10 BORG)					

*Se os sintomas persistirem (os que estão a sublinhado), dar a indicação que deve suspender o exercício físico até reavaliação médica.
*Caso sinta parestesias das extremidades, não necessita de suspender o exercício físico, mas há necessidade de reavaliação médica. Dar indicação que deve realizar o exercício físico com bom apoio/estabilidade dos membros inferiores e tronco.

	Conseguiu registar no relógio?					
Exercício de Força	Com que frequência? (vezes/ semana)					
	Qual o volume? (nº de séries e repetições)					
	Qual elástico utilizou para a realização dos exercícios de força?					
	Qual a perceção do seu esforço? (0 a 10 BORG)					
Treino dos Músculos inspiratórios	Com que frequência? (semanal/ diária)					
	Qual o volume? (nº de séries e repetições)					
	Qual a perceção do seu esforço? (0 a 10 BORG)					
Está a fazer o registo no diário?						
Recomendações/Progressões/Regressões:						
OBSERVAÇÕES:						

Protocolo 1 **ID do Ensaio:** _____	**ETIQUETA**	**Momento:** _____ ☐ Presencial ☐ Telefónica ___/___/___	**Momento:** _____ ☐ Presencial ☐ Telefónica ___/___/___	**Momento:** _____ ☐ Presencial ☐ Telefónica ___/___/___	**Momento:** _____ ☐ Presencial ☐ Telefónica ___/___/___	**Momento:** _____ ☐ Presencial ☐ Telefónica ___/___/___
AVALIAÇÃO DE SINTOMAS E EFEITOS ADVERSOS		☐ **Avaliador:**__ _____	**Avaliador:**__ _____	**Avaliador:**__ _____	**Avaliador:**__ _____	**Avaliador:**__ _____
Esta semana, sentiu algum dos seguintes sintomas (de novo)? *escrever qual(ais) o(s) sintoma(s) na caixa em branco						
• Dor, artralgias/dor óssea, dor abdominal? • Desconforto (ou outro equivalente anginoso) no peito, pescoço, mandibula, membros superiores? • Dispneia em repouso ou esforços/exercício ligeiro? • Ortopneia ou dispneia paroxística noturna? • Taquicardia, palpitações, arritmias? • Claudicação intermitente? • Edema dos membros inferiores? • Sudorese fria ou palidez? • Tonturas, desequilíbrio ou lipotimia? • Confusão/delirium? • Letargia/fraqueza muscular? • **Náuseas? Vómitos?** • **Problemas de memória**? (Leve, moderada ou grave) Interferem com as atividades habituais (instrumentais) ou diárias (autocuidado)? • **Febre?** (se sim, quanto e durante quanto tempo?)						

*Se os sintomas persistirem (os que estão a sublinhado), dar a indicação que deve suspender o exercício físico até reavaliação médica.
*Caso sinta parestesias das extremidades, não necessita de suspender o exercício físico, mas há necessidade de reavaliação médica. Dar indicação que deve realizar o exercício físico com bom apoio/estabilidade dos membros inferiores a tronco

• **<u>Fadiga?</u>** (alivia com repouso? Se não alivia, interfere nas suas atividades habituais ou autocuidado? • **Parestesias nas extremidades?** (Leve, moderada ou grave) Interfere com as atividades habituais ou autocuidado? • **Boca seca/Saliva espessa?** Interfere com a sua alimentação? • **Mucosite oral/Feridas ou dor na boca/garganta?** (pouca/moderada/muita?) Interfere com a sua alimentação? • **Diarreia**? Frequência em relação ao normal (< 4; 4-6; ≥7) • **Obstipação?** Ocasional ou regular? Interferiu nas suas atividades habituais (instrumentais) ou diárias (autocuidado)? • **Alopecia/Queda de cabelo?** Caiu menos (< 50%) ou mais (≥ 50%) de metade o que tinha antes?					
Necessitou de tomar alguma medicação para resolução de algum dos sintomas acima? Se sim, qual? E com que frequência?					
AVALIAÇÃO DA NUTRIÇÃO					
Teve dificuldades em se alimentar?					
Sentiu diminuição do apetite?					
Alterou a quantidade de comida?					
Perdeu peso? Se sim, indicar quanto?					
AVALIAÇÃO DA ADESÃO AO PROGRAMA DE EXERCÍCIO FÍSICO					
Esta semana, conseguiu cumprir o que lhe foi recomendado? (Sim, Não ou em parte)					
Se **NÃO** ou **EM PARTE**, quais os motivos?					
Se **SIM**:					
Com que frequência? (vezes/ semana)					
Qual a duração? (horas/minutos)					
Qual a perceção do seu esforço? (0 a 10 BORG)					
Conseguiu registar no relógio?					
OBSERVAÇÕES:					

	Conseguiu registar no relógio?					
Exercício de Força	Com que frequência? (vezes/ semana)					
	Qual o volume? (nº de séries e repetições)					
	Qual elástico utilizou para a realização dos exercícios de força?					
	Qual a perceção do seu esforço? (0 a 10 BORG)					
Treino dos Músculos inspiratórios	Com que frequência? (semanal/ diária)					
	Qual o volume? (nº de séries e repetições)					
	Qual a perceção do seu esforço? (0 a 10 BORG)					
Está a fazer o registo no diário?						
Recomendações/Progressões/Regressões:						
OBSERVAÇÕES:						