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## Long term improved quality of life by a 2-week group physical and educational intervention shortly after breast cancer chemotherapy completion. Results of the ‘Programme of Accompanying women after breast Cancer treatment completion in Thermal resorts’ (PACThe) randomised clinical trial of 251 patients

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### KEYWORDS

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**Abstract Background:** Quality of life (QoL) after breast cancer is nowadays a major challenge. Complementary interventions are necessary because of frequent depression symptoms after treatment and also to favour return to activity. Besides, radio-chemotherapy has side-effects like weight gain and fatigue. Several strategies including group behavioural-educational interventions, physical training and/or dietary education, have been tested to answer these difficulties with moderate success in the long run.

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**Methods:** Two hundred and fifty-one non-metastatic patients were accrued after chemotherapy in a prospective randomised multicenter trial between 2008 and 2010, testing a 2-week intervention in SPA centres. Intervention comprised group physical training, dietary education and physiotherapy. Selected patients were in complete remission. QoL was evaluated with SF36 questionnaire, anxiety and depression with the hospital anxiety and depression (HAD) one. Anthropometric measures and QoL evaluations were obtained before randomisation and every 6 months during 3 years.

**Results:** Two hundred and twenty patients were evaluable at 1 year. Intervention increased SF36 score by 9.5 points ( $p = 0.000006$ ), 4.6 ( $p = 0.032$ ) and 6.2 ( $p = 0.028$ ) respectively at 6, 12 and 24 months. Effect size (ES) was 0.63 [0.37; 0.90], 0.29 [0.03; 0.55] and 0.41 [0.04; 0.78]. Anxiety score was shortly minored by intervention (6-month ES =  $-0.24$  [ $-0.42$ ;  $-0.05$ ]) and depression score more durably: ES =  $-0.45$  [ $-0.72$ ;  $-0.18$ ],  $-0.34$  [ $-0.61$ ;  $-0.08$ ], and  $-0.26$  [ $-0.63$ ;  $0.11$ ] at 6, 12 and 24 months.

**Conclusion:** This 2-week group intervention seemed to durably influence QoL of breast cancer patients treated by chemotherapy. Differences, smaller at 12 months than at six, suggest that a second but shorter intervention could help maintain the 6-month benefits.

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## 1. Rationale

Thanks to early detection and improved treatment efficacy, breast cancer is becoming a chronic disease with an increasing number of survivors. In Northern America and Western Europe, the 5-year age-standardised relative survival rate is close to 80%.<sup>1</sup> Quality of life (QoL) after treatment is thus a major challenge for oncologists.

QoL is greatly impaired in women immediately after the completion of the surgery-chemotherapy-radiotherapy sequences for breast cancer. Many women present a remission psychopathology linked to the abrupt absence of the medical environment, with transient depression symptoms in the few months following their treatment. Although there seems to be no evidence that major depressive disorder is more frequent in long term cancer survivors,<sup>2</sup> depression prevalence in breast cancer patients during the first year after diagnosis was found to be twice as frequent as in the general female population<sup>3</sup>: half the patients faced either anxiety or depression during this period. Reduced QoL also has health consequences: hopelessness and helplessness seem to favour accelerated disease progression.<sup>4</sup> It has also social consequences, as it often delays the return to work for active patients. In contrast, positive factors such as social support and optimism have been associated with longer survival.<sup>5–8</sup> But these conclusions are still controversial and health effects of coping style and mood may be indirect, being possibly mediated by better lifestyle and/or health behaviour like adherence to treatments.<sup>9</sup> Finally, other works suggest that pejorative psychosocial factors could play a role by disrupting circadian rhythms and thus negatively impact immunity.<sup>10</sup>

Physical capacities represent an important component of QoL. After cancer treatment, these are often reduced because of not only surgical complications (in particular lymphoedema) but also metabolic changes caused by chemotherapy (sarcopenic weight gain).

About half of treated women show weight gain of 2.5–5 kg,<sup>11,12</sup> and only 10% of these women recover their initial weight. Lower levels of physical activity contribute to this weight gain: 75% of cancer survivors have insufficient physical activity.<sup>13</sup> In the NHANES study,<sup>14</sup> participants spent the majority of their day in sedentary time (66%) and in low-intensity activities (33%); low intensity of physical activity was associated with higher body mass index (BMI). Greater exercise and better diet quality correlate with better vitality and physical functioning, whereas greater BMI reduces physical QoL.<sup>15</sup> Finally, physical activity after breast cancer also influences survival: in a recent meta-analysis, mortality was significantly reduced, but only in survivors with BMI > 25 kg/m<sup>2</sup> (hazard ratio (HR) = 0.53 [0.35–0.81]).<sup>16</sup> Another review finds no evidence that physical activity would only benefit overweighted patients.<sup>17</sup>

Considering these interactions between disease prognosis, QoL, physical activity and BMI, in 2008 we started a prospective randomised trial ‘Programme of Accompanying women after breast Cancer treatment completion in Thermal resorts’ (PACThe) for complete responder breast cancer patients after chemotherapy. The main objective was to improve long term QoL (1 year), as short-term QoL improvement was already assessed.<sup>18</sup> Secondary objectives were to reduce weight in women with BMI > 25, to avoid weight gain in all women, and to achieve international recommendations concerning nutrition and regular physical activity.

## 2. Patients and methods

Patients were enrolled from March 2008 to October 2010. Inclusion criteria were:

- Invasive non-metastatic breast carcinoma.
- Less than 9 months after chemotherapy/radiotherapy completion.

- Complete remission.
- No contraindication of physical activity: clinical examination and maximal exercise tests with determination of maximum oxygen consumption ( $VO_{2max}$ ).<sup>19</sup>
- $18.5 < BMI < 40 \text{ kg/m}^2$ .
- No psychiatric illness.
- Informed signed consent.

Characteristics of the 2-week session performed in thermal centres:

- By group including 7–11 patients.
- Three SPA centres: Vichy, Le-Mont-Dore, Châtel-Guyon.
- Medical, nutritionist and psycho-oncologist consultations.
- Training courses lasted 13 full days when arrival and departure days in SPA centre were excluded.
- Physical activity for 2 h daily, supervised by a physiotherapist:
  - Endurance activities: walking over a flat ground or pedal on a cycloergometer.
  - Physical exercises for both strength training and flexibility/stretching: upper and lower limbs and body were concerned.
  - Aquagymnastics.
- SPA cares consist of bath, shower and massage for half an hour per day. Personal physiotherapy cares were also given if needed taking into account the entire body (usually physiotherapy performed in anticancer centres only focus on lymphoedema or pain/difficulties resulting from breast reconstruction).
- Aesthetic care.
- Dietary meals with adapted menus at the thermal resort, and dietary education. Caloric Intake was limited to 1700–2000 cal/day and dietary education was organised daily during SPA: it comprised cooking lessons related to the meals that patients had at lunch or supper. At every meal also, the chef visited the dining room and answered patients' questions about their menu and again the way to perform recipes.

Physical managements were described in detail by the PACThe protocol and physiotherapists of each SPA centre agreed to respect carefully the general training programme. The quality of intervention was also the topic of two meetings organised by the main investigator at the SPA centre, at the beginning and the end of each 2-week stay: besides the investigator, they gathered both SPA staff and patients' group. During the first reunion, participants and staff were introduced and goals and contents of the stay were precisely described. During

the second, a debriefing with the same persons was performed in order to ensure no particular observation could indicate a protocol deviation, to check for patient satisfaction and to collect information that could suggest possible improvements.

Besides standard oncological follow-up of the patients of both groups, personal consultations with a dietician were planned every 6 months until 3 years:

- To perform anthropometric measurements.
- To provide dietary advice with a dietician concerning cooking with less fat, based on a dietary inquiry about meals of previous week.
- To give encouragement for daily physical activity as defined by the American College of Sports Medicine (ACSM)/the American Heart Association (AHA)<sup>20</sup> guidelines.

Measures were taken and questionnaires filled out before randomisation at 6, 12, 18, 24 and 36 months. The French version<sup>21,22</sup> of the SF36 questionnaire was used to evaluate QoL. Secondary endpoints were included:

- Anxiety/depression (hospital anxiety and depression (HAD) questionnaire<sup>23</sup>).
- Sleep (adaptated from Leeds sleep evaluation questionnaire<sup>24</sup>).
- Physical/sedentary activity scores (Ricci & Gagnon questionnaire for physical activity<sup>25</sup> and questionnaire on sitting time<sup>26</sup>).
- Weight, waist circumference, body composition (impedanceometry).

This trial was performed in compliance with the Helsinki declaration. Protocol was approved by the AFSSAPS (French Agency for Sanitary Security of Health Products), the regional Ethics Committee (March 2008), and the French National Committee controlling personal computerised data (CNIL). This trial was registered in ClinicalTrials.gov with the n° NCT01563588.

### 3. Statistical considerations

Experimental design consisted of a multicenter parallel randomised prospective trial. Previous investigations showed variation of SF36 QoL (measured using the mean of all scores by dimension) 6 months after such an intervention of 16% versus 4% in a control group (results not published). At 1 year, we expected a 10% differential increase in SF36 QoL score. With a type one error  $\alpha = 0.05$  and 95% power ( $\beta = 0.05$ ), about 200 patients were necessary per arm. Randomisation was balanced and stratified by menopausal status, BMI less or more than  $25 \text{ kg/m}^2$ , and inclusion centre.

Data were analysed using the intention-to-treat principle. Patients who relapsed during the first year were excluded from the analysis.

Descriptive statistics are presented with mean  $\pm$  standard deviation (SD) for Gaussian quantitative variables. Outcomes are shown with 95% confidence intervals. Because sufficient data were available 2 years after diagnosis, longitudinal analysis included all available data concerning the first 2 years of follow-up.

Comparison of outcomes per allocation group was tested with Student's *t*-test or the Mann–Whitney U-test depending on homoscedasticity or normality of distributions. Two way analysis of variance (ANOVA) was used to compare longitudinal variations between allocation groups, but without interaction test because of unequal class sizes. Categorical data were compared with Chi<sup>2</sup> test. Pearson's correlation coefficient was used for quantitative data, or Spearman's ranks correlation if this was not possible. Comparison of two correlation coefficients was done using Fisher's approximation. To compare our outcomes with published data, effect sizes were computed using differences between pairs of means divided by their pooled standard deviation. Logistic regression and multivariate analysis of variance (MANOVA) were used for multivariate analysis.

The nominal level of significance was 5%. Randomisation and statistics were performed using SEM software.<sup>27</sup>

#### 4. Results

Hereafter, patients belonging to the experimental group are called the 'SPA group' and others the 'control group'. Fig. 1 shows the inclusion flow-chart. Almost half of the eligible patients (44%) refused to participate in the study or were not eligible. Twenty-two randomised patients (9%) withdrew.

Personal reasons were most frequent motif for refusal to participate. This included various motivations, such as 'already feeling well', 'benefiting from sufficient support from relatives', or 'leaving the SPA place to someone else'. Familial reasons concerned mostly women with dependents (children or parents). Health problems included relapses, depression or other psychological difficulties, limited mobility, hypertension and other health problems.

Among the 450 eligible patients, the final proportion of included ones was 66%. Randomisation was balanced in order to take into account immediate withdrawals. In the intervention group, withdrawals after randomisation were mainly due to patient's professional activity and/or the presence of children or relatives at home. In the control group, patients were sometimes so disappointed not to benefit from the SPA stay that they rapidly interrupted their participation. Balance was achieved with 117 patients in the intervention group and 115 in the control group. No patient was lost to follow-up. Six patients

had a relapse of their breast cancer before 1 year of follow-up. At end, 114 patients were analysed in the SPA group and 108 in the control group. After 1 year, much data were not yet available as follow-up was not long enough for many patients: this concerned 30% of randomised patients at 18 months and 50% at 24 months.

The main covariates were distributed similarly between the allocation arms (Table 1): only patients with QoL data 1 year after inclusion were included. No attrition bias could be evidenced: missing QoL data seemed randomly allocated between both intervention groups ( $p = 0.32$  at inclusion, and respectively 0.50, 0.72, 0.67 at 12, 18 and 24 months after inclusion).

Previous smoking was the only factor unequally distributed between arms. All other parameters did not vary significantly between groups. Cancer treatments were similar and standard for invasive tumours. Most patients were RH positive and received hormonotherapy, and a few (Her2+ patients) a targeted therapy.

#### 4.1. Quality of life

QoL evolved differently after inclusion according to allocation group (Fig. 2). The difference between curves was associated to a  $p$ -value  $< 10^{-6}$ .

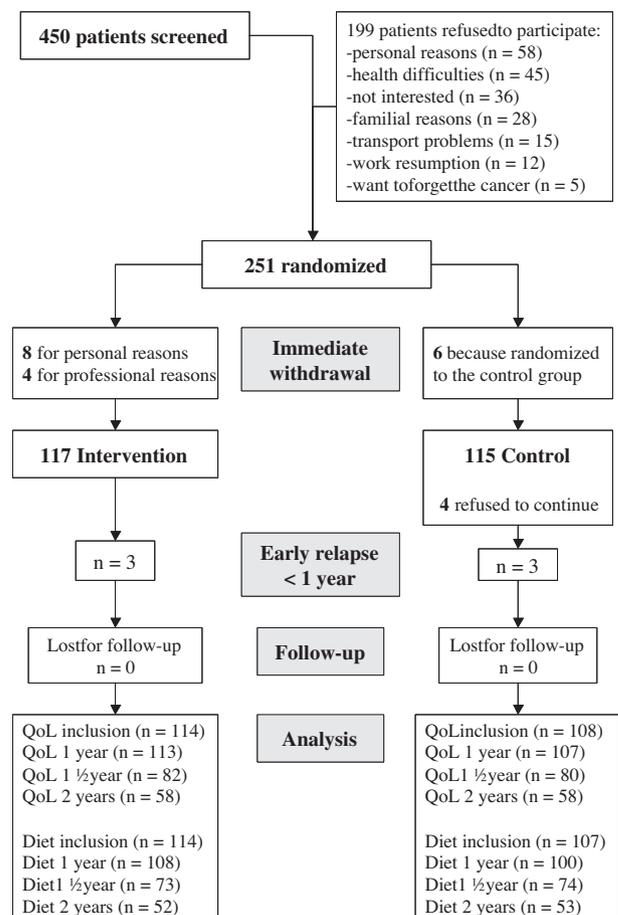


Fig. 1. Inclusion diagram. Abbreviations: QoL, quality of life; Diet, nutritional + anthropometric data.

Differences between mean QoL scores per group at 6 months equalled 9.5 points ( $p = 0.000006$ ) and 4.6 ( $p = 0.032$ ) after 1 year, then 5.4 ( $p = 0.027$ ) and 6.2 ( $p = 0.028$ ) respectively at 18 and 24 months. Corresponding effect sizes, measured by the differences divided by respective pooled standard deviations, were 0.63 [0.37; 0.90], 0.29 [0.03; 0.55], 0.34 [0.04; 0.66] and 0.41 [0.04; 0.78]. If we consider the variation in% ( $\Delta$ ) of QoL score per patient between inclusion and 1 year, the difference between intervention groups did not reach significance:  $\Delta = 26.4\% \pm 44.1\%$  for the SPA group versus  $20.3\% \pm 34.0\%$  ( $p = 0.26$ ) for the control group, while at 6 months the difference  $\Delta = 29.1\% \pm 40.1\%$  versus  $12.1\% \pm 29.1\%$  was significant ( $p = 0.00016$ ). Control group QoL increased steadily during the first two years of follow-up, by 8.7% per year.

At six months when compared to basal values (Table 2), all dimensions except the ‘role-emotional’ one, were significantly improved by SPA stay. At 1 year, all differences between groups disappeared except vitality ( $p = 0.028$ ). General health was close to significance ( $p = 0.053$ ) as well as the aggregated ‘physical health’ score ( $p = 0.076$ ).

The two aggregated SF36 sub-scales, global physical health and global mental health,<sup>28</sup> evolved differently between the groups. The gap between mental and physical dimensions was larger for the control group ( $p = 0.019$ ) than for the SPA group ( $p = 0.19$ ).

Multivariate analysis performed on the global QoL score showed that QoL was improved by following covariates: post-inclusion delay ( $p = 4 \times 10^{-7}$ ), sleep quality ( $p = 7 \times 10^{-7}$ ), physical activity score ( $p = 2 \times 10^{-6}$ ), and being in the SPA arm ( $p = 3 \times 10^{-5}$ ). Overweight ( $p = 0.001$ ) and hormonotherapy ( $p = 0.043$ ) were found to be unfavourable for QoL.

#### 4.2. Anxiety, depression

Depression and anxiety scores showed similar differences according to time and allocation group. Conversely to QoL scores, HAD questionnaire scores are worse when they are higher (Fig. 3).

For the SPA group, anxiety score just after SPA stay (not shown on Fig. 3) was 29.2/100: it was the lowest score obtained for all periods. Although the curves were not significantly different, an overall decrease of anxiety was observed compared to baseline scores ( $p = 0.0005$ ). The descendant trend was stronger for depression ( $p = 0.00014$  for the SPA group and  $p = 0.025$  for the control group). For anxiety, effect size was  $-0.24$  [ $-0.42$ ;  $-0.05$ ] at 6 months but only  $-0.09$  [ $-0.28$ ;  $0.17$ ] at 1 and 2 years. For depression, effect size was respectively  $-0.45$  [ $-0.72$ ;  $-0.18$ ],  $-0.34$  [ $-0.61$ ;  $-0.08$ ], and  $-0.26$  [ $-0.63$ ;  $0.11$ ] at 6, 12 and 24 months.

Depression (Table 3) decreased in both groups, but to a greater degree in the SPA group. This difference was

Table 1  
Repertition of main parameters according to allocation group.

Parameter	SPA group (N = 114)	Control group (N = 108)	p-Value
Menopause	Yes = 69 (61%) No = 45 (39%)	Yes = 69 (64%) No = 39 (36%)	0.61
Age (years)	51.8 ± 8.7 [23–74]	52.3 ± 10.1 [29–71]	0.68
Inclusion centre	CJP = 95 (83%) PSR = 19 (17%)	CJP = 92 (85%) PSR = 12 (15%)	0.71
Body mass index (BMI) (kg/m <sup>2</sup> )	26.1 ± 4.6 [18.4–35.9]	25.5 ± 4.1 [18.0–38.7]	0.36
BMI ≤ 25 kg/m <sup>2</sup>	52 (45%)	49 (45%)	0.15
25 < BMI ≤ 30	35 (31%)	44 (41%)	
30 < BMI ≤ 35	20 (18%)	13 (12%)	
BMI > 35 kg/m <sup>2</sup>	7 (6%)	2 (2%)	
Present smoking	Yes = 6 (5%) No = 70 (61%) Unknown = 38 (34%)	Yes = 5 (5%) No = 67 (62%) Unknown = 36 (33%)	0.81
Previous smoking	Yes = 28 (25%) No = 41 (36%) Unknown = 45 (39%)	Yes = 15 (14%) No = 51 (47%) Unknown = 42 (39%)	0.026
Chemotherapy: number of cycles	6.3 ± 1.2 [5–15]	6.0 ± 0.7 [3–9]	0.33
Radiotherapy	Yes = 107 (94%) No = 7 (6%)	Yes = 99 (82%) No = 9 (8%)	0.37
Hormonotherapy	Yes = 86 (75%) No = 28 (25%)	Yes = 82 (76%) No = 26 (24%)	0.93
Herceptin	Yes = 15 (13%) No = 99 (87%)	Yes = 9 (8%) No = 99 (92%)	0.25
SF36 global score at inclusion	56.6 ± 16.2 [19.4–93.0]	54.4 ± 14.4 [25.2–90.8]	0.30

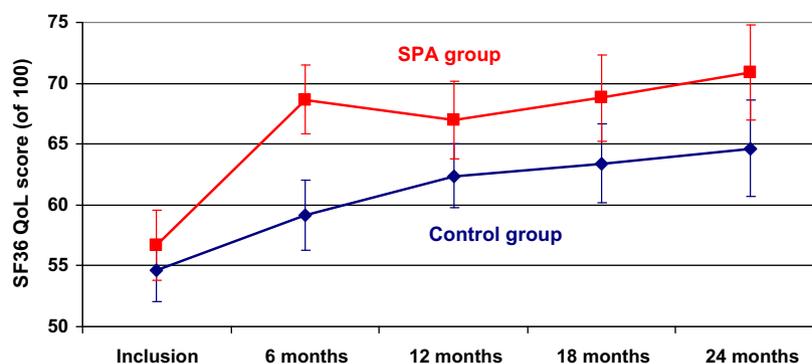


Fig. 2. Evolution of SF36 quality of life (QoL) scores according to allocation group (error bars correspond to 95% confidence interval (CI)).

Table 2  
variation of SF36 sub-scales in % after 6 and 12 months.

SF36 dimensions	Δ 6 months versus inclusion (mean ± standard deviation (SD))			Δ 1 year versus inclusion (mean ± SD)		
	SPA group	Control group	<i>p</i> -Value	SPA group	Control group	<i>p</i> -Value
Physical functioning	25.9 ± 78.6	14.5 ± 50.6	0.034	17.7 ± 42.4	18.6 ± 53.5	0.36
Role physical	61.1 ± 124.3	33.6 ± 86.4	0.042	74.0 ± 139.4	53.6 ± 108.6	0.14
Body pain	53.3 ± 97.8	38.1 ± 100.1	0.07	42.1 ± 100.6	42.1 ± 100.3	0.96
General health	41.5 ± 94.9	22.8 ± 105.9	0.0002	41.3 ± 122.2	23.6 ± 58.9	0.053
Vitality	45.6 ± 79.2	17.7 ± 52.6	0.002	32.5 ± 61.9	17.5 ± 53.7	0.028
Social functioning	45.0 ± 94.1	18.4 ± 61.6	0.032	35.2 ± 79.9	29.7 ± 69.6	0.53
Role-emotional	45.7 ± 97.0	25.8 ± 72.3	0.15	45.0 ± 97.7	47.6 ± 80.1	0.43
Mental health	32.7 ± 69.2	8.2 ± 38.4	0.00058	22.8 ± 46.5	18.0 ± 44.7	0.74
Global physical health	29.3 ± 36.5	14.6 ± 31.1	0.00022	26.0 ± 39.1	19.7 ± 34.9	0.076
Global mental health	33.3 ± 51.0	12.0 ± 37.9	0.00011	27.6 ± 47.8	21.6 ± 44.2	0.40

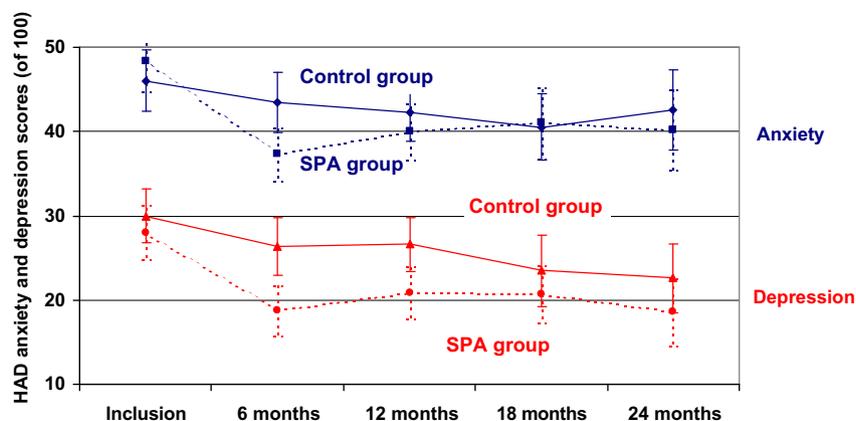


Fig. 3. Hospital anxiety and depression (HAD) anxiety and depression scores. Differences between curves are significant for depression ( $p = 0.00001$ ) but not for anxiety ( $p = 0.19$ ).

slightly significant. Reduction of anxiety was stronger but shorter, as the difference was significant only at 6 months.

Depression syndrome (HAD score  $\geq 11$ ), although reduced by half by intervention in all periods after inclusion, never yielded any significant difference. Conversely, depressive traits (HAD score  $\geq 8$ ) were significantly diminished by the SPA stay at 6 and 12 months ( $p = 0.0003$  and  $0.019$ ).

Finally, HAD depression scores were more strongly correlated to QoL than anxiety ( $r = -0.74 \pm 0.02$  and  $r = -0.58 \pm 0.02$ ).

#### 4.3. Activity, sedentarity and sleep

A score  $> 40/100$  of the physical activity questionnaire corresponds to the World Health Organization (WHO) recommendations for physical activity for

Table 3

Percent variation of anxiety and depression scores ( $\Delta$ ) according to allocation group: 6 months and 1 year versus baseline values (a negative mean value indicates reduction of depression signs).

Dimension of hospital anxiety and depression (HAD) questionnaire	$\Delta$ 6 months versus inclusion (mean $\pm$ standard deviation (SD))			$\Delta$ 1 year versus inclusion (mean $\pm$ SD)		
	SPA group	Control group	<i>p</i> -Value	SPA group	Control group	<i>p</i> -Value
Anxiety	-18.0% $\pm$ 36.7	+2.1% $\pm$ 38.4	0.0002	-11.5% $\pm$ 42.1	-1.6% $\pm$ 39.1	0.06
Depression	-23.8% $\pm$ 56.4	-9.7% $\pm$ 54.1	0.035	-12.4% $\pm$ 78.6	-5.8% $\pm$ 60.8	0.05

adults aged 18–64 years. Score of total physical activity was similar at inclusion (43% of patients in the SPA group and 45% in the control group had a good level of activity) but significantly increased after the SPA stay by 36%, versus 18% in the control group (Fig. 4). Rate of active patients (score  $>$  40) was respectively superior by 8%, 10% and 14% in the SPA group at 6 months, 1 year and 2 years.

Sedentarity levels did not differ between groups ( $p = 0.09$ ) or change over time. Sedentarity score was weakly negatively correlated to QoL ( $r = -0.10$ ,  $p = 0.0012$ ) but activity positively ( $r = 0.33$ ,  $p < 10^{-7}$ ).

Sleep quality was correlated to QoL ( $r = 0.41$ ,  $p < 10^{-7}$ ) and it was durably improved by the SPA stay ( $p = 0.0008$ ). However hypnotics consumption was not changed by the SPA stay ( $p = 0.24$ ).

## 5. Discussion

The primary endpoint of PACThe trial was quality of life 1 year after inclusion. SPA stay improved SF36 QoL by 9.5 points after 6 months and about five points ( $p = 0.032$ ) after 1 year of follow-up. The differential increase was significant at 6 months (17%,  $p = 0.00016$ ), but not at 1 year (6%,  $p = 0.26$ ). A lack of power may explain this result, as recruitment was interrupted before the target sample size was reached. Second, women from the control group increased their QoL more strongly during the second semester than women in the SPA group (these latter even exhibited a 3% reduction after a large initial improvement). The QoL effect sizes of our trial are satisfying as they always stand over the 0.28 reported in the meta-analysis of Duijts.<sup>18</sup> But this meta-analysis

mixed protocols of various duration and also, some occurring during adjuvant treatments and others after treatments (except hormonotherapy).

The slight QoL decrease between 6 and 12 months in the SPA group suggests that a new SPA session, even short, during the second semester after the first one could help sustain the benefits, as noticed by patients' comments. Finally, our QoL outcomes indicate that about 1 year is necessary for breast cancer patients to reach a better QoL level. Post-treatment adequate managements can thus largely reduce this delay. Here, a short 2-week protocol in SPA did significantly accelerate this recovery.

QoL dimensions most favoured by SPA stay were physical (SF36 physical functioning, role physical, general health, vitality). Moreover, evolution of overall mental and physical aggregated scores was different between both allocation groups: for SPA patients, corresponding longitudinal curves were very close while they were not in the control group (figure not shown). The gap between mental and physical dimensions in the only control group may indicate that mental QoL dimension of control patients increases in the long run despite remaining physical difficulties. After our 2-week protocol, patients seemed able to keep to their previous values while others were often forced to alter some personal considerations about their well-being.

Anxiety and depression measured by the HAD questionnaire is another good indicator of QoL. In Duijts' meta-analysis, only three over five trials investigated depression and two over three anxiety with post-treatment managements. When limiting analysis to these trials, no significant impact could be objectivised. In

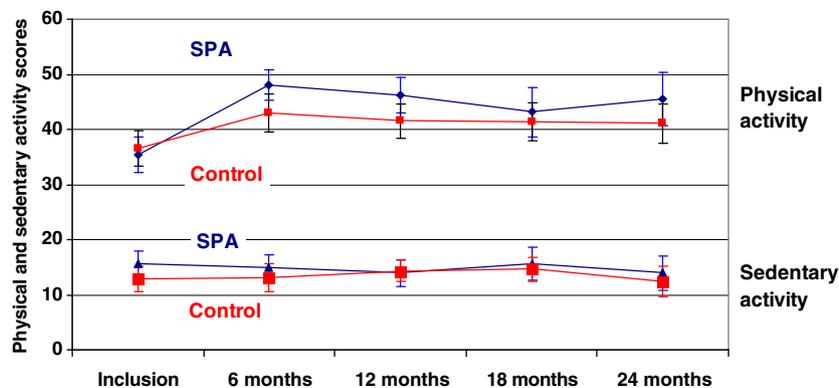


Fig. 4. Physical and sedentary activity scores. Differences were significant for physical activity ( $p = 0.013$ ).

PACThe trial, anxiety appeared a very fluctuant parameter on which interventions had a very quick but not lasting effect. Depression was more influenced in the long term by the intervention than anxiety and this until 2 years. On average after SPA stay, rates of patients either with depression traits (HAD cut-off = 8) or depression syndrome (cut-off = 11) were divided by two at 6 and 12 months. Craft et al.<sup>29</sup> have performed a review and a meta-analysis of prospective trials testing the impact of physical activity on depression. Effect size on depression (0.22) was found slightly significant on the short run but no results were available on the long term. The effect sizes obtained after SPA stay after one and two semesters (−0.45 and −0.34) appear higher suggesting that other managements provided by our protocol (dietary education, physiotherapy, group dynamic... and perhaps SPA cares) have played a complementary role to physical training on outcomes.

## 6. Limitations and strengths

- About half of the eligible patients finally accepted to participate in our study. This percentage can be compared to similar investigations, for example the 'Alberta physical activity and breast cancer prevention trial'<sup>30</sup> proposing a 1 year weekly physical training where only 320 out of 1072 patients entered the trial. This is the first limit of such approaches. Our protocol duration was only 2 weeks, but this duration appeared often even too long, especially for patients with children at home or those still working. However, it is possible that the acceptance of a 2-week protocol in a SPA may increase with time as its benefits become more widely recognised.
- Our protocol, although it included SPA cares, was first of all dedicated to physical exercises and dietary education. Further, interventions were organised by groups of 7–11 patients, and it is likely that this grouping could favour within each group a dynamic with psychotherapeutic effects. Finally, the physiotherapy sessions provided did not focus on local chest or back pains or lymphoedema as usually performed but had a more global purpose considering body functions as a whole. It is possible that only SPA group managements comprising these parts could be really efficient
- Studies on cancer survivor groups are generally highly clinically heterogeneous. PACThe population is much more homogeneous. But this quality may limit the scope of benefits to patients presenting with the same kind of disease, that is invasive tumour treated at least by chemotherapy.

To conclude, PACThe trial testing the impact of a 2-week SPA stay by small groups of patients comprising physical training, dietary education, physiotherapy and SPA cares, suggests that this intervention enabled on the middle run (1 year) an improvement of women's

QoL, a reduction of depression traits, and a better quality of sleep. This comprehensive protocol appears an interesting strategy that requires only a 2-week management disconnecting patients from standard cancer cares immediately after completion of cancer treatment. It was impossible to find what in the protocol was the most effective: physical activity, physiotherapy, dietary education or group dynamics? The protocol seemed to work as a whole, and each piece should not be used apart from the others. It represents a global multidisciplinary supportive and educational intervention. As breast cancer survivors are more and more numerous, this strategy seems well suited to the needs and expectations of patients in complete remission. This approach needs to be validated by other trials, and in other cancers, with adaptations to specific disease characteristics and treatment consequences.

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## Conflict of interest statement

Pr. Roques CF is involved in the AFRETH council. His role was to supervise the global study methodology/design and check for the trial quality. He did not interfere with the management of the trial, nor with statistical calculations and manuscript preparation.

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