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RESEARCH

Adherence, safety, and satisfaction of a cardio-oncology rehabilitation program framework versus community exercise training for cancer survivors: findings from the CORE trial

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Abstract

Purpose To assess safety, satisfaction, and overall adherence of a center-based cardiac rehabilitation (CBCR) program for cancer survivors at increased cardiovascular (CV) risk, compared to community-based exercise training (CBET).

Methods The CORE study was a single-center, prospective, randomized controlled trial enrolling cancer survivors exposed to cardiotoxic cancer treatment and/or with previous CV disease. Participants were randomized to an 8-week CBCR program or CBET, twice a week. Overall feasibility (consent, retention, and completion rates), intervention adherence (percentage of exercise sessions attended), and safety were assessed. Adverse events (AEs) were registered, and participants' satisfaction was measured at the end of the study.

Results Eighty out of 116 potentially eligible individuals were included; consent rate was 72.4%, and 77 (96.2%) started the study (retention rate 100% in CBCR vs 92.5% in CBET); completion rate was 92.5%. Intervention adherence was higher in CBCR ($90.3 \pm 11.8\%$ *vs* $68.4 \pm 22.1\%$, $p < 0.001$). Exercise-related AEs were mainly related to musculoskeletal conditions in both groups (7 in CBCR vs 20 in CBET, $p < 0.001$), accounting for exercise prescription modification in 47 sessions (18 (3.3%) in CBCR vs 29 (7.2%) in CBET, $p = 0.006$), none motivating exercise discontinuation. No participants reported major CV events. Overall, the satisfaction with the different aspects of the programs (e.g., expectations, monitoring) was higher in the CBCR.

Conclusion This exploratory analysis of the CORE trial suggests that both exercise-based interventions are feasible and safe in this setting. The higher intervention adherence and patient satisfaction in CBCR suggest that this comprehensive approach could be of interest in this population.

Keywords Cancer survivors · Cardiac rehabilitation · Cardiovascular risk · Exercise training

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Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in cancer survivors [1–4], with several studies reporting on an important burden in terms of both cardiovascular risk factors (CVRF) and cardiovascular (CV) mortality among these individuals [5–8]. Given these issues, strategies aimed at mitigating CV risk in this population have progressively gained the spotlight [3, 9–11].

The potential benefits of exercise-based interventions across different stages of the cancer continuum have been an area of increasing interest [10–12]. In this regard, current recommendations highlight the importance of risk assessment and the referral for physical activity (PA) and exercise training (ET) [11–15]. Of note, the American Heart Association (AHA) has suggested a framework to refer cancer survivors with higher CV risk to a cardio-oncology rehabilitation program, including several components ranging from ET, nutritional support, psychological counselling, and overall CVRF optimization [16, 17]. These programs comprise several of the core components of contemporary cardiac rehabilitation (CR), while also emphasizing many of the specificities of oncologic settings [16, 18–20].

While over the years different studies have highlighted the possible benefits of these programs, the overall effects of a center-based cardiac rehabilitation (CBCR) program have not been fully ascertained [21, 22]. Moreover, there is still a need for more data on the feasibility, acceptability, and safety of this approach in specific subgroups of cancer survivors and in different settings. Indeed, when addressing the current paradigm concerning CR (as related specifically to CV patients, without a primary focus on cancer survivors), and even when considering the plethora of data attesting to its central role in different CVD, reports have nonetheless underscored several barriers to this intervention, leading to pitfalls such as low adherence rates [23–25]. As such, the question of whether cardio-oncology rehabilitation would be a feasible and acceptable model in different oncological settings is of pivotal importance.

Given this background, we aimed to assess the feasibility and overall safety of a CBCR program framework in cancer survivors exposed to cardiotoxic cancer treatment and/or with previous CVD. Furthermore, this exploratory analysis also aimed to analyze the motives for declining participation in the trial as well as exclusion criteria and subjects' satisfaction with this intervention or with an ET community intervention (the comparator in this trial).

Methods

Study design

The CORE study (NCT05132998) was a single-center, prospective, two-arm randomized controlled trial (RCT) performed in Portugal, assessing the impact of a CBCR framework as compared to a community-based exercise training intervention (CBET) in cancer survivors, with cardiorespiratory fitness (CRF) as the primary endpoint. The present study encompasses a pre-specified secondary analysis from this RCT aiming to assess safety, satisfaction, and overall adherence for both study arms.

Figure 1 shows the study flowchart. A full description of the study protocol design has been provided elsewhere [26], while a brief overview is provided below and in supplementary file 1.

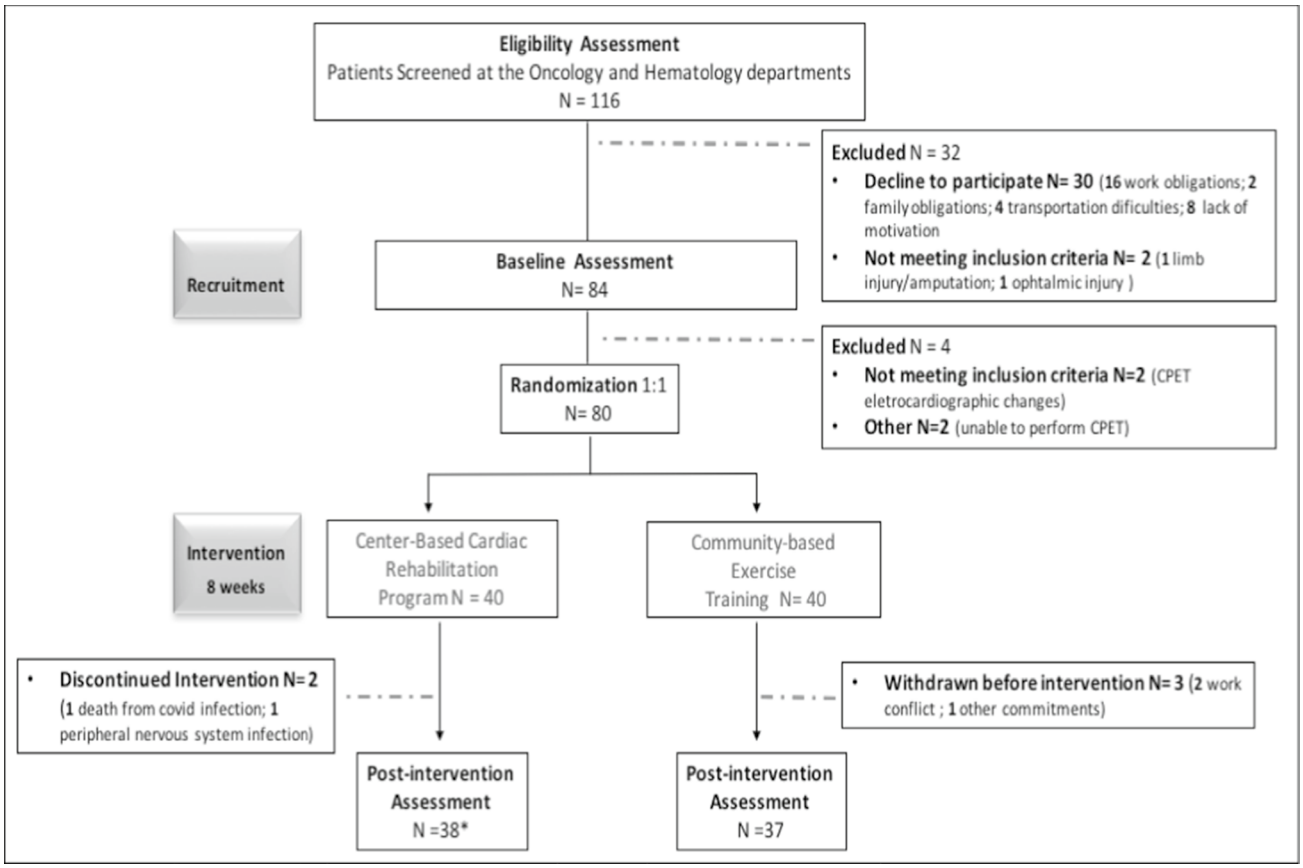
Participant recruitment and eligibility

Potentially eligible participants were recruited in person by assistant physicians at the Oncology and Hematology Departments, Centro Hospitalar Vila Nova de Gaia/Espinho. The principal investigator (PI) subsequently contacted individuals by telephone and arranged a first assessment to determine eligibility. Potentially eligible participants who provided written informed consent were then referred to medical screening and exercise testing (cardiopulmonary exercise stress testing (CPET)), prior to a final decision about eligibility. Reasons for exclusion, declining participation and screening failure were registered. Inclusion criteria were:

1) Cancer survivors aged > 18 years old in follow-up after conclusion of primary treatment with curative intent at least 2 months before enrolment
1.1) exposed to the following therapies: high-dose anthracycline (e.g., doxorubicin ≥ 250 mg/m.^{2}) or high-dose radiotherapy (thoracic wall, (RT ≥ 30 Gy); low-dose anthracycline or anti-human epidermal growth factor receptor-type 2 drugs (anti-HER2) alone plus ≥ 2 CVRF [24, 27] and/or age ≥ 60 years at cancer treatment; low-dose anthracycline followed by anti-HER2

and/or.

1.2) with the following cardiovascular medical background: history of coronary artery disease, moderate valvular disease; left ventricular ejection fraction < 50%.



*One patient completed all final assessments except for CPET. **Abbreviation:** CPET, cardiopulmonary exercise testing

Fig. 1 Participant flowchart

Exclusion criteria were as follows: (1) previous participation in a CR program; (2) contraindications to ET; (3) active cancer; (4) considered unsuitable as per PI judgment (namely due to expected inability to fulfil the proposed trial schedule).

Randomization and blinding

As previously reported [26], after baseline testing, eligible survivors were randomly assigned in a 1:1 ratio to undergo an eight-week CBCR or CBET. Computer-based randomization was generated using a permutated block design with random block sizes (e.g., six or eight) with stratification by two dichotomous variables: gender and age (<65 or ≥ 65 years old), with outcome communicated by telephone.

Intervention

Participants were randomized to either (1) CBCR, consisting of core components of an outpatient CR program [24, 27, 28], delivered by a multidisciplinary rehabilitation team in addition to standard care: ET (center-based, conducted by a physiotherapist and supervised by a physiatrist), nutritional individual counselling, psychological management and lifestyle behavior change (weekly group sessions, scheduled on the same days as the exercise sessions); or (2) CBET, consisting of standard care provided by the cancer survivors' physicians supplemented by ET, as recommended for cancer survivors, performed at a community-based facility, conducted by an exercise physiologist, with on-demand diet/nutritional counselling and psychosocial management [10, 13].

In both groups, participants attended a 1-h exercise class, twice a week for 8 weeks. The detailed exercise protocol has been described in a previous report [26], while an overview of the major components of each program is detailed in supplementary file 1.

Outcomes

Demographics

Demographical data and medical history (including age, sex, marital status, education level, employment status,

medication, CVRF, type of cancer, cancer treatment, time elapsed since cancer diagnosis and treatment, and co-morbidities) were obtained from the electronic medical records.

Feasibility outcomes and adherence

The outcomes used to assess the feasibility of both interventions were [29]:

1) Consent rate: the number of cancer survivors who met inclusion criteria divided by the number who consented to participate. Reasons for not participating in the study were registered.
2) Retention rate: the number of participants who remained in the study after enrollment, divided by the number of randomized patients.
3) Completion rate: the number of cancer survivors that completed all the evaluations during the defined timeline.
4) Intervention adherence: the total percentage of exercise sessions attended by participants allocated to the intervention. Reasons for dropping out were registered.

Safety

All the adverse events (AEs) and exercise-related complications during the intervention were registered based on the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) [30]. The consequences associated with AEs were recorded as follows: permanent discontinuation of ET before week 8 or exercise session treatment interruption, the total number of sessions requiring exercise dose/type modification.

Patient satisfaction

A questionnaire aimed at assessing patient satisfaction was delivered at the end of the study for both groups (5-item, with a 5-point Likert scale; 1 being very dissatisfied and 5 being very satisfied). The questionnaire is displayed in supplementary file 2.

Data analysis

Continuous variables are expressed as means ± standard deviations (SD) or medians with interquartile ranges for variables with skewed distributions. Categorical variables are presented as frequencies and percentages. The normality of the distribution was assessed using the Shapiro–Wilk test or skewness and kurtosis. Between-group differences were tested with unpaired *t*-tests or Mann–Whitney *U* tests. Between-group comparisons in categorical variables were compared with Fisher's exact test or the chi-square test, as appropriate. Statistical analyses were performed using Software Statistical Package for the Social Sciences version 24.0 (SPSS Inc., USA).

Results

Patient demographics, feasibility, and adherence parameters

Eighty-four out of 116 potentially eligible cancer survivors (screened over a 12-month period, from March 2021) consented to participate and completed baseline assessments (consent rate 72.4%). Of those, thirty-two (5 men; 27 women) were excluded; 30 declined to participate, and 2 suffered injuries after the eligibility assessment, not meeting inclusion criteria. The main reasons for not participating in the study are described in Fig. 1.

Briefly, work-related issues accounted for circa half of refusals. Four survivors were excluded after baseline assessment for not meeting inclusion criteria: CPET electrocardiographic (ECG) abnormalities requiring additional investigation ($n=2$); unable to perform treadmill test (inadaptation to treadmill, $n=1$; inadequate ECG display $n=1$). There were no significant differences in baseline characteristics between groups. An overview of patient demographics is depicted in Table 1.

After randomization, 77 (96.3%) cancer survivors remained in the study and started the program: The retention rate was 100% in CBCR vs 92.5% in the CBET group (3 participants withdrew after randomization: 2 mentioned that work-related issues were the reason for dropping out and 1 patient referred personal reasons/other commitments). During the intervention, 2 individuals in the CBCR group were excluded due to medical conditions (Fig. 1). After the 8-week intervention, 74 of the 80 randomized participants completed all the final assessments (completion rate 92.5%), since 1 patient in the CBCR completed all the assessments except the CPET (missed the evaluation schedule).

Intervention adherence (percentage of predicted exercise sessions attended) was significantly higher in the CBCR group in comparison to the CBET group (90.3 ± 11.8% *vs* 68.4 ± 22.1%, $p<0.001$) (Table 2). In the CBRC group, 18 (47.4%) participants attended 100% of the scheduled exercise sessions; 34 (89.5%) and 18 (48.6%) participants in CBCR and CBET respectively attended ≥ 80% of the sessions. In the CBCR group there were 59 missed sessions, whereas there were 187 missed sessions in the CBET group. Some of the reasons for missing exercise sessions were related to family obligations, medical conditions, or medical appointments (Table 2). In accordance with the study protocol, all participants in the CBCR group attended the educational and psychological management sessions. In the CBET group, 11 participants had nutritional follow-up and 24 received psychological support.

Table 1 Baseline patient characteristics

	CBCR ($N=40$)	CBET ($N=40$)
Age (years)	54.5 ± 14.1	53 ± 11.8
Gender		
Female	30 (75%)	31 (77.5%)
Male	10 (25%)	9 (22.5%)
Marital status		
Single	3 (7.5%)	5 (12.5%)
Married	30 (75%)	29 (72.5%)
Divorced	4 (10%)	6 (15%)
Widower	3 (7.5%)	0 (0%)
Highest education level		
Elementary school	24 (60%)	16 (40%)
High school	12 (30%)	17 (42.5%)
University graduate degree	4 (10%)	6 (15%)
Post graduate degree	0 (0%)	1 (2.5%)
Work situation		
Employed	23 (57.5%)	18 (45%)
Unemployed	7 (17.5%)	13 (32.5%)
Retired	10 (25%)	9 (22.5%)
Type of cancer		
Breast	26 (65%)	27 (67.5%)
Colorectal	1 (2.5%)	1 (2.5%)
Gastric	1 (2.5%)	0 (0%)
Prostate	1 (2.5%)	1 (2.5%)
Lymphoma	11 (27.5%)	11 (27.5%)
Time elapsed between cancer diagnosis and study enrollment (months)*	27 [34.5]	26 [21.5]
Cancer treatment		
Chemotherapy	38 (95%)	37 (92.5%)
Anthracyclines	35 (87.5%)	34 (85%)
Thoracic radiotherapy	24 (60%)	25 (62.5%)
Surgery	26 (65%)	27 (67.5%)
Adjuvant hormonal therapy	22 (55%)	21 (52.5%)
Tamoxifen	6 (15%)	12 (30%)
Tamoxifen + goserelin	3 (7.5%)	3 (7.5%)
Exemestan + goserelin	1 (2.5%)	0 (0%)
Letrozol	12 (30%)	6 (15%)
Trastuzumab	5 (12.5%)	2 (5%)
Pertuzumab	3 (7.5%)	1 (2.5%)
Cardiovascular risk factors		
Diabetes mellitus	2 (5%)	4 (10%)
Hypertension	16 (40%)	14 (35%)
Dyslipidemia	20 (50%)	20 (50%)
Smoking habits	5 (12.5%)	5 (12.5%)
Depression	12 (30%)	9 (22.5%)
Overweight	18 (45%)	14 (35%)
Obesity	12 (30%)	11 (27.5%)
Other comorbidities		
Ischemic heart disease	3 (7.5%)	4 (10%)
Atrial fibrillation	0 (0%)	1 (2.5%)
Heart failure	4 (10%)	5 (12.5%)
Valvular disease	1 (2.5%)	0 (0%)
Implantable cardioverter-defibrillator	1 (2.5%)	1 (2.5%)
Respiratory diseases**	7 (17.5%)	7 (17.5%)
Musculoskeletal diseases***	8 (20%)	8 (20%)
Others§	6 (15%)	5 (12.5%)
Left ventricular ejection fraction	59.0 [9.5]	59.0 [8.0]
Medication		
Anticoagulants	0 (0%)	1 (2.5%)
Anti-platelet therapy	3 (7.5%)	3 (7.5%)
Beta-blockers	6 (15%)	5 (12.5%)
Anxiolytics	11 (27.5%)	10 (25%)
Antidepressants	12 (30%)	9 (22.5%)
Diuretics	7 (17.5%)	7 (17.5%)
Statins	16 (40%)	14 (35%)
Nitrates	0 (0%)	1 (2.5%)
Fibrates	3 (7.5%)	2 (5%)
ACEI	5 (12.5%)	6 (15%)
ARA II	4 (10%)	7 (17.5%)
Sacubitril/valsartan	2 (5%)	0 (0%)
Calcium channel blockers	4 (10%)	1 (2.5%)
Insulin	0 (0%)	1 (2.5%)
Anti-diabetic agents****	2(5%)	4(10%)

ACEI angiotensin-converting enzyme inhibitor, *ARA* angiotensin II receptor antagonists, *BMI* body mass index

*Values are median [IQR]

**Asthma; chronic obstructive pulmonary disease

***degenerative joint disease

****Excluding insulin

§Thyroid diseases; hepatitis; human immunodeficiency virus infection; chronic herpes zoster infection; obstructive sleep apnea; chronic renal disease; peripheral artery disease; vertiginous syndrome

Safety

The AEs related and not related to exercise are summarized in Table 3. The CBET reported a significantly higher total number of AEs both related (27 vs 7, $p<0.001$) and not related to exercise (32 vs 18, $p<0.001$) than the CBCR. A full description of each AE per category and grade, as well as the number of modified exercise sessions, can be found in Supplementary file 1. The most common exercise-related AEs reported in both groups were related to musculoskeletal conditions (arthralgia, back pain), with a higher number of cases in CBET versus CBCR (20 vs 7, $p=0.001$) (Table 3). These musculoskeletal AEs led to exercise prescription modification (dose reduction/type modification during training) in 18 sessions (out of 549 attended sessions) in CBCR and 29 sessions (out of 405 attended sessions) in CBET (3.3% vs 7.2%, $p=0.006$) (Supplementary

Table 2 Intervention adherence

	CBCR ($N=38$)	CBET ($N=37$)
Exercise sessions attended (n, %)		
100%	18 (47.4%)	1 (2.7%)
≥ 80%	34 (89.5%)	18 (48.6%)
≤ 50%	0 (0%)	7 (18.9%)
Reasons for missing exercise sessions [no. of missed sessions (% of total prescribed sessions)]		
Family obligations	21 (3.5%)	39 (6.6%)
Scheduled exams/medical appointments	21 (3.5%)	32 (5.4%)
Medical conditions	10* (1.6%)	29** (4.9%)
Others/no reason	5 (0.8%)	84 (14.2%)
Transportation difficulties	2 (0.3%)	3 (0.5%)
Distance from home to intervention site (km)	11.2 ± 6.8	10.2 ± 8.0
Means of transportation (n, %)		
Own transportation	29 (76.3%)	25 (67.6%)
Taxi	1 (2.6%)	2 (5.4%)
Walking	2 (5.3%)	2 (5.4%)
Public transportation	6 (15.8%)	8 (21.6%)

*Covid-19 infection/isolation rules or reaction to vaccine ($n=8$); surgical procedure ($n=1$); gastrointestinal disorders ($n=1$)

**Covid-19 infection/isolation rules or reaction to vaccine ($n=12$); fatigue ($n=5$); tooth infection ($n=3$); gastrointestinal disorders ($n=2$); arthralgia ($n=5$); urinary tract infection ($n=2$)

Table 3 Adverse events (AEs) not related to exercise and AEs related to exercise

	CBCR ($N=38$)	CBET ($N=37$)	P value
AEs related to exercise (n, %)			
Musculoskeletal conditions	7 (18.4%)	20 (54.1%)	0.001
Fatigue	0(0%)	3(8.1%)	0.115
Cardiovascular conditions	0(0%)	4(10.8%)	0.054
Total	7 (18.4%)	27 (73.0%)	< 0.001
AEs not related to exercise (n, %)			
Musculoskeletal conditions	5 (13.2%)	13 (35.1%)	0.026
Fatigue	0 (0%)	6 (16.2%)	0.012
Others*	13 (34.2%)	13 (35.1%)	0.933
Total	18 (47.4)	32 (86.5)	< 0.001

*The full description of each AE category can be found in Supplementary file 1 (Table S2)

file 1 (Table 2)). Most of the AEs related to exercise were grade 1 according to the CTCAE v5.0 classification [30], none motivating exercise disruption or permanent discontinuation (Supplementary file 1). No participants reported major CV events during exercise.

The most common AEs not related to exercise were also associated with musculoskeletal conditions; CBET showed a significantly higher number of musculoskeletal AEs and fatigue not related to exercise than the CBCR (Table 3). Two cancer survivors discontinued the intervention due to serious AEs: 1 death due to severe Covid-19 infection; 1 *Herpes Zoster* infectious disease (grade 3 in CTCAE v5.0 classification [30]), causing exercise session discontinuation (Supplementary file 1 (Table 3)).

Patient satisfaction

The questionnaire applied at the end of the trial revealed an overall higher satisfaction with both programs (Table 4). In both groups, most item scores were between 4 and 5 (out of 5) showing that participants were satisfied or very satisfied with the programs. Yet, the number of participants reporting to be very satisfied was consistently higher in the CBCR vs CBET, e.g., when asked about how satisfied subjects were with the program (question 1), 86.8% of the participants in CBCR reported being very satisfied vs 45.9% in CBET ($p=0.001$). The same pattern was observed regarding program location ($p=0.001$) or monitoring by professionals throughout the intervention ($p=0.013$).

Discussion

This pre-specified analysis from the CORE study is, to the best of our knowledge, the first RCT to compare a contemporary CBCR program framework with CBET in cancer survivors, assessing feasibility, safety, and satisfaction. Overall, the main results suggest that both programs are feasible, as

Table 4 Participants' satisfaction questionnaire responses

Question	CBCR $N=38$					CBET $N=37$					p
	Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied	Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very Satisfied	
Answer	1	2	3	4	5	1	2	3	4	5	
How satisfied are you with the program in which you were included?	0 (0%)	0 (0%)	0 (0%)	5 (13.2%)	33 (86.8%)	0 (0%)	0 (0%)	5 (13.5%)	15 (40.5%)	17 (45.9%)	0.001
How satisfied are you regarding the expectations you had for the program you carried out?	0 (0%)	0 (0%)	0 (0%)	6 (15.8%)	32 (84.2%)	0 (0%)	0 (0%)	10 (27.0%)	8 (21.6%)	19 (51.3%)	0.001
How satisfied are you with the duration of the program in which you were included?	0 (0%)	4 (10.5%)	3 (7.9%)	11 (28.9%)	20 (52.6%)	1 (2.7%)	1 (2.7%)	9 (24.3%)	18 (48.6%)	8 (21.6%)	0.013
How satisfied are you with the place where the program took place?	0 (0%)	0 (0%)	0 (0%)	11 (28.9%)	27 (71.1%)	0 (0%)	2 (5.4%)	10 (27.0%)	12 (32.4%)	13 (35.1%)	0.001
What is your degree of satisfaction with the professionals monitoring throughout the program you have carried out?	0 (0%)	0 (0%)	0 (0%)	2 (5.3%)	36 (94.7%)	0 (0%)	1 (2.7%)	3 (8.1%)	9 (24.3%)	24 (64.9%)	0.013

indicated by recruitment, adherence, and safety outcomes. In several key parameters, including patient satisfaction, CBCR was superior to CBET.

In this study, 72.4% of potentially eligible cancer survivors initially screened accepted to participate and performed baseline assessments, suggesting that participants were motivated to engage in an exercise-based intervention. This value represents a higher rate compared to some of the other reports on this topic [21, 22, 31, 32]. In a study by Hobbard et al. on individuals with colorectal cancer, 31% of potentially eligible patients accepted to participate in the trial (which compared CR to usual care) [22]. While differences in terms of study designs (including populations under study and interventions) should be considered, the fact that in both arms of the CORE study an exercise intervention was delivered may have influenced these results. Indeed, in trials where participants are allocated to a control group with no intervention besides usual care, more dropouts could potentially be present [21, 22]. Interestingly, reviews focusing on barriers and facilitators for PA engagement reported that perceived health benefits, wellbeing, and healthcare professionals' guidance in a tailored exercise intervention could be important facilitators [33, 34]. When assessing the reasons for not participating, work obligations accounted for around half of motives reported. Of note, this may be related to the fact that the exercise sessions took place during working hours. It should also be noted that, to avoid possible confusion in terms of consent rate and adherence, timetables of exercise sessions were the same in both groups. These data are informative, as future studies should attempt to address scheduling issues as potential means to increase overall participation. Moreover, the high retention and completion rates in both groups should also be noted. As mentioned before, the fact that in both trial arms an intervention was delivered should be considered when assessing these data and when comparing these to other studies in the field [21, 22, 29].

In terms of adherence, there were significant differences between groups, favoring CBCR. Notably, absences were more frequent in CBET, with a relevant number of cases (14.2%) of missing sessions without any specific reason attributed to by participants. Several potential factors may be related to these findings. In this regard, the multidisciplinary nature of CR, encompassing close counselling and education, motivational sessions, and peer group support, could potentially help in explaining (at least in part) these data [24]. Moreover, the hospital setting of the CR unit may also have contributed to compliance with the scheduled sessions. It has been suggested that lifestyle behavioral interventions and the encouragement for exercise beyond supervised sessions, as recommended in CR programs, may increase adherence rates [35]. Furthermore, sessions delivered by the program's psychologist addressing self-efficacy and behavioral skills could also have reinforced participant's

motivation [36, 37]. Reports suggest that cancer survivors and individuals with CVD may share common conditions such as those related to sleep disorders, fatigue, sexual problems, anxiety, and depression, suggesting that a comprehensive rehabilitation program could be of interest, so these motivational and educational group sessions may have also contributed to improving adherence rates in CBCR [36–38].

The difficulties encountered due to the pandemic situation experienced along the study period should also be recalled, with some participants, in both groups, missing exercise sessions due to Covid-19 infection or isolation rules, which may have negatively affected feasibility rates.

Safety considerations, especially in high-risk CV patients, constitute a particular concern to determine the appropriate level of medical supervision advised according to clinical determinants [24]. Exercised-based interventions addressing patients living with and beyond cancer have been systematically recognized as safe strategies [39–41]. However, many studies do not present a comprehensive analysis of AEs related or unrelated to exercise during ET interventions. Recent data examining safety profiles in exercise-based interventions in oncologic settings indicate that several studies contain no mention of AEs, suggesting an incomplete report [39, 42]. The present findings suggest that exercise is a safe strategy, with no serious AEs related to ET having been reported in either group. Nonetheless, all participants underwent a CPET before starting the program, making it possible to obtain important information in terms of risk stratification associated with exercise practice [16]. It should be highlighted that two participants were excluded after baseline assessment due to abnormalities during CPET, in need of further investigation. The recent AHA statement illustrates the potential role of the CPET prior to beginning a structured cardio-oncology rehabilitation intervention in high-risk patients, a concept reinforced by the present data [16]. Interestingly, in a previous study comprising a CR program for cancer survivors without prior CVD, 2 patients (out of 25 enrolled) were withdrawn due to serious cardiac AEs (arrhythmias) [32].

As detailed in Table 3 and supplementary file 1, most of AEs were musculoskeletal. This finding underscores the need for an integrative approach, as a multidisciplinary team able to both address these as well as other potential needs specific to cancer survivors can be pivotal in this type of programs [35]. These skills proved to be particularly important in addressing possible musculoskeletal disorders. Of note, differences in aerobic exercise between the two study arms (as depicted in supplementary file 1) may have contributed to the differences found regarding AEs, as well as possibly influencing the adherence and satisfaction results.

Regarding participant's satisfaction, the questionnaire revealed a high level of satisfaction with both interventions, although with higher scores in the CBCR group (Table 4). In this background, the fact that 84.2% of individuals in CBCR indicated that the intervention met initial expectations ("very satisfied") should be highlighted. This contrasts with 51.3% of participants in CBET, suggesting that cancer survivors may prefer an intervention that takes place in a clinical setting with a multidisciplinary outlook.

Given the paramount role of these programs in terms of morbidity and quality of life in CVD in general, and the expanding interest in oncologic settings, current data from these analyses could be highly informative in helping improve future trial designs (namely in comparison to other modalities), to enhance overall access and allow for optimization of tailoring to the needs of different patient groups [18, 27, 43, 44]. In addition, and given the lack of data on this topic, the findings derived from this contemporary pragmatic study could also be of value by providing novel insights into this complex field.

Limitations

Some limitations should be considered when analyzing the present data. Firstly, participants were derived from a single center, on a limited number of individuals [26]. As such, generalization of these findings to other settings should be cautious. Secondly, due to the impossibility of blinding cancer survivors and those who delivered the intervention, the open design of this study may have influenced retention rates in both groups. Moreover, while adherence to exercise sessions was assessed, additional data related to exercise intensity adherence (during exercise sessions) was not analyzed. Thirdly, as described in the "Results" and "Discussion" both the COVID-19 pandemic and timing of the interventions (with possible limitations in terms of access to sessions during work hours) should also be considered. In addition, differences in terms of design between exercise modalities should be further acknowledge, as detailed above. Finally, it should be noted that the primary endpoint in the CORE trial was CRF. Although the present study derives from a pre-specified secondary analysis, this point should be further considered when interpreting the data, which should be viewed, at this point, as hypothesis generating. Albeit this, in view of the major hurdles related to both the implementation and adherence to exercise-based programs (encompassing CR) which have been previously reported in different clinical contexts, specifically addressing these secondary outcomes in detail could be of substantial importance, as to try to optimize and overcome some of these potential barriers [23, 25, 33]. In addition, given the specificities associated with the survivorship continuum (namely when considering different types of cancers, treatments, and comorbidities), assessing the safety of these approaches

based on a framework reflective of clinical practice can also provide important ancillary data [16, 33]. While these points should be acknowledged, we believe that the current data derived from a contemporary RCT provide a useful and pragmatic framework for future larger studies on this topic of major clinical importance.

Conclusion

The CORE trial suggests that both exercise-based interventions are feasible and safe for cancer survivors with high CV risk. The higher adherence to CBCR when compared to CBET, as well as differences in terms of patient satisfaction, suggest that this model may be of particular interest in this challenging and complex population.

Abbreviations *AHA*: American Heart Association; *BMI*: Body mass index; *CBCR*: Center-based cardiac rehabilitation; *CBET*: Community-based exercise training; *CR*: Cardiac rehabilitation; *CRF*: Cardiorespiratory fitness; *CTCAE*: Common Terminology Criteria for Adverse Events; *CV*: Cardiovascular; *CVD*: Cardiovascular diseases; *CVRF*: Cardiovascular risk factors; *ECG*: Electrocardiographic; *ET*: Exercise training; *HER2*: Human epidermal growth factor receptor 2; *HF*: Heart failure; *PA*: Physical activity; *RCT*: Randomized controlled trial

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Author contribution Sofia Viamonte, Ana Joaquim, Alberto Alves, Andreia Capela, Eduardo Vilela, Madalena Teixeira, Ana João Costa, Barbara Duarte, Cristina Ferreira, Aida Tavares, Nuno Rato, and Fernando Ribeiro conceived the design for the study, contributed for acquisition and interpretation of data, formal analysis, and data curation as well as drafting the article. Fernando Ribeiro and Mario Santos contributed to interpretation of data and the revision of the manuscript; all authors approved the final manuscript.

Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki, and ethical approval for this study was obtained from the Centro Hospitalar Vila Nova de Gaia /Espinho Ethics Committee (reference number 168/2020). All patient provided written informed consent.

Competing interests The authors declare no competing interests.

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