Cognitive function after adjuvant treatment for early breast cancer: a population-based longitudinal study

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Abstract

Purpose. To examine cognitive function in patients with early breast cancer before and after adjuvant chemotherapy or six months of tamoxifen.

Methods. We performed a population-based study in the county of North Jutland, Denmark, including 120 women aged less than 60 years who received adjuvant chemotherapy with seven cycles of cyclophosphamide, epirubicin, and fluoruracil or adjuvant tamoxifen for six months for early breast cancer from 2004-2006. They were compared with an aged-matched group of 208 women without previous cancer selected randomly from the same population. Data were collected before start of adjuvant treatment and after six months by neuropsychological tests and questionnaires to evaluate cognitive function, quality of life, and psychological distress.

Results. Neuropsychological tests did not reveal any differences in cognitive function between breast cancer patients after chemotherapy and healthy controls. Patients rated their own cognitive functions as improved after six months, and patients, who did not receive adjuvant medical treatment, reached the same level as controls within 6 months. Patients receiving chemotherapy or tamoxifen were up to three times more likely than controls to rate themselves as impaired at six months.

Conclusion. Our results do not support that adjuvant chemotherapy is associated with cognitive side effects in breast cancer patients.

Keywords:Breast cancer, cognitive function, psychological distress, quality of life, population based longitudinal study.

Background

Adjuvant chemotherapy with antracyclines and endocrine treatment with tamoxifen reduces the risk of dying from breast cancer (BC)[1] . Among side effects to adjuvant treatment, several studies have reported a decline in cognitive function like memory, attention, and executive function [2]. The first studies of cognitive function appeared around 1995 and showed from 28 to 75% impairment in cognitive function [3,4]. However, these studies were small and cross-sectional. Later longitudinal studies including healthy controls and larger patient series have found either lower levels of impairment [5], no difference, or even improvement after chemotherapy [5,6]. Thus, the results are still at variance, probably due to differences in design and methodology [7,8]. An influence of tamoxifen on cognitive function has also been debated with one study showing no association [9] and others demonstrating impairment of memory and processing speed task [10,11].

The purpose of this study was to examine cognitive function, psychological distress, and quality of life (QOL) before the initiation of adjuvant therapy for early BC and at completion of chemotherapy or after six months of tamoxifen compared with an age-matched control group without prior cancer.

Materials and methods

Study population

We identified prospectively 196 women aged less than 60 years who had surgery for primary BC and no evidence of metastatic disease between May 1, 2004 and July 4, 2006. By use of the unique personal ID-numbers issued to all persons residing in Denmark, we were able to select a control group of 531 women who were age-matched to the study

group from the entire female population of North Jutland Country. Among BC patients 124 (63%) accepted to participate and among controls 224 (42%) accepted. The selection process has been described in detail elsewhere [12]. Six months after baseline 120 (61%) of the BC patients and 208 (39%) of the controls remained in the study. Eligibility criteria for the BC patients and controls were: 1) no prior cancer 2) no diseases of the central nervous system; 3) no neurosurgery; 4) no neuropsychological testing within the last year; 5) no use of antidepressants or alcohol abuse; 6) no impairment of eye or hearing; 7) no illiteracy and not having Danish as mother tongue. Adjuvant treatment was given as follows: 75 patients (62.5%) received CEF chemotherapy (cyclophosphamide 600 mg/m^2 intravenously (IV), epirubicin 60 mg/m^2 IV, and 5-fluorouracil 600 mg/m^2 IV every three weeks for seven cycles), and 26 (21.7%) patients received tamoxifen 20 mg/day while 19 (15.8%) received no medical adjuvant treatment. One patient stopped chemotherapy after five cycles, and one patient had only one cycle followed by ovarian ablation but both stayed in the chemotherapy group for the analyses. Radiotherapy (RT) to the chest wall or residual breast with or without the regional lymph nodes was given to 79 patients (66%) of whom 52 (66%) were in the chemotherapy group, 17 (21%) in the tamoxifen group and 10 (13%) in the no medical treatment group. All BC patients receiving chemotherapy were offered standard antiemetic treatment.

Data collection

At baseline (T1) after surgery but before initiation of any adjuvant treatment, data were collected regarding education, occupation, fertility, family history of BC, quality of life, and psychological distress using self-administered questionnaires filled in by the BC patients and controls at home. The questionnaires were checked for completeness by the research staff after the neuropsychological testing had been carried out. The second assessment (T2) was carried out four weeks after the last cycle of CEF or approximately six months after T1. Self-administered questionnaires regarding psychological distress and QOL were mailed to patients and controls and filled in at home before the neuropsychological testing. Data on adjuvant treatment derived from the medical records.

Neuropsychological testing

The neuropsychological status of all participants was assessed by the revised neuropsychological test-battery from the International Study of Postoperative Cognitive Dysfunction [13]. The ISPOCD test battery consists of four tests giving five test measures: 1) Visual Verbal Learning Test (VLT), 2) Concept Shifting Test (CST), 3) Stroop Colour Word Interference Test (SCWT), and 4) Letter-Digit Coding Test (LDCT). Testing was designed to encompass the following cognitive domains: concentration, episodic memory (intermediate and long-term memory), simple and complex attention, cognitive speed and flexibility, visual scanning, and executive function. Alternate forms of the tests were used in random order except for the STROOP test to minimise practise effects. General intelligence was evaluated using The Danish Adult Reading Test (DART) translated from the National Adult Reading

Test (NART). This test was taken once at baseline. All tests were administered in the same quiet room and in a fixed order at the Department of Oncology by four trained research assistants [12].

Rating scales and questionnaires

To measure coping capacity we employed the Danish version of the10-item scale General Perceived Self-Efficacy (GPS) [14]. We used the sum of the 10 items. A high validity and reliability has been documented in various populations [15].

Profile of Mood States (POMS) was administered to all participants to evaluate psychological distress. POMS measures six identifiable mood or affective states including five negative mood factors: tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, confusion-bewilderment, and one positive mood factor, vigour [16].

Subjective cognitive functioning (SCF) was measured by four questions about memory, concentration/attention, mental burden, and vitality from the ISPOCD 2 study concerning change within the last four weeks [13]. The subjects rated themselves for each question on a 7-point scale ranging from (1) *major improvement* to (7) *greatest decline* regarding changes within the last month. In the analysis, scores from 1-3 were considered as improvement, 4 as no change, and 5-7 as impairment.

EORTC QLQ-C30 was used to measure quality of life. The questionnaire is translated into Danish and validated internationally by the EORTC Study Group [17]. It incorporates five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea or vomiting); one global health scale,

and six single items (dyspnoea, sleeplessness, loss of appetite, constipation, diarrhoea, and financial difficulties) [18] and is used widely in Europe for cancer patients [19].

Ethical considerations

Oral and written information was given about the study. Those who accepted to participate gave informed consent before inclusion in the study. The study was approved by the Ethical Committee for Viborg and North Jutland Counties with reference number: VN 2004/15.

Statistical methods

Study population

Normal probability plots were used to assess the normal distribution of data. Measures of central tendency (mean, median) and dispersion (SD, interquartile range (IQR)) were computed initially for continuous variables and frequency counts and percentages for categorical variables. One-Way ANOVA was employed to explore differences between groups for selected variables.

Neuropsychological test battery

The control group was used to predict the difference in test scores between baseline and 6 months. This was achieved by fitting a linear regression model to the difference in test scores for the control group only. Because of a possible confounding effect on the neuropsychological tests, the difference was adjusted for baseline level of the test score, age, DART, educational level, length of retest interval, and difference in depression and

tension between 6 months and baseline. Possible confounders were selected on the basis of theory found to influence test performance, e.g. depression [20], and kept in the model regardless of effects. The regression coefficients obtained from this model were then used to predict the expected differences in test scores for the breast cancer patients, divided into the three treatment groups. In this way, the use of a control group ensured that any practice effects between baseline and 6 months were controlled for. However, the differences in test scores in the control group were not normally distributed. Therefore, in order to classify the patients has having either declined or improved at 6 months we used the 5^{th} and 95^{th} percentiles of the residuals, i.e. the observed difference minus the predicted difference, from the control group to define 90% "distribution-free" prediction intervals. This is similar to the approach recommended by Temkin et al. [21]. Using these distribution-free prediction intervals the BC patients could be classified as either having improved, been stable or declined from baseline to 6 months. We also present results of binomial tests of the assumption of a five percent improvement and a five percent decline for the BC patients for each of the tests in the test battery. We finally calculated the percentage of BC patients who had declined or improved in two or more tests. Assuming that the individual tests in the test battery were independent and that there was no difference between the BC patients and the control group, 2.26% of the BC patients were expected to decline/improve in two or more tests. A binomial test of this assumption was calculated.

To control for type I error across the multiple outcome measures, a two-sided 0.005 critical level for a statistical significance was employed. A strict Bonferroni adjustment would be overly conservative due to correlations among outcomes measures [22].

Psychological distress (POMS)

For POMS, the approach was identical to the one described above for the neuropsychological test battery. The only difference was that the linear regression model fitting the difference in scores between baseline and 6 months for the control group was adjusted for baseline level, age, educational level, working status, smoking status, level of exercise, and self efficacy at baseline. Since the POMS consisted of six tests (compared with five tests in the test battery) we expected 3.28% of the BC patients to decline or improve in two or more tests under the assumption that there was no difference between the BC patients and the control group. Again the use of a control group to predict difference in scores ensured that any retest effects were taken properly care of.

Quality of life

Changes in QLQ-C30 from T1 to T2 were assessed by Wilcoxon sign rank test and the Kruskal Wallis one way ANOVA by ranks for differences between groups at T1 and T2 to account for the skewness in data distribution.

Subjective cognitive functioning

Proportions of patients impaired, unchanged or improved on subjective cognitive functioning (SCF) in each of the four study groups at T1 and T2 and the changes from T1 to T2 were compared by Fisher's exact test. Bivariate correlations using Spearman rank correlations were computed between the neuropsychological test scores and SCF questions.

For all statistical analyses we used the statistical Package Stata version 9.2 for Windows and SAS software (version 9.1, SAS Institute Inc., Cary, NC).

Results

Study population

Table 1 shows the characteristics of the 120 BC patients and 208 controls who completed all tests and questionnaires at T1 and T2. There were no significant differences between the patients and the controls with respect to DART, years in school and education. Patients receiving tamoxifen were significantly older than the patients in the other groups (tamoxifen group: mean 56.2; chemotherapy group: mean 47.2; no medical treatment group: mean 49.7; control group: mean 48.2). The time interval between the two neuropsychological assessments also differed, the interval being shortest for the chemotherapy group. Hence, all neuropsychological change analyses were adjusted for age and retest interval. Few patients in the chemotherapy group had completed radiotherapy at T2 whereas all in the tamoxifen group had. Similarly, none in the chemotherapy group had started endocrine treatment at T2, whereas the tamoxifen group had been treated for approximately six months. There were no significant differences in age or reason to refuse inclusion in the study between the included and excluded participants.

Analyses of changes in scores on the neuropsychological test battery

Between T1 and T2 no evident or consistent pattern of change in cognitive function was observed in the three groups of patients (Table 2). In the chemotherapy group 14.9% showed a decline on concept shifting test ($p=0.002$) but 12.2% showed a trend of improvement on delayed memory ($p = 0.023$). The no medical treatment group was

stable on most tests. In the tamoxifen group a trend of changes in both directions was seen as 19.2% declined on concept shifting test ($p = 0.017$) and 19.2% improved on STROOP test ($p=0.017$).

Table 3 A shows that 15.4% in the Tamoxifen group declined on two or more tests ($p=0.005$). No other changes were found for any of the groups. Using the f-test, the baseline level, age, and intelligence most consistently predicted change from baseline to six month on most tests ($p< 0.001$) (data not shown).

Subjective cognitive functioning

Table 4 illustrates the changes one month preceding T1 and one month preceding T2 in perceived cognitive function. Between T1 and T2 there were significant improvements in the perception of changes in all four cognitive functions in all patient groups, except for memory in the tamoxifen group. At T2, however, patients who had just completed chemotherapy still rated themselves as impaired with respect to cognitive abilities with relative risks (RRs) ranging from 1.2 to 2.8 compared with controls. Similarly, the RRs were between 1.2 and 2.8 in the tamoxifen group, i.e. these patients were still up to three times more likely to perceive themselves as impaired.

At baseline, BC patients who received no adjuvant medical treatment had as poor ratings as the patients who were later treated with chemotherapy or tamoxifen but at T2, this group had achieved almost similar ratings as the controls. As expected, the control group remained stable with similar ratings of subjective change at both T1 and T2. No significant correlations were found between the neuropsychological tests and the subjective ratings of cognitive functions (all $p>0.05$).

Psychological distress (POMS)

Between T1 and T2 patients treated with chemotherapy or tamoxifen improved significantly on the anger and tension dimensions. In the no treatment group there were significant improvements in fatigue and confusion (table 5). The number of patients showing improved mood scores on two or more scales was significantly higher than expected in all three groups, showing improvements from 16 to 32%. (all $p < 0.0001$) (table 3 B). General Perceived Self-efficacy was stable over time and no differences were found between the groups (table 6).

Quality of life

Table 6 shows the symptom scores on EORTC QLQ-C30. All three groups of patients improved their role function ($p< 0.005$). The chemotherapy group improved on emotional function but decreased in cognitive and physical function. The tamoxifen group had better scores on emotional function and global health ($p<0.005$) at T2. On the symptom scores, patients completing chemotherapy had higher scores on fatigue, nausea, dyspnoea, and appetite loss ($p \leq 0.01$) and all patients had significantly less pain. Compared with the control group the BC patients still scored lower at T2 on several functional scores (physical, role, cognitive, and social ($p < 0.005$) and higher on symptom scores (fatigue, nausea, pain ($p=0.02$), dyspnoea, and sleeplessness ($p < 0.005$)). The distribution of data for most scores was skewed which explains why there could be a significant difference between two equal medians e.g. for fatigue in the tamoxifen group.

Discussion

Previously we have reported that before start of adjuvant treatment, BC patients experienced a significant deterioration of their subjectively rated cognitive functioning, quality of life and of psychological well being but at the same time showed no impairment on the neuropsychological tests [12] . In this analysis, we have evaluated the same patients and controls six months later using the same questionnaires and neuropsychological test battery. While we no observed any major changes over time or between the chemotherapy and the no medical treatment groups on the neuropsychological test battery, all patients improved on most measures evaluating their subjectively rated level of cognitive and psychological distress. Patients who did not receive medical adjuvant treatment reached a level almost similar to that of the controls six months after surgery. Patients receiving chemotherapy or tamoxifen also improved but they still rated their cognitive functions as impaired compared with controls.

Our results do not provide evidence that chemotherapy with CEF is associated with cognitive side effects or so called “chemo brain”. This is in agreement with other studies reporting that patients treated with standard dose CEF showed no impairment on test results[5,6,23,24] . Some studies have reported memory and concentration problems during or after treatment with chemotherapy [25-27] but few patients felt these problems had bothered them [28]. It is, however, difficult to make direct comparisons between the studies since the questionnaires as well as the treatment regimens varied. Treatments mostly consisted of CEF, docetaxel, cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), adriamycin, cyclophosphamide (AC) and paclitaxel [6,23,25-27], followed by tamoxifen or aromatase inhibitors. Some gave no specific information

about the cyctotoxic agents used [29]. A likely explanation of previous findings of cognitive impairment after adjuvant chemotherapy may be the lack of a matched control group and using a large number of cognitive tests [25] which may increase the chance of categorising a patient as impaired on one or more tests [30].

Among patients receiving tamoxifen 15.4% declined on two or more tests. This is in agreement with a cross-sectional study of patients who had impaired processing speed and memory after treatment with tamoxifen and / or anastrozole for a longer period [10,11]. Similarly, others have shown a decrease in cognitive function after six months in a prospective study [31] and one year after tamoxifen treatment in a randomised trial [32]. However, the most reliable predictors of change on the neuropsychological tests for all groups were baseline performance, intelligence and age which are well known to influence cognitive tests. Selection of these confounders made it possible to adjust the test results and thereby to predict a more valid change in cognitive function. Temkin et al. [21] have reported that baseline performance level accounted for up to 80% of the variance. We used the test battery from the ISPOCD study [33] because it has shown sensitivity to small and moderate postoperative cognitive decline in European patients and encompasses the same domains most often tested in "chemo brain" studies [2,34]. As in several other studies [35-37] we did not detect any association between neuropsychological test scores and subjective reports of cognitive function. Also, there were no associations between the changes in scores over six months. This discrepancy remains to be fully understood and clearly demands more attention [38] . However, self rating of cognitive capacity may not necessarily be related closely to objective measures, particularly when one is under the strain of a serious illness.

In assessing psychological distress, we found improvements equivalent to those reported in other longitudinal studies [39,40]. In this analysis, we adjusted for several factors and the most reliable predictors of mood function at six months were baseline level and smoking. In a Danish nationwide cohort study [41], smoking was also reported to be associated with depressive symptoms. BC patients generally scored low on depression and anxiety with only 3.8 % of the patients compared with 4.3% among controls scoring above threshold, using the POMS manual for cut off [16]. In our study population, fewer women were depressed than in the Danish nationwide cohort study where 13.7% of BC patients had a major depression three to four months after surgery [41]. This difference may be due either to the use of another questionnaire, the exclusion of major depressed participants, or to improvement during the additional three months after surgery. The ability to cope with life-situations did not change over time and was similar to the control group.

Receiving medical treatment had a negative influence on the QLQ – C30 symptom scores probably related to side effects from treatments [42]. Subjective ratings of memory and concentration abilities decreased after treatment with chemotherapy which is consistent with results from other studies with similarly treated BC patients [26,43]. BC patients treated with chemotherapy seemed to be more likely than controls to perceive themselves as impaired.

The well-being and Global Health scales improved over time even if it did not reach the same level as in the control group. This is consistent with other Scandinavian studies

which also showed improvement over time after treatment. However, other studies showed lower levels of scores than in this study [44,45]. According to EORTC QLQ-C-30 norms for a Danish population-based study, the general level of functional scores in this study was higher and the symptom scores lower. [46].

The strength of our study design is that we included a control group from the same population which allowed us to estimate directly the level of symptoms to expect in women without cancer and to control for individual differences such as intelligence and education. Also, we performed a baseline assessment before start of treatment in order to be able to evaluate whether patients improved or declined, taking practise effects into account. Additionally, all patients received the same type of chemotherapy (CEF).We also included a small group of patients receiving no adjuvant medical treatment. An additional strength is the low attrition rate ranging from three percent among patients to seven percent among controls. Losses to follow-up are thus unlikely to explain the results. Furthermore, the regression-based approach is found to be the most sensitive in detecting cognitive changes and ensures that a reliable and consistent decline in cognitive function would be found if present [47].

However, there are limitations to our study. The relatively low inclusion rate may have caused selection bias but neither patients nor controls declining to participate differed with respect to age and reasons for refusing from those included in the study and all four groups ended up being similar with respect to demographic factors. We therefore think that the participants at baseline were representative for the Danish population in general, i.e. that selection bias did not exert any great influence on the results. Dividing

the patients by treatment, the groups became relatively small and the statistical power to detect small differences was reduced. Although we used well documented assessment tools we cannot rule out that these tools could not capture minute changes in cognitive function. During the data collection period, CEF was the standard chemotherapy. However, our study cannot address side effects of chemotherapy including the potentially neurotoxic taxans.

In conclusion, our results do not support that chemotherapy with CEF is associated with cognitive side effects. Patients who did not receive medical adjuvant treatment reached a subjective level almost similar to the controls six months after surgery.

Acknowledgements

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Characteristics	Patients no medical treatment N = 19 (%)	Patients chemotherapy N = 75 (%)	Patients tamoxifen N = 26 (%)	Controls N = 208 (%)	p-value
Age, years					
Mean	49.7	47.2	56.2	48.1	
Range	39 -59	29 – 59	44 - 59	28 - 59	< 0.001
Years in school					
<= 9 years	4 (21)	8 (11)	9 (35)	44 (21)	
> 9 years	14 (74)	63 (84)	16 (62)	161 (77)	

Other	1 (5.3)	4 (5.3)	1 (3.9)	3 (1.4)	0.08
Education level					
No education	1 (5.3)	6 (8.0)	2 (7.7)	26 (13)	
< 3 years	11 (58)	33 (44)	15 (58)	93 (45)	
3-4 years	4 (21)	24 (32)	6 (23)	72 (35)	
> 4 years	2 (11)	7 (9.3)	2 (7.7)	8 (3.9)	
Other	1 (5.3)	5 (6.7)	1 (3.9)	8 (3.9)	0.62
Menopausal status					
Pre/ perimenopausal	11 (58)	57 (76)	2 (7.7)	134 (64)	
Postmenopausal	8 (42)	18 (24)	24 (92)	74 (36)	<0.001
Danish adult reading test (baseline test)	30.7 (5.3)	30.3 (6.1)	31.0 (8.5)	29.9 (8.1)	0.87
Test interval T1 - T2 Days (SD)	183 (14.6)	167 (14.6)	183 (15.1)	190 (14.9)	<0.001

Table 1 Characteristics of the study population

Table 2. Change in neuropsychological tests between baseline and after six months

Test / group	Number of subjects	% Improved	CI: % improved	Sign. level improved	% Stable	% Declined	CI: % declined	Sign. level declined
Visual verbal learning delayed								
Chemotherapy	74	12.2	(5.7,21.8)	0.023	83.8	4.1	(0.8,11.4)	0.981
No treatment	18	11.1	(1.4,34.7)	0.453	77.8	11.1	(1.4,34.7)	0.453
Tamoxifen	26	3.8	(0.1,19.6)	1.000	80.8	15.4	(4.4,34.9)	0.078
Visual verbal learning total								
Chemotherapy	74	1.4	(0.0,7.3)	0.220	94.6	4.1	(0.8,11.4)	0.981
No treatment	18	.	.	.	77.8	22.2	(6.4,47.6)	0.022
Tamoxifen	26	3.8	(0.1,19.6)	1.000	80.8	15.4	(4.4,34.9)	0.078
Concept shifting test								
Chemotherapy	74	2.7	(0.3,9.4)	0.556	82.4	14.9	(7.7,25.0)	0.002
No treatment	18	.	.	.	94.4	5.6	(0.1,27.3)	1.000
Tamoxifen	26	11.5	(2.4,30.2)	0.277	69.2	19.2	(6.6,39.4)	0.017
Stroop colour word test								
Chemotherapy	73	2.7	(0.3,9.5)	0.573	90.4	6.8	(2.3,15.7)	0.603
No treatment	18	.	.	.	94.4	5.6	(0.1,27.3)	1.000
Tamoxifen	26	19.2	(6.6,39.4)	0.017	73.1	7.7	(0.9,25.1)	0.752
Letter digit coding								
Chemotherapy	74	4.1	(0.8,11.4)	0.981	86.9	9.5	(3.9,18.5)	0.153
No treatment	18	5.6	(0.1,27.3)	1.000	94.4	.	.	.
Tamoxifen	26	.	.	.	92.3	7.7	(0.9,25.1)	0.752

The 5% distribution-free prediction intervals used for the classification are adjusted for practice effects, baseline level, age, dart, educational level, retest interval and difference in depression and tension between 6 months and baseline.

Table 3. Number of patients with changes on more that two neuropsychological tests (A) and on more than two psychological distress scores (B) at six months.

Perceived	Patients	Patients	Patients	Control

A: Test battery*	Chemo-therapy N = 73	Sign. level	Tamoxifen N = 26	Sign. level	No medical treatment N = 18	Sign. level
Declined on ≥ 2 tests	4.1%	0.457	15.4%	0.005	11.1%	0.123
Improved on ≥ 2 tests	2.7%	0.986	7.7%	0.232	.,.	.
B: POMS**	N = 75		N = 26		N = 19	
Declined on ≥ 2 mood functions	6.7%	0.200	.,.	.	5.3%	0.938
Improved on ≥ 2 mood functions	16.0%	<0.0001	30.8%	<0.0001	31.6%	<0.0001

*Expected percentage declined/ improved on tests: 2.26 based on the control group.
**Expected percentage declined/ improved on POMS: 3.28 based on the control group.

Table 4. Change in subjective cognitive function between baseline (T1) and six months (T2)

cognitive function	No treatment N = 19 (%)		Chemotherapy N= 75 (%)		tamoxifen N= 26 (%)		group N = 208 (%)	
Memory	**T1**	**T2**	**T1**	**T2**	**T1**	**T2**	**T1**	**T2**
Impairment	11 (58)	3 (16)	28 (37)	22 (29)	12 (46)	8 (31)	22 (11)	24 (12)
No change	6 (32)	12 (63)	45 (60)	42 (56)	14 (54)	17 (65)	174 (84)	172 (83)
Improvement	2 (10)	4 (21)*	2 (2.7)	11(14)*	0 (0.0)	1 (4.0)	12 (5.8)	12 (5.8)
Concentration								
Impairment	11 (58)	3 (16)	33 (44)	10 (13)	17 (65)	9 (35)	24 (12)	24 (12)
No change	6 (32)	12 (63)	41 (55)	57 (76)	9 (35)	17 (65)	173 (83)	172 (83)
Improvement	2 (10)	4 (21)*	1 (1.3)	8 (11)¤	0 (0.0)	0 (0.0)*	11 (5.3)	12 (5.8)
Mental fatigue								
Impairment	12 (63)	4 (21)	40 (53)	25 (33)	19 (73)	8 (31)	19 (9.1)	28 (14)
No change	4 (21)	10 (53)	34 (45)	36 (48)	7 (27)	17 (65)	179(86)	166 (80)
Improvement	3 (16)	5 (26)*	1 (1.3)	14 (19)§	0 (0.0)	1 (4.0)#	10 (4.8)	14 (6.3)
Vigor								
Impairment	13 (68)	3 (16)	41 (55)	32 (43)	20 (77)	6 (23)	41 (20)	42 (20)
No change	4 (21)	10 (63)	27 (36)	23 (31)	3 (12)	15 (58)	144 (69)	135 (65)
Improvement	2 (11)	6 (31)§	7 (9.3)	20 (27)*	3 (12)	5 (19)¤	23 (11)	31 (15)

Fischer exact test: baseline versus 6 month for each study group and cognitive function *: $p < 0.05$; #: $p < 0.01$; §: $p<0.005$; ¤ $p < 0.001$

Table5. Change in psychological distress (POMS) between baseline and six months.

Test / Group	Number of Subjects	% Improved	CI: % Improved	Sign. Level % Improved	% Stable	% Declined	CI: % Declined	Sign. level Declined
Anger								
Chemotherapy	75	13.3	(6.6,23.2)	0.008	80.0	6.7	(2.2,14.9)	0.642
No treatment	19	15.8	(3.4,39.6)	0.133	84.2	.	.	.
Tamoxifen	26	23.1	(9.0,43.6)	0.003	76.9	.	.	.
Depression								
Chemotherapy	75	10.7	(4.7,19.9)	0.067	85.3	4.0	(0.8,11.2)	0.960
No treatment	19	21.1	(6.1,45.6)	0.027	73.7	5.3	(0.1,26.0)	1.000
Tamoxifen	26	15.4	(4.4,34.9)	0.078	84.6	.	.	.
Tension								
Chemotherapy	75	16.0	(8.6,26.3)	0.001	81.3	2.7	(0.3,9.3)	0.539
No treatment	19	21.1	(6.1,45.6)	0.027	73.7	5.3	(0.1,26.0)	1.000
Tamoxifen	26	34.6	(17.2,55.7)	<0.0001	65.4	.	.	.
Vigor								
Chemotherapy	75	2.7	(0.3,9.3)	0.539	86.7	10.7	(4.7,19.9)	0.067
No treatment	19	15.8	(3.4,39.6)	0.133	78.9	5.3	(0.1,26.0)	1.000

Tamoxifen	26	7.7	(0.9,25.1)	0.752	84.6	7.7	(0.9,25.1)	0.752	
Fatigue									
Chemotherapy	75	6.7	(2.2,14.9)	0.642	82.7	10.7	(4.7,19.9)	0.067	
No treatment	19	26.3	(9.1,51.2)	0.004	63.2	10.5	(1.3,33.1)	0.491	
Tamoxifen		11.5	(2.4,30.2)		84.6	3.8	(0.1,19.6)		

Median (IQR)**	**No medical treatment N = 19**			**Chemo-therapy N= 75**			**Tamoxifen N= 26**		
EORTC QLQ-C30	**T1**	**T2**	***P. value**	**T1**	**T2**	***P. value**	**T1**	**T2**	***P. valu**
Physical function	93.3 (20)	93.3 (6.7)	0.165	100 (13.7)	93.3 (13.4)	0.031	93.3 (6.7)	90.0 (20.0)	0
Role function	50.0 (33.3)	100.0 (16.7)	0.001	66.7 (50.0)	83.3 (33.3)	0.001	50.0 (50.0)	100.0 (16.7)	<0.
Cognitive function	83.3 (33.3)	83.3 (33.3)	0.919	100.0 (16.7)	83.3 (33.3)	0.001	83.3 (33.4)	83.3 (33.39	0
Social function	83.3 (16.7)	100 (16.7)	0.513	100.0 (16.7)	100.0 (16.7)	0.452	100.0 (16.7)	100 (16.7)	0
Emotional function	75.0 (25.0)	83.3 (25.0)	0.072	83.3 (25.0)	91.6 (25.0)	<0.001	79.2 (25.0)	87.5 (25.0)	0
Global health	75.0 (33.3)	83.3 (25.0)	0.018	75.0 (16.7)	75.0 (16.7)	0.858	66.7 (16.7)	79.2 (16.7)	0
Fatigue	33.3 (33.3)	22.2 (33.3)	0.021	22.2 (22.2)	33.3 (11.1)	0.010	33.3 (22.2)	33.3 (22.2)	0

The 5 % distribution-free prediction intervals used for the classification are adjusted for retest effect, baseline level, age, educational level, working status, smoking status, level of exercise and self-efficacy at baseline.

Nausea/Vomiting	0.0 (0.0)	0.0 (0.0)	0.317	0.0 (0.0)	0.0 (16.6)	0.002	0.0 (0.0)	0.0 (0.0)	0
Sleeplessness	33.3 (33.3)	33.3 (33.3)	0.639	0.0 (33.3)	33.3 (33.3)	0.042	33.3 (33.3)	16.7 (66.7)	0
Pain	33.3 (16.7)	16.6 (16.7)	0.006	16.7 (33.3)	0.0 (16.7)	<0.001	33.3 (33.3)	25.0 (33.0)	0
Dyspnoea	0.0 (0.0)	0.0 (0.0)	0.564	0.0 (0.0)	0.0 (33.3)	<0.001	0.0 (0.0)	0.0 (0.0)	0
Appetite loss	0.0 (33.3)	0.0 (0.0)	0.180	0.0 (0.0)	0.0 (0.0)	0.014	0.0 (33.3)	0.0 (0.0)	0
General Perceived self-efficacy		**N = 19**			**N = 75**			**N = 25**	
Mean; (SD)	30.4 (5.4)	28.8 (5.3)	0.126	31.9 (5.1)	31.5 (5.0)	0.451	30.8 (6.3)	30.1 (4.8)	0

Table 6.EORTC QLQ C-30 scores at baseline (T1) and six months (T2)

**(IQR): Interquartile Range. * P-values: change from baseline T1 to six month T2 for each score and groups.