We have extended our previous finding that all subgroups of premenopausal patients benefit significantly from such treatment.

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Effect of Peri-operative Chemotherapy on the Quality of Life of Patients with Early Breast Cancer

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Since chemotherapy is assumed to have a negative impact on quality of life, the impact of peri-operative chemotherapy on physical, psychological and social well-being and on the activity level of patients with early stage breast cancer was investigated. 24 women received peri-operative chemotherapy and 29 did not. They were interviewed 2 months and at a mean of 12 months post-surgery. Although the treated group reported more fatigue and considered hair loss a severe side-effect, no differences were found in overall physical and psychological well-being, perceived social interaction and activity level at 2 months. 1 year after surgery no differences were found between the two groups. Although no substantial effects of peri-operative chemotherapy on quality of life were demonstrated, patients almost unanimously considered peri-operative chemotherapy the most burdensome aspect of the treatment because of alopecia.
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INTRODUCTION

CONSENSUS ABOUT the best treatment regimen for early stage breast cancer has not been reached [1–5]. In 1986 the EORTC Breast Cancer Cooperative Group started a multi-centre randomised study (EORTC 10854) to test the hypothesis that a single peri-operative dose of adjuvant combination chemotherapy increases overall survival compared with an untreated control arm. However, side-effects of chemotherapy have a negative

effect on quality of life [6,7]. It was therefore expected that the patients receiving peri-operative chemotherapy would temporarily differ in their functioning and evaluation of some aspects of quality of life. On the other hand, the degree of social interaction for cancer patients seems to cohere with the perceived seriousness of the situation. This may hold true for alopecia as a side-effect of peri-operative chemotherapy, a toxicity that is clearly visible. For these reasons we have investigated the hypothesis that: (1) treatment with peri-operative chemotherapy would have a short term negative effect on both physical and psychological well-being and on the activity level of patients; (2) there would be a positive effect on social interaction in the sense that the treatment group would report less negative and more positive social experiences than the controls and (3) since peri-operative chemotherapy consists of a single dose, there would be no long-term i.e. 1 year differences in the quality of life between the two treatment arms.

PATIENTS AND METHODS

Patients and treatment

Between September 1986 and December 1988, 94 women with primary operable breast cancer ($T_{1,2}$ $N_{0,1}$ M_0) admitted to the Leiden University Hospital entered the EORTC trial 10854 and were randomised, after informed consent was obtained, to either a peri-operative chemotherapy or an untreated control arm. Those patients who were 6 months or more post-surgery ($N = 70$) were approached to participate in the present study. 56 (80%) agreed to participate; 10 (14%) refused and 4 (6%) could not be contacted by telephone during the period the interviews took place. All the women were interviewed by G.M.K. either at home (49) or in the hospital (7), depending on the personal preference of the patient. The questions were too difficult to answer for 3 women, so that data were collected for 53 subjects. Of this sample 24 had received peri-operative chemotherapy and 29 had not (Table 1). No significant differences were found between the groups in education, occupation, marital status or number of children. Surgical treatment in both groups consisted of either modified radical mastectomy if the tumour size was 3 cm or more in diameter, or a breast conserving procedure plus radiotherapy if the tumour measured less than 3 cm.

Peri-operative chemotherapy consisted of a single intravenous dose of 5-fluorouracil 600 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 600 mg/m^2. A pilot study in 1985 of toxicity had revealed that most patients had transient nausea after receiving chemotherapy which required anti-emetic medication and that 3 weeks post-surgery most patients had alopecia.

In both groups 21% of the premenopausal patients were found to be node-positive after axillary dissection. In line with the recommendations of the National Institutes of Health, these patients received another five (peri-operative chemotherapy group) and six (controls) courses of adjuvant combination chemotherapy.

Assessments

In this study the quality of life is defined as "the subjective evaluation of the good or satisfactory character of life as a whole" [8]. Quality of life is considered to be affected by different aspects [9,10]. In breast cancer, physical and psychological well-being, fears and concerns, perceived social interaction and activity level are the most relevant aspects [11].

Physical and psychological well-being (i.e. symptoms) were measured with the Rotterdam symptom checklist (RSCL) [12]. The impact on body image and fear of recurrence and death were measured by six questions whose reliability had been estimated in a study with breast cancer patients [13]. For perceived social interaction a scale was used that measures both positive and negative experiences [14]. The questions for these variables concerned two periods: retrospectively the first 2 months after surgery and the week before interview (mean = 12 months post-surgery). The answers to the questions were scaled from "not at all" (score 0) to "very much" (score 3). Activity level was measured by asking patients to indicate when they were able to perform certain routine daily activities after their operation. For this purpose we modified a questionnaire, developed by the EORTC Quality of Life Study Group [15]. The patients' subjective evaluation of these variables was also investigated, as well as their overall evaluation of quality of life for both periods [16]. Finally the patients were asked which aspect of the treatment as a whole and which period of their illness they considered the most burdensome.

Analysis

Differences between the two groups were tested by t tests (Tables 2 and 4) and where appropriate by χ^2 tests. Since surgical treatment in breast cancer is known to have an impact on quality of life, it was necessary to explore whether any variance in quality of life could be attributed to surgical treatment (mastectomy vs. breast conserving procedure), to treatment with peri-operative chemotherapy or to an interaction, by two-way analyses of variance.

Table 1. Patients' details

	Peri-operative chemotherapy Yes ($n = 24$)	No ($n = 29$)
Stage of disease		
I	13	15
II	11	14
Type of surgery		
Modified radical mastectomy	7	14
Breast conserving therapy	17	15
Radiotherapy		
Yes	22	20
No	2	9
Adjuvant chemotherapy		
Yes*	5	6
No	19	23
Menopausal status		
Pre-menopausal	14	14
Post-menopausal	10	15
Age (yr)	46 (11.8)†	50 (10.8)
Time since surgery (mo)	12.6 (3.7)	12.3 (3.1)

*If axillary lymph nodes were positive in premenopausal patients (≤ 50 years old), six cycles of combination chemotherapy were given.
†Mean (S.D.).

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Table 2. Impact of chemotherapy on quality of life at 2 months post-surgery

	Peri-operative chemotherapy	
	Yes	No
Physical distress		
Physical symptoms	10.6*	8.0
Evaluation of physical aspect	9.1	9.1
Psychological distress		
Psychological symptoms	7.7	7.5
Evaluation of psychological aspect	8.9	8.2
Fears and concerns		
Impact on body image	2.8	2.9
Fear of recurrence and death	3.8	3.7
Perceived social interaction		
Positive experiences	19.1	17.8
Negative experiences	3.5	3.8
Evaluation of social aspect	11.3	11.0
Activity level		
Daily functioning	3.9	4.0
Evaluation of activity level	7.9	8.7
Global quality of life		
Affective evaluation	4.3	4.4
Cognitive evaluation	4.6	4.6

*Mean.

RESULTS

In the first 2 months after surgery, patients who received peri-operative chemotherapy had in sum no more physical symptoms than the controls (Table 2). There was a significant difference between the two groups in fatigue (the peri-operative chemotherapy group reported more fatigue than the control group) and, as expected, complete hair loss for patients who received peri-operative chemotherapy (Table 3). The subjective evaluation of physical well-being in the patients who had peri-operative chemotherapy did not significantly differ from that in the controls.

No differences in psychological well-being, fears and concerns, performance of daily activities and overall evaluation of life were apparent. There was a non-significant tendency for more positive and less negative social experiences in the group who had received peri-operative chemotherapy.

At a mean of 12 months post-surgery, there were no significant differences between the two groups in any of the variables measured (Table 4).

When asked which aspect of the treatment they considered retrospectively as the most burdensome, 88% of the treatment group named the peri-operative chemotherapy. Further probing elicited hair loss and having temporarily to wear a wig as the most important reason. The answers of the control group were divided over the different aspects (Table 5). When asked which period of their illness they considered retrospectively as the most stressful, 79% of the women in both groups answered that this was the period before surgery. Further probing revealed that this was caused by feelings of anxiety before diagnosis as well as uncertainty about the date and nature of the required treatment.

In the first 2 months after surgery the type of surgery performed had an independent effect on psychological symptoms as well as on the subjective evaluation of psychological well-being (Table 6). Women who underwent mastectomy reported significantly more psychological symptoms and evaluated their psychological well-being as less positive than women who had breast conserving treatment (both $P \leq 0.01$). For body image and fear of recurrence and death, the surgical treatment explained significantly more of the variance than treatment with peri-operative chemotherapy or not. Women who had a mastectomy reported a more impaired body image compared with the breast conserving group ($P \leq 0.03$), but the latter reported more fear of recurrence and death ($P \leq 0.05$).

At 12 months post-surgery, body image was still and even more so affected by the type of surgery. Women who underwent a mastectomy reported a more negative body image than women who had a breast conserving treatment ($P \leq 0.01$) and the difference between both groups had even increased. The difference in fear of recurrence and death was, however, no longer apparent. In both groups fear of recurrence and death had decreased, but the level of fear dropped more in the breast conservation group.

No interaction was found between the type of surgery and peri-operative chemotherapy for any of the variables measured in either period.

DISCUSSION

Since the sample number within our sub-groups was small, the results of the analyses of variance should be interpreted cautiously. Also, we did not differentiate the answers by variables such as cancer stage and treatment regimen (surgical

Table 3. Impact of chemotherapy on physical and psychological symptoms at 2 months post-surgery

	Peri-operative chemotherapy	
	Yes	No
Physical symptoms		
Lack of appetite	0.75	0.24
Tiredness	1.79	1.21*
Sore muscles	0.75	1.24
Lack of energy	0.92	0.93
Lower back pain	0.29	0.48
Nausea/vomiting	0.29	0.34
Dizziness	0.17	0.45
Sore mouth/difficulty swallowing	0.17	0.03
Decreased sexual interest	0.71	0.83
Heartburn/acidity	0.29	0.17
Shivering	0.25	0.24
Tingling of hands or feet	0.13	0.34
Abdominal pain	0.17	0.17
Loss of hair	2.83	0.34†
Burning eyes	0.13	0.24
Shortness of breath	0.25	0.41
Dry mouth	0.71	0.31
Psychological symptoms		
Irritability	0.75	0.55
Worrying	1.25	1.24
Depressed mood	0.54	0.72
Nervousness	0.83	1.00
Desperate feelings about future	0.58	0.45
Difficulty sleeping	0.54	1.00
Headaches	0.58	0.31
Anxious feelings	0.67	0.55
Feeling tense	0.96	1.07
Difficulty concentrating	0.92	0.62

*Significant difference between the groups: *$P \leq 0.04$ and †$P \leq 0.0001$.

Table 4. Impact of chemotherapy on quality of life 1 year after surgery

	Peri-operative chemotherapy	
	Yes	No
Physical distress		
Physical symptoms	5.3	6.2
Evaluation of physical aspect	9.1	9.1
Psychological distress		
Psychological symptoms	4.8	5.5
Evaluation of psychological aspects	9.0	8.8
Fears and concerns		
Impact on body image	1.7	1.9
Fear of recurrence and death	2.4	2.8
Perceived social interaction		
Positive experiences	15.3	14.4
Negative experiences	2.7	2.1
Evaluation of social aspect	10.7	10.7
Global quality of life		
Affective evaluation	4.6	4.6
Cognitive evaluation	4.8	4.7

procedure, radiotherapy and adjuvant chemotherapy), which may substantially influence quality of life. Since both groups did not differ in any of these variables, we have assumed that if an effect had been present, it would have influenced both groups similarly. Finally, we compare the first 2 months after surgery retrospectively with the actual situation at a mean of 12 months, which may be a potential bias.

We found that a single peri-operative dose of adjuvant chemotherapy in early stage breast cancer did not have an important impact on quality of life. Although the treated group felt significantly more tired during the first 2 months after surgery and considered hair loss a severe side-effect, these negative experiences were not prominent enough to cause a substantial change in well-being nor in the overall evaluation of quality of life. It is not clear how short-term effects of fatigue and hair loss should be weighed against a possible gain in survival, but it seems reasonable to assume that such effects on quality of life is not a major argument to withhold peri-operative chemotherapy if this treatment proves to have a notable positive effect on survival.

Nevertheless, 88% of the women who received peri-operative chemotherapy considered alopecia the most burdensome aspect of the treatment. This seemingly contradictory finding might be explained as follows. Alopecia is frequently reported by patients as one of the major side-effects of adjuvant chemotherapy [17–19], but our data suggested no negative correlation between alopecia and quality of life or body image. In our culture the breast is highly associated with femininity and sexuality and cancer of the breast has therefore a different psychological meaning than, for instance, cancer of the lungs. Our study confirmed earlier findings that the type of surgery is an important variable in the adaption process of patients with early breast cancer. Since breast cancer in general and the type of surgery in particular affect the psychological dimension of quality of life, both variables may increase the relative importance of alopecia, which is also often associated with losing part of the feminine identity. In other words, the importance of alopecia is influenced by the psychological impact of a specific sort of cancer and/or a specific kind of treatment. Coates *et al.* reported [20] that different groups of patients indeed differ in their ranking of severity of side-effects of adjuvant chemotherapy, but the hypothesis clearly needs further elaboration and testing.

Another factor which might increase the relative importance of alopecia without a negative effect on quality of life is that to obtain informed consent, all women in the treatment group were told about the nature of the trial and that positive clinical results still had to be proven. It may be that, as long as the (disease-free) survival benefits of peri-operative chemotherapy remain uncertain, the costs of the treatment (i.e. negative side-effects) may become more important for a patient. If so, one would expect few patients to participate in a randomised clinical trial. But the many trials that have applied informed consent suggests that patients who are later assigned to the experimental treatment psychologically compensate the costs of the treatment. This compensation can consist of a perceived better chance of survival which could in turn positively influence quality of life. The high burden of the side-effects of the experimental treatment and the absence of a negative correlation between the side-effects and quality of life would thus be explained.

A final factor that may be at work is the defence mechanism of displacement [21]. Such mechanisms defend against anxiety by distorting reality, by changing the way we perceive objective dangers. In displacement a motive or an emotion is directed into a new channel. It may be that the inevitable feelings of helplessness and anger about the still unexplained cause and onset of breast cancer may be directed towards an additional short-term side-effect such as alopecia with a clear external cause, and thus increase its importance.

Before this study, we assumed that alopecia as a side-effect of chemotherapy would negatively influence quality of life. But we found that the relations between the variables were not as simple. The question still remains how breast cancer and/or its surgical treatment affect the perception of alopecia as a side-effect of adjuvant chemotherapy.

Table 5. Most burdensome aspect of treatment as a whole

	Peri-operative chemotherapy	
	Yes	No
Diagnostic examinations	1 (4%)	10 (34%)
Operation	1 (4%)	8 (28%)
Chemotherapy	21 (88%)	3 (10%)
Radiotherapy	0	4 (14%)
Some other aspect	0	3 (10%)
Unable to decide	1 (4%)	1 (3%)

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Argyrophilic Nuclear Organiser Region Counts in Locally Advanced Breast Carcinoma Treated by Chemotherapy before Surgery

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The value of argyrophilic nuclear organiser region (AgNOR) counts in assessing histologically the effects of combination chemotherapy given to eleven patients with locally advanced breast cancer before mastectomy was studied. AgNOR counts were significantly reduced ($P < 0.001$) in the post-chemotherapy, surgically excised residual tumour specimens compared with the initial diagnostic biopsy specimens. AgNOR counts could be used to monitor the effects of chemotherapy on breast cancer.
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NUCLEOLAR organiser regions (NORs) have attracted much attention in tumour pathology [1–4]. NORs are chromosomal segments containing encoded ribosomal RNA genes, and are likely to play a major role in nucleolar activity, thus contributing to cell proliferation [5]. The number of NORs detected in neoplastic cells may hence reflect tumour cell kinetics, with possible prognostic implications. Being intimately associated with argyrophilic proteins, NORs can be visualised as AgNORs in routine paraffin sections by a modified silver technique [6]. There are significant correlations between AgNOR counts, Ki67 immunostaining and DNA flow cytometry in human breast cancer specimens [7–9]. Our aim was to investigate the usefulness of AgNOR counts in assessing histologically the effects of combination chemotherapy in patients with locally advanced breast cancer before mastectomy.

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PATIENTS AND METHODS

Eleven cases of infiltrating carcinoma of the breast were selected from the files of the Institut Jean Godinot on the following basis: (1) locally advanced breast cancer staged T_3–T_4 (M_0 and irrespective of N status), N_2–N_3 (M_0 and irrespective of T status) or with inflammatory carcinoma (M_0 and irrespective of T and N status); (2) each patient had had one initial diagnostic biopsy of her breast tumour (Tru-cut, drill or incisional biopsy); (3) following histological confirmation of the invasive neoplastic nature of the mammary lesion, each patient had received four cycles of combination chemotherapy (doxorudicin 30 mg/m^2 a total of 50 mg or less on day 1, vincristine 1 mg/m^2 to a total