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Effects of aerobic or resistance exercise during neoadjuvant chemotherapy on tumor response and therapy completion in women with breast cancer: The randomized controlled BENEFIT trial

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Abstract

Background: The potential of exercise as a concurrent therapy for actively treated primary tumors has been suggested by emerging preclinical and observational studies. However, clinical trials regarding this question are scarce. Therefore, we conducted a randomized controlled trial investigating the effects of aerobic or resistance exercise concomitant to neoadjuvant chemotherapy (NACT) on tumor size.

Methods: In the BENEFIT study (German title: Bewegung bei neoadjuvanter chemotherapie zur verbesserung der fitness), patients with breast cancer scheduled for NACT were randomly assigned to supervised resistance training (RT, $n = 60$) or aerobic training (AT, $n = 60$) twice weekly during NACT or to a waitlist control group (WCG, $n = 60$). The primary outcome, "change in tumor size", as well as the secondary clinical outcomes pathologic complete response (pCR), type of surgery (breast conserving/mastectomy), axillary lymph node dissection (ALND, yes/no), premature discontinuation of chemotherapy (yes/no), and relative dose intensity (RDI) were derived from clinical records. Due to the highly skewed distribution, the primary outcome was categorized. Multiple (ordinal) logistic regression analyses were performed.

Results: Overall, there was no significant difference in post-intervention tumor size between RT or AT and WCG. However, there was a significant effect modification by hormone receptor (HR) status ($p_{interaction} = 0.030$). Among patients with HR+ tumors, results suggest a beneficial effect of AT on tumor shrinkage (odds ratio (OR) = 2.37, 95% confidence interval (95%CI): 0.97–5.78), on pCR (OR = 3.21, 95%CI: 0.97–10.61); and on ALND (OR = 3.76, 95%CI: 0.78–18.06) compared to WCG. The effects of RT were slightly less pronounced. For HR−subtypes, beneficial effects on RDI were found for AT (OR = 3.71, 95%CI: 1.20–11.50) and similarly for RT (OR = 2.58, 95%CI: 0.88–7.59). Both AT and RT had favorable effects on premature discontinuation of chemotherapy (OR (no *vs.* yes) = 2.34, 95%CI: 1.10–5.06), irrespective of tumor receptor status.

Conclusion: While there was no significant effect on the primary outcome in the overall group, aerobic and resistance exercise concomitant to NACT seem to beneficially affect tumor shrinkage and pCR, reduce the need for ALND among patients with HR+ breast cancers, and prevent low RDI among patients with HR− breast cancers. These results warrant confirmation in further trials.

Keywords: Supervised exercise; Neoadjuvant chemotherapy; Tumor response; Pathologic complete response; Clinical cancer outcomes

1. Introduction

There is compelling evidence that exercise can positively impact the physical and mental wellbeing and quality of life of cancer patients.[1] It is also of great interest, yet still unclear, whether exercise can reduce tumor size or function.[2,3]

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Preclinical studies suggest that exercise may counteract the growth and spread of certain cancers through mechanisms involving tumor metabolism, immune response, apoptosis, DNA synthesis and repair, or by enhancing the delivery and effectiveness of cancer drugs.[4] Despite these promising preclinical data, clinical studies examining the direct impact of exercise on tumor response or the antitumoral effectiveness of cancer drugs in patients are scarce.[2] Neoadjuvant chemotherapy (NACT), which refers to the application of chemotherapy before tumor surgery, provides a good framework for investigating various clinically relevant outcomes, including tumor shrinkage from pre to post NACT with or without a concomitant exercise intervention. Besides tumor size, a more common clinical outcome for evaluating tumor response to NACT is pathologic complete response (pCR), defined as the complete disappearance of the invasive cancer.[5] In breast cancer, this means the absence of any invasive tumor in the breast and the axillary lymph nodes. Tumor shrinkage during NACT may also be highly relevant for patients with respect to the type and extent of breast surgery and lymph node excision.[6] In previous studies, patients who received a mastectomy self-reported significantly lower global health, physical and social functioning, and a higher burden of pain compared to patients who had a breast conserving surgery.[7] Axillary lymph node dissection (ALND), which is performed when there is residual axillary disease (ypN+) after NACT, is associated with morbidity and pain.[8]

In addition to tumor shrinkage or pCR, chemotherapy compliance is also relevant and has been considered an important treatment goal. Reducing chemotherapy dose intensity through treatment delays, dose reduction, or premature discontinuation can increase the risk for recurrence and death from cancer.[9] Chemotherapy compliance is often assessed by relative dose intensity (RDI), which is the ratio of the amount of chemotherapy delivered *vs.* the amount initially prescribed. An RDI below 85% is commonly regarded as a clinical threshold at which the efficacy of chemotherapy and thus the prognosis deteriorate significantly.[10]

Few observational studies have explored the relationship between exercise or physical activity during NACT and such clinical outcomes, and the results of these studies have been inconsistent. For instance, a study involving 1075 breast cancer patients undergoing NACT as part of the CANcer TOxicities (CANTO) cohort found no significant association between physical activity and pCR or chemotherapy completion, either in the overall cohort or when stratified by tumor subtype based on human epidermal growth factor receptor 2 (HER2) and hormone receptors (HR).[11] A case-control study involving 243 breast cancer patients receiving NACT found that exercise was significantly associated with higher odds for chemotherapy completion but was not associated with pCR.[12]

To our knowledge, only 3 randomized controlled trials (RCTs) have been published that explored the effects of exercise during NACT on tumor response.[13–15] However, the results are inconclusive. The first was a small pilot trial including only 10 patients.[13] The second trial (LEANer study) randomized women with early-stage breast cancer to either a home-based exercise and nutrition intervention or usual care.[14] The intervention consisted of individual in-person, telephone, or video counseling sessions over the course of chemotherapy, conducted weekly for the first month, biweekly for the second and third months, with monthly sessions thereafter. In the subgroup of participants receiving NACT ($n = 72$), the pCR rate was significantly higher in the intervention group compared to the control group. In contrast, in the third RCT, the MAMA_MOVE Gaia on Treatment (MMGOT) trial, where women with early breast cancer undergoing anthracycline-based chemotherapy were randomized to a supervised aerobic and resistance exercise training program (3 sessions per week) or usual care, no differences in pCR rates were observed between the exercise and the control group in the subgroup of patients receiving NACT ($n = 64$).[15]

Thus, more well-designed trials are urgently needed to examine the antitumoral effects of exercise. As emphasized by the "Exercise as Cancer Treatment" framework, it is important to consider tumor and treatment status when assessing the efficacy of exercise as a cancer therapy.[3] Accordingly, in the present study, we focus on patients with a primary tumor (early-stage breast cancer) who have not yet received treatment. We investigated the effects of resistance or aerobic exercise on change in tumor size (primary outcome), as well as on pCR, type of breast surgery, ALND, chemotherapy completion, and RDI in breast cancer patients undergoing NACT, under consideration of HR and HER2 tumor subtypes.

2. Materials and methods

2.1. Study design, population, and randomization

The BENEFIT trial (German title: Bewegung bei neoadjuvanter chemotherapie zur verbesserung der fitness) is a 3-arm RCT investigating the efficacy of resistance training (RT) or aerobic training (AT) in breast cancer patients undergoing NACT compared to a waitlist control group (WCG) that received usual care without any exercise intervention during NACT. The study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg (S-678/2015) and was registered at clinicaltrials.gov (NCT02999074). Written informed consent was obtained from all participants. The participants were recruited between January 2016 and October 2022 mainly, but not exclusively, from the National Center for Tumor Diseases (NCT) Heidelberg.

Adult female breast cancer patients were eligible if they were scheduled for NACT, had a body mass index (BMI) of $\geq 18\ kg/m^2$, sufficient language proficiency, and were willing to participate in the study measurements and engage in twice-weekly exercise sessions at one of the collaborating gyms. Patients who had a health condition that could interfere with their ability to participate in the study or who were already performing regular exercise (i.e., at least 2 sessions of at least 1 h per week) were excluded. Eligible participants were randomly assigned to 1 of 3 groups in a 1:1:1 ratio (AT, RT, or WCG) based on a blocked randomization stratified by tumor type (HR−, HR+/HER2+, and HR+/HER2−). The biometrician, who was not involved in the recruitment of the patients,

performed the allocation after completion of the baseline assessments based on computer-generated lists that were concealed to the other study personnel. The baseline visits and randomization were performed before the start of NACT.

2.2. Study measures

The primary outcome was change in tumor size defined as percentage of change from the maximal diameter of the tumor assessed before NACT (by mammography or sonography) to the maximal diameter assessed after NACT at breast surgery. A major secondary outcome comprised pCR defined as ypT0/is and ypN0. As further outcomes, type of breast surgery (mastectomy/breast conserving surgery) and ALND (yes/no) were derived from clinical records. For each cytostatic drug scheduled at the start of NACT, its RDI was calculated as cumulative dose that had been administered divided by the planned cumulative dose × 100. Then, the overall RDI was calculated as the average of the RDIs of all cytostatic drugs. Irrespective of dose adjustments or delays, we additionally assessed premature discontinuation of chemotherapy (yes/no) on the basis of clinical documentation and patient-reported information regarding whether and why chemotherapy was stopped prematurely. The main reasons for discontinuing NACT prematurely were side effects, such as chemotherapy-induced peripheral neuropathy or cardiotoxicity. Furthermore, the Clinical-Pathologic Stage (CPS-EG) score is an established prognostic factor for HR+/HER2− breast cancer and was assessed for this subgroup. The score combines clinical tumor stage *prior to* neoadjuvant therapy, pathological tumor stage after neoadjuvant treatment, estrogen receptor status, and nuclear grading.[16]

As covariates, age, pre-NACT tumor characteristics (grade, nodal status, ki67), and type of treatment were extracted from the medical records. BMI (kg/m^2) was calculated from measured baseline weight and height.

Cardio-respiratory fitness was measured at baseline (i.e., before the start of NACT) and after NACT via cardio-pulmonary exercise testing (CPET) on an electronically braked cycle ergometer (Ergoselect 100; Ergoline, Bitz, Germany). We measured peak oxygen uptake (VO_{2peak}) for exercise prescription and effect analysis. During the graded exercise test (a 2-min unloaded warm-up, then starting at 20 watts (W) and increasing the load by 10 W every minute) respiratory gas exchange was measured continuously using a breath-by-breath system (Ergostik; Geratherm Respiratory, Bad Kissingen, Germany). Gas exchange data were stationary time averaged over 30 s. VO_{2peak} was considered as the highest 30-s average value during or immediately post-exercise. For safety reasons, a 12-lead electrocardiogram was recorded continuously. Patients were encouraged to spend maximal effort until voluntary exhaustion.

Muscle strength was assessed with the IsoMed 2000-test system (D&R Ferstl GmbH, Hemau, Germany) at baseline and after NACT. Isokinetic dynamometer is considered to be the gold standard method for measuring muscle strength in healthy subjects as well as in cancer patients. Maximal isokinetic peak torque (MIPT) was measured bilaterally for extensors and flexors of the elbow and knee with an angular velocity of 60°/s. Range of motion for isokinetic measurements was from 10° to 90° of flexion in the knee (straight leg is 0°) and from 20° to 110° in the elbow. Patients were instructed to move the machine arm as strong and as fast as they could for 10 repetitions. We further tested maximal voluntary isometric contraction (MVIC) bilaterally for elbow flexors at an angle position of 80° and knee extensors at an angle position of 36°, which were consistently the strongest angle positions for each. Patients were instructed to exert maximum force and to keep it for 6 s. During measurements of the knee and elbow, patients were sitting in an upright position with a fixation belt fastened to the pelvis. An additional fixation was used at the tested thigh at the seating surface for the knee measurement, and at the tested upper arm for the elbow measurement. Values for MIPT and MVIC of the dominant side were included in the analysis.

2.3. Interventions

In the RT and AT groups, patients received a supervised training twice weekly over the whole course of NACT in experienced exercise oncology training facilities (OnkoAktiv Network or physiotherapy practices) close to home. The exercise regimens were in accordance with the guidelines for cancer survivors as set forth by the American College of Sports Medicine.

The AT was typically conducted on a cycle ergometer, though in selected instances it could also be performed on a rowing machine, treadmill, or elliptical trainer. The AT program was divided into 2 phases, allowing for a progressive increase in both duration and intensity:

Weeks 1−6: Continuous training

- Weeks 1 and 2: Each session lasted 15−30 min. The intensity was set at 60% of the patient's VO_{2peak}, which was determined at baseline through CPET.
- Weeks 3−6: Session duration increased to between 30 min and 60 min. The intensity gradually increased, reaching 70% of VO_{2peak} by Week 6.
- Week 7 onwards: Each session lasted approximately 30 min and utilized interval training consisting of 4 higher intensity intervals at 75%−85% VO_{2peak} for 4 min, interspersed with 3-min recovery intervals at 60% VO_{2peak}. Intensity monitoring was based on the patient's heart rate in all phases of the AT program.

The RT was a machine-based resistance training program that targeted major upper and lower muscle groups, and it included the leg extension, leg curl, leg press, shoulder internal and external rotation, seated row, latissimus pull down, butterfly, and butterfly reverse. Participants were instructed to perform 3 sets of 8−12 repetitions with a weight that could be lifted for 8−12 repetitions, corresponding to 60%−80% of the participant's 1-repetition maximum, which was determined after 2 familiarization sessions at each resistance machine.

Additionally, participants in RT and AT were instructed to perform a 15-min home-based exercise regimen once weekly without supervision. The home-based AT consisted of walking, jogging, or cycling, depending on the patient's ability and interests. The home-based RT consisted of core stability exercises without additional weights.

Participants randomized to WCG did not receive any intervention throughout NACT. However, approximately 6 weeks after their breast surgery, they were offered the same training as the RT group.

2.4. Statistical analysis

Power calculations were based on simulation analyses and an anticipated distribution of the primary outcome (change in tumor size, categorized as −100%, >−100% to −75%, >−75% to −25%, and >−25% due to high skewness with inflation on −100%) derived from existing data. It resulted in a sample size of 80 evaluable patients per group to yield a power of about 80% for detecting an overall difference between the 3 groups if the cumulative odds ratio (OR) (exercise *vs.* control) is about 2.3 for one exercise group and at least 1.2 for the other exercise group. Due to the coronavirus disease 2019 (COVID-19) pandemic and financial issues, a final sample size of 60 evaluable patients per group was obtained. A *post hoc* power analysis with the given sample size and distribution of the primary outcome yielded a power of 80% for detecting ORs of about 2.6 for RT and AT *vs.* WCG.

The primary outcome, change in tumor size, was analyzed using ordinal logistic regression with group (RT, AT, and WCG) as independent factor and adjustment for the stratification variable (HR−, HR+/HER2+, HR+/HER2−). The proportional odds assumption was checked with the score test. In addition, adjustment by age, BMI, pre-NACT tumor characteristics (grade, tumor size, nodal status, and ki67), and received cytostatics (taxanes, cyclophosphamide, anthracycline, and platin derivates) was explored for confounding or a better model fit. Further, effect modification by tumor type (HR, HER2, or combined HR/HER2 status) was investigated by testing an interaction term in the model. Interaction terms with $p < 0.20$ gave rise to subgroup analyses.

Analyses for all secondary outcomes are considered to be explorative. Logistic regression analyses were conducted for the intervention effect on the dichotomous secondary outcomes. Due to a highly skewed distribution of RDI with an inflation of the value 100%, we categorized the variable as <75%, 75% to <85%, 85% to <100%, and 100% and applied ordinal logistic regression. Due to the common dichotomization ≥85% *vs.* <85% for prognostic use, we additionally investigated this dichotomous variable for RDI in a logistic regression model.

All statistical analyses were conducted with SAS (Version 9.4; SAS Inc., Cary, NC, USA) according to the intent-to-treat principle. All tests were performed two-sided with $p < 0.05$ considered to be statistically significant.

3. Results

As presented in Fig. 1, 180 patients were eligible and randomized to RT ($n = 60$), AT ($n = 60$), or WCG ($n = 60$). For all patients, the primary and secondary outcomes could be extracted from the medical records, except for ALND, for which data were not available for 2 patients (1 each in AT and WCG). Table 1 presents the baseline characteristics of the

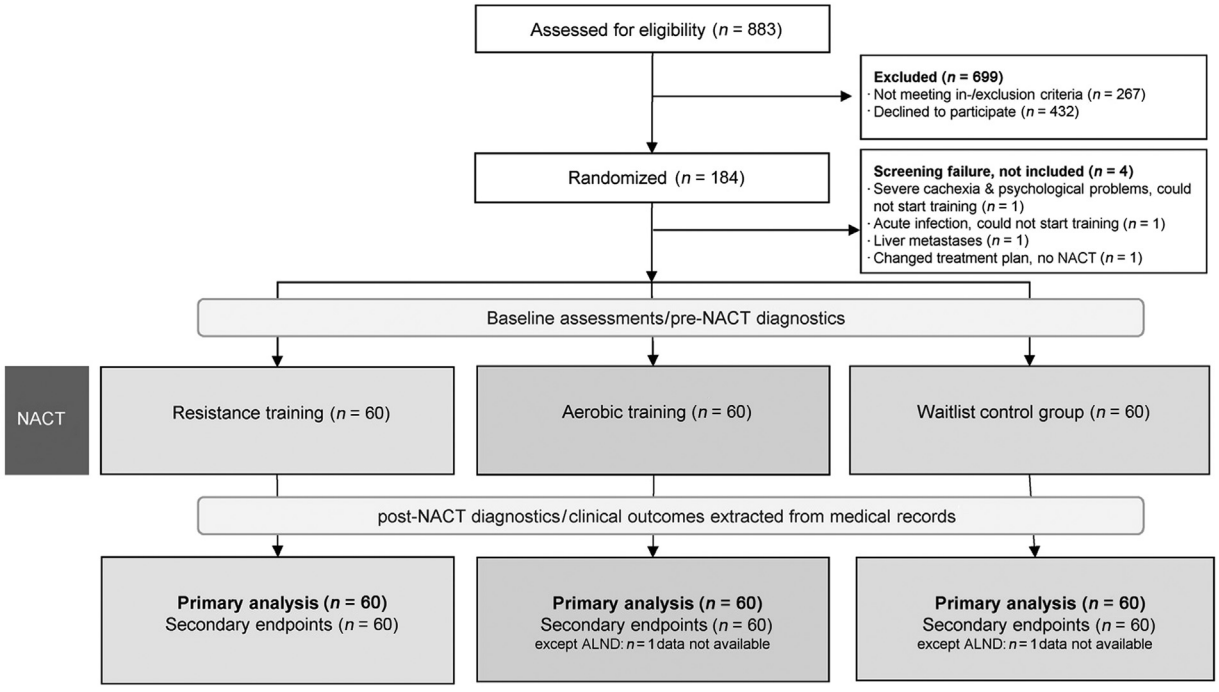

Fig. 1. Study flow chart. ALND = axillary lymph node dissection; NACT = neoadjuvant chemotherapy.

Table 1
Baseline and treatment characteristics of the study population

	Resistance training ($n = 60$)	Aerobic training ($n = 60$)	Waitlist control group ($n = 60$)
Age (year)	48.4 ± 10.9	51.4 ± 11.2	49.7 ± 9.9
Body mass index (kg/m^2)	25.8 ± 4.0	25.7 ± 6.0	27.6 ± 6.0
Education			
University	24 (40.0)	24 (40.0)	17 (28.3)
High school	9 (15.0)	13 (21.7)	21 (35.0‘)
Middle school	21 (35.0)	19 (31.7)	18 (30.0)
Lower education	5 (8.3)	4 (6.7)	4 (6.7)
Missing	1 (1.7)	–	–
Tumor subtype			
HR+	39 (65.0)	38 (63.4)	34 (56.6)
HR+/HER2−	24 (40.0)	25 (41.7)	23 (38.3)
HR+/HER2+	15 (25.0)	13 (21.7)	11 (18.3)
HR−	21 (35.0)	22 (36.7)	26 (43.3)
HR−/HER2+	3 (5.0)	4 (6.7)	2 (3.3)
HR−/HER2− (TNBC)	18 (30.0)	18 (30.0)	24 (40.0)
Nodal status			
cN0	37 (61.7)	41 (68.3)	33 (55.0)
cN1	16 (26.7)	12 (20.0)	19 (31.7)
cN2	3 (5.0)	5 (8.3)	3 (5.0)
cN3	3 (5.0)	2 (3.3)	5 (8.3)
Unknown	1 (1.7)	–	–
Grade			
1	0 (0)	2 (3.3)	1 (1.7)
2	28 (46.7)	27 (45.0)	13 (21.7)
3	32 (53.3)	31 (51.7)	46 (76.7)
Tumor size (mm), pre-NACT	28.1 ± 14.6	27.7 ± 17.6	33.2 ± 22.0
Time since diagnosis (day)	28.4 ± 12.3	31.8 ± 12.7	28.4 ± 13.4
NACT (number of cycles)			
Taxanes (T)			
	60 (100.0)	60 (100.0)	60 (100.0)
	8.4 ± 3.4	8.9 ± 3.2	9.1 ± 3.6
Cyclophosphamide (C)			
	42 (70.0)	40 (66.7)	41 (68.3)
	2.8 ± 2.0	2.7 ± 2.0	2.6 ± 1.9
Anthracycline (A)			
	37 (61.7)	35 (58.3)	42 (70.0)
	2.3 ± 1.9	2.3 ± 2.0	2.8 ± 2.4
Platin derivates (P)			
	29 (48.3)	32 (53.3)	30 (50.0)
	2.9 ± 3.3	3.8 ± 4.0	3.5 ± 4.3
Combinations			
T + A + C	25 (41.7)	21 (35.0)	26 (43.3)
T + P	17 (28.3)	18 (30.0)	15 (25.0)
T + A + C + P	12 (20.0)	14 (23.3)	14 (23.3)
Other	6 (10.0)	7 (11.7)	5 (8.3)

Notes: Data are shown as mean ± SD or *n* (%). Percentages might not add up to 100% due to rounding.
Abbreviations: HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; NACT = neoadjuvant chemotherapy; TNBC = triple-negative breast cancer.

study population by randomization group. Age was equally distributed across groups with an average age of 50 years (SD = 11 years). Despite randomization, patients in WCG had a slightly higher BMI compared to those in RT and AT (27.6 ± 6.0 *vs.* 25.8 ± 4.0, and 25.7 ± 6.0 (mean ± SD), respectively), and were more likely to have a triple-negative breast cancer (TNBC) subtype (40.0% *vs*. 30.0% and 30.0%, respectively) and tumor Grade 3 (76.7% *vs*. 53.3% and 51.7%, respectively). All patients received taxanes as part of their NACT, with a similar number of cycles across all 3 groups. The most frequent NACT ($n = 72$, 40.0%) included taxanes, anthracyclines, and cyclophosphamide, often according to the scheme 4× epirubicin and cyclophosphamide followed by 12× (nab-)paclitaxel. Furthermore, 40 patients (22.2%) received all 4 cytostatic drugs, often following the scheme 4× epirubicin and cyclophosphamide followed by 12× carboplatin and (nab-)paclitaxel, or *vice versa*. Another common NACT combination ($n = 50$, 27.8%) included taxanes and platin derivates—typically 6× docetaxel and carboplatin. The duration of NACT ranged from 6 to 31 weeks, with a mean (SD) of 20.2 ± 4.0 weeks, without differences between RT, AT, and WCG.

Table 2
Effects of the exercise interventions on clinical outcomes: (ordinal) logistic regression models

Outcome	Group comparison	Adjusted for randomization strata OR (95%CI)	*p*	Multiple adjusted model OR (95%CI)	*p*	Test of effect modification
Change in tumor size (−100%, >−100% to −75%, >−75% to −25%, and >−25%)	RT *vs*. WCG	0.92 (0.45–1.87)	0.81	1.01 (0.51–2.22)	0.86	Strata: $p_{inter} = 0.15$
	AT *vs*. WCG	1.16 (0.57–2.38)	0.68	1.36 (0.65–2.86)	0.41	HR: p_{inter} **= 0.030**
						HER2: $p_{inter} = 0.65$
pCR (yes *vs.* no)	RT *vs*. WCG	0.87 (0.39–1.91)	0.72	1.01 (0.43–2.37)	0.98	Strata: $p_{inter} = 0.31$
	AT *vs*. WCG	1.03 (0.46–2.27)	0.95	1.17 (0.49–2.76)	0.73	HR: p_{inter} **= 0.13**
						HER2: $p_{inter} = 0.50$
Breast conserving surgery (yes *vs.* no)	RT *vs*. WCG	1.42 (0.69–2.93)	0.35	1.83 (0.80–4.20)	0.15	Strata: $p_{inter} = 0.68$
	AT *vs*. WCG	1.01 (0.49–2.08)	0.97	0.95 (0.42–2.15)	0.90	HR: $p_{inter} = 0.43$
						HER2: $p_{inter} = 0.71$
ALND (no *vs.* yes)	RT *vs*. WCG	1.01 (0.48–2.16)	0.97	0.90 (0.27–2.95)	0.86	Strata: $p_{inter} = 0.24$
	AT *vs*. WCG	1.98 (0.88–4.48)	0.10	2.46 (0.75–8.06)	0.14	HR: p_{inter} **= 0.17**
						HER2: $p_{inter} = 0.50$
Premature discontinuation of chemotherapy (no *vs.* yes)	RT *vs*. WCG	2.02 (0.86–4.74)	0.12	2.41 (0.97–6.01)	0.058	Strata: $p_{inter} = 0.86$
	AT *vs*. WCG	2.87 (0.82–4.33)	0.14	2.32 (0.95–5.67)	0.064	HR: $p_{inter} = 0.68$
	IG *vs*. WCG	1.95 (0.95–3.97)	0.067	**2.34 (1.10–5.09)**	**0.027**	HER2: $p_{inter} = 0.65$
RDI (100%, 85% to <100%, 75% to <85%, and <75%)	RT *vs*. WCG	1.41 (0.72 –2.74)	0.32	1.39 (0.70–2.75)	0.34	Strata: $p_{inter} = 15$
	AT *vs*. WCG	1.24 (0.62–2.42)	0.52	1.25 (0.63–2.48)	0.52	HR: p_{inter} **= 0.094**
						HER2: $p_{inter} = 0.64$

Notes: The following variables have been investigated for confounding or improvement of model fit: age; body mass index; depressive symptoms; education; HR, HER2, or combined tumor subtypes; tumor grade; cN; cT; baseline ki67; type of NACT: platin (yes/no), anthracycline (yes/no), cyclophosphamide (yes/no), or combinations of all; targeted therapy (other than trastuzumab/pertuzumab, which was identical with HER2). The final models include variables that indicated potential confounding of the group effect or improved the model fit. Odds ratios with $p < 0.05$ or interactions with $p < 0.2$ are marked in bold.
Abbreviations: 95%CI = 95% confidence interval; ALND = axillary lymph node dissection; AT = aerobic training; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IG = exercise intervention group (AT and RT combined); NACT = neoadjuvant chemotherapy; OR = odds ratio; pCR = pathologic complete response; $p_{inter} = p_{interaction}$; RDI = relative dose intensity; RT = resistance training; WCG = waitlist control group.

Regarding training adherence, patients in RT attended a median (Q1, Q3) of 16 (8, 25) sessions, and in AT, 16 (8, 32) sessions. Seven patients (4 in RT and 3 in AT) never started their training due to cancer therapy-related side effects or psychological issues. Attendance above 75% of scheduled sessions twice weekly over the whole course of NACT was reached by only 12% in RT and 13% in AT. Further details on attendance over time have been published previously.[17] The RT group showed significant benefits (adjusted difference (95% confidence interval, 95%CI)) in knee muscle strength compared to the WCG in MVIC (knee extension: 11.37, 95%CI: 1.54−21.21, $p = 0.024$) and non-significant benefits in MIPT (knee extension: 4.20, 95%CI: −2.75 to 11.16, $p = 0.24$; and knee flexion: 2.35, 95%CI: −1.68 to 6.39, $p = 0.25$). AT showed no effects on these measures (Supplementary Table 1). Analysis of elbow muscle strength showed no significant differences. Regarding the CPET testing, the AT group showed significant benefits in aerobic capacity (VO_{2peak}) compared to the WCG (0.15, 95%CI: 0.02−0.29, $p = 0.024$), whereas the RT group did not differ significantly from the WCG.

After NACT, 49.4% of the patients had pCR, with the lowest rates among HR+/HER2− (25.0%) and highest rates among HR− subtypes (HR−/HER2+: 88.9%, TNBC: 70.0%). Detailed data by tumor subtype can be found in Supplementary Table 2. Overall, 45.0% of patients had a mastectomy, and 31.5% had to undergo ALND, with slightly varying rates between tumor subtypes and intervention groups. Chemotherapy was prematurely discontinued by 27.9%, with the highest rate among TNBC patients (41.7%) but overall lower rates in the AT group. Overall, the median (Q1, Q3) RDI was 96.7 (95%CI: 86.6−100.0). In the subgroup of patients who did not complete chemotherapy, the median (Q1, Q3) RDI was 83.9 (95%CI: 73.2−92.3).

The results of the logistic regressions for the primary and secondary clinical outcomes are presented in Table 2. Overall, there was no significant intervention effect on change in tumor size, pCR, type of surgery, ALND, or RDI. Yet, there were similar lower odds for premature discontinuation of chemotherapy for both exercise groups compared to WCG; thus, when both exercise groups were combined, the OR was 2.34 (95%CI: 1.10–5.09, $p = 0.027$) compared to WCG.

Effect modification analyses suggested a modifying effect of the HR status for several outcomes (Table 2). Subsequent subgroup analyses stratified by HR status (Table 3) showed positive effects for AT compared to WCG in the subgroup of patients with HR+ breast cancer (i.e., higher odds for larger reduction in tumor size (OR = 2.37, 95%CI: 0.97–5.78, $p = 0.059$), for pCR (3.21, 95%CI: 0.97–10.61, $p = 0.056$), and a tendency of higher odds for not needing ALND (3.76, 95%CI: 0.78–18.06, $p = 0.10$)). The effects of RT on tumor change, pCR, and ALND were similar but slightly less pronounced. In contrast, among patients with HR− breast cancer, the exercise groups had higher RDI compared to WCG

Table 3
Effects of the exercise interventions on clinical outcomes: multiple adjusted (ordinal) logistic regression models by hormone receptor status.

Outcome	Group comparison	HR+ OR (95%CI)	*p*	HR− OR (95%CI)	*p*
Change in tumor size	RT *vs*. WCG	1.39 (0.58–3.30)	0.46	0.47 (0.09–2.35)	0.36
(−100%, >−100% to −75%, >−75% to −25%, and >−25%)	AT *vs*. WCG	2.37 (0.97–5.78)	0.059	0.43 (0.09–2.14)	0.30
pCR (yes *vs.* no)	RT *vs*. WCG	2.38 (0.71–7.97)	0.16	1.17 (0.17–7.99)	0.87
	AT *vs*. WCG	3.21 (0.97–10.61)	0.056	0.38 (0.07–2.24)	0.29
ALND (no *vs.* yes)	RT *vs*. WCG	2.36 (0.50–11.05)	0.28	0.11 (0.01–1.82)	0.12
	AT *vs*. WCG	3.76 (0.78–18.06)	0.10	1.11 (0.13–9.91)	0.92
RDI (100%, 85% to <100%, 75% to <85%, and <75%)	RT *vs*. WCG	0.92 (0.38–2.23)	0.85	2.58 (0.88–7.59)	0.085
	AT *vs*. WCG	0.71 (0.28–1.81)	0.48	**3.71 (1.20–11.50)**	**0.023**

Notes: Subgroup HR+ includes 39, 38, and 34 patients in RT, AT, and WCG, respectively. Subgroup HR− includes 21, 22, and 26 patients in RT, AT, and WCG, respectively. The following variables have been investigated for confounding or improvement of model fit: age; body mass index; depressive symptoms; education; HR, HER2, or combined tumor subtypes; tumor grade; cN; cT; baseline ki67; type of NACT: platin (yes/no), anthracycline (yes/no), cyclophosphamide (yes/no), or combinations of all; targeted therapy (other than trastuzumab/pertuzumab, which was identical with HER). The final models include variables that indicated potential confounding of the group effect or improved the model fit. Only outcomes considered, where testing interaction with HR status gave rise to subgroup analyses ($p < 0.20$, Table 2).
Abbreviations: 95%CI = 95% confidence interval; ALND = axillary lymph node dissection; AT = aerobic training; HR = hormone receptor status; NACT = neoadjuvant chemotherapy; OR = odds ratio; pCR = pathologic complete response; RDI = relative dose intensity; RT = resistance training; WCG = waitlist control group.

(AT *vs*. WCG: 3.71, 95%CI: 1.20–11.50), $p = 0.023$; RT *vs*. WCG: 2.58, 95%CI: 0.88–7.59, $p = 0.085$). The logistic regression results on the dichotomized RDI variable (≥85% *vs.* <85%) tended in the same direction but were not statistically significant.

The effects of RT and AT on change in tumor size, pCR, and ALND did not alter when the models were adjusted by premature discontinuation of chemotherapy or by RDI. Hence, there seems to be no mediating effect by these variables. Among patients with HR+/HER2− breast cancer, the CPS-EG score did not differ between the 3 intervention groups (Kruskal-Wallis test, $p = 0.97$, Supplementary Fig. 1).

4. Discussion

The randomized controlled BENEFIT trial did not show significant effects of aerobic or resistance training on the primary outcome, change in tumor size, in the overall study sample of breast cancer patients undergoing NACT. However, there was a significant effect modification by HR status. Among patients with HR+ tumors, results suggest some beneficial effects of the exercise interventions on change in tumor size, pCR, and ALND compared to the WCG. Among patients with HR− tumors, the exercise interventions were significantly associated with higher RDI compared to the WCG. Moreover, irrespective of HR status, the rate of premature discontinuation of chemotherapy was significantly lower among patients randomized to any exercise intervention compared to the WCG.

So far, exercise effects on change in tumor size during NACT have been investigated in only 1 small pilot RCT, where in the intervention group ($n = 5$, supervised bootcamp involving aerobic and resistance exercises) the mean tumor size decreased from 5.06 cm at baseline to 2.59 cm post-intervention, which was similar to the control group ($n = 5$, from 4.88 cm to 3.16 cm, $p = 0.76$).[13] Furthermore, 2 RCTs have investigated the effects of exercise during NACT on pCR, but they yielded inconclusive results. The MMGOT trial found no difference in pCR between the exercise and control groups (56.7% *vs*. 55.9%, $p = 0.95$).[15] In contrast, the LEANer study found a significantly higher pCR rate among the women randomized to an intervention combining exercise and nutrition compared to usual care controls (53% *vs*. 28%; χ^2 test: $p = 0.037$).[14] In line with our results, the effect on pCR was seen in the HR+/HER2− subgroup. They also found a significant effect in the TNBC but not the HER2+ subgroup (which however was not further distinguished by HR status).[14] In addition, a single small RCT exists investigating exercise in patients with rectal cancer who are undergoing neoadjuvant chemo-radio-therapy (EXERT study).[18] In this study, 10 of the 18 patients in the exercise group (56%) achieved pCR/near pCR compared to 3 of 17 (18%) in the usual care group ($p = 0.020$). We are not aware of any published exercise RCTs investigating effects on lymph node positivity or ALND.

The observed beneficial effects of exercise on tumor shrinkage and pCR for HR+ breast cancer were not explained by better RDI or lower rates of premature discontinuation of chemotherapy in RT and AT. Thus, the mechanisms underlying the exercise effect warrant further exploration. There is strong evidence that estrogens, progesterone, and androgen levels may decrease in response to exercise or physical activity.[19] Physical activity has been observed as a preventive factor for HR+ (but not HR−) breast cancer.[20,21] Likewise, steroid hormones have been proposed to play a key role in the preventive effect of physical activity on HR+ breast cancer.[19] Thus, it is perceivable that steroid hormones might also play a role in reducing tumor burden by exercise during NACT. However, pCR is commonly lowest in the HR+/HER2− breast cancer subtype (in our study: 25% pCR), whereas it was 72.5% for the HR− subtype. It might be that this strong effect of NACT on pCR among HR− may eclipse other, smaller

potential effects of exercise. Irrespective of HR status, preclinical studies suggest a broad spectrum of potential exercise effects, either directly on the tumor and its microenvironment or systemic effects such as reduced inflammation and improved immune or metabolic function.[4] For example, cancer models in mice and studies in humans have indicated that exercise can upregulate ligands for activating natural killer cell receptors, thereby enhancing their cytotoxic potential.[22] Furthermore, exercise may affect cellular metabolism via mechanical stresses, which trigger the secretion of tumor-impacting cytokines, such as dopamine, nexin, and TNF-related apoptosis-inducing ligand, as has been shown in preclinical and clinical studies.[23] Moreover, hypoxia seems to be a factor that may impair the effectiveness of chemotherapy.[24] Preclinical and clinical studies suggest that (aerobic) exercise may improve tumor blood flow (e.g., via higher tumor microvessel density, increased tumor perfusion, and increased tumor vascularization), thus enhancing the delivery of systemic therapies.[24,25] Indeed, our study showed somewhat higher effect sizes on pCR with aerobic exercise than with resistance exercise.

Premature discontinuation of NACT was significantly less frequent in our exercise groups than in the WCG. Significant exercise effects on RDI, however, were seen only among patients with HR− tumors, which might be due to the often more aggressive NACT for patients with HR− tumors, which can result in greater dose reductions or treatment discontinuation. In contrast, among patients with HR+ tumors, RDI is generally high; thus, there is less potential for further improvement with exercise. Indeed, in our study sample, 33.3% of HR− *vs*. 15.3% of HR+ patients had an RDI < 85%, which is associated with reduced chemotherapy effectiveness and significantly worse prognosis.[10,26] The LEANer study did not show significant intervention effects on RDI, but it did not consider the HR− subgroup, which is where our study observed the significant intervention effects. A review of exercise RCTs irrespective of cancer entity and timing of chemotherapy found that 2 of 8 identified RCTs showed a beneficial effect of exercise intervention on RDI or chemotherapy adherence.[27] Decisions on chemotherapy dose modifications are often based on treatment toxicities, the patient's performance status, presence of comorbidities, and patient-reported outcomes such as fatigue.[27] Increased muscle mass enhances drug metabolism and reduces toxicity;[28] and high fat and low lean mass, low skeletal muscle mass, or sarcopenia have been found to be associated with higher treatment toxicity and poorer chemotherapy tolerance in various studies.[29–31] Our results indicated beneficial effects on RDI for both resistance and aerobic exercise, which were, however, slightly more pronounced in the AT group.

Our results are of high relevance for patients, as larger tumor shrinkage may result in less-extensive surgeries, and avoiding ALND is crucial to reducing the associated patient burden, which encompasses limitations in range of motion, edema, chronic pain, and sensory defects.[8] Moreover, improving chemotherapy completion and RDI is clinically relevant, because dose reductions or premature discontinuation of NACT have been associated with worse prognosis previously.[26,32]

Limitations of our study need to be addressed. First, due to heterogeneous and changing cancer therapies, residual confounding cannot be excluded. Likewise, as a number of secondary exploratory analyses were performed without adjusting for multiple testing, chance finding cannot be excluded. On the other hand, attendance to the training sessions markedly dropped over the course of NACT, as has been described in detail previously,[17] with consequently modest effects on fitness outcomes. Thus, the effects of exercising during NACT on tumor size and other clinical outcomes might even have been underestimated. Finally, the small sample size (especially for subgroup analyses) lacks power for detection of smaller effects as well as for testing superiority of one type of exercise compared to the other. However, BENEFIT is the largest RCT so far, and it contributes valuable insights on the effects of exercise concomitant to NACT on clinical outcomes. The investigation of different types of exercise (i.e., aerobic and resistance training) is a further strength. While aerobic exercise showed more pronounced effects, both exercise modalities demonstrated benefits, suggesting that aerobic and resistance training (or probably a combination of both) can be recommended for breast cancer patients undergoing NACT. Additionally, patient preferences should be considered, as motivation to initiate and sustain exercise is often a limiting factor for effective training.

5. Conclusion

Our results suggest that aerobic and resistance exercise concomitant to NACT may beneficially affect tumor shrinkage and pCR, and reduce the need for ALND among patients with HR+ breast cancers. Furthermore, both aerobic and resistance exercise appeared to significantly reduce premature discontinuation of chemotherapy compared to the control group, irrespective of tumor type, and to prevent low RDI, especially among patients with HR− tumors. These results underline the importance of offering supervised aerobic or resistance exercise (or some combination of both) already during NACT and warrant confirmation in further, even larger trials.

Authors' contributions

MES participated in the conceptualization and supervision of the study, performed the statistical analyses and drafted the manuscript; KS and JW participated in the conceptualization and supervision of the study; FR, SG, CK, and JM participated in project administration and performed the assessments; AS supported recruitment and clinical data collection; AMM supported recruitment. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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Supplementary materials

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