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EFFECTS OF HOME-BASED EXERCISE TRAINING ON VO2 IN BREAST CANCER PATIENTS UNDER ADJUVANT OR NEOADJUVANT CHEMOTHERAPY (SAPA).

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ABSTRACT

Background. Breast cancer chemotherapy is associated with a decline in measured cardiorespiratory fitness and increased fatigue. Physical activity has emerged as a feasible intervention to limit these side effects. Quantitative evaluation is necessary to propose a better-adapted physical activity and to evaluate efficacy.

Aim. We undertook a prospective study to assess the effects of a home-based adapted physical activity (APA) program on aerobic capacity, strength, and fatigue in women treated with adjuvant or neoadjuvant chemotherapy for breast cancer versus usual care.

Design. This was an open two-arm, randomized controlled trial.

Setting. Study included outpatient groups in the Department of Physiology and Medical Oncology, at Limoges University Hospital, France.

Population. Forty-four patients treated with adjuvant or neoadjuvant chemotherapy for breast cancer.

Methods. Patients were randomly assigned to a control group or an APA group. Intervention consisted of a 3-week, home-based, supervised, combined APA program (endurance and resistance training) during 27 weeks. The primary endpoint was cardiopulmonary function assessed by maximal peak oxygen consumption (VO_{2peak}). Secondary endpoints included a 6-minute walking test (6MWT), and assessment of muscular strength, fatigue, quality of life, physical activity level, and anxiety/depression.

Results. At 27 weeks, VO_{2peak} increased by 1.83 ± 0.68 $ml.min^{-1}.kg^{-1}$ in the APA group (P = 0.009) and decreased by 1.31 ± 0.65 $ml.min^{-1}.kg^{-1}$ in the control group (P = 0.046). The difference between the two groups was not significant (2.26 ± 1.53 $ml.min^{-1}.kg^{-1}$, P = 0.140) in intention-to-treat analysis, but it was significant in per protocol analysis (3.49 ± 1.64

ml.min^{-1}.kg^{-1}, P = 0.049). At 27 and 54 weeks, no significant differences were observed between the two groups for the cardiopulmonary exercise test, 6MWT, quadriceps strength, or quality of life.

Conclusion. In breast cancer patients, a home-based supervised program during chemotherapy and radiotherapy treatment may be safe, feasible and increase VO_{2peak}. In this study, heavy evaluation tests explain patient's non-adherence and do not permit to obtain statistically significant results between APA and control groups.

Clinical Rehabilitation Impact: aerobic home-based adapted physical activity is beneficial on aerobic capacity.

Keywords: Oxygen consumption; breast cancer; adapted physical activity; adjuvant chemotherapy; neoadjuvant chemotherapy; home training; maximal peak oxygen consumption.

INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy of women in Western countries. Adjuvant chemotherapy for early stage breast cancer improves survival, but may also associated with unfavourable changes in quality of life (QoL), fatigue, muscle strength and cardiorespiratory fitness (CRF) such as peak oxygen consumption (VO_{2peak}) [21, 40-43]. Emerging evidence indicates that physical activity (PA) during adjuvant treatment may contribute to prevent these changes [20, 44, 45]. Unfortunately, these studies are heterogeneous and have methodological limitations, including different modes (endurance or resistance training), protocols (cycle ergometer or walking), sites (supervised or home exercise), and inconsistency in determining CRF using VO_{2peak} (assessed by cardiopulmonary testing) or non-VO_{2peak} (for example distance walked within a set time-frame), as shown in reviews and meta-analyses[19, 46, 47]. Objective methods to determine PA intensity are needed to better adapt PA program to each patient. The gold standard measure of CRF is maximal peak of oxygen consumption (VO_{2peak}). A correlation between VO_{2peak}, survival and quality of life has been shown on healthy people.[48].

We previously showed that home-based walking training program (WTP) had a beneficial effect on CRF (VO_{2peak} increased by 2.2 $mL.kg^{-1}.min^{-1}$) in patients with breast cancer receiving adjuvant treatment[26]. This pilot study suggests that home-based WTP is feasible, safe, and well tolerated but has no positive influence on cancer-related fatigue. This study was limited because of focus on small numbers of patients; effective home-based exercise programs the frequency and intensity of exercising, which is often a barrier to PA adherence.

The purpose of this phase III trial was to examine the effects of a home-based adapted physical activity (APA) program performed during chemotherapy on CRF (eg, VO2peak and walking test), strength, and fatigue in breast cancer patients receiving adjuvant or neoadjuvant treatment. We hypothesized that home-based, supervised, combined APA program

(endurance and resistance training) would have beneficial effects on CRF measured by VO_{2peak}, and beneficial effects for muscular strength and conditioning.

METHODS

Setting and participants

The SAPA trial was conducted at Limoges University Hospital (France). Patients eligible for study inclusion were women aged 18 to 75 years with early-stage breast cancer treated with chemotherapy (neoadjuvant or adjuvant) followed by radiotherapy. Patients received the same chemotherapy regimen. Six courses (3 FEC100, 3 Taxotere) were administered every 21 days. Exclusion criteria were metastatic disease, symptomatic cardiac or pulmonary disease, a left ventricular ejection fraction <50%, family history of sudden death in a first-degree patient, or ongoing treatment with beta-blockers. Ethical approval was obtained from the ethics committee of Limoges. Medical oncologists enrolled patients, explained the study, and obtained written informed consent. The trial was registered with ClinicalTrials.gov (NCT01322412).

Study design and procedures

The SAPA study was an open interventional single-center, two-arm, randomized, phase III trial. The trial compared two groups: the APA group performed the 27 weeks PA program during the chemotherapy and radiotherapy treatment, The control group received conventional management and was encouraged to remain on their regular activity level during and after chemotherapy and radiotherapy treatment. Patients were randomized with 1:1 allocation to the APA group or control group without stratification.

The study sample completed questionnaires and physical tests prior to chemotherapy (T0), 27 weeks after baseline and at the end of chemotherapy (T1), and 27 weeks after completing the chemotherapy regimen (T2).

The primary endpoint was a between-group comparison of aerobic capacity, measured by $VO_{2peak,}$ at 27 weeks. Secondary endpoints were: functional capacity, muscle strength, fatigue, quality of life, anxiety/depression, at 27 and 54 weeks between the two groups and VO_{2peak} at 54 weeks.

Outcomes measures

Cardiopulmonary exercise test (CPET)

All patients performed and incremental supervised CPET to determine VO_{2peak}, maximum power (P_{max}), and heart rate (HR) at the ventilatory threshold (VT). According to CPET guidelines for clinical and cancer populations.[11] a 12-lead electrocardiographic monitoring (Corina, GE Medical Systems IT Inc., Milwaukee, WI, USA) was performed during the exercise test. All tests were performed on an electronically braked cycle ergometer (Ergoline, model 900, Bitz, Germany) with breath-by-breath expired gas analysis (Vmax spectra metabolic cart, Model 29n, SensorMedics, Yorba Linda, CA, USA). The analysis of expired air allowed the determination of oxygen uptake (VO_2), carbon dioxide production (VCO_2), ventilation (VE), and respiratory exchange ratio (RER; $VCO_2.VO_2^{-1}$) during all rest and exercise periods. Maximal oxygen uptake was the highest oxygen uptake during exercise.

Six minutes walking test (6MWT)

The 6MWT was conducted twice according to the ATS guidelines and administered on a 25-m segment of a quiet corridor.[12] Under the supervision of a respiratory physiologist, patients were instructed to walk as quickly as possible for up to 6 min, and the total distance

walked was recorded. Patients were allowed to quit at any time during the 6-min test. Age- and sex-predicted 6MWT was calculated from Enright's equation.[13]

Muscular strength

Muscular strength of the quadriceps was determined using the best of three repetitions on an isometric bench with a strain gauge (Globus system). The measurement of maximal voluntary strength was realized while sitting, knee flexed to 90 °. The subject was sitting, back straight, no back support (to avoid contraction of the muscles of the trunk as additional force generator). He was asked the patient to hold the bench with hands at hips (maintenance of the basin). In addition, the opposite leg was not to remain placed on the ground but be free. The strength was measured on the right leg, then the left leg, only the value of the dominant leg was reported. For a valid measurement, it was necessary that the patient's strength reaches a plateau and it is supported at least 0.5s. Each test was followed by a minute of rest (3 trials). The force was measured in kg.

Fatigue

Fatigue was evaluated using the Multidimensional Fatigue Inventory (MFI-20),[14] Level of fatigue in 5 dimensions (general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation) was evaluated. A score was calculated for each dimension. The total score was calculated from the sum of the 5 scores. The questionnaire consists of 20 items, with respect to which the patient 's position on a scale of 5 levels, rated from 1 to 5, according to the fatigue experienced the day before the evaluation. A high score corresponds to a significant fatigue.

Quality of life

Quality of life was evaluated using the EORTC QLQ-C30.[15] It includes 30 items with obtaining 15 scores. Five functional scales on general domains (physical, social, cognitive, emotional, functional), a global health scale and 9 symptomatic scales (fatigue, nausea,

vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, financial problems). Measurements are from 0 to 100, a high score indicating a high level in a field of symptoms.

Anxiety and depression

Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS).[16] It was a self-administered questionnaire of 14 items rated from 0 to 3 , evaluating the anxious symptoms (7 items) and depression (7 items). A score (anxiety + depression) of 19 or more indicates a anxiety and depression. A score between 14 and 18 results in anxiety and depressive tendency. A score between 8 and 10 indicates a trend and a score ≥11 indicates anxiety or depression confirmed.

Physical activity questionnaire

The International Physical Activity Questionnaire (IPAQ)[17] was used to determine physical activity of the week preceding the assessment. It included 7 items. The score corresponds to energy expenditure in METs. The interpretation of this questionnaire defines the total activity of the week in three categories: low, moderate, and high.

Exercise training interventions

The APA consisted of a 27-week home-based exercise program that combined strength and aerobic training performed throughout the time period of adjuvant chemotherapy. The main aim for the APA group was to perform PA regularly during the 27 weeks for a minimum of 3 times per week. The APA program was individually tailored to each patient. An exercise specialist provided detailed information about the APA program; the same specialist evaluated the home activity and fitness of patients at each course of chemotherapy. The women in the APA group were supported and encouraged in their exercise by motivational telephone calls from the exercise specialist every week. The telephone calls were also used to

monitor adverse events. Aerobic training was performed at home on a cycle ergometer twice a week or outside by walking. Intensity of the exercise was adapted to HR and power, as determined by the first VT of the CPET. The aerobic session consisted on 5-min warm-up, central phase and cool down. For cycle ergometer training, patient set metronome at the target power and should maintained cycling speeds of 60 revolutions per minute. For walking training, the target was HR determined by the first VT of the CPET. The duration of central phase was 20 min initially, with an increase of 5 min every 6 weeks to achieve 40 min at the end of the program. Strength training was performed once each week on five muscle groups (abdominal, hamstring, quadriceps, triceps, and gluteus maximus), using a resistance bands. Each resistance training session consisted of two sets of 8-12 repetitions.

Assessment of exercise adherence

Exercise adherence was defined as the extent to which the patient in the APA group performed the exercise program as prescribed, operationalized as cycling at intensity corresponding to the first VT for 20 to 40 minutes twice a week and performing the strength training program one time per week. Data on exercise adherence and caloric expenditure were obtained from the exercise diaries and HR monitor (Polar RS400SD).

Adverse events were monitored and registered during the study.

Statistical analysis and sample size calculation

The sample size was calculated in order to detect a difference of 3.3 ml min^{-1} kg^{-1} of VO_{2peak} between the two treatment arms at 27 weeks (T1). Seventeen patients were needed in each arm in order to achieve 90% power with a two-sided 5% significance level. To account for an expected dropout rate of 20%, 22 patients were included in each arm. The analysis was conducted on an intention-to-treat (ITT) basis. For missing data, the Last Observation Carried

Forward (LOCF) method was used. This analysis imputes the last value observed before dropout, regardless of when it occurred.

The primary outcome analysis was also performed using the per protocol (PP) approach based on complete exploratory measures at T1. Quantitative values were expressed as means and standard deviations or medians and ranges. Qualitative values were expressed as percentages and numbers. Comparisons were made using Student's *t*-test or the non-parametric Mann-Whitney U-test, as appropriate, for continuous outcomes. Analysis of variance (ANOVA) was used for repeated measures. $P < 0.05$ was considered statistically significant. All analyses were performed using the SAS system for Windows, v.9.3.1 (SAS Institute, Cary, NC, USA).

RESULTS

From June 2011 to June 2012, 89 patients were eligible and 44 patients enrolled in this study (Figure 1). The main reason for refusal to participate was a lack of interest in performing APA or CPET. Two patients withdrew after randomization. Patient characteristics at baseline are presented in Table 1.

Adherence on the home-based exercise program

Adherence was measured by two methods: Polar monitor and questionnaires. All patients (20) completed the training. Adherence assessment to the entire program as measured by a Polar monitor was registered in only 14/20 patients because of poor use of the monitor. Patient adherence assessed by Polar monitor was 88% (from 10 to 167%) for the complete program; aerobic training adherence was 109% (9-202) and resistance training adherence was 46% (0-96). Reasons for incomplete adherence to the program were feeling overwhelmed, becoming too sick, and refusal to be followed. Sixty-three percent of participants performed training sessions on a bike at home, and 37% did walking. The mean HR during unsupervised exercise

training was 70% to 80% of the measured maximum HR. The majority of patients performed their aerobic APA at moderate intensity (3-6 METs), two performed at low intensity (<3 METs), and two performed at high intensity (>6 METs). For resistance training, four patients performed more than 70% of the APA resistance program, four performed less than 40%, and six performed between 40% and 70%. The assessment of physical activity with the IPAQ (Figure 2) showed that the APA group doubled its total activity between T0 and T1. In addition, at T2, the APA group maintained its level of total activity, without coaching between T1 and T2.

The median number of training sessions per week was 3 (0-15) during FEC chemotherapy and 2 (0-9) during Docetaxel chemotherapy. No adverse events were reported in the APA group.

Effect of home-based exercise training on aerobic and functional capacity (T0-T1)

Changes in VO_{2peak} are presented in Table 2, in intention to treat analysis (ITT), and Table 3, in per-protocol analysis (PP). At T1 compared to T0, the VO_{2peak} increased by 1.83 ± 0.68 $ml.min^{-1}.kg^{-1}$ in the APA group (P = 0.009) and decreased by 1.31 ± 0.65 $ml.min^{-1}.kg^{-1}$ in the control group (P = 0.046). The difference between the two groups was 2.26 ± 1.53 $ml.min^{-1}.kg^{-1}$ in ITT analysis (P = 0.140). PP analysis resulted in a VO_{2peak} difference of 3.49 ± 1.64 $ml.min^{-1}.kg^{-1}$ (P = 0.049).

CPET, 6MWT, and quadriceps strength using the ITT analysis are shown in Tables 2 Multivariate analysis shows a significant improvement in the APA group after training for 6MWT, with an increase of 21.75 ± 7.15 m between T0 and T1 (P = 0.03); in contrast, the control group's walking distance was reduced by 9.54 ± 6.82 m (P = 0.165). No change regarding quadriceps strength was observed in the two groups. Only the P_{max} was significantly reduced in the control group after treatment (6.81 ± 2.83 W, P = 0.019).

Assessment on aerobic and functional capacity in post training period (T2-T0; T2-T1)

At T2 compared to T0, significant VO_{2peak} changes were noted within the groups, with a significant increase of 2.37 ± 0.68 $ml.min^{-1}.kg^{-1}$ (P = 0.001) in the APA group and a decrease of 0.70 ± 0.65 $ml.min^{-1}.kg^{-1}$ (P = 0.284) in the control group; however, at T2, no significant between-group difference was noted in VO_{2peak}. Also, significant increase of P_{max} (p=0.0001), VO_2 threshold (p=0.004), P at threshold (p=0.0001) and 6MWT (p=0.001) was observed between T0 and T2 in the APA group. In the control group our results showed only a significant decrease of P_{max} (p=0.017)

At T2 compared to T1, only P_{max} (p=0.022) and P at threshold (p=0.002) in the APA group were significantly different. No difference was noted in the other parameters for APA or control group.

At T1 and T2, we observed no significant between-group differences for these parameters.

Effect of training and post-training period on quality of life, fatigue, and anxiety depression scales

We observed no between-group differences for MFI-20 or EORTC QLQ-C30 scores at T1 and T2, or before and after treatment. Although the HADS total score improved at T1 in the APA group compared to the control group, the difference was not significant (Table 4).

Effect of training and post training period on BMI.

BMI assessment using the ITT analysis is shown in Table 5. We observed difference between group at T0 and T1. In the APA group, multivariate analysis shows a significant BMI increase of 0.3 ± 0.8 kg/m^2 between T1 and T2 (P = 0.04) and an increase of 0.6 ± 1.3 kg/m^2 between T0 and T2 (P = 0.003). No change was observed for the control group.

Chemotherapy assessment and toxicity evaluation

Chemotherapy was administered to the two groups at the same dose intensity. No difference in chemotherapy toxicity was observed during treatment. In particular, the same decrease in hemoglobin level was noted after chemotherapy in both groups (-2.0g/dl).

DISCUSSION

The SAPA study confirms a physiological functional impact of home-based APA during chemotherapy and radiotherapy in patients with early-stage breast cancer. Although many APA studies involving breast cancer patients have been performed[44], few randomized controlled studies have been conducted during chemotherapy[20]. In addition, two studies have demonstrated that the performance of a home-based training program during chemotherapy increases CRF in breast cancer patients.[18, 19] Although the between-group difference in VO_{2peak} was greater in the SAPA study than in the literature, the difference was not significant. After retraining, Courneya *et al.*[20] observed a difference in VO_{2peak} between aerobic APA and control groups of 0.98 ml min^{-1} kg^{-1}. The difference was explained by the stabilization of VO_{2peak} in the APA group and decreased VO_{2peak} in the control group. Segal *et al.*[18] reported VO_{2peak} differences of 0.7 ml min^{-1} kg^{-1} and 0.5 ml min^{-1} kg^{-1} respectively between the control group and a home-based APA group and a supervised institution APA group. In our control group, the VO_{2peak} decreased by 1.31 ± 0.65 ml min^{-1} kg^{-1}, which is similar to the results of a meta-analysis by Jones *et al.*,[21] who reported a decrease of 1.02 ml min^{-1} kg^{-1} in patients during chemotherapy.

In our study, we observed a relationship between the increase in VO_{2peak} (1.38 ± 2.1 ml min^{-1} kg^{-1} to 2.36 ± 1.99 ml min^{-1} kg^{-1}) and the percentage of aerobic activity performed by the APA group (less than 70% to more than 70%, respectively). Our results are close to those of McNeely *et al.*[19]; their meta-analysis showed an increase in VO_{2peak} of 3.39 ml min^{-1} kg^{-1} after

exercise training in breast cancer patients. However, the three studies included in the meta-analysis were heterogeneous: one was performed during chemotherapy,[22] one was performed during radiotherapy,[23] and the third was performed after treatment.[24] One limitation of our study was non-adherence to CPET evaluations by patients in the control group, which explains the non-significant results for the primary criterion in the ITT approach compared with the PP approach. In the PP analysis, we considered only patients who completed CPET evaluation (main objective). Deviations of participation were known in terms of APA training in the control group; four patients were very active during the study, similar to the study by Griffith[25] in which 32.4% of patients assigned to exercise and 22% of control participants dropped out. Our hypothesis to observe a VO_{2peak} difference of 3.3 ml min^{-1} kg^{-1} between our two groups is questionable. In our previous phase II study,[26] the training improved VO_{2peak} by 2.2 ml min^{-1} kg^{-1}. The value applied in the SAPA trial was obtained from Thorsen *et al.*[27] study. This study included various cancers (breast, lymphoma, gynecological, and testicular) and an APA program immediately after treatment. Moreover, the magnitude of VO_{2peak} after exercise training appears to be lower in cancer patients than in healthy individuals, suggesting that the use of cytotoxic treatment may attenuate normal cardiovascular and/or skeletal muscle adaptations to exercise training; deconditioning depletes the compensatory abilities of the cardiovascular reserve.[28] The decreased hemoglobin level may partly explain this difference in VO_{2peak} compared with the values obtained in healthy patients. However, it did not differ between our two groups, which exhibited an average decrease of 2 g/dl after chemotherapy, similar to the results of Dolan *et al.*[29] We used the 6MWT to assess patients' functional capacity. After training, there was no difference between our two groups, as in the results reported by Haines *et al.*[30]; however, we noted an improvement in the APA group and a decrease in the control group. Another parameter of functional capacity was quadriceps muscle strength. No significant difference was observed between our two groups, despite the

retraining of the lower limbs. A meta-analysis by Speck *et al.*[31] and studies by Schwartz *et al.*[32] and Courneya *et al.*[20] reported improvements in lower-body muscle strength for the APA group after retraining. One possible explanation for these differences from the SAPA study is that our method of assessing quadriceps muscle strength was not the same as in other studies; another explanation is participants' low adherence with muscle-building sessions. Rate of refusal to participate in the SAPA study was 16%, lower than the refusal rates of our previous phase II study (26%)[26] and the literature (33.9% in Courneya's study).[20] In contrast to many other physical activity intervention studies,[18, 20] we chose a home-based training program coached by an exercise expert. We allowed patients to choose between walking and cycling as aerobic activities to reduce the dropout rate and to prolong motivation, which is confirmed by the IPAQ results and quantitative evaluations performed at 54 weeks. The improvements in PA behavior and VO_{2peak} at 27 weeks in the APA group were maintained at 54 weeks, unlike in Thorsen's study.[33] Our program used combined aerobic and resistance training. Resistance training sessions were less effective, with poor motivation and a rate of participation of 46%. The use of the elastic band was considered too difficult without the support of an interactive APA video program.

We observed no changes in quality of life, fatigue, or HADS questionnaires of the two groups. We cannot draw conclusions regarding a relationship between APA training and quality of life, although our training sessions were performed at the best intensity to obtain an impact on quality of life.[34] No adverse events were noted in our study, as in the literature.[21]

CONCLUSION

The SAPA study shows that home-based activity during chemotherapy and radiotherapy was safe, feasible and had beneficial effects on aerobic capacity in breast cancer patients. We chose VO_{2peak} as the primary objective because it is a strong independent predictor of mortality in healthy humans without cardiovascular disease[35] and in breast cancer patients.[36]

The VO_{2peak} value is associated with surgical complications, late effects of therapy, survival in breast cancer patients[36] decreased quality of life, and fatigue in cancer patients.[37, 38] However multiple assessment of VO2peak is an heavy evaluation for patients. That explains patient's dropout in control arm. The non-statistically results of SAPA study are explained by the lack of assessment in the control group. Easier tests should be used to determine APA training target and fitness evaluation.

Some questions remain unresolved, such as the performance of AP initiation compared with that of specific treatment. A new randomized trial is currently being conducted at Limoges University Hospital (APAC study) to answer this question.

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FIGURE AND TABLE LEGENDS

Figure 1. Flowchart

Figure 2. Caloric expenditure during SAPA study

Table 1. Patient characteristics at baseline (N=42)

Abbreviations: BMI, body mass index; APA, adapted physical activity.

Table 2. Evaluation of aerobic and functional capacity by intention-to-treat analysis and cardiopulmonary, six-minute walking test, and quadriceps assessments using intention-to-treat ANOVA (N=42)

Abbreviations: SD, standard deviation; VO_{2peak}, peak volume of oxygen consumed; APA, adapted physical activity; P_{max}, maximal power; RM, repetition maximum.

P-value of the difference between APA and control group

Table 3. Comparison of VO_{2peak} at T1 between the two groups (APA and control)

Abbreviations: SD, standard deviation; VO_{2peak}, peak volume of oxygen consumed; APA, adapted physical activity.

Table 4. Quality of life, fatigue, and anxiety/depression scales

Abbreviations: SD, standard deviation; MFI-20, Multidimensional Fatigue Inventory; EORTC QLQ C30, European Organization of Research and Treatment of Cancer; HADS, Hospital Anxiety and Depression Scale.

P-value was determined by Student's t-test of the difference between the APA group and the control group.

Table 5. Assessment of BMI by intention-to-treat analysis and using intention-to-treat ANOVA (N = 42)

Table 1. Patient characteristics at baseline (N= 42)

	Control group (N = 22)		APA group (N = 20)		
Characteristics	N	%	N	%	P-value
Age, years					0.596
Median	49		52		
Min-Max	37-68		37-73		
Cancer stage					0.131
I	0	0	3	15	
IIA	9	41	8	40	
IIB	9	41	3	15	
IIIA	4	18	5	25	
IIIB	0	0	1	5	
BMI, kg/m^2					0.052
Thin	0	0	1	5	
Normal	7	32	12	60	
Overweight	11	50	7	35	
Obesity	4	18	0	0	

Abbreviations: BMI, body mass index; APA, adapted physical activity.

Table 2. Assessment of aerobic and functional capacity by intention-to-treat analysis and cardiopulmonary, six-minute walking test, and quadriceps assessments using intention-to-treat ANOVA (N = 42)

	T0			T1			T2			T0-T1	T1-T2	T0-T2
Values	Mean	SD	P-value*	Mean	SD	P-value*	Mean	SD	P-value*	P-value	P-value	P-value
VO_{2peak}, ml min^{-1} kg^{-1}			0.829			0.140			0.181			
APA group	22.5	4.4		24.4	4.9		24.9	5.4		**0.009**	0.434	**0.001**
Control group	23.4	5.1		22.1	5		22.7	5.2		**0.046**	0.374	0.284
P max, W			**0.020**			0.561			0.776			
APA group	90.1	16.1		94.5	24.9		101.4	29.3		0.144	**0.022**	**0.000**
Control group	105.8	24.6		99	25.5		98.9	27.2		**0.019**	0.975	**0.017**
VO_2 at threshold, ml min^{-1} kg^{-1}			0.90			0.378			0.315			
APA group	16.1	3		17.1	3.4		17.8	3.7		0.104	0.187	**0.004**
Control group	16.5	3.3		16.1	3.6		16.7	3.3		0.492	0.258	0.655
P at threshold, W			**0.007**			0.365			0.717			
APA group	56.8	10.1		60.6	14.2		68.2	19.6		0.109	**0.002**	**0.000**
Control group	67.1	13.9		65.2	17.9		66	19.5		0.408	0.716	0.642
6-min walk, m			0.735			0.108			0.118			
APA group	527.3	46.1		549	53		552	54.2		**0.003**	0.676	**0.001**
Control group	527.1	61.5		517.5	69.3		522.3	65.2		0.165	0.486	0.486
1 RM leg, kg			0.152			0.062			0.111			
APA group	25.3	8.7		24	5.5		24.6	7.1		0.283	0.540	0.680
Control group	28.7	8.4		28.2	8.3		28.6	8.8		0.557	0.493	0.902

Abbreviations: SD, standard deviation; VO_{2peak}, peak volume of oxygen consumed; APA, adapted physical activity; P max, maximal power; RM, repetition maximum.

* P-value of the difference between APA and control group.

Table 3. Comparison of VO_{2peak} at T1 between the two groups (APA and control)

	Intention-to-treat analysis (N=42)			Per-protocol analysis (N=34)		
Values	Mean	SD	P-value	Mean	SD	P-value
VO_{2peak}, $ml.min^{-1}.kg^{-1}$			0.14			**0.049**
APA group	24.4	4.9		24.4	4.9	
Control group	22.1	5		21	4.8	

Abbreviations: SD, standard deviation; VO_{2peak}, peak volume of oxygen consumed; APA, adapted physical activity.

Table 4. Quality of life, fatigue, and anxiety depression scales

	T0				T1				T2			
Values	Mean	SD		P-value	Mean	SD		P-value	Mean	SD		P-value
MFI 20				0.817				0.438				0.157
APA group	48.8	20.1	(N = 11)		41.9	14.8	(N = 10)		38	12.3	(N = 14)	
Control group	54.4	19.4	(N = 13)		49.8	18.4	(N = 9)		44.2	13.9	(N = 12)	
EORTC QLQ C30				0.778				0.414				0.644
APA group	62.1	25.1	(N = 11)		71.7	18.9	(N = 10)		75	16.7	(N = 13)	
Control group	59.1	27.5	(N = 10)		64.8	17.1	(N = 9)		69.9	21.7	(N = 13)	
HADS				0.744				0.055				0.453
APA group	12.1	5.6	(N = 10)		9.8	1.9	(N = 10)		9.8	4.2	(N = 9)	
Control group	15.3	7.2	(N = 9)		15.9	5.4	(N = 9)		14.3	3.5	(N = 9)	

Abbreviations: SD, standard deviation; MFI 20, Multidimensional Fatigue Inventory; EORTC QLQ C30, European Organization of Research and Treatment of Cancer; HADS, Hospital Anxiety and Depression Scale.

P-value was determined by Student's t-test of the difference between the APA group and control group.

Table 5. Assessment of BMI by intention-to-treat analysis and using intention-to-treat ANOVA (N = 42)

	T0			T1			T2			T0-T1	T1-T2	T0-T2
Values	Mean	SD	P-value*	Mean	SD	P-value*	Mean	SD	P-value*	P-value	P-value	P-value
BMI kg/m^2			**0.002**			**0.031**			0.078			
APA group	23,8	3,8		24,1	3,3		24,4	3,4		0.368	**0.040**	**0.003**
Control group	26,6	3,7		26,4	3,4		26,2	2,9		0.374	0.521	0.359

*P-value was determined by Student's t-test of the difference between the APA group and control group.

Figure 1. Flowchart

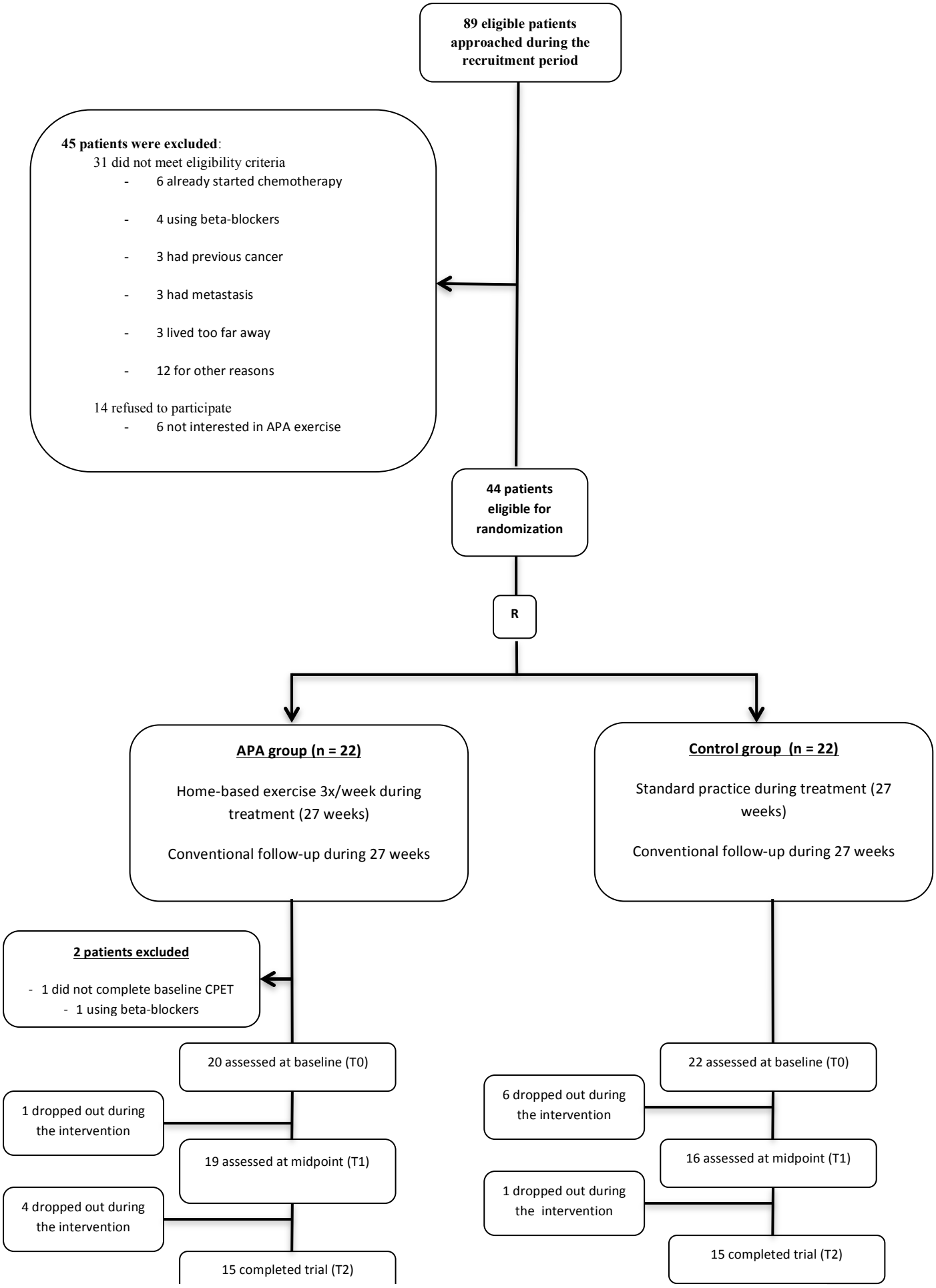

Figure 2. Caloric expenditure during SAPA study

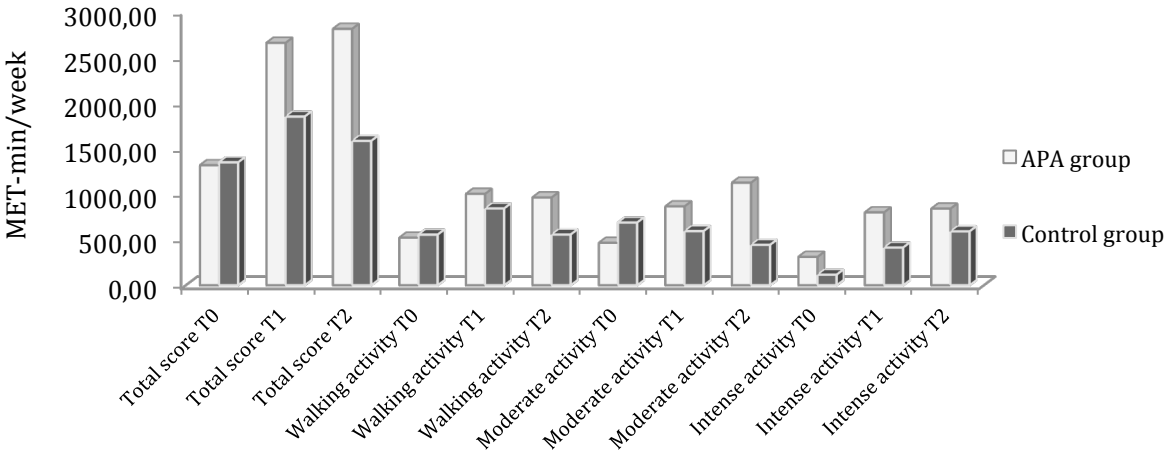

Figure 2. Caloric expenditure during SAPA study