

Psychological Stress and Coping Resources during Primary Systemic Therapy for Breast Cancer. Results of a Prospective Study

Psychische Belastungen und Patientinnenressourcen während einer primär systemischen Therapie bei Brustkrebs. Ergebnisse einer prospektiven Studie

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ABSTRACT

Introduction This prospective study reports on the impact of psychological factors on women with primary breast cancer undergoing neoadjuvant chemotherapy. These women are in a special situation, where they not only have to deal with the shock of the cancer diagnosis but also with the fact that the malignant tumor will not be removed immediately but only after completing chemotherapy. A situation like this is stressful and requires a personal strength which not every woman may have.

Methods In a prospective study 53 patients were assessed using various psychological and psycho-oncological questionnaires which aimed to evaluate their psychological stress and their coping resources. The women were evaluated before starting systemic treatment (t-1) and

again immediately after completing chemotherapy but prior to surgery (t-2). The patients were also asked about their coping strategies at t-1 and t-2. Using the Ulm Coping Manual (UCM) the interviews were rated by independent assessors blinded to the respective patient's medical data. Patients were followed up for 3.7–5.5 years after completing chemotherapy.

Results Patients with poor psychosocial adjustment to the situation were identified prior to starting treatment (at t-1). The social coping strategies of these women were found to be inadequate. Their coping behavior was characterized by resignation and they did not attempt to seek social support. This was found to increase their overall risk of recurrence or of developing another type of malignancy during the follow-up period. The study also identified patients who coped significantly better with primary systemic treatment by strengthening their coping strategies.

Conclusion Careful psychological screening of women's vulnerabilities or strengths immediately after the diagnosis and prior to any oncological treatment is strongly recommended. This would help to identify those patients early on who will require additional psycho-oncological support due to their psychological vulnerability.

ZUSAMMENFASSUNG

Einleitung Diese prospektive Studie berichtet über die Auswirkungen psychologischer Faktoren bei Patientinnen mit primärer Mammakarzinomkrankung, die sich einer neoadjuvanten Chemotherapie unterzogen haben. Die spezielle Situation dieser Frauen ist nicht nur gekennzeichnet durch den Schock der Krebsdiagnose, sondern auch durch die Tatsache, dass der bösartige Tumor nicht sofort, sondern erst nach Abschluss der Chemotherapie entfernt wird. Eine solche Situation belastet und benötigt persönliche Stärken, über die nicht jede Frau verfügt.

Methoden In einer prospektiven Studie wurden 53 Patientinnen vor dem Staging und der systemischen Therapie mithilfe verschiedener psychologischer und psychoonkologischer Fragebögen und Interviews auf ihre psychische Belastung und ihre Bewältigungsressourcen hin untersucht (t 1). Unmittelbar nach Abschluss der Chemotherapie und noch vor dem operativem Eingriff erfolgte eine weitere Testung mit denselben Messinstrumenten (t 2). Zusätzlich wurden die Patientinnen zu t 1 und t 2 bezüglich ihrer Bewältigungsstrategien interviewt. Die Interviews wurden mit dem Ulmer Coping-Manual (UCM) von bezüglich der medizinischen Informationen blinden Ratern objektiv geratet.

Ergebnisse Patientinnen mit einer schlechten psychosozialen Anpassung an die Situation konnten zum Zeitpunkt t 1 identifiziert werden. Sie wiesen Defizite im sozialen Bewältigungsverhalten auf. Weiterhin wiesen sie höhere Werte in resignativem Bewältigungsverhalten und niedrigere Werte in der Suche nach sozialer Unterstützung auf, was

insgesamt das Risiko für das Auftreten eines Rezidivs bzw. einer anderen Krebserkrankung im Betrachtungszeitraum von 3,7 bis 5,5 Jahren nach der chemotherapeutischen Behandlung erhöhte. Im Gegensatz dazu konnten wir über unsere Studie Patientinnen identifizieren, die über eine Stärkung ihrer Copingfaktoren die primär systemische Therapie signifikant besser bewältigten.

Schlussfolgerung Ein sorgfältiges psychologisches Screening unmittelbar nach der Diagnose und noch vor der onkologischen Behandlung ist dringend empfohlen. Über diese Maßnahmen könnten jene Patientinnen identifiziert werden, die aufgrund ihrer psychisch hohen Vulnerabilität eine zusätzliche psychoonkologische Unterstützung erhalten sollten.

Introduction

The treatment of breast cancer has changed significantly in the last few decades. After the introduction of the first cytostatic agents and anti-hormonal drugs between 1960 and 1970, cytostatic treatments were refined even further in the 1990s. This was followed, at the beginning of this millennium, by the era of targeted therapies. The significant progress achieved in the systemic treatment of breast cancer combined with other procedures such as surgery and radiotherapy has meant that currently more than 80% of patients with breast cancer can be cured.

In the last few decades, there has also been an important change in thinking with regard to the sequence of the individual therapies. For many years, the standard order of treatment consisted of surgery followed by systemic therapy. While primary systemic/preoperative treatment was considered the standard approach and an essential part of the therapy concept for locally advanced disease and for inflammatory breast cancer, in recent years, following the results of several studies, the neoadjuvant therapy sequence has become more important when treating operable non-metastatic breast cancer. The improvement in prognosis with regard to disease-free survival and overall survival is similar for both adjuvant and neoadjuvant therapy [1].

There are a number of arguments which support a preoperative systemic therapy sequence:

- breast-conserving therapy rates are increased and surgical morbidity is reduced
- achieves operability of primary inoperable tumors
- improves prognosis, with pathological complete remission (pCR) found to be associated with longer disease-free survival and overall survival, particularly in women with TNBC, HER2-positive breast cancer, G3 tumors, etc.
- patient's response to chemotherapy can be evaluated early through in-vivo chemosensitivity testing, leading subsequently to better patient compliance
- therapy can be individualized depending on the patient's response [1, 2]

As with adjuvant therapy, the indication for primary systemic therapy is based on the estimated prognosis and predictions regarding the effect of therapy using traditional parameters such as nodal status, grading, degree of proliferation, hormone receptor status, HER2 overexpression and patient age.

Using these and other parameters, the individual risk of recurrence of disease is estimated for every patient. Chemotherapy is therefore indicated in patients with a high risk of recurrence.

Various psycho-oncological studies have already shown that around one third of breast cancer patients experience serious psychological stress and urgently require professional psychological support. Between 41 and 64% of all patients were found to have significantly increased rates of depression, anxiety and stress, and between 8 and 40% were traumatized by the diagnosis or the oncological treatment [3]. A systematic analysis of 89 original articles and reviews in English or German, published between 1995 and 2010, showed that cancer patients had an adjusted point prevalence of 11.1% for affective disorders and an adjusted point prevalence of 10.2% for anxiety disorders [4].

Accordingly, the quality of life of patients is generally lower than that of the healthy population. The health-related quality of life is essentially the result of existing medical factors (stage of disease, treatment options, therapy-related side-effects, prognosis), but it is also affected by sociocultural and psychological factors [5].

The results of most research studies into psychological factors affecting breast cancer patients have shown that active coping behavior on the part of the patient has a more beneficial effect compared to passive-anxious coping behavior, and that the latter type of coping behavior is correlated with a poorer adaptation to disease and its requirements [6–16]. The quality of life of oncology patients is certainly affected by their psychological state of mind [17]. Breast cancer patients, for example, are afraid of side-effects of chemotherapy such as nausea, loss of hair, and anemia. During chemotherapy, the health-related quality of life of breast cancer patients often decreases; this is associated with the risk that patients will prematurely discontinue therapy [18]. Friedman et al. were able to show that a positive approach to life also had a beneficial effect on the quality of life of breast cancer patients [19]. One possible reason for this could be that a positive approach to life is more likely to enable the patient to seek out and accept social support and it could also be the trigger for the patient to try to find ways of coping [20, 21].

However, some scientists doubt whether there is a significant link between the quality of the coping, the psychological situation, and quality of life and particularly whether there is any correlation with survival [22–27], as the majority of studies did not find an association. Based on a meta-analysis of 26 studies, Petticrew et al. came to the conclusion that the quality of coping in cancer patients was not consistently correlated with overall survival, despite the fact that the meta-analysis also included complex studies, which used interviews instead of questionnaires to capture the actual coping behaviors used by patients. The overwhelming majority of these more complex studies came to the conclusion that the quality of the coping was significantly positively correlated with survival [27, 28]. Questionnaires are basically flawed,

particularly if they are recording subjective opinions about one's own behavior, as the correlation between stated opinion and actual behavior is only around .15 [3, 29].

The psychological situation of women with a diagnosis of primary breast cancer is made more difficult by the fact that – for patients undergoing neoadjuvant chemotherapy – surgery is delayed by several months. For many women this means they are additionally burdened by the knowledge that the tumor is still in their body. We have not found any studies which have examined the psychological situation and attempts at coping of breast cancer patients receiving neoadjuvant chemotherapy.

Based on the findings of most psycho-oncological studies on primary breast cancer, we suggest that patients receiving neoadjuvant chemotherapy who have an active coping behavior (this includes a “fighting spirit” attitude, an active search for social support, the inner acceptance of the existing situation and active compliance) demonstrate a significantly better adaptation to disease and its treatment, both at the start of treatment and after completing chemotherapy, compared to those patients with passive-resigned coping behavior (this includes a resigned or fatalistic attitude, stoic-passive acceptance, little or no attempt to search for social support).

Method

This was a prospective study. Standardized interviews were carried out with breast cancer patients immediately after receiving the diagnosis, before staging was done and before the start of chemotherapy. Established psycho-oncological questionnaires – POMS (Profile of Mood States), BSI (Brief Symptom Inventory), HADS (Hospital Anxiety and Depression Scale), BFI (Brief Fatigue Inventory) and F-SOZU (Fragebogen zur sozialen Unterstützung; Engl.: Questionnaire on Social Support) – were used to record patients' psychological state of mind and stress levels. Semi-structured interviews (before and immediately after chemotherapy but before patients underwent surgery) which included the same psycho-oncological tests were done on inclusion into the study and repeated again before surgical extirpation of the tumor, i.e. after the patient had completed chemotherapy. Patients had a medical follow-up examination between 3.7 and 5.5 years after the first oncological treatment. This was to investigate the question whether the extent of psychological stress recorded at t-1 permitted a prediction to be made regarding the patient's psychological adjustment recorded at t-2 and whether the patient's own coping resources permitted predictions to be made regarding progression-free survival, disease-free survival and overall survival. Not much research has been done into coping strategies and psychological stress, and many of the findings must be classified as inconsistent.

Patients and treatment

Fifty-three breast cancer patients out of a total of 356 female patients with primary breast cancer treated between June 2008 and May 2010 at the Breast Center of St. Martinus Hospital in Olpe were included in the study. Key criteria for inclusion in the study were breast cancer confirmed by punch biopsy, the recommenda-

tion to undergo neoadjuvant chemotherapy based on existing indications, the patient's written consent to participate in the study, age over 18 years, and a sufficient knowledge of German (required for the tests and the interviews). Exclusion criteria were linguistic and communication problems, evidence of primary metastasis already present at the time of the primary diagnosis, and existing co-morbidities which meant that cytostatic therapy was contraindicated. Only one of the patients considered suitable for inclusion in the study did not consent to participate in the study.

Study participants therefore represent an incidental sample of patients who may not be representative. All patients treated in this period were approached and asked about participating in the study, meaning that the investigators did not select patients for inclusion in the study (exception: language skills).

Those patients for whom the interdisciplinary tumor board recommended primary systemic chemotherapy based on their oncologic parameters were admitted to hospital for staging. On the day of their admission, Dr. Jürgen Schwickerath, the department's medical director, gave a presentation on the study to all German-speaking patients. After patients had been informed about the study they were given consent forms for inclusion in the study. Patients who were included in the study were interviewed by two ward physicians previously trained in the use of the interview technique required to implement the Ulm Coping Manual (UCM). Interviews were carried out using a semi-structured format. The Breast Center of the St. Martinus Hospital in Olpe participates in many scientific clinical trials and its staff have a lot of experience in carrying out scientific studies.

The semi-structured interview covered all topics relevant at the time of carrying out oncological treatment, including the experience of receiving the diagnosis, the decision to undergo systemic treatment, the relevant feelings, expectations, hopes, and fears, the patient's personal and professional situation, and other current personally relevant topics. The psychological questionnaires were handed to patients for completion on the same day or on the following day. The tumor stage – TNM stage – of disease was not known at the time of the interview by either the patient or the two physicians carrying out the interview.

After being apprised of the histological findings, patients were informed by the head of the department about the diagnosis “breast cancer”, about potential treatment options and the oncological course of treatment. No statements were made about the potential prognosis.

The risk for each patient was determined during a meeting of the interdisciplinary tumor board which also took the St. Gallen risk parameters into account. Patients with an indication for neoadjuvant chemotherapy were informed about the recommended therapy and the possibility of participating in the study after the interdisciplinary tumor board had met.

Patient received a standard chemotherapy regimen consisting of 4 × EC q3W, followed by 4 × docetaxel q3W on an outpatient basis. The efficacy of the primary systemic chemotherapy, i.e. the rate of response, was re-evaluated by the head of the department Dr. Jürgen Schwickerath based on sonographic examinations performed after 2–3 cycles of chemotherapy.

After patients had completed chemotherapy, they were admitted to hospital for surgery. Patients were once again given the

standardized psychological questionnaires to complete, and were again investigated in another semi-structured interview (t-2). This time the focus was also on the patient's experiences during the period she received chemotherapy. This included her experience of chemotherapy (including side-effects), the impact on her everyday life and on her private life and situation (relationship, family, work), her social contacts during the treatment period, her hopes and fears, her thoughts about the further progress of disease and convalescence, etc. A total of ten questions structuring the interview were specified by the head of the department Dr. Jürgen Schwickerath in consultation with the head of the study and of the Department of Medical Psychology at Cologne University Hospital, Prof. Dr. Volker Tschuschke, and were the same for all of the patients in the study.

Psychological stress and coping

Patients' coping behavior was evaluated using the Ulm Coping Manual (UCM) [30], a rating tool designed to objectively rate the coping resources or coping strategies of adults with somatic disease. Rating is based on content analysis. Every single grammatical sentence of the patient during the semi-structured interview is objectively evaluated by independent, trained and blinded raters using the 36 categories of the Manual (six scales). The UCM was developed and applied as part of a DFG study into leukemia patients who were undergoing allogeneic bone marrow transplantation. The coping strategies of the leukemia patients determined with the help of the manual predicted disease survival on a 6- to 10-year basis [31, 32].

The semi-structured interviews were carried out immediately prior to primary staging by physicians trained in the interview techniques and again after completing chemotherapy and prior to undergoing surgery. The structured interviews focused on up to ten topics which were relevant at the time of the interview (t-1: prior to staging and chemotherapy, t-2: after concluding chemotherapy and immediately prior to surgery). Topics were referred to flexibly and extensively, according to the needs of every individual patient, with each patient allowed to comment extensively and exhaustively on every topic. All of the interviews were digitally recorded and subsequently coded in accordance with the Ulm Coping Manual (UCM) by three independent raters blinded to the patient's medical data [30]. The length of the interview varied considerably between individual patients, as the semi-structured interview only sets the topics to be addressed during the interview but does not determine how long and to what extent patients may comment on individual topics. The time used for the interview therefore ranged from a minimum of 18–20 minutes to around one hour. The time taken for the interview (allowing for the interviewer's share of the conversation) was taken into account when calculating the score, so the ensuing scores are independent of time. Scores were calculated according to the following formula:

$Score_{scale} = \text{raw value} \times 100/N \times \text{time (duration) of the interview,}$

where "raw value" represented the sum of ratings for every scale, "N" stood for the number of subcategories of a scale and "time" was the duration of the interview in minutes and seconds. The resulting scores are interval scaled and normally distributed.

With a mean kappa of 0.86, the inter-rater reliability showed a high degree of agreement between the three raters. The evaluation method and the calculation of the scores are described in detail elsewhere [30]. Ratings with the UCM allowed a prediction to be made regarding the probability of survival over 6- to 10-years in 52 and 72 leukemia patients, respectively, undergoing allogeneic bone marrow transplantation [31, 32].

The interviews in our study were also examined with regard to the presence of subjective theories about the possible cause of disease. Patients were *not* explicitly questioned about possible subjective assumptions about the cause of their disease (lay theories), but theories spontaneously mentioned in the interview were evaluated as the patient's personal views about the cause of her cancer. This is a conservative approach to recording lay theories. We are of the opinion that unprompted comments by a patient (versus the non-existence of a lay theory) on possible causes of disease reflect the patient's need to explain her own situation to herself (to find an explanation for the inexplicable), and explanations demonstrably result in the patient becoming calmer and less despairing. This assumption is based on the findings of a study of leukemia patients undergoing allogeneic bone marrow transplantation: patients with a subjective assumption about the possible cause of their leukemia suffered significantly less from depressive symptoms [33, 34].

The psycho-oncological tests were carried out at t-1 (after receiving the diagnosis, prior to undergoing staging, i.e. without knowing the stage of disease and prior to primary systemic chemotherapy) and at t-2 (after completing chemotherapy and immediately prior to surgical extirpation). All of the tests administered to patients were validated and reliable instruments used in psycho-oncological research [35].

The following tests were employed at both time points:

- Profile of Mood States (POMS) are established scales commonly used in psycho-oncology research; they are well validated and known to be reliable [36, 37]. The German version consists of the four scales Depression, Fatigue, Anger and Vigor.
- The Brief Symptom Inventory (BSI) is a short version of the Symptom Check List (SCL-90-R) [38]. It consists of nine scales (ranging from Somatization, Anxiety, and Depression to Psychopathologies such as Paranoia or Psychosis) and is widely used as one of the best validated psychological tests. We used the Global Severity Index (GSI) in our study to depict the overall symptomatic burden.
- The Hospital Anxiety and Depression Scale (HADS) [39, 40] is widely used as a screening tool in psycho-oncological research and its quality criteria are rated as good.
- The Brief Fatigue Inventory (BFI) [41, 42] is a short test used to assess the severity of the cancer-specific fatigue. The inventory's criteria for psychometric quality are rated as excellent.
- The Questionnaire on Social Support (F-SOZU) [43, 44] is an instrument used in Germany in psycho-oncology research which aims to capture the extent of perceived social support. Its criteria for psychometric quality are considered medium to good.

Statistical analysis

Psychological assessments of the 53 patients were evaluated based on the "multiple outcomes criterion" [45, 46]. This ap-

proach takes account of the combination of results from different psychological instruments; it is therefore based on the results for all psychological tests taken in combination and not just on the partial results for individual tests. To do this, the scores of every individual psychological test (POMS scales “Depression”, “Fatigue”, “Anger” and “Vigor”; BSI-GSI; HADS [Anxiety and Depression], BFI und F-SOZU) were converted into T-scores for each measurement time point. The t-scores for all nine scales were added together for each measurement time point (t-1 und t-2), i.e. before and after chemotherapy. The final result for the t-scores after chemotherapy was subtracted from the final result of the scores calculated prior to chemotherapy, resulting in an “outcome t-score”. The sum of the t-scores prior to chemotherapy served to measure the severity of the patient’s psychological problems prior to treatment and the patient’s adaptation to the situation at time point t-1. This approach allowed a summary assessment to be made of the patient’s overall state and is an established procedure in research [45, 46]. It was also used in the large study conducted by the Techniker health insurance company into the impact of outpatient psychotherapy [47]. The multitude of individual test results is reduced to a date which prevents potential misinterpretations arising from alpha error inflation.

A fixed effects model (mixed model analysis of variance) was calculated using the difference in the t-scores at time points t-1 and t-2 as a dependent variable and using the coping strategies (scales of the UCM) at time point t-1 along with other predictor variables such as age, St. Gallen risk status and interactions between some of these individual variables as independent variables. This method was used to examine which of the somatic and psychological variables can predict the change in the psychological situation from time point t-1 (immediately after the diagnosis and prior to neoadjuvant chemotherapy) to time point t-2 (immediately after completing neoadjuvant chemotherapy and prior to surgery).

Using the SPSS program (version 23), Kaplan-Meier survival analyses were calculated (using log-rank test) to estimate whether coping strategies prior to chemotherapy predicted recurrence-free or overall long-term survival. The classification into high or low values was done using the median of the distribution of the total sample for every coping scale: scores below the median were classified as belonging to the group of “low values”; scores above the median were classified as part of the group “high values”.

In this calculation, the dependent variable was survival time after diagnosis and chemotherapy or for censored/incomplete data, the time to the last visit (follow-up) to the treating physician recorded in the patient’s medical file.

Results

► **Table 1** shows the basic demographic and medical data. The patients lived in a predominantly rural area and the average patient only had a basic school education. Only a small percentage of patients had an advanced technical college entrance qualification or a university degree. This corresponds to the general information regarding education and school-leaving certificates obtained dur-

ing the questioning of patients with a primary diagnosis of breast cancer. Around 70% of recorded patients had no high-school diploma or advanced technical college entrance qualification [48, 49].

The average age of the patients in our study was 50 years (range: 34 to 74 years). The mean age at disease onset in Germany is 63 years [49]. The women in our sample were therefore comparatively young. Forty percent of patients had a high risk according to the St. Gallen criteria and sixty percent had an intermediate risk.

Lymph node involvement was present in more than half of the patients; all tumors were moderately or poorly differentiated (grading). Thirteen out of 53 of the patients included in the study had a positive HER2-neu status.

Seven patients (13.2%) either died, suffered recurrence (n = 3) or went on to develop another type of cancer (n = 1) during the follow-up period of between 3.7 and 5.5 years; 42 patients (79.2%) were disease-free and presented with complete remission.

Patient’s psychological state before and after neoadjuvant chemotherapy

► **Table 2** shows that all patients at t-1 had slightly higher psychological symptoms (BSI) compared to the norm. This was no longer the case after chemotherapy had been completed (t-2). None of the patients had either requested or received psychological support, nor had they received any additional psychosocial support from the hospital staff. Only the POMS depression scale showed a highly significant drop from t-1 to t-2. The scores for social support (F-SOZU) did not differ: the fatigue scores (BFI) had a slight tendency to increase during chemotherapy. Anxiety (HADS) showed a highly significant reduction over the treatment period while Depression (HADS) did not.

In important areas (Anxiety, Depression, overall psychological pressure) the figures showed, on average, a reduction in psychological stress over the course of chemotherapy treatment – without patients having received additional psychological support. On average, the sample adapted well in important areas to the demands created by the situation.

► **Table 3** depicts the coping resources of patients at time points t-1 and t-2. On average, “resigned coping” was relatively low but nevertheless showed a highly significant decrease for all patients over the course of chemotherapy (from t-1 to t-2). “Distraction coping” increased slightly during chemotherapy, while there was an extreme reduction in “cognitive-restructuring coping”. The latter points to a tendency towards a defensive attitude (the aspect of defensiveness is not examined further here).

On average for the total sample, there was a highly significant increase in scores from t-1 to t-2 for “social support” as a means of coping. The most impressive figures were calculated for “fighting spirit coping”, which was already higher than the other scales at time point t-1 and continued to increase during chemotherapy (t-2), even if the increase was not statistically significant.

► **Table 4** shows that “active coping strategies” (the use of “cognitive restructuring”, from looking for “social support”, “complying” with treatment and showing a “fighting spirit”) correlated with better psychological adaptation. Patients with higher

► **Table 1** Demographic and medical indicators of the overall sample (n = 53).

	n	%	Mean	SD	Range
Age	53		50.2	9.5	34–74
Nationality					
▪ German	48	90.6			
▪ non-German	5	9.4			
Education					
▪ primary school/ housewife	18	34.0			
▪ blue-collar worker	1	1.9			
▪ employee	17	32.1			
▪ high school diploma/ university degree	9	17.0			
▪ freelancer	2	3.8			
▪ pensioner	5	9.4			
▪ no data available	1	1.9			
St. Gallen risk category					
▪ high	21	39.6			
▪ medium	32	60.4			
Tumor thickness at t-1 (in mm)	53		25.9	8.6	14–50
▪ T1	12	22.6			
▪ T2	35	66.0			
▪ T3	1	1.9			
▪ T4	5	9.4			
Tumor thickness at t-2 (in mm)	50	94.3	8.7	15.1	0–70
Nodal status					
▪ no involvement	24	45.3			
▪ 1–3 lymph nodes	19	35.8			
▪ 4–9 lymph nodes	9	17.0			
▪ > 10 lymph nodes	1	1.9			
Grading					
▪ Grade 2	27	50.9			
▪ Grade 3	26	49.1			
HER-2					
▪ positive	13	24.5			
▪ negative	40	75.5			
Medical status after 3–5 years					
▪ CR (complete remission)	42	79.2			
▪ Died or recurrence of disease	11	20.8			

“cognitive restructuring” scores at time point t-1 experienced significantly lower psychological stress. This also tended to be the case during chemotherapy (t-2). Patients who were resigned showed significantly poorer psychological adaptation at t-2; in contrast, patients with a higher score for “fighting spirit” adapted significantly better to treatment.

► **Table 2** Psychological stress pre (t-1) and post neoadjuvant chemotherapy (t-2).

T-tests	n	MW	SD	T-score	p
Brief Symptom Inventory BSI-GSI				2.17	0.035*
▪ pre	48	0.65	0.63		
▪ post	48	0.49	0.41		
Depression POMS				6.18	0.000***
▪ pre	48	2.47	0.93		
▪ post	48	1.66	0.62		
Fatigue POMS				-0.75	0.459
▪ pre	47	2.50	1.10		
▪ post	47	2.64	0.88		
Vigor POMS				-0.91	0.371
▪ pre	45	2.43	0.75		
▪ post	45	2.56	0.86		
Despondency POMS				1.65	0.106
▪ pre	48	1.83	0.86		
▪ post	48	1.63	0.82		
Social support F-SOZU				0.24	0.813
▪ pre	48	61.92	9.26		
▪ post	48	61.58	9.78		
Brief Fatigue Inventory BFI				-1.74	0.089
▪ pre	48	3.43	2.12		
▪ post	48	4.04	1.82		
Anxiety HADS				6.71	0.000***
▪ pre	49	9.16	4.37		
▪ post	49	5.33	3.72		
Depression HADS				1.60	0.116
▪ pre	49	5.80	4.86		
▪ post	49	4.76	3.89		

* p < 0.05, ** p < 0.01, *** p < 0.001

POMS = Profile of Mood States

F-SOZU = Questionnaire on Social Support

HADS = Hospital Anxiety and Depression Scale

Predictions for tumor reduction, survival and psychological situation

Fifty-one of 53 patients attended follow-up examinations between 3.7 and 5.5 years after chemotherapy. The average follow-up examination was carried out 4.6 years after chemotherapy (minimum: 3.7 years; maximum: 5.5 years). The St. Gallen risk was found to offer the best predictive score for tumor reduction, but only as a trend (p < 0.08). No psychological test or coping strategy proved to have any predictive value for tumor reduction. Seven patients died in the interval between chemotherapy and follow-up; three developed recurrence and one developed another form of cancer. There was no statistical correlation between a higher St. Gallen risk and recurrence, new onset of disease or

► **Table 3** Scores for coping strategies prior to (t-1) and after (t-2) chemotherapy (t-tests).

T-tests	n	MW	SD	T-score	p
Resignation/despair				3.88	0.000***
▪ pre	49	2.10	1.73		
▪ post	49	1.21	1.11		
Distraction coping				- 1.73	0.089
▪ pre	49	2.96	1.76		
▪ post	49	3.61	1.97		
Cognitive restructuring				4.62	0.000***
▪ pre	49	4.06	1.83		
▪ post	49	2.60	2.47		
Social support				- 3.23	0.002**
▪ pre	49	3.95	2.47		
▪ post	49	5.57	2.88		
Compliance				- 1.45	0.154
▪ pre	49	3.37	2.33		
▪ post	49	4.03	2.88		
Fighting spirit				- 1.45	0.154
▪ pre	49	4.83	3.45		
▪ post	49	5.50	3.65		

* p < 0.05, ** p < 0.01, *** p < 0.001

► **Table 4** Scores for the individual coping strategies and psychological adjustment (t-scores) prior to (t-1) and after (t-2) chemotherapy (t-tests).

T-tests	n	Stress (MW) ^a	SD	T-score	p
Cognitive restructuring at t-1				2.203	0.033*
▪ low	22	269.20	75.65		
▪ high	22	228.47	42.38		
Resigned coping at t-2				- 2.194	0.034*
▪ low	22	228.55	49.23		
▪ high	22	269.12	71.42		
Cognitive restructuring at t-2				1.954	0.057
▪ low	21	267.95	69.20		
▪ high	23	231.38	54.64		
Fighting spirit at t-2				2.362	0.023*
▪ low	22	270.50	70.23		
▪ high	22	227.17	49.72		

^a psychological stress (T-score standardization)

* p < 0.05

death ($\chi^2 = 0.403$, $p < 0.525$). In the high-risk group 68.4% remained disease-free to the end of follow-up, as did 76.3% of the relatively low-risk group. With a hazard ratio of 1 there was no difference between both groups with regard to the prognostic power of the variable "St. Gallen risk".

In an extreme group comparison – between the group of patients with higher levels of resigned coping and the group of patients with lower levels of resigned coping – patients with lower "resigned coping" or for whom "resigned coping" decreased during chemotherapy or with higher levels of resigned coping which decreased towards time point t-2, were found to have significantly higher overall or disease-free survival rates compared to patients with higher levels of resignation which remained constant over time at the second time point or in whom resignation increased or who showed an overall increase in "resigned coping" (log rank-test [Mantel-Cox]: $\chi^2 = 4.882$, $p < 0.03$) (► **Fig. 1**).

► **Fig. 2** shows the correlation between "resigned coping" and "fighting spirit coping". In an extreme group comparison – patients with higher levels of "resigned coping" and lower levels of "fighting spirit coping" and patients with lower levels of "resigned coping" and higher levels of "fighting spirit coping" – the first group had significantly lower overall or disease-free survival rates compared to patients with lower levels of "resigned coping" and higher levels of "fighting spirit coping" (log rank-test [Mantel-Cox]: $\chi^2 = 4.253$, $p < 0.050$).

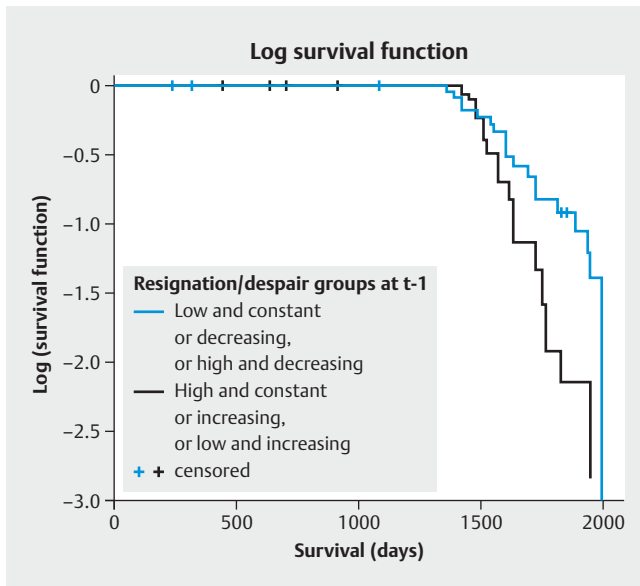
A mixed model analysis (mixed design analysis of variance) with fixed effects was done with the St. Gallen risk as the medical

variable, "resigned coping" and "socially supported coping" as the coping variables, age as the critical variable for breast cancer, and the existence or absence of a possible explanation for the cause of disease (lay theory). The aim was to examine the psychological changes which occurred from one measuring time point to the next, i.e. before and after treatment (psychological adaptation was the dependent variable) (► **Table 5**).

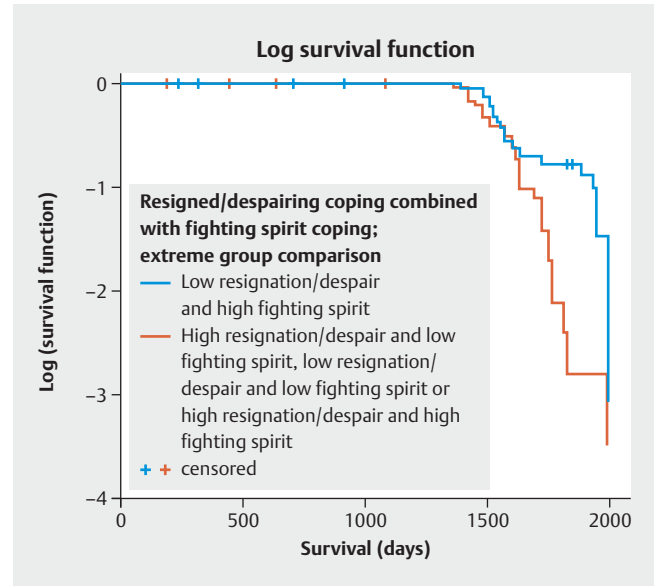
Age and the St. Gallen risk had no impact on the psychological adaptation of patients at t-2. In contrast, the existence of a possible explanation for the onset of disease (lay theory) and higher levels of "socially supported coping" at t-1 were found to be associated with a highly significant predictive effect (lay theory) or a significant prediction (good social support) of the psychological adaptation at t-2. Patients who subjectively attributed the onset of disease to a cause and patients who actively sought social support showed better psychological adaptation at t-2. Similarly, marked resignation as a coping behavior was a negative predictor, just as a marked search for social support was a positive predictor for better psychological adaptation at t-2.

There was also an interactive effect between age and resigned coping as a significant predictor for poorer psychological adaptation at t-2. Older patients were more resigned before starting neoadjuvant chemotherapy, which predicted a significantly poorer psychological adaptation at t-2.

Older patients were significantly less likely to look for social support, and this was clearly followed by poorer psychological



► **Fig. 1** Extreme group comparison: patients with unchanged or increasingly “resigned/despairing coping” strategy (black) vs. patients with low or decreasing “resigned/despairing coping” strategy (blue) (log-rank test: $\chi^2 = 4.882$; $df = 1$; $p < 0.03$).



► **Fig. 2** Extreme group comparison: patients with high “resigned/despairing coping” and low “fighting spirit coping” (red) versus patients with low “resigned/despairing coping” and high “fighting spirit coping” (blue) (log-rank test: $\chi^2 = 4.253$; $df = 1$; $p < 0.05$).

► **Table 5** Dependent variable: t-score “beneficial psychological change” (from t-1 to t-2) and predictors (mixed model analysis, fixed effects).

Variable	Estimate	SD	df	T	P	95% Confidence interval	
						Lower limit	Upper limit
Intercept	-165.87	120.45	54	-1.377	0.174	-407.36	75.62
St. Gallen risk category	-105.66	53.12	54	-1.989	0.052	-212.16	0.84
Age	3.38	2.32	54	1.458	0.151	-1.27	8.03
Lay theory	54.50	15.96	54	3.414	0.001***	22.49	86.50
Social support for coping at t-1	191.63	72.23	54	2.653	0.010**	46.81	336.45
Resigned coping at t-1	-51.73	19.20	54	-2.694	0.009**	-90.23	-13.24
St. Gallen risk category* resigned coping	70.75	34.00	54	2.081	0.042*	2.58	138.91
Social support for coping at t-1* age	-3.30	1.39	54	-2.368	0.022*	-6.09	-0.51

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

adaptation. Conversely, younger patients were more likely to look for social support and adapted better to the situation.

Discussion

This was a prospective study into the psychological adaptation of breast cancer patients scheduled for neoadjuvant chemotherapy prior to surgery. The criteria for inclusion into the study were breast cancer confirmed by punch biopsy, the patient’s written consent to participate in the study, age over 18 years, and a sufficient knowledge of German (for the tests and interviews which were held in German). The investigated psychological variables in-

cluded psychological stress, social support, fatigue, subjective ideas about the cause of disease (lay theory), and the patients’ coping strategies and resources. Coping strategies were investigated prospectively and recorded objectively with the help of semi-structured interviews; this was done immediately before undergoing neoadjuvant chemotherapy and after completing chemotherapy but before undergoing surgery. Medical data were recorded and examined at a follow-up examination which took place between 3.7 and 5.5 years after chemotherapy for possible correlations with psychological and coping variables.

Overall, the average level of psychological stress at the time of receiving the diagnosis and prior to starting systemic treatment (t-1) was higher for all patients. While important psychological

variables such as overall symptoms of psychological stress (BSI), depression (POMS) and anxiety (HADS) tended to decrease over the course of chemotherapy (t-2 compared to t-1), levels for other variables remained constantly elevated. Patients who spontaneously offered an explanation for the cause of their disease during the first interview at t-1 showed significantly better levels of psychological adaptation over the course of chemotherapy and at t-2. There are very few studies which have reported on correlations between psychological adaptation and attributing the disease to a specific cause. The results to date are inconsistent and contradictory. The few studies on this topic showed no correlation between attribution (lay theories on the possible cause of disease) and the patient's adaptation to breast cancer [50, 51]; other studies have shown significant correlations between a better adaptation to leukemia and to treatment consisting of allogeneic bone marrow transplantation [33, 34]. Research on coping with disease by recording coping strategies and patients' subjective theories on why they developed disease is fraught with numerous difficulties. Given that many cancer patients have their own theories about the causes which led to their disease, this aspect is becoming more important for future research [50, 51].

Causal thinking is an integral component of human nature. People search for causes and reasons for the events which occur in their lives. One can speculate whether subjective theories on the cause of disease may be helpful and tend to soften anxieties in contrast to feeling powerless, helpless and inexplicable bafflement. Physicians and healthcare staff should take note of patients' personal beliefs with regard to their potential consequences: Are patient-held beliefs ("lay etiologies") more beneficial – because they tend to have a calming effect on patients – or are they dysfunctional with regard to compliance with therapy and building-up hope and are more likely to hamper therapy-related compliance – because the patients remain agitated and they are not reassured by their own theories on disease? If the latter is the case, a psycho-oncological intervention would be needed because the patient would otherwise remain in an elevated state of stress, which would prevent the patient from adapting to her disease and could act as a brake or even make it impossible to carry out the necessary treatment which would additionally diminish the patient's chance of overall or disease-free survival. This could have been the case with our patient sample.

Our study showed that some breast cancer patients could be identified as having greater difficulties in adapting to their situation before starting (neoadjuvant) therapy. They tended to be older and had deficits in asking for social support from family members and friends. They usually had no theory of their own (lay etiology) to explain the cause of disease, were often depressed, took a more pessimistic view of the future, appeared despondent and had high levels of "resigned coping". These women clearly had difficulty in coming to terms with their situation, which could put them at higher risk during the further course of disease.

In contrast to this problematic subgroup, women with better social support showed a better adaptation to the situation after they had received the diagnosis and even before they had started chemotherapy. They were more likely to demonstrate a strong "fighting spirit" and had their own theories about the cause of disease. They also tended to be younger. These patients showed sig-

nificantly better psychological adaptation to disease and to systemic therapy. Patients without or with lower levels of "resigned coping" at t-1 and during treatment and with a greater "fighting spirit" had significantly better disease-free and overall survival rates.

"Resigned coping" and "fighting spirit coping" were significantly negatively correlated at t-1 ($r = -0.360$, $df = 52$, $p < 0.009$). The coping strategy of seeking "social support" and "fighting spirit coping" were significantly positively correlated at t-1 ($r = 0.296$, $df = 52$, $p < 0.033$).

In our study, the quality of how patients processed and coped with the diagnosis of cancer at the time of primary diagnosis and before starting oncological treatment predicted the patient's psychological adaptation and influenced the course of disease and convalescence. Patients at risk should be identified at primary diagnosis as they will require additional support [52].

The results of this study show that patients with a primary diagnosis of breast cancer have a high need of psychosocial support from family, friends and acquaintances. Both in our and in other studies it appears that a good network of social support is decisive for the patient's psychological adaptation and possibly even her survival with cancer [52–58]. The women in our study who demonstrated better coping behavior with regard to "social support" also had better "cognitive restructuring", a stronger "fighting spirit" and less or no "resigned coping". Early and careful psychological screening with regard to the coping resources of breast cancer patients is therefore recommended. Vulnerable patients require additional psychological measures to give them the opportunity to improve their ability to cope. Several methodologically precise studies have shown that the quality of the patient's coping resources has a greater predictive power for the patient's psychological adaptation and also her survival [6, 7, 14–16, 27, 31, 32, 52–58]. An investigation of patients with gynecological malignancies receiving chemotherapy found that even before starting chemotherapy – after surgery – the patients' perceived quality of life before chemotherapy already predicted their quality of life after their sixth chemotherapy cycle [59].

The resources of patients at the time of receiving the diagnosis could be correspondingly influenced by short but intensive psycho-oncological interventions [59–63]. Although many studies found no significant association between psycho-oncological interventions and effects on survival [64–68], there is at present no conclusive answer to this question. Most of these studies used inadequate methods which did not allow the patients' coping resources to be adequately recorded. They used questionnaires to measure coping behavior. However, questionnaires are not a valid instrument to identify the real coping behavior. They tend to measure what is socially desirable or the patient's resistance rather than the often painful self-revelation.

The low number of participants is one of the limitations of this study. One of the strengths of the study is its prospective nature and its 3–5 year follow-up, the objective assessment of patients' coping behavior, the use of well-established psycho-oncological measurement methods and the multiple measurements of outcome criteria.

The follow-up data on non-recurrence, no new disease, no tumor-related mortality and the elevated scores for the coping

strategies assessed as positive suggest a connection between disease-free and overall survival, which – in addition to another follow-up examination – should definitely be verified in further studies using a significantly larger sample of patients. At all events, the findings presented here already indicate the need for a greater sensitivity and careful psycho-oncological screening of patients scheduled to undergo neoadjuvant chemotherapy in order to arrange beneficial psycho-oncological interventions in good time if required.

Conclusion

Patients with breast cancer scheduled to undergo neoadjuvant chemotherapy experience considerable psychological stress when they first receive the diagnosis. Their special situation does not just include the shock of diagnosis but also the fact that because of their risk situation neoadjuvant chemotherapy is carried out first and the tumor is only surgically resected after competing chemotherapy and thus initially remains in the body. This is a big challenge for affected women, who do not just have to come to terms with the difficult situation of a “diagnosis of breast cancer” but also have to live with the fear of a persistent threat in their body. This situation requires a strength which not every woman may have. Women without active and helpful coping strategies are at increased risk of psychological maladaptation.

Careful psycho-oncological screening with regard to possible psychosocial deficits or a lack of coping resources on the part of affected women is urgently recommended. Screening should be done immediately after diagnosis and before starting any oncological treatment. This could be used to detect potentially vulnerable women and arrange suitable psycho-oncological support.

Conflict of Interest

None.

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