UNIVERSIDADE BEIRA INTERIOR

Effects of physical exercise concomitant with chemotherapy on cardiac functionality of women with breast cancer

Pedro Miguel da Silva Antunes

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Dedication

Aos meus queridos Pais, Benilde Antunes e Vítor Antunes.

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Preface

[*]Vai ser dia feliz
Nem interessa o que diz
A sorte do zodíaco,
Vestida a preceito
Com a banda ao peito
Do ritmo cardíaco

Com água no saco,
E prudente casaco
P'ra quando acabar,
E sem um cosmético
Para efeito estético
Só creme solar.

Dar a trela à língua,
Que não fica à míngua
É preliminar,
É um dialeto
Que eu interpreto
P'ros males expiar

Próximo momento
É o aquecimento
E toca a mexer,
Do braço à perna
De forma alterna
Doa a quem doer.

Ninguém acredita
O estado em que fica
O meu coração
É coisa estranha
E energia tamanha
Em vez de exaustão
Pois na carreira,
Desta vida sã
Mais nada me dá
A genica e pica
Qu'o cardio me dá.

S' a batida acelera
De forma sincera
Não é da paixão,
Eu até me torço
Com tanto esforço
Que ponho na ação,

Com vigor esdrúxulo
Trabalhar o músculo
Do coração,
Pois esse, eu declaro
É um bem tão caro
Merece atenção,

E não é sacrifício
Tanto exercício
De musculação,
É por bom motivo
E o objetivo
É um corpo são,

Vida é movimento
Ouve o chamamento
Do teu coração,
E se querer é poder
Vem então viver
É esta a lição.

[*]Letra escrita em homenagem ao Mama Move on Treatment trial, autorizada pela autora.

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List of Publications

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- **Study 1** – Journal article.

  Antunes, P., Esteves, D., Nunes, C., Amarelo, A., Fonseca-Moutinho, J., Afreixo, V., Costa, H., Alves, A., & Joaquim, A. (2019). Effects of physical exercise on outcomes of cardiac (dys)function in women with breast cancer undergoing anthracycline or trastuzumab treatment: study protocol for a systematic review. *Systematic reviews, 8*(1), 239. https://doi.org/10.1186/s13643-019-1154-x.

- **Study 2** – Journal article.

Antunes, P., Esteves, D., Nunes, C., Amarelo, A., Fonseca-Moutinho, J., Afreixo, V., Costa, H., Alves, A., & Joaquim, A. (2021). Effects of Exercise on Cardiac Function Outcomes in Women Receiving Anthracycline or Trastuzumab Treatment for Breast Cancer: A Systematic Review and Meta-Analysis. *Applied Sciences, 11*, 8336. https://doi.org/10.3390/app11188336.

- **Study 3** – Journal article.

Antunes, P., Esteves, D., Nunes, C., Sampaio, F., Ascensão, A., Vilela, E., Teixeira, M., Amarelo, A. L., & Joaquim, A. (2019). Impact of exercise training on cardiotoxicity and cardiac health outcomes in women with breast cancer anthracycline chemotherapy: a study protocol for a randomized controlled trial. *Trials, 20*(1), 433. https://doi.org/10.1186/s13063-019-3499-9.

- **Study 4** – Journal article.

Antunes, P., Joaquim, A., Sampaio, F., Nunes, C., Ascensão, A., Vilela, E., Teixeira, M., Capela, A., Amarelo, A., Marques, C., Viamonte, S., Alves, A., & Esteves, D. (2023). Effects of exercise training on cardiac toxicity markers in women with breast cancer undergoing chemotherapy with anthracyclines: a randomized controlled trial. *European Journal of Preventive Cardiology, 30*(9), 844–855. https://doi.org/10.1093/eurjpc/zwad063.

- **Study 5**

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Apart from these papers, the author of this dissertation also conducted preliminary study as an initial exploration into the field of exercise oncology:

- **Antunes, P.,** Esteves, D., Nunes, C., Joaquim, A., Pimentel, F. L., & Fonseca-Moutinho, J. (2019). Health-related quality of life and physical fitness in breast cancer patients: the impact of a supervised physical exercise program in women with no exercise experience. *Psychology, health & medicine,* 24(9), 1038–1046. https://doi.org/10.1080/13548506.2019.1597978.

List of Communications

Preliminary results were presented at national and international conferences:

- **Communication 1** – Poster presentation.

Antunes, P., Esteves, D., Nunes, C., Sampaio, F., Ascensão, A., Vilela, E., Teixeira, M., Amarelo, A., & Joaquim, A. (2019). Could physical exercise prevent anthracycline-related cardiotoxicity in breast cancer patients? Rationale and design of a intra-hospital randomized controlled trial. *Supportive care in cancer, 27 (Suppl 1)*, s264-s265. https://doi.org/10.1007/s00520-019-04813-1.

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- **Communication 5** – Poster presentation.

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List of Honours

The journal article included in this thesis, entitled “Effects of exercise training on cardiac toxicity markers in women with breast cancer undergoing chemotherapy with anthracycline: a randomized controlled trial” published by Pedro Antunes, Ana Joaquim, Francisco Sampaio, Célia Nunes, António Ascensão, Eduardo Vilela, Madalena Teixeira, Andreia Capela, Anabela Amarelo, Cristiana Marques, Sofia Viamonte, Alberto Alves & Dulce Esteves in the *European Journal of Preventive Cardiology*, **received an honourable mention in the context of an application for the Sports Science Awards 2022/2023, in the Sports Medicine category, promoted by the Portuguese Olympic Committee**.

Resumo

A quimioterapia contendo antraciclinas é frequentemente utilizada no tratamento de neoplasias hematológicas e tumores sólidos, incluindo o cancro da mama. Apesar do seu reconhecido valor clínico, a utilização de antraciclinas é limitada pela subjacente cardiotoxicidade dose-dependente e cumulativa. Adicionalmente, o tratamento do cancro da mama é tipicamente multimodal, o que pode agravar o dano cardíaco. A toxicidade cardíaca é um problema *major* com implicações na decisão terapêutica e na morbi/mortalidade destes doentes. Estudos longitudinais têm demonstrado que as doenças cardiovasculares são uma das principais causas de morte entre mulheres sobreviventes de cancro da mama. Por estes motivos, diversas agências internacionais, como a American Society of Clinical Oncology e a European Society of Cardiology, salientam a importância de implementar intervenções de prevenção primária, incluindo o exercício físico, uma intervenção acessível e de baixo custo, com benefícios comprovados na saúde global. Estudos pré-clínicos demonstraram resultados promissores na atenuação da cardiotoxicidade associada ao tratamento com antraciclinas. Contudo, o efeito cardioprotetor em humanos carece de informação adicional, incluindo a análise de marcadores de integridade e funcionalidade cardíaca, da aptidão cardiorrespiratória e fatores associados, assim como indicadores de adesão, segurança e qualidade de vida. Após a realização de uma revisão da literatura sobre a temática (**Estudos 1 e 2**) e do desenho de um ensaio randomizado controlado, unicêntrico, com dois braços (grupo de exercício vs. grupo de controlo) (**Estudo 3**), foi objetivo principal da presente dissertação avaliar o impacto de um programa de exercício de físico supervisionado em marcadores estabelecidos de toxicidade cardíaca (i.e., fração de ejeção do ventrículo esquerdo, strain longitudinal global e biomarcadores cardíacos) em mulheres com cancro da mama a realizar quimioterapia contendo antraciclinas em contexto curativo. Foram ainda definidos, como objetivos secundários, avaliar a segurança do exercício físico e o seu efeito na aptidão cardiorrespiratória, funcionalidade física e qualidade de vida relacionada com a saúde. O programa consistiu em 3 sessões semanais de treino combinado (i.e., treino aeróbio e treino resistido) durante o período de quimioterapia (duração ~5 meses). Da análise da literatura, apoiada numa revisão sistemática com meta-análise de ensaios randomizados controlados (**Estudos 2**), verificámos que a evidência sobre o efeito do exercício físico em parâmetros estabelecidos de toxicidade cardíaca era escassa, tendo sido identificados apenas quatro estudos elegíveis. Além disso, a maioria apresentava limitações relevantes, incluindo um desenho não específico para avaliar a eficácia do exercício físico nos parâmetros de

interesse, tamanho da amostra reduzido, programas de treino e seguimentos curtos. Os resultados da meta-análise não mostraram um efeito significativo do exercício físico em relação ao controlo. Uma análise exploratória, que incluiu estudos que implementaram programas de treino com pelo menos 36 sessões de treino (n=3), revelou um efeito superior do exercício físico na fração de ejeção do ventrículo esquerdo em repouso, podendo sugerir que a duração da intervenção possa estar associada ao efeito do exercício físico na função cardíaca. Por sua vez, os resultados do nosso ensaio randomizado controlado demonstraram que o exercício físico não preveniu significativamente o declínio de marcadores estabelecidos de toxicidade cardíaca (**Estudo 4**). No entanto, verificou-se que realizar exercício físico durante a quimioterapia foi seguro- não foi registado qualquer evento adverso grave durante as sessões de treino-, e que este preveniu significativamente o declínio da aptidão cardiorrespiratória, da qualidade de vida relacionada com a saúde e da funcionalidade física (**Estudos 4 e 6**). Adicionalmente, constatou-se uma resposta heterogénea da aptidão cardiorrespiratória ao exercício, o que justificou a análise de potenciais preditores através de um estudo exploratório (**Estudo 5**). Os resultados evidenciaram o índice de massa corporal e o equivalente metabólico de tarefa por hora (MET/h) total de treino aeróbio como fatores associados à resposta da aptidão.

Em resumo, os nossos resultados sugerem que a realização de exercício físico complementarmente ao cuidado *standard* em mulheres com cancro da mama a realizar quimioterapia contendo antraciclinas, não se traduz em benefícios nos marcadores estabelecidos de toxicidade cardíaca. No entanto, a implementação de um programa de exercício físico supervisionado nesta fase revelou ser uma estratégia segura, viável e eficaz para melhorar a aptidão cardiorrespiratória, prevenir o declínio da funcionalidade física e da qualidade de vida relacionada com a saúde nesta população. Os nossos resultados sugerem, ainda, o dispêndio energético do treino aeróbio (i.e., MET/h) como a componente de treino com poder preditivo mais elevado da resposta da aptidão cardiorrespiratória ao exercício físico.

Palavras-chave

Exercício físico; cancro da mama; quimioterapia; cardiotoxicidade; função cardíaca; aptidão física; aptidão cardiorespiratória; capacidade funcional; qualidade de vida.

Abstract

Anthracycline-containing chemotherapy is commonly used in the treatment of hematologic cancers and solid tumors, including breast cancer. Despite its well-recognized clinical efficacy, the use of anthracyclines is limited by dose-dependent and cumulative cardiotoxic risk. Additionally, breast cancer treatment is often multimodal, which can further increase the cardiac damage. The cardiac toxicity poses significant challenges, influencing therapeutic decision-making and exacerbate patients' morbidity and mortality. Longitudinal studies have shown that cardiovascular diseases are one of the leading causes of death among women with breast cancer. As a result, various international agencies, such as the American Society of Clinical Oncology and the European Society of Cardiology, emphasize the importance of implementing primary prevention interventions. Exercise training is an accessible and cost-effective intervention with well-documented benefits for overall health. Preclinical studies have shown promising results in mitigating the cardiotoxic impact of anthracyclines. However, whether this potential cardioprotective effect translates to humans is a question that remains to be clarified. The objectives of this thesis were to conduct a literature review on this topic (**Study 1 and 2**) and, as the core of this doctoral program, to design a single-center, randomized controlled trial with two arms (exercise group vs. usual care group) (**Study 3**). The main objective of this trial was to analyze the impact of a supervised exercise training program on established markers of cardiac toxicity (i.e., left ventricular ejection fraction, global longitudinal strain, and cardiac biomarkers) in women with breast cancer undergoing curative anthracycline-containing chemotherapy. Secondary objectives included analyzing the safety of exercise training and its effect on cardiorespiratory fitness, physical functionality, and health-related quality of life. The program consisted of three sessions per week of combined training (i.e., aerobic and resistance training) during each participant's chemotherapy length (approximately 5-months). Through the literature review, supported by a systematic review with meta-analysis of randomized controlled trials (**Study 2**), we found that evidence on the effect of physical exercise on established parameters of cardiac toxicity was limited, as only four eligible studies were identified. Most of these studies had significant limitations, including designs not specifically aimed at evaluating the efficacy of physical exercise on the parameters of interest, small sample sizes, short training programs, and brief follow-up periods. The results of the meta-analysis did not show a significant effect of exercise training compared to non-exercise. However, an exploratory analysis, which included studies with training programs consisting of at least 36 sessions (n=3), revealed a

superior effect of exercise training on resting left ventricular ejection fraction. This suggests that the length of the exercise training programs might be associated with the effect of exercise training on cardiac function. The results of the randomized controlled trial demonstrated that exercise training did not significantly prevent the decline in established markers of cardiac toxicity compared to control (**Study 4**). However, it was found that exercising was safe—no serious adverse events were reported during the exercise training sessions—and it significantly prevented the decline in cardiorespiratory fitness, physical functionality, and health-related quality of life (**Study 4 and 6**). Additionally, we found that the response of cardiorespiratory fitness among participants randomized to the exercise group was heterogeneous, which justified the analysis of potential predictors through an exploratory study (**Study 5**). The results revealed that the parameters associated with the response in cardiorespiratory fitness to training were baseline body mass index and total aerobic training metabolic equivalent of task per hour (MET-hour).

In summary, the results of this thesis suggest that adding exercise training to standard breast cancer care does not provide benefits on established markers of cardiac toxicity in women undergoing anthracycline-containing chemotherapy. However, the findings of experimental works indicate that implementing a supervised exercise training program during chemotherapy is safe and can be a viable and effective approach for improving cardiorespiratory fitness, preventing the decline in physical functionality and health-related quality of life in this challenging patient population. Additionally, our study suggests that the total energy expenditure of aerobic exercise (i.e., MET-hour) may be a predictor of cardiorespiratory response.

Keywords

Exercise training; breast cancer; chemotherapy; cardiotoxicity; cardiac function; physical fitness; cardiorespiratory fitness; functional capacity; quality of live.

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List of Acronym

A-Ct	Anthracycline-containing chemotherapy
a-vO_2diff	Arteriovenous oxygen difference
BC	Breast cancer
CTRCD	Cancer therapy-related cardiac dysfunction
CV	Cardiovascular
CI	Confidence interval
CAD	Coronary artery disease
CRF	Cardiorespiratory fitness
EORTC	European Organization for Research and Treatment of Cancer
GLS	Global longitudinal strain
HRQoL	Health-related quality of life
HF	Heart failure
HER2	Human epidermal growth factor receptor 2
IARC	International Agency for Research on Cancer
ISRCTN	International standard randomized controlled trial number
LVEF	Left ventricular ejection fraction
MCT	Metabolic equivalent of task
MET	Metabolic equivalent of task
NT-proBNP	N-terminal pro b-type natriuretic peptide
VO_2peak	Peak oxygen uptake
QLQ-C30	Quality of Life Questionnaire
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SETP	Supervised exercise training program
US	Usual care

Chapter 1 – Introduction

Breast cancer (BC) stands as the most prevalent tumor among women globally (Bray et al., 2024). According to GLOBOCAN data, approximately 2.3 million new cases of BC were diagnosed worldwide in 2022, accounting for 11.6% of all cancer cases (Bray et al., 2024). The incidence of BC has been rising annually by about 0.6%, largely attributed to the implementation of mammography screening programs, population growth and aging (Siegel et al., 2023, 2024). Projections suggest that by 2040, new BC cases could exceed 3 million (Arnold et al., 2022; Ju et al., 2023). Despite this surge, the cure rate has consistently improved over recent decades, driven by early diagnosis, advances in therapeutic research and its integration in clinical practice (Siegel et al., 2023). As a result, the 5-year survival rate for BC now exceeds 90% in most developed countries, contributing to a steady increase in the number of BC survivors (Siegel et al., 2023).

The treatment of BC is typically multimodal, involving local therapies such as surgery and radiotherapy, alongside systemic treatments (Cardoso et al., 2019; Korde et al., 2021; Loibl et al., 2024). Among systemic treatments, anthracycline-containing chemotherapy (A-Ct) is traditionally employed in curative setting (Cardoso et al., 2019; Korde et al., 2021; Loibl et al., 2024). The clinical benefit of anthracyclines (e.g., doxorubicin and epirubicin) is well established, with numerous clinical trials demonstrating their significant impact on BC overall survival (Early Breast Cancer Trialists' Collaborative Group, 2012). However, its use is limited by the well-documented cumulative and dose-dependent direct toxic effects on cardiac myocytes (Lyon et al., 2022; McGowan et al., 2017; Zamorano et al., 2016). The cardiotoxicity risk of BC patients taking A-Ct may be further exacerbated by the additional use of other cardiotoxic cancer therapies, including cytotoxic drugs (e.g., alkylating agents, taxanes, small molecule tyrosine kinase inhibitors), radiotherapy to the thoracic wall or mediastinum, and trastuzumab, as well as the presence of risk factors such as advanced age, pre-existing hypertension, obesity, diabetes mellitus, or coronary artery disease (Curigliano et al., 2012; Lyon et al., 2022; McGowan et al., 2017; Zamorano et al., 2016).

The cardiovascular (CV) side effects of BC-related therapies are diverse and include, among others, an increased risk of cardiac dysfunction (Herrmann et al., 2022; Lyon et al., 2022; Zamorano et al., 2016). Cancer therapy-related cardiac dysfunction (CTRCD) is the most severe form of cardiac toxicity associated with anthracyclines and can present clinically with cardinal symptoms of heart failure (HF) (Herrmann et al., 2022; Lyon et al., 2022). It may also be detected in asymptomatic patients through changes in left ventricular systolic function, often observed during cancer treatment (Cardinale et al., 2015; Herrmann et al., 2022; Lyon et al., 2022). Left ventricular ejection fraction (LVEF) is the most common parameter used to monitor these changes (Herrmann et al., 2022). However, because LVEF may not detect subtle changes in cardiac function, alternative imaging markers of cardiotoxicity such as global longitudinal strain (GLS) and cardiac biomarkers (troponin or natriuretic peptide) are recommended for a

comprehensive assessment (Plana et al., 2014; Sawaya et al., 2011). Studies have demonstrated that these markers can be useful in predicting early cardiac dysfunction; accordingly, they were recently incorporated in the definition of asymptomatic CTRCD in the cardio-oncology guidelines from the European Society of Cardiology (Lyon et al., 2022).

Notably, CV disease poses a significant burden during cancer survivorship, emerging as the leading cause of non-cancer-related death (Armenian et al., 2016; Paterson et al., 2022; Patnaik et al., 2011; Strongman et al., 2022). Therefore, developing and implementing effective prevention strategies to mitigate and/or prevent the cancer-related CV toxicity, while ensuring effective and safe cancer treatment, has become a matter of interest and a research priority (Alexandre et al., 2020; Armenian et al., 2017; Curigliano et al., 2020; Lyon et al., 2022; Zamorano et al., 2016). Preventive strategies include baseline screening, CV imaging surveillance, and primary prevention measures, such as active management of modifiable CV risk factors and promotion of healthy lifestyle habits, in which physical activity and nutrition seem to be key (Alexandre et al., 2020; Armenian et al., 2017; Curigliano et al., 2020; Lyon et al., 2022; Zamorano et al., 2016). Modifications of A-Ct administration, and the potential use of HF pharmacotherapy in certain cases are also mentioned (Alexandre et al., 2020; Armenian et al., 2017; Curigliano et al., 2020; Lyon et al., 2022; Zamorano et al., 2016).

Among healthy lifestyle routines, regular physical activity is widely recognized as a crucial component for preventing and managing CV disease in the general population (Visseren et al., 2021). Particularly, in the oncology field, mounting body of epidemiological evidence supports a significant inverse relationship between self-reported physical activity and cancer-specific mortality, with a risk reduction ranging from 33% to 85% (Scott et al., 2011). Additionally, some evidence suggests that pre-and post-treatment physical activity exposure may also reduce the risk of CV events and CV disease-specific mortality (Alexandre et al., 2020; Gilchrist et al., 2019; Kim et al., 2021; Lavery et al., 2023; Okwuosa et al., 2019).

Exercise training—a planned, structured, and repetitive form of physical activity aimed at improving or maintaining physical fitness (American College of Sports Medicine, 2021)— is a cornerstone in cardiac rehabilitation, but only since the middle of the first decade of the 2000s has gained acceptance as a potential key adjunct therapy following a cancer diagnosis (Rock et al., 2012; Schmitz et al., 2010). The initial exercise guidelines for cancer survivors, introduced by the American College of Sports Medicine in 2010, emphasized the importance of cancer patients engaging in physical activity, while discouraging prolonged inactivity (Schmitz et al., 2010). These guidelines determined that exercise training is generally safe and confers benefits on physical functioning, quality of life, and cancer-related fatigue, during and after cancer treatments (Schmitz et al., 2010). The recommendations of physical activity for cancer survivors aligned with guidelines for adults with chronic diseases, advocating for a minimum of 150 minutes per week of moderate-intensity aerobic activity (or 75 minutes if vigorous-intensity), and incorporating resistance training on two or more days per week for overall health and fitness (Schmitz et al.,

2010). Since then, the number of randomized controlled exercise trials (RCTs) in exercise oncology field increased by 281%, and in 2019 an updated of the initial guidelines was published (Campbell et al., 2019). The conclusions in terms of safety have remained consistent and accumulated evidence showed that the benefits of exercise training were significant in important health-related outcomes, including physical fitness levels, anxiety and depressive symptoms, fatigue, and lymphoedema (Campbell et al., 2019). A pivotal feature of this guideline document was the definition of specific evidence-based FITT principles of exercise training (i.e., frequency, intensity, time, type of training) for targeting these health-related outcomes. Whilst the efficacy of the proposed evidence-based FITT prescription is still under research, these new guidelines suggested that an effective exercise prescription should include moderate-intensity aerobic training at least 3 times per week for at least 30 minutes, over a period of 8 to 12-weeks (Campbell et al., 2019). The addition of resistance training, at least twice a week, consisting of at least 2 sets of 8 to 15-repetitions at a minimum of 60% of one repetition maximum, is anticipated to provide comparable benefits (Campbell et al., 2019).

Several RCTs have provided evidence that exercise training, particularly if it includes aerobic training, may help to preserve or enhance cardiorespiratory fitness (CRF) in cancer patients (Scott et al., 2018a). While most evidence is derived from studies in non-oncology populations, it is now recognized that aerobic training plays a role in mitigating left ventricular remodeling and enhancing myocardial contractility, stroke volume, diastolic relaxation, and filling (Clark et al., 1992; Hambrecht, 2000; Haykowsky et al., 2012, 2022; Scott et al., 2013). Moreover, aerobic training has been shown to elicit adaptations extending beyond the heart, promoting enhancements in peripheral vascular function (Clark et al., 1992; Hambrecht, 2000; Haykowsky et al., 2012, 2022; Scott et al., 2013). This includes enhanced oxygen utilization in skeletal muscles resulting from increased capillary surface area and oxidative capacity, beneficial adaptations that can be further optimized when combined with resistance training (Beever et al., 2020; Foulkes et al., 2024; Kirkham et al., 2021; Okushima et al., 2016; Segerström et al., 2011).

Preclinical studies in rodents have suggested that aerobic/endurance training may mitigate or prevent cardiac damage induced by anthracyclines (Kirkham & Davis, 2015; Naaktgeboren et al., 2022; Scott et al., 2018b). For example, research in animal models indicate that aerobic exercise, whether performed before or during doxorubicin treatment, can alleviate harmful effects such as increased leakage of cardiac troponin I levels as a measure of cardiac myocyte structural integrity, left ventricular dysfunction, increased levels oxidative stress markers, cardiac mitochondrial dysfunction with consequent increased apoptotic signaling and (auto)mitophagy deregulation, as well as drug accumulation in cardiac tissue (Ascensão et al., 2005b, 2005a, 2006; Chicco et al., 2006; Morton et al., 2019). These promising findings, along with an understanding of the positive effects of exercise training on key cardiac function endpoints, provide a solid foundation to transition from preclinical research to clinical studies.

In a 2016 position paper addressing cancer treatments and CV toxicity, the European Society of Cardiology recommend aerobic training as a non-pharmacological intervention to prevent or attenuate CTRCD (Zamorano et al., 2016). This recommendation was primarily supported on preclinical evidence, as at that point, only one RCT had published data on the potential cardioprotective effect of exercise (Hornsby et al., 2014). Involving 20 women with BC receiving A-Ct, Hornsby et al. (2014) found that a 12-week aerobic training completely abrogated the decline in CRF seen in non-exercise group, although no significant effects were noted in LVEF or other conventional echocardiographic parameters. Subsequently, three other studies provided data that added to the existing literature. Some failed to validate the favorable outcomes observed in animal models, finding that exercise training did not significant role preserve cardiac function in BC patients undergoing doxorubicin (Howden et al., 2019; Kirkham et al., 2018b). In contrast, Ma (2018) reported, in a RCT that included 64 women with BC receiving A-Ct, that a 16-week interval aerobic training program, consisting of three sessions per week of 50 minutes each, significantly attenuated the decline in LVEF compared to a non-exercise control group. Despite these encouraging results, the inconsistencies among studies, their limited number and modest sample size, constrain our ability to ascertain the effectiveness of exercise training in this context. The uncertainty regarding the potential cardioprotective role of exercise training during cardiotoxic treatment advocates the need to replicate Ma's (2018) findings in a larger cohort of cancer patients, complemented by appropriate follow-up assessments including novel subclinical markers of cardiac toxicity.

Recognizing the growing evidence from RCTs investigating the impact of exercise on established markers of cardiac toxicity in women with BC undergoing A-Ct and trastuzumab, we identified the need to review their findings and methods, particularly the FITT principles. Indeed, there were systematic reviews available on the effects of exercise in animal models, but none specifically addressed its impact in human subjects (Chen et al., 2017; Kirkham & Davis, 2015; Scott et al., 2011, 2018a). To achieve this purpose, a study protocol (**Study 1**) for a systematic review was developed and registered on the PROSPERO database. This protocol outlined the research rationale and detailed the methodology for conducting a systematic review. A systematic review of RCTs was subsequently conducted (**Study 2**).

Regarding patients-related experimental contribution, the main objective of this thesis was to design and conduct a two-arm, single-center RCT, the Mama Move Gaia on treatment trial. This trial aimed to assess whether a supervised exercise training program (SETP), combining aerobic and resistance training could serve as a primary prevention intervention against the decline in cardiac function in women with early-stage BC undergoing A-Ct. The first step involved the development of a study protocol for a RCT (**Study 3**), which established the rationale and methodology for conducting this trial. This protocol was registered in the International Standard Randomized Controlled Trial Number (ISRCTN), in accordance with best research practices. Three experimental studies (**Studies 4, 5, 6**) were implemented following the design of the Mama Move Gaia on treatment trial. **Study 4** was the cornerstone of this thesis. In this study, we

report data regarding the impact exercise training on established markers of cardiac toxicity including LVEF, GLS, and circulating biomarkers, as well on secondary endpoints, including CRF, safety and tolerance to exercise training. Although some RCTs and non-RCTs have examined the effects of exercise training on cardiac function in BC patients receiving A-Ct, these studies often had relatively modest sample sizes and implemented short-term exercise training programs (12 to 16-weeks) (Costello et al., 2019; Haykowsky et al., 2009; Hornsby et al., 2014; Howden et al., 2019; Kirkham et al., 2018b). Furthermore, not all these studies assessed subclinical parameters, potentially more sensitive markers of early toxicity, such as GLS or cardiac biomarkers. It is our belief that data presented in our study can further contribute strengthen the body knowledge of the specific literature by addressing some of the limitations identified in previous research.

Subsequently, we conducted the **Study 5**. This was unplanned exploratory analysis, prompted by the heterogeneity in CRF responses observed in the data from **Study 4**. Understanding individual CRF responses to exercise training is a critical question in personalized exercise medicine, and there is growing interest in identifying the factors influencing patients' CRF responsiveness to exercise (Ross et al., 2019). While some studies in the oncology context have assessed the impact of physiological variables, there is still a lack of information regarding the influence of training variables (Foulkes et al., 2023a, 2024; Kirkham et al., 2021). For instance, some studies suggest that, during chemotherapy, women with BC who had better attendance at exercise sessions experienced greater gains in CRF (Foulkes et al., 2023b; Haykowsky et al., 2009). However, attendance rates may not fully capture the true exercise dose, particularly in patients undergoing training programs during chemotherapy (Kirkham et al., 2018a). This underscores the importance of assessing CRF responsiveness with other training components, alongside socio-demographic, clinical, and physiological characteristics.

Finally, it is widely recognized that chemotherapy is associated with a large spectrum of physiological and psychological side effects that negatively impact patients' health-related quality of life (HRQoL) (Denlinger et al., 2018; Loibl et al., 2024; Sheng et al., 2019). Evidence indicates that exercise training programs implemented during active cancer treatment can serve as a non-pharmacological, cost-effective intervention to alleviate some associated toxicities (e.g., fatigue, anxiety) (Campbell et al., 2019; Cormie et al., 2018; Rock et al., 2012). While trials have consistently demonstrated a significant positive effect of exercise on physical function, the extent to which exercise prevents a decline in HRQoL remains uncertain with the literature showing inconsistent findings (Courneya et al., 2007; Hornsby et al., 2014; Mijwel et al., 2018; Schmidt et al., 2015; Travier et al., 2015). Findings from a recent meta-analysis have proposed that combined training may offer greater benefits compared to single-modality exercise programs; however, the supporting literature is still insufficiently robust (Martínez-Vizcaíno et al., 2023). Researchers have primarily assessed the impact of exercise on HRQoL through mean differences between groups, often neglecting clinically relevant changes at the individual patient level, which could provide insights into shifts in patients' supportive care needs (Giesinger et al., 2020; Snyder et al., 2015). For example, Mijwell et al. (2018) showed that a 16-week exercise training program

mitigated declines in physical function and reduced fatigue compared to standard care in women with BC receiving chemotherapy, although no differences were observed in the general quality of life scale. Analyzing data at the individual patient level—specifically examining the prevalence of patients who experience clinically significant changes and those who report scores below the clinical importance threshold for functional domains (or above for symptom domains)—could provide a more comprehensive understanding of the role of exercise training. Considering this rational, we conducted **Study 6** analyzing the impact of physical exercise on HRQoL and function capacity.

1.1. Thesis organization

This thesis is organized in eight main chapters and adopts a modern format, comprising a series of chapters that include a review of the literature and original data from the experimental works, presented in the form of research papers as follows:

- Chapter 1 introduces the thesis, establishing the research framework and defining the general objective.
- Chapter 2 describes the specific objectives of this thesis.
- Chapter 3 provides a comprehensive background on the key concepts relevant to this thesis.
- Chapter 4 presents a protocol for a systematic review of RCTs that analyzed the effects of exercise training on cardiac function and circulating biomarkers in women with early-stage BC undergoing A-Ct or trastuzumab (**Study 1**).
- Chapter 5 presents the results of a systematic review and meta-analysis (**Study 2**), based on the protocol presented in the previous chapter.
- Chapter 6 includes the results of the experimental work and is organized into four sub-chapters:
    - **Study 3** – This subchapter outlines the rationale and design of a RCT aimed at evaluating the effects of a SETP in women with early-stage BC undergoing A-Ct.
    - **Study 4** – Based on RCT described in Study 3, this subchapter presents the effects of a SETP on established markers of cardiac toxicity and CRF.
    - **Study 5** – This subchapter presents an exploratory analysis, based on data from Study 4, which aimed to study the CRF responsiveness among patients who underwent the SETP during A-Ct and to identify predictors of CRF response.

- **Study 6** –This subchapter presents the effects of a SETP on HRQoL and functional capacity.

- Chapter 7 provides a general discussion of the key results from the experimental works and suggests potential directions for future research.

- Chapter 8 provides the main remarks of the experimental works.

Chapter 2 – Specific Objectives

This thesis aims to enhance scientific understanding of the role of exercise training during chemotherapy in women with early-stage breast cancer (BC), with a central focus on its potential cardioprotective effect on cardiac function. Additionally, the thesis analyzes the effects of exercise training on cardiorespiratory fitness (CRF), health-related quality of life (HRQoL) and functional capacity. To achieve these objectives, we undertook six studies with the following specific aims:

- **Study 1 –** To describe the rationale and methods for a systematic review of randomized controlled exercise trials (RCTs) that analyzed the effects of exercise training on cardiac function and circulating biomarkers in women with early-stage BC undergoing anthracycline-containing chemotherapy (A-Ct) or trastuzumab.

- **Study 2 –** A systematic review and meta-analysis of RCTs on the effects exercise training (i.e., aerobic, resistance, or combined training) on established cardiac toxicity markers in women with BC undergoing A-Ct or trastuzumab.

- **Study 3 –** To describe the rationale for two-arm, single-center RCT, designed to evaluate the efficacy of a supervised exercise training program (SETP), compared to usual care, on established markers of cardiac toxicity in women with early-stage BC receiving A-Ct.

- **Study 4 –** Aimed to analyze the efficacy of exercise training in mitigating the decline on established markers of cardiac toxicity, namely: resting left ventricular ejection fraction (LVEF); global longitudinal strain (GLS); and circulating biomarkers (N-terminal pro-brain natriuretic peptide and high-sensitivity cardiac troponin T).

  Additionally, we aimed to analyze effects on CRF and to assess the safety and tolerability of the exercise training.

- **Study 5 –** Aimed to analyze the CRF responsiveness among the BC patients who performed the SETP during A-Ct and to identify what variables are associated with this response.

- **Study 6 –** Aimed to analyze the efficacy of exercise training on HRQoL and functional capacity (i.e., maximum voluntary handgrip strength and muscle strength and endurance of the lower limbs). In addition, to investigate patient-level changes in HRQoL, two exploratory secondary analyses were also carried out:

    - To analyze the proportion of patients who experienced clinically significant worsening in the different domains of HRQoL.

- To analyze the proportion of patients that reach thresholds for clinical importance in the different domains of HRQoL.

Chapter 3 – Background

3.1. Epidemiology

Cancer is a major global public health concern. The International Agency for Research on Cancer (IARC), a specialized agency of the World Health Organization, has been providing comprehensive global data on cancer epidemiology for many years (Saracci & Wild, 2016). In its latest report, the IARC released updated global statistics, offering insights into the incidence and mortality rates of 36 cancer types across 185 countries for the year 2022 (Bray et al., 2024). In that year alone, approximately 20 million new cancer cases were diagnosed worldwide, marking a 10% increase from the figures in 2018 (Bray et al., 2018, 2024). Of these cases, lung cancer and female breast cancer (BC) were the most incident, accounting for approximately 12.4% (i.e., 2.5 million cases) and 11.6% (i.e., 2.3 million cases) of all newly diagnosed cases, respectively (Bray et al., 2024).

Among women, BC is by far the most incident cancer and the leading cause of cancer-related mortality in many countries worldwide (Bray et al., 2024). Specifically, in 2022, BC was responsible for approximately 670,000 deaths globally, representing 15.4% of cancer-related mortality (Bray et al., 2024). This pattern is notably observed in Portugal as well. According to GLOBOCAN 2022 data, there were an estimated 8,954 new cases of female BC diagnosed, making up 12.9% of all new cancer cases in Portugal (Ferlay et al., 2024). The mortality rate for BC in Portugal was projected at 15.5%, constituting approximately 2,200 deaths (Ferlay et al., 2024).

Globally, the incidence rate of BC has been steadily rising by approximately 0.6% per year (Siegel et al., 2024). Recent projections indicate that 8% of women (i.e., 1 in 12) will be diagnosed with BC before the age of 75 (Dyba et al., 2021). If current trends persist, along with population growth and aging, it is anticipated that the annual global burden of BC will exceed 3 million new cases by the year 2040 (Arnold et al., 2022; Ju et al., 2023). Fortunately, the increase in BC incidence has been accompanied by a substantially decline in mortality since 1990, resulting in a consistent increase in BC survivors (Sung et al., 2021). In most high-income countries, the 5-year survival rate for early-stage BC (i.e., non-metastatic) now exceeds 90% (Siegel et al., 2023). This progress is largely attributed to remarkable advancements in BC research and cancer-related therapies, coupled with the widespread implementation of mammography screening programs and awareness campaigns (Siegel et al., 2023).

3.2. Breast cancer treatment

The treatment for early-stage BC involves a multimodal approach, integrating local treatments, such as surgery and radiotherapy, with systemic therapies (Cardoso et al., 2019; Korde et al., 2021; Loibl et al., 2024). Systemic treatments can be delivered before (neoadjuvant) or after BC sugery (adjuvant) and may include chemotherapy, biologic targeted therapies (for tumors expressing human epidermal growth factor receptor 2 [HER2]), endocrine therapy (for hormone receptor-positive tumors), and, more recently, immunotherapy (Cardoso et al., 2019; Korde et al., 2021; Loibl et al., 2024).

Chemotherapy is indicated for the majority of triple-negative and HER2-positive BC, as well as high-risk luminal-like HER2-negative BC (Cardoso et al., 2019; Korde et al., 2021; Loibl et al., 2024). Anthracyclines (e.g., doxorubicin, epirubicin), taxanes (e.g., docetaxel, paclitaxel), and platinum (e.g., carboplatin) are the most used drugs in chemotherapy protocols for early-stage BC (Loibl et al., 2024). For patients with early-stage HER2-positive BC, HER2-targeted therapies, such as trastuzumab and pertuzumab, are added to these protocols. The HER2-targeted therapy is administered for 12-months, covering both the neoadjuvant and adjuvant phases of treatment (Cardoso et al., 2019; Korde et al., 2021; Loibl et al., 2024). An overview of typical chemotherapy protocols for early-stage BC is provided in table 1.

Table 1. Characteristics of planned systemic therapy

Protocol	Protocol Description
AC-T	▪ 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks; **followed** by 12 cycles of Paclitaxel (80 mg/m², IV) weekly
AC-TH	▪ 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every three weeks; **followed** by 4 cycles of Docetaxel (75 mg/m², IV) plus Trastuzumab SC (600 mg, SC) and Pertuzumab (loading dose 840 mg/m²; subsequent doses 420 mg/m², IV) every three weeks ▪ 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks; **followed** by 4 cycles of Docetaxel (75 mg/m², IV) plus Trastuzumab SC (600 mg, SC) and Pertuzumab (loading dose 840 mg/m²; subsequent doses 420 mg/m², IV) every three weeks ▪ 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks; **followed** by 12 cycles of Paclitaxel (80 mg/m², IV) weekly plus Trastuzumab SC (600 mg, SC) and Pertuzumab (loading dose 840 mg/m²; subsequent doses 420 mg/m², IV) every three weeks ▪ 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks; **followed** by 12 cycles of Paclitaxel (80 mg/m², IV) weekly plus Trastuzumab SC (600 mg, SC) every three week

Table 1. Continued

CP-AC	▪ 4 cycles of Carboplatin (AUC 6, IV) every three weeks and Paclitaxel (80 mg/m², IV) weekly; **followed** by 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks

Legend:
AC-T: anthracycline-based chemotherapy followed by taxane-based chemotherapy.
AC-TH: anthracycline-based chemotherapy followed by taxane-based chemotherapy with anti-HER2 therapy.
AUC: area under the curve.
CP-AC: taxane-based chemotherapy with carboplatin followed by anthracycline-based chemotherapy.
IV: intravenous.
SC: subcutaneous.

3.3. Cardiovascular risk in breast cancer

The overall 5-year survival rate for BC exceeds 90%, meaning that at least 90 out of 100 people are alive 5 years after they've been diagnosed with BC. The improvement in overall survival among cancer patients has brought attention to their susceptibility to chronic morbidity and highlighted the long-term consequences of the disease and related therapies (Du et al., 2008; Riihimäki et al., 2012). Particularly, numerous clinical trials and large retrospective studies have consistently reported that BC survivors have an increased cardiovascular (CV) risk and a higher likelihood of premature CV-related mortality compared to women without a history of cancer (Abdel-Qadir et al., 2019; Armenian et al., 2016; Chavez-MacGregor et al., 2013; Perez, I. E et al., 2004, 2008; Pinder et al., 2007; Thavendiranathan et al., 2016). In a retrospective cohort study involving 36,232 cancer survivors, with a median follow-up of 4.4 years from diagnosis, Armenian et al. (2016) aimed to assess the extent of CV disease. They found that BC survivors had a 13% greater risk of developing CV disease compared to age- and sex-matched non-cancer controls, and a notably 35% increased risk of cardiomyopathy or heart failure (HF) incidence [incidence rate ratio (IRR): 1.35; 95% confidence interval (CI): 1.19 to 1.54; $p<0.01$)] (Armenian et al., 2016). Additionally, cancer survivors who developed CV disease showed a 3.78-fold higher risk of all-cause mortality (95% CI: 3.55 to 4.01; $p<0.01$), and their 8-year overall survival was significantly lower compared to those without CV disease (60% vs. 81%; $p<0.01$) (Armenian et al., 2016). Prospective studies have also demonstrated that, as time passes since BC diagnosis, CV disease becomes a leading cause of mortality, often surpassing primary cancer mortality within 5 to 10 years, especially in survivors over 60 years old (Patnaik et al., 2011; Strongman et al., 2022).

The etiology CV disease in BC survivors is likely multifactorial, involving the effects of various cardiotoxic anti-cancer therapies, along with pre-existing CV risk factors (e.g., hypertension, coronary artery disease, dyslipidemia), and lifestyle factors (e.g., unhealthy diet, sedentary lifestyle, or reduced physical activity) that can elevate the long-term risk of CV disease (Curigliano

et al., 2016; Lyon et al., 2022; Perez, I. E et al., 2019; Zamorano et al., 2016). When considering therapeutic exposures in BC patients, the increased risk of cancer-related CV toxicity is particularly associated with anticancer treatments such as anthracyclines, trastuzumab, and radiotherapy (Curigliano et al., 2016; Perez, I. E et al., 2019; Lyon et al., 2022; Zamorano et al., 2016).

3.4. Cancer therapy-related cardiac dysfunction

Definition and diagnosis

Recent advancements in the field of cardio-oncology have considerable enhanced knowledge regarding the diverse range of conditions involved in cancer-related CV toxicity (Curigliano et al., 2020; Herrmann et al., 2022; Lyon et al., 2022; Zamorano et al., 2016). The Scientific Council of the International Cardio-Oncology Society has recently introduced a classification of the most common adverse CV events that can occur during anticancer treatment, identifying five main categories: (i) cardiac dysfunction, including cardiomyopathy and HF; (ii) myocarditis; (iii) vascular toxicity; (iv) hypertension; and (v) arrhythmias and QT interval prolongation (Herrmann et al., 2022; Lyon et al., 2022).

Cancer therapy-related cardiac dysfunction (CTRCD), commonly referred to as cardiotoxicity, is a major CV complication that can impact therapeutic decision-making and worsen patients' outcomes in terms of morbidity and mortality (Armenian et al., 2017; Curigliano et al., 2020; Lyon et al., 2022; Zamorano et al., 2016). This condition encompasses "cardiac dysfunction or structural injury associated with cancer therapy, which can remain asymptomatic, or present as clinical HF, each defined ranging from mild to severe degree" (Herrmann et al., 2022). The symptomatic form of CTRCD is typically observed post-treatment and is characterized by the HF syndrome, marked by hallmark symptoms such as breathlessness, ankle swelling, and fatigue, along with signs of volume overload and inadequate perfusion (Herrmann et al., 2022; Lyon et al., 2022). These clinical manifestations reflect structural or functional abnormalities in the heart, consistent with the HF stage C/D classifications outlined by the American Heart Association and American College of Cardiology and are directly linked to survival rates (Herrmann et al., 2022; Lyon et al., 2022). In line with the 2022 European Society of Cardiology guidelines on cardio-oncology, symptomatic CTRCD can been categorized as (Lyon et al., 2022):

- **Very Severe:** HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation. HF that necessitates inotropic support, mechanical circulatory assistance, or consideration for heart transplantation.
- **Severe:** HF that necessitates hospitalization.
- **Moderate:** Need for outpatient intensification of diuretic and HF therapy.

- **Mild:** Mild HF symptoms, no intensification of therapy required.

Asymptomatic CTRCD is more prevalent during anticancer therapy (Herrmann et al., 2022; Lyon et al., 2022). Its diagnosis often relies on resting systolic measures, with left ventricular ejection fraction (LVEF) being the most used parameter for monitoring changes in left ventricular function (Plana et al., 2014; Zamorano et al., 2016). Echocardiography continues to be the primary method for assessing LVEF due to its accessibility, portability, safety, and cost-effectiveness (Plana et al., 2014). One of the most widely accepted definitions of asymptomatic CTRCD, based solely on LVEF—endorsed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging—characterizes it as a decrease in LVEF of ≥10% from baseline to a value below 53% (Plana et al., 2014).

Early detection of declining left ventricular function can help prevent irreversible damage, but relying only on LVEF, particularly using echocardiography to diagnose CTRCD has several limitations (Cardinale et al., 2015; Henriksen et al., 2023; Plana et al., 2014). A normal LVEF doesn't rule out CTRCD due to dependence on image quality, intra- and inter-observer variability, geometric assumptions and inability to detect regional myocardial abnormalities (Lang et al., 2015; Plana et al., 2014). Furthermore, LVEF is often insensitive to asymptomatic and subtle alterations in left ventricular function, and by the time a decline is detected, the cardiac damage may already be irreversible (Lang et al., 2015; Plana et al., 2014). Consequently, there was a growing interest in developing imaging techniques that can identify cardiac injury before a decrease in LVEF occurs (Sawaya et al., 2011). Myocardial strain imaging has been suggested as particularly valuable parameter for identifying subclinical left ventricular dysfunction related to cardiotoxic cancer therapies (Oikonomou et al., 2019; Thavendiranathan et al., 2014). Strain quantifies the percentual variation in cardiomyocyte length between end-diastole and end-systole (Lang et al., 2015). Specifically, global longitudinal strain (GLS) is the most widely used strain-based parameter of left ventricular function (Lang et al., 2015). Numerous studies have demonstrated that GLS is robust and reproducible, offering additional predictive value in detecting CTRCD or HF in BC patients treated with anthracycline-containing chemotherapy (A-Ct) and trastuzumab (Oikonomou et al., 2019; Thavendiranathan et al., 2014). A relative change in sequential GLS measurements >15% (e.g., decline in absolute GLS of -22% to -18%) has been proposed as a significant threshold for indicating subclinical left ventricular dysfunction, suggesting that GLS-guided cardioprotective therapy could potentially reduce the incidence of asymptomatic CTRCD (Negishi et al., 2023; Plana et al., 2014; Thavendiranathan et al., 2021). Furthermore, cardiac biomarkers play a crucial role in risk stratification for HF patients and are increasingly recognized for their predictive value in the context of CTRCD (Lyon et al., 2022; Yancy et al., 2013; Zamorano et al., 2016). Emerging evidence suggests that the assessment of cardiac natriuretic peptides and cardiac troponins can serve as early indicators of future CTRCD, underscoring their utility as minimally invasive tools for diagnosing and monitoring cancer-related cardiotoxicity (Díaz-Antón et al., 2022; Ky et al., 2014; Mecinaj et al., 2024). Therefore, a decline in resting GLS and elevations in cardiac biomarkers have been incorporated into the

diagnosis of asymptomatic CTRCD, as proposed by the 2022 European Society of Cardiology guidelines on cardio-oncology (Lyon et al., 2022). Asymptomatic CTRCD has been categorized as follows (Lyon et al., 2022):

- **Severe:** defined as a new decrease in LVEF to value <40%.
- **Moderate:** defined as a new LVEF ≥10% to value between 40% and 49% OR defined as a new LVEF <10% to value between 40% and 49% AND new relative decline in GLS by >15% from baseline OR a new increase in cardiac biomarkers.
- **Mild:** defined as LVEF ≥50% AND a new relative decline by >15% GLS from baseline AND/OR a new rise in troponins/natriuretic peptides.

All guidelines underscore the need of identifying high-risk patients for developing cancer-related CV toxicity, at the onset of anticancer treatment and during survivorship (Alexandre et al., 2020; Armenian et al., 2017; Curigliano et al., 2020; Zamorano et al., 2016). While there are variations in how high-risk patients are defined, common criteria across these include individuals with a history of CV disease or risk factors, those receiving high-dose anthracycline treatment, and patients undergoing combination therapy. The criteria proposed in the cardio-oncology guidelines from the American Society of Clinical Oncology classifies are presented in table 2 (Armenian et al., 2017).

Table 2. Patients with cancer are at increased risk for developing cancer-related therapy cardiac dysfunction adapted from Armenian et al. (2017)

Treatment that includes any of the following:
▪ High-dose anthracycline (eg, doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2). ▪ High-dose radiotherapy (≥30 gy) where the heart is in the treatment field. ▪ Lower-dose anthracycline (e.g., doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) in combination with lower-dose radiotherapy <30 gy) where the heart is in the treatment field.
Treatment with lower-dose anthracycline (e.g., doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) or trastuzumab alone, and presence of any of the following risk factors:
▪ Multiple CV risk factors (≥two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy. ▪ Older age (≥60 years) at cancer treatment. ▪ Compromised cardiac function (e.g., borderline low LVEF [50% to 55%], history of myocardial infarction, moderate valvular heart disease) at any time before or during treatment.
Treatment with lower-dose anthracycline followed by trastuzumab (sequential therapy).

3.5. Anthracycline-related cardiac dysfunction

Incidence

There are several cancer-related therapies that can cause direct myocardial damage, leading to a significant risk of CTRCD (Curigliano et al., 2020; Lyon et al., 2022; McGowan et al., 2017; Zamorano et al., 2016). Regarding BC treatment, CTRCD is particularly associated with exposure to anthracyclines, trastuzumab, alkylating agents (e.g., cyclophosphamide), antimicrotubule agents (e.g., docetaxel, paclitaxel), and tyrosine kinase inhibitors (e.g., lapatinib) (Curigliano et al., 2020; McGowan et al., 2017; Zamorano et al., 2016). Among these therapies, doxorubicin-related cardiac dysfunction has been the most extensively studied, as it remains the most used anthracycline. Moreover, multiple studies have demonstrated that A-Ct regimens are associated with frequent decrease in systolic function and, when compared to non-anthracycline chemotherapy, carry a significantly higher risk of CV toxicity (Advani et al., 2016; Perez, E. A et al., 2004; Romond et al., 2005; Slamon et al., 2011; Smith et al., 2010; Tan-Chiu et al., 2005; Thavendiranathan et al., 2016). In a meta-analysis of randomized controlled trials (RCTs), Smith et al. (2010) demonstrated that A-Ct was associated with an odds ratio of 5.43 (95% CI: 2.34 to 12.62; $p<0.0001$) for clinical cardiotoxicity and 6.25 (95% CI: 2.58 to 15.13; $p<0.0001$) for subclinical cardiotoxicity compared to non-anthracycline regimens.

The prevalence of anthracycline-induced cardiac dysfunction varies in the literature due to factors such as the definitions used, study setting and design (i.e., clinical trial vs. community cohort study), the population and cancer type (e.g., pediatric vs. adult), and the duration of follow-up (Herrmann et al., 2022). Nevertheless, a meta-analysis indicated that in contemporary anthracycline-containing regimens for BC, the incidence of HF was approximately 2%, while subclinical cardiac dysfunction occurred in about 10% of cases (Jang et al., 2019).

Risk factors and mechanisms

The cumulative dose is the most significant risk factor for anthracycline-induced cardiac dysfunction. Early evidence demonstrated that HF occurs in approximately 3%–5% of patients at a cumulative doxorubicin dose of 400 mg/m², but this incidence markedly increases to 18%–48% at a dose of 700 mg/m² (Swain et al., 2003; Von Hoff et al., 1979). Swain et al. (2003) also demonstrated that the earliest step-up in cardiac events occurred from 250 to 350 mg/m² (9%–18%), but histopathologic changes can be detected in endomyocardial biopsy specimens from patients who have received 240 mg/m² of doxorubicin (Bristow, 1978). The risk of anthracycline-induced cardiac dysfunction may be further exacerbated by several factors, including: i) history of CV disease, including HF, cardiomyopathy, valvular heart disease, and coronary artery disease; ii) advanced (≥65 years) or pediatric age; iii) CV risk factors such as hypertension, obesity, diabetes mellitus, and chronic kidney disease; iv) lifestyle choices (e.g., smoking) (Curigliano et al., 2020; Lyon et al., 2020; Zamorano et al., 2016). Additionally, the use of other cytotoxic agents (e.g., cyclophosphamide), trastuzumab, or mediastinal radiation therapy can increase

susceptibility to cardiac toxicity in BC patients (Curigliano et al., 2020; Lyon et al., 2020; Zamorano et al., 2016).

Anthracyclines exhibit a variety of mechanisms of action, including the generation of reactive oxygen species (ROS), intercalation into DNA, and inhibition of the topoisomerase II enzyme, which is crucial for DNA transcription and repair (Hahn et al., 2014; McGowan et al., 2017; Rawat et al., 2021). Currently, the primary mechanism of cardiotoxicity is believed to involve the formation of topoisomerase 2β-anthracycline complexes, which impair mitochondrial function and biogenesis (Henriksen, 2018) . In mitochondria affected by anthracyclines, iron accumulation occurs, resulting in iron-dependent ROS generation. This damage is further exacerbated by impaired autophagic clearance of dysfunctional mitochondria. The combined effects of ROS generation and mitochondrial dysfunction ultimately lead to apoptosis, with myocytes being particularly vulnerable to anthracycline-induced cellular damage due to their limited capacity to scavenge ROS.

Classification

Anthracycline-induced cardiac dysfunction was initially proposed to be i) acute, occurring after a single dose, with symptoms onset within 14-days of treatment cessation—this is uncommon but usually reversible upon discontinuation; ii) early-onset chronic, occurring within; and iii) late-onset chronic, developing years, or even decades, after the end of chemotherapy (Cardinale et al., 2015, 2020; Perez, I. E et al., 2019; Zamorano et al., 2016). However, this classification was based on retrospective studies where declines in cardiac function were identified only after the development of HF, suggesting a delayed diagnosis of an initially early-onset condition rather than a distinct late-onset disease (Cardinale et al., 2015). Subsequent research supports the hypothesis that these observations may represent different stages of the same pathological process rather than separate diseases (Cardinale et al., 2015). Indeed, studies have suggested that anthracycline-induced cardiac dysfunction likely follows a continuous trajectory that begins with myocardial cell damage, initially detectable by circulating biomarkers, followed by a decline in LVEF that may eventually progress to symptomatic HF (Cardinale et al., 2020; Curigliano et al., 2020; McGowan et al., 2017).

3.6. Cardiac toxicity beyond the heart

Cardiorespiratory fitness (CRF) is considered an objective and comprehensive measure of CV function, serving as a key clinical endpoint (Gilchrist et al., 2019; Jones et al., 2007; Ross et al., 2016). Physiologically, CRF reflects the integrated capacity of the cardiac, pulmonary, and circulatory systems to uptake, transport, and deliver oxygen and substrates to active skeletal muscles, as well as their ability to resynthesize adenosine triphosphate (Ross et al., 2016). From a practical standpoint, CRF represents the capacity to sustain dynamic exercise involving large

muscle groups at moderate to vigorous intensity for extended durations (American College of Sports Medicine, 2021).

Peak oxygen uptake (VO_{2peak}), measured through cardiopulmonary exercise testing, is the gold standard for assessing CRF (Ross et al., 2016). Supported by robust evidence, VO_{2peak} is widely recognized as one of the strongest independent predictors of all-cause mortality across adult populations (Han et al., 2022; Imboden et al., 2018; Khan et al., 2014; Kupsky et al., 2017; Ross et al., 2016). Emerging research has increasingly demonstrated that low CRF correlates with poor outcomes in cancer survivors, including diminished quality of life, heightened symptom burden, morbidity, and mortality (Ekblom-Bak et al., 2023; Fardman et al., 2021; Groarke et al., 2020; Han et al., 2022; Herrero et al., 2006; Lakoski et al., 2015; Schmid & Leitzmann, 2015).

The progressive decline in CRF is a hallmark of senescence, with some longitudinal research indicating that VO_{2peak} declines by approximately 10% per decade (Letnes et al., 2023). Over the course of the cancer care, patients frequently experience a notable decline in CRF, with the most pronounced reductions typically occurring during cancer-related therapy, which may persist for several months to years afterward (Jones et al., 2012; Khouri et al., 2014; Klassen et al., 2014; Lakoski et al., 2013; Peel et al., 2014, 2015). Jones et al. (2012) were the first to document CRF impairment throughout the entire continuum of BC, from diagnosis to metastatic disease. Their findings revealed that even among patients with normal left ventricular systolic function (defined as LVEF ≥50%) VO_{2peak} was, on average, 27% lower compared to an age-matched sedentary cohort of healthy women without a history of BC (Jones et al., 2012). This difference increased to 31% when focusing solely on patients undergoing adjuvant treatment (Jones et al., 2012).

During standard chemotherapy regimens for BC, contemporary trials have demonstrated that VO_{2peak} can decrease by approximately 5% to 15%, a decline comparable to the functional reduction typically seen over 5 to 15 years of aging (Courneya et al., 2007; Foulkes et al., 2023b; Howden et al., 2019; Scott et al., 2023; Van Der Schoot et al., 2022). Notably, many patients show reduced CRF pre-treatment, exacerbating the severity of this decline (Howden et al., 2021; Jones et al., 2012; Peel et al., 2014). A review evaluating the CRF of 493 women with BC before adjuvant therapy found that their VO_{2peak} was 83% of the predicted values (Peel et al., 2014), in line with recent data (Howden et al., 2021). Therefore, it is not surprising that a considerable percentage of patients exhibit a VO_{2peak} ≤18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ by the end of chemotherapy, a level of fitness used to define *functional disability*, which is associated with an increased need for assistance in daily activities and nearly a seven to nine-fold increase in the risk of HF (Howden et al., 2019).

For instance, a cross-sectional study by Howden et al. (2021), involving 173 participants with various cancers and treatments, found that, within 6-months after finishing treatment (median follow-up of 4-months), the percentage of patients falling below this threshold nearly doubled compared to baseline (15% vs. 26%; p=0.016). Similarly, in a study of 147 women with HER2+ BC who had undergone surgery, anthracyclines and trastuzumab, with or without radiotherapy (median follow-up of 14 to 15 months duration), Bonsignore et al. (2021) found that 44% of

patients had a VO_{2peak} ≤18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. It is possible that the longer follow-up in this study may more accurately uncover the persistent impact of cancer treatment on CRF, thereby explaining the higher percentage observed (Bonsignore et al., 2021). Findings from a recent cross-sectional study suggest that long-term CRF impairment (median follow-up of 7 years since trastuzumab completion) may be particularly exacerbated in patients who developed asymptomatic CTRCD (Yu et al., 2020). Specifically, these patients exhibited VO_{2peak} values that were 15% lower than those without CTRCD history and 25% lower than healthy controls (Yu et al., 2020).

Understanding the mechanisms underlying the impairment VO_{2peak} in cancer survivors is crucial for developing new strategies and enhancing the effectiveness of recommended interventions, such as exercise training (Dillon et al., 2024; Foulkes et al., 2023a, 2024; Haykowsky et al., 2022). According to the Fick equation, VO_{2peak} is determined by the product of cardiac output and the arteriovenous oxygen difference (a-vO_2diff) (Koelwyn et al., 2012). Thus, reduced VO_{2peak} may arise from compromised cardiac, vascular, and skeletal muscle functions, leading to decreased oxygen delivery to active skeletal muscles (Dillon et al., 2024; Foulkes et al., 2023a, 2024; Haykowsky et al., 2022). Studies indicate that both central (oxygen delivery) and peripheral (skeletal muscle oxygen extraction) factors contribute to VO_{2peak} decline in BC patients treated with A-Ct (Dillon et al., 2024; Foulkes et al., 2023a, 2024; Haykowsky et al., 2022; Kirkham et al., 2021). Specifically, the decline in VO_{2peak} has been closely linked to a reduction in peak cardiac output, primarily due to decreased peak stroke volume (Howden et al., 2019). In a prospective study, Foulkes et al. (2019) noted that impairments in CRF could persist for up to 12-months after A-Ct, correlating with a decline in peak exercise cardiac function (Foulkes et al., 2019). Additionally, they found that the a-vO_2diff was significantly lower in patients experiencing *functional disability* and was strongly correlated with VO_{2peak} at 16-months post-chemotherapy (Foulkes et al., 2019). Furthermore, Kirkham et al. (2021) demonstrated that other skeletal muscle-driven peripheral factors, such as muscle fatty infiltration, may contribute to reduced VO_{2peak} in BC patients treated with anthracyclines by impairing oxygen extraction and affecting a-vO_2diff.

3.7. Managing cancer-related cardiovascular toxicity

The risk of cancer-related CV toxicity varies throughout cancer care and maybe be influenced by multiple factors, including individual patient characteristics, the type of malignancy, the therapeutic regimen (i.e., type of treatment, dose, frequency, and duration of treatment), pre-existing CV risk factors, the onset and severity of CV complications (Bloom et al., 2016; Herrmann et al., 2022; Lyon et al., 2022; Zamorano et al., 2016). Specifically, A-Ct can lead to immediate cardiac damage, making it essential to implement preventive CV strategies at the time of diagnosis, before treatment starts (Bloom et al., 2016; McGowan et al., 2017; Von Hoff et al., 1979; Zamorano et al., 2016). Clinical guidelines support this approach, emphasizing that early

intervention can improved CV risk assessment and personalized monitoring, which can mitigate CV risk, enhance treatment adherence, and improve overall survival (Armenian et al., 2017; Curigliano et al., 2020; Lyon et al., 2022; Zamorano et al., 2016). This process begins with a baseline CV toxicity risk assessment, which includes screening for pre-existing CV conditions and reviewing the patient's cancer history, including the cardiotoxic risks associated with past and planned cancer therapies. Based on this risk, tailored cardiac surveillance (e.g., electrocardiograms, biomarkers, imaging) and primary prevention measures are considered (Lyon et al., 2022).

Active management of modifiable CV risk factors and encouragement of healthy lifestyle habits (including physical activity and nutrition) are key for primary prevention (Lyon et al., 2022; Zamorano et al., 2016). This is particularly important given the high prevalence of CV risk factors—such as advance age, smoking, unhealthy diet, obesity, and sedentary lifestyle—among women with BC (Obeidat et al., 2023). Moreover, modifications of anthracycline administration (i.e., dose reduction; administration via continuous infusion, or liposome encapsulation), the use of cardioprotective agent in conjunction with treatment (e.g., dexrazoxane) or the use of HF pharmacotherapy (i.e., including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins and beta-blockers), have been also suggested as primary strategies for preventing anthracycline-related cardiac dysfunction in patients with high to very high baseline risk (Henriksen et al., 2023; Lyon et al., 2022; Vejpongsa & Yeh, 2014). However, these approaches have significant limitations. Firstly, reducing the cumulative dose of anthracyclines in patients with aggressive malignancies may increase the risk of cancer recurrence and cancer-related mortality. Secondly, the use of liposome encapsulation, though promising, is limited due to its high cost and in BC setting, its current approval only for metastatic BC patient with an increased cardiac risk (European Medicines Agency, 2019). Thirdly, conventional HF therapies have demonstrated limited effectiveness in preventing anthracycline-related cardiac dysfunction (Henriksen et al., 2023). As a potential alternative to reduce the risk of long-term cardiac issues, there is a suggestion to focus on managing risk factors such as blood pressure and lipid profiles (Avila et al., 2018; Heck et al., 2018; Henriksen et al., 2023). Additionally, these medications are often not administered until after CTRCD symptoms appear, due to the challenges in early detection (Henriksen et al., 2023). Finally, all these approaches are unlikely to address the indirect effects of chemotherapy (Jones et al., 2007). Given these limitations, it is crucial to explore alternative and complementary treatment interventions.

3.8. The role of physical activity and exercise training in mitigating cancer-related cardiovascular toxicity

The importance of physical activity and exercise training in preventing and mitigating CV disease has long been recognized (Visseren et al., 2021). In the field of oncology, several observational

studies have demonstrated that pre-diagnosis and post-diagnosis leisure-time physical activity are associated with a graded reduction in the risk of cancer, all-cause mortality, and CV events, such as new diagnoses of coronary artery disease (CAD), HF, or stroke (Alexandre et al., 2020; Gilchrist et al., 2019; Kim et al., 2021; Lavery et al., 2023; Okwuosa et al., 2019). For instance, in a 13-year follow-up study of 4,015 BC patients, those with pre-treatment physical activity levels of ~18 MET-h/week experienced a 37% reduction in the risk of any CV event (95% CI: 0.45 to 0.88; p=0.016) and a 31% reduction in the risk of CAD-related mortality (95% CI: 0.21 to 0.78; p=0.006) compared to those engaging in less than 2 MET-h/week (Okwuosa et al., 2019). Additionally, Jones et al. (2016) found that self-reported physical activity after treatment in 2,973 women with early-stage BC was associated with a dose-dependent reduction in the risk of CV events. Specifically, meeting guidelines for vigorous-intensity physical activity (i.e., ≥9 MET-h/week) was linked to a 33% reduction in CV event risk (95% CI: 0.67 to 0.88; p=0.002) compared to those who did not meet these guidelines (Jones et al., 2016). Similarly, Naaktgeboren et al. (2022) reported that higher post-treatment leisure-time physical activity was linked to a lower cumulative risk of impaired GLS in BC survivors (n= 559 patients; median time since treatment of 10.2 years) and may delay the development of diastolic dysfunction after A-Ct, as noted by Nagy et al. (2017).

Exercise training has also progressively been established as a safe and well-tolerated intervention that may be effective in mitigating some cancer- and treatment-related symptoms (e.g., fatigue, anxiety and depression), preserving physical fitness and health-related quality of life (HRQoL) (Aune et al., 2022; Campbell et al., 2019; Schmitz et al., 2010). Beyond this, exercise training has emerged as a promising cardioprotective strategy to counteract the cardiac toxicity associated with cancer treatments (Gilchrist et al., 2019; Lyon et al., 2020; Wilson et al., 2023; Zamorano et al., 2016). In sedentary, overweight, or obese women with BC post-adjuvant treatment, Lee et al. (2019) reported that a 16-week exercise program combining aerobic and resistance training reduced in 11% the estimated 10-year CV risk, as assessed by the Framingham Risk Score, compared to non-exercising individuals. However, to date, most studies conducted have primarily examined the effects of exercise training on CRF, with evidence suggesting that exercise, particularly aerobic training, has a beneficial effect on VO_{2peak} of BC patients undergoing cardiotoxic treatment (Gilchrist et al., 2019; Scott et al., 2018a).

In a phase II RCT (n=20), Hornsby et al. (2014) found that a 12-week aerobic training performed concurrently with A-Ct in BC patients led to a marked improvement in VO_{2peak} by approximately 13%, whereas the non-exercise group experienced a decline of about 9% (between-group mean difference: +4.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; p=0.004). In the landmark START trial involving 242 women with early-stage BC undergoing adjuvant chemotherapy, the impact of aerobic training alone, resistance training alone or usual care on various cancer-related health outcomes, including CRF, was analyzed (Courneya et al., 2007). The study revealed that standard dose aerobic training (15-45 min of aerobic exercise) completely abrogated the decline in CRF seen in the usual care group, although resistance training did not have the same effect (Courneya et al., 2007). Subsequently,

the CARE trial, a three-arm study involving 301 women with BC undergoing adjuvant chemotherapy, examined the effects of different exercise regimens: standard-dose aerobic training (3-days/week for 25-30 minutes/session), combined aerobic and resistance training (3-days/week for 25-30 minutes/session plus a standard strength training program 3-days/week), and high-dose aerobic training (3-days/week for 50-60 minutes/session) (Courneya et al., 2013). Contrary to the START trial findings, all groups showed a substantial decrease in CRF (Courneya et al., 2013). However, high-dose aerobic training partially mitigated this decline, resulting in a reduction of approximately 1.0 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, which has recently been linked to a 16% decrease in cancer-related mortality (Imboden et al., 2019).

It is also noteworthy that some trials have reported no effect on preventing CRF declines (Scott et al., 2023; van Waart et al., 2015). These discrepancies may be explained, at least in part, by differences in training prescriptions, patient and treatment characteristics, and exercise training adherence. Furthermore, a meta-analysis of RCTs indicated that exercise training may exert a pronounced effect on CRF when implemented post-treatment and following on a non-linear training schedule (Scott, Zabor, et al., 2018). However, studies testing this hypothesis failed to confirm a superior effect of non-linear training prescriptions and demonstrated that exercise should ideally begin early in treatment and continue thereafter to help mitigate and potentially reverse CRF impairment (Scott et al., 2021, 2023; Van Der Schoot et al., 2022).

More recently, researchers have also focused on identifying key exercise prescription variables that influence the CRF response to exercise training. In a single-arm study involving women with BC undergoing adjuvant trastuzumab, Haykowsky et al. (2009) found that patients who adhered to at least 55% of their planned aerobic training sessions experienced greater improvements in VO_{2peak}. This finding has been supported by subsequent studies in the oncology field and aligns with data from trials involving patients with CV disease (Foulkes et al., 2023b; Little et al., 2022). However, focusing solely on the number of sessions attended may not fully reflect the true exercise dose; for example, a patient might attend all scheduled sessions but achieve only 90% of the prescribed duration and 70% of the intended intensity. This variability was elegantly reported by Kirkham et al. (2018b), demonstrating that BC patients undergoing an exercise training program during chemotherapy exhibited inconsistent adherence to prescribed aerobic training duration and intensity due to treatment-related symptoms. This underscores the need to explore how different training components—such as frequency, duration, intensity, and energy expenditure—affect CRF responsiveness in cancer patients.

Pre-clinical studies have also demonstrated that aerobic training, performed before or concurrently with doxorubicin treatment, can play a crucial role in preserving mitochondrial function, enhancing the antioxidant capacity of cardiomyocytes, maintaining systolic function (as measured by echocardiogram-derived fractional shortening), and limiting the accumulation of the drug in cardiac tissue (Ascensão et al., 2005a, 2005b, 2006; Chicco et al., 2006; Morton et al., 2019; Naaktgeboren et al., 2022). These findings offer a compelling rationale for translating these

pre-clinical results into clinical studies aimed at evaluating the cardioprotective potential of exercise during A-Ct.

Over the past five years, this call has been acknowledged, leading to a growing body of research focused on examining the effect of exercise training on preserving cardiac function in early-stage BC patients undergoing A-Ct (Murray et al., 2022; Naaktgeboren et al., 2021; Scott et al., 2018a). For example, a RCT from Kirkham et al. (2018) involving 24 women with BC found that a single exercise session conducted 24 hours before each doxorubicin-based chemotherapy cycle (totaling 4 exercise sessions) improved systemic vascular resistance and reduced N-terminal pro b-type natriuretic peptide (NT-proBNP) levels compared to usual care in women with BC undergoing A-Ct (Kirkham et al., 2018b). However, this intervention did not result in significant changes in LVEF or strain rate. Similarly, Haykowsky et al. (2009) found that exercise training failed to mitigate the decline in resting LVEF in BC patients receiving adjuvant trastuzumab. In contrast, Ma (2018) and Costello et al. (2019) reported a significant effect of exercise training at mitigating the decline in LVEF and GLS, respectively. The conflicting results, coupled with the considerable limitations of the preliminary evidence—such as modest sample sizes, short-term physical training interventions, and limited follow-up—emphasizes the need for well-designed and well-executed trials. Indeed, the most recent American College of Sports Medicine roundtable on exercise guidelines for cancer survivors has highlighted this knowledge gap (Campbell et al., 2019).

Chapter 4 – Protocol for a Systematic Review

Study 1

Effects of physical exercise on outcomes of cardiac (dys)function in women with breast cancer undergoing anthracycline or trastuzumab treatment: study protocol for a systematic review [1]

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Abstract

Background Cardiotoxicity is a known complication and one of the most adverse effects from the use of conventional treatments such as anthracyclines and trastuzumab in breast cancer (BC) care. This phenomenon has been associated with the restriction of therapeutic options and the increase of cardiovascular complications, which may compromise the survival of patients. Implementation of preventive strategies is an important approach for the management of this issue. Physical exercise has been proposed as a non-pharmacological strategy to counteracting cardiotoxicity. The aim of this protocol is to describe the rationale and methods for a systematic review of published randomized controlled trials (RCTs) that have analysed the effects of physical exercise on outcomes of cardiac (dys)function in women with BC undergoing neoadjuvant or adjuvant treatment containing anthracyclines and/or trastuzumab.

Methods and analysis This is a protocol for a systematic review reported according to the PRISMA-P 2015 checklist. RCTs will be included. The literature will be screened on MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, ISI Web of Science and Scopus. The risk of bias of the included RCTs will be assessed using the Cochrane Collaboration's tool. The primary outcomes will be systolic function (left ventricular ejection fraction), diastolic function (E/A' ratio, deceleration time of early left ventricular filling, isovolumetric relaxation time, E/E' septal and lateral ratio) and myocardial deformation imaging outcomes (strain and strain rate [measured in longitudinal, radial, or circumferential directions]). Secondary outcomes will be cardiac biomarkers (troponin I or T, high-sensitivity troponin I or T, brain natriuretic peptide, amino terminal of B-type natriuretic peptide). Data will be descriptively reported, and quantitative synthesis will also be considered if the included studies are sufficiently homogenous.

Discussion This systematic review will help to understand the effectiveness of physical exercise on counteracting cardiotoxicity related to anticancer therapies in women with BC.

Systematic review registration PROSPERO CRD42018096060.

Keywords

Breast cancer; exercise; cardiotoxicity; cardiovascular function; systematic review.

Background

Breast cancer (BC) is the most diagnosed malignancy and the major cause of cancer-related death in the female gender (Torre et al., 2016). Over the past two decades, due to preventive actions, early screening and advances in anticancer therapies, the BC management has been marked by a notable progress reflected by the improvement in survival rates (Bray et al., 2018). However, despite the optimistic prospects in the fight against BC, survivorship is often marked by several treatment-related side effects and poor quality of life (Binkley et al., 2012; McNeely et al., 2012). Notably, cardiotoxicity has been recognized as a serious issue in clinical practice, restricting treatment options and contributing to morbidity and mortality among BC patients (Armenian et al., 2017; Gernaat et al., 2017).

Cardiac dysfunction, which involves direct effects of the treatment on heart function and structure (Zamorano et al., 2016), is a well-established side effect from the use of conventional cardiotoxic drugs such as anthracyclines (the cornerstone of BC chemotherapy) and trastuzumab [the standard of care for the treatment of human epidermal growth factor receptor 2 (HER2) positive] in BC treatment (Valachis & Nilsson, 2015). Anthracycline-induced cardiotoxicity is mostly influenced by cumulative dose, leading to an irreversible cardiac damage (type I cardiotoxicity) (Swain et al., 2003). The anthracycline-related cardiac effects are commonly manifested by asymptomatic or symptomatic left ventricular dysfunction leading to HF, myocardial ischemia, arrhythmias, hypertension, myocarditis, pericarditis and thromboembolism (Colombo et al., 2013). On the other hand, trastuzumab-related cardiotoxicity is not dose-dependent and is often reversible (type II cardiotoxicity) after treatment discontinuation (Ewer & Lippman, 2005). Nevertheless, the elevated incidence of cardiac dysfunction in patients treated with trastuzumab after anthracyclines is a growing concern (Seicean et al., 2013).

According to the American Society of Echocardiography and the European Association of Cardiovascular Imaging, cardiotoxicity is defined by a decrease in left ventricular ejection fraction (LVEF) of > 10% to a value of < 53% (Plana et al., 2014). Currently, serial determination of LVEF is the standard marker for reporting cardiotoxicity related to anticancer therapies (Zamorano et al., 2016). However, the determination of LVEF has substantial limitations and is considered a poor sensitivity parameter to detect cardiotoxicity at an early stage (Ewer & Lenihan, 2008). As such, an integrated approach that includes the assessment of echocardiographic parameters (diastolic function and myocardial deformation imaging) and biomarkers of cardiac injury has been recommended for a better monitoring of cardiac (dys)function (Plana et al., 2014; Schwartz et al., 2013). Besides the importance of screening, the implementation of preventive strategies that optimize cardiovascular care in patients with BC treated with cardiotoxic agents is also an important component to avoid this issue, but currently, they are limited (Clarke & Lenihan, 2015).

Physical exercise is recognized as a viable non-pharmacological approach for the management of several cardiovascular risk factors (Al-Mallah et al., 2018; Lavie et al., 2015) and as a safe and

effective supportive care for cancer survivors (Schmitz et al., 2010). Evidence from meta-analysis highlights its beneficial effects on physiological and psychological outcomes, during or after treatment, as well as its important role in surveillance and disease recurrence (Furmaniak et al., 2016; Ibrahim & Al-Homaidh, 2011; Lahart et al., 2018). Furthermore, exercise has also been proposed as a promising strategy to prevent cardiotoxicity related to anticancer therapies (Nair & Gongora, 2016; Zamorano et al., 2016). There are several review studies that analysed and described the potential protection mechanisms of physical exercise against cardiotoxicity, but most of these have reported data from animal studies (Chen et al., 2017; Kirkham & Davis, 2015; Scott et al., 2011, 2018). To the best of our knowledge, no systematic review has summarized the effects of physical exercise on cardiac (dys)function induced by neoadjuvant or adjuvant treatment containing anthracyclines and/or trastuzumab in adult women with BC. Therefore, this systematic review will aim to analyse the existing evidence regarding the role of physical exercise on outcomes of cardiac (dys)function in intervention studies that involved women with BC who were undergoing neoadjuvant or adjuvant treatment containing anthracyclines and/or trastuzumab.

Methods and analysis

Study design

This is a protocol for a systematic review which is registered in the international Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42018096060) and has been developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (Moher et al., 2015; Shamseer et al., 2015).

Patient and public involvement

No patients will be involved in this study.

Eligibility criteria

We will include studies that meet the following criteria:

- Study type: Published randomized controlled trials (RCTs) will be eligible. Due to funding restraints, we will include studies in English, French, Germany, Portuguese and Spanish language.

- Participants: Studies that involving adult women (>18 years old) with BC, who were undergoing in a neoadjuvant or adjuvant treatment containing anthracyclines and/or

trastuzumab and performed concurrently a physical exercise intervention, were included. Studies which involved other cancer types beyond BC will be excluded.

- Intervention: Studies that involved aerobic training (any exercise form that uses large muscle groups which predominately stresses the cardiovascular system, such as walking, jogging, cycling) and resistance training (any exercise form that requires a muscle or a muscle group to work against external resistance which predominately stresses the musculoskeletal system, such as squats, chest press), according to the American College of Sports Medicine (Garber et al., 2011), isolated or in combination, will be included.

Trials will not be considered if:

- Yoga, tai chi chuan, qigong or pilates was defined as physical intervention.
- The physical exercise intervention group performed other supportive care (e.g., dietary plan).

Comparator(s)

Comparators will include non-exercise group (i.e., waiting list, control or placebo).

Outcomes

Studies that report the absolute and/or percentage change from baseline to the end of the intervention and/or at follow-up, on at least one of the following outcomes, will be considered:

- Primary outcomes: resting LVEF.
- Secondary outcomes: resting parameters of diastolic function (E/A' ratio; deceleration time of early left ventricular filling [DT]; isovolumetric relaxation time [IVRT]; E/E' lateral and E/E' septal); resting parameters of myocardial deformation imaging (strain and strain rate); cardiac biomarkers (troponin I or T; high-sensitivity troponin I or T; brain natriuretic peptide; amino terminal of B-type natriuretic peptide).

Search methodology for identification of studies

Electronic databases

Literature search will be performed in the following electronic bibliographic databases: MEDLINE (via PubMed), EMBASE (Via embase.com), the Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Science and Scopus. Moreover, clinical trial registers such as ClinicalTrials.gov (https://ClinicalTrials.gov), World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) and International Clinical Trials Registry Platform registry

(http://www.isrctn.com) will be also scanned to identify ongoing and/or protocols trials. Furthermore, the references of the included manuscripts and relevant reviews will be checked. No restriction will be applied regarding the year of publication and the language of the study. This researching process will be independently conducted by two review authors (PA and DE).

Search terms and keywords

The specific search strategies were created through a consensus between all the authors and will include the following four concepts and their related terms: (1) condiction (i.e., breast cancer), (2) cancer treatment (i.e., anthracyclines and trastuzumab), (3) exercise (i.e., aerobic exercise and resistance exercise) and (4) study type (i.e., controlled trial). It will be used as text terms and indexing terms from the thesaurus of the databases (i.e., Medical Subject Headings (MeSH) for MEDLINE and CENTRAL and Emtree for EMBASE) and Boolean operators. The search strategy for MEDLINE is outlined at Table 1 and will be adapted for the further databases. This researching process will be independently conducted by two review authors (PA and DE).

Table 1. Search strategy for MEDLINE (via PubMed)

#1 condition	((breast neoplasms[MeSH]) OR ((breast[MeSH] OR breast diseases[MeSH]) AND neoplasms[MeSH])) OR ((Breast[tiab] OR mammary[tiab]) AND cancer*[tiab] OR carcinoma*[tiab] OR tumour*[tiab] OR malignant*[tiab] OR neoplasm*[tiab]))
#2 cancer treatment	((chemotherapy[MeSH]) OR anthracycline[MeSH]) OR trastuzumab[MeSH]) OR Antibodies, Monoclonal, Humanized[MeSH]) OR (chemotherap*[tiab] OR anthracycline*[tiab] OR trastuzumab[tiab] OR herceptin[tiab]))
#3 exercise	((Exercise training[MeSH]) OR Resistance training[MeSH]) OR Exercise therapy[MeSH]) OR ((Exercise[tiab] OR training[tiab] OR sport*[tiab]) AND aerobic*[tiab] OR resistance*[tiab] OR strength*[tiab] OR weight [tiab] OR endurance*[tiab]))
#4 study type	((randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR (randomized[tiab] OR randomly[tiab] OR trial[tiab]))
#1 AND #2 AND #3 AND #	

Data management

Studies selection

Screening search results will be entered into the latest version of EndNote (Clarivate Analytics) and duplicates will be removed. These procedures will be independently conducted by two review authors (PA and DE). After this, to test the eligibility criteria, the same two review authors will

independently evaluate the title and abstract of the studies. The manuscripts that appear to meet the eligibility criteria will be recorded using an Excel predesigned criterion data collection form. Then, the same two review authors (PA and DE) will meet in person and perform a non-blind full-text screening to take a final inclusion decision. Reasons for exclusion will be recorded. Possible disagreements will be resolved by discussion or, if necessary, by the judgement of a third author (AAl). Whenever required, the study's corresponding authors will be contacted to provide possible ambiguous or lack of necessary information.

Data extraction

Two review authors (CN and VA) will independently perform data extraction using a Microsoft Office Excel version 2016 (Microsoft Corporation, Redmond, WA, USA) predesigned criterion data collection form. The following data will be collected:

- Study characteristics: primary aim, authors, year of publication, journal name, country and sample size.
- Participant characteristics: mean age, disease stage and treatment scheme.
- Intervention characteristics: exercise type, intensity, frequency, time, supervision, location and, if provided, we will also highlight safety and feasibility.
- Comparison details: placebo or control group.
- Interested study outcomes: data of the study outcomes (effect size, 95% CI, standard mean deviation) and its measuring methods.

When ambiguous or clarification of data is required, the study's corresponding authors will be contacted (via email). Possible disagreements during this process will be resolved by consensus or, if necessary, by a third review author's judgement (AAl).

Assessment risk of bias of the included studies

Two review authors (AJ and AA) will independently assess and score the methodological quality of the included trials using the Cochrane Collaboration's tool for assessing risk of bias, according to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential sources of bias (Higgins & Green, 2011). The level of risk of bias will be determined for each domain: (1) high risk, (2) unclear risk or (3) low risk. Possible disagreements shall be resolved by discussion and, if necessary, by consulting a third review author (AAl). We will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the quality of the evidence across studies (Guyatt et al., 2008).

Heterogeneity assessment

Statistical heterogeneity will be tested by the χ^2 test and quantified by the I^2 statistic. Heterogeneity will be assumed if we verified a p value of < 0.1 for χ^2 and I^2 of ≥50% (Egger et al., 1997). We will perform sensitivity analyses stratified according to the risk of bias.

Data synthesis

Data will be managed using the Review Manager software version 5.3 (Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark). The characteristics and findings extracted from the included studies will be exposed in a descriptive way, through tables, and complemented with a synthetic narrative which explores the relationship between the trials. If heterogeneity is found in most studies, regarding design and comparator, random effects model meta-analyses will be performed. For continuous outcomes, we planned to estimate standardized mean difference (SMD) with a 95% confidence interval (95% CI). When standard deviations are not available, they will be calculated from standard errors, CI or p-values for both groups for each study included. The magnitude of the effect size will be reported according to Cohen's classification with the following: small (SMD = 0.2–0.5), moderate (SMD = 0.5–0.8) and large (SMD > 0.8) (Cohen, 1988).

Assessment of reporting bias

We will examine funnel plots corresponding to meta-analysis of the primary outcomes to assess the potential for small-study effects such as publication bias if we include more than 10 studies in an analysis.

Subgroups analyses

If sufficient data is available, we will perform subgroup analyses according to the following:

- Intervention type (aerobic or resistance, concomitant or isolated).
- Exercise intensity (light, moderate, vigorous).
- Treatment scheme (including anthracyclines or trastuzumab, concomitant or isolated).

Ethics and dissemination

Ethics approval is not required because this is a protocol for a systematic review not involving personal data or the exercise of any intervention in patients. The findings of this study will be submitted to a peer-reviewed journal for publication, will be presented at relevant conferences and will be also part of the main author's PhD thesis.

Discussion

The notable progress in the care of BC has led to a marked improvement in survival rates (Bray et al., 2018). Despite the optimistic prospects in the fight against BC, these patients face several treatment-related side effects (Binkley et al., 2012; McNeely et al., 2012). Cardiac dysfunction has been recognized as a major concern from the use of conventional cardiotoxic drugs (Gernaat et al., 2017), such as anthracyclines and trastuzumab, which can occur either during treatment or after it (Zamorano et al., 2016). The implementation of preventive strategies to optimize and balance cardiac health is needed. Physical exercise has been emerging as a potential approach for counteracting cardiotoxicity related to anticancer therapies (Nair & Gongora, 2016; Zamorano et al., 2016). Previous review studies have analysed and described the potential protection mechanisms of physical exercise against cardiotoxicity (Chen et al., 2017; Kirkham & Davis, 2015; Scott et al., 2011, 2018), but most of these have reported data from animal studies. Until now, no systematic review has summarized the effects of physical exercise on cardiac (dys)function induced by neoadjuvant or adjuvant treatment containing anthracyclines and/or trastuzumab in adult women with BC.

Limitations

We anticipate some limitations. There may be a risk of bias as we only include published articles. Moreover, this systematic review may be limited by the lack of studies and significant heterogeneity among them.

Conclusion

In this systematic review, we will conduct a comprehensive and rigorous research to summarize and clarify the potential cardioprotective effect of physical exercise at mitigating cardiotoxicity in women with BC undergoing neoadjuvant or adjuvant treatment containing anthracyclines and/or trastuzumab. We expect to present solid findings in this work that it may facilitate the integration of future policies which aim at balancing the negative cardiac effects related to the use of cardiotoxic drugs in the care management of BC, making decisions regarding the practice of exercise.

Chapter 5 – Systematic Review and Meta-analysis

Study 2

Effects of Exercise on Cardiac Function Outcomes in Women Receiving Anthracycline or Trastuzumab Treatment for Breast Cancer: A Systematic Review and Meta-Analysis [1]

Pedro Antunes [1,2], Dulce Esteves[1], Célia Nunes [3], Anabela Amarelo [2,4], José-Fonseca Moutinho [5], Vera Afreixo [6], Henrique Costa [7], Alberto Alves [2,8], Ana Joaquim [2,3]

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[1] This chapter is based on the work publised in the *Applied Sciences*
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Abstract

Objective We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy of exercise training on cardiac function and circulating biomarkers outcomes among women with breast cancer (BC) receiving anthracycline or trastuzumab-containing therapy.

Methods PubMed, EMBASE, Cochrane Library, Web of Science and Scopus were searched. The primary outcome was change on left ventricular ejection fraction (LVEF). Secondary outcomes included diastolic function, strain imaging and circulating biomarkers.

Results Four RCTs were included, of those three were conducted during anthracycline and one during trastuzumab, involving a total 161 patients. All trials provided absolute change in LVEF (%) after a short to medium-term of treatment exposure (≤ 6-months). Pooled data revealed no differences in LVEF in the exercise group versus control (mean difference [MD]: 2.07%; 95% CI: −0.17 to 4.34). Similar results were observed by pooling data from the three RCTs conducted during anthracycline. Data from trials that implemented interventions with ≥36 exercise sessions (n= 3) showed a significant effect in preventing LVEF decline favoring the exercise (MD: 3.25%; 95% CI: 1.20 to 5.31). No significant changes were observed on secondary outcomes.

Conclusion Exercise appears to have a beneficial effect in mitigating LVEF decline and this effect was significant for interventions with ≥36 exercise sessions.

Keywords

Breast cancer; cardiac function; cardiotoxicity; exercise.

Introduction

Breast cancer (BC) is the most common malignant disease among women, accounting for more than two million new cases diagnosed worldwide in 2018 (Bray et al., 2018). Since 2004, we are noticing a slight increase in BC incidence rate, by 0.6% per year, a trend that is expected to continue to rise over the coming decades (American Cancer Society, 2020). Fortunately, this trend has been followed by the progress in cancer management, including primary prevention, screening, and curative-intent therapies, leading to a notable improvement in specific survival. Globally, the five-years survival rate of women with BC is 91% (American Cancer Society, 2020). As a result of this growing population of survivors, patients living with and beyond BC face a multiple short and long-term treatment-related side effects (American Cancer Society, 2019; Bodai & Tuso, 2015).

Cardiotoxicity has been raised as a major concern in clinical practice, that may restrict or delay treatment options, contributing to long-term cardiovascular morbidity and mortality among women with history of BC (Abdel-Qadir et al., 2017; Bradshaw et al., 2016; Chuy & Yu et al., 2019). Despite playing a crucial role for BC treatment, the exposure to drugs such as anthracyclines or to the anti-HER2 newer molecular targeted therapies such as trastuzumab are clinically associated with cardiotoxicity, usually manifested by, but not limited to, left ventricular dysfunction to overt HF (Armenian et al., 2017; Chuy & Yu et al., 2019; Zamorano et al., 2016). Currently, recommendations for monitoring treatment-related cardiotoxicity entail clinical examination and serial echocardiographic assessments (Plana et al., 2014). Resting left ventricular ejection fraction (LVEF) is the standard marker for reporting anticancer therapy-related cardiotoxicity (Plana et al., 2014). Cardiotoxicity is defined by a decrease LVEF of >10% to a value below the lower limit of normal (Plana et al., 2014; Zamorano et al., 2016). However, the determination of LVEF has substantial technical limitations and is considered a poor sensitivity parameter to detect cardiotoxicity at an early stage (Plana et al., 2014). As such, an integrated approach that includes the assessment of other echocardiographic outcomes (diastolic function and strain imaging) and circulating biomarkers has been recommended (Plana et al., 2014; Sawaya et al., 2012). Besides the importance of screening and detection, the implementation of preventive strategies to optimize cardiovascular health of BC patients treated with cardiotoxic therapies is also an important component to be considered.

Exercise training is a core component of cardiac rehabilitation and has a major role in primary and secondary prevention of cardiovascular disease (Piepoli et al., 2016). In oncology, exercise has been widely accepted to be a safe and tolerable approach, during or after treatment, playing a beneficial effect on a wide range of physiological and subject-reported outcomes (Campbell et al., 2019; Cave et al., 2018; Furmaniak et al., 2016). Furthermore, exercise has been associated with a substantial decrease in the risk of cardiovascular disease and, thus, there has been an increasing interest in exploring the role of exercise for mitigating cancer treatment-related cardiotoxicity (Jones et al., 2016; Kyuwan Lee et al., 2019).

This systematic review aims to analyze the effects of exercise, performed during anthracycline or trastuzumab-containing therapy (TC-T), on conventional cardiac function outcomes and circulating biomarkers among women with BC.

Materials and methods

Protocol and registry

This systematic review is registered on PROSPERO (registry number: CRD42018096060) and was conducted according to a previously published protocol (Antunes et al., 2019a), which addressed the PRISMA recommendations (Moher et al., 2015).

Data sources and search terms

Our search strategy was conducted up to 18 May 2020 in: MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Scopus. No restriction were applied. The references of the included manuscripts and relevant reviews were checked. We also searched three trial register platforms: ClinicalTrials.gov (https://clinicaltrials.gov/) (accessed on 24 May 2020), World Health Organization trials portal (https://www.who.int/clinical-trials-registry-platform) (accessed on 24 May 2020), International Clinical Trials Registry (https://www.isrctn.com/) (accessed on 24 May 2020) to identify ongoing trials.

The search strategy were defined by a consensus among the authors of this study and included keywords related to: (1) condition (i.e., breast cancer); (2) treatment (i.e., anthracycline, trastuzumab); (3) exercise training (i.e., aerobic exercise, resistance exercise); and (4) study design (i.e., RCT). The text terms and indexing terms were modified according to the searched database.

Eligibility criteria

- Study type: published randomized controlled trials (RCTs) in English, French, Germany, Portuguese or Spanish languages.
- Participants: trials involving adult women with BC undergoing neoadjuvant or adjuvant anthracycline-containing therapy (A-Ct) or TC-T.
- Intervention: Trials delivering an exercise training intervention involving aerobic exercise (i.e., any exercise form that uses large muscle groups which predominately stresses the cardiovascular system) and/or resistance exercise (i.e., any exercise form that requires a muscle or a muscle group to work against external resistance which predominately stresses

the musculoskeletal system), comparing to a non-exercise group. To be eligible, the exercise intervention had to be performed during A-Ct or TC-T. Trials were not considered if Yoga, Tai Chi Chuan, Qigong or Pilates was defined as the exercise modality.

- Outcomes: Resting LVEF was defined as primary outcome. Secondary outcomes included diastolic function (E/A' ratio, isovolumetric relaxation time, E/E' lateral, and E/E' septal), strain imaging and circulating biomarkers (troponin I or T; high-sensitivity troponin I or T; brain natriuretic peptide; amino terminal of B-type natriuretic peptide or n-terminal pro-b-type natriuretic peptide).

Data management and analysis

The search results were managed using the EndNote software X9 version (Clarivate Analytics, Philadelphia, PA, USA). Two authors (P.A., D.E.) independently reviewed the titles and abstracts of the retrieved results and selected the studies that appeared to meet the predefined population-intervention-control outcome (PICO) criteria. Then, the same two authors performed a non-blind full-text screening to take a final decision. Reasons for exclusion were recorded. Disagreements were resolved by discussion or by judgement of a third author (A.J.).

Three authors (P.A., C.N., V.A.) independently extracted data from the included RCTs. Two authors (An.A., H.C.) extracted data from the identified ongoing trials. In both processes, it was used a predesigned data collection form.

Risk of bias assessment

Two authors (An.A., A.J.) independently assessed risk of bias using the Cochrane collaboration's risk-of-bias tool (Higgins & Green, 2011). Random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting of outcomes, other possible sources of bias and, additional the adherence to exercise intervention were graded as high ('+'), low ('–') or unclear ('?') quality.

Statistical analysis

We used the mean difference (MD) as the effect size measure to assess the effect of exercise on several quantitative outcomes. We calculated the MD by subtracting the mean change in the exercise group from the mean change in the control group. Homogeneity among studies was computed using the Cochran's Q statistic and I^2 statistic. The I^2 provides an estimate of proportion of the variance in the pooled effect size that is attributable to between-studies heterogeneity (low heterogeneity [0% to 25%], moderate [26% to 75%], and high [76% to 100%]). A $p<0.1$ for the Cochran's Q-test was considered as a significant heterogeneity among the studies (Higgins et al., 2003). Due to the significant heterogeneity between the studies, the pooled MD for each outcome was estimated using the random-effects model and the DerSimonian-Laird estimator for τ^2

(Borenstein et al., 2009). The analysis included calculating the mean effect size with its 95%CI and we considered a statistically significant effect when $p<0.05$. We used a correlation value of 0.5 to calculate the variance of each study group when the studies did not report the change standard deviation (SD) or the correlations between pre-intervention and post-intervention measures. We evaluate the sensitivity of the meta-analytic results for distinct correlation values for pre-intervention and post-intervention values (0.25, 0.5, 0.75). We conduct a sensitivity analysis to the sequential omission of every study in turn, to reflect the influence of the data from individual studies on the pooled MDs and evaluate the stability of the results. We also analyzed the impact of excluding trials that involved a small number of exercise sessions. The statistical analyses were performed using software R version 3.6.1© 2019 (R Foundation for Statistical Computing, Vienna, Austria), in RStudio environment version 1.2.1578© 2009–2019 R Studio, Inc. Narrative synthesis was carried out for outcomes where meta-analysis was not possible.

Results

Study selection

The PRISMA flow diagram is outlined in Figure 1. Our search in the five databases yielded 6203 records. Through other resources, we identified three additional studies. After removing duplicates, title and abstract of the remaining 5354 results were screened. We retained 14 articles for full-text assessment and, of those, 10 did not meet eligibility criteria for reasons highlighted in Figure 1.

Four unique RCTs (Hojan et al., 2020; Hornsby et al., 2014; Kirkham et al., 2018a; Ma, 2018) were included (Table 1). Furthermore, we identified ten ongoing trials (ACTRN12617001408370; ISRCTN3261790; NCT03131024; NCT02454777; NCT03027063; NCT03748550; NCT01621659; NCT03850171; NCT03964142; TCTR20190330002) and four published study protocols (Antunes et al., 2019b; Jacquinot et al., 2017; Kirkham et al., 2018b; Pituskin et al., 2016) that appear to meet the predefined PICO criteria.

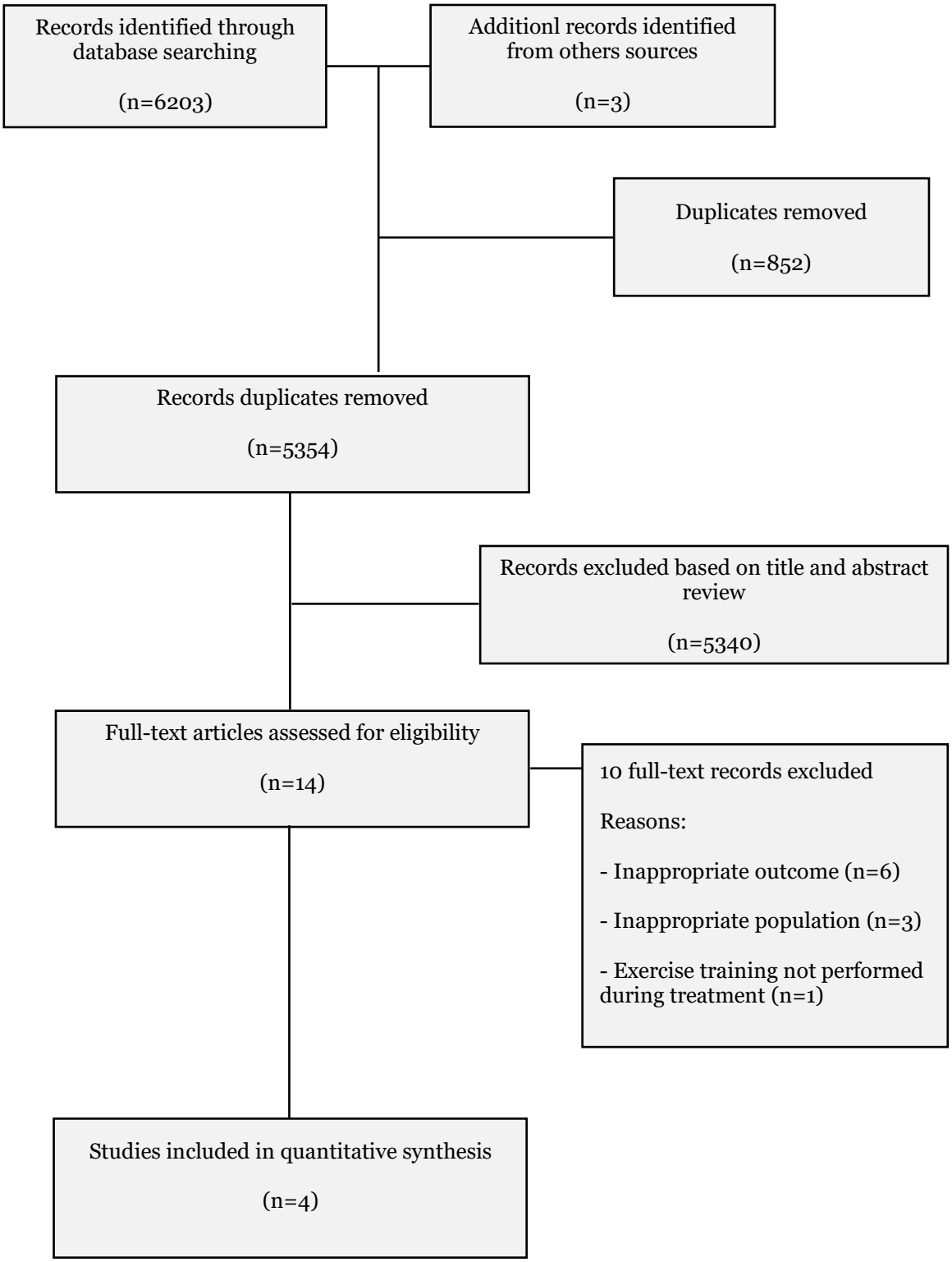

Figure 1. Flow of trials through the selection process.

Table 1. Characteristics of the included trials

	Hojan et al., (2020)	**Hornsby et al., (2014)**	**Kirkham et al., (2018a)**	**MA (2018)**
Study register	NR	NR	NCT02006979	NR
Randomly assigned / withdrawals	n=68 / n=21	n=20 / n=1	n=27 / n=3	n=70 / n=6
Sample size	EG=26; CG=21	EG=9; CG=10	EG=13; CG=11	EG=31; CG=33
Patients' characteristics	Stage: IB-IIIA; Age: EG: 54.4±6.2; CG: 54.6±5.2	Stage: IIB-IIIC; Age: EG: 46±11; CG: 51±6	Stage: I-III; Age: EG: 51±9; CG: 50±10	Stage: NR; Age: EG: 44.2±5.7; CG: 43.5±6.3
Treatment type	TC-T	A-Ct	A-Ct	A-Ct
▪ Neoadjuvant	---	n=19; EG: n=9; CG: n=10	n=8; EG: n=4; CG: n=4	---
▪ Adjuvant	n=47; EG: n=26; CG: n=21	---	n=16; EG: n=9; CG: n=7	n=64; EG: n=31; CG: n=33
Type of exercise training	Aerobic training + Resistance training	Aerobic training	Aerobic training	Aerobic training
Sequence	Linear Progressive	Non-linear	Linear	Linear
Supervision	Supervised Supervised	Supervised	Supervised	Supervised
Volume / intensity	Warm-up: 5 min / NR; Cool-down: 3 min / NR; Aerobic training: 45 min / 40% to 80% HRmax; Sets: 1–3; Reps: 8–10; Load: NR;	Warm-up: NR / NR; Cool-down: NR / NR; Aerobic training: range from 15–20 min to 30–45 min / range from 60% to 100% of PO	Warm-up: 10 min / NR; Cool-down: 5 min / NR; Aerobic training: 30-min / 70% of HRR;	Warm-up: 10 min / 60–70% HRmax; Cool-down: 10 min / 60–70% HRmax; Aerobic training: 30 min / 50–95% HRmax;

Table 1. Characteristics of the included trials

	Hojan et al., (2020)	**Hornsby et al., (2014)**	**Kirkham et al., (2018a)**	**MA (2018)**
Length / frequency	9-weeks / 5 TPW (TNES= 45)	12-weeks / 3 TPW (TNES= 36)	Single exercise session prior to each A-Ct (TNES= 4)	16-weeks / 3 TPW (TNES= 48)
Attendance rate to exercise intervention	98.7%	82%	100%	NR
Safety	No adverse events	One non-serious event (leg pain)	No adverse events	NR
Outcomes of interest				
Cardiac outcomes	LVEF; GLS; E/A ratio	LVEF	LVEF; LV longitudinal strain; E/A ratio	LVEF; E/A ratio
Circulating biomarkers	NR	NR	NT-proBNP; cTnT	NT-proBNP
Timeline assessments	Baseline (3 to 6-months after the start of trastuzumab)	Baseline	Baseline (0 to 14-days prior the start of A-Ct)	Baseline
	Post-intervention (after 9-weeks of exercise intervention)	Post-treatment (after 12-weeks of exercise intervention)	Post-treatment (7 to 14-days after A-Ct)	Post-treatment (after 6 and 12-months A-Ct)

Legend:
Aerobic training: (duration/target intensity); cool-down: (duration/target intensity); warm-up: (duration/target intensity).
A-Ct: anthracycline-containing therapy; CG: control group; cTnT: cardiac Troponin T; EG: exercise group; GLS: global longitudinal strain; HRmax: heart rate maximum; HRR: heart rate reserve; LV: left ventricular; LVEF: left ventricular ejection fraction; NR: not reported; PO: power output; Reps: repetitions; TC-T: trastuzumab-containing therapy; TPW: times per week; TNES: total number of exercise sessions.

Overview of the included trials

Main characteristics are described in Table 1. The four included trials involved a total of 161 women with BC. Provided cohort were middle age (mean age = 49; SD: 4.3). Three trials (Hornsby et al., 2014; Kirkham et al., 2018a; Ma, 2018) were conducted during A-Ct (114 patients) and one trial (Hojan et al., 2020) during adjuvant trastuzumab (47 patients). All the trials implemented supervised exercise interventions. One trial delivered an exercise intervention, with five sessions per week for 9-weeks, combining aerobic training (AT) and resistance training (RT) (Hojan et al., 2020. The AT was performed at very light to vigorous intensity (40% to 80% of maximum heart rate) for 45-minutes following a linear approach and the RT involved eight different exercises, with one to five sets of eight to ten repetitions, with a progressive increase in training load. The three remaining trials adopted exercise interventions involving only AT. Kirkham et al. (2018a) explored the effect of a "short dose" exercise intervention which involved a single 30 min bout of aerobic exercise, at a vigorous intensity, performed 24-hours prior to each A-Ct cycle (i.e., maximum of four exercise sessions). The two other trials implemented an exercise intervention with three sessions per week for 12 (Hornsby et al., 2014) and 16-weeks (Ma, 2018), respectively. Hornsby et al. (2014) implemented a nonlinear exercise approach with duration ranging from 15 to 20-mininutes to 30 to 45-minutes and intensity ranging from 60% to 100% of power output. Lastly, Ma (2018) adopted a linear exercise intervention, with 50-minutes at intermittent intensity ranging 50% to 95% of maximum heart rate.

Risk of bias

A summary of the judgements for the risk of bias is presented in Figure 2. Selection bias has clearly been described in three trials. The remaining trial was judged to be at unclear risk for adequate random sequence generation, given the lack of clarity in methods, and to be at high risk for concealment of participant, because the allocation process was not mentioned. All trials were considered at high risk for performance bias because it was not possible to blind the participants to exercise intervention. All trials reported blinded assessment of outcomes. Two trials was judged at high risk of bias concerning incomplete data. The outcomes described in the methods section were reported in all trials. Three trials reported adherence to exercise sessions and were judged at low risk.

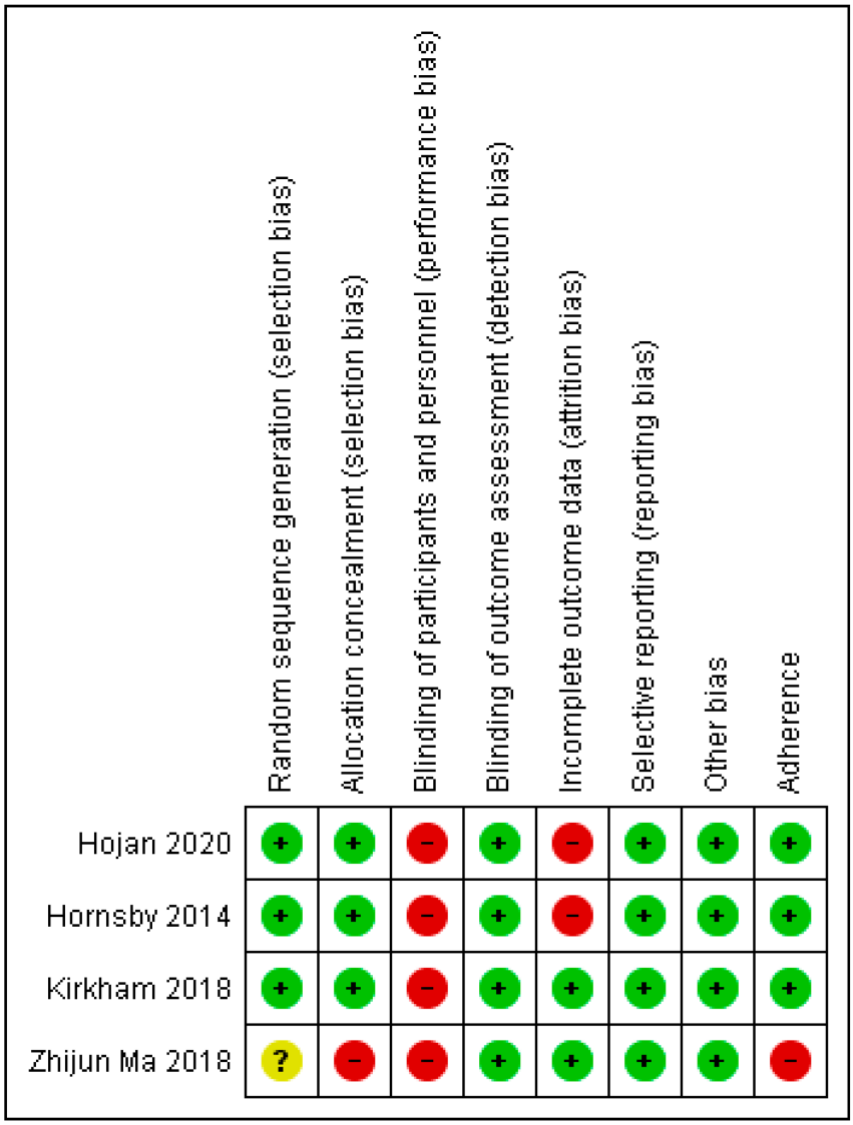

Figure 2. Summary of the judgements for the risk of bias of each study.

Effects of intervention on primary outcome

Resting left ventricular ejection fraction

All the studies provided data concerning absolute change on LVEF. Three trials (Hornsby et al., 2014; Kirkham et al., 2018a; Ma, 2018) reported data from baseline to after a short to medium-term A-Ct exposure (< 6-months) and one trial (Hojan et al., 2020), conducted during adjuvant trastuzumab, provided data from baseline to after the exercise intervention. Pooling data across the four trials showed no significant change between the exercise group compared to control (MD: 2.07%; 95% CI: −0.17 to 4.34; I^2= 38%; Figure 3A). Similar results were verified by pooling results from the three trials conducted during A-Ct (MD: 1.44%; 95% CI: −1.76 to 4.65; I^2=43%; Figure 3B). The pooled data from trials that implemented interventions involving ≥36 exercise sessions (i.e., excluding data from Kirkham et al. [2018a]), showed a significant effect in preventing LVEF

decline favoring the exercise (MD: 3.25%; 95% CI: 1.20 to 5.31; I^2=0% Figure 3C). Ma (2018) was the only author that reported data on LVEF following a long-term follow-up (after 12-months of A-Ct). The results demonstrated a significant attenuation in LVEF decline in the exercise group compared to control (MD: 3.80%; 95% CI: 0.49 to 7.11).

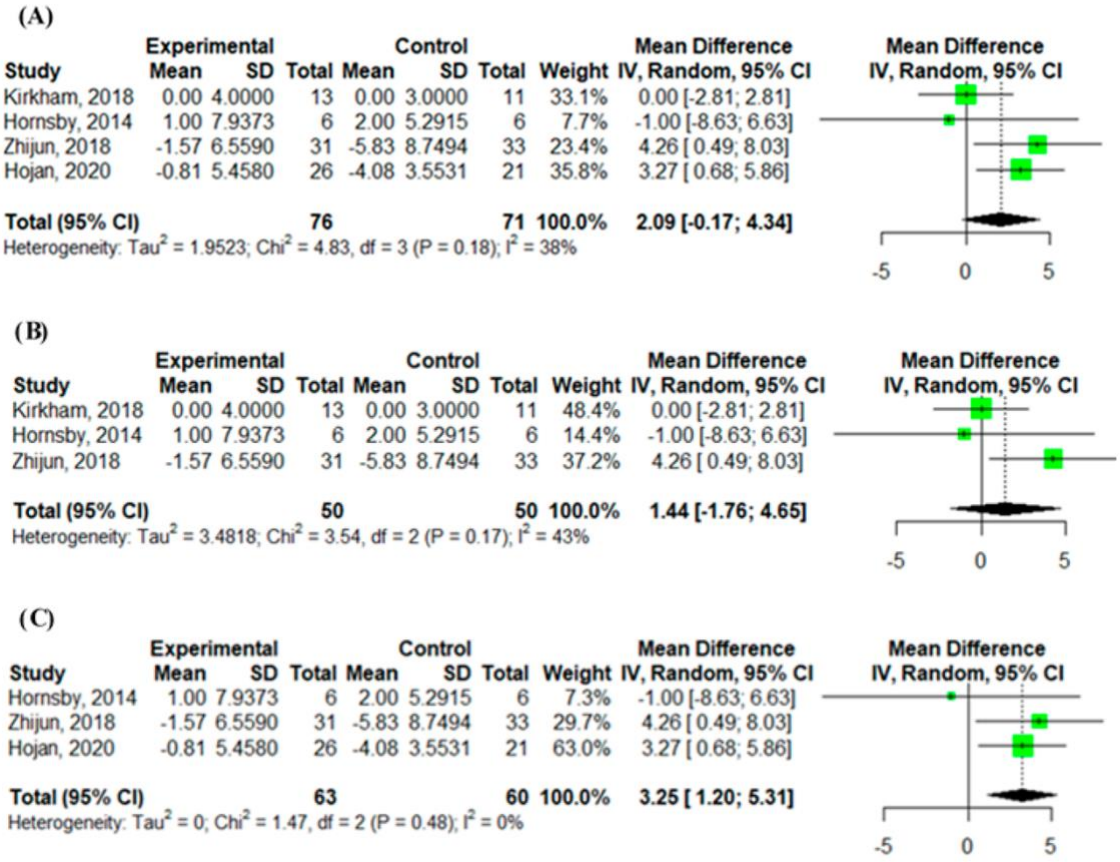

Figure 3. Forest plot showing the effect of exercise intervention compared to control on resting left ventricular ejection fraction: (A) from the included trials; (B) from the trials conducted during anthracycline-containing therapy; (C) from the trials that implemented interventions involving ≥36 exercise sessions.

Effects of intervention on secondary outcome

Resting Parameters on Strain Imaging

Kirkham et al. (2018a) reported data for left ventricular longitudinal strain and Hojan et al. (2020) analyzed global longitudinal strain (GLS). Pooled data demonstrated no differences (MD: −0.31%; 95% CI: −2.07 to 1.46; I^2= 68%; Figure 4). Kirkham et al. (2018a) also presented data on left ventricular twist but it was observed a null effect (MD: 0.12°; 95% CI: −0.1 to 0.35).

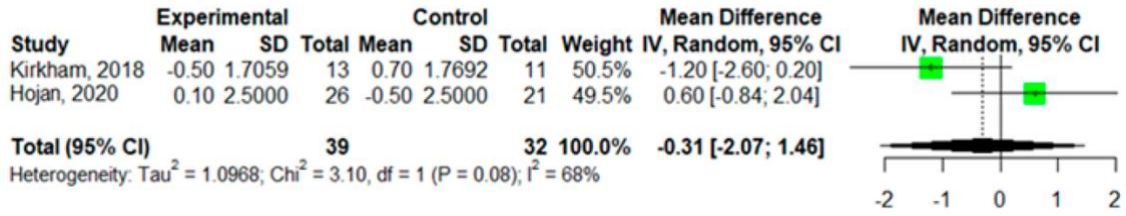

Figure 4. Forest plot showing the effect of exercise intervention compared to control on longitudinal strain.

Resting E/A ratio

Three trials (Hojan et al., 2020; Kirkham et al., 2018a; Ma, 2018) reported data on E/A ratio. The pooled data revealed a null effect (MD: 0.12; 95% CI: −0.1 to 0.35; I^2= 25%) (Figure 5).

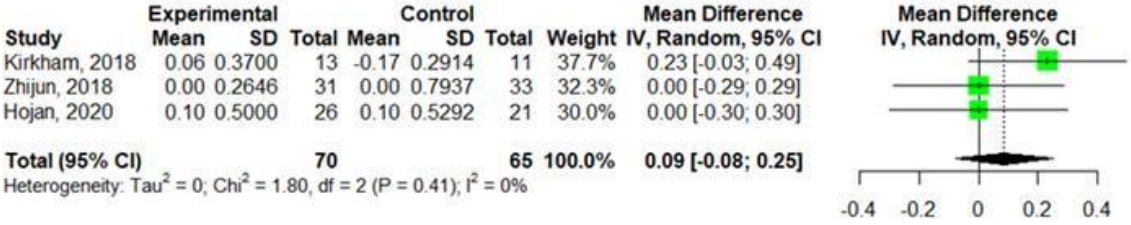

Figure 5. Forest plot showing the effect of exercise intervention compared to control on longitudinal strain.

NT-proBNP and troponin I

Two studies (Kirkham et al., 2018a; Ma, 2018) provided results concerning NT-proBNP. Pooling data showed a null effect (MD: −13.91pmo/L; 95% CI: −49.32 to 21.51; I^2=99%) (Figure 6). Only Kirkham et al. (2018a) reported data regarding troponin I, but no significant changes were verified (MD: 2.20 pg/mL; 95%CI: −4.92 to 9.32).

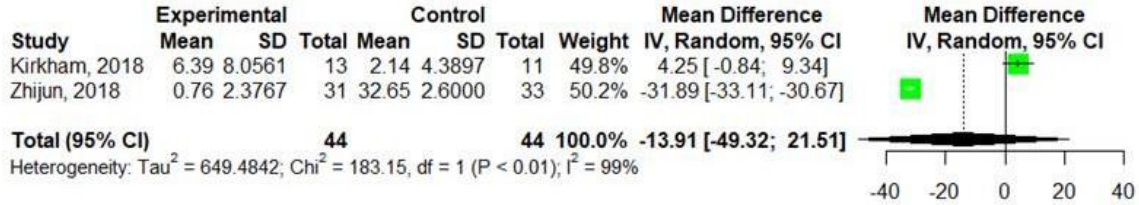

Figure 6. Forest plot showing the effect of exercise intervention compared to control on NT-proBNP.

Discussion

Exercise training has been suggested as a potential approach to mitigate cancer treatment-related cardiotoxicity (D'Ascenzi et al., 2019; Gilchrist et al., 2019). There are several reviews that describe the potential protective mechanisms of exercise against cardiotoxicity, but most of these only provide narrative synthesis, data from animal studies or are limited to cardiorespiratory fitness outcomes (Chen et al., 2017; Ginzac et al., 2019; Kirkham & Davis, 2015; Maginador et al., 2020; Nair & Gongora, 2016; Scott et al., 2018a). The present systematic review adds to existing literature by providing the first report of pooled data from RCTs that analyzed the impact of exercise on cardiac function outcomes and circulating biomarkers among women with BC receiving A-Ct or TC-T, and a systematic compilation of ongoing trials which are researching this subject. This work demonstrated that exercise appears to have a beneficial effect to mitigating LVEF decline in women with BC receiving A-Ct or TC-T, and this effect was significant for interventions with ≥36 exercise sessions. Although this new finding supports the rationale of exercise as a promising approach for preventing cardiac dysfunction, this result should be interpreted cautiously, because it was based on a limited number of RCTs which involved a small sample size, considerable methodological bias, different exercise interventions, and short-term follow-up.

Anthracycline-related cardiotoxicity is often characterized by a continuous progressive decline in LVEF, which predisposes for the development of overt HF (Zamorano et al., 2016). Three included trials compared the effects of aerobic exercise versus usual care in LVEF among women with BC receiving A-Ct (Hornsby et al., 2014; Kirkham et al., 2018a; Ma, 2018). Two of those studies reported a null effect (Hornsby et al., 2014; Kirkham et al., 2018a), while Ma (2018) found a significant efficacy of exercise (MD: 4.26%; 95% CI: 0.49 to 8.03). This discrepancy is likely to be explained by differences in sample size, protocol of exercise intervention, and, perhaps above all, due to the fact that MA (2018) has presented data following 6-months of A-Ct exposure, which represented a longer follow-up compared to the other two studies. More recently, in a non-randomized trial, Howden et al. (2019) tested the effects of an exercise intervention (8 to 12-weeks), combining AT and RT, on cardiac function of 28 women with BC receiving A-Ct. The authors found a significant efficacy of exercise to mitigating cardiorespiratory fitness impairment (VO_{2peak}), but the results regarding LVEF were congruent with the findings from Hornsby et al. (2014) and Kirkham et al. (2018a) and no significant changes were verified after a short-term A-Ct exposure. However, in a long-term follow-up analysis (12-months after A-Ct T) involving 17 participants (61%) from the initial cohort, Foulkes et al. (2019) observed that compared to baseline, LVEF did not change significa[36]ntly in the exercise group (MD: −3.1%; 95% CI: −8.4, to 2.1), whereas it statistically decreased in control (MD: −6.9%; 95% CI: −11.1 to −2.0). Moreover, two participants from the control group were diagnosed with asym[36]ptomatic cardiotoxicity. Although a possible cardioprotective effect of exercise can be hypothesized, it is plausible that these differences may also be justified by the fact that the control group has presented: older age (58±8 years vs. 46±9 years; p=0.012); higher body mass index (28.1±5.5 kg/m² vs. 24±3.3 kg/m²;

p=0.07) and a larger rate of patients undergoing trastuzumab (63% vs. 22%; p=0.15); which are recognized factors to further compound the risk for cardiotoxicity. Furthermore, one included trial reported data on LVEF decline from a long-term follow-up (12-months after A-Ct), verifying a significant attenuation in the exercise group compared to control (MD: 3.80%; 95% CI: 0.49 to 7.11) (Ma, 2018). Together, these facts may hint that the effect of exercise in preventing cardiac dysfunction, assessed by LVEF, may only be detected after long-term of A-Ct, which suggests that studies designed to explore this topic need to include a long-term follow-up. Moreover, further studies are needed to conclude whether the exercise training performed during A-Ct provides adaptations to protect the heart in the long-term and whether this potential cardioprotective effect would extend to prevent cardiotoxicity during trastuzumab.

Regarding the setting of TC-T, we only have identified one RCT (Hojan et al., 2020) and one published study protocol (Jacquinot et al., 2017) which aimed to evaluate the effects of a high-intensity interval training (HIIT) intervention. In the unique RCT conducted during adjuvant trastuzumab, Hojan et al. (2020) showed that an exercise intervention combining AT and RT was able to significantly alleviate the decline in LVEF and in aerobic capacity (assessed by the six minutes walk test) among the exercise group, a phenomenon that occurred in the control. Previously, in a single-arm trial, Haykowsky et al. (2009) verified that AT did not prevent a significant decline in LVEF and this was not related to previous A-Ct, trastuzumab dose and adherence to training sessions. The authors also reported that trastuzumab was discontinued in three patients (18%) before the post-intervention assessment. Asymptomatic decline in LVEF is the most common manifestation of cardiotoxicity during trastuzumab and can lead to premature interruption or discontinuation of therapy (Chuy & Yu, 2019).

Although often considered reversible after treatment discontinuation (Type II cardiotoxicity) (Chuy & Yu, 2019), Yu et al. (2020) verified that patients with versus without history of trastuzumab-related cardiotoxicity presented lower mean values of resting LVEF (56.9±5.2% vs. 62.4±4%; p<0.001), GLS (−17.8±2.2% vs. −19.8±2.2%; p<0.001) and VO_{2peak} (22.9±4.4 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ vs. 27±5.3 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; p<0.001) after a mean seven-year follow-up. These novel findings suggest that the development of cardiotoxicity during trastuzumab may lead to a persistent long-term impairment on cardiac function, which extends beyond the heart, affecting the cardiorespiratory capacity, emphasizing the need to implement holistic strategies for support cardiovascular health. Previous meta-analysis have highlighted the effectiveness of exercise training to prevent or mitigate the decline of cardiorespiratory capacity (Furmaniak et al., 2016; Maginador et al., 2020 Scott et al., 2018b). Although widely used for monitoring cardiac function in cardio-oncology setting, LVEF has important limitations (Plana et al., 2014; Sawaya et al., 2012), thus, an integrated approach which includes the assessment of other echocardiographic outcomes (parameters of diastolic function and strain imaging), and biomarkers has been recommended. Three (Hojan et al., 2020; Kirkham et al., 2018a; Ma, 2018) and two (Kirkham et al., 2018a; Ma, 2018) included trials reported, respectively, data on diastolic function (measured by E/A ratio), and NT-proBNP. For both outcomes, pooled analysis did not reveal significant changes. Regarding strain imaging outcomes, two studies analyzed longitudinal strain (Hojan et

al., 2020; Ma, 2018) and GLS (Hojan et al., 2020), but no changes were verified. In contrast, findings from a non-randomized study showed that exercise training, combining AT and RT, during A-Ct, mitigated the GLS decline (Costello et al., 2019). This is a relevant finding, that needs to be confirmed, as GLS has been suggested to early predicts subclinical cardiac dysfunction (Plana et al., 2014; Zamorano et al., 2016).

The limited number of trials in this review did not allow us to analyze the role of different training types and intensity on study outcomes. In light of the literature of the cardiac rehabilitation field, continuous aerobic exercise, at moderate intensity, has been associated to improve LVEF in heart failure patients, but that benefit was not evident when RT was performed alone or combined with AT (Chen et al., 2012; Jewiss et al., 2016; Tucker et al., 2019). However, Hojan et al. (2020) demonstrated that AT combined to RT had a favorable effect in preventing LVEF decline among women with BC receiving adjuvant trastuzmab. Furthermore, Tucker et al. (2019) highlight that the efficacy of moderate intensity continuous aerobic exercise on LVEF and VO_{2peak} are greatest in long-term interventions (length ≥ 6-months). Such results emphasize the importance of implementing interventions that last longer than the A-Ct regime; which range from 8 (dose-dense protocol) to 12-weeks (every 3-weeks protocol). Therefore, additional research is needed to identify a safe and optimal dose of FITT (frequency, intensity, time, type) prescription to target this issue. We identified ten ongoing trials (ACTRN12617001408370; ISRCTN3261790; NCT03131024; NCT02454777; NCT03027063; NCT03748550; NCT01621659; NCT03850171; NCT03964142; TCTR20190330002) and four published study protocols (Antunes et al., 2019b; Jacquinot et al., 2017; Kirkham et al., 2018b; Pituskin et al., 2016) which are exploring this topic and their results might help to address some research gaps in a near future.

Despite of its originality and adherence to a published protocol and to PRISMA guidelines, when interpreting the findings of this review, one should bear in mind a few limitations. The main limitation of this review was the scarce of RCTs included, which reflects the lack of clinical trial evidence in the literature addressing this topic. It is possible that the strict eligibility criteria applied (only RCTs) and the fact that this is relatively recent research topic, have contributed to this limited selection. Moreover, included trials presented methodological differences and are constrained by its methodological quality (i.e., underpowered studies, high risk of bias, and short-term follow-up data to evaluate clinical events). Second, there was observed a considerable heterogeneity in the components of the exercise training interventions (i.e., F = frequency, I = intensity, T = time, and T = type) across the included studies. Third, we only identified one trial conducted during TC-T. Fourth, outcomes of diastolic function and strain imaging were not consistently assessed among the trials. Fourth, trials had a relatively short-term follow-up, and a longer-term follow-up may be needed to understand the real impact of exercise on cardiac function of cancer patients treated with cardiotoxic therapies. Finally, cardiorespiratory fitness is well established as a strong predictor of cardiovascular and all-cause mortality among healthy individuals and in several patient populations, including cancer survivors, and thus, it should be addressed in future updates of this review.

Therefore, future RCTs with the following focus is widely encouraged: (a) trials designed for a long-term intervention and follow-up; (b) enroll elderly patients; (c) explore the effects of different training modalities (i.e., AT combining RT; HIIT combining or not with RT) and characteristics (i.e., linear vs. non-linear approach); (d) implement exercise interventions during A-Ct and which may also be extensible for TC-T; (e) consider the analysis of promising parameters for the prediction of subclinical cardiotoxicity (i.e., as strain imaging; diastolic function outcomes and circulating biomarkers).

Conclusion

Exercise appears to exert a beneficial effect for mitigating LVEF decline in women with BC receiving A-Ct or TC-T, and this effect was significant for interventions with ≥36 exercise sessions. Although this finding supports the rationale of exercise as a promising approach for preventing cancer therapy-related cardiotoxicity, this result should be interpreted cautiously, because it was based on a limited number of RCTs. Thus, more trials are warranted to validate the efficacy of exercise in preventing cancer therapy-related cardiotoxicity and to analyze its effects on subclinical cardiotoxicity outcomes (strain imaging, diastolic function and circulating biomarkers). We identified ten ongoing trials researching this issue and their future results can be used to upgrade this review.

Chapter 6 – Experimental Works

Study 3

Impact of exercise training on cardiotoxicity and cardiac health outcomes in women with breast cancer undergoing anthracycline chemotherapy: a study protocol for a randomized controlled trial [2]

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[2] This chapter is based on the work publised in the *Trials*
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Abstract

Objective Anthracyclines are chemotherapeutic agents frequently used in breast cancer (BC) treatment. Although it improves disease-free and overall survival, the use of anthracyclines is associated with a cumulative risk of cardiac toxicity. Preventive strategies to optimize cardiac health are needed and exercise is proposed as a potential non-pharmacological approach for counteracting anthracycline-related cardiotoxicity. Most of the data on the effects of exercise to reduce anthracycline-related cardiotoxicity are from animal studies, with only a few studies in a limited number of patients indicating beneficial effects. To better understand the effectiveness of exercise in the mitigation of anthracycline-related cardiotoxicity, clinical, real-world trials claim require a larger sample size and more accurate and valuable clinical biomarkers. In this study, we intend to include a large sample and investigate cardiac function through serial measures of biomarkers and imaging techniques.

Methods This protocol describes a two-arm, prospective, randomized controlled trial that will explore the cardioprotective effect of a structured exercise program in women with BC undergoing anthracycline-containing chemotherapy (A-Ct). Ninety adult women with early BC and recommended to receive A-Ct will be randomly assigned (1:1) to an intervention group or usual care group. Patients allocated to the intervention group will perform a supervised exercise program three times per week, consisting of a combination of aerobic and resistance training with progressive intensity and volume, during the time period they receive A-Ct. The usual care group will receive standard BC care. Primary outcomes related to cardiac (dys)function will be resting left ventricular (LV) longitudinal strain, resting LV ejection fraction and circulating N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Secondary outcomes will include the assessment of resting blood pressure, resting heart rate (HR), resting HR variability (HRV), recovery HR, physical function outcomes, self-reported physical activity level, health-related quality of life, and fatigue. Data will be obtained at baseline (t_0), after the end of anthracycline-treatment (t_2), and 3-months after t_2 (t_3). Additionally, NT-proBNP will be measured 1–24 hours prior to each anthracycline cycle (t_1).

Discussion The implementation of the present study design, using novel clinical biomarkers, will determine the effect of structured exercise interventions at mitigating anthracycline-related cardiotoxicity, with the overall aim of finding means to further improve BC care.

Keywords

Breast cancer, cardiotoxicity, cardiac healthcare, supervised exercise, supportive cancer care.

Introduction

Over the last three decades the epidemiology of breast cancer (BC) has been marked by the clear increase in survival rate (American Cancer Society, 2018). The accessibility of screening and the discovery of new therapeutic options are among some relevant factors related to the improved management of cancer. However, despite their undeniable clinical importance, anti-cancer treatments are also associated with frequent induction of side effects. Among those, cardiotoxicity emerges as a major challenge, limiting treatment options and contributing to morbidity and mortality in this patient population (Armenian et al., 2017; Bradshaw et al., 2016; Gernaat et al., 2017; Patnaik et al., 2011).

In the BC setting, cardiotoxicity is typically associated with exposure to traditional cytotoxic therapies and particularly with the use of anthracyclines (Smith et al., 2010). Anthracyclines are important and effective chemotherapeutic agents, frequently administered in curative and palliative regimens for BC, although their clinical use is limited by cardiac dysfunction, usually seen as cardiotoxicity (Sawyer et al., 2010). The American Society of Echocardiography and European Association of Cardiovascular Imaging defines cardiotoxicity as a decrease in left ventricular ejection fraction (LVEF) of > 10% to a value of < 53% (Plana et al., 2014). However, it has been proposed that anthracycline-related cardiotoxicity is a continuous and dose-dependent phenomenon that starts with acute myocardial damage, which can be detected by elevation of circulating cardiac biomarkers and by impairment of left ventricular (LV) longitudinal strain, in turn preceding the commonly reported progressive decline in LVEF (Cardinale et al., 2015; Romano et al., 2011; Thavendiranathan et al., 2014; Von Hoff et al., 1979; Witteles et al., 2011). Anthracycline-related cardiotoxicity may ultimately lead to overt heart failure, particularly when underestimated, not prevented or insufficiently prevented, or untreated (Cardinale et al., 2015).

Unfortunately, and in addition to the manifestations associated with anthracycline treatment, BC survivors often exhibit a phenotype characterized by the presence of risk factors for cardiovascular disease (CVD), including advanced age, obesity, prior CVD, poor cardiorespiratory fitness, and inappropriate lifestyle habits (smoking, alcoholism, and sedentary lifestyle) (Jones et al., 2007; Mehta et al., 2018). It is therefore not surprising that when compared to healthy individuals of a similar age, these patients have higher prevalence of CVD and greater mortality (Gernaat et al., 2017). Considering the high risk of cardiac dysfunction, the study of preventive strategies is an emerging and unmet need, as these strategies may mitigate cardiac damage associated with the use of cardiotoxic agents and could lead to improvements in overall cardiovascular health.

In adults with CVD without cancer, exercise training is recognized as an important approach in cardiac rehabilitation (Buckley et al., 2013). Particularly, two meta-analyses have shown favorable effects of exercise on attenuation of N-terminal pro-brain natriuretic peptide (NT-proBNP) and mitigation of LV remodeling in patients with heart failure (Pearson et al., 2018; Tucker et al., 2019). Also, in the oncological setting, it has become clear that exercise is a safe and effective

supportive therapy in the management of several treatment-related side effects and in improving overall physical fitness (Furmaniak et al., 2016; Lahart et al., 2018). Furthermore, in a recent position paper the European Society of Cardiology task force for cancer treatments and cardiovascular toxicity suggests the possible utility of aerobic exercise as a promising strategy to attenuate anthracycline-related cardiotoxicity (Zamorano et al., 2016). However, this position remains to be complementarily analyzed as the evidence so far is mainly from studies in animal models (Chen et al., 2017; Scott et al., 2018), with only a few studies, with a limited number of patients, evaluating the cardioprotective role of exercise in cardiac function among women with BC receiving cardiotoxic treatments (Howden et al., 2019; Kirkham et al., 2017, 2018). Further clinical studies involving a large sample size and accurate clinical biomarkers are thus warranted to better understand the effectiveness of exercise in the mitigation of anthracycline-related cardiotoxicity.

Hypothesis

The primary aim of this study is to ascertain whether a structured exercise program mitigates anthracycline-related cardiotoxicity, measured by change in the levels of circulating biomarkers (NTproBNP) and cardiac (dys)function endpoints (LVEF and LV global longitudinal strain). The secondary aim is to evaluate the effectiveness of the intervention in the regulation of some cardiac health parameters: resting blood pressure, resting heart rate (HR), resting HR variability (HRV) and recovery HR. As exploratory objectives, we will assess physical function (cardiorespiratory capacity, upper limb strength, and lower limb functionality), self-reported physical activity level, health-related quality of life (HRQoL), and fatigue. We hypothesize that exercise may limit the degradation of cardiac function and structure and benefit cardiac outcomes. We also believe that patients in the intervention group will improve overall physical fitness, HRQoL, decrease their perception of fatigue, and increase physical activity levels.

Method

Study Design

This is a study protocol for a two-arm, prospective, randomized controlled trial that will explore the cardioprotective effect of a structured exercise program, compared to standard care, in adult women undergoing anthracycline-containing chemotherapy (A-Ct) for early BC. The study design and protocol adhere to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The study design is outlined in Figure 1.

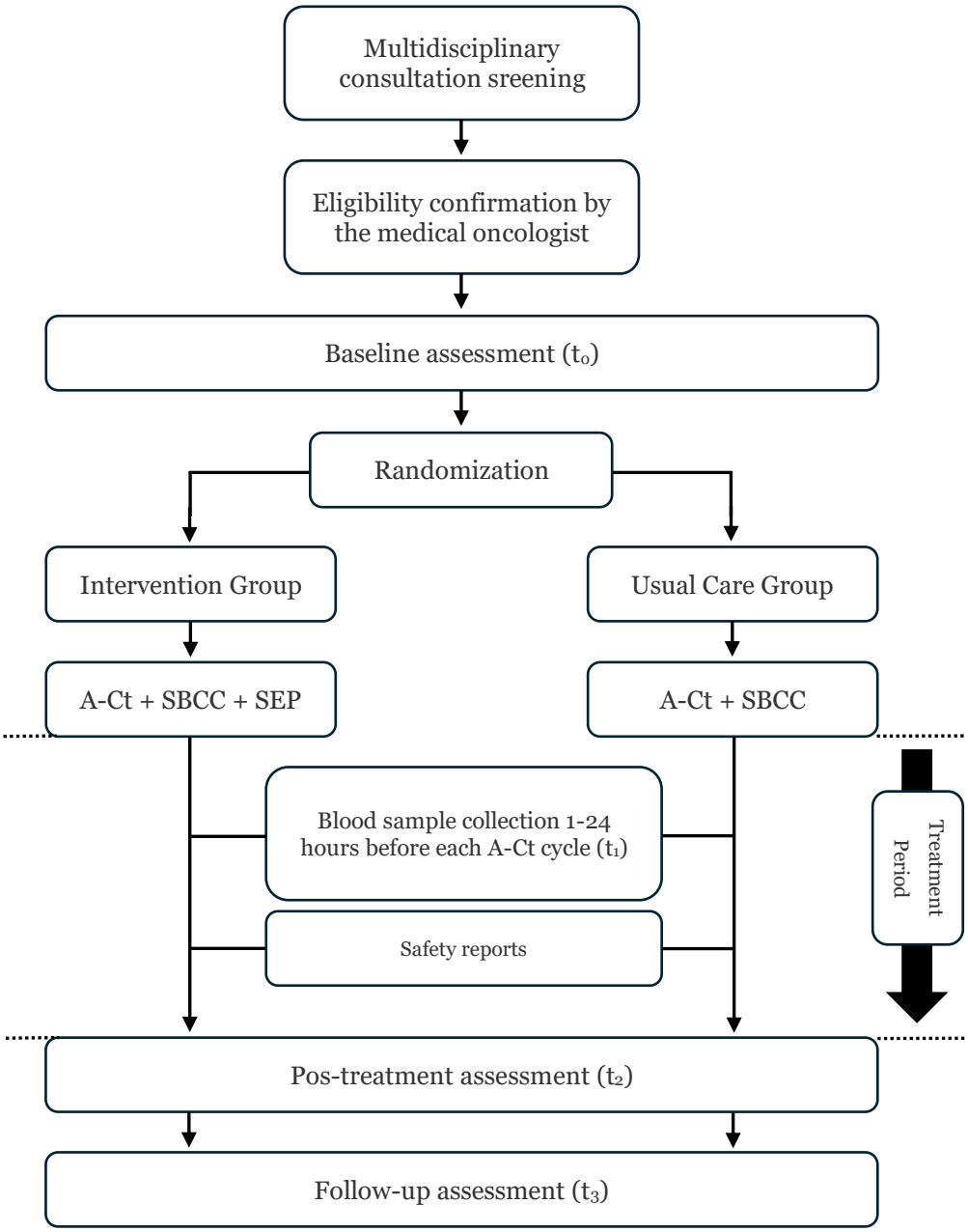

Figure 1. Study flow.

A-Ct, anthracycline-containing chemotherapy; SBCC, standard breast cancer care; SEP, structured exercise program.

Ethical approval

This study will be conducted in compliance with the Declaration of Helsinki Ethical Principles (1975) and it received approval by the Ethics Committee of the Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E; Vila Nova de Gaia, Portugal) (reference number: 145/ 2018–1). The study is registered in the International Standard Randomised Controlled Trial Number

(ISRCTN32617901). Any protocol amendments will be submitted to the CHVNG/E for ethical approval and updated on the ISRCTN.

Participant recruitment

We intend to recruit 90 adult women with early invasive BC, scheduled to receive A-Ct and follow-up in the Medical Oncology Department of the CHVNG/E. Participants will be recruited based on the eligibility criteria presented in Table 1. Recruitment will take place in two distinct phases. In the first instance, potential participants will be identified in the multidisciplinary consultation involving medical oncologists, surgeons, and radio-oncologists. After this preliminary phase, the eligibility of each patient will be confirmed by the oncologist during a medical consultation. The oncologist will present the study to the patients who are considered eligible, explaining the study, offering participation and requesting written informed consent. Written informed consent will be obtained from all patients, and they will be informed that they are under no obligation to participate, and they may withdraw their consent at any time. Withdrawal from the study or non-participation will have no consequences for medical follow-up and care. Where possible, the reasons for withdrawal from the study will be recorded. All the participants will be followed from the acceptance period and 3-months after the end of the anthracycline-based chemotherapy (t_3). If recruitment is not achieving the target sample size, we will extend recruitment to additional hospitals.

Table 1. Eligibility criteria

Inclusion criteria	Exclusion criteria
Female gender.	Contraindications to maximal exercise testing.
Aged 18 years or older.	Decompensated diabetes mellitus.
Histological diagnosis of stage IA–IIIC BC.	Severe anemia (hemoglobin < 8 g/dL) uncorrectable with transfusion and/or iron and/or vitamin deficiency replacement.
Scheduled to receive A-Ct.	Pregnancy.
Follow up at the Medical Oncology clinic at the CHVNG/E.	Known significant heart disease (myocardial infarction, congestive heart failure, cardiomyopathy).
Consent of the assistant oncologist for exercising.	Usual medication containing beta-blockers.
Able to provide informed consent.	
Acceptance of randomization to intervention group or usual care group.	

Randomization

After confirmation of eligibility and baseline assessments (t_0), patients will be randomized using Internet software (www.sealedenvelope.com), in a 1:1 ratio, to the supervised exercise group (intervention group) or the usual care group (control group), using a permutated block design with random block sizes (4, 6, 8) with stratification by two dichotomous variables, which are known risk factors for anthracycline-related cardiotoxicity:

- Age (< 50 years or older)
- Receiving anti human epidermal growth factor receptor 2 (HER2) therapy (Yes/No)

This process will be performed by an external individual who is blinded to the study and who will place the sequence in a numbered, opaque, sealed envelope. The allocation of participants will then be reported to an oncologist (AJ) who will subsequently inform the patients about the assignment group.

Study arms

Intervention group

Patients allocated to the intervention group will perform a supervised exercise program specifically developed for patients with BC, based on the guidelines of the American College of Sports Medicine (Schmitz et al., 2010) and in a close cooperation between physical sports researchers (PA, DE, AA) and medical staff (oncologists, surgeons, radiologists, physiatrist, and physiotherapist) of the CHVNG/E.

The exercise program comprises three sessions per week guided in small groups (< 5 patients) in an appropriately equipped room at the CHVNG/E, supervised by the main author (PA) and a physiotherapist. Each session will involve an initial warm up (5-minutes), followed by arobic and resistance training (~60-minutes), and ending with a cooldown phase (5-minutes). The program will be started 1 or 2-days after the first A-Ct cycle and will be conducted over the respective treatment of each patient. It should be noted that the proposed exercise intervention will never be intended to replace or interfere with the current standard BC care.

Aerobic training

It will include the combination of treadmill, stationary bike, and stepping. This phase will be monitored through HR (each participant will wear a HR monitor during exercise training sessions) and rate of perceived exertion (RPE) measured by a 0–10 point modified Borg scale (minimal effort: 0; maximum effort: 10) (Borg, 1982). During the first 2-weeks, the participants will perform 20 min (divided equally among the three exercise modes) of light-intensity, aerobic

training (at <50% of measured HR reserve [based on maximum HR reached in the cardiorespiratory test], with a reported rating of 2–4 [“easy” to “somewhat easy”] on the modified Borg scale). After this period, 3-minutes will be added every 2-weeks until a volume of 30-minutes of aerobic training is reached. At this stage, participants will be encouraged to perform high-intensity training (at 65–80% of measured HR reserve, with a reported rating of 5–8 [“somewhat hard” to “hard”] on the modified Borg scale) until the end of the intervention.

Participants will be reminded weekly (by email or phone) of their exercise training schedule and the importance of adherence to achieve the established objectives.

Resistance training

Resistance training will include upper body (shoulder press, chest press, lateral pulldown, biceps curls, and triceps extension) and lower body (squat, calf raise, leg press, leg extension, and leg curl) weight-training exercises. All the exercises will be performed at the maximum possible joint range of motion, using resistance machines and free weights. RPE will be measured using a 0–10-point OMNI-Resistance Exercise Scale (OMNI-RES, minimal effort: 0; maximum effort: 10) (Robertson et al., 2003). During the first week, participants will perform 2 sets and 10 repetitions of each exercise without additional resistance or with the lowest available (reported rating of 2–4 [“easy” to “somewhat easy”] on the OMNI-RES). After this phase, if no adverse events or symptoms were reported for a specific exercise, resistance will be added so that each participant could be able to perform 3-sets with 12 maximal repetitions (12-RM) of each exercise. When the participants can complete 3-sets and more than 12-RM at the set weight in three consecutive sessions, then the resistance will be increased by between 5% and 10%.

Usual care group

Patients allocated to the usual care group will receive standard BC care. The usual care group will not receive any specific advice about physical activity and will not be asked to be inactive. In compensation for participation in this study, patients in this group will be offered the possibility to follow the same exercise program as in the intervention group, after the final assessments are completed.

Study assessments

The schedule of study outcome assessments is outlined in Figure 2. Study assessments will be scheduled upfront and participants will be regularly reminded (by email or phone) to ensure complete follow-up. Primary, secondary, and exploratory outcomes will be measured in all participants at three different time points:

- t_0 (baseline assessments): between 0 and 14-days prior to the first chemotherapy session.
- t_2 (post-treatment assessments): between 1 and 5-days after the end of anthracycline-based chemotherapy.

- t_3 (follow-up assessments): after 3-months of t_2.

In addition, for analysis of circulating NT-proBNP, blood samples will be collected between 1 and 24-hours before each anthracycline-based chemotherapy cycle (t_1: during treatment assessments).

Patients will be instructed and reminded to avoid drinking beverages containing alcoholic or caffeine, and to abstain from smoking for 12-hours prior to, and avoid vigorous physical activities for 24-hours prior to all examinations.

	Enrolment	**Allocation**	**Post-allocation**			**Follow-up**
TIMEPOINT	**$-t_0$**	**0**	**t_0**	**t_1**	**t_2**	**t_3**
Enrolment:						
Eligibility screen	✓					
Informed consent	✓					
Demographic data	✓					
Anthropometric data	✓		✓		✓	✓
Clinical data	✓		✓		✓	✓
Allocation		✓				
Interventions:						
Supervised exercise program			◆———		———◆	
Usual cancer care			◆———		———◆	
Assessments						
Primary outcomes						
NT-proBNP			✓	✓	✓	✓
Resting LV global longitudinal strain			✓		✓	✓
Resting LV ejection fraction			✓		✓	✓
Secondary outcomes						
Resting blood pressure			✓		✓	✓
Resting heart rate			✓		✓	✓
Resting heart rate variability			✓		✓	✓
Heart rate recovery			✓		✓	✓
Physical Function			✓		✓	✓
Cardiorespiratory fitness			✓		✓	✓
Upper limb strength			✓		✓	✓
Lower limb functionality			✓		✓	✓
Self-reported physical activity level			✓		✓	✓
Helath-related Quality of life			✓		✓	✓
Fatigue			✓		✓	✓

Figure 2. The schedule of enrolment, interventions, and assessments.
$-t_0$, enrolment process; t_0, baseline; t_1, during anthracycline-containing chemotherapy; t_2. post-anthracycline-containing chemotherapy (which coincides with the end of the intervention); t_3, 3-months after t_2; NT-proBNP, N-Terminal pro-brain natriuretic peptide; LV, left ventricular.

Study outcomes

The primary outcomes are:

- Resting LVEF and LV global longitudinal strain.
- Circulating NT-proBNP levels.

The secondary outcomes are:

- Resting blood pressure, resting HR, resting HRV, recovery HR.
- Cardiorespiratory fitness, upper and lower limb strength.
- Self-reported physical activity level, HRQoL, fatigue.

Assessment of the primary outcomes

Resting LV ejection fraction and resting LV longitudinal strain

Resting LVEF will be calculated using the biplane method of disks (modified Simpson's rule) from the apical four-chamber and two-chamber view (Lang et al., 2015). For resting LV global longitudinal strain assessment, two-dimensional grayscale images will be acquired in the apical four-chamber, two-chamber, and three-chamber views, with a frame rate of 60–100 frames per second. Three cardiac cycles will be digitally stored and Velocity Vector Imaging software (Siemens Medical Solutions United States of America Inc) will be used in the analysis. Echocardiographic acquisitions will be performed by a single experienced cardiologist blinded to the patient assignment group.

Assessment of the primary outcomes

Resting blood pressure and resting HR

Resting blood pressure (systolic and diastolic blood pressure) and resting HR will be measured using a standard automated device (Philips SureSignsVM6, Philips Medical System, Andover, USA). Two measurements will be carried out. The first measurement will be preceded by a 5-minutes resting period and a second reading will be taken after 3-minutes. If necessary, additional records shall be obtained until two consecutive stable measurements (differences <5 mmHg for blood pressure and <7 bpm for HR) are obtained. The average of the two stable measurements will be used in the analysis. This procedure will be carried out by a study investigator (ALA) not blinded to the patient assignment group.

Resting HRV

HRV is a non-invasive method used to analyze cardiac autonomic function through the measurement of successive heartbeat variations (R-R). Resting HRV will be analyzed using a HR monitor Polar V800 (Polar Electro Oy, Kempele, Finland) with a Polar H7 chest strap. During the

R-R recording, patients will be seated in a comfortable position. They shall be required to breathe spontaneously, to avoid any movements, and to maintain neutral thoughts during the data acquisition. The first 5-minutes will be excluded (stabilization period) and the remaining 5-minutes will be used to calculate the time-domain (standard deviation of successive normal R-R (SDNN), and root mean square of successive normal R-R (RMSSD)) and frequency-domain indices (low-frequency spectral component (LF), and high-frequency spectral component (HF). In all cases, the R-R recordings will be exported to the Kubios v2 HRV software (Biosignal Analysis and Medical Imaging Group at the Department of Applied Physics, University of Kuopio, Kuopio, Finland). Occasional artifact noise shall be automatically replaced with the interpolated adjacent RR interval values (filter power < low). This procedure will be carried out by the first author (PA) who will not be blinded to the patient assignment group.

Recovery HR

Recovery HR will be determined as the absolute difference between the HR at peak effort during the cardiorespiratory exercise test (CRET) and the HR at 60 s, and 120 s post-exercise. HR values will be derived from a continuous record obtained via CRET (Mortara X-Scribe, Mortara, USA). This procedure will be carried out by study investigators (EV, MT), blinded to the patient assignment group.

Cardiorespiratory fitness

Cardiorespiratory fitness will be evaluated by means of a symptom-limited CRET on a treadmill (Mortara X-Scribe, Mortara, USA), using a modified version of the Bruce protocol (Bruce & McDonough, 1969). Expired gases will be continuously collected throughout exercise and analyzed for ventilatory volume (VE) and for oxygen (O_2) and carbon dioxide (CO_2) content, using dedicated analyzers. Standard spirometry (forced expiratory volume in first second (FEV_1)) and forced vital capacity (FVC) will also be undertaken before the test. Equipment calibration and measurements will be in accordance with the recommendations of the American Thoracic Society and American College of Chest Physicians (American Thoracic Society & American College of Chest Physicians, 2003).

The following parameters will be calculated and considered for analysis: peak oxygen consumption (VO_{2peak}, measured in mL $O_2 \cdot kg^{-1} \cdot min^{-1}$), peak respiratory exchange ratio (RER), defined by the ratio of CO_2 production to O_2 consumption at peak effort, oxygen consumption at the anaerobic threshold (AT), defined as the point at which CO_2 production increases disproportionately in relation to O_2 consumption, obtained from a graph plotting O_2 consumption against CO_2 production, and total exercise duration (measured in seconds). The maximum HR achieved will also be recorded. The CRET will be conducted on a separate day to the remaining outcomes assessments out by study investigators (EV, MT) blinded to the patient assignment group. Patients will be in a fasted state and will not be asked to discontinue current medication before the test. Upper limb strength will be evaluated by maximal voluntary grip strength

(measured in kilograms), using a digital handgrip dynamometer (Saehan Corporation, Masan, South Korea - model SH5003). Each subject will perform six trials, three in each arm, with an alternating bilateral sequence. The results will based on the average of the three trials, respectively. This procedure will be carried out by the first author (PA), not blinded to the patient assignment group.

Upper limb strength

Upper limb strength will be evaluated by maximal voluntary grip strength (measured in kilograms), using a digital handgrip dynamometer (Saehan Corporation, Masan, South Korea - model SH5003). Each subject will perform six trials, three in each arm, with an alternating bilateral sequence. The results will based on the average of the three trials, respectively. This procedure will be carried out by the first author (PA), not blinded to the patient assignment group.

Lower limb functionality

Lower limb functionality will be evaluated by the 30-seconds sit-to-stand test using a straight-backed chair (40-cm high). Each subject will be required to keep plantar support while flat on the floor with arms crossed at the chest, and sit and stand as many times as possible for 3- seconds. The score for the test will be determined by the number of repetitions achieved during this procedure. The procedure will be carried out by the first author (PA), not blinded to the patient assignment group.

Self-reported physical activity level

The International Physical Activity Questionnaire-Short (IPAQ-SF) will be used to calculate the metabolic equivalent task (MET)/minutes per week spent in walking and in moderate and vigorous activities. Sedentary behavior will be determined based on time spent sitting per day (minutes). Based on their scores, participants will be categorized as having a low, moderate, or high physical-activity level. The Portuguese language version of the IPAQ-SF will be used (Craig et al., 2003). Scoring will be analyzed by the first author (PA), not blinded to the patient assignment group.

Health-related quality of life and fatigue

The European Organization for Research and Treatment in Cancer (EORTC) Quality of Life C-30 (QOL-C30) is a self-administered, validated questionnaire to assess HRQoL in patients with cancer (Aaronson et al., 1993). It is composed of nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. Additionally, there are five single items of symptoms commonly reported by patients with cancer (dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea), and an item that evaluates the perceived financial

impact of the disease. In this study, the third version of this questionnaire will be used, in the portuguese language (Franceschini et al., 2010). Analyses will include the five functional scales, fatigue scale, and the global health and quality-of-life scale. The scoring of the several scales will be carried out by the first author (PA), not blinded to the patient assignment group.

Demographic, anthropometric, and clinical data

Demographic, anthropometric, and clinical data will be recorded during the enrolment process ($-t_0$). Demographic data include age, sex, and education. Anthropometric data include weight, height, and body mass index. Clinical data include disease, treatment information, past medical history, and current medication. These data will be extracted from the patients' electronic medical files by two study coordinators (ALA, AJ) not blinded to the patient assignment group.

Safety

The safety of the intervention will be assessed by weekly tracking and monitoring the number of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. A meeting between the study investigators will be held weekly to review and discuss the reported adverse events. All serious adverse events will be immediately reported to the CHVNG/E ethics commission and to all study members, and will be reported in the study results. Adverse events will be evaluated by the study investigators who will make the decision to stop the study early if there is a clinically relevant increased risk.

Bliding

This study will involve the prescription of exercise sessions. To carry out a rigorous exercise prescription and to ensure adequate follow up of each patient, participants, the physical trainer (PA), the medical oncologist (AJ), and the nurse oncologist (ALA) will not be blinded to group assignment. Due to the lack of resources, only the evaluators acquiring the echocardiographic outcomes (resting LVEF and LV global longitudinal strain), circulating NTproBNP levels, cardiorespiratory fitness, and recovery HR data, will be blinded to the group assignment.

Data management

Study data will be managed by two study investigators (PA, AJ) using a predesigned data collection form (Microsoft Office Excel version 2016; Microsoft Corporation, Redmond, WA, USA) and Statistical Package for the Social Sciences files version 23.0 (IBM Corporation, Armonk, NY, USA) with double data-entry. Data checks will be regularly performed to ensure data quality. Patients will be identified by codes to ensure their anonymity, and only the authors involved in the trial will have access to their full identification details. The total number of patients who meet the study eligibility criteria will be recorded, as will the number of patients who agree or not agree to participate in the study, the number of patients assigned to each study arm, the number of

patients who participate in all sessions, the attendance of each patient in the intervention sessions, the number of patients who provide follow-up data, the number of patients included in the final analysis, and the number of withdrawals.

Sample size calculation

The sample size was determined by a power calculation based on resting LVEF outcome, using a non-commercial statistical power analysis program (G*Power Version 3.1.9.2). Based on an effect size of 0.6 for resting LVEF presented in a previous study (Howden et al., 2019), to ensure statistical power of 80% and a significance level of 0.05, using the *t* test for two independent groups, the recruitment of 72 participants is required. Predicting a 20% dropout rate (Furmaniak et al., 2016), we estimate that a total of 90 patients will be needed (45 patients in each arm). There are no planned early stopping rules. Adverse events will be evaluated by the study investigators, who will make the decision to stop the study early if there is a clinically relevant increased risk.

Statistical analysis

Statistical data analysis will be performed using the Statistical Package for the Social Sciences. The statistical significance will be set at a p-value <0.05. Intention-to-treat and per-protocol approaches will be used both for all analyses. Data analysis will start with standard descriptive methods to describe the data (means and standard deviations will be calculated for continuous variables and absolute and relative frequencies for categorical variables). Continuous variables will be compared between the two study groups using one-way analysis of covariance (ANCOVA), adjusted for the effect of the baseline values (covariate). A linear two-way mixed ANCOVA model with repeated measures (t_1, t_2 and t_3) will be performed to test the difference over time between the two study groups and interaction (Group × Time), on primary and secondary outcomes, with the same covariate as the one-way ANCOVA. Bonferroni's post-hoc procedure will be performed to locate the pairwise differences. Normality will be verified by the Kolmogorov-Smirnov test and the homogeneity of the variance will be validated by Levene's test. Effect size will be calculated to estimate variance between moments through partial eta-squared. The cutoff values were defined as 0.02 for small effect size, 0.13 for moderate, and 0.26 for large effect sizes (Cohen, 1988). The chi-squared test will be used to check for a relationship between categorical variables. The effect size will be calculated using Cramer's V test and interpreted based on the following cutoff values: 0.10 for a small effect, 0.30 for a medium effect, and 0.50 for a large effect (Cohen, 1988). No interim analyses will be conducted.

Discussion

CVD is one of the leading causes of death among women with BC and a foremost concern in the clinical practice of oncology (Armenian et al., 2017; Bradshaw et al., 2016; Gernaat et al., 2017;

Patnaik et al., 2011). According to Gernaat et al. (2017), BC survivors have an absolute risk of dying from CVD that ranges from 1.6% to 10.4%. The recurrent use of cardiotoxic therapies and the presence of risk factors for the development and worsening of cardiovascular health problems are the main factors related to this phenomenon. The implementation of preventive strategies aiming to optimize cardiovascular care in BC survivors is therefore an emerging need. To date these include early identification of potential risk factors, the management of anthracycline cumulative dose (and possible use of ancillary therapies), or the use of drugs for heart failure (beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor antagonists) (Zamorano et al., 2016). However, these approaches were mainly established to reduce the toxicity of therapeutic agents and ensure their efficacy, but not to provide a general preventive cardiovascular approach. It is thus pivotal to investigate the effects of non-pharmacological prevention strategies in order to counteract anthracycline-related cardiotoxicity and related complications in patients with BC.

Currently, exercise is recognized as a safe and effective, supportive intervention to improve physical function and HRQoL in BC survivors during or after treatment (Furmaniak et al., 2016; Lahart et al., 2018). Furthermore, exercise has also been proposed as a potential tool to mitigate anthracycline-related cardiotoxicity in humans, although this remains uncertain as it is mainly supported by data from animal studies and/or using less accurate biomarkers (Chen et al., 2017; Scott et al., 2018; Virani et al., 2016; Zamorano et al., 2016). In fact, there are limited data on whether the benefits of exercise also include protection from anthracycline-related cardiac damage in women with BC. To the best of our knowledge, Kirkham et al. (2018) were the first to test this hypothesis by analyzing the efficacy of a single aerobic bout performed 24-hours prior to each treatment. The authors observed positive effects on systemic outcomes (cardiac output, resting HR, body weight, and psychological symptoms), but did not observe relevant changes in echocardiographic outcomes (LV mass, LVEF, strain imaging, and the E/A ratio) or circulating cardiac biomarkers (troponin t and NT-proBNP). In a recent non-randomized trial, Howden et al. (2019) verified that performing a 2-weekly supervised exercise program plus a weekly unsupervised aerobic session attenuated the reduction in VO_{2peak} and the increase of troponin levels in women with BC undergoing A-Ct, when compared to a usual care group. However, these authors did not observe any relevant changes in the measured echocardiographic outcomes. So far, the overall clinical significance of exercise in preventing cardiac dysfunction associated with anthracycline treatment remains to be clarified in controlled clinical settings.

The present study will explore the cardioprotective role of exercise and potential mitigation of anthracycline-related cardiotoxicity, and establish the possible effect of exercise on different health outcomes in women with BC. A total of 90 adult women with early BC and prescribed A-Ct at the CHVNG/E will be enrolled. Recruitment will take place between 1 November 2018 and 31 November 2020 (expected date of recruitment completion). Follow up is expected to be completed by 30 June 2021.

We anticipate that the results of this study will add new knowledge to what the literature currently offers, clarifying the effects of a supervised exercise program on different established markers and more accurate biomarkers of cardiotoxicity in women with BC undergoing A-Ct. Furthermore, we expect that the findings from this study may help in future policies related to cancer care management and contribute to the ascertainment of the role of exercise programs during anti-neoplastic treatment in hospital.

Limitations

There are some limitations to this study, which should be noted. First, we will only include patients followed at CHVNG/E. Second, due to the impossibility of blinding patients and some of the researchers to study group assignment, the open design of this study may influence the assessment retention rate of participants allocated to the usual care group. Third, we will stratify our sample based on age (under/over 50 years) and use of trastuzumab (yes/ no). However, there are other risk factors associated with anthracycline-related cardiotoxicity, including total cumulative anthracycline dose, preexisting cardiac disease, and treatment with mediastinal radiation, that should also be considered (Furmaniak et al., 2016). Although these hinderances should be acknowledged, we believe the findings from the present study will provide important data, which will be of relevance to the contemporary literature on this subject.

Dissemination

The findings of this study will be reported in a doctoral thesis by the main author, will be submitted to a peer reviewed journal for publication, and will be presented at relevant conferences and disseminated to the public in partnership with CHVNG/E, Universidade da Beira Interior (Covilhã, Portugal), and community stakeholders.

Study 4

Effects of exercise training on cardiac toxicity markers in women with breast cancer undergoing chemotherapy with anthracycline: a randomized controlled trial [3]

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Abstract

Objectives Exercise training has been suggested to prevent anthracycline-related cardiac dysfunction, but clinical-based evidence is scarce. We investigated the effects of a supervised exercise training program (SETP) on cardiac toxicity markers in women with breast cancer receiving anthracycline-containing chemotherapy.

Methods Ninety-three women with early-stage breast cancer were randomly allocated to a SETP plus usual care group (Exercise, n=47) or usual care alone group (UC, n=46). The SETP consisted of 3 sessions per week, combining aerobic and resistance training, conducted concurrently across the anthracycline-containing chemotherapy length. The primary endpoint was the change in left ventricular ejection fraction (LVEF) from baseline to the end of anthracycline cycles. Secondary endpoints included global longitudinal strain (GLS) and other conventional echocardiographic outcomes, exercise capacity (estimated VO_{2peak}), circulating biomarkers (N-terminal pro-brain natriuretic peptide [NT-proBNP] and high-sensitivity cardiac troponin T [hs-TnT]), and safety of the SETP. The study endpoints were also assessed 3-months after the end of anthracycline cycles.

Results All patients were prescribed four cycles of doxorubicin plus cyclophosphamide (AC). No significant between-group differences in LVEF change at end of AC (mean difference [MD]: 0.7%, 95% confidence interval [CI]: -0.8 to 2.3; p=0.349) and 3-months after AC (MD: 1.1%; 95% CI: -0.5 to 2.6; p=0.196) were seen. Compared to the UC group, the estimated VO_{2peak} increased in exercise group at end of AC (MD: 1.6 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI: 0.06 to 3.1; p=0.041) and 3-months after AC (MD: 3.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI: 1.4 to 4.7; p<0.001). No between-group differences were found in the remaining secondary endpoints. No serious adverse events were observed during exercise training sessions.

Conclusion Exercise training was safe during chemotherapy and significantly improved aerobic exercise capacity. No significant effects were seen on cardiac toxicity markers (LVEF and GLS) as compared to usual care.

Keywords

Exercise; supportive therapy; breast cancer; chemotherapy; quality of life; physical fitness.

Introduction

Anthracycline-containing chemotherapy is frequently recommended in the curative treatment plan for breast cancer (BC) (Cardoso et al., 2019). Studies have shown the benefits of its use on disease-free survival and overall survival in patients with early-stage BC (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2012). Whilst this, it is well recognized that anthracyclines increase the risk of cancer therapy-related cardiac dysfunction (CTRCD), typically defined by left ventricular ejection fraction (LVEF) decline, with or without symptoms of heart failure (HF) (Armenian et al., 2017; Bloom et al., 2016). A recent meta-analysis found a clinical HF incidence of 2% and a 10.3% incidence of subclinical anthracycline-related cardiac dysfunction in BC survivors (Jang et al., 2019). Although the incidence of CTRCD varies according to the definition used, this is in line with previous literature (McGowan et al., 2017). Furthermore, it is well established that anthracycline-related cardiac dysfunction is a progressive, cumulative, and dose-dependent process, which can affect patients' treatment strategies (Armenian et al., 2017). Therefore, effective interventions to prevent or limit CTRCD are warranted.

In the past few years, guidelines (Alexandre et al., 2020; Armenian et al., 2017; Lyon et al., 2022) and expert position statements (Curigliano et al., 2020; Zamorano et al., 2016) have proposed different measures aiming to prevent CTRCD. These recommendations comprise baseline screening (including cardiotoxicity risk assessment of anticancer therapies and baseline screening of pre-existing cardiovascular [CV] disease or CV risk factors), CV imaging surveillance, and primary prevention measures such as i) active management of modifiable CV risk factors; ii) encouragement of healthy lifestyle habits (including physical activity [PA] and nutrition), and iii) the possible use of pharmacotherapy for HF in certain cases.

Among healthy lifestyle routines, regular PA has long been recognized as an essential component for the primary and secondary prevention of CV disease (Visseren et al., 2021). In addition to its beneficial role in the general population (Lee et al., 2022; Saint-Maurice et al., 2020), studies have reported the potential relevance of leisure-time PA and exercise training in reducing the risk and incidence of CV events in BC survivors (Jones et al., 2016; Kim et al., 2021; Lee, T. K., et al., 2019). Recently, Naaktgeboren et al. (2022) expanded on this field, by demonstrating that higher levels of PA were associated with more favorable global longitudinal strain (GLS; a subclinical cardiac dysfunction marker) in women with BC at a median of 10 years of follow-up after treatment. Data from preclinical studies have also shown promising evidence that exercise training could have a potential cardioprotective effect by preserving mitochondrial function, preventing an anthracycline-induced increase in oxidative stress markers, and the accumulation of this drug in cardiac tissue (Ascensão et al., 2006; Naaktgeboren et al., 2022). Despite this valuable body of knowledge, there are a limited number of randomized clinical trials (RCTs) that have evaluated the effect of exercise on cardiac outcomes beyond cardiorespiratory capacity (Murray et al., 2022a; Naaktgeboren et al., 2021; Scott et al., 2018b). Recently, Murray et al. (2022a) conducted a systematic review to describe the effect of exercise training, concomitant

with chemotherapy in women with BC, on LVEF and GLS. The authors found similar effects of exercise compared to control groups. However, this systematic review included only 8 studies, of which only 3 were RCTs that involved small samples (the largest trial involved 64 participants), short exercise interventions (4 to 48 exercise training sessions) and no follow-up period (Hornsby et al., 2014; Kirkham et al., 2018b; Ma, 2018). As such, the overall effect of structured exercise on the prevention of cardiac function decline during potentially cardiotoxic treatment remains to be fully ascertained.

Accordingly, we conducted a RCT to evaluate the effects of a supervised exercise training program (SETP) on established markers of cardiac toxicity in women with early-stage BC undergoing anthracycline-containing chemotherapy. The primary endpoint was the change in LVEF at the end of anthracycline cycles. Secondary endpoints included the change in GLS, other conventional echocardiographic parameters, exercise capacity, and circulating cardiac biomarkers.

Methods

Study design and ethical approval

We conducted a RCT with a parallel 2-arm group design (Antunes et al., 2019), at Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E; Vila Nova de Gaia, Portugal). This trial is registered in the International Standard Randomised Controlled Trial Number (trial identifier: ISRCTN32617901) and was approved by the Ethics Committee of the CHVNG/E (reference: 145/2018–1). All patients provided written informed consent before enrolment.

Patients

Adult (i.e., ≥18 years of age) women diagnosed with early-stage BC, scheduled to receive anthracycline-containing chemotherapy, and followed up at the CHVNG/E, were considered eligible and recruited by medical oncologists of the CHVNG/E. Early-stage BC describes non-metastatic BC that, taking in account only the disease stage, is possible to treat with curative intente (Cardoso et al., 2019). Exclusion criteria were contraindication to maximal exercise testing; decompensated diabetes mellitus; severe anemia (hemoglobin < 8 g/dL) despite blood transfusion and/or iron supplementation and/or vitamin deficiency replacement; history of CV disease such as myocardial infarction, congestive HF, cardiomyopathy; and taking usual medication containing beta-blockers.

Recruitment was conducted from January 2019 to March 2020 and from September 2020 to January 2022. The interruption (March 2020 to September 2020) was due to COVID-19 pandemic measures.

Randomization

Patients were randomly assigned, in a 1:1 ratio, to a SETP plus usual care group (Exercise) or usual care alone (UC) group. Randomization was stratified according to age (≤ 50 years vs. > 50 years) and the clinical decision to receive anti-human epidermal growth factor receptor 2 (anti-HER2) therapy (Yes vs. No) using an electronic software (www.sealedenvelope.com) with a permuted block design with random block sizes (4; 6; 8). Data on randomization and allocation were maintained in opaque envelopes and were managed by an external blinded individual.

Primary and secondary endpoints

The primary efficacy endpoint was the absolute change in LVEF from baseline to the end of anthracycline cycles. We also analyzed the incidence of CTRCD based on the change in LVEF. The CTRCD was defined by a decrease in LVEF of ≥10% from baseline to a value of LVEF under 53%, according to the criteria described by American Society of Echocardiography and the European Association of Cardiovascular Imaging (Plana et al., 2014). Secondary endpoints included the absolute change in GLS and other echocardiographic measures of cardiac remodeling (left ventricular [LV] end-diastolic volume, LV end-systolic volume, LV mass index, left atrial volume index); diastolic (E/E' mean ratio, E/A ratio) and systolic function (cardiac output, stroke volume); exercise capacity (estimated peak oxygen consumption [VO_{2peak}]); and circulating CV biomarkers (N-terminal pro-brain natriuretic peptide [NT-proBNP], high-sensitivity cardiac troponin T [hs-TnT]). These outcomes were assessed at baseline (i.e., before the start of the first cycle of chemotherapy), after the last anthracycline cycle, and 3-months after that (follow-up visit) (Figure 1). Circulating CV biomarkers were further assessed in the 24 hours preceding each anthracycline cycle.

In addition, the tolerability and safety of the SETP were also reported.

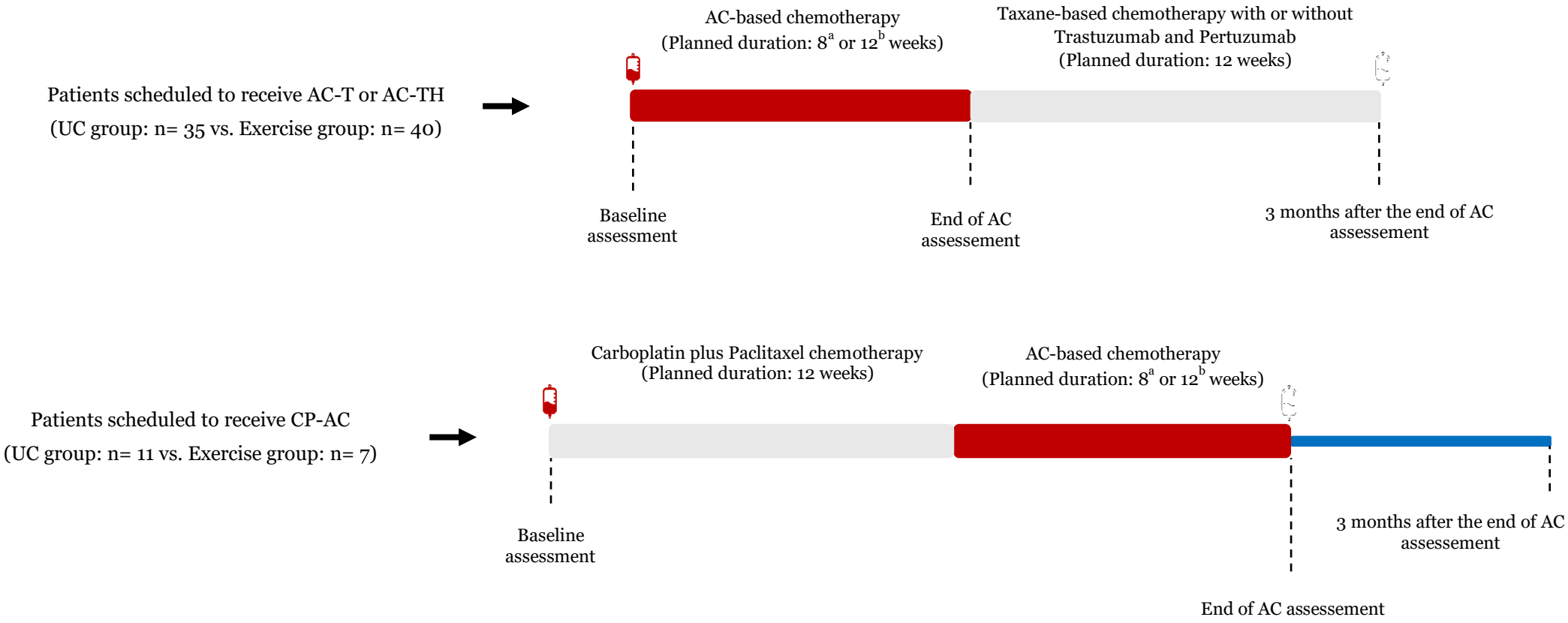

Figure 1. Description of the Assessments Timeline.

AC: Doxorubicin plus Cyclophosphamide; AC-T: Doxorubicin plus Cyclophosphamide followed by taxane-based chemotherapy; AC-TH: Doxorubicin plus Cyclophosphamide followed by taxane-based chemotherapy plus trastuzumab with or without pertuzumab; CP-AC: Carboplatin and Paclitaxel followed by Doxorubicin plus Cyclophosphamide; : denotes the begin of chemotherapy; : denotes the end of chemotherapy.

aAC was delivered every 2-weeks; bAC was delivered every 3-weeks.

Echocardiography

A single experienced cardiologist, blinded to the patient assignment group, performed all echocardiographic studies using a commercially available ultrasound system (Acuson SC2000, Siemens Medical Solutions USA, Inc, Mountain View, CA, USA) equipped with a broadband 4V1c transducer. Resting LV ejection fraction was calculated using the biplane method of disks (modified Simpson's rule) from the apical four- and two-chamber views (Lang et al., 2015). For resting LV GLS assessment, two-dimensional grayscale images were acquired in the apical four-, two- and three-chamber views, with a frame rate of 60–100 fps. Three cardiac cycles were digitally stored and the Velocity Vector Imaging software (Siemens Healthineers USA) was used in the analysis.

Exercise capacity

Exercise capacity was evaluated through a symptom-limited treadmill exercise stress test on a treadmill (Mortara X-Scribe, Mortara, USA), using a modified version of the Bruce protocol (Bruce & McDonough, 1969). Exercise capacity was planned to be assessed by directly measuring VO_{2peak} (by means of a cardiopulmonary exercise stress test), but due to the COVID-19 pandemic, most symptom-limited treadmill exercise stress tests were conducted without gas analysis. Thus, VO_{2peak} was estimated using the following equation, which was recently validated in treated BC patients: VO_{2peak} (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) = [speed (m/min) × (0.17 + fractional grade × 0.32) + 3.5]) (Michalski et al., 2022).

Circulating biomarkers

The assessment of NT-proBNP and hs-TnT levels was conducted in the local clinical analysis laboratories at the CHVNG/E, which are certified by the United Kingdom National External Quality Assessment Service. These were blinded to the patient assignment group. Clinical records were consulted to collect circulating biomarkers data.

Tolerability and safety

Tolerability was assessed by the rates of adherence to the planned exercise training frequency; adherence to the prescribed duration and intensity of aerobic training; and adherence to the prescribed volume (sets, repetitions) and intensity (training load) of resistance training (Kirkham et al., 2018a). To assess the safety of the exercise program, type and prevalence of serious adverse events (i.e., "events that results in death or persistent or significant disability/incapacity, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization") and non-serious adverse events (e.g., general fatigue and pain in the extremities) that occurred during exercise training sessions were recorded (Scott et al., 2018a). Only patients who have performed at least one exercise training session were included in the tolerability and safety analysis.

Exercise training program

Patients allocated to the Exercise group underwent a SETP concomitant to each patient's anthracycline-containing chemotherapy. The exercise training program involved 3 sessions per week, combining aerobic and resistance training. The exercise training sessions started 1 or 2-days after the first cycle of chemotherapy and were supervised by an exercise physiologist and a physiotherapist. Each training session involved a warm-up (5-10 minutes) and ended with a cool-down phase with stretching exercises (5 minutes). Patients scheduled to receive four cycles of doxorubicin plus cyclophosphamide (AC) every 2-weeks were planned to perform 60 exercise sessions, whereas patients scheduled to receive AC every 3-weeks were planned to perform 72 exercise sessions.

Continuous aerobic training was performed on a treadmill, stationary bike, or stepping. During the first 2-weeks of training, patients performed 20 minutes of aerobic training at an intensity <50% of heart rate (HR) reserve. After this period, 3 minutes were increased every 2-weeks until a total duration of 30 minutes was reached and patients were encouraged to exercise at 65-80% of HR reserve. Exercise intensity was continuously monitored during sessions with HR monitors (Firstbeat Sports, Firstbeat Sport®, Finland). The average HR and the amount of time spent at the target HR were recorded. The HR reserve was calculated considering the maximum HR achieved in the symptom-limited treadmill exercise stress test and resting HR, which was assessed in every exercise session. For the resting HR assessment, the participants were instructed to remain seated, at rest, in a chair with a back, keeping their backs against the chair, feet flat on the floor, arms and legs relaxed, for 3 to 5 minutes.

Resistance training involved upper body (shoulder press, chest press, lateral pulldown, biceps curls, and triceps extension) and lower body weight-training exercises (squat, calf raise, leg press, leg extension, and leg curl). Patients were encouraged to perform the exercise at the maximum possible joint range of motion, using resistance machines and free weights. During the first 2-weeks of training, patients performed 2 sets and 10 repetitions of each exercise without additional resistance or with the lowest load available. After this period, if no adverse events or symptoms were reported for a specific exercise, resistance was added so that each patient could be able to perform 3 sets with 12 maximal repetitions (RM). When patients were able to complete 3 sets and more than 12-RM at the set weight in three consecutive sessions, an increased load of 5-10% was considered.

Statistical analysis

The sample size was based on an effect size for LVEF of a previous study (Howden et al., 2019). With a power of 80%, a significance level of 5%, and a predicted dropout rate of 20%, a total of 90 patients were considered. The primary efficacy analysis was performed on an intention-to-treat sample consisting of all validly randomized patients. We also performed a non-planned per-

protocol analysis that included the UC group and patients who had an adherence to training frequency equal or higher than the median.

Continuous variables are expressed by means and standard deviation or medians with 25-75th percentile and mean differences are expressed with their two-sided 95% confidence interval (CI). Categorical variables are expressed by frequencies (percentages). To compare baseline characteristics between groups an independent sample t-test was used for continuous variables. The Mann-Whitney test was used whenever the normality assumption could not be assumed. The normality assumption was assessed by the Kolmogorov-Smirnov test. The Chi-squared test and Fisher's exact test were used to analyze the existence of a relationship between categorical variables. Linear mixed models (LMMs) were used to estimate longitudinal within-group and between-group differences in mean change of the primary and secondary endpoints, with fixed effects for group and time. The choice of LMMs analysis is justified by the existence of some missing data points in the dataset. The covariance type was set to scaled identity. The between-group difference in mean change for the echocardiographic outcomes was adjusted for baseline values of the endpoint, HR, and total cumulative doxorubicin dose. Because of the nonnormal distribuition of NT-proBNP and hs-TnT data, the LMMs analysis was performed using the log-transformed values. However, untransformed data are presented for ease of reading. The level of significance was set as 5%. All analyses were conducted using SPSS Statistics 26.0 (IBM Corporation., Armonk, NY, USA).

Results

Study Population

Of the 119 screened patients, 93 eligible patients (78.2%) were randomly assigned to the UC group (n=46) or the Exercise group (n=47) (Figure 2). The two groups were well-balanced concerning patient characteristics at baseline (Table 1). Four cycles of AC, followed by taxanes (75; 80.6%) were prescribed to all patients, except for 18 patients (19.4%; UC group: n=11 vs. Exercise group: n=7) with triple-negative tumors, who received carboplatin and paclitaxel first, followed by AC, according to local practice. Anti-HER2 therapy was added in HER2 positive tumors (trastuzumab plus pertuzumab in 23 patients [24.7%] and trastuzumab alone in 2 patients [2.1%]). The total cumulative doxorubicin dose was similar among the groups, although the UC group had a higher number of patients who did not complete their planned AC dose (UC group: n=6 (13%) vs. Exercise group: n=1 (2%); p=0.059). Considering the proforma for anthracycline-containing chemotherapy designed by the Cardio-Oncology Study Group from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) in collaboration with the International Cardio-Oncology Society (ICOS) (Lyon et al., 2020), 68 patients (73.1%) had low risk, 24 patients (25.8%) were medium risk, and 1 patient (1.1%) were high risk for CTRCD.

Details of baseline tumor characteristics are outlined in Table 2. Cancer treatment characteristics of the included patients are described in Table A1 (Appendixes - Study 4). Both groups were similar considering tumor characteristics, except for a larger number of patients in the Exercise group who underwent axillary dissection (UC group: n=2 vs. Exercise group: n=12; p=0.008).

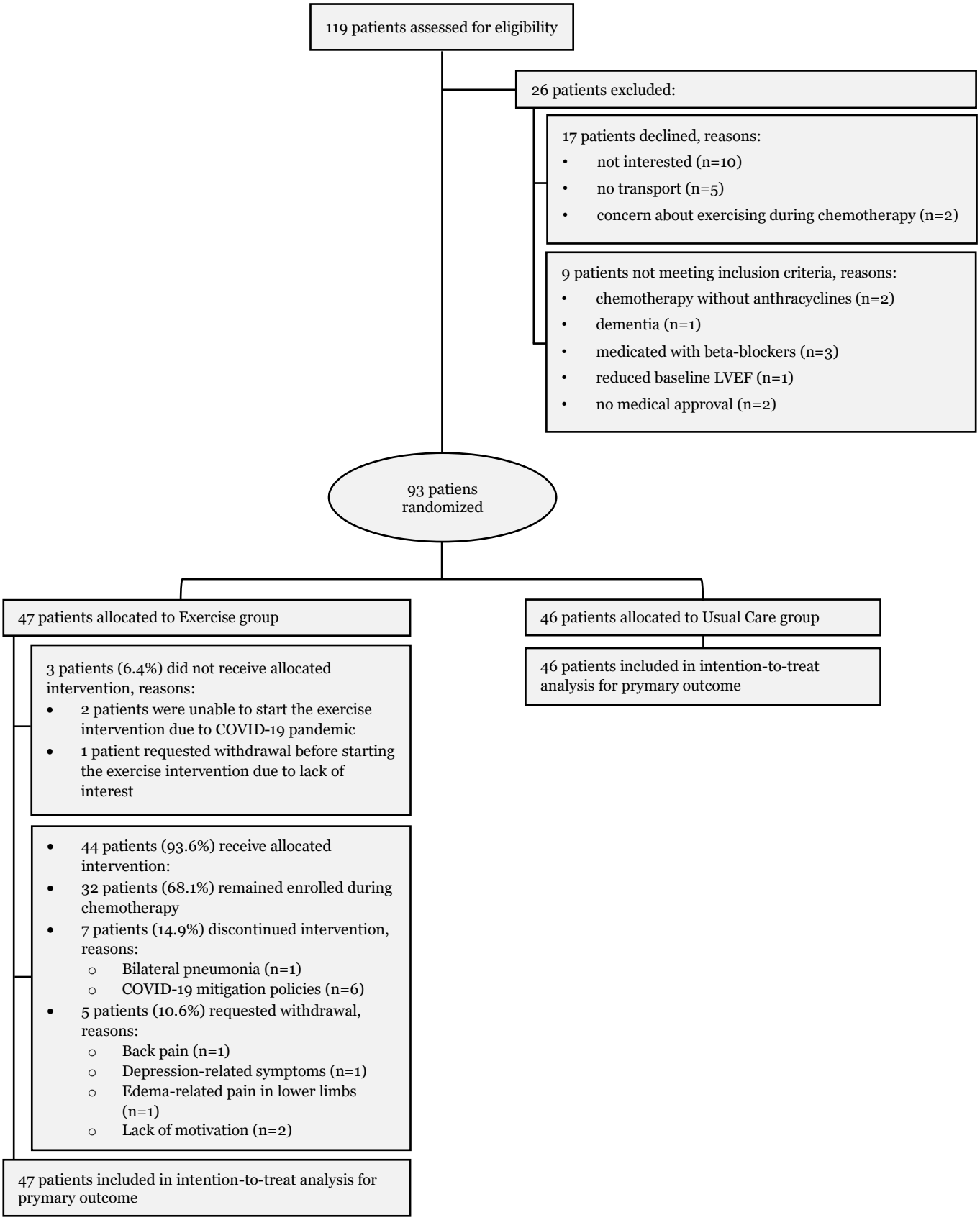

Figure 2. Study enrollment, randomization, follow-up and analysis (CONSORT flow).

Table 1. Baseline characteristics of the study patients

Characteristics	Total (n=93)	Usual Care (n=46)	Exercise (n=47)	*P*
Age (years)	50.33±9.46	51.02±9.54	49.66±9.43	0.491[a]
Body Mass Index (kg/m²)	27.82±5.73	28.69±6.82	26.94±4.32	0.138[a]
Eastern Cooperative Oncology Group (ECOG) Performance Status				
ECOG score of 0	74 (79.6%)	36 (78.3%)	38 (80.9%)	0.802[c]
ECOG score of 1	19 (20.4%)	10 (21.7%)	9 (19.1%)	
Premenopausal	53 (57%)	24 (52.2%)	29 (61.7%)	0.406[c]
Postmenopausal	40 (43%)	22 (47.8%)	18 (38.3%)	
Cardiovascular Risk Factor				
Current Smoker	18 (19.3%)	8 (17.4%)	10 (21.3%)	0.794[c]
Diabetes	7 (7.5%)	5 (10.9%)	2 (4.3%)	0.267[d]
Hypertension	27 (29.0%)	14 (30.4%)	13 (27.7%)	0.768[c]
Obesity	27 (29.0%)	15 (32.6%)	12 (25.5%)	0.499[c]
Pre-treatment Cancer Therapy-related CardiovascularToxicity Risk[e]				
Low risk	68 (73.1%)	34 (73.9%)	34 (72.3%)	1[c]
Medium risk	24 (25.8%)	11 (23.9%)	13 (27.7%)	0.813[c]
High risk	1 (1.1%)	1 (2.2%)	0 (0%)	0.495[d]
Usual Antihypertensive Medication	24 (25.8%)	14 (30.4%)	10 (21.3%)	0.822[c]
Aldosterone Receptor Antagonism	10 (10.8%)	7 (15.2%)	3 (6.4%)	0.198[d]
Angiotensin-Converting Enzyme Inhibitors	11 (11.8%)	6 (13%)	5 (10.6%)	0.759[c]
Calcium Channel Blockers	1 (1.1%)	1 (2.2%)	0 (0%)	0.495[d]
Diuretic	11 (11.8%)	7 (15.2%)	4 (8.5%)	0.355[c]
Chemotherapy Intent				
Neoadjuvant	64 (68.8%)	34 (73.9%)	30 (63.8%)	0.294[c]
Adjuvant	29 (31.2%)	12 (26.1%)	17 (36.9%)	
Sytemic Treatment Protocols				
AC-T	50 (53.8%)	23 (50%)	27 (57.4%)	0.535[c]
AC-TH	25 (26.9%)	12 (26.1%)	13 27.7%)	1[c]
CP-AC	18 (19.4%)	11 (23.9%)	7 (14.9%)	0.304[c]
Anti-HER2 Therapy				
Trastuzumab	2 (2.2%)	1 (2.2%)	1 (2.1%)	1[d]
Trastuzumab and Pertuzumab	23 (24.7%)	11 (23.9%)	12 (25.5%)	1[c]
Doxorubicin Cumulative Dose (mg/m²)	416.4 [377.4, 444.0]	417.6 [364.1, 442.2]	411.6 [390, 446.4]	0.456[b]
Incomplete AC Planned Dose	7 (7.5%)	6 (13%)	1 (2%)	0.059[d]
Meeting Exercise Guidellines for Healthy Adultsf	7 (7.5%)	4 (8.7%)	3 (6.4%)	0.714[d]

Legend:

Data are expressed as mean+SD, median [25th-75th percentile], or numbers (percent).

AC: Doxorubicin plus Cyclophosphamide; AC-T: Doxorubicin plus Cyclophosphamide followed by taxane-based chemotherapy; AC-TH: Doxorubicin plus Cyclophosphamide followed by taxane-based chemotherapy plus trastuzumab whit or without pertuzumab; CP-AC: Carboplatin and Paclitaxel followed by Doxorubicin plus Cyclophosphamide.

Eastern Cooperative Oncology Group Performance Status: was used by the medical oncologists, responsible for recruitment, to evaluate each patient's performance status at enrollment. An ECOG score of 0 indicated that the patient was fully active, able to carry on all predisease performance without restriction; an ECOG score of 1, indicated that the patient was restricted in physically strenuous activity but ambulatory and able to perform light work.

Table 1. Continued

[a] t-test for independent samples.
[b] Mann-Whitney test.
[c] Chi squared test.
[d] Fisher's exact test.
[e] Pre-treatment cancer therapy-related cardiovascular toxicity risk was retrospectively assessed accordingly with HFA/ICOS proforma for anthracycline chemotherapy (Lyon et al., 2020).
[f] Perform at least 150 minutes a week of moderate-intensity aerobic physical activity, or 75 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity.

Table 2. Breast tumour characteristics

Characteristics	Total (n=93)	Usual Care (n=46)	Exercise (n=47)	*p*
Breast Cancer Stage, American Joint Committee on Cancer Eighth Edition				
Stage I	14 (15.1%)	7 (15.2%)	7 (14.9%)	1[a]
Stage II	47 (50.5%)	21 (45.7%)	26 (55.3%)	0.409[a]
Stage III	32 (34.4%)	18 (39.1%)	14 (29.8%)	0.388[a]
Immunohistology				
HER2+	25 (26.9%)	12 (26.1%)	13 (27.7%)	1[a]
ER+	65 (69.9%)	30 (65.2%)	35 (74.5%)	0.372[a]
PR+	62 (66.7%)	29 (63%)	33 (70.2%)	0.514[a]
Ki-67 ≥30%	47 (50.5%)	31 (67.4%)	28 (59.6%)	0.520[a]
Breast Cancer Phenotype				
ER/PR+ and HER2-	48 (51.6%)	21 (45.6%)	27 (57.4%)	0.181[a]
ER/PR+ and HER2+	19 (20.4%)	9 (19.6%)	10 (21.3%)	0.565[a]
ER/PR- and HER2+	6 (6.5%)	3 (6.5%)	3 (6.4%)	0.250[b]
ER/PR- and HER2-	20 (21.5%)	13 (28.3%)	7 (14.9%)	0.353[a]
Nottingham Tumor Grade				
Grade 1	5 (5.4%)	2 (4.3%)	3 (6.4%)	1[b]
Grade 2	46 (49.5%)	21 (45.7%)	25 (53.2%)	0.536[a]
Grade 3	42 (45.2%)	23 (50%)	19 (40.4%)	0.408[a]
Breast Cancer Laterality				
Left Side	49 (52.7%)	25 (54.3%)	24 (51.1%)	0.836[a]
Right Side	44 (47.3%)	21 (45.7%)	23 (48.9%)	
Adjuvant Setting	29 (31.2%)	12 (26.1%)	17 (36.2%)	0.372[a]
Pathologic Tumor Sizec				
pT1	13 (44.8%)	6 (50%)	7 (41.2%)	1[a]
pT2	13 (44.8%)	6 (50%)	7 (41.2%)	1[a]
pT3	3 (10.3%)	0 (0%)	3 (17.7%)	0.242[b]
Pathologic Lymph Nodec				
pN0	13 (44.8%)	7 (58.3%)	6 (35.3%)	0.773[a]
pN1	13 (41.4%)	3 (25%)	10 (52.9%)	0.120[b]
pN2	3 (13.8%)	2 (16.7%)	1 (11.8%)	1[b]
Breast Cancer Surgery Before Systemic Treatment				
Lumpectomy	14 (48.3%)	7 (58.3%)	7 (41.2%)	0.462[a]
Mastectomy	15 (51.7%)	5 (41.7%)	10 (58.8%)	
Sentinel Lymph Node Biopsy	15 (51.7%)	10 (83.3%)	5 (29.4%)	0.008[a]
Axillary Dissection	14 (48.3%)	2 (16.7%)	12 (70.6%)	
Neoadjuvant Setting	64 (68.8%)	34 (73.9%)	30 (63.8%)	0.372[a]
Clinical Tumour Sized				
cT1	9 (14.1%)	4 (11.7%)	5 (16.7%)	0.723[b]
cT2	37 (57.8%)	20 (58.8%)	17 (56.7%)	1[a]
cT3	13 (20.3%)	7 (20.6%)	6 (20%)	1[a]
cT4	5 (7.8%)	3 (8.8%)	2 (6.7%)	1[b]
Clinical Lymph Node				
cN0	34 (53.1%)	16 (47.1%)	18 (60%)	1[b]
cN1	8 (12.5%)	5 (14.7%)	3 (10%)	0.529[a]
cN2	20 (31.3%)	11 (32.4%)	9 (30%)	0.773[a]
cN3	2 (3.1%)	2 (5.9%)	0 (0%)	0.677[b]

Table 2. Continued

Legend:
Data are expressed as numbers (per cent).
ER: Oestrogen Receptor; HER2: Human Epidermal Growth Factor Receptor 2; PR: Progesterone Receptor; +: positive; -: negative.
[a] Chi-squared test.
[b] Fisher's exact test.
[c] the relative distribution (per cent) was calculated considering the number of patients who underwent chemotherapy in an adjuvant adjuvant setting.
[d] the relative distribution (per cent) was calculated considering the number of patients who underwent chemotherapy in an adjuvant neoadjuvant setting.

Exercise training tolerability and safety

Of the 47 patients assigned to the Exercise group, 3 patients (6.4%) did not start the SETP, 12 patients (25.5%) discontinued the SETP, and 32 patients (68.1%) remained enrolled during the whole period of chemotherapy. The reasons for the SETP discontinuation are described in Table 3. During patients' chemotherapy, 1664 exercise sessions were attended out of 2634 planned (ranging from 60 to 72 planned exercise sessions), corresponding to a mean adherence of 63.2±26.9% (median adherence of 72.5% [44.16% to 78.33%]) of the planned exercise sessions. Considering aerobic training, median adherence to duration was 100% [98% to 100%], and mean adherence to aerobic intensity was 77.9±14.3%. Median adherence to resistance training prescription (considering prescribed load, sets, and repetitions) was 74.5±11.5%.

A total of 149 non-serious adverse events were registered during the exercise training sessions, and 37 patients (84.1%) experienced at least 1 non-serious adverse event (Table 3). The most common non-serious adverse events were generalized fatigue (38.2%), pain in the extremities (12.1%), and dizziness (7.4%). No serious adverse events were observed during exercise training sessions.

Table 3. Description of the adverse events that occurred during the exercise training sessions

	No. patients (%)[1]	Incidence (%)
Total	37 (84.1%)	149
Abnormal heart rate response	1 (2.3%)	1 (0.7%)
Anal fistula-related pain	1 (2.3%)	1 (0.7%)
Anxiety	1 (2.3%)	1 (0.7%)
Arthralgia	5 (11.4%)	8 (5.4%)
Asthma-related symptmos	2 (4.5%)	4 (2.7%)
Cramps	2 (4.5%)	4 (2.7%)
Diarrhea	3 (6.4%)	3 (2%)
Dizziness	8 (18.2%)	11 (7.4%)
Edema-related pain in lower limbs	4 (9.1%)	10 (6.7%)
Fear of dislodging the central venous catheter	1 (2.3%)	1 (0.7%)
Fear of walking on treadmill	1 (2.3%)	1 (0.7%)
Fever (found at pre-session screening)	2 (4.5%)	2 (1.3%)
General fatigue	20 (45.4%)	57 (38.2%)
Hemorrhoid-related pain	1 (2.3%)	2 (1.3%)
Nausea	4 (9.1%)	6 (4%)
Pain in the extremities	9 (50.4%)	18 (12.1%)
Pain in the operated arm	2 (2.3%)	5 (3.4%)
Presyncope	2 (4.5%)	2 (1.3%)
Syncope	3 (6.4%)	3 (2%)
Sudden extreme fatigue	2 (4.5%)	3 (2%)
Tremor	1 (2.3%)	1 (0.7%)
Weak emotional state	3 (6.4%)	5 (3.4%)

Legend:
Data are expressed as numbers (percent).
[1] Considering the total of patients that performed at least 1 exercise training sessions (n=44).

Primary endpoint

Data on patients' echocardiographic outcomes across the study are reported in Table 4.

The mean baseline LVEF was 61.2±3.3% (range from 54% to 67%) in the UC group and 60.1±2.9% (range from 51% to 66%) in the Exercise group. There was no significant interaction on the primary endpoint (p=0.408) or any of the secondary endpoints. As estimated from the LMMs, we observed a decrease in LVEF at the end of AC, namely 1.6% (95% CI: -3.0 to -0.1; p=0.022) in the UC group and 0.8% (95% CI: -2.2 to 0.5; p=0.411) in the Exercise group. Both groups showed a significant decrease at 3-months after AC, namely 3% (95% CI: -4.5 to -1.6; p<0.001) in the UC group and 1.9% (95% CI: -3.4 to -0.57; p=0.003) in the Exercise group. Despite the smaller decline seen in the Exercise group, the adjusted between-group differences were not statistically significant in any time-point assessment.

Per-protocol analysis revealed similar results (Table A2, in Appendixes - Study 4). At the end of AC, one patient (triple-negative subtype) from the UC group experienced an absolute decline of 10% in LVEF to an absolute value of 52%. At the follow-up visit, the previously mentioned patient experienced a worsening of the LVEF decline to an absolute value of 47%, and 3 additional patients (2 luminal-b subtype in the UC group vs. 1 HER2-positive subtype in the Exercise group) experienced an absolute decline of at least 10% in LVEF to an absolute value bellow than 50%.

Table 4. Change in echocardiogram endpoints (intention-to-treat analysis)

	Usual Care			Exercise			*P* (Interaction)†	Adjusted Between-group Difference from Baseline‡		
	n	**Mean±SD**	**Within-group Difference in Mean Change from Baseline†**	***n***	**Mean±SD**	**Within-group Difference in Mean Change from Baseline†**		***n***	**Mean (95%CI)**	***P***
Left Ventricular Ejection Fraction (%)							0.408			
Baseline	45	61.2±3.3		46	60.1±2.9					
End of AC	45	59.6±3.3	-1.6 (-3.0, -0.1)*	47	59.2±3.1	-0.8 (-2.2, 0.5)		91	0.7 (-0.8, 2.3)	0.349
3 months after AC	43	58.1±4.4	-3.0 (-4.5, -1.6)*	44	58.1±3.6	-1.9(-3.4, -0.5)*		86	1.1 (-0.5, 2.6)	0.196
Global Longitudinal Strain (%)							0.299			
Baseline	37	-21.3±2.2		39	-21.1±1.9					
End of AC	39	-20.1±2.1	1.1 (0.2, 2.1)*	38	-20.1±1.8	0.8 (-0.1, 1.8)		73	-0.3(-1.4, 0.7)	0.500
3 months after AC	34	-18.8±2.0	2.4 (1.4, 3.4)*	33	-19.4±2.1	1.5 (0.6, 2.5)*		63	-1.0(-2.1, 0.1)	0.095
Cardiac Output (L.min)							0.339			
Baseline	45	3.5±0.6		46	3.4±0.7					
End of AC	45	3.7±0.7	0.1 (-0.1, 0.4)	47	3.8±0.9	0.4 (0.1, 0.6)		91	0.2 (-0.1, 0.5)	0.107
3 months after AC	43	3.5±0.7	-0.01 (-0.2, 0.2)	44	3.5±0.7	0.1 (-0.1, 0.4)		86	0.1 (-0.1, 0.4)	0.446
Stroke Volume (mL)							0.454			
Baseline	45	46.5±9.7		46	46.4±10.6					
End of AC	45	45.8±10.6	-0.7 (-4.0, 2.6)	47	47.1±11.4	0.9 (-2.2, 4.2)		91	1.9 (-1.9, 5.7)	0.323
3 months after AC	43	44.7±11	-1.5 (-4.9, 1.7)	44	44.4±8.2	-2.2 (-5.6, 1.1)		86	-0.9 (-4.9, 2.9)	0.618
Left Atrium Volume Index (mL/m^2)							0.376			
Baseline	45	23.4±5.8		45	24.3±8.6					
End of AC	45	26.4±7.2	2.9 (0.3, 5.5)*	47	26.1±8.4	1.9 (-0.6, 4.5)		90	-0.8 (-3.7, 2.1)	0.584
3 months after AC	42	25.1±5.7	1.6 (-1.0, 4.3)	43	23.3±6.4	-0.5(-3.1, 2.1)		83	-2.0 (-5.0, 1.0)	0.193
Left Ventricular End-diastolic Volume (mL)							0.344			
Baseline	45	76.1±16.6		46	77.2±16.9					
End of AC	45	76.9±17.1	0.8 (-4.1, 5.8)	47	79.5±18.2	2.7 (-2.1, 7.7)		91	2.3 (-3.5, 8.1)	0.436
3 months after AC	43	77.4±18.3	1.4 (-3.6, 6.5)	44	76.6±13.1	-0.9 (-5.9, 4.1)		86	-2.8 (-8.7, 3.1)	0.353

Table 4. Continued

Left Ventricular End-systolic Volume (mL)						0.422			
Baseline	45	29.6±7.6		46	30.9±6.8				
End of AC	45	31.1±7.6	1.5 (-0.8, 3.9)	47	32.4±7.5	1.6 (-0.6, 4)	91	0.2 (-2.5, 3.3)	0.854
3 months after AC	43	32.6±9.2	3.0 (0.6, 5.4)*	44	32.6±6.9	1.4 (-0.8, 3.8)	86	-1.6 (-4.5, 1.1)	0.242
Left Ventricular Diameter (mm)						0.824			
Baseline	46	46.9±4.2		47	46.5±3.0				
End of AC	45	47.6±3.8	0.6 (-0.5, 1.8)	47	47.3±3.2	0.7 (-0.3, 1.9)	91	0.2 (-1.1, 1.6)	0.733
3 months after AC	43	47.0±4.2	-0.03 (-1.2, 1.1)	45	47.0±3.2	0.3 (-0.7, 1.5)	87	0.4 (-1.0, 1.8)	0.556
Left Ventricular Mass Index (g/m^2)						0.665			
Baseline	46	78.1±16.1		47	76.8±14.3				
End of AC	45	80.3±16.5	1.9 (-2.3, 6.2)	47	80.2±14.7	3.3 (-0.8, 7.6)	91	1.7 (-3.4, 6.9)	0.507
3 months after AC	43	79.3±17.9	1.1 (-3.4, 5.4)	45	77.1±13.1	0.2 (-4.1, 4.5)	87	-0.5 (-5.7, 4.7)	0.848
EA ratio						0.911			
Baseline	46	0.9±0.3		47	1.0±0.3				
End of AC	45	0.9±0.3	0.004 (-0.08, 0.09)	47	1.0±0.3	0.01 (-0.07, 0.1)	91	0.01 (-0.09, 0.1)	0.872
3 months after AC	43	0.9±0.3	-0.03 (-0.1, 0.05)	45	1.0±0.2	-0.05 (-0.1, 0.03)	87	-0.01 (-0.1, 0.09)	0.833
Ee ratio						0.509			
Baseline	46	7.9±2		45	7.8±1.9				
End of AC	44	8.1±1.7	0.09 (-0.4, 0.6)	45	8.2±1.9	0.4 (-0.09, 1.0)	86	0.3 (-0.2, 0.9)	0.268
3 months after AC	43	7.8±1.8	-0.2 (-0.7, 0.3)	45	7.9±1.9	0.04 (-0.5, 0.5)	85	0.1 (-0.4, 0.8)	0.543

Legend:

Data are expressed as mean±standard deviation or mean (95% CI).

AC: doxorubicin plus cyclophosphamide; SD: standard deviation.

† Within-Group Difference in Mean Change and Interaction was based on linear mixed models, controlling for group, time and interaction (fixed effects).

‡ Adjusted Between-Group Difference was based on linear mixed models, controlling for group, time and interaction (fixed effects) and for baseline outcome, heart rate, and total cumulative doxorubicin dose (covariate).

* Denotes a significant p-value<0.05.

1

Secondary endpoint

GLS, cardiac output and stroke volume

Global longitudinal strain was obtained in 76 (81.7%), 77 (82.8%), and 67 patients (72.0%) at baseline, end of AC, and 3-months after AC, respectively, with no differences found between groups. The mean baseline GLS was -21.3±2.2% (ranging from -17.2% to -26.2%) in the UC group and -21.1±1.9% (ranging from -16.6% to -24.8%) in the Exercise group (Table 4). As estimated from LMMs, we observed a decrease at the end of AC, namely 1.1% (95% CI: 0.2 to 2.1; p=0.009) in UC group and 0.8% (95% CI: -0.1 to 1.8; p=0.068) in the Exercise group. Both groups showed a significant reduction at the follow-up visit, namely 2.4% (95% CI: 1.4 to 3.4; p<0.001) in the UC group and 1.5% (95% CI: 0.6 to 2.5; p<0.001) in the Exercise group. The adjusted between-group differences at the end of AC and the follow-up visit were not significant. Moreover, no differences were observed in cardiac output and stroke volume.

Per-protocol analysis revealed an attenuation in the GLS decline in Exercise group compared to the baseline (Table A2, in Appendixes - Study 4). A statistical adjusted between-group difference of 1.5% (95% CI: 2.9 to 0.2; p=0.025) was observed at 3-months after AC, favoring the Exercise group.

Left ventricular diastolic function

Estimated LMMs revealed no differences between-group in the EA ratio and E/E' (Table 4).

Cardiac remodelling

In the UC group, a significant increase of 2.9% (95% CI: 0.3 to 5.5; p=0.019) in left atrium volume index at end of AC and of 3.0% (95% CI: 0.6 to 5.4; p=0.008) in left ventricular end-systolic volume at 3-months after AC was found (Table 4). However, no changes in the adjusted between-group difference were found (Table 4).

Exercise capacity

Data on patients' exercise capacity are reported in Table 5. There was a significant interaction (p=0.001) on estimated VO_{2peak}. Estimated VO_{2peak} remained unchanged throughout the study in the UC group, whereas the Exercise group showed an increase compared to baseline by 3.9% (p=0.160) and 11.2% (p<0.001) at the end of AC and 3-months after AC, respectively. The adjusted between-group difference in mean change revealed that the Exercise group increased estimated VO_{2peak} by 1.6 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (95% CI: 0.06 to 3.1; p=0.041) at the end of AC and by 3.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (95% CI: 1.4 to 4.7; p<0.001) at 3-months after AC, compared to the UC group.

Table 5. Change in cardiorespiratory fitness (intention-to-treat analysis)

	Usual Care			Exercise			*P* (Interaction)†	Adjusted Between-group Difference from Baseline‡		
	n	**Mean±SD**	**Within-group Difference in Mean Change from Baseline†**	***n***	**Mean±SD**	**Within-group Difference in Mean Change from Baseline†**		***n***	**Mean (95%CI)**	***P***
Estimated VO_{2peak} (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)							0.001			
Baseline	40	21.5±4.8		45	23.1±3.3					
End of AC	35	20.8±4.4	-0.9 (-2.2, 0.4)	41	24.2±4.0§	0.9 (-0.2, 2.2)		71	1.6 (0.06, 3.1)	0.041
3 months after AC	31	21.2±4.2	-0.5 (-1.9, 0.9)	35	25.8±4.2§	2.59 (1.2, 3.9)*		61	3.1 (1.4, 4.7)	<0.001

Legend:

Data are expressed as mean±standard deviation or mean (95% CI).

AC: doxorubicin plus cyclophosphamide; SD: standard deviation.

† Within-Group Difference in Mean Change and Interaction was based on linear mixed models, controlling for group, time and interaction (fixed effects).

‡ Adjusted Between-Group Difference was based on linear mixed models, controlling for group, time and interaction (fixed effects) and for baseline outcome, and total cumulative doxorubicin dose (covariate).

* Denotes a significant p-value<0.05.

§ Denotes a significant p-value<0.05 between groups.

Circulating biomarkers

Changes in serum levels of NT-proBNP and hs-TnT are described in Table 6. As estimated from LMMs, compared to the baseline, the UC group showed a significant increase in NT-proBNP at end of AC (mean: 38.64 pg/mL; 95% CI: 1.73 to 79.02; p=0.007). Compared to the baseline, both groups experienced a significant increase in serum troponin I level in subsequent time-point assessments (p<0.001). There were no alterations in the adjusted between-group differences for NT-proBNP and troponin I

Table 6. Change in circulating biomarkers (intention-to-treat analysis)

	Usual Care			Exercise			*p* (Interaction)†	Adjusted Between-group Difference from Baseline ‡		
	n	Mean ± SD	Within-group Difference in Mean Change from Baseline†	*n*	Mean ± SD	Within-group Difference in Mean Change from Baseline†		*n*	Mean (95%CI)	*p*
N-terminal pro-brain natriuretic peptide (pg/mL)							0.561			
Baseline	44	66.97±79.62		44	67.43±47.88					
Before AC Cycle 2	33	72.06±56.04	10.71 (-30.4 to 51.83)	31	65.38±50.60	0.03 (-41.93 to 42.0)		61	-9.20 (-50.49 to 32.09)	0.107
Before AC Cycle 3	36	83.90±87.71	14.34 (-26.80 to 55.49)	40	88.07±74.63	19.74 (-18.9 to 58.42)		69	-9.58 (-30.22 to 49.39)	0.664
Before AC Cycle 4	37	95.88±95.45	27.54 (-16.35 to 71.43)	38	99.68±93.01	30.84 (-8.43 to 70.12)		64	-5.33 (-35.95 to 46.62)	0.589
End of AC	35	106.28±124.25	38.64 (1.73 to 79.02)*	39	96.48±76.36	27.61 (-11.40 to 66.61)		70	-15.74 (-55.35 to 23.86)	0.282
3 months after AC	26	55.80±42.30	-6.81 (-51.42 to 37.78)	32	50.31±29.99	-15.08 (0.51 to 84.86)		57	-7.70 (-50.14 to 34.73)	0.439
hs-TnT (ng/L)							0.938			
Baseline	42	4.90±3.50		43	5.83±10.94					
Before AC Cycle 2	33	8±5.64	2.59 (0.26 to 5.45)**	31	6.69±2.93	1.89 (0.94 to 4.73)**		61	0.1 (-2.73 to 2.53)	0.998
Before AC Cycle 3	29	8.51±4.65	3.95 (1.20 to 6.70)**	35	7.62±3.60	3.13 (0.56 to 5.70)**		59	0.91 (-3.35 to 1.53)	0.556
Before AC Cycle 4	22	10.68±5.32	5.37 (2.35 to 8.39)**	27	10.0±6.10	4.88 (2.08 to 7.68)**		47	0.11 (-2.54 to 2.77)	0.893
End of AC	35	14.66±7.33	9.67 (7.03 to 12.31)**	37	13.59±6.64	9.08 (6.55 to 11.61)**		64	0.22 (-2.14 to 2.60)	0.490
3 months after AC	26	11.4±5.47	6.87 (3.95 to 9.78)**	32	12.03±4.89	6.95 (4.32 to 9.58)**		57	0.42 (-2.11 to 2.97)	0.503

Legend:

Data are expressed as mean±standard deviation or mean (95% CI). The statistical analysis was performed using the log-transformed values.

AC: doxorubicin plus cyclophosphamide; hs-TnT: high-sensitivity cardiac troponin T.

† Within-Group Difference in Mean Change and Interception was based on linear mixed models, controlling for group, time and interaction (fixed effects).

‡ Adjusted Between-Group Difference was based on linear mixed model, controlling for group, time and interaction (fixed effects) and for baseline outcome and total cumulative doxorubicin dose (covariate).

* denotes a significant p-value<0.05.

** denotes a significant p-value <0.001.

Discussion

This prospective RCT was conducted to analyze primarily the effects of a SETP on cardiac toxicity markers in women with early-stage BC undergoing anthracycline-containing chemotherapy. In this study, we found that concomitant exercise training during anthracycline-containing chemotherapy did not significantly prevent the decline of cardiac toxicity markers, such as LVEF and GLS, compared to UC. There was also no significant effect of exercise neither on conventional echocardiographic indices of cardiac function and structure, nor on serum levels of NT-proBNP and hs-TnT. However, exercise training significantly improved exercise capacity and was safe as a supportive approach, with no serious adverse events occurring during exercise training sessions, a finding consistent with prior studies (Hornsby et al., 2014; Scott et al., 2020).

LVEF is the most used parameter for identifying CTRCD (Zamorano et al., 2016). In this trial, we observed a less pronounced LVEF decline in the Exercise group, but this finding was not significantly different as compared to the UC group. This potential attenuating effect of exercise did not persist after 3-months of AC, and a significant decline in LVEF was seen in both groups compared to baseline. To date, research on the role of exercise in mitigating CTRCD is limited by the paucity of studies, and those that address this topic have included small sample sizes, short-duration exercise interventions, and short follow-up periods (Murray et al., 2022a; Naaktgeboren et al., 2021). Similar to our results, several studies reported a non-significant effect of exercise in preventing the decline in LVEF and GLS during anthracycline-containing chemotherapy (Haykowsky et al., 2009; Hornsby et al., 2014; Howden et al., 2019; Kirkham et al., 2018b). In contrast, a RCT involving women receiving adjuvant anthracycline-containing chemotherapy, found a significant improvement in LVEF after a 16-week interval aerobic training program (Ma, 2018). Despite promising, the risk of bias assessed by a systematic review (Murray et al., 2022a) and a meta-analysis (Naaktgeboren et al., 2021) point out possible methodological issues (inaccurate information about participant selection and randomization), which suggests caution in interpreting this result. The high prevalence of patients at low risk (73.1%) to develop CTRCD in the present study might explain, at least partially, the absence of a significant effect of exercise. Moreover, the mean decline of LVEF in our UC group was lower than the expected magnitude of impairment observed after anthracycline-containing chemotherapy (mean difference: 5.62%; 95% CI: 3.5 to 7.6) according with a recent meta-analysis of RCTs (Jeyaprakash et al., 2021). In addition, as cardiac toxicity can manifest months to years after the end of therapy, the follow-up period of this trial may have been too short to detect differences between groups (Cardinale et al., 2015).

In our trial, we observed a total of 4 CTRCD events (4.3%; UC group: n=3 vs. Exercise group: n=1). Previous studies, with shorter follow-up, have not reported any events (Hornsby et al., 2014; Howden et al., 2019; Kirkham et al., 2018b). Foulkes et al. (2019) were the first to analyze the long-term (12-months) effect of exercise training performed during AC by extending the follow-up of a non-RCT. The authors found 2 cases of CTRCD in the control group and noted an

attenuation in LVEF decline at 12-months in the exercise group compared to usual care -3.1% (95% CI: -8.4 to 2.1) vs. -6.9% (95% CI: -11.1 to -2.0), although without significant interaction effect (3.8%; 95% CI: -2.9 to 10.4) (Foulkes et al., 2019). Note that this study included 61% of the original study cohort (n=28), nevertheless, these results reinforce the importance of an extended follow-up analysis of the long-term effect of exercise on markers of cardiac toxicity, contributing, in turn, to better understand the possible role of exercise on the early attenuation of cardiac function, a subject not yet entirely clear (Gulati et al., 2016).

GLS has been recognized as a valuable parameter for detecting subclinical ventricular dysfunction (Oikonomou et al., 2019). We found a significant decline in GLS at the end of the study in both groups, slightly attenuated in the Exercise group at the end of the AC. Other studies have also reported a null effect of exercise at preventing the decline of GLS during anthracycline-containing chemotherapy, compared to usual care (Howden et al., 2019; Kirkham et al., 2018b). In contrast to our results, Costello et al. (2019) found, in a non-RCT with a smaller sample size (n=27), a significant effect of a nonlinear exercise program, combining moderate-to-vigorous intensity aerobic and resistance training, in the prevention of GLS decline in women with BC receiving anthracycline-containing chemotherapy. A recent meta-analysis also stated that exercise training significantly improves GLS in patients with CV disease (mean difference: 0.59; 95% CI: 0.16 to 1.02; p=0.01) compared to the non-intervention group, although with no significant effect in patients with CV risk factors and healthy subjects (Murray et al., 2022b). Moreover, the different method used in this non-RCT for assessing GLS (cardiac magnetic resonance) may explain the differences to our results. Furthermore, the higher adherence to the exercise training frequency reported by Costello et al. (2019) (76% vs. 63%) should be considered, as the training volume can be a significant determinant in the magnitude of the change in GLS (Murray et al., 2022a). Our per-protocol analysis involving participants with an adherence to planned exercise training frequency equal or higher than the median observed (≥72.5%), revealed a significant change between-group favoring the Exercise group; however, this observation should be cautiously interpreted due to the limited number of individuals (n=48; UC group: n=31 vs. Exercise group: n=17). Future trials should explore this hypothesis.

Although there was a small increase in hs-TnT at all time-point measurements and a significant increase in NT-ProBNP in UC at the end of AC, no significant between-group differences were found in these biomarkers. This is an expected result as there were no differences in systolic and diastolic function parameters between the groups. This finding is in line with a previous RCT (Kirkham et al., 2018b).

In this study, the Exercise group progressively improved exercise capacity (by 3.8% at end of AC and by 11.2% 3-months after AC). This result is in line with a previous phase II RCT that directly assessed VO_{2peak} in women with BC undergoing anthracycline-containing chemotherapy (Hornsby et al., 2014). Interestingly, a smaller magnitude of exercise-induced VO_{2peak} improvement was found in other studies, which have shown mitigation in the decline of the cardiorespiratory capacity (Howden et al., 2019; Lee, K. K., et al., 2019). Importantly, differences

in terms of study design (namely the shorter duration of the interventions, around 8-weeks) may explain the differences in relation to our results. In fact, we observed a progressive improvement in VO_{2peak} throughout the study, which reinforces the importance of performing exercise interventions throughout the systemic treatment period. Cardiorespiratory capacity provides an integrative outlook concerning global CV function, being inversely associated with CV disease and all-cause mortality (Jones et al., 2011; Ross et al., 2016). The 3.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ between-group difference obeserved in this study was a considerable result and may contribute to reducing all-cause mortality, cancer-related mortality, and CV mortality (Imboden et al., 2019). The decline in cardiorespiratory capacity is a chemotherapy-related toxicity often seen in cancer patients (Scott et al., 2018c). Particularly, it has previously been reported that the cardiorespiratory capacity of BC survivors is lower compared to healthy age- and sex-matched subjects and is particularly affected during anticancer treatment (Jones et al., 2012; Plana et al., 2014). Data also highlights that a considerable number of patients after anthracycline-containing chemotherapy can present VO_{2peak} corresponding to important impairments in functional capacity and that their full recovery is not always achieved, even after a long period of treatment cessation (Foulkes et al., 2019; Jones et al., 2012). Although we did not assess the long-term effects of exercise training, these observations support the relevance of exercise as a therapeutic support measure in the challenging subset of cancer survivors.

Strengths and limitations

The strengths of the current study include the randomized controlled design, coupled with the blinded evaluation of the study parameters conducted by the same highly trained and experienced professionals. In addition, our exercise training intervention was implemented during the entire systemic treatment of each patient and not limited to a part of it. This trial also has some limitations that deserve consideration. First, the current trial included a short follow-up period, which was limited to 3-months after the end of AC. Second, our findings are limited to BC survivors who underwent anthracycline-containing chemotherapy and therefore should not be generalized to other cancer patient populations undergoing treatment at different doses. Third, it is possible that the inclusion criteria may have limited the participation of patients at high risk of developing CTRCD, therefore, studies comparing subjects with more severe disease conditions are needed. Fourth, we used two-dimensional echocardiography by measuring LVEF which has well-recognized limitations (Thavendiranathan et al., 2013). Still, two-dimensional echocardiography is the most widely used imaging modality in clinical practice (Edvardsen et al., 2021) and the measurements conducted in this trial were performed by a single experienced cardiologist. Fifth, we were only able to record the adverse events that occurred during the training sessions. Future exercise training trials should include the assessement and analysis of adverse events that occur throughout the trial. Sixth, due to the prospective design, the contingencies related to COVID-19 had a significant impact on the recruitment, follow-up and assessments, leading to to 6 patients (12.7%) discontinuing SETP, some missing endpoints values and to the inability to perform a direct assessment of VO_{2peak}. Surprisingly, we found that

adherence to training frequency was not affected during the pandemic period (September 2020 to June 2022), which included a lockdown phase.

Conclusion

In conclusion, this RCT suggests that concomitant exercise training during anthracycline-containing chemotherapy was not associated with a significant effect on cardiac toxicity markers (LVEF and GLS), conventional echocardiographic indices of cardiac function and structure, or on serum levels of NT-proBNP and hs-TnT. However, exercise training was safe and significantly improved exercise capacity.

Study 5

Predictors of cardiorespiratory responsiveness in women with breast cancer undergoing exercise training during chemotherapy

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Abstract

Objective To analyze factors associated with cardiorespiratory fitness (CRF) responsiveness in women with breast cancer (BC) undergoing a supervised exercise training program (SETP), consisted at aerobic and resistance training, during anthracycline-containing chemotherapy.

Methods In this secondary analysis of the Mama Move Gaia on Treatment randomized controlled trial, CRF responsiveness of patients randomized to the Exercise group was assessed. Patients who completed CRF assessments at both baseline and post-STEP (n=41) were included and categorized as CRF Responders if exhibiting improvements in peak oxygen consumption (VO_{2peak}) ≥1 mL $O2 \cdot kg^{-1} \cdot min^{-1}$, or as CRF Non-responders if otherwise. Multiple logistic regression (MLR) analysis was performed to determine independent predictors of the CRF responsiveness considering baseline socio-demographic, clinical, and physiological factors, as well as the adherence to exercise training components.

Results Twenty-five patients (63%) were Responders. Compared to Non-responders, they had lower baseline body mass index (BMI) (p=0.045), fewer patients with obesity (p=0.049), and higher baseline left ventricular ejection fraction (LVEF) (p=0.021). Responders also showed greater adherence to training frequency (p=0.002) and considering aerobic training, performed a longer total duration (p=0.002), and accumulated more minutes at target intensity (p=0.002) and total aerobic training MET-hour (p<0.001). No differences were observed in resistance training adherence. MLR analysis confirmed that baseline BMI (OR: 0.796; 95% CI: 0.634 to 0.999; p=0.049) and total aerobic training MET-hour (OR: 1.038; 95% CI: 1.012 to 1.064; p=0.004) were significantly associated with patients' responsiveness.

Conclusions These findings suggest that baseline BMI and total energy expenditure may predict CRF responsiveness in BC patients undergoing exercise training during chemotherapy.

Keywords:

Exercise training; exercise prescription; cancer; cardiorespiratory fitness.

Introduction

Peak oxygen uptake (VO_{2peak}), the gold standard measure for assessing cardiorespiratory fitness (CRF), is a pivotal marker of cardiovascular health (Ross et al., 2016). Over the years, data has consistently reinforced the association between low CRF and increased risk of cardiovascular disease (CVD) and mortality across a broad range of settings (Ekblom-Bak et al., 2019; Han et al., 2022).

Throughout the cancer care continuum, a notable decline in CRF is often present with the most considerable decrease typically occurring during cancer-related therapy (Scott et al., 2018). This decline can be substantial, with reductions of up to 26% even among those with normal left ventricular systolic function (Jones et al., 2012; Peel et al., 2014; Scott et al., 2018). Moreover, studies indicate that CRF impairment tends to persist post-therapy, with patients often failing to regain pre-treatment levels (Foulkes et al., 2023b; Jones et al., 2012). In cancer patients, poor CRF has been associated with a higher symptom burden and risk of cancer-related mortality (Ekblom-Bak et al., 2023; Fardman et al., 2021; Herrero et al., 2006; Schmid & Leitzmann, 2015). Interestingly, data shows that an increase of 1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in VO_{2peak} was associated with a 16% reduction in cancer-related mortality, underscoring the relevance of addressing the trajectory of CRF in this population as well as key influencing factors on this important hallmark (Imboden et al., 2019).

Exercise training has progressively been established as a useful intervention in cancer care (Campbell et al., 2019). Several studies have documented that exercise training may mitigate the declines in CRF, physical functioning and health-related quality of life (Antunes et al., 2023; Foulkes et al., 2023b; Joaquim et al., 2022; Mijwel et al., 2018). We recently found that a supervised exercise training program (SETP), combining aerobic and resistance training, implemented throughout anthracycline-containing chemotherapy (A-Ct) for women with early-stage breast cancer (BC), significantly prevented the decline in VO_{2peak} as compared to usual care (Antunes et al., 2023). Other studies have demonstrated similar favorable effects (Foulkes et al., 2023b; Howden et al., 2019). Albeit this, it is acknowledged that substantial variations may exist among individuals regarding their CRF response to exercise training (Ross et al., 2019).

There has been growing interest at understanding the factors that influence patients' CRF response to exercise training. Indeed, the effects of socio-demographic, clinical, and physiological features as well as the impact of different exercise training components have been under study, to allow optimization of exercise training prescriptions (Foulkes et al., 2023a, 2024; Gevaert et al., 2020; Iannetta et al., 2023; Sweegers et al., 2019). However, most of the data so far falls outside the field of exercise oncology frameworks.

Given this background, we aimed to assess potential predictors of CRF responsiveness in individuals undergoing a SETP during A-Ct, as well as to explore differences between Responders

and Non-responders to this program. The knowledge of potential modified predictors of CRF responsiveness in this populational set will allow, not only individualization of exercise prescription, but also anticipate the strengthening of modified features in an attempt to possibly shift Non-responsiveness into responsiveness to exercise regimens in these patients.

Methods

Study design

This study was a secondary analysis of a parallel 2-arm group RCT, registered in the International Standard Randomized Controlled Trial Number registry (ISRCTN32617901) and approved by the local Ethics Committee (reference number: 145/2018–1). Detailed information on the study's rationale and design have been previously reported (Antunes et al., 2019).

Participants

This RCT included adult women (≥18 years old) diagnosed with early-stage BC scheduled to undergo A-Ct. Patients were randomly assigned, in a 1:1 ratio, to a SETP plus usual care (Exercise group) or usual care alone.(Antunes et al., 2019) For this study, we exclusively analyzed data from patients assigned to the Exercise group who completed two symptom-limited treadmill exercise stress tests during the study (Figure 1).

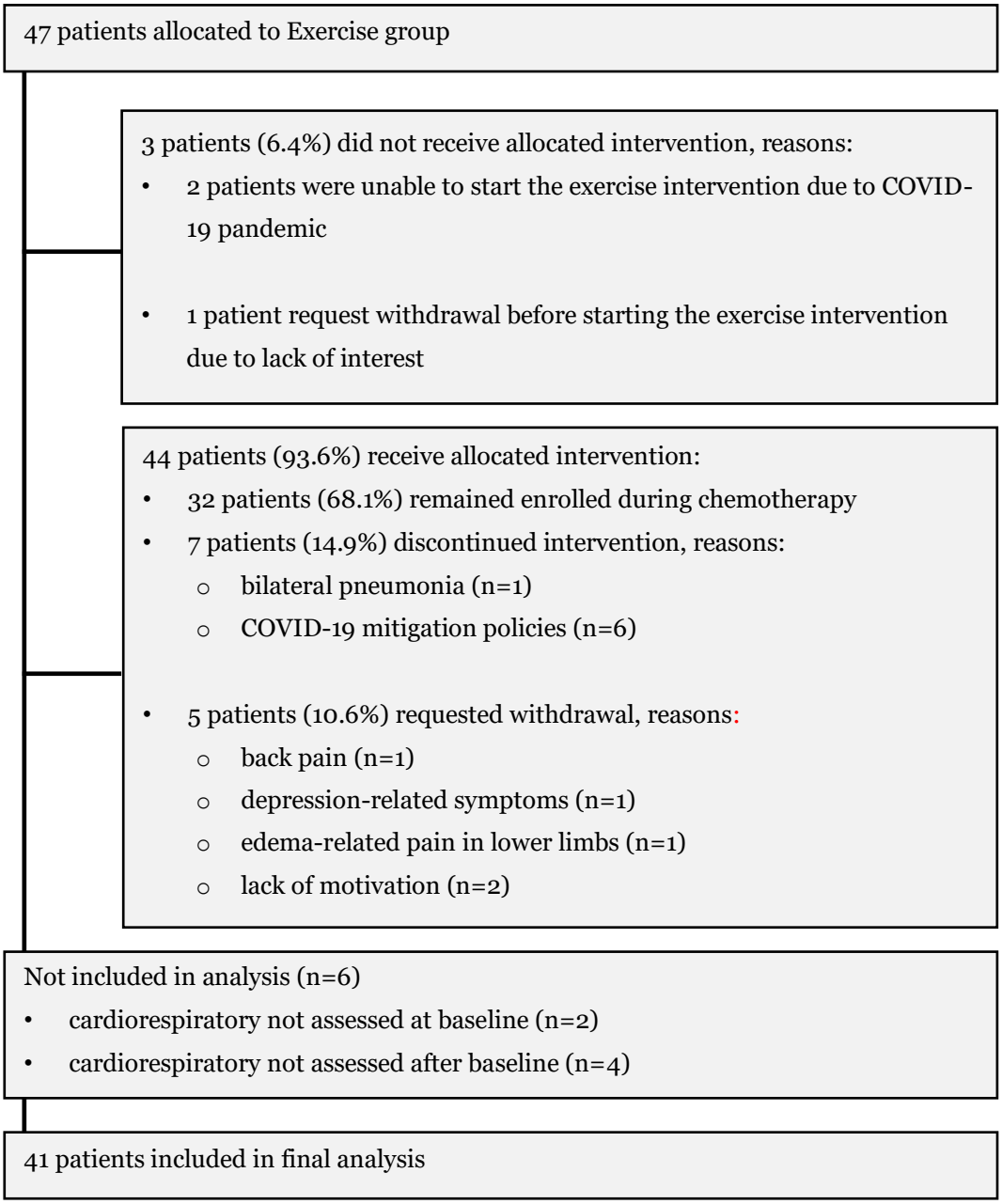

Figure 1. Study flow.

Exercise training program

The exercise program has been described in detail previously (Antunes et al., 2023). Briefly, the SETP was implemented concurrently with A-Ct, and involved three sessions per week combining aerobic and resistance training. Each training session initiated with a warm-up (5-10 minutes) and concluded with a 5-minute cool-down.

Continuous aerobic training was performed using a treadmill, stationary bike, or stepping. During the initial 2-weeks, patients were engaged in 20 minutes of aerobic training at an intensity below

50% of heart rate (HR) reserve. Subsequently, every 2-weeks, the duration increased by 3 minutes until reaching a total of 30 minutes. Patients were encouraged to exercise at an intensity ranging from 65% to 80% of HR reserve. Throughout sessions, HR monitors (Firstbeat Sports, Firstbeat Sport®, Finland) were used to continually monitor exercise intensity. The average HR and the duration spent at the target HR were recorded.

Resistance training encompassed both upper (shoulder press, chest press, lateral pulldown, biceps curls, and triceps extension) and lower body exercises (squat, calf raise, leg press, leg extension, and leg curl). During the initial 2-weeks, patients performed 2 sets and 10 repetitions of each exercise without load or with the lowest load available. Following this period, and in the absence of reported adverse events or symptoms, resistance was added. The goal for each patient to perform 3 sets with 12 maximal repetitions (RM). Once a patient consistently completed 3 sets with more than 12-RM at the set weight over three consecutive sessions, an increased load of 5-10% was introduced.

Cardiorespiratory fitness testing

CRF was assessed through a symptom-limited exercise stress test on a treadmill (Mortara X-Scribe, Mortara, USA), employing a modified version of the Bruce protocol. The original framework was to assess VO_{2peak} using a cardiopulmonary exercise stress test. However, due to the COVID-19 pandemic, most exercise stress tests were conducted without gas analysis. Consequently, VO_{2peak} was estimated using a validated equation for treated BC patients: VO_{2peak} (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) = [speed (m/min) × (0.17 + fractional grade × 0.32) + 3.5] (Michalski et al., 2022).

Functional capacity

Functional capacity was assessed by the maximum voluntary handgrip strength (MVHS) and by the 30-s chair sit to stand test (30-s CST). Both protocols were previously described (Antunes et al., 2023).

Study endpoints

CRF responsiveness (i.e., Non-responders vs. Responders) was defined as the dependent variable and the main endpoint of this study. CRF responsiveness was determined based on changes in VO_{2peak} from baseline to post-SETP (i.e., ΔVO_{2peak}). Responders were defined as those participants who exhibited a gain in $VO_{2peak} \geq 1$ mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. This criterion has been applied in other studies, being associated with a 16% predicted reduction in cancer-related mortality (Imboden et al., 2019; Lin et al., 2021; McGregor et al., 2023).

Potential predictors of CRF responsiveness (i.e., independent variables) included demographic and clinical factors, baseline physical fitness (CRF and functional capacity), attendence to exercise training (i.e., frequency) and adherence to aerobic training and resistance training prescription.

Frequency was calculated by dividing the number of attended exercise sessions by the number of planned exercise sessions (Kirkham et al., 2018).

Regarding adherence to aerobic training prescription, duration, intensity and metabolic equivalent task (MET) hours (MET-hour) per session were considered. Duration (i.e., total aerobic training duration performed) was calculated by summing the total minutes of aerobic training performed, excluding warm-up and cool-down periods. Intensity (i.e., total duration of aerobic training performed at target intensity) was calculated by summing the total minutes of aerobic training performed at target intensity. MET-hour was calculated by summing the total MET-hour of aerobic training performed. MET-hour of each exercise session was estimated using the following equation: VO_{2peak}= (0.1 × Speed in m.min-1) + (1.8 × Speed in m.min-1 × Grade in decimal) + 3.5. MET-hour was calculated by summing the total MET-hour of aerobic training performed (American College of Sports Medicine, 2021). As an example, an exercise session involving walking for 30 minutes at 5 km/h (83.33 m/min) with an 8% grade slope is estimated to have an energy expenditure of 3.40 MET-hour.

Adherence to resistance training prescription was calculated by dividing the number of sessions that each patient performed the prescribed volume (sets, repetitions) and intensity (training load) by the number of prescribed exercise training sessions (Kirkham et al., 2018).

Statistical analysis

Continuous and categorical variables were expressed as mean (± standard deviation) and absolute and relative frequencies (%), respectively. To compare baseline characteristics and post-SETP changes (Δ) between CRF Responders and Non-responders, we used independent sample t-tests when the normality assumption was verified. If normality could not be assumed, the Mann–Whitney test was applied. The normality assumption was assessed by the Shapiro-wilk test. The Chi-squared test and Fisher's exact test were used to examine relationships between categorical variables. A binary logistic regression analysis was conducted to identify predictors of CRF responsiveness, employing the Forward Stepwise Likelihood Ratio method. Variables that demonstrated significant differences between groups were selected for this analysis. The results were reported using the odds ratio (OR) estimates and their 95% confidence intervals (CI). To evaluate the quality of the adjustment, the Nagelkerke's R squared was used. Its interpretation as an effect size measure was made based on the following criteria: 0.02–0.13 small, 0.13–0.26 medium, and > 0.26 large effect size (Cohen, 1988). The level of significance was set as 5%. All analyses were conducted using SPSS Statistics 26.0 (IBM Corporation., Armonk, NY, USA).

Results

Study population

Of the 47 patients randomly assigned to the Exercise group, CRF was not assessed in 2 patients at baseline. Additionally, CRF could not be assessed in 11 patients at the end of A-Ct (including one of the patients who was not assessed at baseline). However, 6 patients who were schedule to receive doxorubicin plus cyclophosphamide followed by taxane-based chemotherapy had their CRF assessed at the end of doxorubicin plus cyclophosphamide (i.e., after 8 weeks of exercise training), so this data was considered in the analysis as VO_{2peak} post-SETP. Therefore, a total of 41 participants (87% of the initial cohort) were included in the analysis (Figure 1).

Of those included in this analysis, 26 patients (63%) exhibited an improvement in VO_{2peak} ≥1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (Responders), while 15 (37%) were Non-responders. Baseline characteristics are described in Table 1. No differences regarding age, HER2 status, systemic treatment protocol or chemotherapy intent were found between groups. Responders had lower baseline body mass index (BMI) (p=0.045) and lower percentage of patients with obesity (p=0.049). Moreover, Responders had a higher baseline left ventricular ejection fraction (LVEF) (p=0.021), whereas no differences were present in baseline VO_{2peak}, functional capacity or on health-related quality of life (EORTC QLQ-C30 domains).

Table 1. Baseline characteristics according to cardiorespiratory responsiveness

	VO_{2peak} responsiveness		*P*
	Non-responders (n=15)	**Responders (n=26)**	
Age, years	47.73±8.70	49.53±8.86	0.531[a]
Body mass index, kg/m²	28.25±5.02	25.55±3.35	0.045[a]
Obesity, n (%)	6 (40%)	2 (11%)	0.019[b]
Hypertesion, n (%)	5 (33%)	4 (15%)	0.248[b]
Dislipidemia, n (%)	3 (20%)	3 (11%)	0.651[b]
Diabetes, n (%)	1 (7%)	0 (0%)	0.366[b]
HER2 status, n (%)	3 (20%)	7 (30%)	0.720[b]
Chemotherapy intent, n (%)			
Neoadjuvant	11 (73%)	15 (56%)	0.330[c]
Systemic treatment protocol, n (%)			
AC-T	10 (67%)	17 (63%)	1[c]
AC-TH	2 (13%)	7 (30%)	0.445[b]
CP-AC	3 (20%)	2 (7%)	0.336[b]
GLS, %	-21.30±1.90	-21.07±1.77	0.723[a]
LVEF, %	58.93±3.67	60.92±2.28	0.021[d]
VO_{2peak}, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$	23.14±3.70	23.59±2.94	0.673[a]
MVHS Tumor/surgery upper limb side, kg	26.28±6.72	25.34±4.39	0.591[a]
MVHS Contralateral upper limb side, kg	27.14±5.15	25.34±4.11	0.225[a]
30-s CST, repetitions	15.20±3.54	16.03±4.11	0.614[d]
EORTC QLQ-C30			
QLQ-C30 summary score	84.12±11.17	85.94±8.77	0.094[d]
Global health status/QoL	55.0±16.30	63.46±16.51	0.636[d]
Physical Functioning	82.66±19.64	88.97±9.41	0.647[d]
Fatigue	25.18±23.18	25.21±15.88	0.639[d]

Legend:
Data are expressed as mean±SD or numbers (percent).
AC-T: doxorubicin plus cyclophosphamide followed by taxane-based chemotherapy.
AC-TH: doxorubicin plus cyclophosphamide followed by taxane-based chemotherapy plus trastuzumab whit or without pertuzumab.
CP-AC: carboplatin and paclitaxel followed by doxorubicin plus cyclophosphamide.
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-of-Life-Questionnaire-Core-30.
LVEF: left ventricular ejection fraction.
GLS: global longitudinal strain.
MVHS: maximum voluntary handgrip strength.
30-s CST: 30-seconds chair sit-to-stand test.
[a] t-test for independent samples.
[b] Fisher's exact test.
[c] Chi-squared test.
[d] Mann–Whitney test.

Differences between Responders and Non-Responders

Cardiorrespiratory fitness

There was a large variability in ΔVO_{2peak} (from -4.27 to 8.95 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$). Individual changes in CRF are displayed in Figure 2. Responders had higher VO_{2peak} post-SETP than Non-responders (Responders: 27.68±2.00 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ vs. Non-responders: 21.92±4.52 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; $p<0.001$). Significant differences in ΔVO_{2peak} were also verified (Responders 4.08±2.11 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ vs. Non-responders: -1.22±1.42 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; $p<0.001$).

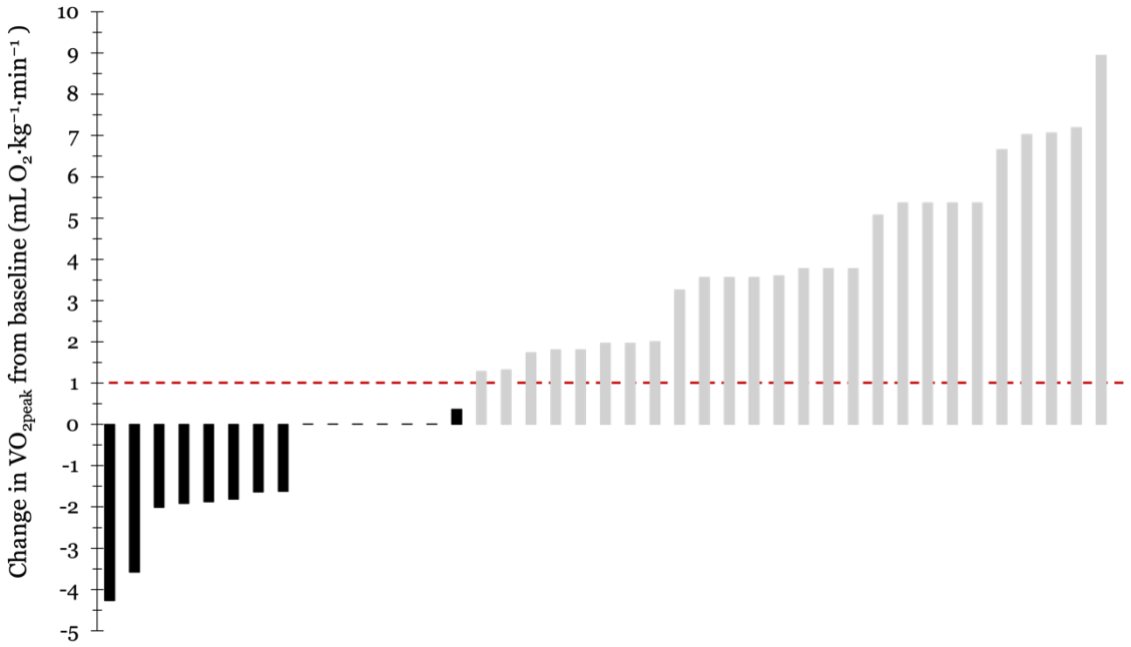

Figure 2. Individual cardiorespiratory fitness responsiveness.
Black bars depict Non-responders and grey bars depict Responders. Red line (1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) indicates the threshold for defining cardiorespiratory fitness responsiveness.

Adherence to exercise training prescription

Details on adherence to exercise training prescription are displayed in Table 2. We found that Responders had a higher adherence to training frequency ($p=0.002$), performed higher aerobic training duration ($p=0.002$) and accumulated more minutes of aerobic training at target intensity ($p=0.002$). Responders performed higher aerobic training MET-hour ($p<0.001$), with no differences regarding adherence to resistance training prescription ($p=0.064$).

Table 2. Adherence to exercise training prescription

	Non-responders (n=15)	Responders (n=26)	*P*
Adherence to planned exercise training frequency, %	51.33 ± 25.08	74.25±24.53	0.002[a]
Duration, min[c]	682.20±379.52	1131.84±480.61	0.002[a]
Intensity, min[d]	475.60±317.33	905.15±425.51	0.002[b]
MET-hour[e]	53.60±32.06	116.62±61.46	<0.001[b]
Adherence to resistance training, %	64.49±20.07	71.57±18.68	0.064[b]

Legend:
Data are expressed as mean±SD.
[a] Mann–Whitney test.
[b] *t*-test for independent samples.
[c] Total aerobic training duration performed.
[d] Total aerobic training duration performed at target intensity.
[e] Total aerobic training MET-hour performed.

Predictors of cardiorespiratory fitness responsiveness

We found that adherence to planned exercise training frequency (r=0.371; *p*=0.017), total aerobic training duration (r=0.311; *p*=0.048), intensity (r=0.309; *p*=0.049) and MET-hour (r=0.326; *p*=0.037) were significantly associated with ΔVO_{2peak}. No correlation was found between adherence to resistance training prescription and ΔVO_{2peak} (r=0.271; *p*=0.086). These variables were selected as potential predictors of CRF responsiveness and were included in the multiple logistic regression analysis, adjusted for baseline BMI, and baseline LVEF.

Multiple logistic regression analysis found baseline BMI and total aerobic training MET-hour as independent predictors of CRF responsiveness (Table 3). Specifically, higher baseline BMI (OR: 0.796; 95% CI: 0.634 to 0.999; *p*=0.049) was associated with lower odds of achieving a gain in VO2peak ≥1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. In contrast, performing more MET-hour was associated with higher odds of being Responder (OR: 1.038; 95% CI: 1.012 to 1.064; *p*=0.004).

Table 3. Results of logistic regression analyses for cardiorespiratory fitness responsiveness

Independent Variables	B	P_{Wald}	OR (95% CI)
Constant	3.615	0.201	
MET-hour[a]	0.037	0.004	1.038 (1.012; 1.064)
Baseline BMI, kg/m^2	-0.228	0.049	0.638 (0.634; 0.999)

Legend:
B: partial regression coeficiente.
BMI: body mass index.
OD: odd ratio.
R^2 Nagelkerke= 0.545; Hosmer and Lemeshow p= 0.589; % Global Correct= 75%.
[a]Total aerobic training MET-hour performed.

Discussion

The purpose of this study was to assess predictors of CRF responsiveness in a cohort of BC patients undergoing a SETP concurrently to A-Ct. Our analysis showed that 63% of patients (n=26) were CRF Responders (i.e., exhibited a gain in VO_{2peak} ≥ mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ post-SETP) and found baseline BMI and total aerobic training MET-hour as independent predictors of CRF responsiveness.

Understanding individual CRF response to exercise training is a key question for personalized exercise medicine (Ross et al., 2019). This subject has been particularly addressed in the setting of cardiovascular rehabilitation, with studies revealing that up to 33% of patients may not experience increases in VO_{2peak} (Gevaert et al., 2020). In the context of exercise oncology, however, this issue was not fully ascertained so far (Foulkes et al., 2024; Scott et al., 2020, 2021). In a 16-week aerobic training RCT in BC patients post-adjuvant therapy, Scott and colleagues. (2020) found that 36% and 40% were responders (defined as ΔVO_{2peak} ≥ 1.32 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) to a linear and non-linear prescription, respectively. In a four-arm trial involving post-therapy lung cancer patients, Scott et al. (2021) found that 13%, 50% and 50% of patients were responders (defined as ΔVO_{2peak} ≥ 1.12 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) following a resistance training, aerobic training and combined training program, respectively. More recently, a third study, comprising a sub-analysis of the BREXIT trial, which involved a 12-month exercise training program, combining aerobic and resistance training, in BC undergoing A-Ct, showed that 46% of subjects achieved a meaningful improvement in CRF (defined as ΔVO_{2peak} ≥ Δ1.65 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) (Foulkes et al., 2023b). Differences in terms of training prescriptions, participant adherence, and the assessment of CRF responsiveness may explain, at least in part, some of the discrepancies observed in the percentage of CRF responders between studies. These findings on CRF responsiveness, coupled with the growing data base supporting the clinical relevance of CRF, underscore the need to address factors which may allow optimization of exercise interventions to improve their overall impact (Foulkes et al., 2023a; Gevaert et al., 2020; Ross et al., 2016; Scott et al., 2020, 2021).

Several factors may influence VO_{2peak}, including age, sex, BMI, and physical fitness among those affecting the CRF response, which seem to be among those affecting the CRF response (Gevaert et al., 2020). In this study, we found that patients with lower baseline BMI had a higher likelihood of being Responders to exercise training, which is consistent with previous data. For instance, Scott et al. (2020) have previously reporting that post-treatment BC patients with lower baseline BMI had greater improvements in VO_{2peak} following a non-linear aerobic training program.

Regarding exercise training characteristics, and as expected, we verified that CRF Responders had higher adherence to exercise training frequency, performed longer aerobic training duration (overall and at target intensity) and accumulated more total aerobic training MET-hour (Table 2). Recent findings from the BREXIT trial revealed that BC patients who achieved a meaningful increase in VO_{2peak} had higher exercise training adherence (78% vs. 68%; p=0.005) (Foulkes et al., 2023a). Little et al. (2022) previously highlighted the importance of training frequency adherence, showing that the attendance to each cardiac rehabilitation session increased the likelihood of being a VO_{2peak} responder by 4%.

Nonetheless, adherence to training frequency may not be the accurate predictor of response, as it may not fully reflect the exercise dose performed, especially in oncology settings where adherence to the prescribed exercise dose often exhibits considerable variability (Kirkham et al., 2018). Moreover, studies in non-cancer patients have also demonstrated substantial variation in CRF response despite training adherence, underscoring the importance of analyzing the impact of other training componentes (Gevaert et al., 2020; Ross et al., 2015). In this study, we found total aerobic training MET-hour as a stronger and independent predictor of CRF responsiveness. This is, to the best of our knowledge, a novel insight in exercise oncology and grees with the results of systematic reviews that found the total energy expenditure as the strongest predictor of CRF responsiveness among heart failure patients (Ismail et al., 2014; Vromen et al., 2016).

In BC patients undergoing chemotherapy, Courneya et al. (2013) found that a higher aerobic exercise dose (average of 120±39 min weekly) was safe and blunted a decline in VO_{2peak} of 1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ when compared to a standard exercise dose (average of 73±17 min weekly). Research conducted in sedentary postmenopausal women and in obese adults has also demonstrated that increasing exercise dose, either by extending volume or increasing intensity, could improve the likelihood of being a CRF responder (Lin et al., 2021; Ross et al., 2015; Sisson et al., 2009). Importantly, cancer patients often experience challenges in adhering to prescribed aerobic training regimens, especially regarding exercise intensity (Antunes et al., 2023; Courneya et al., 2007; Kirkham et al., 2018). When patients face inability to maintain prescribed exercise intensity, a typical approach can involve reducing the workload—by adjusting speed, grade, or watts—to help them to sustain exercise effort and adhere to the prescribed training duration. Our results suggest that adjusting aerobic exercise dose, via MET-hour, may be a suitable prescription approach to mitigate VO_{2peak} decline while maintaining planned energy expenditure levels (an illustrative example is provided bellow). The effectiveness of this approach needs to be confirmed in future studies, which, if validated, could lead to the determination of minimum, maximum, and

optimal therapeutic doses required to enhance CRF responsiveness. This concept could help streamline patient-centered strategies, thus aiding in the refinement of individualized exercise training prescriptions.

Illustrative example

A patient has been prescribed 30 minutes of aerobic training on a treadmill at a speed of 5 km/h and an 8% grade. Based on duration and workload, this session is estimated to have an energy expenditure of **3.40 MET-hour**.

Scenario A: the patient adheres to the planned exercise training prescription and no changes are made.

- The energy expenditure was **3.40 MET-hour** at the end of the aerobic training.

Scenario B: Symptomatic patient at pre-exercise training screening, which justifies pre-aerobic training dose modification (duration and workload).

- Possible aproach: The exercise supervisor decided to reduce the speed by 10% (to 4.5 km/h) and the grade by 2% (to 6% grade), while maintaining the training duration (30 min). In this case the energy expenditure will be **2.73 MET-hour** at the end of the aerobic training, approximately 20% below the planned.
- Possible aproach: The exercise supervisor decided to reduce the speed by 10% (to 4.5 km/h) and the grade by 2% (to 6% grade) and, to maintain the initial energy expenditure, extended the aerobic training duration by 8 minutes (total exercise duration: 38 min). The energy expenditure was **3.40 MET-hour** at the end of the aerobic training.

Scenario C: Asymptomatic patient at pre-exercise training screening, who starts the exercise sessions with the planned prescription. After 10 minutes, shows inability to mantain the prescribed aerobic training dose (duration and workload).

- Possible aproach: The exercise supervisor decided to reduce the speed by 10% (to 4.5 km/h) and the grade by 2% (to 6% grade), while maintaining the training duration (30 min). In this case, the energy expenditure will be **2.95 MET-hour** (1.13 Met-hours in the firt 10 minutes and 1.82 Met-hours in the remaining 20 minutes), approximately 13% below the planned.
- Possible aproach: The exercise supervisor decided to reduce the speed by 10% (to 4.5 km/h) and the grade by 2% (to 6% grade) and, to maintain the initial energy expenditure, extended the aerobic training duration by 5 minutes (total exercise duration: 35 min). The energy expenditure was **3.40 MET-hour** at the end of the aerobic training.

Moreover, other studies, on the other hand, indicated that changes in VO_{2peak} among BC treated with A-Ct were mainly driven by reductions in peak cardiac function (cardiac output and stroke volume), with no significant impact from resting LVEF or global longitudinal strain (Foulkes et al., 2023b, 2023b; Kirkham et al., 2021). In this study, we found that the CRF response was not influenced by resting cardiac function. Recently, an exploratory analysis of the BREXIT trial (n=48) was conducted to assess physiological factors associated with VO_{2peak} responsiveness to aerobic training (Foulkes et al., 2024). The authors found no differences in peak cardiac function change but, interestingly, verified that VO_{2peak} responders improve skeletal muscle diffusive oxygen conductance, a change not seen in non-responders (Foulkes et al., 2024). As mentioned above, these data reinforce the evidence previously observed by Kirkham et al. (2021), suggesting that skeletal muscle-driven peripheral metabolic factors may play an important role in CRF of BC patients. Indeed, despite no relation between CRF responsiveness and resistance training adherence was found, which seems to be anticipated, at least in the time range of the present interventional study, a step further on this matter should be aimed. Considering the importance of muscular strength on physical fitness and life quality of these patients as well as the possible contribution of muscle-peripheral adaptations for the obtained results, we believe that the mitigation effect provided by resistance training routines in the decline of patients' strength should not be discouraged.

Strengths and limitations

The primary strengths of this study lie on its novelty in great extent due to the control of training variables, a factor often referred as a limitation in other similar studies. However, several limitations must be acknowledged. Firstly, the retrospective, single-center design of this study should be considered. Furthermore, the small sample size limited statistical power and precluded analysis of data from those with consistent adherence to training frequency. Additionally, selection bias may have occurred as only patients with both baseline and post-SETP CRF assessments were included. Secondly, although a $\Delta VO_{2peak} \geq 1$ mL $O2 \cdot kg^{-1} \cdot min^{-1}$ was used to define Responders (given data in the literature supporting its importance), alternative thresholds have also been reported. Finally, given the nature of this analysis (and as discussed above), results should be considered as hypothesis-generating. Despite these limitations, we believe that this study provides relevant insights into CRF responsiveness to exercise training performed concurrently during A-Ct in BC patients, a growing research field limited so far.

Conclusion

CRF responsiveness to exercise training varies significantly among women with BC undergoing A-Ct. Baseline BMI and total aerobic training MET-hour may be associated with CRF responsiveness, with this last one being the strongest predictor among exercise training parameters. Although more research is needed to fully understand the relative impact of exercise

training components, this study highlights energy expenditure as a potential key prescription factor in attenuating CRF decline in this challenging patient population.

Study 6

Exercise training benefits health-related quality of life and functional capacity during breast cancer chemotherapy: a RCT [4]

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Abstract

Objective To examine the effectiveness of a SETP on health-related quality of life (HRQoL) and functional capacity in women with BC undergoing chemotherapy.

Methods Ninety-three women with early-stage BC were randomly allocated to a SETP plus usual care (Exercise, n=47) or usual care alone (UC, n=46). The SETP included 3 sessions per week, combining aerobic and resistance training, conducted concurrently over the chemotherapy. The EORTC Cancer Quality-of-Life-Questionnaire-Core-30 (QLQ-C30) and the BC-specific module (QLQ-BR23) were used to assess HRQoL. Functional capacity was analyzed by maximum voluntary handgrip strength (MVHS) and by the 30-second chair sit-to-stand test (30-s CST). These endpoints were assessed at baseline (t_0); middle (t_1; after 8 or 12-weeks of t_0); and at the end of chemotherapy (t_2; after 20-weeks of t_0). Mean changes from baseline were assessed by an intention-to-treat approach.

Results LMMs analyses showed that Exercise group experienced less deterioration in several domains of QLQ-C30 at t_2, including in global health status/ QoL (Δ=9.39 units; p=0.034), QLQ-C30 summary score (Δ=8.08 units; p<0.001), physical (Δ=15.14 units; p<0.001), role (Δ=21.81 units; p<0.001), cognitive (Δ=9.16 units; p=0.032) and social functioning (Δ=11.67 units; p=0.038) domains, compared to the UC group. Similarly, Exercise group exhibited significant lower levels of fatigue (Δ=-20.19 units; p<0.001) and appetite loss (Δ=-13.69 units; p=0.034), compared to UC group. Significant between-group differences were observed on MVHS of the tumor/surgery upper limb side (Δ=2.64kg; p 0.001) and contralateral limb (Δ=2.22kg; p<0.001), and on the 30-s CST score (Δ=3.56 repetitions; p<0.001), favoring the Exercise group. No differences were observed on QLQ-BR23 domains.

Conclusion Exercise training was an effective complementary therapy to prevent the deterioration of HRQoL and functional capacity during chemotherapy in women with early-stage BC.

Keywords

Exercise training; exercise prescription; cancer; cardiorespiratory fitness

Introduction

Anthracycline and taxane-based chemotherapy are frequently recommended in the curative treatment plan for BC (Cardoso et al., 2019). While the clinical benefits of these treatments have been demonstrated (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2012), these may nonetheless have adverse effects on patient-reported outcomes, including in health-related quality of life (HRQoL) (Sheng et al., 2019).

HRQoL is a multidimensional measure that encompasses multiple aspects which capture a patient's perception of the illness effects or treatment on their health and well-being (including physical, social, emotional, cognitive, and role-related aspects) (Karimi & Brazier, 2016). HRQoL progressively become a crucial endpoint in oncology clinical trials, supplementing classical efficacy endpoints such as overall and progression-free survival (Marandino et al., 2018). This is primarily due to its ability to assist in providing a more comprehensive understanding of the overall burden of cancer and its treatments on patients' daily lives (Marandino et al., 2018).

Chemotherapy-related toxicities may potentially exacerbate the challenges posed by cancer diagnosis, including symptom burden, exercise intolerance, and physical deconditioning (Braithwaite et al., 2010; Smit et al., 2019). Importantly, cancer patients frequently undergo a decrease in PA, reduced fitness, and weakened muscle strength (Neo et al., 2017). Notably, impairment of health-related fitness can negatively affect the patients' ability to perform both basic and instrumental activities of daily living (Neo et al., 2017), as well as their ability to participate in social and vocational roles (Stout et al., 2021), leading to a diminished QoL as compared to the general population (LeMasters et al., 2013). Providing optimized rehabilitation support during active cancer treatment may assist BC patients in reducing the impact of some cancer treatment-related toxicities, ultimately leading to an optimization in HRQoL (Vaz-Luis et al., 2022).

Structured exercise is a core component of rehabilitation strategies and is increasingly recognized as an important part of cancer care continuum (Silver et al., 2013). RCTs encompassing exercise training interventions have demonstrated positive effects across a wide range of cancer types, mitigating side-effects of cancer therapies and improving physical fitness during and after active cancer treatment (Courneya et al., 2007; Hathiramani et al., 2021; Quist et al., 2020; Samuel et al., 2019; Taaffe et al., 2023; van Vulpen et al., 2016; Wall et al., 2017). Healthcare providers generally acknowledge the potential of exercise training as a adjunct therapy in cancer care continuum (Kennedy et al., 2022), and international societies guidelines have endorsed the positive effects of exercise training on HRQoL (Lyon et al., 2022; Rock et al., 2012). Nevertheless, the integration of exercise training into supportive cancer care is still limited (Kennedy et al., 2022). Indeed, patients during active treatment often receive only general recommendations for increase PA (i.e., without specific advice on the frequency, duration, intensity, and type of

exercise) without access to a structured exercise program included as part of their rehabilitation care (Kennedy et al., 2022).

Given this background, we conducted a RCT (the Mama Move Gaia on Treatment trial) consisting of a SETP for women with early-stage BC undergoing neoadjuvant or adjuvant chemotherapy. In this study, we focused on the effects of the SETP on HRQoL and functional capacity, which were pre-defined as secondary endpoints of this trial (Antunes et al., 2019). We hypothesized that the SETP concurrently over the chemotherapy may reduce the deterioration of HRQoL and functional capacity in this patient population.

Methods

Study design and ethical approval

This study was a parallel 2-arm group RCT, having been registered in the International Standard Randomised Controlled Trial Number registry (ISRCTN32617901) and approved by the local Ethics Committee (reference: 145/2018–1). Full details regarding the study's rationale and design have been provided elsewhere (Antunes et al., 2019). Briefly, adult (i.e., ≥18 years-old) women diagnosed with early-stage BC scheduled to receive neoadjuvant or adjuvant anthracycline-containing chemotherapy and followed up at the oncology department of CHVNG/E were considered potentially eligible. Recruitment was conducted from January 2019 to March 2020 and from September 2020 to January 2022 (the interruption from March 2020 to September 2020 was due to COVID-19 pandemic restrictions). All patients provided written informed consent.

Patients were randomly assigned, in a 1:1 ratio, to a SETP plus usual care (Exercise group) or usual care alone (UC group). Randomization was stratified according to age (≤ 50 years vs. > 50 years) and the clinical decision to receive anti-HER2 therapy (Yes vs. No), using an electronic software (www.sealedenvelope.com).

Study endpoints

The endpoints of this study were HRQoL and functional capacity. These endpoints were assessed at three time points (Figure 1):

- baseline (t_0; before the start of the first cycle of chemotherapy).
- middle of chemotherapy (t_1; after 8 or 12-weeks of t_0).
- the end of chemotherapy (t_2; after 20-weeks of t_0).

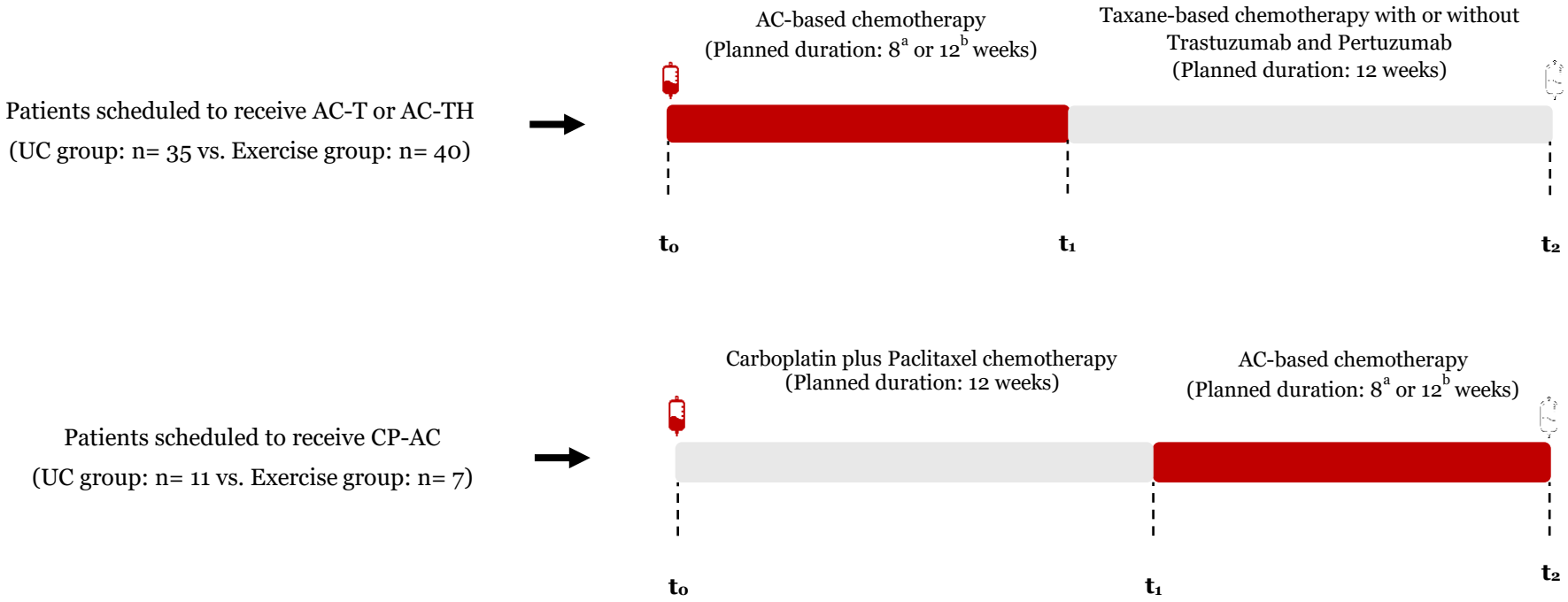

Figure 1. Description of the time points assessments.

AC: Doxorubicin plus Cyclophosphamide; AC-T: Doxorubicin plus Cyclophosphamide followed by taxane-based chemotherapy; AC-TH: Doxorubicin plus Cyclophosphamide followed by taxane-based chemotherapy plus trastuzumab with or without pertuzumab; CP-AC: Carboplatin and Paclitaxel followed by Doxorubicin plus Cyclophosphamide; t_0: baseline assessment (i.e., before the start of the first cycle of chemotherapy); t_1: assessment after 8 or 12-weeks of t0; t_2: assessment after 20-weeks of t0 (i.e., end of chemotherapy); : denotes the begin of chemotherapy; : denotes the end of chemotherapy; [a] if AC was delivered every 2-weeks; [b] if AC was delivered every 3-weeks.

Health-related quality of life

The EORTC QLQ-C30 (version 3.0) was used to assess HRQoL (Aaronson et al., 1993). This questionnaire contains 30 items arranged into 15 domains (all ranging from 0 to 100 units): a two-item global health status /QoL domain; five multi-item functioning domains (physical; role; emotional; cognitive; and social); three multi-item symptom domains (fatigue; nausea and vomiting; pain); and six single-item symptom domains (dyspnea; sleep disturbances; appetite loss; constipation; diarrhea; and financial difficulties).

The QLQ-C30 was scored according to the Scoring Manual (Fayers et al., 2001). Additionally, the QLQ-C30 summary score was calculated as the mean of the combined 13 QLQ-C30 scale and item scores (excluding global health status /QoL and financial difficulties domains) (Giesinger et al., 2020). The symptom domains were reverse scored (e.g., 100 minus fatigue domain score) prior to calculation of the QLQ-C30 summary score to obtain a uniform direction of all scales. This score was only calculated when all the required 13 scale and item scores were available (Giesinger et al., 2020).

Higher scores on the global health status /QoL, QLQ-C30 summary score and functioning domains represented better QoL/functioning, whereas higher scores on symptom domains correspond to a greater symptom burden.

In addition, the 23-item BC-specific module (EORTC QLQ-BR23) comprising four functional scales (body image; sexual functioning; sexual enjoyment; and future perspective) and four symptom scales (systemic therapy side effects; breast symptoms; arm symptoms; and hair loss) was applied.

Functional capacity

Functional capacity was assessed by the MVHS and by the 30-s CST.

MVHS was measured using a digital hand dynamometer (Saehan model SH1001, DHD-1, Saehan Corp. South Korea) with the participants in the sitting position, with the elbow flexed at 90° and a neutral wrist. Each participant performed six trials, three on each hand, with an alternating bilateral sequence. The mean score of the respective tests of each limb (kg) was determined and used for analysis.

The 30-s CST was used to assess muscle strength and endurance of the lower limbs (Jones et al., 1999). Each participant was instructed to stand up and sit as many times as possible on a 40-cm-high chair for 30 seconds, keeping arms crossed close to the chest. The score of this test was determined by the number of repetitions.

Exercise training program

The SETP was conducted concomitant with anthracycline-containing chemotherapy and comprised 3 sessions per week, combining aerobic and resistance training. The exercise training sessions were guided in small groups (up to 5 patients), supervised by an exercise physiologist (certified in exercise for cancer patients [http://canrehab.co.uk/]) and a physiotherapist. Patients were proposed to start the training sessions 1 or 2-days after the start of chemotherapy.

Each training session included a warm-up (5-10 minutes) and ended with a cool-down phase with stretching exercises (5 minutes). Patients scheduled to receive AC every 2-weeks were planned to perform 60 exercise sessions, whereas patients scheduled to receive AC every 3-weeks were planned to perform 72 exercise sessions.

Continuous aerobic training was performed on a treadmill, stationary bike, or stepping. During the first 2-weeks of training, patients performed 20 minutes of aerobic training at an intensity <50% of heart rate (HR) reserve. After this period, 3 minutes were increased every 2-weeks until a total duration of 30 minutes was reached, and patients were encouraged to exercise at 65-80% of HR reserve. Exercise intensity was continuously monitored during sessions with HR monitors (Firstbeat Sports, Firstbeat Sport®, Finland). The average HR and the amount of time spent at the target HR were recorded.

Resistance training involved upper body (shoulder press, chest press, lateral pulldown, biceps curls, and triceps extension) and lower body weight-training exercises (squat, calf raise, leg press, leg extension, and leg curl). Patients were encouraged to perform the exercises at the maximum possible joint range of motion, using resistance machines and free weights. During the first 2-weeks of training, patients performed 2 sets and 10 repetitions of each exercise without additional resistance or with the lowest load available. After this period, if no adverse events or symptoms were reported for a specific exercise, resistance was added so that each patient could be able to perform 3 sets with 12 maximal repetitions (RM). When patients were able to complete 3 sets and more than 12-RM at the set weight in three consecutive sessions, an increased load of 5-10% was considered.

Statistical analysis

The sample size of this RCT was determined based on the primary endpoint which was the change in LVEF from baseline to the end of anthracyclines-based chemotherapy, as previous described (Antunes et al., 2019). The longitudinal changes from baseline in HRQoL and functional capacity were pre-specified as secondary endpoints (Antunes et al., 2019).

LMMs, with fixed effects for group and time and patient as a random effect in the model, were used to estimate mean difference within-group and between-group changes in the study endpoints, even when the assumption of normality is not verified, due to their robustness against

violation of model assumptions (Knief & Forstmeier, 2021; Schielzeth et al., 2020). The covariance type was set to scaled identity. LMMs were based on intention-to-treat analyses. The mean differences between-group in the QLQ-C30 scores were classified according to published guidelines (Cocks et al., 2011). We also carried out a sensitive analysis to explore the effect of exercise training in neoadjuvant and adjuvant setting.

To investigate changes at the patient level in HRQoL, two exploratory secondary analyses were further conducted. These included the status change analysis (Lenz et al., 2019) and the thresholds for clinical importance (TCI) analysis (Giesinger et al., 2020). The status change analysis evaluated the proportion of patients who experienced, from baseline (t_0) to the end of chemotherapy (t_2), a clinically meaningful worsening (CMW; corresponding to a decrease of 10 or more units); clinically meaningful improvement (corresponding to an increase of 10 or more units); or stabilization (neither showing improvement nor worsening) in the QLQ-C30 domains (Snyder et al., 2015). A simple logistic regression was used to compare the proportion of patients with CMW between the two study groups. The results were reported by the Wald test p-value, odds ratio (OR) estimates and their 95% CI.

In contrast with previous analyses that assess changes over time, TCIs were established to identify clinical significance of single values of the QLQ-C30 domains (Giesinger et al., 2020). The TCIs determined by Giesinger et al. (2020) were used. Scores below the TCI in the functioning domains indicated clinically important functional impairment, whereas scores above the TCI in the symptom domains indicated clinically important symptomatology (Snyder et al., 2015). In our TCI analysis we assessed the proportion of patients that reach TCI for functioning domains (i.e., patients that reported values below the TCI) and symptom domains (i.e., patients that reported values above the TCI). For this analysis, within-group differences over time were assessed by Cochran's Q test, whereas between-group relationship was determined by Chi-squared test.

Results

Patients Characteristics

Patients flow through the trial, demographics and baseline clinical characteristics, and details of chemotherapy has been reported elsewhere (Antunes et al., 2023). Briefly, 93 of the 119 eligible patients were randomly assigned to the UC group (n=46) or the Exercise group (n=47) (Figure 2). The patients' demographics and baseline clinical characteristics were generally balanced between the two groups (Table 1), except for a higher incidence of axillary dissection in the Exercise group (UC group: n=2 vs. Exercise group: n=12; p=0.008). Regarding chemotherapy, four cycles of AC, followed by taxane-based chemotherapy (n=75; 80.6%) were prescribed to the majority of patients, except for 18 patients (19.4%; UC group: n=11 vs. Exercise group: n=7) with

triplenegative tumors, who received carboplatin and paclitaxel first, followed by AC, according to local practice. Anti-HER2 therapy was added in HER2 positive tumors (trastuzumab plus pertuzumab in 23 patients [24.7%] and trastuzumab alone in 2 patients [2.1%]).

Regarding the SETP, the mean adherence to training frequency was 63.2±26.9% (73.8±17.8% considering the 32 patients that remained enrolled during chemotherapy) and no serious adverse events were reported during the training sessions (Antunes et al., 2023). Details regarding the safety and tolerability of the SETP are provided elsewhere (Antunes et al., 2023).

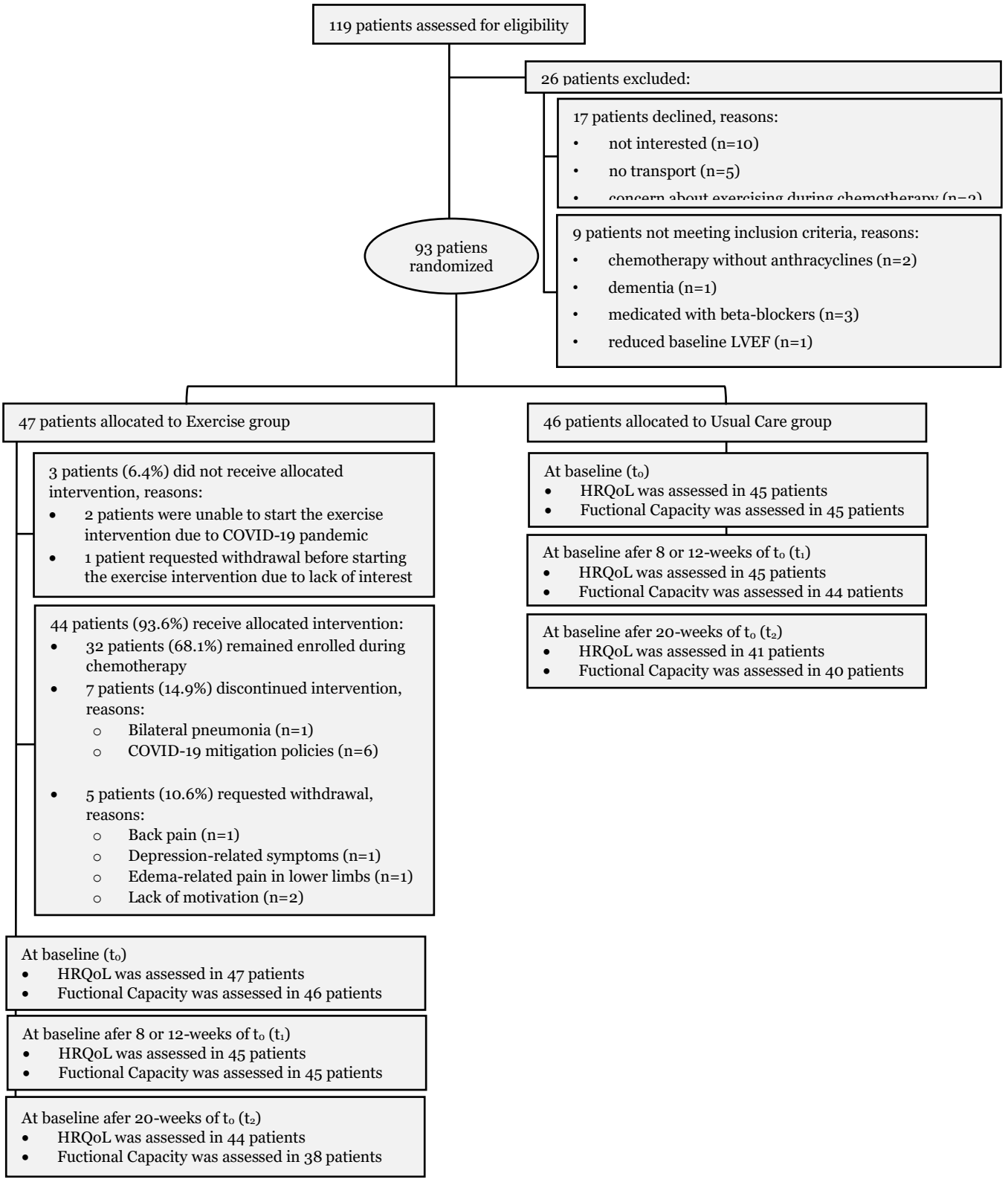

Figure 2. Study enrollment, randomization, follow-up and analysis (CONSORT flow).

Table 1. Baseline characteristics of the study patients

Characteristics	Total (n=93)	Usual Care (n=46)	Exercise (n=47)	*P*
Age (years)	50.33±9.46	51.02±9.54	49.66±9.43	0.491[c]
Body Mass Index (kg/m²)	27.82±5.73	28.69±6.82	26.94±4.32	0.138[c]
Eastern Cooperative Oncology Group (ECOG) Performance Status[a]				
ECOG score of 0	74 (79.6%)	36 (78.3%)	38 (80.9%)	0.802d
ECOG score of 1	19 (20.4%)	10 (21.7%)	9 (19.1%)	0.802[d]
Meeting Exercise Guidellines for Healthy Adults[b]	7 (7.5%)	4 (8.7%)	3 (6.4%)	0.714[e]
Breast Cancer Stage, American Joint Committee on Cancer Eighth Edition				
Stage I	14 (15.1%)	7 (15.2%)	7 (14.9%)	1[d]
Stage II	47 (50.5%)	21 (45.7%)	26 (55.3%)	0.409[d]
Stage III	32 (34.4%)	18 (39.1%)	14 (29.8%)	0.388[d]
Immunohistology				
HER2+	25 (26.9%)	12 (26.1%)	13 (27.7%)	1[d]
ER+	65 (69.9%)	30 (65.2%)	35 (74.5%)	0.372[d]
PR+	62 (66.7%)	29 (63%)	33 (70.2%)	0.514[d]
Ki-67 ≥30%	47 (50.5%)	31 (67.4%)	28 (59.6%)	0.520[d]
Breast Cancer Phenotype				
ER/PR+ and HER2-	48 (51.6%)	21 (45.6%)	27 (57.4%)	0.181[d]
ER/PR+ and HER2+	19 (20.4%)	9 (19.6%)	10 (21.3%)	0.565[d]
ER/PR- and HER2+	6 (6.5%)	3 (6.5%)	3 (6.4%)	0.250[e]
ER/PR- and HER2-	20 (21.5%)	13 (28.3%)	7 (14.9%)	0.353[d]
Breast Surgery				
Lumpectomy	14 (48.3%)	7 (58.3%)	7 (41.2%)	0.462[d]
Mastectomy	15 (51.7%)	5 (41.7%)	10 (58.8%)	0.462[d]
Axillary Surgery				
Sentinel Lymph Node Biopsy	15 (51.7%)	10 (83.3%)	5 (29.4%)	0.008[d]
Axillary Dissection	14 (48.3%)	2 (16.7%)	12 (70.6%)	0.008[d]
Chemotherapy Intent				
Neoadjuvant	64 (68.8%)	34 (73.9%)	30 (63.8%)	0.294[d]
Adjuvant	29 (31.2%)	12 (26.1%)	17 (36.9%)	0.294[d]
Sytemic Treatment Protocols				
AC-T	50 (53.8%)	23 (50%)	27 (57.4%)	0.535[d]
AC-TH	25 (26.9%)	12 (26.1%)	13 (27.7%)	1[d]
CP-AC	18 (19.4%)	11 (23.9%)	7 (14.9%)	0.304[d]
Anti-HER2 Therapy				
Trastuzumab	2 (2.2%)	1 (2.2%)	1 (2.1%)	1[e]
Trastuzumab and Pertuzumab	23 (24.7%)	11 (23.9%)	12 (25.5%)	1[d]

Legend:
Data are expressed as mean±standard deviation or numbers (percent).

Table 1. Continued

Legend:
[a]Eastern Cooperative Oncology Group Performance Status: was used by the medical oncologists, responsible for recruitment, to evaluate each patient's performance status at enrollment. An ECOG score of 0 indicated that the patient was fully active, able to carry on all predisease performance without restriction; an ECOG score of 1, indicated that the patient was restricted in physically strenuous activity but ambulatory and able to perform light work.
[b] Perform at least 150 minutes a week of moderate-intensity aerobic physical activity, or 75 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity.
[c] t-test for independent samples.
[d] Chi squared test.

Change in HRQoL and QLQ-BR23 from baseline

The compliance rate with the QLQ-C30 and QLQ-BR23 questionnaires, defined as the percentage of completed questionnaires in relation to the total number of patients on the study, was 98.9% at t0, 96.8% at t1, and 91.4% at t_2.

Table 2 presents the mean estimated scores by treatment group and time point assessment for each QLQ-C30 domain. Except for the constipation domain (UC group: 4.44±11.45 units vs. Exercise group: 13.47±23.73 units; p=0.023), the QLQ-C30 domain scores were balanced at baseline between the study groups.

The Exercise group demonstrated less deterioration in global health status/ QoL scores over the chemotherapy compared to the UC group, with significant difference in mean changes observed at the end of chemotherapy (Δ=9.39 units; 95% CI: 0.71 to 18.08; p=0.034). Considering the QLQ-C30 functioning domains, the Exercise group showed a smaller decline over treatment. Particularly for physical functioning domain, significant differences in mean changes were observed at t_1 (Δ=8.82 units; 95% CI: 2.81 to 14.83; p=0.004) and t_2 (Δ=15.14 units; 95% CI: 9.00 to 21.29; p<0.001), favoring the Exercise group. Similar results were found at t2 on the role (Δ=21.81units; 95% CI: 10.73 to 32.90; p<0.001); cognitive (Δ=9.16 units; 95% CI: 0.77 to 17.56; p=0.033); and social functioning domains (Δ=11.67 units; 95% CI: 0.68 to 22.66; p=0.038). No significant differences were observed on emotional functioning domain.

Regarding symptom domains, significant between-group differences were observed in fatigue and appetite loss. Specifically, the UC group had significantly higher levels of fatigue at t_1 (Δ=-14.01 units; 95% CI: -23.37 to -4.65; p=0.004) and t_2 (Δ=-20.19units; 95% CI: -29.74 to -10.63; p<0.001), as well as significantly higher levels of appetite loss at t_2 (Δ=-13.32units; 95% CI: -25.56 to -1.08; p=0.033), compared to the Exercise group. No significant between-group differences were found in the other symptom domains.

At the end of chemotherapy, the Exercise group exhibited less deterioration in QLQ-C30 summary score, with a significant difference of 8.08 units (95% CI: 3.56 to 12.60; $p<0.001$) compared to the UC group.

The sensitivity analysis, which assessed the impact of exercise training on patients who underwent neoadjuvant (Table A1, in Appendixes - Study 6) and adjuvant chemotherapy (Table A2, in Appendixes - Study 6) separately, revealed a comparable response in both sub-cohorts.

Regarding the QLQ-BR23, no significant differences were observed in any domain between groups (Table 3).

Table 2. Changes in EORTC QLQ-C30 domains over the chemotherapy

	Usual Care			Exercise			Time	Interaction	Between-group Difference in mean Change			CRD between groups[a]
	n	Mean±SD	Difference in Mean Change (95%CI)	n	Mean±SD	Difference in Mean Change (95%CI)			n	Mean (95%CI)	*P*	
EORTC QLQ-C30 Summary Score							<0.001	<0.003				
t_0	45	87.64±8.52		47	85.66±9.15							
t_1	45	80.51±11.65	-7.13 (-11.03; -3.24)**	45	82.54±10.08	-3.43 (-7.30; 0.44)			90	3.55 (-0.85; 7.96)	0.111	NI
t_2	41	76.96±13.98	-10.94 (-14.96; -6.92)**	44	82.78±10.65	-2.96 (-6.86; 0.94)			85	8.08 (3.56; 12.60)	<0.001	NI
Global Health Status/ Quality of Life							0.038	0.090				
t_0	45	64.25±16.72		47	61.17±16.69							
t_1	45	58.14±19.42	-6.11 (-13.22; 0.99)	45	60.55±15.73	-0.58 (-7.64; 6.47)			90	5.64 (-2.89; 14.17)	0.193	Small
t_2	41	54.47±18.92	-9.97 (-17.30; -2.65)*	44	60.60±14.74	-0.75 (-7.85; 6.35)			85	9.39 (0.71; 18.08)	0.034	Small
Functional Domains												
Physical Functioning							<0.001	<0.001				
t_0	45	88.88±10.54		47	86.09±14.09							
t_1	45	75.85±18.38	-13.03 (-18.26; -7.80)**	45	82.51±12.33	-4.01 (-9.20; 1.18)			90	8.82 (2.81; 14.83)	0.004	Small
t_2	41	71.86±18.64	-17.17 (-22.57; -11.78)**	44	84.69±14.12	-1.89 (-7.12; 3.34)			85	15.14 (9.00; 21.29)	<0.001	Medium

Table 2. Continued

Role Functioning							<0.001	0.001				
t_0	45	88.14±20.90		47	80.49±22.87							
t_1	45	74.81±20.90	-13.33 (-22.59; -4.06)*	45	78.88±20.22	-2.16 (-11.36; 7.03)			90	10.82 (-0.04; 21.69)	0.051	Small
t_2	41	65.44±27.98	-23.53 (-33.07; -13.99)**	44	77.65±20.31	-2.78 (-12.05; 6.47)			85	21.81 (10.73; 32.90)	<0.001	Medium
Emotional Functioning							0.044	0.331				
t_0	45	70.92±18.93		47	68.61±23.26							
t_1	45	74.25±17.83	3.33 (-4.56; 11.23)	45	76.48±19.24	7.86 (0.01; 15.70)*			90	4.68 (-10.54; 5.92)	0.342	NI
t_2	41	69.51±23.98	-2.01 (-10.15; 6.13)	44	73.67±20.08	4.83 (-3.06; 12.74)			85	7.26 (-6.02; 10.56)	0.148	NI
Cognitive Functioning							0.010	0.050				
t_0	45	88.14±19.33		47	84.04±20.83							
t_1	45	81.85±19.40	-6.29 (-13.09; 0.50)	45	85.92±15.87	1.30 (-5.47; 8.09)			90	7.29 (-0.95; 15.54)	0.082	Small
t_2	41	77.23±21.65	-10.88 (-17.90; -3.86)*	44	82.57±18.66	-1.58 (-8.41; 5.24)			85	9.16 (0.77; 17.56)	0.033	Medium
Social Functioning							<0.001	0.112				
t_0	45	90.37±20.86		47	84.75±17.66							
t_1	45	78.14±25.57	-12.22 (-21.12; -3.32)*	45	77.77±25.12	-7.45 (-16.18; 1.27)			90	4.41 (-6.39; 15.22)	0.421	Trivial
t_2	41	75.60±23.59	-15.77 (-24.83; -6.71)**	44	80.30±21.04	-4.78 (-13.57; 4.01)			85	11.67 (0.68; 22.66)	0.038	Medium
Symptoms Domains												
Fatigue							<0.001	<0.001				
t_0	45	17.77±18.41		47	24.34±18.18							
t_1	45	38.27±21.65	20.49 (12.46; 28.52)**	45	30.36±14.48	6.36 (-1.60; 14.33)			90	-14.01 (-23.37; -4.65)	0.004	Medium
t_2	41	43.63±25.01	26.06 (17.79; 34.34)**	44	30.30±21.87	6.09 (-1.92; 14.12)			85	-20.19 (-29.74; -10.63)	<0.001	Large

Table 2. Continued

Nausea and Vomiting							<0.001	0.093			
t_0	45	1.48±4.79		47	2.48±6.93						
t_1	45	8.88±15.32	7.40 (1.38; 13.42)*	45	10.37±15.19	7.86 (1.90; 13.83)*			90	-0.36 (-6.14; 6.86)	0.913	Trivial
t_2	41	10.16±17.43	8.58 (2.41; 14.76)*	44	4.54±10.39	2.00 (-3.99; 8.00)			85	-6.54 (-13.23; 0.14)	0.055	Small
Pain							0.001	0.717			
t_0	45	13.70±15.19		47	15.95±20.83						
t_1	45	18.51±20.48	4.81 (-3.95; 13.58)	45	16.66±18.80	1.64 (-7.02; 10.32)			90	-2.31 (-12.39; 7.76)	0.651	Trivial
t_2	41	24.79±26.90	11.54 (2.50; 20.58)*	44	23.48±23.92	7.82 (-0.91; 16.56)			85	-3.88 (-14.18; 6.41)	0.457	Trivial
Dyspnoea							0.001	0.838			
t_0	45	5.18±12.21		47	1.41±6.80						
t_1	45	8.14±14.48	2.96 (-2.79; 8.72)	45	2.22±8.40	1.08 (-4.63; 6.79)			90	-1.53 (-7.99; 4.92)	0.639	Trivial
t_2	41	11.38±19.16	6.45 (0.52; 12.137)*	44	7.57±15.85	6.10 (0.35; 11.86)*			85	-0.82 (-7.43; 5.79)	0.806	Trivial
Insomnia							0.595	0.137			
t_0	45	34.81±30.11		47	25.53±22.21						
t_1	45	31.10±28.78	-3.70 (-16.23; 8.82)	45	34.81±34.04	9.35 (-3.06; 21.78)			90	13.20 (-1.57; 27.97)	0.079	Medium
t_2	41	32.51±27.37	-2.61 (-15.50; 10.27)	44	34.84±27.80	9.73 (-2.77; 22.24)			85	13.29 (-1.77; 28.36)	0.083	Medium
Appetite Loss							0.014	0.015			
t_0	45	8.88±17.97		47	5.67±14.44						
t_1	45	14.81±29.77	5.92 (-4.21; 16.07)	45	14.18±22.81	9.04 (-1.02; 19.10)			90	2.95 (-9.03; 14.95)	0.627	Trivial
t_2	41	23.57±35.93	14.34 (3.88; 24.78)*	44	6.81±16.20	0.89 (-9.24; 11.02)			85	-13.32 (-25.56; -1.08)	0.033	Small

Table 2. Continued

Constipation							0.008	0.440				
t_0	45	4.44±11.45		47	13.47±23.73							
t_1	45	12.59±22.79	8.14 (-0.59; 16.89)	45	15.55±26.20	2.05 (-6.62; 10.72)			90	-6.17 (-16.03; 3.68)	0.218	Small
t_2	41	4.06±13.32	-0.38 (-9.38; 8.61)	44	8.33±20.49	-5.53 (-14.27; 3.19)			85	-5.62 (-15.72; 4.47)	0.273	Small
Diarrhea							<0.001	0.607				
t_0	45	0.74±4.96		47	1.41±6.80							
t_1	45	5.92±12.88	5.18 (-0.78; 11.15)	45	3.70±10.59	2.25 (-3.66; 8.16)			90	-2.99 (-9.41; 3.42)	0.358	Trivial
t_2	41	8.94±16.70	8.47 (2.34; 14.60)*	44	6.81±19.79	5.35 (-0.59; 11.31)			85	-3.74 (-10.34; 2.84)	0.263	Small
Financial Difficulties							0.129	0.995				
t_0	45	11.85±25.77		47	16.31±28.55							
t_1	45	17.77±24.20	5.92 (-5.27; 17.12)	45	22.22±28.42	6.48 (-4.62; 17.59)			90	0.95 (-12.42; 14.32)	0.888	Trivial
t_2	41	17.07±21.24	4.91 (-6.61; 16.44)	44	21.21±29.71	5.45 (-5.74; 16.64)			85	1.33 (-12.28; 14.95)	0.847	Trivial

Legend:

Within-group and Between-group Difference in Mean Change was based on linear mixed models, controlling for group, time and interaction (fixed effects), and patient as a random effect and the baseline outcome and chemotherapy intent (neoadjuvant or adjuvant) were entered as covariates.

Correction for multiple comparisons for Within-group and Between-group Difference in Mean Change analysis was performed by the Bonferroni method.

[a] Interpreted as clinically relevant as defined by Cocks et al. (2011).

* Denotes a significant p-value <0.05 from baseline.

** Denotes a significant p-value <0.001 from baseline.

NI: not included in the guidelines defined by Cocks et al. (2011).

Table 3. Changes in EORTC QLQ-BR23 domains over the chemotherapy

	Usual Care			Exercise			Time	Interaction	Between-group Difference in mean Change		
	n	**Mean ± SD**	**Difference in Mean Change (95%CI)**	***n***	**Mean ± SD**	**Difference in Mean Change (95%CI)**			***n***	**Mean (95%CI)**	***p***
Body Image							<0.001	0.936			
t_0	45	89.81±20.01		47	87.58±21.34						
t_1	45	82.22±25.35	-7.59 (-14.50; -0.67)*	45	82.22±22.93	-6.62 (-13.73; 0.15)			90	0.41 (-7.29; 9.14)	0.921
t_2	41	84.95±23.95	-6.05(-13.19; 1.09)	44	82.95±25.91	-6.54 (-13.47; 0.39)			85	-0.85 (-8.08; 8.70)	0.842
Sexual Functioning							<0.001	0.670			
t_0	43	24.41±23.66		47	26.59±22.87						
t_1	43	15.50±18.68	-8.91 (-16.39; -1.43)*	45	19.99±17.87	-7.08 (-14.35; 0.18)			88	1.43 (-8.12; 10.98)	0.767
t_2	39	14.95±17.84	-9.69 (-17.42; -1.95)*	44	15.53±18.84	-11.82 (-19.15; -4.50)**			83	-2.681 (-12.33; 6.97)	0.583
Sexual Enjoyment							0.002	0.241			
t_0	24	52.77±29.35		29	57.47±28.02						
t_1	15	51.11±24.77	-3.69 (-18.21; 10.82)	21	42.85±21.45	-16.26 (-27.17; 1.94)			36	-12.09 (-28.93; 4.74)	0.155
t_2	13	46.15±25.60	-10.19 (-25.51; 5.13)	16	41.66±22.77	-20.10 (-33.89; -6.31)*			29	-10.68 (-28.52; 7.15)	0.235
Future perspective							0.331	0.661			
t_0	45	41.48±34.92		47	38.29±31.83						
t_1	45	45.18±34.19	3.70 (-9.24; 16.64)	45	46.66±32.09	7.5 (-5.34; 20.35)			90	2.88 (-13.05; 18.82)	0.721
t_2	41	40.64±32.07	-1.15 (-14.49; 12.18)	44	44.69±31.28	5.82 (-7.12; 18.77)			85	6.71 (-9.47; 22.9)	0.413
Systemic Therapy Side Effects							<0.001	0.391			
t_0	45	10.15 ± 7.96		47	10.73±10.98						
t_1	45	32.69 ±17.51	22.50 (16.41; 28.66)**	45	33.33±17.16	22.5 (16.41; 28.57)**			90	-0.17 (-7.41; 7.06)	0.961
t_2	41	30.89±19.63	20.45 (14.14; 28.66)**	44	26.40±14.24	16.06 (9.93; 22.19)**			85	-3.66 (-11.48; 3.71)	0.328

Table 3. Continued

Breast Symptoms							<0.001	0.341			
t_0	45	17.77±23.40		47	17.37±18.12						
t_1	45	10.37±15.40	-7.40 (-12.73; -2.08)*	45	5.92±8.99	-10.48 (-15.78; -5.19)*			90	-3.06 (-10.05; 3.91)	0.386
t_2	41	8.94±13.09	-8.21 (-13.71; -2.71)*	44	4.54±7.29	-12.75 (-18.08; -7.41)*			85	-4.61 (-11.65; 2.42)	0.197
Arms Symptoms							0.020	0.203			
t_0	45	15.55±15.60		47	15.36±17.87						
t_1	45	11.60±14.78	-3.95 (-9.88; 1.98)	45	8.88±13.31	-5.85 (-11.75; 0.03)			90	-1.49 (-8.78; 5.79)	0.685
t_2	41	15.71±19.24	0.80 (-5.31; 6.92)	44	9.34±16.41	-5.40 (-11.34; 0.53)			85	-6.24 (-13.64; 1.16)	0.098
Upset by hair loss							0.025	0.319			
t_0	20	8.33±14.80		20	9.99±15.67						
t_1	37	25.22±29.81	17.78 (3.02; 32.38)*	35	19.04±31.60	5.78 (-9.28; 20.84)			33	-13.13 (-32.27; 5.99)	0.173
t_2	19	19.29±23.08	11.57 (-5.64; 28.78)	26	21.79±29.72	8.20 (-8.01; 24.43)			20	-18.09 (-39.03; 3.74)	0.102

Legend:

Data are expressed as mean±standard deviation or mean (95% CI).

Within-group and Between-group Difference in Mean Change was based on linear mixed models, controlling for group, time and interaction (fixed effects), and patient as a random effect and the baseline outcome and chemotherapy intent (neoadjuvant or adjuvant) were entered as covariates. Correction for multiple comparisons for Within-group and Between-group Difference in Mean Change analysis was performed by the Bonferroni method.

* Denotes a significant p-value <0.05 from baseline.

** Denotes a significant p-value <0.001 from baseline.

HRQoL status change analysis

In general, a larger proportion of patients in the UC group experienced a CMW of the QLQ-C30 domains from the baseline to the end chemotherapy (Figures 2, 3, and 4). An exception was observed in the sleep disturbance domain, where a higher proportion of patients in the Exercise group experienced a CMW than those in the UC group (UC group: 22% vs. Exercise group: 43.2%; *p*=0.040) (Table 4). For this domain, a patient in the UC group decreases the chance of experienced CMW when compared to a patient in the Exercise group in 63% (OR=0.37; 95% CI: 0.14 to 0.95).

The UC group had significantly higher rates of CMW in the physical functioning (UC group: 61% vs. Exercise group: 27.3%; *p*=0.002) and fatigue domains (UC group: 82.9% vs. Exercise group: 47.7%; *p*=0.001), as reported in Table 4. A patient in the UC group is four times more likely to present CMW of physical functioning compared to a patient in Exercise group (OR=4.16; 95% CI: 1.67 to 10.38). Similarly for fatigue domain, a patient in the UC group is 5.32 times more likely to present CMW comparing to a patient in the Exercise group (OR=5.32; 95% CI: 1.94 to 14.54).

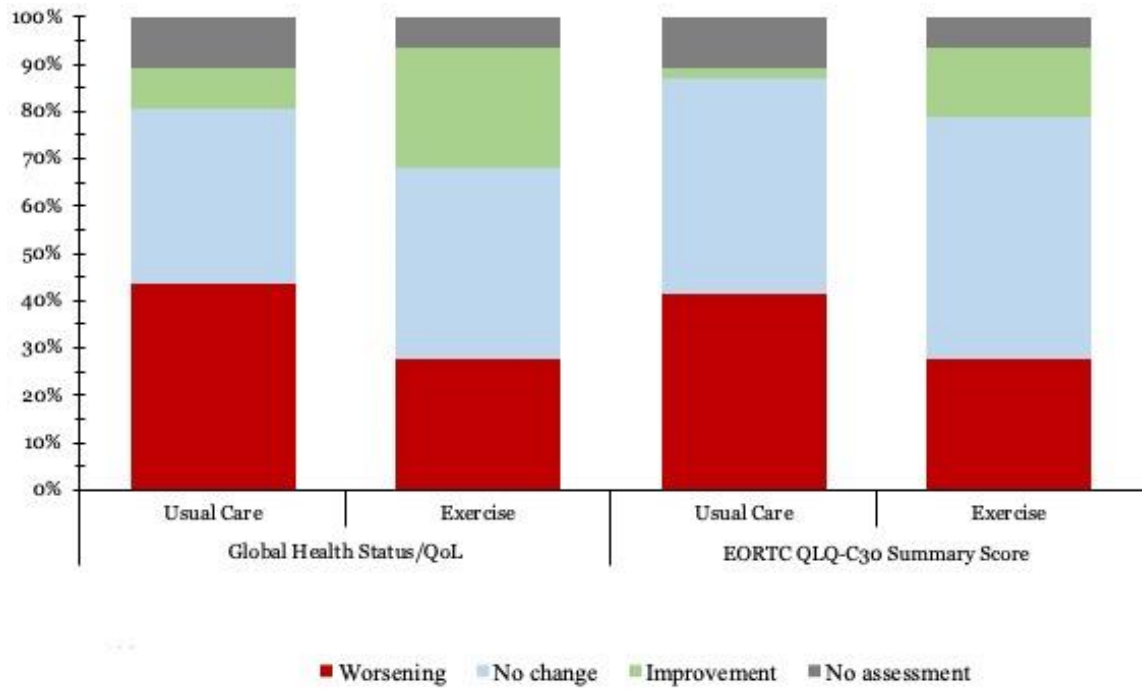

Figure 3. Status change of the Global Health Status/ Quality of Life domain and Summary Score of the EORTC QLQ-C30.

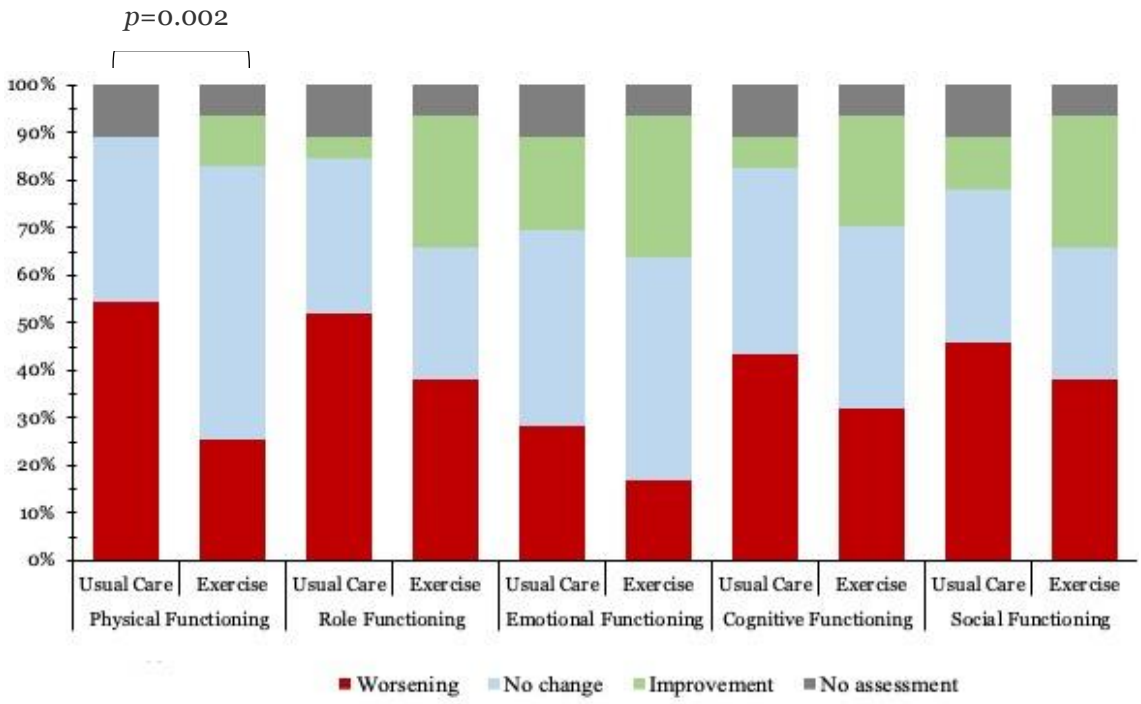

Figure 4. Status change of the functioning domains of the EORTC QLQ-C30.
P-value represents between-group difference in the proportions of patients with clinical meaningful worsening (worsening vs. improvement or no change) using Wald test.

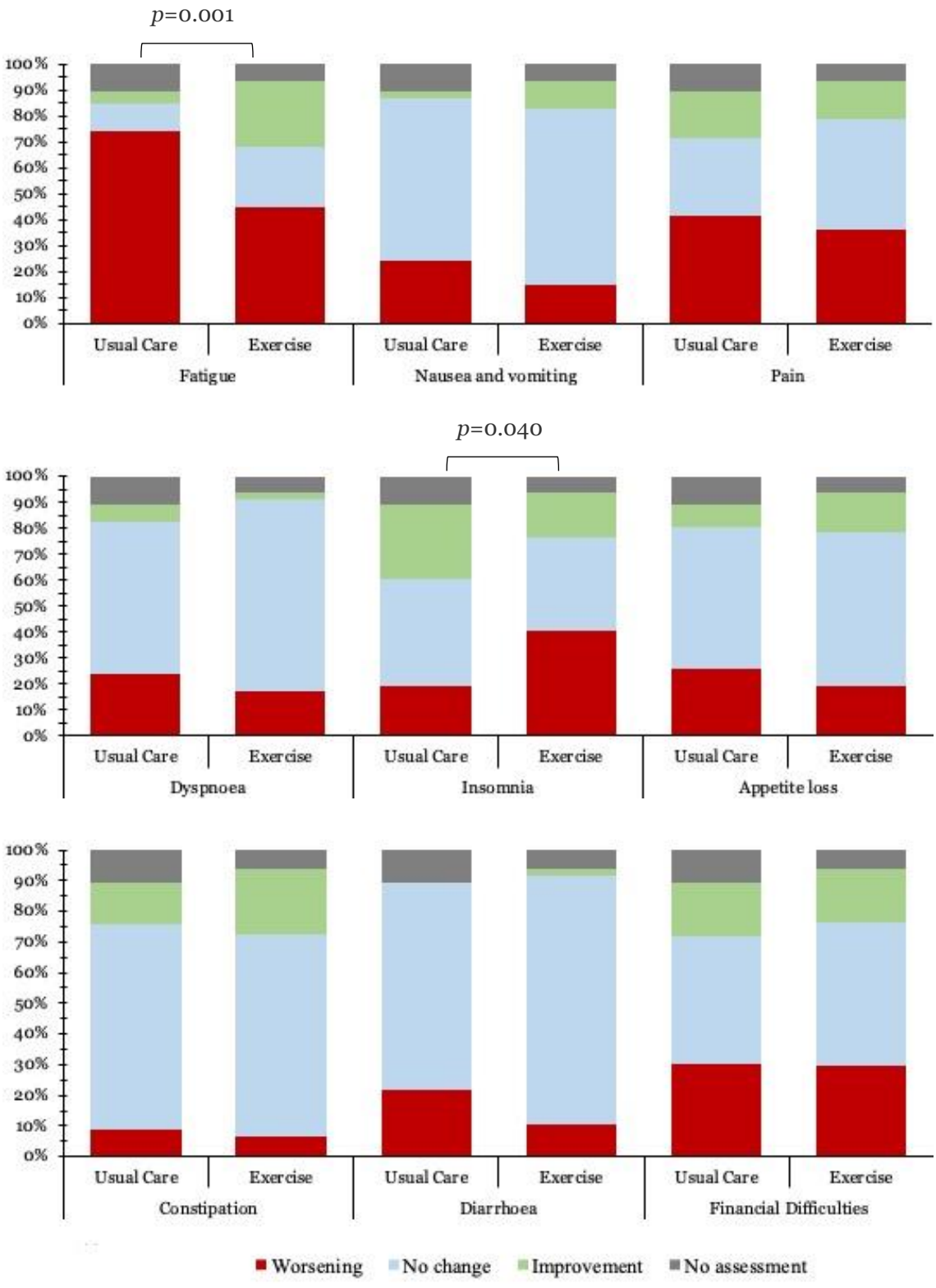

Figure 5. Status change of symptoms domains of the EORTC QLQ-C30.

P-value represents between-group difference in the proportions of patients with clinical meaningful worsening (worsening vs. improvement or no change) using Wald test.

Table 4. Proportion of patients with clinically meaningful worsening of the EORTC QLQ-C30 domains at the end of chemotherapy from baseline

	Total[c] (n=85)	Usual Care[c] (n=41)	Exercise[c] (n=44)	Odds ratio (95% CI)[d]	*P*[e]
EORTC QLQ-C30 Summary Score[a]	32 (37.7%)	19 (43.3%)	13 (29.6%)	2.05 (0.84; 5.02)	0.113
Global Health Status/ QoL[a]	33 (38.8%)	20 (48.8%)	13 (29.6%)	2.27 (0.93; 5.53)	0.071
Functional Domains[a]					
Physical Functioning	37 (43.5%)	25 (61%)	12 (27.3%)	4.16 (1.67; 10.38)	0.002*
Role Functioning	42 (49.4%)	24 (58.5%)	18 (40.9%)	2.03 (0.85; 4.84)	0.106
Emotional Functioning	21 (24.7%)	13 (31.7%)	8 (18.2%)	2.08 (0.76; 5.73)	0.153
Cognitive Functioning	35 (41.2%)	20 (48.8%)	15 (34.1%)	1.84 (0.76; 4.41)	0.171
Social Functioning	39 (45.9%)	21 (51.2%)	18 (40.9%)	1.51 (0.64; 3.57)	0.341
Symptom Domains[b]					
Fatigue	56 (65.9%)	34 (82.9%)	21 (47.7%)	5.32 (1.94; 14.54)	0.001*
Nausea and Vomiting	18 (21.2%)	11 (26.8%)	7 (15.9%)	1.93 (0.66; 5.61)	0.222
Pain	36 (42.4%)	19 (43.3%)	17 (38.6%)	1.37 (0.57; 3.25)	0.473
Dyspnea	19 (22.4%)	11 (26.8%)	8 (18.2%)	1.65 (0.58; 4.62)	0.341
Sleep Disturbance	28 (32.9%)	9 (22%)	19 (43.2%)	0.37 (0.14; 0.95)	0.040*
Appetite Loss	21 (24.7%)	12 (29.3%)	9 (20.5%)	1.60 (0.59; 4.35)	0.348
Constipation	7 (8.2%)	4 (9.8%)	3 (6.8%)	1.47 (0.31; 7.04)	0.624
Diarrhea	15 (17.7%)	10 (24.4%)	5 (11.4%)	2.51 (0.77; 0.81)	0.123
Financial Difficulties	28 (32.9%)	14 (34.1%)	14 (31.8%)	1.11 (0.449; 2.74)	0.820

Legend:
Data are expressed as numbers (percent).
[a] Clinical meaningful worsening is defined as a decrease of 10 or more points.
[b] Clinical meaningful worsening is defined as an increase of 10 or more points.
[c] This analysis only included patients who were assessed at both baseline (t_0) and at the end of chemotherapy (t_2).
[d] Odds ratio greater than 1 indicates a beneficial effect in the Exercise group, while an odds ratio less than 1 indicates a beneficial effect in the Usual Care group.
[e] Wald test.

Thresholds for clinical importance

Table 5 shows the proportion of patients reaching the TCI (i.e., proportion of patients below and above the TCI for functioning and symptom domains, respectively) by treatment group and time point assessment for the QLQ-C30 domains. Particularly in the UC group, significant differences were observed in physical (p<0.001), role (p=0.005), cognitive (p=0.001), and social functioning (p=0.025) domains, as well as for symptom domains such as fatigue (p=0.002), nausea and vomiting (p=0.007), appetite loss (p=0.016), and diarrhea (p<0.001) domains. These differences indicated an increase in the proportion of reaching the TCI over time. In contrast, the Exercise group exhibited a significant increase in the proportion of patients reaching the TCI in the nausea and vomiting (p=0.014) and dyspnea (p=0.036) domains. The between-group analysis reveals

a significant relationship for some of the QLQ-C30 domains. Compared with Exercise group, the UC group had a higher proportion of patients reaching the TCI in the physical functioning domain at t1 (UC group: 64.4% vs. Exercise group: 40%; p=0.034) and t_2 (UC group: 73.2% vs. Exercise group: 40.9%; p=0.004). A similar result was found for dyspnea at t1 (UC group: 24.4% vs. Exercise group: 6.7%; p=0.039) and for appetite loss at t_2 (UC group: 22% vs. Exercise group: 4.5%; p=0.023).

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Table 5. Proportion of patients reaching the threshold for clinical importance for the EORTC QLQ-C30 domains over the chemotherapy

	Total				Usual Care				Exercise				Between-group difference[d]		
	t_0 (n=92)	t_1 (n=90)	t_2 (n=85)	*P*[c]	t_0 (n=45)	t_1 (n=45)	t_2 (n=41)	*P*[c]	t_0 (n=47)	t_1 (n=45)	t_2 (n=44)	*P*[c]	t_0	t_1	t_2
Functional Domains[a]															
Physical Functioning (TCI: 83 units)	25 (27.2%)	47 (52.2%)	48 (56.4%)	<0.001	10 (22.2%)	29 (64.4%)	30 (73.2%)	<0.001	15 (31.9%)	18 (40%)	18 (40.9%)	0.177	0.353	0.034	0.004
Role Functioning (TCI: 58 units)	9 (9.8%)	11 (12.2%)	17 (20)	0.089	3 (6.7%)	6 (13.3%)	11 (26.8%)	0.005	6 (12.8%)	5 (11.1%)	6 (13.6%)	1	0.486	1	0.176
Emotional Functioning (TCI: 71 units)	39 (42.4%)	35 (38.9%)	35 (41.2%)	0.887	21 (46.7%)	17 (37.8%)	17 (41.5%)	0.652	18 (38.3%)	18 (40%)	18 (40.9%)	0.873	0.527	1	1
Cognitive Functioning (TCI: 75 units)	17 (18.5%)	29 (32.2%)	28 (32.9%)	0.015	5(11.1%)	16 (35.6%)	16 (39%)	0.001	12 (25.5%)	13 (28.9%)	12 (27.3%)	0.947	0.107	0.652	0.356
Social Functioning (TCI: 58 units)	6 (6.5%)	14 (15.6%)	13 (15.3%)	0.011	3 (6.7%)	8 (17.8%)	7 (17.1%)	0.025	3 (6.4%)	6 (13.3%)	6 (13.6%)	0.261	1	0.772	0.767
Symptom Domains[b]															
Fatigue (TCI: 39 units)	14 (15.2%)	26 (28.9%)	28 (32.9%)	0.002	6 (13.3%)	15 (33.3%)	16 (39%)	0.002	8 (17%)	11 (24.4%)	12 (27.3%)	0.397	0.773	0.486	0.356
Nausea and vomiting (TCI: 8 units)	10 (10.9%)	31 (34.4%)	21 (24.7%)	<0.001	4 (8.9%)	14 (31.1%)	13 (31.7%)	0.007	6 (12.8%)	17 (37.8%)	8 (18.2%)	0.014	0.740	0.658	0.209

Table 5. Continued

Pain (TCI: 25 units)	24 (26.1%)	32 (35.6%)	37 (43.5%)	0.011	11 (24.4%)	16 (35.6%)	18 (43.9%)	0.063	13 (27.7%)	16 (35.6%)	19 (43.2%)	0.193	0.814	1	1
Dyspnea (TCI: 17 units)	9 (9.8%)	14 (15.6%)	21 (24.7%)	0.003	7 (15.6%)	11 (24.4%)	12 (29.3%)	0.080	2 (4.3%)	3 (6.7%)	9 (20.5%)	0.036	0.087	0.039	0.452
Insomnia (TCI: 50 units)	13 (14.1%)	17 (18.9%)	19 (22.4%)	0.328	9 (20%)	7 (15.6%)	9 (22%)	0.829	4 (8.5%)	10 (22.2%)	10 (22.7%)	0.106	0.141	0.591	1

Legend:
Data are expressed as numbers (percent).
TCI: thresholds for clinical importance, defined by Giesinger et al. (2020).
[a] Proportion of patients that reach TCI for functioning domains (i.e., patients that self-reported QLQ-C30 values below the TCI). Scores below the TCIs for the functioning domains indicate clinically important functional impairment.
[b] Proportion of patients that reach TCI for symptom domains (i.e., patients that self-reported QLQ-C30 values above the TCI. Scores above the TCIs for the symptom domains indicate clinically important symptomatology.
[c] Cochran's Q test.
[d] Chi square test p-value.

Change in functional capacity from baseline

Table 6 presents the mean estimated changes in MVHS and 30-s CST.

Exercise group exhibited a mitigation in the decline of the functional outcomes over the study. At t_2, significant between-group differences were observed on MVHS of the tumor/surgery upper limb side (Δ=2.64kg; 95% CI: 3.41 to 0.79; p<0.001) and in contralateral upper limb (Δ=2.22kg; 95% CI: 1.2 to 3.25; p<0.001), favoring the Exercise group. Similar results were found for 30-s CST score, with between-group differences favoring the Exercise group verified at t_1 (Δ=2.80 repetitions; 95% CI: 1.36 to 4.24; p<0.001) and t_2 (Δ=3.56 repetitions; 95% CI: 2.07 to 5.05; p<0.001).

The sensitivity analysis showed a comparable result in sub-cohorts (Tables A3 and Table A4, in Appendixes - Study 6).

Table 6. Changes in functional capacity parameters over the chemotherapy

	Usual Care			Exercise			Time	Interaction	Between-group difference in mean change from baseline		
	n	Mean±SD	Difference in mean change from baseline (95%CI)	n	Mean±SD	Difference in mean change from baseline (95%CI)			n	Mean (95%CI)	*P*
Maximum voluntary handgrip strength											
Tumor/surgery upper limb side (kg)							0.005	<0.001			
t_0	45	25.57±5.43		46	25.56±5.13						
t_1	44	24.16±5.26	-1.39 (-2.47; -0.32)*	45	25.51±4.34	-0.07 (-1.13; 0.98)			90	1.31 (0.85; 7.96)	0.039
t_2	40	23.50±4.62	-2.34 (-3.46; -1.23)**	38	25.79±3.76	0.26 (-0.87; 1.39)			85	2.64 (3.41; 0.79)	<0.001
Contralateral upper limb (kg)							0.002	<0.001			
t_0	45	25.30±4.58		46	26.04±4.51						
t_1	44	24.35±4.45	-0.90 (-1.73; -0.07)*	45	26.13±3.87	0.03 (-0.78; 0.85)			90	0.92 (-0.05; 1.90)	0.065
t_2	40	23.48±4.38	-2.02 (-2.88; -1.16)**	38	26.08±3.77	0.19 (-0.68; 1.06)			85	2.22 (1.20; 3.25)	<0.001
30-second chair sit-to-stand test (repetitions)							0.003	<0.001			
t_0	45	15.22±4.03		46	15.47±3.85						
t_1	44	14.88±4.09	-0.27 (-1.44; -0.88)	45	18.13±4.09	2.58 (1.43; 3.73)**			90	2.80 (1.36; 4.24)	<0.001
t_2	40	14.20±4.41	-1.13 (-2.34; -0.06)	38	18.15±3.97	2.50 (1.28; 3.72)**			85	3.56 (2.07; 5.05)	<0.001

Legend:

Within-group and Between-group Difference in Mean Change was based on linear mixed models, controlling for group, time and interaction (fixed effects), and patient as a random effect and the baseline outcome and chemotherapy intent (neoadjuvant or adjuvant) were entered as covariates. Correction for multiple comparisons for Within-group and Between-group Difference in Mean Change analysis was performed by the Bonferroni method.

* Denotes a significant p-value <0.05 from baseline.

** Denotes a significant p-value <0.001 from baseline.

Discussion

The purpose of this study was to assess the effectiveness of exercise training on HRQoL and functional capacity parameters in women with BC undergoing chemotherapy. The findings of this RCT support the hypotheses that a SETP, combining aerobic and resistance training, could offer significant benefits in BC patients undergoing chemotherapy. Specifically, the integration of a SETP into cancer care resulted in i) a lower decline in the global health status/ QoL domain; ii) better functional aspects of HRQoL, such as physical, role, cognitive and social functioning domains; iii) lower levels of fatigue and appetite loss; iv) prevention of handgrip strength decline; and v) improvement of muscle strength and endurance of lower limbs. These findings remained consistent when we conducted separate analyses on subcohorts of patients who underwent neoadjuvant and adjuvant chemotherapy.

Neoadjuvant and/or adjuvant BC treatments have a deleterious impact on HRQoL (Sheng et al., 2019). Chemotherapy, in particular, is often associated with impaired health-related fitness, emotional and social functioning, as well as acute and long-term symptoms, such as fatigue, pain, nausea/vomiting, and menopausal symptoms, contributing to a decline in QoL (Cardoso et al., 2019; Sheng et al., 2019). In this study, BC patients on a SETP during chemotherapy experienced less decline in QoL compared to those who received usual care alone. Notably, at the end of chemotherapy, the Exercise group had a significant mean difference of 9.4 units in the global health status/ QoL domain of the QLQ-C30 when compared to the UC group. Previous studies have reported beneficial effects of exercise training in mitigating QoL decline in BC patients during chemotherapy, but several have not found significant differences from control groups (Courneya et al., 2007; Hornsby et al., 2014; Mijwel et al., 2018; Schmidt et al., 2015; Travier et al., 2015). Interestingly, in a recent meta-analysis, combined exercise training during cancer treatment was shown to provide greater benefits than only aerobic or resistance training (Martínez-Vizcaíno et al., 2023). This may possibly explain, at least in part, the discrepancies in results between this RCT and previous studies that employed single modality exercise programs (Courneya et al., 2007; Hornsby et al., 2014; Schmidt et al., 2015). In fact, a specific FITT prescription model including moderate intensity aerobic and resistance training performed 2-3 times per week for at least 12-weeks has been suggested to improve HRQoL during cancer treatment (Campbell et al., 2019). Moreover, the CARE trial showed that, compared to aerobic training prescriptions (STAN and HIGH), combined exercise training (COMB) during chemotherapy resulted in important long-term effects, namely better lower body strength and upper body endurance at 12-months follow-up, and better adherence to resistance exercise at 6 and 24-months follow-up (An et al., 2020).

Another important finding from this RCT was that a SETP was effective in reducing the decline in important functional aspects of HRQoL during chemotherapy. Specifically, a significant ≥10 units difference between groups were observed at the end of chemotherapy on physical, role, and social functioning domains of the QLQ-C30. Some exercise training trials in women with BC receiving

chemotherapy have reported similar results, albeit with lesser magnitude (Courneya et al., 2007; Hornsby et al., 2014; Mijwel et al., 2018; Schmidt et al., 2015; Travier et al., 2015; van Waart et al., 2015). Indeed, this positive impact of exercise training on functional aspects may have contributed in large part to the higher self-reported global health status/ QoL observed in this study.

Cancer patients often experience reductions in health-related fitness during and after cancer treatments, typically marked by a decline in time spent in PA, cardiorespiratory fitness and muscle strength (Stout et al., 2021). Overall, over 40% of patients in this study showed a CMW in physical and role functioning from baseline to the end of chemotherapy. However, the Exercise group had a significantly lower proportion of subjects with CMW in the physical functioning domain of the QLQ-C30 (UC group: 61% vs. Exercise group: 23%, p=0.002). The significant benefits observed in MVHS and in the 30-s CST, along with the previously reported significant improvement in cardiorespiratory fitness (Antunes et al., 2023), may account for the differences in the number of patients with CMW on the physical functioning domain, between the two groups. In this study, there was also a significant effect of exercise on self-reported cognitive functioning, consistent with the findings from the OptiTrain and PACES trials (Mijwel et al., 2018; van Waart et al., 2015). Albeit promising, the positive effects of exercise training on self-reported cognitive functioning should further ascertained, namely in settings including additional measures such as objective tests of cognition (Koevoets et al., 2023). Further research is currently ongoing in this under-researched topic (Kiesl et al., 2022).

Cancer-related fatigue is a prevalent and distressing symptom experienced by patients throughout the cancer trajectory, particularly during chemotherapy (Fabi et al., 2020). In the present study, 56% of patients had a CMW of fatigue from baseline to the end of chemotherapy. Importantly, a clinically meaningful difference in fatigue levels was present at both the middle (t_1) and end of chemotherapy (t_2). In addition, a significantly lower proportion of women in the Exercise group had a CMW on the fatigue domain of the QLQ-C30, as compared to the UC group, at the end of chemotherapy (UC group: 83% vs. Exercise group: 48%; p=0.001). Our results are consistent with previous research showing that a combined exercise program can effectively prevent fatigue during chemotherapy (Mijwel et al., 2018; Schmidt et al., 2015; van Vulpen et al., 2016). Moreover, patients in the Exercise group reported significantly lower levels of appetite loss. Appetite loss is commonly experienced during chemotherapy due to direct effects on the gastrointestinal system, changes in taste and smell perception, and psychological factors such as anxiety, depression, and stress (Hariyanto & Kurniawan, 2021). A decrease in energy intake due to loss of appetite can have adverse effects on physical, emotional, and social aspects. However, it is important to note that weight gain after a BC diagnosis has also associated with increased cardiovascular and BC-specific mortality (Nichols et al., 2009). As this study did not evaluate changes in body composition, this finding must be interpreted with caution.

As described, in this study the QLQ-C30 summary score was also assessed. The QLQC30 summary score is a newly developed endpoint providing a comprehensive assessment of patients'

HRQoL (Giesinger et al., 2016). At the end of chemotherapy, patients in the Exercise group had a significant mean difference of 8.1 units in the QLQ-C30 summary score, suggesting a substantial mitigation in HRQoL decline compared to those who received usual care. The potential relevance of this finding is further underscored by the strong prognostic value of this score in terms of overall survival in cancer patients, which goes beyond the value provided by clinical and sociodemographic variables (Husson et al., 2020). While previous studies have shown the positive effect of exercise training on the QLQ-C30 summary score in post-treatment breast (Koevoets et al., 2022), lymphoma (Hathiramani et al., 2021), and esophageal cancer patients (van Vulpen et al., 2021), our results provide novel data during chemotherapy. These findings could thus provide a useful framework for further larger studies on this topic.

Our study also provides novel information about TCIs for the QLQ-C30 recently developed by Giesinger et al., (2020), which aim to determine the clinical relevance of individual scores rather than changes over time. Interestingly, a significant increase in the proportion of UC group patients that reach TCI was observed in fatigue, nausea and vomiting, appetite loss and diarrhea, as well as in all functioning domains except emotional functioning domain. Conversely, a significant increase in the proportion of Exercise group patients that reach TCI was only observed in nausea and vomiting and dyspnea domains. Nonetheless, significant differences between groups were only seen in physical functioning and appetite loss. In addition to a study that included data from prostate cancer patients receiving androgen deprivation therapy with or without radiotherapy (Schumacher et al., 2021), this is the first exercise trial that performed a TCI analysis.

Strengths and limitations

Several strengths concerning this trial should be highlighted such as the randomized controlled design, the inclusion of a structured exercise training intervention throughout the entire systemic treatment of each patient and not limited to a part of it, the intention-to-treat analysis, and the high completion rate must be underlined. Additionally, to the best of our knowledge, this was the first exercise training RCT conducted in Portugal for BC patients undergoing chemotherapy. The findings of this study may encourage healthcare professionals in the incorporation of exercise training in supportive care for cancer patients and contribute to raising awareness in terms of its positive impact.

While these aspects should be highlighted, some limitations should also be considered. Firstly, the statistical analyses dimensions were based on the primary endpoint. Thus, the issue of multiple testing when interpreting results from the analyses on secondary endpoints should be noted. Secondly, the QLQ-C30 status change analysis and TCI analysis presented should be considered as hypothesis-generating due to the small sample size. Thirdly, the assessment of cancer-related fatigue relied on the QLQ-C30 questionnaire, which primarily focuses on its physical impact and may not provide a complete overview of its multidimensional nature. In this regard, application of a multidimensional tool such as the Piper Fatigue Scale-Revised or the

newly developed QLQ-FA12 alongside the QLQ-C30 could allow for a more comprehensive evaluation of cancer-related fatigue (Fabi et al., 2020). Fourthly, the prospective design of the study had a substantial impact from the contingencies related to the COVID-19 pandemic, leading to discontinuation of the SETP by 6 patients (12.8%; Figure 2) and missing values for some endpoints. Of mention, adherence to the exercise training frequency was not affected during the pandemic period (September 2020 to June 2022), which included a lockdown phase. Fifthly, the exercise prescription in our study followed a linear model, which may not fully accommodate the fluctuations in physiological and psychosocial symptoms that arise during systemic therapy. A non-linear approach has been recently suggested as a potentially more suitable alternative, although data examining its application in cancer patients are currently limited (Fairman et al., 2022). Finally, as a limitation inherent to exercise trials, patients cannot be blinded to group allocation. However, both groups had similar baseline HRQoL and functional capacity values.

While these limitations should be acknowledged, we consider the current trial to be a valuable contribution to the literature, as it provides significant insights into the potential benefits of exercise training as a supportive care approach for BC patients undergoing chemotherapy. The pragmatic contemporary design of the study adds to the relevance and applicability of the findings to real-world clinical settings.

Conclusion

The present RCT provides data that a supervised exercise program, combining both aerobic and resistance training, can mitigate the decline of HRQoL in BC patients receiving chemotherapy. Exercise training had a positive impact in important functioning domains (physical, role, cognitive, and social functioning) and functional capacity measures, while also preventing the increase of fatigue and appetite loss. Given cancer survivors are at risk of developing long-term symptoms, these findings may be of contemporary importance in the management of these patients.

Chapter 7 – General Discussion

The main aim of this thesis was to implement and conduct a randomized controlled trial (RCT) to analyze the potential cardioprotective effect of exercise training in women with breast cancer (BC) undergoing anthracycline-containing chemotherapy (A-Ct). Additionally, we aimed to assess the role of exercise on health-related quality of life (HRQoL) and functional capacity and, in an exploratory manner, to identify predictors of the cardiorespiratory fitness (CRF) response to training in these patients. To achieve these objectives, we undertook 3 experimental works (i.e., **study 4, 5, 6**).

The analysis of **Study 4** leads to the suggestion that integrating a supervised exercise training program (SETP), which combined aerobic and resistance training, into standard care for women with BC undergoing A-Ct did not mitigate the short-term decline of cardiac toxicity markers, including left ventricular ejection fraction (LVEF) (the considered primary endpoint), as well as potentially more sensitive indicators of early toxicity like global longitudinal strain (GLS) or cardiac biomarkers. These findings are consistent with other studies in which aerobic training programs, with or without resistance training, failed to antagonize the decline in subclinical parameters of cardiac function (Haykowsky et al., 2009; Hornsby et al., 2014; Howden et al., 2019; Kirkham et al., 2018b). In the line of these findings, a recent meta-analysis of RCTs (n=8) revealed that exercise training did not prevent the LVEF [mean difference: 1.18%; 95% confidence interval (CI): -0.45, to 2.81; p=0.16)] and GLS decline (0.42%; 95% CI: -0.52 to 1.37; p=0.38) in cancer patients receiving cardiotoxic chemotherapy compared to non-exercise cohort (Amin et al., 2024). In **study 4**, we also found no differences between groups in cancer-therapy related cardiac dysfunction (CTRCD) incidence [Usual Care (UC) group: n=3 (~7%) vs. Exercise group: n=1 (~2%); p=0.361]. The incidence of CTRCD is often underreported in exercise training trials, possibly due to the absence of events, which is particularly expected in studies with a short follow-up after A-Ct (Cardinale et al., 2015). Despite this, studies reporting CTRCD events have been indicated that exercise training is not associated to a reduction in its incidence, at least at short-term (i.e., ≤ 1-year) (Díaz-Balboa et al., 2024; Foulkes et al., 2023b; Howden et al., 2019).

Despite lacking exercise effects on the considered cardiac function endpoints reported in our study, others have presented contrasting findings in women with BC receiving A-Ct or adjuvant trastuzumab (Díaz-Balboa et al., 2024; Hojan et al., 2020; Ma, 2018). For instance, recent data from the ONCORE trial demonstrated that women with BC who performed a SETP during A-Ct, with or without trastuzumab, experienced a mean decrease in LVEF decline of -1.5% (95% CI: -2.9 to -0.1; p=0.006) when compared to UC (Díaz-Balboa et al., 2024). Data demonstrated that the end-chemotherapy LVEF may be an independent predictor of subsequent cardiac dysfunction, including trastuzumab-related cardiac dysfunction. For instance, in a prospective study, which included 2625 cancer patients treated with A-Ct, Cardinale et al. (2015) found that

each percentage unit decrease in LVEF was associated with a hazard ratio of 1.37 (95% CI: 1.33 to 1.42) for developing asymptomatic CTRCD. The risk seems to be substantially increased for every 5% decrease, and this magnitude of change has been used as a clinically important difference in cancer studies, despite its exact clinical significance is yet to be determined (Breathett et al., 2016; Gulati et al., 2016). In patients with heart failure (HF) with reduced LVEF a 5% increase in LVEF was suggested to be a powerful predictor of survival and reduced HF-related hospitalization. Therefore, while acknowledging the positive impact on preserving cardiac function demonstrated in the mentioned ONCORE trial, the question remains whether the early and relatively small changes, in a population with preserved LVEF (>60%), could potentially influence the long-term risk of developing cardiac dysfunction related to cancer therapy.

The factors contributing to the divergent findings between the ONCORE trial and our **study 4** remain inadequately understood. Notably, the participants' baseline sociodemographic and clinical characteristics, and the method to assess cardiac function were identical in both trials. Furthermore, the exercise training protocols shared similarities, with the primary differences being the lower training frequency (twice weekly) and the longer duration of training for human epidermal growth factor receptor 2 (HER2)-positive BC patients (12-months; n=12) in the ONCORE trial. It could be relevant to compare the susceptibility to developing CTRCD between participants in the two studies, but this comparison was not feasible as this info was not provided in the ONCORE trial.

The results of our **Study 4** also demonstrated that exercise training improved CRF (a secondary endpoint). In cancer patients, poor CRF has been associated with a higher symptom burden and risk of cancer-related mortality (Ekblom-Bak et al., 2023; Fardman et al., 2021; Herrero et al., 2006; Schmid & Leitzmann, 2015). Moreover, each 1 metabolic equivalent of task (MET) (i.e., 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) increment was found to decrease in 14% the risk cardiovascular (CV)-related mortality among cancer survivors post-treatement (Groarke et al., 2020) but, more recently, Imboden et al. (2019) found that even a modest increase of 1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in peak oxygen uptake (VO_{2peak}) was associated with a 15% and 16% reduction in CV-related and cancer-related mortality, respectively. Overall, these findings support the clinical relevance of our study's results.

Research have been indicated that the marked decline in VO_{2peak} experienced by cancer patients, treated with A-Ct occurs independently of changes in resting LVEF and GLS, which emphasizes the weak association between CRF and the clinical standards used to identify CTRCD (Foulkes et al., 2019; Howden et al., 2021; Jones et al., 2007, 2012; Khouri et al., 2014). Conversely, studies conducted in hematologic and BC patients treated to A-Ct found that they exhibit impairments in CRF secondary to reduce submaximal and peak exercise cardiac function (such as LVEF, stroke volume, and cardiac output), which appear to correlate with persistent reduction in VO_{2peak} (Foulkes et al., 2019; Jones et al., 2007; Kirkham et al., 2021). Jones et al. (2007) were pioneers at exploring the value of peak exercise cardiac function in BC survivors treated with A-Ct (n=47). In a cross-sectional study, the authors found that BC survivors (34±18-months after A-Ct) exhibited a marked impairment in CRF compared to age- and sex-matched healthy control

subjects (n=11), despite preserved resting systolic function (LVEF: 64±19%). Specifically, the BC survivors' VO_{2peak} was 20% lower compared to controls, which was mostly attributed to a blunted increase in peak exercise cardiac output (10.4±1.5 vs. 11.7±2.4 L/minute; $p<0.05$) and stroke volume (68±9 vs. 76±15 mL/beat; $p<0.05$), as chronotropic response and systemic vascular resistance were similar between groups (Jones et al., 2007). Subsequent research has confirmed these results, underscoring that the decline in CRF is, in part, a result of subclinical reductions in cardiac reserve (Foulkes et al., 2019, 2023b, 2024; Kirkham et al., 2021). This knowledge provided a compelling rationale for assessing the impact of exercise training on peak exercise cardiac function, as it may enhance our understanding of this non-pharmacological strategy's role in cardiac health.

The Brexit trial was the first large-scale RCT analysing the efficacy of exercise training on cardiac reserve by using cardiac magnetic resonance imaging to assess peak exercise and reserve cardiac function in women early-stage BC receiving A-Ct (Foulkes et al., 2023b). While no alterations in resting cardiac parameters were observed, including markers of cardiac dysfunction induced by cancer therapies (LVEF and GLS), exercise training significantly blunted the decline in peak exercise cardiac output, stroke volume, LVEF, and right-ventricular ejection fraction at the end and 12-months after A-Ct, compared to the control group (Foulkes et al., 2023b). These findings provided the first robust evidence that exercise training during A-Ct has a beneficial impact on cardiac reserve, contributing to mitigate the decline CRF. Notably, the authors also demonstrated that 12-months ΔVO_{2peak} was significantly associated with alterations in peak cardiac output (per 1 L/min: β, 0.76, R_2=0.22, $p<0.001$), but not with resting LVEF and GLS (Foulkes et al., 2023b). This supports earlier findings that indicated that CTRCD identified by resting cardiac parameters has poor sensitivity to functional decline. Consequently, the question arises as to whether the current definitions of CTRCD could be adjusted by incorporating cardiac reserve parameters to better identify patients at CV risk (Foulkes et al., 2023a; Haykowsky et al., 2022; Howden et al., 2021). To date, the effectiveness of these metrics in detecting subclinical dysfunction remains uncertain, as results have been inconsistent (Civelli et al., 2006; Foulkes et al., 2020; Howden et al., 2021; Khouri et al., 2014). This is an important subject for future research. Nonetheless, CRF is a relevant therapeutic target among cancer patients, given its significance in survival and the management of cancer-related treatment toxicities.

Research involving BC patients undergoing A-Ct typically shows that 2-4 sessions per week of exercise training —including moderate continuous training (MCT), MCT combined with resistance training, or a combination of MCT, resistance training, and high-intensity interval training— helps to attenuate the CRF decline associated with A-Ct (Beaudry et al., 2015; Scott et al., 2018). Particularly, a recent meta-analysis of RCTs focused on cancer survivors undergoing cardiotoxic therapy found a net increase of 1.9 mL·kg−1·min−1 in VO_{2peak} with exercise training (Amin et al., 2024). Likewise, we observed a significant effectiveness of exercise training at the group level (in **Study 4**); however, we also noted a considerable variability in ΔVO_{2peak} 3-months after doxorubicin-based chemotherapy, ranging from -4.27 to 8.95 mL O_2·kg^{-1}·min^{-1}. This finding

prompted us to conduct **Study 5**, which aimed to evaluate the CRF responsiveness to exercise training.

Our analysis in **Study 5** showed that 63% of patients (n=26) were Responders. This aligns with data from CV rehabilitation trials, where it is observed that up to 33% of patients may not experience an increase in VO_{2peak} (Gevaert et al., 2020). However, our findings are slightly higher than those reported in exercise oncology trials, where the percentage of responders varies from 13% to 50% (Foulkes et al., 2024; Scott et al., 2020, 2021). Although this issue has not been fully ascertained in exercise oncology, it is plausible that differences in patient characteristics, training prescriptions, exercise training adherence, and the assessment of CRF responsiveness may explain, at least in part, some of the discrepancies observed between studies.

In **Study 5** we also aimed to identify potential predictors of CRF responsiveness. Our analysis indicated total MET-hour of aerobic training and baseline body mass index (BMI) were independent predictor of CRF responsiveness. Particularly, total MET-hour of aerobic training serves as an exercise dose metric, and their association with CRF response provides a novel insight into exercise oncology. Previous studies in this field, as well as in cardiac rehabilitation, have indicated that higher attendance is associated with better CRF response (Beaudry et al., 2015; Foulkes et al., 2023a; Haykowsky et al., 2009; Little et al., 2015). Specifically, Haykowsky et al. (2009) showed that exercise attendance was a predicter of ΔVO_{2peak} (r=0.77; p<0.001) in BC undergoing adjuvant trastuzumab. Additionally, data from the BREXIT trial revealed that participants with over 66% attendance during the 12-month intervention experienced greater improvements in CRF (+2.45 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ vs. +0.11 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; p=0.037) and were completely protected against *functional disability*, defined as a VO_{2peak} ≤18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (Foulkes et al., 2023a). However, during chemotherapy, patients commonly experience fluctuations in adherence to prescribed exercise duration and intensity, often linked to the accumulation of symptoms and chemotherapy-related toxicities—such as fatigue, low mood, sleep and autonomic disturbances—especially prominent in the first 7-days following chemotherapy infusion (Kirkham et al., 2018a, 2019, 2020). Therefore, attendance rates alone may not accurately reflect the actual exercise dose performed, as when patients face inability to adhere training prescription, a typical approach involve reducing the workload—by adjusting speed, grade, or watts—to help them to sustain exercise effort (Courneya et al., 2007; Kirkham et al., 2018a, 2020; Scott et al., 2020).

Recently, nonlinear (periodized) exercise training prescription, which incorporates a prophylactic adjustment of exercise duration and/or intensity during the week of chemotherapy infusion, has been suggested has a better approach for optimizing exercise adaptations than the traditional standard linear prescriptions (Sasso et al., 2015). Kirkham et al. (2020) found that nonlinear prescription enhanced exercise attendance in BC patients undergoing taxane-based chemotherapy. Despite this, studies to date have not confirmed that this approach provides better tolerance compared to linear prescriptions, and its effectiveness on CRF remains uncertain (Scott et al., 2020, 2021). Additionally, nonlinear prescription may not be viable for patients undergoing

weekly chemotherapy. Indeed, the optimal exercise training prescription for cancer populations —one that maximizes exercise adherence, delivers optimal physical and psychological benefits, and is feasible for implementation in real-world settings— continues to be a topic of debate. The results of **Study 5** suggest that adjusting aerobic exercise dose, via MET-hour, may be a suitable prescription approach to mitigate VO_{2peak} decline while maintaining planned energy expenditure levels. The effectiveness of this approach was not tested in exercise oncology trials, but research conducted in sedentary postmenopausal women and obese adults indicates that increasing the volume of aerobic training —whether through extended duration or heightened intensity— enhances the responsiveness of CRF to exercise (Lin et al., 2021; Ross et al., 2015; Sisson et al., 2009).

In addition to the training components, several factors are known to influence VO_{2peak}, including age, sex, BMI, and baseline physical fitness, which seem to significantly affect the CRF response (Bonsignore & Warburton, 2013; Gevaert et al., 2020; Pandey et al., 2021). In **study 5**, we found that patients with lower baseline BMI had a higher likelihood of improve >1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in VO_{2peak} in response to exercise training. Early findings indicated that post-treatment BC patients with lower baseline BMI had greater improvements in VO_{2peak} following a non-linear aerobic training program (Scott et al., 2020). The analysis of appropriate body composition measurements could have contributed to a better understanding of the factors that influence the CRF response to exercise training, as literature indicates that changes in the musculoskeletal system induced by chemotherapy affect the oxygen cascade (Bonsignore & Warburton, 2013; Dillon et al., 2024; Foulkes et al., 2023a, 2024; Gevaert et al., 2020; Pandey et al., 2021). Unfortunately, these parameters were not assessed in our study.

Skeletal muscle deconditioning is a (in)direct detrimental effect of systemic anti-cancer treatment, marked by abnormalities in skeletal muscle mass, including reduced muscle size, fiber cross-sectional area, and myocyte size, as well as in muscle mass quality indicators, such as myosteatosis, altered fiber type distribution, and a decreased capillary to fiber ratio (Beaudry et al., 2020; Kirkham et al., 2021; Mallard et al., 2021, 2022; Mijwel et al., 2018; Reding et al., 2019). These skeletal muscle impairments have been associated with CRF decay and poor quality of life in BC cancer patients (Cespedes Feliciano et al., 2020; Mijwel et al., 2018). Furthermore, such deconditioning may exacerbate treatment-related toxicities, ultimately reducing adherence to systemic therapies and increasing the risk of mortality (Caan et al., 2018; Cespedes Feliciano et al., 2020; Mijwel et al., 2018).

Finally, regardless the uncertainties and potential lack of alterations here reported in some endpoints, namely in CRF, the following aspects would complement the present discussion and can possibly reinforce the usefulness and the efficacy of physical exercise training practice in the context of these subjects, Therefore, (i) the usual low physical fitness levels of cancer patients undergoing chemotherapy, including CRF and lower limb muscle mass and functionality (Mijwel et al., 2018), (ii) the coordinated central and peripheral dependency of VO_{2peak} as a gold standard of CRF, (iii) the used estimation method for CRF assessment in the present study based on

external workload variables and, straightly derived from the pointed features, (iv) the possible higher contribution of skeletal adaptations muscle than the cardiac ones (induced by exercise training in this scenario) to the estimated VO_{2peak} as a measure of CRF, which seems established as more easily accomplished (Foulkes et al., 2023a, 2024). In addition, if we consider the systemic biological relevance of skeletal muscle mechanical work in the release of the so-called exerkines in exercise-induced hormesis phenomenon, further general health benefits are obtained from chronic exercise practice in these subjects seen in other systems and tissues such as liver, brain, bones, adipose or kidney, rather than the studied cardiovascular-related under the scope of the present work (Foulkes et al., 2023a, 2024; Haykowsky et al., 2022).

Changes in skeletal muscle architecture were further associated with peripheral (mal)adaptations (Beaudry et al., 2020; Mallard et al., 2021, 2022; Mijwel et al., 2018). Notably, studies using obtained skeletal muscle tissue from biopsies demonstrated peripheral chemotherapy-related abnormalities, including reduced mitochondrial content (evidenced by lower citrate synthase protein levels) and compromised biogenesis, shown through impaired protein turnover (Mallard et al., 2022; Mijwel et al., 2018). These mitochondrial alterations may contribute to VO_{2peak} impairment in BC patients treated with A-Ct and were linked to cancer-related fatigue exacerbation (Mallard et al., 2022; Mijwel et al., 2018). A recent secondary analysis of the BREXIT trial, employing hemodynamic monitoring during exercise, added to the understanding of CRF responsiveness in BC patients treated with A-Ct, demonstrating that oxygen extraction capacity (assessed by arteriovenous oxygen difference) and skeletal muscle diffusive oxygen conductance are pivotal factors (Foulkes et al., 2024). Overall, these data emphasize the crucial role of strength training in enhancing physical fitness for these patients through its ability to counteract musculoskeletal toxicity (Courneya et al., 2007; Mijwell et al., 2018).

It is now widely acknowledged and valued that patient-reported outcomes offer a unique perspective, without interpretation or amendment by others, on disease, symptoms, and HRQoL (Liang & Ye, 2023; Kluetz et al., 2016; Di Maio et al., 2022). This direct perspective can enhance clinicians' decision-making regarding symptom management, treatment response, supportive care measures, and patient satisfaction (Di Maio et al., 2022). Prospective trials and population-based studies have indicated that the assessment of patient-reported outcomes during cancer care was associated with better physical function, symptom management, HRQoL, reduced hospitalizations, and increased overall survival (Di Maio et al., 2022). Particularly, HRQoL has emerged as an important prognostic factor for survival among cancer patients (Marandino et al., 2018). When assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), recent findings indicate that the QLQ-C30 summary score a strong prognostic value (Husson et al., 2020).

Research has consistently demonstrated that exercise training can alleviate the decline in HRQoL, during and after treatment, in patients with various types of tumors (Aune et al., 2022; Buffart et al., 2017; Campbell et al., 2019; Furmaniak et al., 2016). The results of **Study 6** reinforced this prior knowledge by confirming that the integration of a SETP into BC care effectively mitigated

the decline in HRQoL during chemotherapy. Specifically, we found that at the end of chemotherapy, the Exercise group had a significant mean difference of 8.1 units in the QLQ-C30 summary score, suggesting a substantial mitigation in HRQoL decline compared to UC. Additionally, a novel finding from our **Study 6** was that exercise training effectively prevented a clinically significant deterioration in all domains of functioning, except for emotional functioning. It also reduced the prevalence of clinically important symptoms, including fatigue, nausea and vomiting, loss of appetite, and diarrhea. The substantial effects of exercise training on physical fitness components, metabolic and inflammatory profile, and social engagement are critical in mitigating some of the toxicities associated with treatments.

Despite the positive short-term effects of exercise training, with some evidence suggesting that benefits may persist into the medium term (~ 1-year later), the long-term value of these results markedly diminishes over time (Anandavadivelan et al., 2024; Binyam et al., 2024; Bolam et al., 2020; Goldschmidt et al., 2023). The literature indicates that this decline may largely be due to a return to pre-diagnosis levels of physical activity, which are generally lower (Goldschmidt et al., 2023). This understanding underscores the need to implement strategies that foster long-term adherence to physical activity from the outset. Studies in this filed have primarily focused on identifying predictors and barriers to physical activity (Schmidt et al., 2017), but; they have often overlooked the importance of the meanings that patients ascribe to exercise after active treatment, as well as their knowledge regarding the role of physical activity during the survivorship.

Strengths and limitations

The strengths and main limitations of the work conducted have been detailed in each study. However, when considering the overall perspective of this doctoral thesis, additional factors must also be considered.

One of the key strengths of this research is its multidisciplinary team, which brings a wealth of knowledge and expertise in the key scientific areas relevant to thesis, including exercise physiology, sports science, cardiology, oncology, and medicine and rehabilitation. The resilience of this team deserves special recognition, as they demonstrated their capability to implement this project while overcoming significant obstacles, even during the challenges posed by the pandemic. Additional strengths include the establishment of a robust rationale for conducting innovative experimental work, grounded in sound methodological principles, aimed at contributing to the existing body of knowledge. Furthermore, in addition to its scientific contributions—potentially raising awareness of the beneficial role of exercise training in supportive care for cancer patients—this work has also made a meaningful social impact.

Nonetheless, some limitations must be acknowledged. The work conducted had a relatively short follow-up period, which limited the analysis of medium- to long-term results and focused particularly on systolic function. Additionally, certain methodological issues arose, particularly due to the challenges posed by the SARS-CoV-2 pandemic. This required adjustments to the

experimental work, such as altering the locations of training sessions, modifying the assessment of cardiorespiratory fitness, revising the pre-defined statistical methodology. The pandemic-related confinement also hindered the collection of some data and led to the early suspension of the exercise training program by some participants. Furthermore, due to constraints in resource and time management, we were unable to present results for several relevant secondary variables, such as heart rate variability.

Future research

This work has brought several promising directions for future research, including:

- Optimizing aerobic training prescription: investigating whether prescribing aerobic training based on energy expenditure might enhance the training response—measured through CRF responsiveness and other cardiac function parameters—compared to traditional methods, such as those based on maximum heart rate or heart rate reserve. Within this scope, further analysis and comparison of exercise tolerance would also be valuable to better understand individual responses.

- Exercise training for patients at higher risk or with history of CTRCD: given the primary focus of this study, there is a significant gap in the literature on the effects of exercise in individuals with an elevated baseline risk of CTRCD. Furthermore, limited research has examined the role of exercise specifically in patients who have already developed CTRCD, highlighting a critical need to investigate the potential of exercise as a secondary prevention strategy within this population.

- CRF as a stratification tool for cardiac dysfunction risk: the design of prospective studies would allow evaluating whether changes in CRF could improve the stratification of patients at risk of cardiac dysfunction.

Chapter 8 – Conclusion

The experimental works of this thesis suggest that:

- Exercise training did not prevent the decline of established markers of cardiac toxicity—specifically, left ventricular ejection fraction, global longitudinal strain, and circulating biomarkers—in women with breast cancer undergoing anthracycline-containing chemotherapy.

- The implementation of a training program during systemic treatment for early-stage breast cancer has been shown to be safe, with no reported serious adverse events. It's important to highlight the positive results in feasibility outcomes, particularly the recruitment rate of 78% and the retention rate of 68%, despite the significant challenges posed by the SARS-CoV-2 pandemic. These parameters are not only essential for conducting clinical trials but also indicate that these patients are interested in participating in multidisciplinary supervised exercise training programs during chemotherapy.

- Exercise training played a crucial role in enhancing cardiorespiratory fitness and physical function during this challenging phase of breast cancer treatment. Furthermore, exercise training demonstrated a significant effect in alleviating declines across various domains of health-related quality of life, as well as in reducing fatigue, which is one of the most common and detrimental symptoms in this patient population.

Chapter 9 – References

References of chapter 1

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Appendixes

Appendixes – Study 4

Table A1. Characteristics of Planned Systemic Therapy

Chemotherapy Protocol	Protocol Description	Total (n=93)	Usual Care (n=46)	Exercise (n=47)	Chemotherapy Length (weeks)	Planned Exercise Sessions (sessions)	*p*
AC-T	• 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks; followed by 12 cycles of Paclitaxel (80 mg/m², IV) weekly	50 (53.8%)	23 (50%)	27 (57.4%)	20	60	0.535[a]
AC-TH	• 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every three weeks; followed by 4 cycles of Docetaxel (75 mg/m², IV) plus Trastuzumab SC (600 mg, SC) and Pertuzumab (loading dose 840 mg/m²; subsequent doses 420 mg/m², IV) every three weeks	2 (2.1%)	1 (2.2%)	1 (2.1%)	24	72	1[b]
	• 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks; followed by 4 cycles of Docetaxel (75 mg/m², IV) plus Trastuzumab SC (600 mg, SC) and Pertuzumab (loading dose 840 mg/m²; subsequent doses 420 mg/m², IV) every three weeks	12 (12.9%)	4 (8.7%)	8 (17%)	20	60	0.355[a]
	• 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks; followed by 12 cycles of Paclitaxel (80 mg/m², IV) weekly plus Trastuzumab SC (600 mg, SC) and Pertuzumab (loading dose 840 mg/m²; subsequent doses 420 mg/m², IV) every three weeks	9 (9.7%)	6 (13%)	3 (6.4%)	20	60	0.316[b]
	• 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks; followed by 12 cycles of Paclitaxel (80 mg/m², IV) weekly plus Trastuzumab SC (600 mg, SC) every three week	2 (2.1%)	1 (2.2%)	1 (2.1%)	20	60	1[b]
CP-AC	• 4 cycles of Carboplatin (AUC 6, IV) every three weeks and Paclitaxel (80 mg/m², IV) weekly; followed by 4 cycles of Doxorubicin (60 mg/m², IV) plus Cyclophosphamide (600 mg/m², IV) every two weeks	18 (19.4%)	11 (23.9%)	7 (14.9%)	20	60	0.304[a]

Table A1. Characteristics of Planned Systemic Therapy

Legend:
Data are expressed as numbers (per cent).
AC: Doxorubicin plus Cyclophosphamide; AC-T: Doxorubicin plus Cyclophosphamide followed by taxane-based chemotherapy; AC-TH: Doxorubicin plus Cyclophosphamide followed by taxane-based chemotherapy plus trastuzumab with or without pertuzumab; CP-AC: Carboplatin and Paclitaxel followed by Doxorubicin plus Cyclophosphamide; IV: intravenous; SB: subcutaneous; p: represents the difference in chemotherapy protocols between groups.
[a] Chi-squared test.
[b] Fisher's exact test.

Table A2. Change in Echocardiogram Endpoints (per-protocol analysis)

	Usual Care			Exercise			*p* (Interaction)†	Adjusted Between-group Difference from Baseline ‡		
	n	Mean ± SD	Within-group Difference in Mean Change from Baseline†	*n*	Mean ± SD	Within-group Difference in Mean Change from Baseline†		*n*	Mean (95%CI)	*p*
Left Ventricular Ejection Fraction (%)							0.460			
Baseline	46	61.2±3.3		22	60.4±2.9					
End of AC	45	59.6±3.3	-1.6 (-3.0, -0.1)*	22	59.6±2.7	-0.7(-2.2, 0.5)		67	0.8(-1.1, 2.8)	0.415
3 months after AC	43	58.1±4.4	-3.0 (-4.5, -1.6)*	21	58.6±3.7	-1.7(-3.4, -0.5)		64	1.2(-0.7, 3.3)	0.216
Global Longitudinal Strain (%)							0.108			
Baseline	37	-21.3±2.2		20	-20.8±1.6					
End of AC	39	-20.1±2.1	1.1(0.2, 2.1)*	20	-19.9±1.6	0.8(-0.3, 2.1)		55	-0.4(-1.7, 0.8)	0.487
3 months after AC	34	-18.8±2.0	2.4(1.5, 3.4)*	17	-19.6±1.9	1.1(-0.2, 2.4)		48	-1.5(-2.9, -0.2)	0.025*
Cardiac Output (L.min)							0.241			
Baseline	45	3.5±0.6		22	3.3±0.6					
End of AC	45	3.7±0.7	0.1(-0.1, 0.4)	22	3.7±0.7	0.4 (0.04, 0.7)*		67	0.2 (-0.1, 0.6)	0.210
3 months after AC	43	3.5±0.7	-0.01(-0.2, 0.2)	21	3.6±0.7	0.3 (-0.1, 0.6)		64	0.3 (-0.1, 0.6)	0.113
Stroke Volume (ml)							0.542			
Baseline	45	46.5±9.7		22	44.7±8.8					
End of AC	45	45.8±10.6	-0.7(-3.9, 2.5)	22	46.6±10.5	1.8 (-2.7, 6.4)		67	2.5 (-2.0, 7.1)	0.268
3 months after AC	43	44.7±11.0	-1.5(-4.8, 1.6)	21	44.4±8.2	-0.5 (-5.2, 4.1)		64	0.9 (-3.6, 5.6)	0.678
Left Atrium Volume Index (ml/m^2)							0.315			
Baseline	45	23.4±5.8		22	22.5±6.1					
End of AC	45	26.4±7.2	2.9 (0.7, 5.2)	22	23.3±5.3	0.8 (-2.3, 4.0)		67	-2.1 (-5.1, 0.9)	0.171
3 months after AC	42	25.1±5.7	-1.6 (-0.6, 3.9)	21	22.0±5.7	-0.5 (-3.7, 2.7)		63	-2.1 (-5.3, 0.9)	0.168
Left Ventricular End-diastolic Volume (ml)							0.622			
Baseline	45	76.1±16.6		22	74.1±14.2					
End of AC	45	76.9±17.1	0.8 (-4.0, 5.7)	22	78.0±17.0	3.8 (-3.1, 10.9)		67	3.0(-4.0, 10.1)	0.398
3 months after AC	43	77.4±18.3	1.4 (-3.5, 6.4)	21	76.0±14.5	1.4 (-5.6, 8.6)		64	-0.1(-7.2, 7.1)	0.981
Left Ventricular End-systolic Volume (ml)							0.625			
Baseline	45	29.6±7.6		22	29.9±6.0					
End of AC	45	31.1±7.6	1.5 (-0.8, 3.9)	22	31.4±7.2	1.5 (-1.9, 5.0)		67	-0.01(-3.5, 0.5)	0.995
3 months after AC	43	32.6±9.2	3.0 (0.5, 5.4)*	21	31.6±7.3	1.5 (-1.9, 5.0)		64	-1.5(-5.1, 2.0)	0.394
Left Ventricular Diameter (mm)							0.930			
Baseline	46	46.9±4.2		22	46.4±2.8					
End of AC	45	47.6±3.8	0.6 (-0.5, 1.8)	22	47.1±2.9	0.6 (-1.0, 2.3)		67	0.1 (-1.7, 1.9)	0.930
3 months after AC	43	47.0±4.2	-0.03 (-1.2, 1.1)	22	46.7±2.6	0.2 (-1.4, 1.9)		65	0.3 (-1.5, 2.2)	0.708

Table A2. Continued

Left Ventricular Mass Index (g/m^2)							0.659			
Baseline	46	78.1±16.1		22	74.4±10.4					
End of AC	45	80.3±16.5	1.9 (-2.3, 6.2)	22	78.8±13.4	4.4 (-1.7, 10.6)		67	2.6 (-3.8, 9.0)	0.422
3 months after AC	43	79.3±17.9	1.0 (-3.3, 5.2)	22	77.9±11.7	3.5 (-2.7, 9.7)		65	2.8 (-3.5, 9.3)	0.376
E/A ratio							0.688			
Baseline	46	0.9±0.3		22	1.0±0.3					
End of AC	45	0.9±0.3	0.005 (-0.07, 0.08)	22	1.0±0.3	0.05(-0.06, 0.1)		67	0.04 (-0.06, 0.1)	0.416
3 months after AC	43	0.9±0.3	-0.03 (-0.1, 0.04)	22	0.9±0.3	-0.03(-0.1, 0.08)		65	0.006 (-0.1, 0.1)	0.916
E/e ratio							0.201			
Baseline	46	7.9±2		22	7.7±1.9					
End of AC	44	8.1±1.7	0.09 (-0.4, 0.6)	22	8.4±2.0	0.7(0.01, 1.5)*		66	0.6 (-0.03, 1.4)	0.062
3 months after AC	43	7.8±1.8	-0.2 (-0.7, 0.3)	22	7.9±1.8	0.2(-0.5, 0.9)*		65	0.4 (-0.2, 1.2)	0.212

Legend:

Data are expressed as mean ± standard deviation or mean (95% CI).

AC: doxorubicin plus cyclophosphamide; SD: standard deviation.

†Within-Group Difference in Mean Change and Interception was based on linear mixed models, controlling for group, time and interaction (fixed effects).

‡Adjusted Between-Group Difference was based on linear mixed model, controlling for group, time and interaction (fixed effects) and for baseline outcome, heart rate, and total cumulative doxorubicin dose (covariate).

*denotes a significant p-value<0.05.

Appendixes – Study 6

Table A1: Changes in EORTC QLQ-C30 domains in patients performed neoadjuvant chemotherapy

	Usual Care			Exercise					Between-group Difference in mean Change from Baseline			Clinically relevant differences between groups[a]
	n	Mean ± SD	Difference in Mean Change from Baseline Mean (95%CI)	*n*	Mean ± SD	Difference in Mean Change from Baseline Mean (95%CI)	Time	Interaction	n	Mean (95%CI)	*p*	
EORTC QLQ-C30 Summary Score							<0.001	0.097				
t0	34	87.40±8.65		30	87.93±6.73							
t1	34	80.71±11.94	-6.69 (-11.07; -2.31)**	29	83.33±8.45	-4.56 (-9.29; 0.15)			63	2.15 (-2.86; 7.17)	0.397	NI
t2	30	77.13±14.43	-10.62 (-15.19; -6.05)**	28	83.50±9.46	-4.72 (-9.50; 0.05)			58	5.91 (0.72; 11.10)	0.026	NI
Global Health Status/ Quality of Life							0.002	0.357				
t0	34	66.91±13.98		30	65.27±17.79							
t1	34	58.57±17.10	-8.33 (-16.55; -0.11)*	29	59.19±17.30	-5.98 (-14.83; 2.86)			63	2.58 (-7.32; 12.49)	0.606	Trivial
t2	30	55.27±18.75	-11.96 (-20.51; -3.41)*	28	60.71±14.31	-5.30 (-13.67; 4.21)			58	7.55 (-2.65; 17.75)	0.145	Small
FUNCTIONAL DOMAINS												
Physical Functioning							<0.001	<0.001				
t0	34	90.39±9.45		30	90.22±9.11							
t1	34	80.39±13.02	-10.00 (14.74; -5.25)**	29	83.36±10.76	-5.92 (-11.03; -0.80)*			63	4.02 (-1.70; 9.74)	0.166	Trivial
t2	30	75.55±15.98	-15.34 (-20.29; -10.39)**	28	87.14 ± 11.70	-3.75 (-8.92; 1.42)			58	11.49 (5.60; 17.38)	<0.001	Small

Table A1: Continued

Role Functioning							<0.001	0.043			
t0	34	91.17±18.45		30	87.77±15.73						
t1	34	75.00±22.19	-16.17 (-26.35; -6.00)**	29	81.03±18.75	-6.61 (-17.56; 4.33)			63	9.85 (-2.34; 22.05)	0.112	Small
t2	30	68.33±27.45	-23.99 (-34.56; -13.41)**	28	79.77±18.88	-8.16 (-19.23; 2.90)			58	17.09 (4.54; 29.65)	0.008	Small
Emotional Functioning							0.042	0.707			
t0	34	69.11±17.94		30	70.83±22.71						
t1	34	74.75±16.08	5.63 (-3.35; 14.63)	29	78.16±18.42	7.60 (-2.08; 17.29)			63	2.40 (-8.76; 13.58)	0.670	NI
t2	30	68.88±22.41	-0.93 (-10.30; 8.43)	28	75.00±19.24	3.71 (-6.08; 13.51)			58	5.07 (-6.37; 16.53)	0.381	NI
Cognitive Functioning							0.109	0.202			
t0	34	86.76±20.42		30	86.66±19.27						
t1	34	80.88±18.86	-5.88 (-13.31; 1.54)	29	86.78±14.34	-0.24 (-8.26; 7.76)			63	5.30 (-4.29; 14.91)	0.275	Small
t2	30	77.77±21.59	-8.84 (-16.59; -1.08)*	28	86.30±13.64	-0.81 (-8.92; 7.29)			58	7.53 (-2.25; 17.33)	0.130	Small
Social Functioning							<0.001	0.703			
t0	34	88.23±23.03		30	88.33±16.46						
t1	34	77.45 27.79	-10.78 (-21.47; -0.09)*	29	78.73±23.10	-9.90 (-21.41; 1.61)			63	0.44 (-13.11; 13.99)	0.949	Trivial
t2	30	74.99±25.80	-14.48 (-25.61; -3.34)**	28	79.76±20.96	-9.22 (-20.87; 2.41)			58	5.66 (-8.17; 19.49)	0.418	Small

Table A1: Continued

SYMPTOMS DOMAINS											
Fatigue							<0.001	0.025			
t0	34	15.35± 16.41		30	20.73±16.69						
t1	34	36.27± 20.15	20.91 (11.69; 30.13)**	29	31.41±14.48	10.45 (0.53; 20.37)*			63	-10.95 (-21.93; 0.02)	0.051	Small
t2	30	41.11± 24.26	26.14 (16.55; 35.72)**	28	31.34±19.13	10.88 (0.85; 20.91)*			58	-15.64 (-26.95; 4.33)	0.007	Medium
Nausea and Vomiting							0.001	0.351			
t0	34	1.47±4.79		30	2.22±5.76						
t1	34	8.33±14.36	6.86 (-0.38; 14.10)	29	9.77±14.44	7.54 (-0.23; 15.32)			63	-0.60 (-7.25; 8.47)	0.879	Trivial
t2	30	11.11±17.68	9.62 (2.13; 17.10)*	28	6.54±12.28	4.31 (-3.53; 12.16)			58	-5.19 (-13.36; 2.97)	0.210	Small
Pain							0.001	0.856			
t0	34	13.72±14.48		30	12.22±15.74						
t1	34	21.07±21.44	7.35 (-2.21; 16.92)	29	17.81±19.88	5.64 (-4.65; 15.94)			63	-1.60 (-13.38; 10.16)	0.787	Trivial
t2	30	26.11±26.14	12.89 (2.94; 22.85)*	28	21.42±20.71	9.59 (-0.82; 20.00)			58	-3.40 (-15.49; 8.69)	0.578	Trivial
Dyspnoea							0.041	0.905			
t0	34	5.88±12.89		30	1.11±6.08						
t1	34	8.82±14.92	2.94 (-3.61; 9.49)	29	2.29±8.59	1.75 (-5.87; 8.22)			63	-1.79 (-9.35; 5.77)	0.639	Trivial
t2	30	11.11±20.21	5.55 (-1.25; 12.37)	28	5.95±12.99	4.79 (-2.33; 11.93)			58	-1.37 (-9.19; 6.44)	0.728	Trivial

Table A1: Continued

Insomnia							0.854	0.328			
t0	34	36.27±30.00		30	28.88±24.34						
t1	34	32.35±27.81	-3.92 (-17.95; 10.11)	29	33.33±35.63	4.49 (-10.61; 19.60)			63	8.52 (-8.42; 25.46)	0.321	Small
t2	30	33.33±26.26	-3.55 (-18.15; 11.05)	28	35.71±28.58	8.08 (-7.19; 23.36)			58	13.58 (-3.85; 31.01)	0.125	Medium
Appetite Loss							0.084	0.179			
t0	34	10.78±19.62		30	5.55±15.37						
t1	34	13.72±28.56	2.94 (-8.73; 14.61)	29	13.79±22.30	8.16 (-4.40; 20.74)			63	5.10 (-9.03; 19.23)	0.475	Small
t2	30	23.33±37.29	11.97 (-0.17; 24.13)*	28	9.52±18.93	3.71 (-8.99; 16.42)			58	-8.03 (-22.58; -6.50)	0.276	Small
Constipation							0.119	0.759			
t0	34	4.90±11.98		30	8.88±17.36						
t1	34	11.76±23.03	6.86 (-2.87; 16.59)	29	11.49±18.42	2.55 (-7.91; 13.02)			63	-4.56 (-15.92; 6.79)	0.427	Trivial
t2	30	4.44±14.47	-0.45 (-9.38; 8.61)	28	7.14±20.99	-1.89 (-12.47; 8.67)			58	-1.80 (-13.54; 9.93)	0.761	Trivial
Diarrhea							<0.001	0.088			
t0	34	0.98±5.71		30	1.11±6.08						
t1	34	6.86± 3.67	5.88 (-0.44; 12.20)	29	5.74±12.81	4.62 (-2.17; 11.42)			63	-1.28 (-8.53; 5.96)	0.726	Trivial
t2	30	12.22±18.53	11.75 (5.18; 18.32)**	28	4.76±14.94	3.58 (-3.29; 10.46)			58	-8.82 (-16.31; 1.32)	0.022	Medium

Table A1: Continued

Financial Difficulties							0.385	0.612				
t0	34	9.80±26.62		30	13.33±25.67							
t1	34	17.64±24.93	7.84 (-4.91; 20.59)	29	13.79±20.92	0.34 (-13.37; 14.06)			63	-7.84 (-23.54; 7.85)	0.324	Small
t2	30	17.77±22.71	7.68 (-5.55; 20.93)	28	15.47±27.93	2.54 (-11.32; 16.40)			58	-4.41 (-20.53; 11.70)	0.588	Small

Legend:

Data are expressed as mean ± standard deviation or mean (95% CI).

Within-group and Between-group Difference in Mean Change was based on linear mixed models, controlling for group, time and interaction (fixed effects), and patient as a random effect and the baseline outcome and chemotherapy intent (neoadjuvant or adjuvant) were entered as covariates. Correction for multiple comparisons for Within-group and Between-group Difference in Mean Change analysis was performed by the Bonferroni method. [a]Interpreted as clinically relevant as defined by Cocks et al. 2011(11).

*Denotes a significant p-value <0.05 from baseline.

**Denotes a significant p-value <0.001 from baseline.

NI: not included in the guidelines defined by Cocks et al. 2011 (30).

Table A2: Changes in EORTC QLQ-C30 domains in patients receiving adjuvant chemotherapy

	Usual Care			Exercise					Between-group Difference in mean Change from Baseline			Clinically relevant differences between groups[a]
	n	Mean ± SD	Difference in Mean Change from Baseline Mean (95%CI)	*n*	Mean ± SD	Difference in Mean Change from Baseline Mean (95%CI)	Time	Interaction	n	Mean (95%CI)	*p*	
EORTC QLQ-C30 Summary Score							0.023	0.031				
t0	11	88.39±8.48		17	81.67±11.57							
t1	11	79.89±11.24	-8.50 (-17.05; 0.07)	16	81.10±12.40	-1.49 (-8.05; 5.89)			27	6.65 (-2.57; 15.88)	0.153	NI
t2	11	76.51±13.30	-11.88 (-20.39; -3.37)*	16	81.52±12.33	0.18 (-6.80; 7.16)			27	12.30 (3.06; 21.53)	0.010	NI
Global Health Status/ Quality of Life							0.393	0.355				
t0	11	56.06±22.07		17	53.92±11.82							
t1	11	56.81±26.30	0.75 (-13.30; 14.81)	16	63.02±12.53	8.99 (-2.90; 20.80)			27	7.94 (-8.35; 24.25)	0.337	Small
t2	11	52.27±20.10	-3.78 (-17.84; 10.27)	16	60.41±15.95	6.17 (-5.36; 17.70)			27	9.62 (-6.67; 25.93)	0.198	Small
FUNCTIONAL DOMAINS												
Physical Functioning							0.007	0.005				
t0	11	84.24±12.74		17	78.82±17.12							
t1	11	61.81±25.31	-22.42 (-37.08; -7.76)*	16	79.16±14.80	0.52 (-12.54; 11.50)			27	21.16 (6.11; 36.21)	0.007	Medium
t2	11	61.81±22.32	-22.42 (-37.08; -7.76)*	16	80.41±18.03	1.39 (-10.63; 13.42)			27	23.55 (8.50; 38.60)	0.003	Large
Role Functioning												
t0	11	78.78±25.91		17	67.64±27.93		0.300	0.045				
t1	11	74.24±17.26	-4.54 (-25.59; 16.50)	16	75.08±22.77	5.55 (-11.69; 22.81)			27	8.71 (-14.20; 31.85)	0.450	Small
t2	11	57.57±29.21	-21.21 (-42.25; -0.16)*	16	73.95±22.74	6.73 (-10.51; 23.99)			27	28.64 (5.05; 51.78)	0.017	Medium
Emotional Functioning							0.889	0.311				
t0	11	76.51±21.67		17	64.70±24.38							
t1	11	72.72±23.29	-3.78 (-21.09; 13.51)	16	73.43±20.90	8.14 (-6.06; 22.34)			27	11.65 (-9.00; 32.32)	0.259	NA
t2	11	71.21±28.95	-5.30 (-22.61; 12.00)	16	71.35±21.93	6.91 (-7.29; 21.11)			27	12.53 (-8.13; 33.19)	0.225	NA

Table A2: Continued

Cognitive Functioning							0.054	0.218			
t0	11	92.42±15.57		17	79.41±23.22						
t1	11	84.84±21.62	-7.57 (-23.63; 8.48)	16	84.37±18.72	4.14 (-9.02; 17.32)			27	11.34 (-5.81; 28.51)	0.189	Medium
t2	11	75.75±22.80	-16.66 (-32.72; -0.60)*	16	76.04±24.31	-2.94 (-16.12; 10.23)			27	13.97 (-3.19; 31.13)	0.108	Medium
Social Functioning							0.044	0.029			
t0	11	96.97±10.04		17	78.43±18.41						
t1	11	80.30±17.97	-16.66 (-32.58; -0.75)*	16	76.04±29.16	-3.25 (-16.31; 9.80)			27	13.13 (-5.67; 31.94)	0.164	Medium
t2	11	77.27±17.11	-19.69 (-35.61; -3.78)*	16	81.25±21.83	-3.07 (-9.98; 16.13)			27	23.62 (-26.95; -4.33)	0.015	Large
SYMPTOMS DOMAINS											
Fatigue							0.028	0.009			
t0	11	25.25±22.81		17	30.71±19.45						
t1	11	44.44±25.82	19.19 (2.30; 36.08)*	16	28.47±17.67	-0.4 (-14.31; 13.40)			27	-18.65 (-37.24; -0.07)	0.049	Medium
t2	11	50.50±26.92	25.25 (8.36; 42.14)*	16	28.47±26.59	-2.3 (-16.22; 11.50)			27	-27.79 (-46.38; -9.21)	0.004	Large
Nausea and Vomiting							0.012	0.316			
t0	11	1.51±5.02		17	2.94±8.80						
t1	11	10.60±18.66	9.09 (-2.02; 20.38)	16	11.45±16.90	8.46 (-0.79; 17.71)			27	-0.60 (-7.25; 8.47)	0.879	Trivial
t2	11	7.57±17.26	6.06 (-5.23; 17.35)	16	1.04±4.16	2.10 (-11.36; 7-14)			27	-5.19 (-13.36; 2.97)	0.210	Small
Pain							0.159	0.959			
t0	11	13.63 17.97		17	22.54±20.83						
t1	11	10.60±15.40	-3.03 (-23.34; 17.28)	16	14.58±17.07	-5.39 (-22.05; 11.25)			27	-2.3.1 (-12.39; 7.76)	0.651	Trivial
t2	11	21.21±29.89	7.57 (-12.73; 27.88)	16	27.08±29.10	4.71 (-11.94; 21.36)			27	-3.88 (-14.18; 6.41)	0.457	Trivial
Dyspnoea							0.028	0.937			
t0	11	3.03±10.04		17	1.96±8.08						
t1	11	6.06±13.48	3.03 (-9.69; 15.75)	16	2.08±8.33	0.70 (-9.71; 11.11)			27	-1.53 (-7.99; 4.92)	0.639	Trivial
t2	11	12.12±16.81	9.09 (-3.63; 21.81)	16	10.41±20.06	8.40 (-2.01; 18.82)			27	-0.82 (-7.43; 5.79)	0.806	Trivial

Table A2: Continued

Insomnia							0.539	0.358				
t0	11	30.30 ± 31.46		17	19.60 ± 16.90							
t1	11	27.27 ± 32.72	-3.03 (-31.21; 25.15)	16	37.49 ± 31.91	17.98 (-5.06; 41.03)			27	13.20 (-1.57; 27.97)	0.079	Medium
t2	11	30.30 ± 31.46	-3.55 (-28.18; 28.18)	16	33.33 ± 27.21	13.34 (-9.70; 36.39)			27	13.29 (-1.77; 28.36)	0.083	Medium
Appetite Loss							0.071	0.065				
t0	11	3.03 ± 10.04		17	5.88 ± 14.44							
t1	11	18.18 ± 34.52	15.15 (-6.23; 36.55)	16	16.66 ± 24.34	10.72 (--6.79; 28.23)			27	2.59 (-9.03; 14.95)	0.627	Trivial
t2	11	24.24 ± 33.63	21.21 (-0.19; 42.61)*	16	2.08 ± 8.33	-3.98 (-21.49; 13.52)			27	-13.32 (-25.56; -1.08)	0.033	Small
Constipation							0.059	0.448				
t0	11	3.03 ± 10.49		17	21.56 ± 31.04							
t1	11	15.15 ± 22.91	12.12 (-7.68; 31.92)	16	22.91 ± 35.93	1.39 (-14.85; 17.63)			27	-6.17 (-16.03; 3.68)	0.218	Small
t2	11	3.03 ± 10.49	-3.55 (-19.80; 19.80)	16	10.41 ± 20.06	-12.00 (-28.25; 4.24)			27	-5.62 (-15.72; 4.47)	0.273	Small
Diarrhea							0.435	0.168				
t0	11	0.00 ± 0.00		17	1.96 ± 6.80							
t1	11	3.03 ± 10.49	3.03 (-10.38; 16.44)	16	0.00 ± 0.00	-1.96 (-12.91; 8.99)			27	-2.99 (-9.41; 3.42)	0.358	Trivial
t2	11	0.00 ± 0.00	-7.10 (-13.41; 13.41)*	16	10.41 ± 26.43	8.45 (-2.49; 19.41)			27	-3.74 (-10.34; 2.84)	0.263	Small
Financial Difficulties							0.349	0.323				
t0	11	18.18 ± 22.91		17	21.56 ± 33.21							
t1	11	18.18 ± 22.91	0.00 (-23.59; 23.59)	16	37.49 ± 34.15	17.97 (-1.37; 37.33)			27	18.90 (-7.64; 45.44)	0.157	Medium
t2	11	15.15 ± 17.40	-3.03 (-26.62; 20.56)	16	31.24 ± 30.95	10.38 (-8.96; 29.73)			27	14.83 (-11.711; 41.37)	0.264	Medium

Legend:

Data are expressed as mean ± standard deviation or mean (95% CI).

Within-group and Between-group Difference in Mean Change was based on linear mixed models, controlling for group, time and interaction (fixed effects), and patient as a random effect and the baseline outcome and chemotherapy intent (neoadjuvant or adjuvant) were entered as covariates. Correction for multiple comparisons for Within-group and Between-group Difference in Mean Change analysis was performed by the Bonferroni method. [a]Interpreted as clinically relevant as defined by Cocks et al. 2011 (30).

*Denotes a significant p-value <0.05 from baseline.

**Denotes a significant p-value <0.001 from baseline.

NI: not included in the guidelines defined by Cocks et al. 2011 (30).

Table A3: Changes in functional capacity parameters in patients receiving neoadjuvant chemotherapy

	Usual Care			Exercise					Between-group Difference in mean Change from Baseline		
	n	**Mean ± SD**	**Difference in Mean Change from Baseline Mean (95%CI)**	***n***	**Mean ± SD**	**Difference in Mean Change from Baseline Mean (95%CI)**	**Time**	**Interaction**	**n**	**Mean (95%CI)**	***p***
Maximum Voluntary Handgrip Strength											
Tumor/Surgery Upper Limb Side (kg)							<0.001	0.095			
t0	34	26.11±5.03		29	26.54±5.68						
t1	33	24.30±4.90	-1.81 (-2.98; -0.64)**	28	25.97±4.65	-0.64 (-1.91; 0.62)**			61	1.14 (-0.29; 2.59)	0.118
t2	30	24.05±4.24	-2.38 (-3.59; -1.17)**	23	25.78±4.06	-0.83 (-2.20; 0.52)**			53	1.57 (0.05; 3.09)	0.043
Contralateral Upper Limb (kg)							0.001	0.020			
t0	34	25.55±4.69		29	26.36±4.86						
t1	33	24.37±4.60	-1.12 (-2.04; -0.21)*	28	26.42±4.32	-0.03 (-1.02; 0.95)			61	1.07 (-0.05; 2.20)	0.062
t2	30	23.91±4.48	-1.89 (-2.84; -0.94)**	23	25.92±4.30	-0.28 (-1.34; 0.78)			53	1.63 (0.44; 2.82)	0.008
30-second Chair Sit-to-Stand Test (repetitions)							0.032	<0.001			
t0	34	15.82 4.01		29	15.34±3.48						
t1	33	15.03±3.90	-0.72 (-2.06; 0.60)	28	18.32±3.87	2.87 (1.42; 4.32)**			61	3.51 (1.72; 5.31)	<0.001
t2	30	14.93±4.10	-0.96 (-2.34; 0.41)	23	17.82±3.80	2.23 (0.68; 3.79)*			53	3.10 (1.25; 4.94)	0.001

Legend:

* Denotes a significant p-value <0.05 from baseline.

** Denotes a significant p-value <0.001 from baseline.

Within-group and Between-group Difference in Mean Change was based on linear mixed models, controlling for group, time and interaction (fixed effects), and patient as a random effect and the baseline outcome and chemotherapy intent (neoadjuvant or adjuvant) were entered as covariates. Correction for multiple comparisons for Within-group and Between-group Difference in Mean Change analysis was performed by the Bonferroni method.

Table A4: Changes in functional capacity parameters in patients receiving adjuvant chemotherapy

	Usual Care			Exercise			Time	Interaction	Between-group Difference in mean Change from Baseline		
	n	**Mean ± SD**	**Difference in Mean Change from Baseline Mean (95%CI)**	***n***	**Mean ± SD**	**Difference in Mean Change from Baseline Mean (95%CI)**			**n**	**Mean (95%CI)**	***p***
Maximum Voluntary Handgrip Strength											
Tumor/Surgery Upper Limb Side (kg)							0.704	0.004			
t0	11	23.89±6.47		17	23.88±3.51						
t1	11	23.75±6.47	-0.13 (-2.45; 2.17)	17	24.76±3.19	0.87 (-0.98; 2.74)			28	1.01 (-1.31; 3.35)	0.385
t2	10	21.84±5.52	-2.24 (-4.64; 0.14)	15	25.79±3.38	1.99 (0.04; 3.94)*			25	4.29 (1.85; 6.73)	<0.001
Contralateral Upper Limb (kg)							0.257	0.003			
t0	11	24.50±4.34		17	25.50±3.91						
t1	11	24.29±4.17	-0.21 (-2.05; 1.63)	17	25.66±3.06	0.15 (-1.33; 1.63)			28	0.36 (1.65; 2.38)	0.716
t2	10	22.17±3.99	-2.39 (-4.31; -0.48)**	15	26.31±2.91	0.91 (-0.64; 2.46)			25	3.31 (1.23; 5.39)	0.003
30-second Chair Sit-to-Stand Test (repetitions)							0.040	0.002			
t0	11	13.36±3.64		17	15.70±4.51						
t1	11	14.45±3.93	1.09 (-1.28; 3.46)	17	17.82±4.54	2.11 (0.20; 4.03)*			28	1.02 (-1.53; 3.58)	0.421
t2	10	12.00±4.78	-1.65 (-4.11; 0.80)	15	18.66±4.30	2.90 (0.90; 4.90)*			25	4.55 (1.02; 7.20)	0.001

Legend:

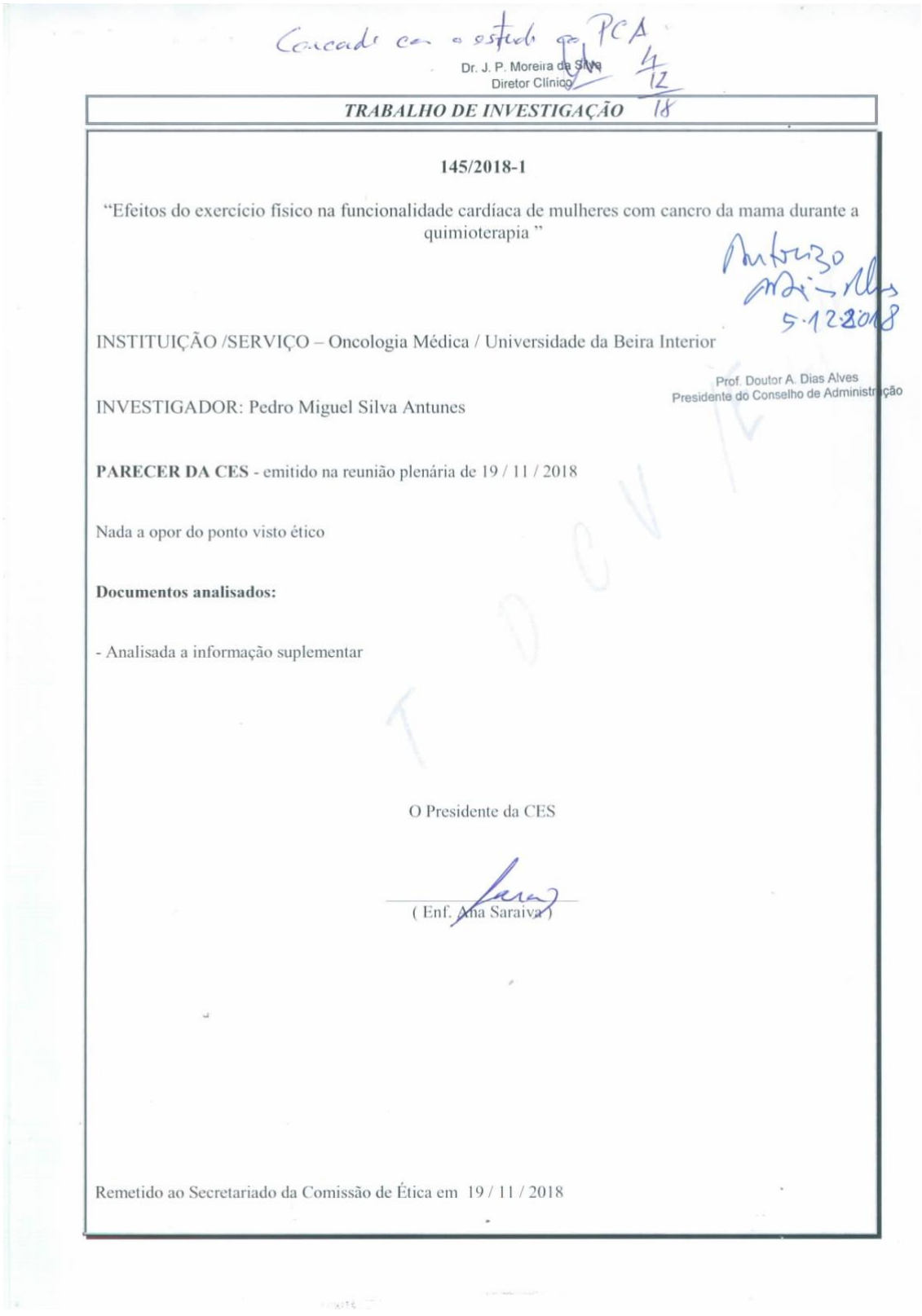
* Denotes a significant p-value <0.05 from baseline.

** Denotes a significant p-value <0.001 from baseline.

Within-group and Between-group Difference in Mean Change was based on linear mixed models, controlling for group, time and interaction (fixed effects), and patient as a random effect and the baseline outcome and chemotherapy intent (neoadjuvant or adjuvant) were entered as covariates. Correction for multiple comparisons for Within-group and Between-group Difference in Mean Change analysis was performed by the Bonferroni method.

Annexes

Opinion of the Ethics Committee of the Centro Hospitalar Vila Nova de Gaia/Espinho.



Concede-se o estudo do PCA
Dr. J. P. Moreira da Silva
Diretor Clínico
4/12/18

TRABALHO DE INVESTIGAÇÃO

145/2018-1

"Efeitos do exercício físico na funcionalidade cardíaca de mulheres com cancro da mama durante a quimioterapia "

Autorizo
5-12-2018
Prof. Doutor A. Dias Alves
Presidente do Conselho de Administração

INSTITUIÇÃO /SERVIÇO – Oncologia Médica / Universidade da Beira Interior

INVESTIGADOR: Pedro Miguel Silva Antunes

PARECER DA CES - emitido na reunião plenária de 19 / 11 / 2018

Nada a opor do ponto visto ético

Documentos analisados:

- Analisada a informação suplementar

O Presidente da CES

(Enf. Ana Saraiva)

Remetido ao Secretariado da Comissão de Ética em 19 / 11 / 2018

Free and Informed Consent to participate in research.

CENTRO HOSPITALAR VILA NOVA DE GAIA/ESPINHO

CONSENTIMENTO INFORMADO, LIVRE E ESCLARECIDO PARA PARTICIPAÇÃO EM INVESTIGAÇÃO

de acordo com a Declaração de Helsínquia[1] e a Convenção de Oviedo[2]

Por favor, leia com atenção a seguinte informação. Se achar que algo está incorrecto ou que não está claro, não hesite em solicitar mais informações. Se concorda com a proposta que lhe foi feita, queira assinar este documento.

Título do estudo: Efeitos do exercício físico na funcionalidade cardíaca de mulheres com cancro da mama durante o tratamento de quimioterapia neoadjuvante ou adjuvante.

Enquadramento:

Esta investigação, que decorre no Serviços de Oncologia Médica do Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E), é realizada num âmbito académico, da Universidade da Beira Interior, através do doutorando Pedro Miguel da Silva Antunes, orientado pela professora dra. Dulce Esteves, dra. Ana Joaquim.

Explicação do estudo:

O tratamento com quimioterapia afeta substancialmente a capacidade física, a funcionalidade cardíaca e, consequente, a qualidade de vida. Para o presente estudo, pretende-se avaliar os efeitos que o exercício físico exerce na capacidade física, funcionalidade cardíaca e na qualidade de vida de mulheres com cancro da mama durante o tratamento com quimioterapia.

São selecionadas mulheres com confirmação histológica de carcinoma invasor da mama em estádio I-III e decisão de quimioterapia neoadjuvante ou adjuvante pela Consulta de Grupo Multidisciplinar. As pacientes que aceitem participar no presente estudo serão aleatoriamente divididas em:

- Grupo de Intervenção: realizará um programa de exercício físico supervisionado durante o tratamento de quimioterapia.

- Grupo de controlo: não realiza um programa de exercício físico supervisionado durante o tratamento de quimioterapia.

Desta forma, será objeto de estudo a análise dos efeitos de um programa de exercício físico supervisionado nos parâmetros relativos à:

- Funcionalidade cardíaca

a) Fração de ejeção do ventrículo esquerdo, avaliada, como habitualmente, por ecocardiograma

b) Biomarcadores cardíacos, em análise sanguínea habitualmente realizada para a validar os tratamentos de quimioterapia.

c) A variabilidade da frequência cardíaca que é um método não invasivo que permite determinar o tempo entre os batimentos cardíacos. Este parâmetro é avaliado com um cardiofrequêncimetro. É pretendido que a recolha seja feita durante 10 minutos, numa sala adequada, e que os doentes permaneçam confortavelmente sentados.

d) Frequência cardíaca de repouso, número de batimentos cardíacos por minuto.

[1] http://portal.arsnorte.min-saude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf

[2] http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf

e) Frequência cardíaca de recuperação, diferença entre o número de batimentos cardíacos por minuto observado nos 60 e 120 segundos após o término do teste cardiopulmonar.

- Aptidão física

a) Avaliação da capacidade cardiopulmonar: avaliada através de um teste cardiopulmonar numa passadeira, controlado e monitorizado por profissionais do serviço de cardiologia do CHVNG/E. Neste caso é pedido que a paciente caminhe ou corra numa passadeira até à fadiga voluntária.

b) Força de preensão, medida com ajuda de um dinamómetro manual.

c) Funcionalidade dos membros inferiores, analisada através do teste levantar e sentar durante 30 segundos.

- **Qualidade de vida relacionada com a saúde e fadiga**, pela aplicação de um breve questionário ao qual que lhe pedimos que responda.

Estes parâmetros serão recolhidos em três momentos distintos (na semana anterior ao início do tratamento, na semana seguinte à conclusão do tratamento e passados três meses deste período) que corresponderão a vindas programadas ao Hospital.

Confidencialidade e anonimato:

Informa-se que a sua participação é voluntária, podendo desistir a qualquer momento sem que por isso venha a ser prejudicado nos cuidados de saúde prestados pelo CHVNG/E.

Identificação Investigador

Nome: Pedro Miguel da Silva Antunes

Assinatura: _____

Identificação da pessoa que pede o consentimento (preencher se for diferente do investigador)

Nome:

N.º Cédula Profissional:

Assinatura: _____

Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pela/s pessoas/s que acima assina/m. Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências. Desta forma, aceito participar neste estudo e permito a utilização dos dados que de forma voluntária forneço, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pelo/a investigador/a.

Nome: _____ Processo Clínico n.º _____

Assinatura: _____ Data: __ /__ /_____

ESTE DOCUMENTO, COMPOSTO DE ... PÁGINA/S, É FEITO EM DUPLICADO:
UMA VIA PARA O/A INVESTIGADOR/A, OUTRA PARA A PESSOA QUE CONSENTE

Mod. CIELPI01