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EXERCISE AND EDUCATION PROGRAM AFTER BREAST CANCER: BENEFITS ON QUALITY OF LIFE AND SYMPTOMS AT THREE, SIX, TWELVE AND TWENTY-FOUR MONTHS OF FOLLOW-UP

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Microabstract

This trial identifies the benefits on quality of life and symptoms of a three-month exercise and education program over a follow-up of 24 months among a population of 209 women who have been treated for a breast cancer.

Abstract

BACKGROUND: Various clinical trials show benefits of physical training offered during and / or after breast cancer treatments. However, given the variety of side effects that may be encountered, physical training could be combined with psychological, relational and social guidance. This kind of multidisciplinary program, just like their long-term effects, have been little studied so far. Therefore, the objective of our study is to determine the benefits at 3, 6, 12 and 24 months of a three-month exercise and education program among women after breast cancer treatment.

MATERIALS AND METHODS: Two hundred and nine outpatients who have been treated for a primary breast carcinoma were divided into a control group (n=106) and an experimental group (n=103) which has benefited from a three-month rehabilitation program including physical training and psycho-educational sessions. The assessments, performed before the program and at 3, 6, 12 and 24 months after inclusion, included validated questionnaires on quality of life and symptoms.

RESULTS: The analyses show an improvement in quality of life and symptoms following the exercise and education program within the experimental group and a maintenance of these improvements

during the two years of follow-up. These improvements are significantly superior to those presented in the control group, demonstrating the programs benefits.

CONCLUSIONS: This trial identifies the benefits of a well detailed three-month exercise and education program over a follow-up of 24 months among women after breast cancer treatment.

Key words: Breast cancer, exercise and education program, long-term benefits, quality of life.

Introduction

Although the incidence of mortality due to breast cancer has declined in recent years due to early detection and improved treatment, it remains the most frequently diagnosed cancer in women with 1 671 149 new cases reported worldwide in 2012 (25 % of all cancers in women)[1,2].

After completion of treatment (generally a combination of surgery, radiotherapy, chemotherapy, hormonal therapy and / or targeted therapy), the majority of patients suffer from a high number of side effects, such as fatigue[3–9], weight gain[3–5,8,9] alopecia[5,8], lymphedema[10], pain[11], loss of functional capacity[3,4,12] or anxiety[5,8,13], all having a negative impact on quality of life.

Fatigue[3–9,14], for example, is the most common symptom reported. It is observed in 70 to 100 % of women who have undergone chemotherapy[8] and generally, patients continue to experience fatigue after completion of their treatment[6,8,9,15]. Because of it, many women often avoid physical efforts and reduce their physical activity levels[16–18]. However, inactivity, causing muscle catabolism, is likely to increase the feeling of fatigue.

Different clinical trials[4,19,20] show beneficial effects of physical training offered during and / or after oncological treatments. However, physical training should ideally be combined with psychological, relational and social guidance to reduce fatigue and to improve quality of life, especially as the benefits of psycho-educational care have also been proven[21–23]. Few studies have investigated the effects of a multidisciplinary approach and these are rarely carried out on a large sample of patients with a long-term follow-up[20].

Therefore, this study aims to evaluate, by validated questionnaires, the long-term impact (over a follow-up of 24 months) of a three-month exercise and education program, comprising physical re-conditioning and psycho-educational sessions, on quality of life and symptoms of a high number of patients who have been treated for breast cancer.

Results obtained at three months, concerning the overall quality of life, but also physical function and body composition data, are presented in another article previously published[24]. This approach, if proven beneficial, could contribute to the development of hospital quality standards for oncologic rehabilitation.

Materials and methods

DESIGN

Two hundred and nine voluntary women who had completed their treatments for breast cancer, except for hormonal therapy and / or targeted therapy (which could be continued), were divided into two groups, an experimental group and a control group. The patient could choose to participate in either group. All participants were assessed at baseline and at 3, 6, 12 and 24 months. The experimental group participated in an exercise and education program including supervised physical training and psycho-educational sessions for 12 weeks while the control group did not receive any special medical care and were asked not to change their habits (especially in terms of physical activity) during the follow-up.

PARTICIPANTS

Participants were recruited, by phone, from a prospective registry of all patients. There was a rolling admission over a period of three years. Seven groups of about thirty patients (15 for the experimental group and 15 for the control group) successively participated in the experimentation.

Eligibility criteria were: surgery of a primary breast carcinoma, a minimum period of three weeks and a maximum of one year elapsed since the end of adjuvant chemotherapy and / or radiotherapy (hormonal therapy and targeted therapy could be continued) and the opportunity to participate in group programs. Participants were excluded if they had severe neurological, orthopedic or rheumatic disabilities, heart failure, a previous or synchronous other malignancy.

The trial received ethical approval from the Ethics Committee of the Liège University (Belgium) (B67020084166) and informed consent was signed by all individual participants included in the study.

MEASURES

Both groups completed assessments at admission to the study (M0) and at 3 (M3), 6 (M6), 12 (M12) and 24 (M24) months. The 3-month point coincided with the end of the 12week rehabilitation program.

At each measurement time, each patient was subjected to a battery of validated questionnaires including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[25], EuroQol-5 Dimension (EQ-5D)[26], Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)[27], State-Trait Anxiety Inventory (STAI)[28], Hospital Anxiety and Depression Scale (HADS)[29] and Flemish physical activity computerized questionnaire (FPACQ)[30]. At M0, participants also completed another questionnaire to gather biometric data, data on the history of the disease, on treatment modalities and on their professional status.

Quality of life and various symptoms and functions were assessed by the EORTC QLQ-C30[25]. This questionnaire assesses six functional areas (health status or quality of life, functional role, emotional state, physical, cognitive and social functions) and nine symptoms caused by cancer or its treatments (fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea and financial difficulties). For functions, the higher the score, the better the quality of life and for

symptoms, the higher the score, the worse the quality of life. This questionnaire is validated for people with cancer[31] and more specifically breast cancer[32].

The EQ-5D[26] provides a simple and generic measure of health from a clinical and economical point of view. From this questionnaire, we used the visual analogue scale that evaluates the patient's overall health status (overall quality of life) between 0 and 100 (0: worst possible state of health, 100: best imaginable state of health). The questionnaire is standardised[33] and applicable to a wide range of health issues, including cancer[34].

The FACIT-Fatigue[27] measures the impact of fatigue induced by the treatment of chronic diseases. This questionnaire includes thirteen items, eleven with a negative tendency and two with a positive tendency for which the patient must position herself on a scale ranging from 0 to 4. To calculate the final score, the degree of the scale of each negative item must be subtract to 4 and then all the scores obtained (including those of the two positive items) must be added, the maximum score being 52. The higher the score, the lesser fatigue. This questionnaire is also validated and used for cancer patients[27].

The STAI[28,35] is a validated questionnaire that assesses the state of anxiety corresponding to a state of temporary anxiety experienced in specific situations and the trait of anxiety corresponding to the general tendency to perceive the situations as a threat. The questionnaire is composed of two sets of 20 items rated from 1 to 4. The sum of the results gives a score of 80 and the higher the score, the higher the anxiety. In addition, threshold scores are established (score less than or equal to 35: very low anxiety, from 36 to 45: low anxiety, from 46 to 55: average anxiety, from 56 to 65: high anxiety, greater than 65: very high anxiety).

The level of anxiety and depression is assessed by the HADS[29]. The questionnaire consists of 7 items assessing anxiety and 7 items assessing depression. Each has four response possibilities rated from 0 to 3. Thus, a score of 21 is obtained for each dimension and the higher the score, the greater the anxiety and / or depression. In addition, threshold scores are established (score below 7: absence of anxiety / depression, between 8 and 10: state of anxiety / depression doubtful and greater than 10: state of anxiety / depression certain). The HADS scale is not only validated in a hospital environment[36,37], but also in an outdoor environment[38].

Finally, the validated FPACQ[30], with its closed questions, was used to assess the level of physical activity (MET/week) practiced by each group.

Intervention for the experimental group

The experimental group, unlike the control group, participated in a rehabilitation program including physical training and psycho-educational sessions.

PHYSICAL TRAINING

The training period lasted twelve weeks and consisted of three sessions of one hour and thirty minutes per week. Workouts were done in groups of twelve to fifteen people under the supervision of two physiotherapists specialized in oncology care. Participants each spent thirty minutes at three different workshops (cardiovascular training, muscular endurance training and a varied activity) and ended the session by stretching for five to ten minutes. The entire training protocol was based on the

recommendations of the American College of Sports Medicine (ACSM) on physical activity and cancer[4,39].

Cardiovascular training was performed on a bicycle ergometer at constant wattage. Participants began to pedal three series of eight minutes at 60 % of their maximal aerobic power (MAP) (previously evaluated by a maximal incremental exercise protocol on a cycle ergometer) with one-minute rest intervals, and gradually rode thirty minutes continuously at 70 % of their MAP.

Muscular endurance training was performed on weight machines. The exercises were leg presses, leg extensions, leg curls, biceps curls and triceps extensions. The “10RM” or the load that a muscle can lift ten times at full amplitude was evaluated on each machine for each patient. The 1RM was then extrapolated and used as a base for further training. Participants started with two sets of twenty repetitions at 30 % of their estimated 1RM and gradually, the difficulty was increased to three sets of thirty repetitions at 35 % of their 1RM.The varied activity, used to add a more entertaining activity to the program, consisted of group gymnastics with hypopressive exercises or exercises on a mat, on an aerobic stepper or on a Swiss ball, with or without dumbbells (0,5 to 1 kg), elastics, foam balloons or sticks. The exercises were given by one of the two physiotherapists and each exercise was repeated ten times. They were different at each training session.

Finally, the training session ended with stretching the specific muscle groups that were solicited throughout all the session. Each stretch was maintained twenty to thirty seconds.

PSYCHO-EDUCATIONAL SESSIONS

Two-hour psycho-educational sessions were also provided once a week over eleven weeks of the program. These sessions, described in Table 1, were given to groups of twelve to fifteen participants. After a first introductory session where people got to know each other, a specific topic was approached by a specialist at each session: a psychologist supervised sessions on psychological aspects (discussion about the anxiety of relapse, self-esteem, the desire to regain one's physical form and the look and expectations of the family and social entourage) (twice two-hours), on stress management (presentation of different stress management tools such as relaxation, meditation, breathing, yoga and visualization) (twice two-hours) and on sexuality (link between breast cancer and sexuality, problems encountered and opportunities for help); a professor in physiotherapy and rehabilitation was responsible for the session on the health benefits of physical activity (justification of the benefits of physical activity, potential risks and recommended modalities); a dietician discussed good nutrition practices in two sessions (presentation of a healthy diet, recommendations in the context of cancer, effects of drugs on body composition, explanation of body mass index and practical advice) and finally, a neurologist presented sleep disorders commonly encountered and their treatments (explanation on normal sleep, on insomnia and hypersomnia, consequences of insomnia and possible treatments). Thus, participants were given information, advice and tips on all these topics and had the opportunity to ask questions to the various specialists. A final session was given by a psychologist and a physiotherapist to find out what participants think about the program and encourage them to continue a regular physical activity.

STATISTICAL ANALYSIS

Results are presented as means and standard deviations (SD) for continuous variables (all continuous variables followed the normal distribution) and as absolute and relative frequencies for categorical variables. Comparisons between groups were done by a Student t-test for continuous variables and by a Chi-square test for categorical variables. General linear mixed (GLMM) model was used to study the evolution of each variable as a function of time, group and interaction between time and group. This model takes into account the fact that a variable was measured at several times within the same group. Results were considered to be significant at the 5 % level ($p < .05$). All statistical calculations were done with the maximum available data at each time. Calculations were done using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

SAMPLE CHARACTERISTICS

Biometric, medical and professional data for all participants at baseline are listed in Table 2. The experimental group and control group were composed respectively of 103 people and 106 people. Both groups were mostly homogenous: the average age for the experimental group was 53.0 ± 8.9 years compared with 53.7 ± 9.8 years in the control group ($P = .59$), the experimental group had completed treatment 5.5 ± 2.5 months ago on average and the control group 5.3 ± 2.1 months ago ($P = .43$), the majority of participants had had a tumor of stage I (43.6 % of the experimental group and 44.7 % of the control group) ($P = .78$) and all participants underwent surgery. The groups were homogeneous with regards to their professional status: 25.5 % of the participants in the experimental group had returned to work at the initial stage of the study, compared with 33.3 % in the control group ($P = .13$).

The reasons why the patients chose to join the control group were, in descending order of importance: fear of the cumbersome nature of the proposed program, lack of time to participate, lack of means of travel, too long distance between home and hospital, parking difficulties and the desire not to hear about the disease.

The patients flow throughout the study is presented in the Figure 1. At M3, 39 women (15 from the experimental group and 24 from the control group) dropped out and did not provide data. At M6, 49 people did not answer the questionnaires compared to the initial stage (17 from the experimental group and 32 from the control group). At M12, we count 112 dropouts (54 from the experimental group and 58 from the control group), but among the 112 dropouts, we must account 60 questionnaires that were not able to be sent following a delay error. Finally, at M24, 108 dropouts are counted compared to the initial stage (53 from the experimental group and 55 from the control group).

At all measurements times, reasons for drop out included personal reasons such as lack of time, transportation difficulties and return to work, but the majority of people did not give any reason or could not be contacted. No complication due to the program has been identified.

If we do not count dropouts, patients of the experimental group participated in an average of 80 % of the program and 70 to 90 % of the patients were present at each physical training and psycho-educational session.

QUALITY OF LIFE, SYMPTOMS AND FUNCTIONS FROM THE EORTC QLQ-C30

Table 3 lists the items of the EORTC QLQ-C30 at each measurement time and presents their evolution by the GLMM model. As a reminder, for functions, the higher the score, the better the quality of life and for symptoms, the higher the score, the worse the quality of life.

With regard to the “function” parts, the two groups significantly differ from each other initially; more deleterious scores were observed in all functional areas within the experimental group. At the end of the three months, that is to say directly after the intervention for the experimental group, only one significant difference persists between the two groups and concerns cognitive functions, with a better score in the control group. Finally, after twenty-four months, no significant difference between the two groups is observed.

The GLMM model indicates a significant difference between groups globally (“*P* group”) for all functional domains, except for health status. It demonstrates a significant overall evolution of all functional domains as a function of time (“*P* time”), but with a significant difference between the two groups for the overall evolution (“*P* group and time”) of the health status, functional role, emotional state and physical functions in favor of the experimental group. These results show a greater subjective improvement of these functional domains within the experimental group.

Concerning the “symptom” parts, at M0, the two groups also significantly differ with regards to the scores obtained for fatigue, pain, dyspnea, insomnia, diarrhea and financial difficulties, the experimental group being more symptomatic. At M3, the two groups differ significantly from each other only in financial difficulties, with a score that reports fewer difficulties in the control group. At M24, no more significant difference between groups appears.

A significant difference between groups overall is defined by the GLMM model for fatigue, dyspnea and financial difficulties. All symptoms, except diarrhea and nausea and vomiting, changed significantly as a function of time, but with a significant difference between the two groups for the evolution patterns of fatigue, pain, insomnia and diarrhea, in favor of the experimental group. Thus, the improvement of these four last scores appears significantly greater in the group that benefited from the exercise and education program.

QUALITY OF LIFE FROM THE EQ-5D

The evolution of health status (quality of life) is presented in Table 4. As a reminder, we used the visual analogue scale of the EQ-5D that evaluates patient's health status between 0 and 100 (0: worst possible state of health, 100: best imaginable state of health).

At M0, there is a significant difference between the two groups concerning health status, the control group judging itself to be in better health than the experimental group. This difference is then reduced to reappear significantly at M12 and to disappear at M24.

The GLMM model indicates a significant difference between the groups globally. It demonstrates a significant overall improvement in health status over time as well as a significant difference between the two groups for the overall evolution of the variable, in favor of the experimental group. The health status improves significantly more within the experimental group.

FATIGUE FROM THE FACIT-FATIGUE

Table 5 presents the evolution of fatigue. As a reminder, in this questionnaire, the higher the score, the lesser fatigue.

A significant difference is observed between the two groups at the initial stage. The control group obtains a higher fatigue score than the experimental group, reporting less felt fatigue. This difference is reduced at M3 and M6 to become significant again at M12 and then disappear at M24.

The GLMM model does not indicate a significant difference between the groups overall and it demonstrates a significant overall improvement of fatigue as a function of time as well as a significant difference between the two groups for the overall evolution of the variable, in favor of the experimental group. The overall improvement of fatigue appears significantly greater in the experimental group.

STATE AND TRAIT OF ANXIETY FROM THE STAI

The evolution of anxiety (state of anxiety and trait of anxiety) is presented in Table 6. In this questionnaire, as a reminder, the higher the score, the higher anxiety.

At M0, a significant difference is observed between the two groups for the state of anxiety and for the trait of anxiety. The experimental group, with higher scores, indicates feeling more anxiety. After three months, this significant difference between the two groups disappears and no longer appears until the end of the twenty-four months of follow-up.

The GLMM model does not reveal a significant difference between the groups overall, but it demonstrates a significant global evolution of the state and trait of anxiety as a function of time and a significant difference between the two groups for the overall evolution of the two variables, in favor of the experimental group.

The values in the table illustrate these significant changes as a function of time and show not only the increase of anxiety in the control group between M0 and M24, but also the reduction of anxiety in the experimental group at M3 and its increase to return to a value close to, but lower than, the initial value at M24.

ANXIETY AND DEPRESSION FROM THE HADS

Table 7 presents the evolution of anxiety and depression. As a reminder, in the HADS, a score of 21 is obtained for each dimension and the higher the score, the greater the anxiety and / or depression.

A significant difference is observed between the two groups at the initial stage with regards to anxiety and depression, these being felt more intensely within the experimental group. After three months, this significant difference between the two groups disappears, for both anxiety and depression, and it no longer reappears.

Overall, no significant difference between groups is defined by the GLMM model, but it demonstrates a significant overall improvement in anxiety and depression over time and a significant difference between the two groups with respect to the overall evolution of the variables, in favor of the experimental group. The subjective improvement of anxiety and depression appears to be greater in the experimental group.

LEVEL OF PHYSICAL ACTIVITY FROM THE FPACQ

Finally, the evolution of the level of physical activity practiced by each group is presented in Table 8.

At any measurement time, the two groups differ significantly from each other.

The GLMM model does not indicate significant difference between the groups overall. It shows a significant change in the level of physical activity as a function of time, but no significant difference between the two groups for the evolution of the variable. The level of physical activity increases over time in both groups.

Discussion

Various clinical trials[4,19,20] show the benefits of a physical training or of a psychoeducational care[21–23] offered during and / or after breast cancer treatments, but few studies have evaluated the benefits of a multidisciplinary approach comprised of both. In addition, they are rarely carried out on a large sample and with a long term follow-up[20].

Therefore, the aim of this study was to demonstrate the long-term benefits (at 3, 6, 12 and 24 months) of an exercise and education program in women having been treated for breast cancer. Results indicate that participants which have received the three-months intervention significantly improved their health status (overall quality of life), functional role, emotional state, physical functions, fatigue, pain, insomnia, diarrhea, state and trait of anxiety and state of depression when compared to control participants.

With respect to the questionnaires, overall health status (quality of life) was assessed using the EORTC QLQ-C30 questionnaire and the visual analogue scale of the EQ-5D. As predicted in the literature[21,23,40–50], the score of the two questionnaires increased during the rehabilitation phase (between M0 and M3) in the experimental group. After M3, less important variations were observed, but we observed nevertheless a high significant improvement of the score for each questionnaire between M0 and M24 (*P* time < .0001). Although these positive results do not yet reach the standards of a healthy female population of the same average age, described by Michelson et al.[51] and other authors[52,53] for the EORTC QLQ-C30, they are close to them. Indeed, at the end of the two years of follow-up, the score of health status (quality of life) is 72 ± 15 in our experimental group and the standard value is 77 ± 21. Thus, although the scores obtained at M24 remain below average, they are close to established standards and they show the benefit of this kind of rehabilitation, including physical training and psycho-educational sessions, on the quality of life of patients. As far as the control group is concerned (who had better data initially), the results were relatively stable throughout the experiment. The values obtained at M24 are similar to those of the experimental group but there was a significantly greater improvement in the group that benefited from rehabilitation compared to the control group (*P* group and time < .0001 for the EORTC QLQ-C30 and for the EQ-5D), which also proves the benefits from the rehabilitation program.

Although the majority are carried out in the short term, various studies report similar results to ours for physical training[23,40–47] and psycho-educational sessions[21,48–50]. The clinical trial of Haines et al.[40] especially showed at six months of follow-up the significant health benefits (on overall quality of life) of an exercise program including strength, balance and endurance training elements similar to ours

and the clinical trial of Stagl et al.[50] demonstrated the long-term benefits (at eleven years of follow-up) on the quality of life of a ten-week cognitive behavioral treatment offered to patients at most ten weeks after their breast cancer surgery.

Fatigue is one of the most common symptoms associated with breast cancer treatments[6–8]. This variable was evaluated using two questionnaires, the EORTC QLQ-C30 and the FACIT-Fatigue. The evolution of fatigue in the experimental group assessed using the two questionnaires showed a decrease during rehabilitation (M0 to M3) followed by an increase at M6 and at M12 (EORTC QLQ-C30) to finally show a new decrease at M24. In both questionnaires, the fatigue state is significantly lower at M24 than at M0 (*P* time < .0001). In comparison with the reference values associated with the EORTC QLQ-C30 questionnaire[51], the state of fatigue at M24 is always greater in our population compared to a healthy sample: 33 ± 23 against 21 ± 22 / 100. However, the average of the starting score being 50 ± 27, we note a marked improvement of the state of fatigue whereas it varies only very little within the control group. As for health status, similar values are observed at M24 between the two groups, but with a significant difference in terms of evolution between M0 and M24 (*P* group and time < .0001 for EORTC QLQ-C30 and for the FACIT-Fatigue), in favor of the experimental group.

Other studies also observe a beneficial effect of physical training[45,54,55] and psychoeducational sessions[21–23] on fatigue. They therefore corroborate our results.

Pain is also one of the most common symptoms[5,56,57]. It was evaluated from the EORTC QLQ-C30 questionnaire. The pain experienced by members of the experimental group decreased between M0 and M3, stabilised between M3 and M6, increased between M6 and M12, and again decreased between M12 and M24. Overall, the pain significantly decreased between M0 and M24 from 40 ± 27 to 31 ± 25 / 100 (*P* time = .001). As for the previous items, the final score does unfortunately not yet reach the standard established by Michelson et al.[51] which is 21 ± 29 / 100 for a healthy female population of the same average age. The control group showed an increase of pain over time, but with a similar score to that of the experimental group at M24. Again, there is a significantly greater change between M0 and M24 in the group that benefited from the rehabilitation than in the control group (*P* group and time = .0004), which also shows us the benefits of the program.

Anxiety, associated with a lower quality of life[58], was assessed by the STAI and HADS questionnaires. For this variable, the evolution of the results is different from the previous ones. Indeed, the experimental group presented a high decrease in scores of anxiety between M0 and M3, as in other studies including physical rehabilitation[59–61] or psychoeducational support[21,23,49,48], but then presented an increase in scores over time to obtain, at M24, scores close to the initial values without however reaching them (43 ± 6 / 80 for the state of anxiety, 45 ± 6 / 80 for the trait of anxiety from the STAI and 7 ± 8 for the anxiety from the HADS). It is not surprising that there is little change in the trait of anxiety from the STAI because it is a character trait and not a temporary feeling. In a surprising and original way, the control group presented an increase in anxiety evaluated using the STAI questionnaire between M0 and M24, but according to the HADS scale[29], the averages of the two groups obtained at M24 corresponded to the absence of anxiety (0 to 7 / 21) and at M0, only the score of the experimental group corresponded to a state of doubtful anxiety. Therefore, an improvement is observed in the experimental group and the GLMM model also shows this. It indicates a significantly more favorable evolution within the experimental group than in the control group (*P* group and time < .0001 for the STAI and = .0003 for the HADS), which shows, once again, the benefits of the program.

Depression was also assessed using the HADS questionnaire. The GLMM model indicates, as for anxiety, a significant difference between the two groups with respect to the overall evolution of the variable (*P* group and time < .0001), in favor of the experimental group. The subjective improvement of depression appears to be greater in the experimental group. This shows again the positive impact of the exercise and education program. Although they did not analyse the depressive state with the same scale, Mutrie et al.[62], who evaluated breast cancer patients 18 and 60 months after rehabilitation, also found a decrease in depressive status in their experimental group. While they also observe a decrease in depression in their control group with very little difference in terms of evolution between the two groups, our research reveals, on the contrary, a significant difference in the evolution presented by the two groups. These results must still be nuanced since, throughout the study, the averages of the two groups remain between 0 and 7, corresponding to an absence of depression[29], but the decrease of the score can only be beneficial from a quality of life point of view.

Finally, we observe that the evolution of the level of physical activity does not differ significantly between groups, but that it changes significantly as a function of time (*P* time = .002). An increase in the level of physical activity is observed in both groups. The program does not seem to have further modified the level of physical activity, but we must note that in the FPACQ, it is calculated from the energy expended during work, active recreation, sleep, meals and during periods spent in front of the television / computer. It would therefore be interesting to evaluate, in future studies, the characteristics of the physical activities practiced in order to see if there is, for example, a change in intensity, duration or frequency.

To conclude, for all these variables (except for the level of physical activity measured by FPACQ), the improvement observed in our experimental group, directly after the rehabilitation, but also after the two years of follow-up, may probably be explained in part by the care of the patient as a whole. So, the psycho-educational sessions probably gave many tips to participants allowing them to better manage stress and daily activities, balance their diet, better control their pain, improve their sleep and thus reduce their fatigue[21–23,48,49,63], the physical rehabilitation certainly promotes improvements in physical function, endurance and functional role that probably also improve overall quality of life[4,19,20,23,40–47,64] and finally, the meeting of other people and the group cohesion certainly allowed patients to regain confidence and maybe helped to a reintegration into the social, professional and family environments. In this way, the multidisciplinary approach seems to be necessary to improve all quality of life variables touched by breast cancer and its treatments[65–67].

Nevertheless, the fact that the quality of life of the patients who participated in the rehabilitation was so low at the inclusion of the study certainly influences the evolution of the variables. This leads us to wonder what would have happened if the control group had followed the same care. Would they have also improved their quality of life and this, in order to reach established standards? In the event that the values would not have increased significantly, we can question the need to propose exercise and education program to all patients. Indeed, the fact that the intervention has generated such significant results may be related to the voluntary participation of patients (according to their perceived needs), which could have led them to be more receptive and inclined to change.

This leads us to the limits and strengths of our study.

The most important weakness is that our study was not randomized and that there were differences between groups baseline, not about biometric, professional and level of physical activity, but about some medical and quality of life aspects (the experimental group had baseline a greater tumor grade,

less had radiotherapy and hormone therapy and was more symptomatic than the control group). The free choice of participation could have influenced the results. Indeed, based on the theory of self-determination[68], Ryan et al.[69] have shown that patients who are more motivated and involved in their treatments, whether medical or lifestyle-based, maintain better long-term outcomes. We must thus take this into account in the interpretation of our results even if our conclusions remain legitimate since we have observed that the differences in evolution between the two groups were significant and that the literature corroborated our results.

A strength of our study is the large sample size. Indeed, 209 voluntary women meeting inclusion criteria were included baseline (103 in the experimental group and 106 in the control group). At the end of the two years of follow-up, the number of subjects who answered the questionnaires decreased by about half compared to the start (101 responses, ie 48 %, with 50 in the experimental group and 51 in the control group). This response rate can be explained by several reasons described in the literature, including too long questionnaires, lack of monetary incentive or the non-personalization of the questionnaires[70–72]. In addition, Baruch et al.[73] analyzed 1607 studies that collected data through questionnaires and obtained an average response rate of 52.7 %. Thus, although our response rate is lower than this at M24, it is well above at all other measurements times: 100 % at M0, 81 % at M3, 77 % at M6 and 65 % at M12, which constitutes a strength for our study. A second strength is the exhaustive and validated questionnaires used, which cover most of the areas of quality of life and finally, we note the long-term follow-up with measurements at three, six, twelve and twenty-four months and the multidisciplinary care, with supervised exercises and psychological, relational and social guidance, which seems necessary in view of the variety of side effects encountered by patients[65–67].

Conclusions

Although they should be interpreted with caution, our results demonstrate the benefits of a well detailed exercise and education program, including physical reconditioning and psycho-educational sessions, with important improvements in quality of life, functions and symptoms among women who have been treated for breast cancer. Indeed, the breast cancer survivors which have receive the three-month intervention significantly improved their health status (overall quality of life), functional role, emotional state, physical functions, fatigue, pain, insomnia, diarrhea, state and trait of anxiety and state of depression when compared to control participants.

Thus, the results obtained may guide the practice of clinicians. The establishment of exercise and education rehabilitations should be encouraged in patients who have undergone aggressive treatment for breast cancer. In our opinion, it should certainly be offered to all patients, but without doubt to those who present a quality of life greatly diminished as a result of cancer.

Finally, these encouraging results should obviously not be taken for granted, but should instead be the basis for the establishment of future long-term studies. These subsequent studies could therefore confirm or refute our results as well as evaluate various other issues raised through this discussion. Indeed, it would be interesting to compare patients who all participated in this kind of rehabilitation but who have quality of life scores more or less important at the inclusion of the study to see the influence that the quality of life of departure can have on the evolution of parameters. These data

could therefore help to orient the rehabilitation proposal according to the patients' profile and to individualize the care according to the everyone’s needs.

Clinical practice points

Various clinical trials show benefits of physical training offered during and / or after breast cancer treatment. However, given the variety of side effects that may be encountered, physical training could be combined with psychological, relational and social guidance, especially as the benefits of psycho-educational care have also been proven. This kind of multidisciplinary program, just like their long-term effects, have been little studied so far. Therefore, the objective of our study was to determine the benefits at 3, 6, 12 and 24 months of a three-month exercise and education program, including physical training and psychoeducational sessions, among women after breast cancer treatment and this, through a controlled trial based on a sample of 209 patients.

The results show an improvement in quality of life and symptoms following the rehabilitation within the experimental group and a maintenance of these improvements during the two years of follow-up, with improvements significantly superior to those presented in the control group, demonstrating the large program benefits. The results of our study therefore encourage the establishment of exercise and education programs for breast cancer patients to improve their long-term quality of life and the management of side effects.

Acknoledgements

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Declarations of interest

None.

Conflict of interest page

The authors report no declaration of interest.

Tables

Table 1. Psycho-educational sessions

Theme of the session	Description of the content, educational objective(s)	Health professional(s) in charge of the session	Number of sessions	Duration of each the sessions (hours)
Introduction of the program	Meeting of the participants, reminder of the progress of the study	A physiotherapist and a psychologist	1	2
Psychological aspects	Discussion with the participants about the anxiety of relapse, the self-esteem, the desire to regain one's physical form and the look and expectation of the family and social entourage, answers to the questions, advice and tips on these topics	A psychologist	2	2
Stress management	Theoretical and practical presentation of different stress management tools such as relaxation, meditation, breathing, yoga and visualization	A psychologist	2	2
Sexuality	Explanation of the link between breast cancer and sexuality, discussion with the participants about the problems encountered, advice and information on the opportunities for help	A psychologist	1	2
Physical activity	Justification of the health benefits of physical activity, especially in the context of cancer, explanation of the potential risks and recommended modalities, practical advice	A professor in physiotherapy and rehabilitation	1	2
Nutrition	Presentation of a healthy diet and of the recommendations in the context of cancer, explanation of the effects of drugs on body composition and on body mass index, practical advice	A dietician	2	2
Sleep	Explanation on normal sleep, on insomnia and hypersomnia, on consequences of insomnia and on possible treatments	A neurologist	1	2
Closure of the program	Collection of participants appreciation of the program, thanks and encouragement to the maintain of a regular physical activity	A physiotherapist and a psychologist	1	2

Table 2. Biometric, medical and professional characteristics of the sample

Characteristic	Experimental group (n = 103)		Control group (n = 106)		*P*
	No.	%	No.	%	
Biometric data					
Age (years)					.59
Mean	53.0		53.7		
Standard deviation	8.9		9.8		
BMI (kg/m²)					.43
Mean	26.2		25.7		
Standard deviation	4.6		5.1		
Medical data					
Time since the end of treatments (months)					.43
Mean	5.5		5.3		
Standard deviation	2.5		5.1		
Type of tumor					.36
Ductal carcinoma in situ	12	11.8	11	10.5	
Lobular carcinoma in situ	2	2	0	0	
Invasive ductal carcinoma	76	74.5	76	72.4	
Lobular invasive carcinoma	12	11.8	18	17.1	
Tumor grade					**.022**
I	10	10.3	25	24.8	
II	54	55.7	43	42.6	
III	33	34	33	32.7	
Classification of tumor					.78
Stage 0 (TisN0)	6	5.9	7	6.8	
Stage I (T1N0)	44	43.6	46	44.7	
Stage IIa (T1N1, T2N0)	26	25.7	29	28.2	
Stage IIb (T2N1, T3N0)	17	16.8	11	10.7	
Stage III (T1N2, T2N2, T3N1-2)	8	7.9	10	9.7	
Axillary dissection					.54
Yes	60	60	58	55.8	
No	40	40	46	44.2	
Chemotherapy					.052
No	42	40.8	61	57.5	
Neoadjuvant	17	16.5	12	11.3	
Adjuvant	44	42.7	33	31.1	
Radiotherapy					**.040**
Yes	99	96.1	106	100	
No	4	3.9	0	0	
Hormonotherapy					**.030**
Yes	76	73.8	91	85.8	
No	27	26.2	15	14.2	
Targeted therapy					.15
Yes	20	19.8	13	12.4	
No	81	80.2	92	87.6	
Professional status					.13
Active	26	25.5	34	33.3	
Inactive	55	53.9	40	39.5	
Pensioned	21	20.6	28	27.5	

Table 3. Quality of life, symptoms and functions from the EORTC QLQ-C30 between groups at each measurement time and analysis of their evolution by the GLMM model

Variable	M0 Mean ± SD	M3 Mean ± SD	M6 Mean ± SD	M12 Mean ± SD	M24 Mean ± SD	*P* group	*P* time	*P* group and time
EORTC QLQ-C30 (/100)								
Health status (quality of life)						.13	< .0001	< .0001
Control group	68 ± 15*	69 ± 18	71 ± 14	73 ± 16	73 ± 19			
Experimental group	57 ± 19*	73 ± 17	70 ± 16	68 ± 17	72 ± 15			
Functional role						**.014**	**.004**	**.036**
Control group	81 ± 20*	83 ± 20	85 ± 23	86 ± 22*	81 ± 25			
Experimental group	71 ± 25*	83 ± 25	79 ± 25	74 ± 27*	80 ± 26			
Emotional state						**.040**	< .0001	**.003**
Control group	74 ± 24*	78 ± 21	77 ± 25	76 ± 22	78 ± 23			
Experimental group	60 ± 25*	78 ± 22	74 ± 20	69 ± 22	73 ± 24			
Physical functions						**.008**	< .0001	**.042**
Control group	85 ± 14*	88 ± 11	88 ± 15	90 ± 12*	86 ± 16			
Experimental group	77 ± 17*	84 ± 16	84 ± 19	81 ± 17*	85 ± 16			
Cognitive functions						**.006**	< .0001	**
Control group	74 ± 24*	80 ± 20*	80 ± 20*	76 ± 24	77 ± 22			
Experimental group	64 ± 26*	73 ± 22*	72 ± 23*	66 ± 28	74 ± 25			
Social functions						**.002**	< .0001	**
Control group	78 ± 25*	86 ± 22	90 ± 16*	87 ± 22	87 ± 23			
Experimental group	68 ± 29*	80 ± 26	81 ± 26*	77 ± 29	83 ± 22			
Fatigue						**.037**	< .0001	**.0001**
Control group	35 ± 25*	29 ± 22	29 ± 20	34 ± 32	33 ± 24			
Experimental group	50 ± 27*	28 ± 22	35 ± 22	43 ± 31	33 ± 23			
Nausea and vomiting						.30	.13	**
Control group	3 ± 10	3 ± 10	2 ± 8	4 ± 9	5 ± 12			
Experimental group	5 ± 11	3 ± 11	4 ± 9	6 ± 13	3 ± 9			
Pain						.39	**.001**	**.0004**
Control group	27 ± 26*	29 ± 29	27 ± 25	29 ± 26	29 ± 29			
Experimental group	40 ± 27*	26 ± 24	27 ± 24	35 ± 29	31 ± 25			
Dyspnea						**.016**	**.002**	**
Control group	22 ± 27*	17 ± 23	18 ± 22	18 ± 22	22 ± 27			
Experimental group	34 ± 31*	23 ± 26	22 ± 26	25 ± 27	23 ± 28			
Insomnia						.051	< .0001	**.020**
Control group	40 ± 33*	36 ± 32	35 ± 31	37 ± 36	35 ± 35			
Experimental group	53 ± 33*	34 ± 34	36 ± 34	51 ± 34	40 ± 31			
Loss of appetite						.21	**.019**	**
Control group	6 ± 17	5 ± 14	5 ± 15	10 ± 22	7 ± 18			
Experimental group	11 ± 22	6 ± 16	7 ± 16	13 ± 22	9 ± 20			
Constipation						.42	**.002**	**
Control group	17 ± 26	12 ± 21	15 ± 25	16 ± 24	12 ± 22			
Experimental group	17 ± 25	10 ± 20	14 ± 24	18 ± 31	13 ± 24			
Diarrhea						.13	.52	**.026**
Control group	3 ± 11*	4 ± 16	5 ± 13	8 ± 16	5 ± 13			
Experimental group	11 ± 22*	6 ± 16	8 ± 21	8 ± 20	10 ± 19			
Financial difficulties						**.0001**	**.003**	**
Control group	12 ± 25*	8 ± 14*	10 ± 20*	11 ± 26	8 ± 20			
Experimental group	29 ± 35*	20 ± 29*	18 ± 28*	18 ± 31	15 ± 35			

* Significant difference ($p < .05$) between the control and experimental groups at the indicated measurement time.

** GLMM model was done without interaction between time and group as the interaction was not significant in the model with the interaction.

Table 4. Quality of life from the EQ-5D between groups at each measurement time and analysis of its evolution by the GLMM model

Variable	M0 Mean ± SD	M3 Mean ± SD	M6 Mean ± SD	M12 Mean ± SD	M24 Mean ± SD	*P* group	*P* time	*P* group and time
EQ-5D (/100)								
Health status (quality of life)						**.02**	**< .0001**	**< .0001**
Control group	72 ± 13*	75 ± 13	77 ± 11	76 ± 14*	77 ± 14			
Experimental group	63 ± 14*	77 ± 12	74 ± 14	69 ± 16*	75 ± 14			

* Significant difference ($p < .05$) between the control and experimental groups at the indicated measurement time.

Table 5. Fatigue from the FACIT-Fatigue between groups at each measurement time and analysis of its evolution by the GLMM model

Variable	M0 Mean ± SD	M3 Mean ± SD	M6 Mean ± SD	M12 Mean ± SD	M24 Mean ± SD	*P* group	*P* time	*P* group and time
FACIT-Fatigue (/52)								
Fatigue						.69	**< .0001**	**< .0001**
Control group	37 ± 11*	40 ± 9	36 ± 14	42 ± 9*	41 ± 10			
Experimental group	31± 12*	40 ± 10	32 ± 15	36 ± 12*	41 ± 10			

* Significant difference ($p < .05$) between the control and experimental groups at the indicated measurement time.

Table 6. State of anxiety and trait of anxiety from the STAI between groups at each measurement time and analysis of their evolution by the GLMM model

Variable	M0 Mean ± SD	M3 Mean ± SD	M6 Mean ± SD	M12 Mean ± SD	M24 Mean ± SD	*P* group	*P* time	*P* group and time
STAI (/80)								
State of anxiety								
Control group	40 ± 12*	39 ± 11	39 ± 11	43 ± 5	43 ± 6	.23	**< .0001**	**< .0001**
Experimental group	47 ± 13*	37 ± 11	39 ± 10	44 ± 5	43 ± 6			
Trait of anxiety								
Control group	41 ± 11*	40 ± 11	40 ± 11	46 ± 5	46 ± 5	.38	**< .0001**	**< .0001**
Experimental group	47 ± 11*	39 ± 10	41 ± 10	45 ± 5	45 ± 6			

* Significant difference ($p < .05$) between the control and experimental groups at the indicated measurement time.

Table 7. Anxiety and depression from the HADS between groups at each measurement time and analysis of their evolution by the GLMM model

Variable	M0 Mean ± SD	M3 Mean ± SD	M6 Mean ± SD	M12 Mean ± SD	M24 Mean ± SD	*P* group	*P* time	*P* group and time
HADS (/21)								
Anxiety						.13	**< .0001**	**.0003**
Control group	7 ± 4*	6 ± 4	6 ± 4	6 ± 4	6 ± 4			
Experimental group	9 ± 4*	6 ± 4	7 ± 4	6 ± 4	7 ± 8			
Depression						.052	**< .0001**	**< .0001**
Control group	4 ± 3*	3 ± 3	4 ± 3	3 ± 3	3 ± 4			
Experimental group	6 ± 4*	3 ± 3	4 ± 4	4 ± 4	4 ± 4			

* Significant difference ($p < .05$) between the control and experimental groups at the indicated measurement time.

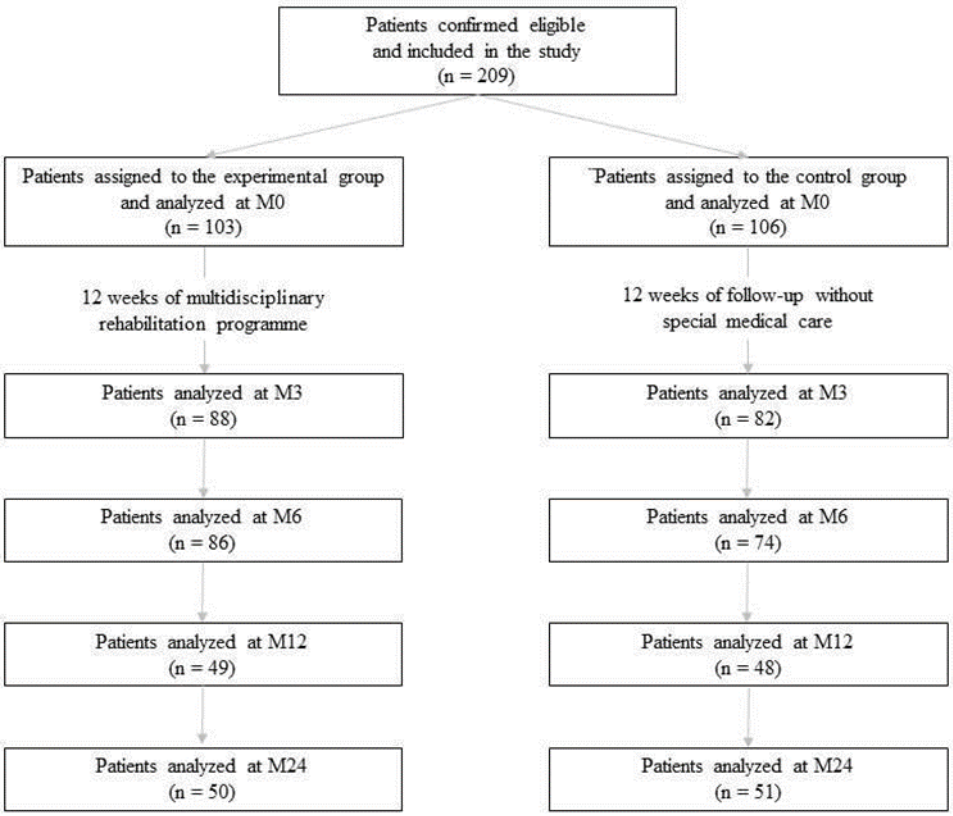
Table 8. Level of physical activity from the FPACQ between groups at each measurement time and analysis of its evolution by the GLMM model

Variable	M0 Mean ± SD	M3 Mean ± SD	M6 Mean ± SD	M12 Mean ± SD	M24 Mean ± SD	*P* group	*P* time	*P* group and time
FPACQ								
Level of physical activity (MET/week)								**
Control group	1.6 ± 0.1	1.6 ± 0.2	1.6 ± 0.1	1.7 ± 0.3	1.8 ± 0.7	.47	**.002**	
Experimental group	1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.1	1.6 ± 0.2	1.8 ± 0.6			

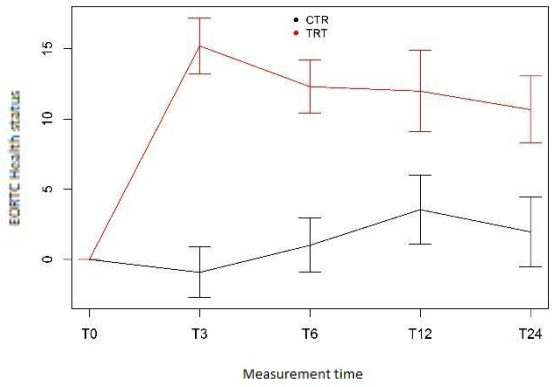
** GLMM model was done without interaction between time and group as the interaction was not significant in the model with the interaction.

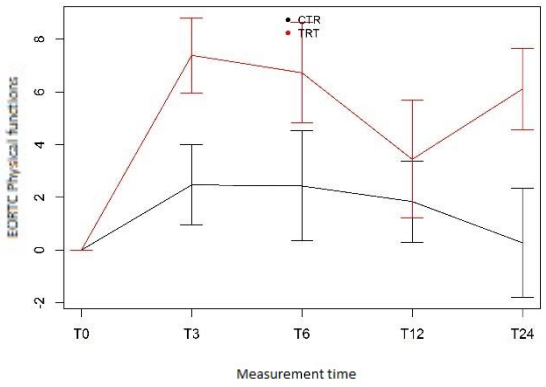
Figures

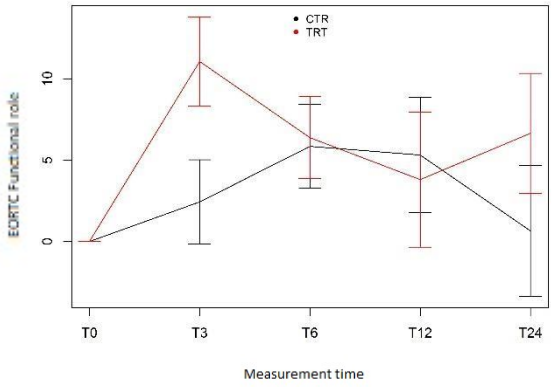
Figure 1. *Flow chart of the patients through the study.*

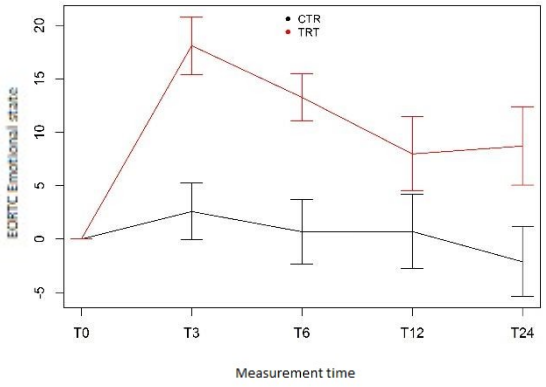


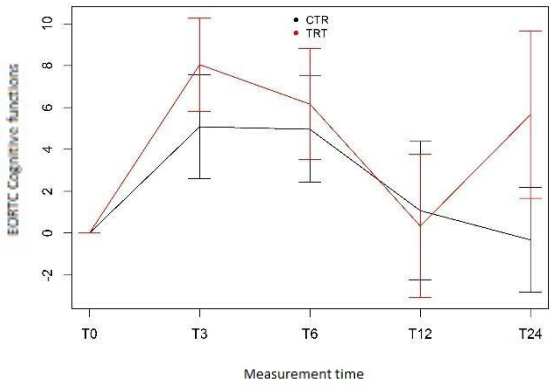
Figures: evolution of the data (mean +/- standard errors (SE)) within the control (CTR) and experimental (TRT) groups calculated from the variation of the data with respect to T0.

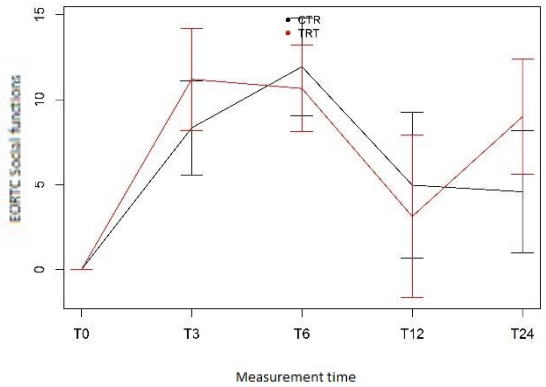


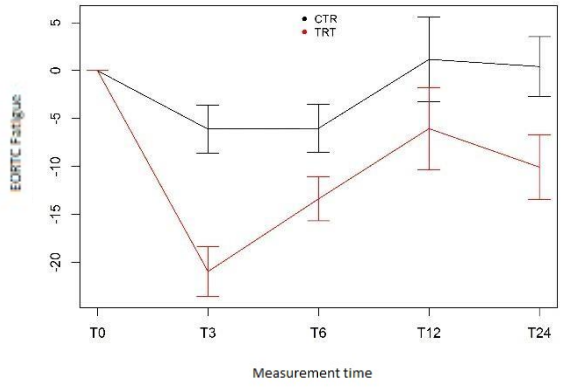


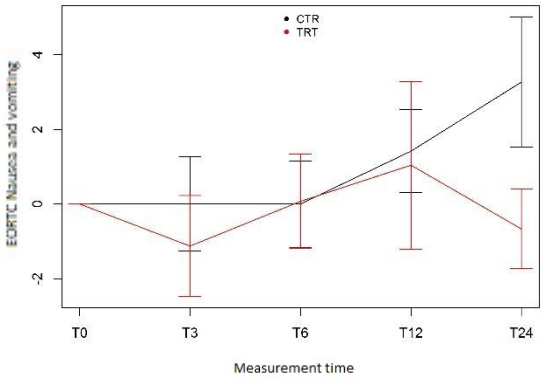


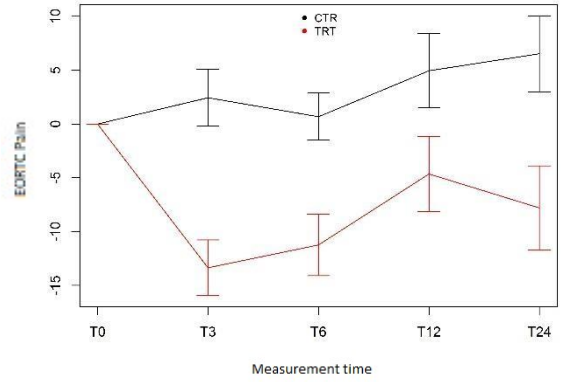


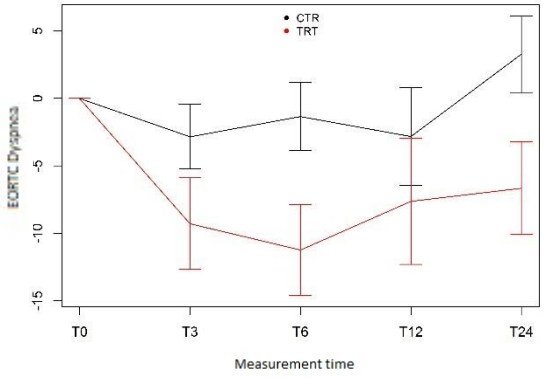


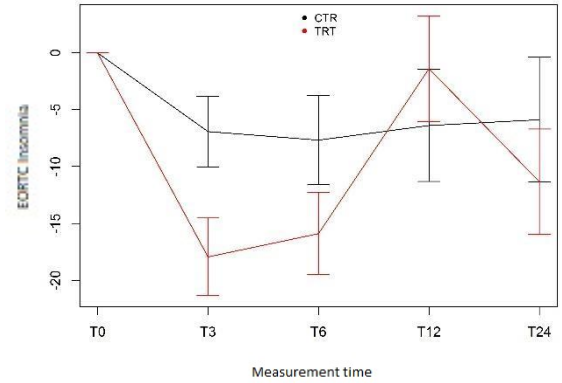


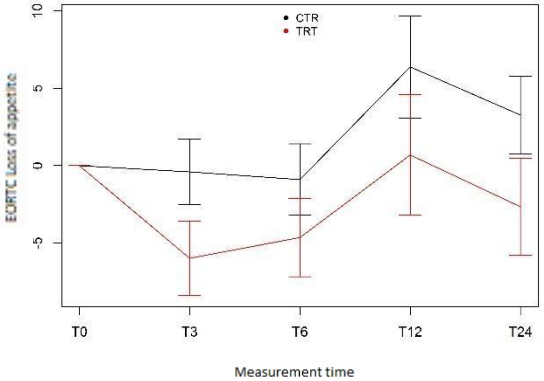

CTR
TRT
EORTC Fatigue
5
0
-5
-10
-15
-20
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
EORTC Nausea and vomiting
4
2
0
-2
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
EORTC Pain
10
5
0
-5
-10
-15
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
EORTC Dyspnea
5
0
-5
-10
-15
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
EORTC Insomnia
0
-5
-10
-15
-20
T0
T3
T6
T12
T24
Measurement time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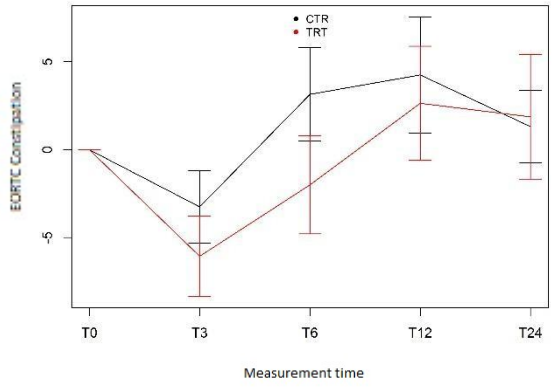
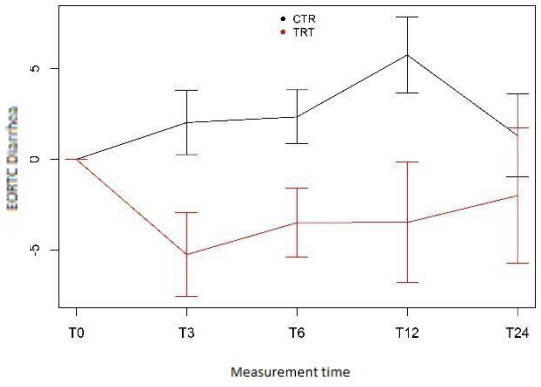
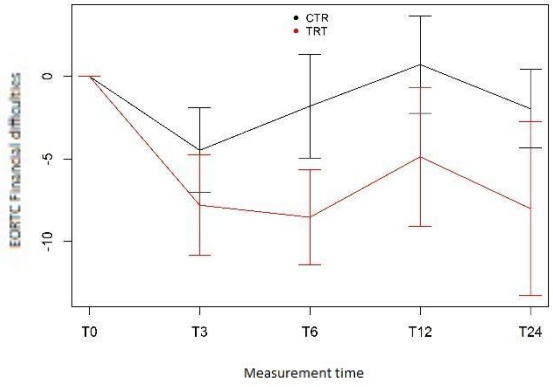
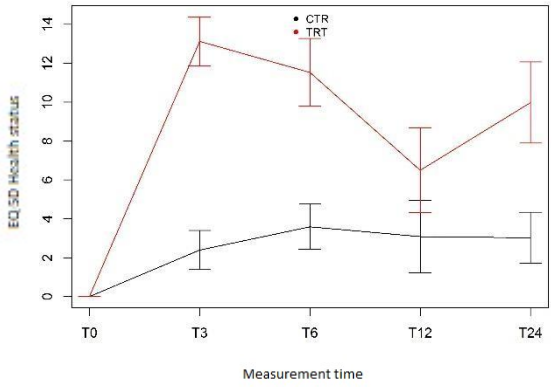
TRT
EORTC Loss of appetite
10
5
0
-5
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
EORTC Constipation
5
0
-5
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
EORTC Diarrhea
5
0
-5
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
EORTC Financial difficulties
0
-5
-10
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
EQ 5D Health status
14
12
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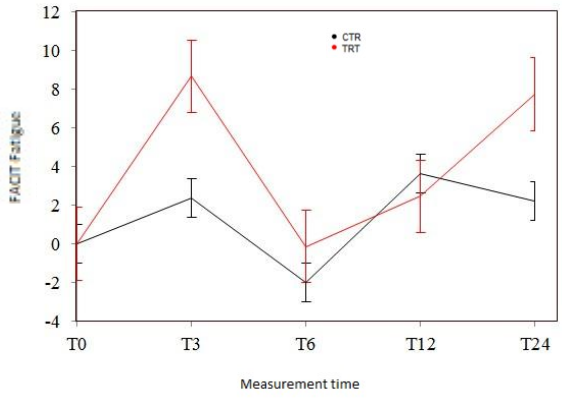
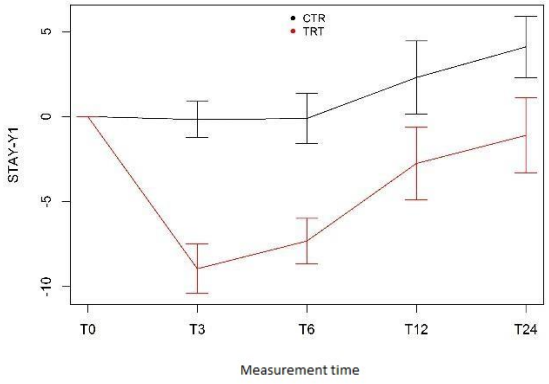
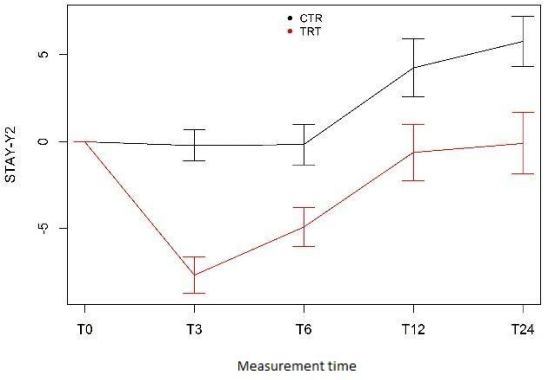
8
6
4
2
0
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
FACIT Fatigue
12
10
8
6
4
2
0
-2
-4
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
STAY-Y1
5
0
-5
-10
T0
T3
T6
T12
T24
Measurement time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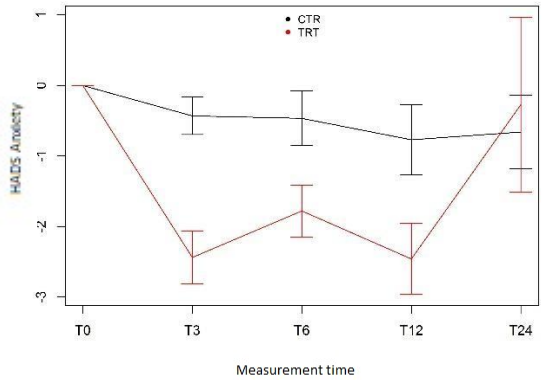
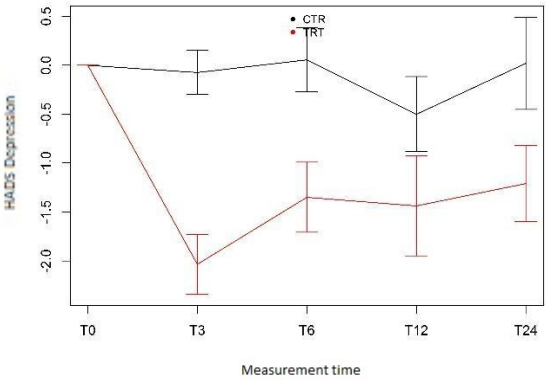
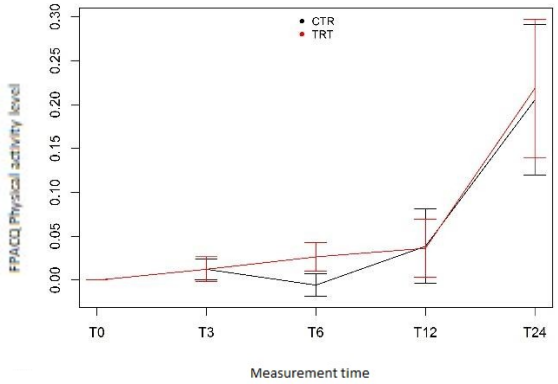
TRT
STAY-Y2
5
0
-5
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
HADS Anxiety
1
0
-1
-2
-3
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
HADS Depression
0.5
0.0
-0.5
-1.0
-1.5
-2.0
T0
T3
T6
T12
T24
Measurement time


CTR
TRT
FPACQ Physical activity level
0.30
0.25
0.20
0.15
0.10
0.05
0.00
T0
T3
T6
T12
T24
Measurement time

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