Timing of cardio-oncological rehabilitation and cardiorespiratory fitness in patients receiving cardiotoxic chemotherapy: a longitudinal observational study

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Summary

AIMS: Anthracycline-based chemotherapy has well-known cardiotoxic effects, butmay also cause skeletal muscle myopathy and negatively affect cardiorespiratory fitness and quality of life. The effectiveness of exercise training in improving cardiorespiratory fitness and quality of life during chemotherapy is highly variable. We set out to determine how the effect of exercise training on cardiorespiratory fitness (primary outcome) and quality of life (secondary outcome) in cancer patients is affected by the type of therapy they receive (cardiotoxic therapy with or without anthracyclines; non-cardiotoxic therapy) and the timing of the exercise training (during or after therapy).

METHODS: Consecutive patients with cancer who participated in an exercise-based cardio-oncology rehabilitation programme at a university hospital in Switzerland between January 2014 and February 2022 were eligible. Patients were grouped based on chemotherapy (anthracycline vs non-anthracycline) and timing of exercise training (during vs after chemotherapy). Peak oxygen uptake (VO_2) was assessed with cardiopulmonary exercise testing (n = 200), and quality of life with the Functional Assessment of Cancer Therapies questionnaire (n = 77). Robust linear models were performed for change in peak VO_2 including type and timing of cardiotoxic therapies, age, training impulse and baseline peak VO_2; change in quality of life was analysed with cumulative linked models.

RESULTS: In all patients with valid VO_2 (n = 164), median change in peak VO_2 from before to after exercise training was 2.3 ml/kg/min (range: −10.1–15.9). The highest median change in peak VO_2 was 4.1 ml/kg/min (interquartile range [IQR]: 0.7–7.7) in patients who completed exercise training during non-anthracycline cardiotoxic or non-cardiotoxic therapies, followed by 2.8 ml/kg/min (IQR: 1.2–5.3) and 2.3 ml/kg/min (IQR: 0.1–4.6) in patients who completed exercise training after anthracycline and after non-anthracycline cardiotoxic or non-cardiotoxic therapies, respectively. In patients who completed exercise training during anthracycline therapy, peak VO_2 decreased by a median of −2.1 ml/kg/min (IQR: −4.7–2.0). In the robust linear model, there was a significant interaction between type and timing of cancer treatment for anthracycline therapy, with greater increases in peak VO_2 when exercise training was performed after anthracycline therapy. For quality of life, higher baseline scores were negatively associated with changes in quality of life.

CONCLUSION: In our cohort, the increase in cardiorespiratory fitness was diminished when exercise training was performed concurrently with anthracyclines. For patients with cardiotoxic treatments other than anthracyclines, cardiorespiratory fitness and quality of life was not associated with timing of exercise training.

Introduction

Lower cardiorespiratory fitness has been observed in patients with cancer compared to healthy age- and sex-matched sedentary individuals [1–3]. While lower levels of physical activity due to diagnosis and treatment may be a driving factor in the decline of cardiorespiratory fitness, measured as peak oxygen consumption (peak VO_2), there is increasing interest in understanding other physiological mechanisms that may be driving this observation. Reduced cardiorespiratory fitness may compromise health-related quality of life and is a strong independent predictor of cancer- and cardiac-specific mortality as well as overall mortality in cancer survivors [4, 5]. A better understanding of these mechanisms will allow for the development of interventions to improve cardiorespiratory fitness during and following cancer diagnosis and treatment.

Lower cardiorespiratory fitness has been found in the absence of cancer treatment (surgery and/or chemotherapy and/or radiotherapy). This finding may be explained by tumour-induced damage and resulting systemic inflammation, affecting multiple organs [6]. Moreover, cancer therapies may cause skeletal muscle myopathy [6, 7] and can have a direct negative effect on the heart and vascular endothelial function [8], further reducing peak VO_2 [9]. A

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proposed mechanism for cancer therapy-associated toxicity is the generation of reactive oxygen species (ROS), induced by anthracycline-based chemotherapy [10, 11], that may negatively affect both skeletal and cardiac muscle tissue [6]. In the muscle, ROS may induce mitochondrial dysfunction, contribute to the inflammation process and can affect muscle repair by reducing the replenishment of the satellite pool [12]. These combined mechanisms amplify the myopathy process and may ultimately result in skeletal muscle wasting and dysfunction, leading to reduced peak oxygen uptake [12]. In the heart, increased ROS production may cause cardiac myocyte apoptosis and necrosis (i.e. anthracycline-induced cardiac toxicity) [13], thereby negatively affecting oxygen transport. Deconditioning and weight gain, occurring secondary to therapies, may result in suboptimal cardiovascular disease prevention. Moreover, the presence of shared risk factors occurring in combination (i.e. inactive lifestyle, obesity and smoking) may adversely affect cardiorespiratory fitness and predispose patients with cancer to the development of cardiovascular disease [14].

Structured exercise training as part of cardio-oncology rehabilitation (CORE) programmes has the potential to prevent and/or restore loss in cardiorespiratory fitness and to alleviate side effects of cancer therapies (i.e. reduce fatigue and improve quality of life) [15]. While the increase in peak VO_2 with exercise training was generally found to be greater when it was done after rather than during cancer treatment [16, 17], no study has compared the timing effect in patients receiving cardiotoxic vs those receiving non-cardiotoxic treatments.

We therefore aimed to evaluate the association of timing of exercise-based CORE with change in cardiorespiratory fitness (primary outcome), quality of life and cancer-related fatigue (secondary outcomes) in patients with anthracyclines, other cardiotoxic therapies (non-anthracycline) and non-cardiotoxic therapies.

Methods

Study population

We included patients with cancer who participated in a 3-month exercise-based CORE programme at the University Hospital of Bern, Switzerland, between January 2014 and the end of January 2022 and who underwent a cardiopulmonary exercise test (CPET) at the beginning and end of the programme. The indication for cardio-oncological rehabilitation in Switzerland depends on referral by oncologists and by different reimbursement strategies of different health insurance schemes. Upon referral, patients underwent a cardiorespiratory fitness assessment at the Centre of Rehabilitation & Sports Medicine and completed the CORE programme at the Department of Physiotherapy.

Patients with a missing follow-up CPET or invalid peak VO_2 at one or both visits, but available data on training characteristics and participation were included in the analysis of adherence and training characteristics but excluded from the primary analysis on predictors for change in peak VO_2.

We categorised disease as early stage or advanced stage using the UICC (Union for International Cancer Control) classification and the International Staging System (ISS), which is used for classifying multiple myeloma. "Early stage" was defined as all cancers classified as UICC 0 to III and ISS I, whereas "advanced stage" included cancers classified as UICC IV and ISS II to III [18].

Cardiovascular risk factors were recorded and a sum score was calculated. The presence of established atherosclerotic cardiovascular disease (ASCVD, i.e. prior myocardial infarction, stroke or presence of atherosclerosis) or other cardiovascular disease (i.e. thrombosis, hypertensive cardiomyopathy, pulmonary embolism) at the beginning of the programme was documented.

Data collection and processing

For patients who had provided signed general consent, non-genetic, health-related data such as age, sex and medical history were derived from the electronic health record. Every training session was recorded and stored in the training monitoring system until the time of data extraction in January 2022. Likewise, CPET data was stored in the databank of the cardiopulmonary exercise test software and extracted at the same time point. CPET data was merged with clinical data and data of monitored training sessions if available. The study was approved by the local ethics committee of the canton of Bern as part of the CAPRICE study (NCT03850171).

Outcomes

The primary outcome of the study was change in cardiorespiratory fitness (peak VO_2) from before to after CORE according to type of therapy, namely anthracycline-based chemotherapy, other cardiotoxic therapies (non-anthracycline) and non-cardiotoxic therapies and timing of exercise training. As secondary outcomes, the study evaluated the association of timing of exercise training with changes in quality of life and cancer-related fatigue in patients with anthracyclines, non-anthracyclines or non-cardiotoxic therapies.

Cardiopulmonary exercise test (CPET)

Cardiopulmonary exercise tests were performed on a cycle ergometer with an individualised ramp protocol aiming to achieve exhaustion within 8 to 12 minutes of ramp duration. The protocol consisted of a 3-minute warm-up at a workload of 5–50 watts followed by an increase of 10, 15 or 20 watts every minute until voluntary exhaustion then a 2-minute active cool-down period. Throughout the cardiopulmonary exercise test, patients were monitored by a cardiologist with continuous assessment of a 12-lead ECG. Gas exchange was measured using the spirometry system Jaeger Oxycon Pro (Masterscreen CPX, PanGas Healthcare GmbH) up to the end of February 2020, then using the Quark spirometry system (Cosmed, Rome, Italy). Peak values from the cardiopulmonary exercise tests were determined and included VO_2, power, heart rate as well as ventilatory and gas exchange parameters. Ventilatory thresholds (VT_1 and VT_2) were determined using established criteria [19]. To ensure that only valid peak VO_2 values were used in our analysis, we excluded cardiopulmonary exer-

cise tests with a respiratory exchange ratio below 1.05, since below this value the identified peak VO_2 is from a submaximal test and does not indicate a true peak value.

Assessment of quality of life and fatigue

Quality of life was assessed with the validated Functional Assessment of Cancer Therapy–General (FACT-G) scale, which contains subscales for physical, functional, emotional and social/family wellbeing. These questionnaires were routinely administered from the beginning of 2019. The subscales were summed to obtain a FACT-G score, which ranged from 0 to 108, with higher values indicating better quality of life. Fatigue was assessed using the 13-item Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), the fatigue scale of the FACT measurement system which gives a score ranging from 0 to 52, with lower values indicating a higher level of fatigue [20]. Patients completed the FACT-G and FACIT-F questionnaires on the days of their cardiopulmonary exercise test visits either electronically or on a print-out.

Training monitoring

Methods for training monitoring and characteristics can be found in the data supplement in the appendix.

Exposures

The following clinical factors were assessed for their predictive value for change in peak VO_2 with exercise training: type of chemotherapy (categorical variable), timing of exercise training (categorical variable) in relation to cancer treatment, exercise training compliance and number of cardiovascular risk factors. Type of cancer and disease classification were not used in the model because they were collinear with type of chemotherapy. Age, sex, change in body fat percentage and baseline peak VO_2 were included as confounding variables. To avoid entering too many training-related variables into the models, we calculated a composite training impulse variable (including endurance sessions only) according to the following formula: Total number of training sessions [n] × average duration of training sessions [min] × average training load as percentage of peak power at baseline [%]. Training impulse was included in the model for patients completing centre-based exercise training only and tested interchangeably with exercise training compliance to assess whether one factor was a better predictor. Since the model did not change substantially when compliance was included, these results are not shown. The type of chemotherapy was categorised into the following groups: anthracycline-based chemotherapy with or without other cardiotoxic treatment; cardiotoxic treatment other than anthracycline-based chemotherapy, e.g. trastuzumab, left-sided radiotherapy, fluorouracil or cyclophosphamide; and non-cardiotoxic treatment. Timing of exercise training was categorised as "during cancer treatment" or "following cancer treatment". For patients who did not receive cardiotoxic therapies, exercise training participation during cancer treatment refers to any other therapy that was prescribed. For patients receiving anthracyclines, irrespective of whether other cardiotoxic therapies were administered, timing of exercise training participation refers to anthracyclines. For patients who participated in the exercise programme during other cardiotoxic treatment but did not receive anthracycline-based chemotherapy, timing of exercise training refers to other cardiotoxic therapies. Since the group of patients receiving no treatment was small (five patients), they were included in the non-cardiotoxic therapy "during" cancer treatment group.

Statistical analyses

All statistics were performed with R Studio (version 2022.02.0 +443) and SPSS (version 25). Baseline data was described as frequencies or means with standard deviations (or medians with interquartile ranges [IQRs]) as appropriate. Differences at baseline between patients receiving anthracycline-based chemotherapy vs those not receiving anthracycline-based chemotherapy were assessed with the Wilcoxon rank-sum test, the chi-squared test or Fisher's exact test as appropriate.

Robust linear models were performed for change in peak VO_2 [ml/kg/min] between baseline and conclusion cardiopulmonary exercise tests (lmrob function from the robustbase package). Robust regression was used since it is less sensitive to outliers than standard linear regression. The following factors were included as predictor variables: type and timing of exercise training; and the interaction effect of type of therapy and timing of exercise training. Age and peak exercise capacity at baseline were included as confounding variables. Cardiovascular risk factors (sum score), sex and change in body fat were included as additional predictor variables in the main model; however since results did not change substantially, we removed these factors from the analysis. We could not enter change in presence of anaemia at baseline as a confounding factor into the model because this data was only available in 62.2% of our patients. Therefore we only performed Pearson correlation between changes in haemoglobin with changes in VO_2 to assess the influence of this variable on our primary outcome. Given that patients with no pharmaceutical or other cancer therapies and those receiving other cardiotoxic treatment showed comparable improvements in peak VO_2 in the linear model, results of these patients were summarised in one group for presentation in tables (the without-anthracyclines group) and compared to the anthracycline therapy group (tables 1, 2 and 3). Furthermore, a corresponding model was performed for the subpopulation of patients attending the centre-based programme only (excluding patients enrolled in hybrid or pure tele-rehab programmes during the COVID-19 pandemic). In the subpopulation model, exercise training compliance or training impulse (in % to peak power at baseline) were included as additional predictor variables. Additionally, cumulative linked models (clm function from the ordinal package) were performed for change in quality of life and fatigue including type and timing of exercise training and the interaction effect of type of therapy and timing of exercise training as predictor variables, adjusted for FACT-G and FACIT-F scores at baseline. Cumulative linked models are used for regression analysis of dependent variables with ordinal data (rather than continuous numerical data that can be analysed with linear regression models). Missing data was not imputed. The alpha level was set at 0.05 for all analyses (two-tailed for Wilcoxon rank-sum test).

Results

Study population

We collected the data of 262 patients at the beginning of their CORE (figure 1).

Adherence to exercise training during CORE was assessed in 260 patients whereas analysis on training characteristics was performed in 245 patients. A total of 205 patients (78.2%) completed the CORE with centre-based exercise training sessions only, whereas 54 patients (20.6%) attended a hybrid programme with both centre-based and home-based exercise training. Three additional patients completed the CORE programme as tele-rehabilitation with no centre-based exercise training. Hybrid and tele-rehabilitation was mainly offered to patients due to COVID-19-related closure of centre-based training facilities. Baseline characteristics of all included patients are shown in table 1.

Of patients with available data on haemoglobin levels, 31.9% and 27.3% of patients with and without anthracyclines, respectively, had anaemia (table S1 in the appendix). Patients with anthracyclines were 9 years younger than patients without anthracyclines (p <0.001). Cardiorespiratory fitness at baseline (when related to age- and sex-matched predicted values) did not differ between the two groups. Patients were comparable with regard to the sum of cardiovascular risk factors. A total of 141 patients received anthracyclines, of whom 94 patients received anthracyclines only (35.9%) and 47 patients (17.9%) additionally received another cardiotoxic therapy (i.e. trastuzumab, left-sided radiotherapy). Forty-nine patients (18.7%) re-ceived other cardiotoxic treatments without anthracyclines and 72 patients (27.5%) had surgery only or were treated with a non-cardiotoxic therapy. Some patients received both, chemotherapy and radiotherapy.

Changes in peak VO2

Of 262 available patients, 62 were excluded from the analysis of peak VO_2 due to a missing conclusion visit, leaving 200 patients with complete CPET data from the beginning to the end of the CORE programme. Of these patients, 36 did not reach sufficient metabolic exhaustion (respiratory exchange ratio ≥1.05) in either the baseline or conclusion CPET or both and were also removed from the dataset, leaving 164 patients for the final analysis. Missing data was not imputed. In these 164 patients, median (IQR) peak VO_2 was 23.1 (18.9–26.9) ml/kg/min, corresponding to 92% (IQR: 77–106%) of sex- and age-predicted value before exercise training and increased to 25.6 (20.7–30.3) ml/kg/min, corresponding to 103% (IQR: 85–118%) after completion of exercise training. Median changes in peak VO_2 from before to after exercise training were 2.3 ml/kg/min (range: –10.1–15.9), with 71.3% of patients showing an improvement in peak VO_2 and 28.7% showing no changes or a decrease in oxygen uptake (see figure S1 in the appendix). Thirteen patients (6.5%) did not perform both CPETs on the same spirometry system; their median change in peak VO_2 from before to after exercise training was 2.4 ml/kg/min (IQR: 1.2–3.7).

Figure 1: Study flow. CORE: Cardio-oncology rehabilitation programme; ET: Exercise training; CPET: Cardiopulmonary exercise test; RER: Respiratory exchange ratio.
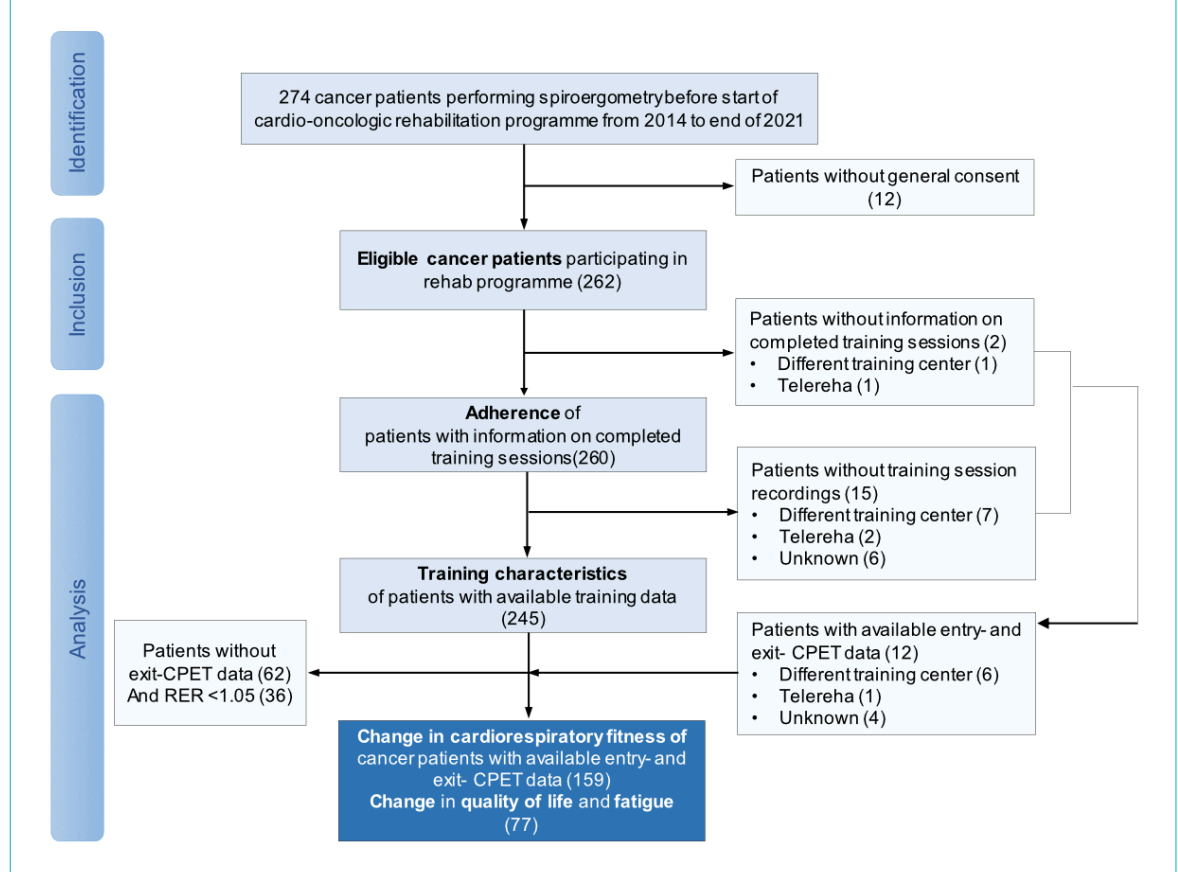
Effect of anthropometric, clinical and exercise training-related moderators on change in VO2 changes in quality of life and fatigue

The final model included 156 of 164 patients and is shown in table 3. The centre-based model only included 108 of 125 patients, with missing data related to unavailable training data.

We found a significant interaction effect for cardiotoxic therapy and timing of CORE with regard to these therapies on change in peak VO_2 (figure 2, table 3). Patients per-

forming exercise training during anthracycline therapy had a mean adjusted decrease of –1.0 ml/kg/min, while those performing exercise training after anthracycline therapy had a mean adjusted increase of 3 ml/kg/min. In patients performing CORE during or after cardiotoxic treatment without anthracyclines (non-anthracycline), the adjusted increases were 4 ml/kg/min and 3 ml/kg/min, respectively. Changes in peak VO_2 of 4 ml/kg/min and 2.0 ml/kg/min were found in patients without other cardiotoxic therapy who completed the exercise training during and after treatment, respectively. Older age (per 1 year) and higher base-

Table 1:

Baseline characteristics of the study population, expressed as n (%) or median (interquartile range).

Characteristics		All cancer patients	AC group	Without-AC group*	p value
		n = 262	n = 141	n = 121	
Female		180 (68.7%)	103 (73.0%)	77 (63.6%)	0.132
Age (years)		52 (40–61)	47 (37–57)	56 (47–64.5)	<0.0001
Body mass index (kg/m^2)		24.7 (22.1–28)	24.5 (21.9–27.8)	25.1 (22.7–28.5)	0.447
Systolic blood pressure (mm Hg)		117 (109–130)	115 (107–127)	120 (110–130)	0.013
Diastolic blood pressure (mm Hg)		70 (62–80)	70 (62–80)	72 (63–80)	0.063
Haemoglobin (g/l) **		123 (110–135)	122 (111–133.5)	123 (108.3–137.5)	0.801
Time from haemoglobin assessment to spiroergometry (weeks)		0 (-2.0–2.0)	0 (-1.8–0.0)	-0.29 (-2.1–0)	0.473
Cardiorespiratory fitness (ml/min/kg)		21.0 (17.2–25.7)	21.7 (18.2–26.6)	20.2 (16.2–24.8)	0.029
Cardiorespiratory fitness (% of predicted)		87% (71.0–103%)	87.1% (70–103%)	86.3% (71.2–102.9%)	0.943
Tumour site	Breast	107 (40.8%)	80 (56.7%)	27 (22.3%)	<0.0001
	Lymphoma	52 (19.8%)	44 (31.2%)	8 (6.6%)	
	Blood cancer	32 (12.2%)	11 (7.8%)	21 (17.4%)	
	Other	71 (27.1%)	6 (4.3%)	65 (53.7%)	
Disease stage (I, II, III, IV)	Stage 0	2 (0.8%)	1 (0.7%)	1 (0.8%)	0.937
	Stage I	48 (18.3%)	27 (19.1%)	23 (19.0%)	
	Stage II	39 (14.9%)	24 (17.0%)	15 (12.4%)	
	Stage III	85 (32.4%)	46 (32.6%)	39 (32.2%)	
	Stage IV	37 (14.1%)	22 (15.6%)	16 (13.2%)	
Disease stage (early, advanced, other)	Early stage (UICC 0-III and ISS I)	182 (69.5%)	99 (70.2%)	86 (71.1%)	0.184
	Advanced stage (UICC IV and ISS II-III)	48 (18.3%)	22 (15.6%)	26 (21.5%)	
	Leukaemia, other classification or unknown	27 (10.3%)	19 (13.5%)	9 (7.4%)	
Cancer therapy	Anthracycline-containing	141 (53.8%)			
	Herceptin (trastuzumab)	20 (7.6%)	14 (9.9%)	5 (4.1%)	0.118
	Radiotherapy	118 (45.0%)	65 (46.1%)	53 (43.8%)	0.804
	Left-sided	55 (21.0%)	37 (26.2%)	18 (23.1%)	0.036
	Other cardiotoxic treatment (cyclophosphamide, 5-fluorouracil)	28 (10.7%)	0 (0%)	28 (23.1%)	<0.0001
Smoking	Never	153 (58.4%)	80 (56.7%)	73 (60.3%)	0.843
	Current	30 (11.5%)	17 (12.1%)	13 (10.7%)	
	Former (more than 3 months ago)	79 (30.2%)	44 (31.2%)	35 (28.9%)	
Pre-existing cardiovascular conditions / comorbidities	Diabetes mellitus	29 (11.1%)	12 (8.5%)	17 (14.0%)	0.220
	Hyperlipidaemia	47 (17.9%)	18 (12.8%)	29 (24.0%)	0.028
	Obesity	49 (18.7%)	25 (17.7%)	24 (19.8%)	0.782
	Hypertension	57 (21.8%)	23 (16.3%)	35 (28.9%)	0.021
	Anaemia**	78 (48.4%)	45 (31.9%)	33 (27.3%)	0.494
	Sum score for cardiovascular risk factors	1 (0–2)	1 (0–1)	1 (0–2)	
	Existing atherosclerotic cardiovascular disease (e.g. myocardial infarction, coronary vascular disease, stroke, peripheral artery disease)	16 (6.1%)	5 (3.5%)	11 (9.1%)	0.107
	Other cardiovascular disease (e.g. thrombosis, pulmonary embolism, hypertensive cardiopathy)	61 (23.3%)	24 (17.0%)	37 (30.6%)	0.015

AC: anthracycline therapy; ISS: International Staging System; UICC: Union for International Cancer Control.

* The without-anthracyclines group consists of patients who received cardiotoxic therapy other than anthracyclines (non-anthracyclines group) and patients who received non-cardiotoxic therapy (non-CTOX group).

** 163 patients had haemoglobin data at baseline, of whom 97 were in the anthracycline group and 66 in the non-anthracycline group. Anaemia was defined as haemoglobin level <120 g/l for women and <130 g/l for men.

line VO_2 (per 1 ml/kg/min lesser increase in peak VO_2) were negatively associated with changes in peak VO_2 with a 0.07 ml/kg/min lesser increase in peak VO_2 per year of increasing ageand a 0.11 ml/kg/min lesser increase per additional 1 ml/kg/min of higher baseline peak VO_2. On the other hand, training impulse or compliance were positively associated with changes in peak VO_2. However even in the centre-based model including training impulse or compliance, the large independent interaction effect of timing and type of chemotherapy persisted. Changes in haemoglobin were available in 105 patients and declines were greatest with anthracyclines (see table S1 in the appendix).

Changes in quality of life and fatigue

Baseline data and changes in the FACT-G and FACIT-F scores after exercise training participation were available in 77 patients only, given that routine assessment and storage in the clinical database started in January 2021 only (table 4). Missing data was not imputed. Both quality of life and fatigue were lowest in the groups who attended the exercise training programme after chemotherapy completion. Exercise training participation during chemotherapy did not prevent a reduction in general wellbeing in either the anthracycline group or the without-anthracycline group whereas clinically meaningful increases occurred in the groups attending the exercise training programme after chemotherapy completion. Fatigue decreased with ex-

Figure 2: Interaction plot showing changes in peak oxygen uptake (VO2) depending on timing of exercise training (ET) and cancer treatment adjusted for age, change in body fat percentage, baseline peak VO2 and training impulse. AC: anthracycline treatment; Non-AC: cardiotoxic treatment other than AC; Non-CTOX: non-cardiotoxic cancer treatment.
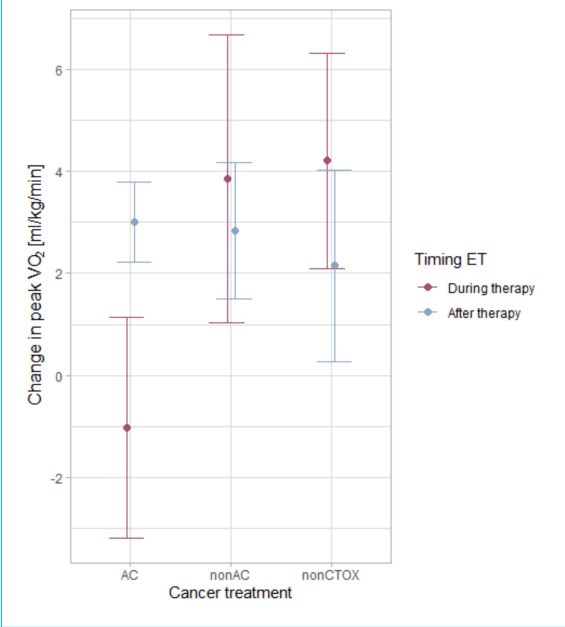
Table 2:
Baseline values and changes in cardiorespiratory fitness from baseline to conclusion cardiopulmonary exercise test in patients with respiratory exchange ratio (RER) ≥1.05. Values are expressed as median (interquartile range). n refers to the number of patients with available data for calculation of the change from the baseline to the conclusion cardiopulmonary exercise test.

	AC group (n = 97)						Without-AC group* (n = 67)					
	ET during therapy (n = 21)			ET after therapy (n = 76)			ET during therapy (n = 25)			ET after therapy (n = 42)		
Resting parameters	Baseline	Change	n	Baseline	Change	n	Baseline	Change	n	Baseline	Change	n
Heart rate (/min)	77 (67–82)	–4.0 (–7.5–10.0)	19	74 (69–86)	–2.0 (–7.5–3.5)	75	77 (72–93)	–8.0 (–13–3)	25	74 (65–85)	–6.0 (–13.3–5.0)	40
VO2 (ml/min/kg)	5.1 (4.8–6.8)	–0.6 (–1.2–0.3)	21	5.1 (4.2–5.9)	0.0 (–1.0–3.8)	75	5.3 (4.7–6.3)	–0.5 (–1.5–0.9)	25	5.3 (3.9–6.1)	0.1 (–1.1–0.9)	41
Ventilation (l/min)	12.3 (11.2–14.0)	–0.8 (–2.3–1.0)	20	12.0 (10.6–15.0)	0.0 (–2.0–2.0)	75	13 (11.0–15.5)	–1.0 (–3.0–0.8)	25	12.4 (10.2–15.0)	0.0 (–2.0–1.1)	41
Respiratory exchange ratio	0.83 (0.80–0.88)	–0.01 (–0.04–0.06)	20	0.83 (0.78–0.87)	–0.01 (–0.05–0.04)	75	0.82 (0.80–0.86)	0.00 (–0.06–0.05)	25	0.79 (0.76–0.85)	0.02 (–0.04–0.1)	41
Parameters at VT1												
Power output (W/kg)	0.9 (0.6–1.1)	–0.1 (–0.2–0.2)	19	0.8 (0.6–1.0)	0.2 (0.0–0.4)	71	0.6 (0.4–0.8)	0.1 (–0.02–0.3)	23	0.7 (0.5–1.01)	0.2 (0.0–0.3)	41
Heart rate (/min)	121 (111–126)	2.0 (–7–12)	21	118 (110–132)	–2.0 (–11.8–9.8)	74	119 (114–131)	–11.0 (–15.3–0.5)	24	113 (102–125)	–0.5 (–9.3–6.0)	40
VO2 (ml/min/kg)	14.1 (13.2–15.9)	–0.2 (–1.5–2.5)	21	13.5 (11.1–16.1)	1.8 (0.5–4.0)	74	12.8 (11.2–14.2)	0.8 (–0.8–2.4)	25	13.7 (11.4–16.2)	1.2 (–0.5–2.5)	42
VO2 (% of peak)	58.6 (52.4–62.9)	2.2 (–3.1–11.0)	21	60.7 (53.6–66.7)	1.5 (–6.7–6.5)	74	59.7 (53.6–68.7)	–2.9 (–13.1–4.0)	25	61.9 (56.9–69.2)	–0.6 (–8.8–4.3)	41
Parameters at peak												
Power output (W/kg)	2.4 (2.1–2.7)	0.1 (–0.3–0.1)	15	1.9 (1.5–2.4)	0.4 (0.2–0.5)	73	1.8 (1.3–2.1)	0.4 (0.1–0.5)	23	1.8 (1.3–2.1)	0.3 (0.2–0.5)	40
Heart rate (/min)	168 (157–180)	0.0 (–5.0–6.0)	21	167 (155–185)	–1.0 (–7.0–7.5)	75	171 (153–179)	–3.0 (–9.0–4.0)	25	156 (137–168)	4.0 (–1.5–12.0)	39
VO2 (ml/kg/min)	24.7 (21.7–29.2)	–2.1 (–4.7–2.0)	21	23.0 (18.7–28.2)	2.8 (1.2–5.3)	76	21.6 (17.3–25.8)	4.1 (0.7–7.7)	25	21.5 (18.4–25.4)	2.3 (0.1–4.6)	42
VO2 (% of predicted)	97.0 (84.0–113.0)	–5.2 (–13.0–6.0)	21	90.9 (75.7–106.3)	11.2 (5.4–23.0)	76	92.1 (77.0–102.6)	16.0 (1.4–32.0)	25	93.0 (77.6–103.8)	7.6 (1.4–19.7)	42
Ventilation (l/min)	72 (63–85)	–1.0 (–7.0–10.6)	21	69 (51–84)	8.0 (–2.0–15.2)	75	77 (62–88.0)	4.0 (–3.3–16.0)	25	69 (56.0–80.0)	6.0 (–1.0–13.0)	41
Respiratory exchange ratio	1.22 (1.16–1.29)	0.01 (–0.08–0.07)	21	1.22 (1.16–1.26)	–0.02 (–0.08–0.03)	76	1.21 (1.16–1.32)	–0.07 (–0.09–0.01)	25	1.16 (1.11–1.24)	0.02 (–0.04–0.08)	42

AC: anthracycline therapy; ET: exercise training; VO2: Oxygen uptake; VT1: Ventilatory threshold 1.

*The without-AC group consists of patients who received cardiotoxic therapy other than anthracyclines (non-AC group) and patients who received non-cardiotoxic therapy (non-CTOX group).

ercise training participation after cancer treatment, while an increase occurred in the anthracycline group with exercise training participation during anthracycline therapy (figure 3), with both changes being clinically meaningful [21]. In the linear model (table 5), neither timing nor cancer therapies had an effect on prediction of changes in general wellbeing. We found a trend for a greater decrease

in the FACIT-F score (indicating an improvement in fatigue) when exercise training was completed after cancer treatment; however anthracycline-based chemotherapy or other cardiotoxic therapies did not affect changes in fatigue. For both quality of life and fatigue, higher FACT-G and FACIT-F scores at baseline were negatively associated with changes in quality of life and fatigue.
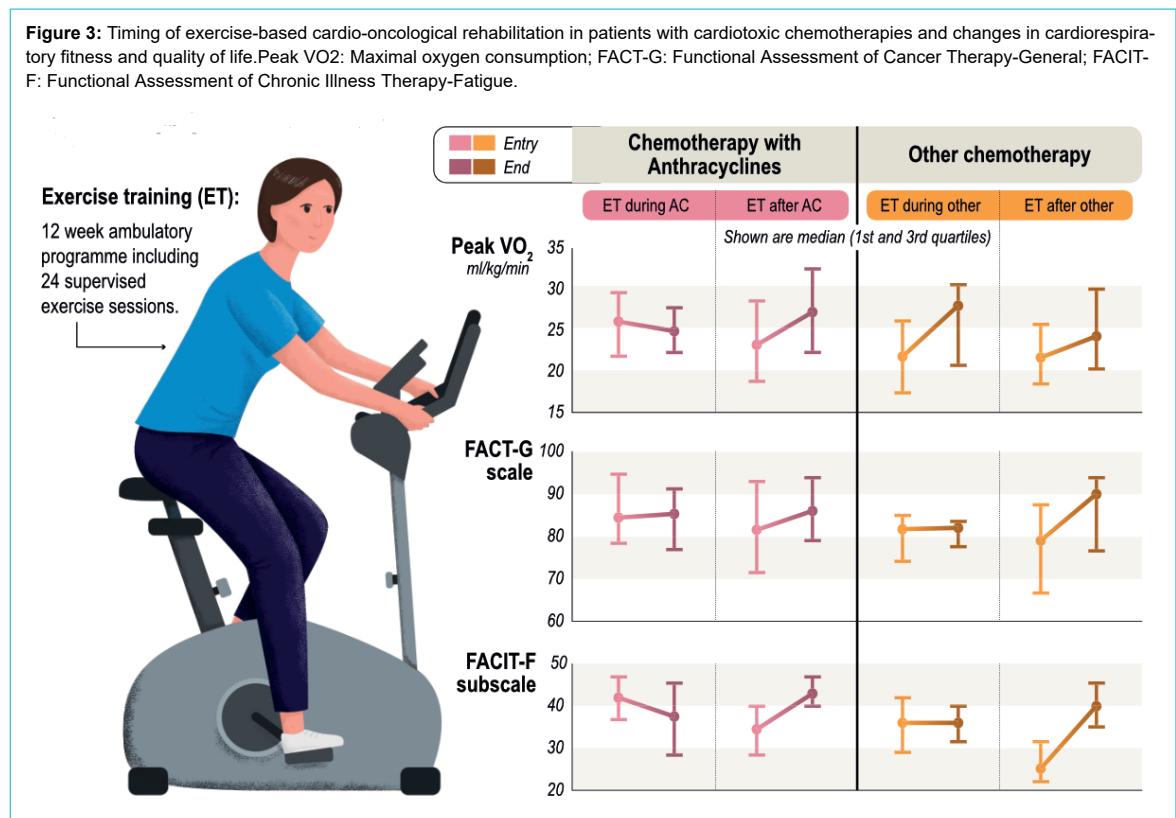
Table 3:

Robust linear models for change in peak VO_2 from before to after exercise training. Independent parameters were age, peak VO_2 at baseline, therapy (non-cardiotoxic therapy, anthracycline, non-anthracycline), timing of exercise training participation (during or after cancer therapy). The reference category for chemotherapy (anthracycline and non-anthracycline) was non-cardiotoxic therapy; for exercise training after cancer therapy, it was exercise training during cancer therapy. The model for change in peak VO_2 explained 14.1% of total variance. In the subgroup of patients participating in the centre-based programme only, training impulse was included as an additional independent parameter. The model for change in peak VO_2 explained 23.8 % of total variance.

Change in peak VO [ml/kg/min]	Estimate (95% confidence interval)		t value	p value
Model 1: all patients (n = 156)				
Intercept	10.29	(5.81–14.76)	4.51	<0.0001
Age (years)	−0.07	(−0.12—0.02)	−2.87	0.0046
Peak VO_2 at baseline (ml/kg/min)	−0.11	(−0.22—0.01)	−2.07	0.0398
Anthracycline treatment	−5.24	(−8.23—2.25)	−3.43	0.0008
Non-anthracycline treatment	−0.36	(−3.84–3.12)	−0.20	0.8407
Exercise training after cancer therapy	−2.05	(−4.84–0.73)	−1.45	0.1503
Anthracycline treatment X exercise training after cancer therapy*	6.10	(2.54–9.65)	3.36	0.0010
Non-AC X exercise training after cancer therapy*	1.04	(−3.05–5.12)	0.50	0.6193
Model 2: centre-based only (n = 108)				
Intercept	8.51	(2.25–14.77)	2.66	0.0089
Age (years)	−0.09	(−0.15—0.03)	−2.98	0.0035
Peak VO_2 at baseline (ml/kg/min)	−0.11	(−0.24–0.02)	−1.66	0.0992
Training impulse (% power baseline)	0.01	(0.00–0.01)	3.09	0.0025
Anthracycline treatment	−5.41	(−8.54—2.28)	−3.39	0.0010
Non-anthracycline treatment	−0.46	(−4.58–0.33)	−0.19	0.8537
Exercise training after cancer therapy	−2.12	(−4.58–0.14)	−1.69	0.0934
AC X exercise training after cancer therapy*	6.08	(−2.53–9.63)	3.36	0.0011
Non-AC X exercise training after cancer therapy*	0.85	(−4.58–6.27)	0.31	0.7608

VO_2: oxygen uptake; Non-AC: cardiotoxic treatment other than anthracyclines.

* X indicates the interaction between cancer treatment (anthracycline therapy and cardiotoxic treatment other than anthracycline therapy) and exercise training timing.

Figure 3: Timing of exercise-based cardio-oncological rehabilitation in patients with cardiotoxic chemotherapies and changes in cardiorespiratory fitness and quality of life. Peak VO2: Maximal oxygen consumption; FACT-G: Functional Assessment of Cancer Therapy-General; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue.

Training characteristics

Training characteristics according to type and timing of anthracycline treatment are summarised in table S2 in the appendix. Median compliance for all patients (centre-based and hybrid exercise training) was 91.6% (IQR: 62.5–100%; range: 4–100%), with higher compliances after compared to during cancer therapy, particularly when exercise training during anthracycline treatment was compared to exercise training after anthracycline treatment (75% vs 96%, table S2).

Discussion

The key finding of our study was that the increase in cardiorespiratory fitness with exercise training was diminished by concurrent anthracycline treatment in our cohort. For patients with cardiotoxic treatments other than anthracycline-based chemotherapy, cardiorespiratory fitness and fatigue were not associated with timing of exercise training (figure 3). Overall, greater positive changes in peak VO_2 were seen in individuals who achieved a greater training impulse, whereas higher age and higher baseline VO_2 resulted in smaller gains in peak VO_2. This is to our knowledge the first study to evaluate changes in cardiorespiratory fitness, quality of life and fatigue with regard to timing of exercise training in patients with anthracycline treatment and other cardiotoxic chemotherapies.

Our findings of a median increase in peak VO_2 of 2.3 ml/kg/min are in line with two meta-analyses in patients with cancer, reporting a weighted mean difference of 2.1 ml/kg/min [16] and 2.9 ml/kg/min [17] from before to after exercise training in exercising patients compared to the usual care group. Interestingly, in both studies changes in peak VO_2 in exercising patients were greater following the completion of adjuvant therapy, compared to exercise training during therapies. Scott et al. describe a weighted mean difference of -1.1 ml/kg/min between groups participating in exercise training during vs after therapy and Jones et al. report an increase of 3.4 ml/kg/min in the three included studies conducting exercise training after chemotherapy [22–24] compared to 1.2 ml/kg/min for the two studies conducting exercise training during adjuvant treatment [25, 26]. In both meta-analyses, a great proportion of the included studies were conducted in middle-aged women with breast cancer; thus it can be expected that most patients were treated with anthracycline treatment. The meta-analysis by Scott et al. further investigated the effect of intervention timing (during vs before surgery and during vs after primary adjuvant therapy); however, they could not identify any moderating effect on the response in exercise capacity, contradicting our findings. Neither of the two meta-analyses differentiated anticancer treatment into anthracycline-based chemotherapy, cardiotoxic and non-cardiotoxic therapies. Our study extends the current literature by suggesting that for anthracycline treatment, changes in peak VO_2 are time-dependent, but that for other cardiotoxic or non-cardiotoxic therapies, timing is not as-

Table 4:

Quality of life (FACT-G) and fatigue (FACIT-F) scores at baseline and changes with exercise training programmes. Values expressed as median (interquartile range).

	AC group				Without-AC group*				
	Exercise training during therapy		Exercise training after therapy		Exercise training during therapy			Exercise training after therapy	
	Baseline	Change	Baseline	Change	Baseline	Change		Baseline	Change
	n = 18	n = 18	n = 34	n = 33	n = 7	n = 7		n = 19	n = 19
FACT-G	84.8 (78.3–94.8)	0.8 (–5.8–6.5)	81.5 (71.3–93.1)	5.7 (0.0–10.0)	81.6 (74–85)	–1.0 (–7.5–9.5)		79.0 (66.5–87.5)	10.0 (5.0–14.0)
FACIT-F	42 (36.8–47.0)	–1.5 (–14.5–6.5)	34.5 (28.3–40.0)	8.0 (2.0–12.0)	36.0 (29.0–42.0)	0.0 (–5.5–5.5)		25.0 (22.0–31.5)	13.0 (5.5–20.5)

AC: anthracyclines.

* The without-AC group consists of patients who received cardiotoxic therapy other than anthracyclines (non-AC group) and patients who received non-cardiotoxic therapy (non-CTOX group).

Table 5:

Cumulative linked models for change in quality of life and fatigue from before to after exercise training. Independent parameters were type of therapy (non-cardiotoxic treatment, anthracycline, other cardiotoxic treatment), timing of exercise training participation (during or after cancer therapy) and baseline quality of life and fatigue levels. Other predictor variables (e.g. age or training impulse) were not assessed due to the small number of patients with available data. The reference category for anthracycline therapy and non-anthracycline therapy was non-cardiotoxic treatment; for exercise training after cancer therapy, it was exercise training during cancer therapy.

	Estimate (95% confidence interval)		t value	p value
Change in quality of life: Subset of patients with available data on quality of life (n = 77)				
Anthracycline therapy	0.69	(–1.64–3.02)	0.58	0.5650
Non-anthracycline therapy	1.24	(–1.66–4.14)	0.84	0.4030
Exercise training after cancer therapy	1.91	(–0.54–4.36)	1.52	0.1280
FACT-G score at baseline	–0.08	(–0.12–0.04)	–4.14	0.0000
Anthracycline therapy x exercise training after cancer therapy	–1.20	(–3.85–1.45)	–0.89	0.3740
Cardiotoxic treatment other than anthracycline therapy x exercise training after cancer therapy	–1.05	(–4.38–2.28)	–0.62	0.5350
Change in fatigue: Subset of patients with available data on fatigue (n = 77)				
Anthracycline therapy	0.98	(–0.80–2.76)	1.08	0.2811
Non-anthracycline therapy	2.26	(–0.50–5.02)	1.61	0.1085
Exercise training after cancer therapy	2.02	(–0.02–4.06)	1.94	0.0524
Fatigue subscale at baseline	–0.19	(–0.25–0.13)	–6.87	0.0000
Anthracycline therapy x exercise training after cancer therapy	–0.54	(–2.77–1.69)	–0.47	0.6378
Cardiotoxic treatment other than anthracycline x exercise training after cancer therapy	–1.03	(–4.24–2.18)	–0.63	0.5290

FACT-G: Functional Assessment of Cancer Therapy–General.

sociated with reduced benefits on cardiorespiratory fitness, with the greatest changes seen in patients completing exercise training during these therapies.

The finding that quality of life decreased (anthracycline and non-anthracycline groups) and fatigue increased (anthracycline group only) in the groups performing exercise training during cancer treatment is in contrast to the results from a recent meta-analysis by Buffart et al., which reported a beneficial effect of exercise training on quality of life and did not find differences in the groups who exercised during compared to after cancer treatment [27]. However, cancer treatment was not categorised into anthracyclines and other non-cardiotoxic therapies. Another meta-analysis by McNeely et al. found a greater increase (by 4.6 points) in quality of life analysed by the FACT-G scale with exercise training compared to usual care in female breast cancer patients during and after cancer treatment (including anthracyclines) [28]. They also found a reduction in fatigue with exercise training. However, of the individual studies included, the two with exercise training performed following cancer treatment showed significant fatigue reductions, whereas the other four studies with exercise training performed during adjuvant cancer treatment showed non-significant improvements in fatigue, underpinning our findings. It should be noted that exercise training is only one component of a comprehensive CORE programme, which further includes counselling on psychosocial issues, nutrition, cardiovascular risk factors and pain management. Thus, changes in quality of life could have resulted from participation in other components of CORE and/or social interactions during exercise training. However, participation in other modules of CORE was very heterogeneous between patients and evaluation of comprehensive CORE was not the aim of the study.

The overall median increase of 2.3 ml/kg/min in peak VO_2 in our cohort is likely to be of clinical importance, given the inverse association of cardiorespiratory fitness with all-cause and cardiovascular mortality in the general population and in patients with cancer [4, 5]. In an observational cohort study including 1691 male cancer survivors, high cardiorespiratory fitness (defined as those above the 60th percentile, achieving mean metabolic equivalent of task [MET] of 13.0 ± 1.8 in a treadmill test) was associated with a 32% risk reduction of cancer mortality and a 68% reduction of cardiovascular disease mortality, compared with patients with low cardiorespiratory fitness (defined as those below the 20th percentile, achieving 8.4 ± 1.2 MET) [29]. In the same study, every 1 MET increase in cardiorespiratory fitness corresponded to 17% and 9% relative risk reductions in lung and colorectal cancer risk, respectively. A population-based follow-up study in 579 apparently healthy men observed changes in peak VO_2 over 11 years and found that after adjusting for various risk factors, baseline VO_2 and physical activity, a 1 ml/kg/min lesser decrease in peak VO_2 was associated with a 9% relative risk reduction of all-cause mortality after approximately 13 years of follow-up [30].

The increase in peak VO_2 was highest when patients completed the exercise training during non-anthracycline therapies (4.1 ml/kg/min) and after receiving anthracyclines (2.8 ml/kg/min), even if they received other cardiotoxic therapies during exercise training. It is difficult to judge whether changes in exercise capacity occurred due to exercise training participation and factors related to exercise intensity and dose, spontaneous recovery of peak VO_2 or due to unmeasured confounders. However, since training impulse was highest in the exercise training after anthracycline group, followed by the exercise training after non-anthracycline group, exercise training during non-anthracycline and exercise training during anthracycline group (table S2 in the appendix), it does not sufficiently explain the highest changes seen in patients completing exercise training during non-anthracycline therapies. In addition, cardiorespiratory fitness can be reduced due to prevailing anaemia, which often develops over the course of anti-cancer therapy with haemoglobin levels lowest immediately post-therapy, but generally recovering within 12 weeks of treatment cessation [31]. Since patients in the exercise training during non-anthracycline therapies and exercise training after anthracycline groups showed the lowest haemoglobin values at baseline and the greatest increase over the course of exercise training (table S1 in the appendix), the larger improvement in peak VO_2 may be partly explained by spontaneous recovery of haemoglobin values. In fact, haemoglobin only declined in the group performing exercise training during anthracycline therapy (table S1). However, when changes in haemoglobin levels from before to after exercise training were included in the model for change in peak VO_2, this factor was not significant, possibly due to the reduced sample size of patients with haemoglobin data. There was a significant albeit weak correlation between changes in peak VO_2 and changes in haemoglobin level (0.260, p <0.001), suggesting at best a minor role of anaemia on changes in peak VO_2.

Our finding that training impulse (and compliance) was positively and independently associated with changes in peak VO_2 is in line with results by Bjørke et al. who evaluated the effects of training modes and intervention duration on peak VO_2 in patients exercising during (neo-) adjuvant treatment [32]. Indeed, other studies in patients with cancer and sedentary older adults have shown that higher weekly exercise durations and intensities are associated with greater improvements in peak VO_2 [33–35]. It should be noted that part of the poor improvement in peak VO_2 in the exercise training during anthracycline therapy group may have resulted from lower compliance with the exercise programme, resulting in a lower training impulse (table S3 in the appendix). However, a recent study by Foulkes et al. observed similar changes in peak VO_2 from before to after a 12-week supervised exercise programme (–1.5 ml/kg/min, 6% reduction compared to baseline) with higher exercise compliance (median 83%) and greater training impulse (3 exercise sessions per week, including 1 interval session) [36]. This suggests that the systemic adverse effect of anthracycline therapy may counteract exercise training-induced beneficial adaptations.

Clinical implications

This is the first study to suggest that timing of exercise training participation with regard to cancer treatment should be considered when analysing changes in peak VO_2, quality of life and fatigue.

Exercise training during anthracycline-based chemotherapy was not associated with improvements in cardiorespiratory fitness, quality of life or fatigue.

Limitations

Inherent to the study's observational design, no conclusions can be made about the causal association between anthropometric, clinical and exercise training-related moderators (i.e. training characteristics) and changes in peak VO_2 and quality of life. The observational design of the study further prevents the appraisal of the potential of exercise training to mitigate a larger decline of cardiorespiratory fitness and quality of life during anthracycline therapy. In addition, our sample size allowed for a somewhat crude analysis only and did not permit differentiation into further subgroups based on timing of exercise training with regard to primary cancer diagnosis, type of cardiotoxic treatments other than anthracycline therapy or cancer treatments additional to anthracyclines. Furthermore, the timing with regard to anthracyclines always overrode other categories (even if they were cardiotoxic, such as trastuzumab) and the exercise training after anthracycline therapy group included 12 patients on trastuzumab, which may have led to an underestimation of recovery of peak VO_2 with exercise training after anthracycline therapy. Unfortunately, 62 patients had to be excluded from our primary outcome analysis of peak VO_2 due to a missing conclusion visit, mainly related to the COVID-19 pandemic. Based on the baseline characteristics of these patients, it was not possible to estimate how the missing data would have affected our results; therefore data was not imputed.

Another limitation linked to the clinical setting of this study was that patients did not complete a familiarisation CPET. In a study by Jones et al., an increase in peak VO_2 of 0.9 ml/kg/min was found from the first to the second CPET. Nevertheless, when subtracting 0.9 ml/kg/min from the median improvement in peak VO_2 observed in our study, our patients still show a clinically meaningful improvement of 1.4 ml/kg/min. 6.5% of our patients had follow-up CPETs on a different spirometry system; however changes in peak VO_2 were comparable to those observed in the other patients.

Despite the limitations of observational design, our real-life setting of patients with cancer participating in an exercise training programme make our study more representative than randomised trials with strict selection criteria. Indeed, with 59% of the study cohort consisting of patients with various cancer diagnoses, our findings expand on data that has typically been obtained from studies consisting of exclusively or primarily breast cancer patients.

Conclusion

The present study evaluated the predictive value of clinical and training-related factors on short-term changes in cardiorespiratory fitness, quality of life and fatigue with exercise training participation. This is the first study to suggest that the change in peak VO_2, quality of life and fatigue may be dependent on type and timing of exercise training with regard to cardiotoxic cancer treatment. The modest (negative) changes in peak VO_2 observed in our study may be explained by simultaneous adverse effects of anthracy-

cline therapy on skeletal and cardiac muscle tissue, impairing oxygen transport and utilisation. For patients with cardiotoxic treatments other than anthracycline therapy, timing had a minimal effect and was not related to reduced benefits on cardiorespiratory fitness and fatigue with exercise training. Higher age and higher baseline VO_2 were negatively associated with changes in peak VO_2 while greater training impulse was positively associated with them. The observational study design precludes the assessment of the potential of exercise training to mitigate a larger decline of cardiorespiratory fitness, quality of life and fatigue during anthracycline therapy. Nevertheless, whether changes in exercise capacity occurred secondary to changes in haemoglobin values, to factors related to exercise intensity and dose or to unmeasured confounders remains to be determined in future studies.

Data availability

Data sharing may be available upon request to the corresponding author.

Potential competing interests
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix: supplementary data, figure and tables

Data supplement: Training monitoring

The exercise-based CORE programme is a 12-week ambulatory multidisciplinary programme, including 24 supervised exercise sessions, counselling on physical activity, psychosocial aspects, nutrition, cardiovascular risk factors and pain. The exercise training is offered twice per week to groups of up to 10 cancer patients with exercise sessions lasting 90 minutes and supervised by experienced exercise therapists. Sessions start with approximately 30–40 minutes of cycling on an ergometer at moderate intensity, increased on a weekly basis if possible. After the cycling training, patients continue the exercise session with 45 minutes of strength, coordination and/or balance training. As a consequence of COVID-19, in June 2020, CORE was changed to a hybrid model comprising one supervised individual ET session and one non-supervised ET session at home. During COVID-19, some patients completed a CORE without centre-based sessions. All patients were encouraged to perform at least 150 minutes of moderate physical activity per week, and two weekly strength sessions for major muscle groups [37].

Training workload and duration of endurance training sessions on cycle ergometers were monitored using the Ers2 system, version 1.01 (ergoline GmbH, Bitz, Germany). In addition, heart rate and rhythm were continuously recorded with 3-lead ECG. During every training session, patients were asked about their perceived exertion using the established Borg scale (scale of perceived exertion from 6 to 20). Resistance, coordination or other endurance sessions performed outside the centre (outdoors, at home or at a different training centre) were not recorded.

For the descriptive analysis of training characteristics, we calculated means from all sessions of each patient for the following parameters: training load, duration and heart rate (HR). Training load was expressed in percent of peak power achieved at baseline CPET and also in percent of the mean from peak power at baseline and conclusion CPET. HR was also expressed as HR relative to peak HR achieved at baseline CPET and also relative to the mean from peak HR at baseline and conclusion CPET. The same was done for expressing HR relative to HR reserve (difference between resting HR and peak HR).

For patients completing all exercise training sessions at the centre (i.e. the centre-based cohort), weekly exercise volume and MET-minutes per week including endurance and strength training were calculated. For endurance sessions on stationary bikes, the following ACSM formula was used to estimate oxygen consumption based on the individual training load: $10.8 \times$ average training load/weight $+ 7$ [38]. Subsequently, VO_2 values were divided by 3.5 (1 MET = 3.5 ml/kg/min) to obtain MET values for each endurance session and then multiplied by the average duration of the endurance session. Each centre-based training session typically included 40 minutes of strength training, performed either on weight machines or as circuit training in the gym. Average intensity during strength training was estimated based on the Compendium for Physical Activity table [39] with 3.5 MET (low to moderate intensity). Therefore, 140 MET-minutes were added for each strength session to the endurance-based exercise volume to approximate overall MET-minutes per week.

Compliance with exercise training was determined by the number of planned training sessions divided by the number of completed training sessions. In order to achieve 100% compliance, two supervised centre-based training sessions per week had to be completed over the duration of the exercise training programme (12 weeks). For patients enrolled in the hybrid rehabilitation model, full compliance was achieved when patients attended one centre-based exercise session per week, assuming an additional non-monitored training session was completed at home. For patients without centre-based sessions, compliance was not documented, which is why these patients were excluded from the analysis of compliance.

Figure S1: Changes in peak VO2 from before to after exercise training (ET) relative to peak oxygen uptake (VO2) at baseline, depending on timing of exercise training and cancer treatment. AC: anthracycline treatment; Non-AC: Cardiotoxic treatment other than AC; Non-CTOX: Non-cardiotoxic cancer treatment.
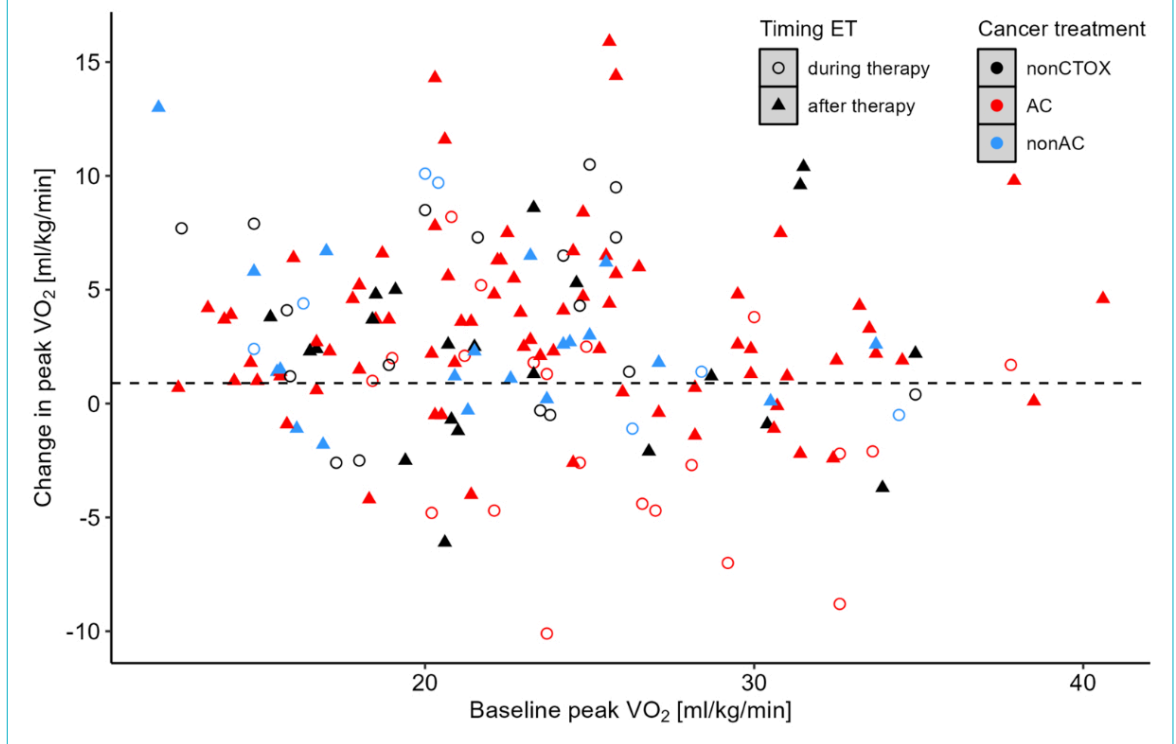
Table S1:

Anaemia status at baseline and changes after exercise training programme. Values expressed as median (interquartile range).

	AC group				Without-AC group*			
	ET during therapy		ET after therapy		ET during therapy		ET after therapy	
	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
	n = 22	n = 19	n = 75	n = 51	n = 28	n = 12	n = 40	n = 23
Haemoglobin (g/l)	126 (113–134)	-12 (-26–0.5)	120 (111–132.5)	7 (-1–18.5)	117 (102–129)	6 (4.3–7.5)	126 (113–138)	0 (-6–5)

ET: exercise training.

* The without-AC group consists of patients who received cardiotoxic therapy other than anthracyclines (non-AC group) and patients who received non-cardiotoxic therapy (non-CTOX group).

Table S2:

Training data from patients with available baseline and conclusion cardiopulmonary exercise tests performing exercise training during or after cancer therapy. Values expressed as median (interquartile range).

Training characteristics	AC group (n = 141)		Without-AC group* (n = 121)	
Timing of exercise training	**During cancer therapy**	**After cancer therapy**	**During cancer therapy**	**After cancer therapy**
Exercise training sessions per week	1.1 (0.6–1.7)	1.3 (0.9–1.6)	1.3 (0.8–1.6)	1.3 (0.8–1.7)
Compliance with exercise training (%)	75% (45.8–95.8%)	95.8% (70.8–100%)	83.3% (63.5–100%)	91.7% (50–100%)
	Centre-based (n = 19): 70.8% (43.8–87.5%)	Centre-based (n = 85): 87.5% (66.7–100%)	Centre-based (n = 40): 83.3% (65.6–100%)	Centre-based (n = 61): 91.7% (50–100%)
	Hybrid (n = 6): 100% (81.3–100%)	Hybrid (n = 28): 100% (100–100%)	Hybrid (n = 6): 100% (62.5–100%)	Hybrid (n = 13): 100% (50–100%)
Time from cancer diagnosis to start of exercise training (weeks)	8.7 (5.9–12.3)	40.0 (29.9–66.1)	41.9 (30.2–119.1)	41.5 (30.7–89.3)
Training intensity relative to mean peak power (%)*	46.7% (44.4–50.8%)	46.7% (41.8–50.7%)	48.8% (41.6–51.7%)	47.3% (42.0–51.3%)
Training intensity relative to peak power at baseline (%)	46.2% (42.3–49.4%)	50.5% (45.7–56.7%)	50.1% (42.3–56.7%)	50.7% (43.6–56.6%)
Training intensity relative to mean power at VT_1 (%)*	114.9% (104.4–128.4%)	118.5% (93.9–164.5%)	130.9% (106.2–160.3%)	115.3% (90.3–140.2%)
Training intensity relative to mean HR peak (%)*	81.5% (78.9–83.6%)	79.9% (75.4–85.4%)	77.5% (74.3–84.8%)	77.0% (74.2–83.9%)
Training intensity relative to heart rate reserve (%)**	65% (60.8–69.7%)	62.4% (54.6–69.0%)	59.7% (55.6–66.1%)	57.2% (47–67.3%)
Mean MET	5.3 (5.1–5.8)	4.6 (3.9–5.5)	4.0 (3.5–4.8)	4.4 (3.8–5.2)
Weekly endurance volume (MET-minutes/week)	228 (149–276)	192 (121–257)	160.7 (98.2–219)	188 (128–245)
Weekly exercise volume including strength and endurance training (MET-minutes/week)	427 (297–519)	405 (294–487)	370 (286–433)	386 (272–475)
Training impulse based on peak power at baseline (min × %)	241 (193–335)	351 (259–451)	314 (201–430)	330 (192–447)
Training impulse based on mean peak power (min × %)*	248 (189–338)	341(268–407)	324 (249–394)	348 (276–404)

MET: metabolic equivalent of task.

Training impulse: number of training sessions × session duration [min] × load [% of peak power at baseline].

Missing cases in each group were 13 for anthracycline-based chemotherapy (AC) during therapy, 48 for AC after therapy, 20 for non-AC during therapy and 29 for non-AC after therapy.

* The without-AC group consists of patients who received cardiotoxic therapy other than anthracyclines (non-AC group) and patients who received non-cardiotoxic therapy) non-CTOX group).

** calculated as mean from cardiopulmonary exercise tests at exercise trainings baseline and conclusion.

*** two patients were removed for calculation of intensities based on erroneous values.