

Predictors of the course of quality of life during therapy in women with primary breast cancer

Achim Wöckel¹ · L. Schwentner² · M. Krockenberger¹ · R. Kreienberg³ ·
W. Janni² · M. Wischnewsky⁴ · Kühn Thorsten⁵ · Flock Felix⁶ · Felberbaum Riccardo⁷ ·
M. Blettner⁸ · S. Singer⁸

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Abstract

Purpose Multimodal therapies affect the quality of life (QoL) of patients with primary breast cancer (PBC). The objectives of this prospective study were to explore the changes in QoL from diagnosis to conclusion of adjuvant therapy and to identify predictive factors of QoL.

Methods Before surgery (t1), before onset of adjuvant treatment (t2) and after completion of adjuvant chemo- or radiotherapy (t3), patients with PBC ($n = 759$) completed the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, Charlson Comorbidity Index, Patient Health Questionnaire and Perceived Involvement in Care Scales. Predictors of the course of global QoL were estimated using multinomial

logistic regression. Effect estimates are odds ratios (OR) and their 95% confidence intervals (CIs).

Results Global QoL improved between t1 and t3, while physical functioning, emotional functioning and fatigue deteriorated. QoL before surgery was more often poor in patients <60 years (OR 2.2, 95% CI 1.5–3.1) and in those with comorbid mental illnesses (OR 8.6, CI 5.4–13.7). Forty-seven percentage reported good global QoL both at t1 and at t3. QoL improved in 28%, worsened in 10% and remained poor in 15%. Compared to patients with consistently good global QoL, a course of improving QoL was more often seen in patients who had received a mastectomy and in those with intense fear of treatment before surgery. A course of decreasing QoL was more often found in patients who were treated with chemotherapy. QoL stayed poor in patients with chemotherapy, mastectomy and intense fear. There was no evidence that radiotherapy, progressive disease or perceived involvement impact the course of QoL.

Conclusions Younger age and comorbid mental illnesses are associated with poor QoL pre-therapeutically. QoL is more likely to stay or become poor in patients who receive chemotherapy.

✉ Achim Wöckel
Markert_F@ukw.de

¹ Department of Obstetrics and Gynecology, Würzburg University Hospital, Würzburg, Germany

² Department of Obstetrics and Gynecology, Ulm University Hospital, Ulm, Germany

³ Landshut, Germany

⁴ eScience lab, University Bremen, Bremen, Germany

⁵ Department of Obstetrics and Gynecology, Esslingen Hospital, Esslingen am Neckar, Germany

⁶ Department of Obstetrics and Gynecology, Memmingen Hospital, Memmingen, Germany

⁷ Department of Obstetrics and Gynecology, Clinic of Kempten, Academic Teaching Hospital - University of Ulm, Ulm, Germany

⁸ Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Centre, Mainz, Germany

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Introduction

Cancer patients are confronted with multiple stress factors that can affect their quality of life (QoL). These include pain, fatigue, adverse reactions and sequelae of the treatment, emotional distress like the fear of disease recurrence, functional limitations in their daily life, problems with

returning to work, existential and spiritual issues among others [25].

Breast cancer patients may experience cosmetic problems and pain after surgical interventions, vaginal problems, cognitive impairment and weight problems during and after adjuvant chemo- and radiotherapy [7]. Chronic fatigue can likewise persist for many months after various treatments [9]. Another sequela is chemotherapy-induced peripheral neuropathy [26]. Lymphedema and restricted arm mobility secondary to lymph node dissection can be added to the above [14]. All problems associated with breast cancer can affect the somatic and emotional functioning of patients, their return to work and their day-to-day competency [3]. These breast-cancer-specific sequelae likewise impact QoL along the different phases of the therapeutic process. A better understanding about the course of QoL and its predictors may help identify patients in need of specific emotional support and better pinpoint the time for special care.

To date, only a few studies have investigated QoL in patients with primary breast cancer throughout the entire clinical course from diagnosis to conclusion of adjuvant therapeutic measures [12, 13, 22]. Similarly, data on predictors of the course of QoL have been rarely prospectively collected in these patients. The objective of the present study was therefore to prospectively assess QoL in patients with primary breast cancer at various post-diagnosis endpoints during acute therapy and after conclusion of adjuvant therapy. In particular, the following questions were asked: (1) what factors are predictive of pre-therapeutic QoL and (2) what factors predict the course of QoL over time.

Methods and patients

Design and study participants

This prospective longitudinal cohort study (BRENDA-II) in patients with primary breast cancer measured QoL at three endpoints: t1 (at diagnosis, before surgery), t2 (after surgery, before onset of adjuvant therapy) and t3 (after conclusion of adjuvant chemo- and/or radiotherapy). After breast-conserving or ablative surgery, personalized or multimodal therapy (chemotherapy, radiotherapy, endocrine therapy) was given to all participants.

Sampling

All patients with primary breast cancer treated from 2009 to 2012 in the Departments of Obstetrics and Gynecology at four breast cancer centers were eligible for this study, independent of histological tumor type and stage, as long

as their treatment strategy was of a curative nature and their tumors had not metastasized. All study centers (Ulm, Memmingen, Kempten and Esslingen) were in Germany and certified by the German Cancer Society. Exclusion criteria were metastatic disease, recurrent disease, bilateral breast cancer, primary occult disease, phyllodes tumor, inability to complete a questionnaire and the absence of written informed consent.

Instruments

Demographic and clinical characteristics

Demographic data like length of education, cohabitation and employment status were self-reported. Clinical data were gathered from the medical records by trained data managers. Disease severity, i.e., each patient's individual risk of dying from the malignancy, was defined according to the Nottingham Prognostic Index (NPI) [5] based on lesion size, number of lymph nodes involved and tumor grade.

Quality of life

The European Organization for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30) version 3 was used to assess health-related quality of life (HRQoL). It surveys a global health status/QoL scale, five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, pain and nausea/vomiting) and six single-item scales (appetite loss, insomnia, dyspnea, constipation, diarrhea and financial difficulties).

All scales were converted to scores ranging from 0 to 100. A high score represented good QoL on the global health and functioning scales and poor QoL on the symptom scales. The EORTC QLQ-C30 is one of the most widely used QoL questionnaires in randomized trials in oncology. The EORTC QLQ-C30 (as evidenced by signed user agreements) has been used in more than 9000 clinical trials or academic studies worldwide [6]. It has been translated into more than 85 languages [6]. To prevent the problem of multiple testing, the global scale was defined as the primary outcome measure with physical and emotional functioning and fatigue as secondary endpoints.

Comorbid diseases

Comorbid somatic diseases were assessed by the attending physician and documented and subsequently coded according to the Charlson Comorbidity Index [2]. This index assigns a weighting to a disease depending on the risk of dying from it. Existence of a comorbid somatic

disease was rated with a score ≥ 1 on the Charlson Comorbidity Index.

Comorbid psychiatric diseases were assessed using the Patient Health Questionnaire (PHQ), a self-administered instrument assessing common mental health conditions according to ICD-10 criteria [17]. The PHQ has demonstrated good agreement with gold-standard structured clinical interviews and exhibits a high test–retest reliability [20].

The PHQ-assessed comorbid psychiatric diseases and their ICD-10 codes were: major depression (F32, F33), other depression (F32.9, F33.9, F34.1), agoraphobia with panic disorder (F40.01), panic syndrome (F41.0), generalized anxiety disorder (F41.1), other anxiety disorders (F41.9), bulimia nervosa (F50.2), binge eating (F50.9), alcohol abuse (F10.1), alcohol dependence (F10.2) and somatoform disorders (F45.0, F45.1, F45.3). Existence of a comorbid psychiatric disease was rated with a score ≥ 1 .

Perceived involvement

Perceived involvement was measured using the Perceived Involvement in Care Scales (PICS). On the PICS, patients indicate their perception of extent of their involvement in their care and the treatment decisions relating thereto [16]. We applied the “patient decision-making” subscale that measures the degree to which a patient feels involved in decisions relating to her treatment.

Data collection

The study was approved by the local institutional review board. A patient information leaflet was handed out that explained all relevant study details and endpoints. All participants gave their consent to participate in the study first orally and subsequently in writing. At inclusion, the questionnaires were collected at the hospital. At the follow-up endpoints, the questionnaires accompanied by an information letter and a stamped envelope were mailed to the participants.

Statistical analyses

The characteristics of patients who completed the EORTC QLQ-C30 were compared with patients who had participated in the BRENDA-II study but had not completed the questionnaire regarding age, stage of disease and subsequent therapy. Patients were grouped into “poor QoL” versus “good QoL” if their QoL score on the EORTC QLQ-C30 was below the 25th percentile of the general German population’s age- and sex-matched norms. This approach was based on previous studies [23, 24].

We analyzed the course of QoL by comparing QoL at t1 and t3. Patients were ranked into one of four groups: always good, always poor, deteriorating (good at t1 and poor at t3) or improving (poor at t1 and good at t3).

Potential predictors of pre-treatment QoL were assessed with binary logistic regression. We deemed the following variables potentially predictive of QoL: severity of the disease (NPI—higher risk vs. lower risk of dying), age at study entry, cohabitation (currently living without/with partner), somatic comorbidity (yes/no), psychiatric comorbidity (yes/no) and employment status (unemployed vs. other). These potential predictors were entered simultaneously into the model.

Predictors of the course of QoL were tested with multinomial logistic regression. We considered the following variables predictive of the course of QoL: adjuvant therapy (radiotherapy yes/no, chemotherapy yes/no), type of surgery (breast-conserving vs. mastectomy), disease progression during follow-up (metastases, recurrent disease), fear of treatment and perceived involvement.

We used 95% confidence intervals (CIs) to quantify statistical uncertainty. The statistical analyses were performed using STATA 12.1 (StataCorp 2011, College Station, TX: StataCorp LP).

Results

Sample characteristics

A total of 759 patients participated in the study. In total, 857 patients were treated at the participating hospitals during the study period; 849 met the inclusion criteria and were contacted for participation; 90 patients declined participation or could not be included due to dementia or language problems.

A total of 753 women completed the EORTC QLQ-C30 at least once, 726 women completed it at t1 and 582 completed it at all three time-points (t1, t2 and t3). Six women never completed the EORTC QLQ-C30 during the entire course of the study. The mean time between t1 and t3 was 8.6 months (SD 2.4, range 4.4–29.3, median 8.1).

The mean age of the patients at baseline was 58 years (youngest patient 23 and oldest patient 87 years). A large proportion of patients (46%) had a length of education of less than 10 years (vocational and no academic education) and were currently living with a partner or spouse (82%). The majority of the patients (83%) had undergone breast-conserving surgery followed by multimodal therapy (44% chemotherapy, 88% radiotherapy, 81% endocrine therapy).

The demographic and clinical data are summarized in Table 1.

Quality of life and its changes over time

Overall, the global QoL in the patients improved from t1 to t3, while the other domains (emotional functioning, physical functioning and fatigue) showed a decreasing tendency (Table 2).

Regarding their global QoL, 47% of patients reported good QoL both at t1 and at t3 (“always good”). The proportion of patients whose QoL improved, i.e., went from “poor” to “good,” was 28%, and the proportion whose QoL worsened, i.e., went from “good” to “poor,” was 10%. In total of 15%, the QoL stayed at its originally low level (Table 3). The scores for fatigue, physical functioning and emotional functioning worsened (23, 23 and 12%) more often than they improved (14, 7 and 5%; Table 4).

Correlates of baseline QoL

A poor global QoL at baseline was associated with age <60 years (OR 2.2; 95% CI 1.5–3.1) and a psychiatric comorbidity (OR 8.6, 95% CI 5.4–13.7). There was no evidence for an association of somatic comorbidity, breast cancer risk group, unemployment and cohabitation with global QoL (Table 5).

Poor physical functioning at baseline was a predictor for psychiatric comorbidity (OR 4.2), somatic comorbidity (OR 2.7) and age <60 years (OR 4.6). Similarly, poor emotional functioning was a predictor for psychiatric comorbidity (OR 6.7), somatic comorbidity (OR 3.9), and age <60 years (OR 0.4). Fatigue was a predictor for psychiatric comorbidity (OR 5.8), somatic comorbidity (OR 2.3), and age <60 years (OR 3.2).

Predictors of the course of QoL

Compared to patients with consistently good global QoL, an improvement in the course of QoL was more often seen in patients who had undergone mastectomy (OR 2.1) and suffered from an intense fear of the proposed treatment before surgery (OR 2.2; Table 6). A worsening in the course of QoL was more often found in patients treated with chemotherapy (OR 2.5). Consistently poor global QoL was reported more often by patients receiving chemotherapy (OR 2.9), mastectomy (OR 2.2) and suffering from fear of treatment (OR 1.9).

There was no evidence for an impact of radiotherapy, disease progression or perceived involvement on the course of global QoL.

Table 1 Patient characteristics at baseline ($n = 759$)

	<i>N</i>	(%)
Age (in years)		
<40	40	5
40–49	154	20
50–59	206	27
60–69	212	28
70–79	117	16
80+	24	3
Cohabitation		
Lives without partner	132	18
Lives with partner	621	82
Education		
<10 years	348	46
10 years	248	33
>10 years	148	20
Unknown	9	1
Employment		
Employed, retired or homemaker	695	92
Unemployed	16	2
Unknown	42	6
T stage (pathological)		
0	10	1
1	377	50
2	305	41
3	42	6
4	17	2
Unknown	2	0
N stage (histological)		
Negative	500	66
Positive	247	33
Unknown	6	1
Nottingham Prognostic Index		
Low risk	66	9
Medium risk	343	46
High risk	247	33
Very high risk	97	13
Somatic comorbidity		
No comorbid disease	520	69
Comorbid disease	190	25
Unknown	43	6
Psychiatric comorbidity		
No comorbid disease	581	77
Comorbid disease	160	21
Unknown	12	2
Nottingham Prognostic Index		
Low risk	66	9
Medium risk	343	46
High risk	247	33
Very high risk	97	13

Table 1 continued

	<i>N</i>	(%)
Type of surgery		
Mastectomy	126	17
Received adjuvant therapy		
Chemotherapy	330	44
Radiotherapy	665	88
Endocrine therapy	612	81

Discussion

This study was designed to identify patients with a special need for QoL-impacting interventions like psychological support during their treatment cycles. Our results showed an average improvement in or a stable course of global QoL in patients with primary breast cancer during the course of therapy. Many past studies have reported divergent results on how QoL changes in breast cancer patients over time [11, 13, 22]. Some studies reported significant improvements in most QoL scores in their patients 6 months after diagnosis [4, 18], although some problems still remained (e.g., poor body image and an uncertain future outlook, in addition to systemic side effects of therapy) [21]. Other studies reported reduced [13, 18] or stable QoL [22] within the first 6 months after treatment.

Most prospective QoL studies focused on scores taken at the time of cancer diagnosis [15] or in the post-diagnosis period [12].

The differences between studies on how breast cancer patients perceive their QoL may depend on how QoL is defined and measured [8]. Assessment of QoL prior to diagnosis may be crucial to providing a true baseline for later comparison, thereby allowing a more reliable interpretation of outcomes [10]. However, enrolling patients to a QoL study with written informed consent before they are informed about their cancer diagnosis may prove ethically difficult.

The patients in our study reported a pattern of increased fatigue after adjuvant treatment in contrast to improved global QoL. A similar pattern was reported in a prospective study 3 months after treatment initiation in breast cancer patients [19]. A Scandinavian study reported decreased physical, role and social functioning, and exacerbated emotional functioning and fatigue in women with breast cancer. However, those women showed a deterioration in global QoL up to 25 weeks after chemotherapy, which is contrary to our findings [1]. This might be explained by patients recovering emotionally during the first 6 months after diagnosis [12] although the impact of different adjuvant treatments and their side effects on QoL is likely to increase [21].

Table 2 Quality of life (QoL) in patients with primary breast cancer before and after surgery and after adjuvant treatment (mean of EORTC QLQ-C30 subscales and percentage of women with poor QoL). Poor QoL is reflected by scores worse than the 25th percentile of the age- and gender-matched general population

	t1 Preoperative	t2 Postoperative	t3 Post-adjuvant therapy
Mean			
Global QoL	60.5	61.4	69.3
Physical functioning	88.5	82.7	82.5
Emotional functioning	53.6	60.0	68.9
Fatigue	25.3	34.6	32.0
Percentage with poor QoL			
Global QoL	43%	40%	25%
Physical functioning	25%	40%	39%
Emotional functioning	10%	16%	17%
Fatigue	42%	57%	51%

Table 3 Quality of life (QoL) over time (before surgery to after adjuvant treatment)

	Global QoL		Physical functioning		Emotional functioning		Fatigue	
	<i>N</i>	(%)	<i>N</i>	(%)	<i>N</i>	(%)	<i>N</i>	(%)
Always good	276	47	323	54	468	78	213	36
Improving	166	28	41	7	31	5	81	14
Decreasing	61	10	136	23	73	12	139	23
Always poor	87	15	100	17	28	5	166	28

Number and percentage of patients with stable, improving and decreasing QoL

Table 4 Predictors of poor global QoL before surgery (t1)

	OR ^a	95% CI ^b	P
NPI ^c 2 vs. 1	1.1	(0.6–2.3)	0.72
NPI 3 vs. 1	1.7	(0.8–3.5)	0.14
NPI 4 vs. 1	1.7	(0.7–3.7)	0.21
Age <60 years	2.2	(1.5–3.1)	<0.001
Lives with partner	1.4	(0.9–2.1)	0.17
Somatic comorbidity	1.4	(0.9–2.1)	0.14
Psychiatric comorbidity	8.6	(5.4–13.7)	<0.001
Unemployed	2.0	(0.5–7.4)	0.29

^a Odds ratio

^b Confidence interval

^c Nottingham Prognostic Index

Other prospective studies reported different results within the first 6 months. One prospective study with a 3-month follow-up after diagnosis showed no change in overall QoL, physical functioning, fatigue, nausea/vomiting or financial difficulties in breast cancer patients compared to the general population, although role, emotional, cognitive and social functioning deteriorated and pain decreased in the breast cancer patients [22]. The findings of a 2-year follow-up study indicated that the greatest improvements appeared in almost all QoL scores during the first 6 months after surgery [12].

Table 5 Predictors of fatigue, poor physical and emotional functioning before surgery (t1)

	Physical functioning		Emotional functioning		Fatigue	
	OR ^a	95% CI ^b	OR	95% CI	OR	95% CI
NPI 2 vs. 1	1.6	(0.7–3.8)	2.1	(0.5–8.1)	0.3	(1.6–0.0)
NPI 3 vs. 1	2.2	(0.9–5.3)	2.9	(0.7–11.3)	1.1	(0.5–2.1)
NPI 4 vs. 1	1.5	(0.6–3.9)	1.5	(0.3–6.9)	0.7	(0.3–1.5)
Age <60 years	4.6	(2.9–7.4)	0.4	(0.2–0.8)	3.2	(2.2–4.8)
Lives with partner	0.8	(0.5–1.2)	0.6	(0.3–1.1)	0.8	(0.5–1.2)
Somatic comorbidity	2.7	(1.7–4.3)	3.9	(2.2–7.0)	2.3	(1.6–3.6)
Psychiatric comorbidity	4.2	(2.8–6.4)	6.7	(3.7–12.1)	5.8	(3.8–8.9)
Unemployed	2.8	(0.9–9.0)	1.2	(0.2–6.3)	2.3	(0.6–8.4)

^a Odds ratio

^b Confidence interval

^c Nottingham Prognostic Index

Table 6 Predictors of the course of global quality of life (QoL) over time (improving, decreasing, or poor QoL compared to good QoL)

	Improving		Decreasing		Always poor	
Radiotherapy	1.7	(0.7; 4.0)	0.9	(0.3; 2.8)	1.4	(0.5; 4.0)
Chemotherapy	1.3	(0.8; 2.0)	2.5	(1.4; 4.5)	2.9	(1.7; 5.1)
Mastectomy	2.1	(1.1; 4.2)	1.2	(0.5; 2.9)	2.2	(1.0; 4.7)
Recurrence or metastasis	0.3	(0.0; 3.0)	1.1	(0.2; 5.9)	2.1	(0.5; 8.2)
Fear of treatments	2.2	(1.6; 3.0)	1.0	(0.7; 1.5)	1.9	(1.3; 2.8)
Shared decision making	1.1	(0.9; 1.4)	1.1	(0.8; 1.4)	0.9	(0.7; 1.2)

The disparities across study results may be due to several factors, such as different treatment regimens with different side effects, different instruments used for scoring QoL and the definition of baseline and follow-up endpoints in relation to diagnosis.

Our study showed younger age (<60 years) and psychiatric comorbidity to be relevant predictors for poor global QoL before the initiation of multimodal breast cancer treatment. Fear of treatment and mastectomy as a surgical procedure were major predictors for a deterioration in global QoL during therapy.

Schou et al. [22] prospectively investigated QoL in 161 women newly diagnosed with breast cancer. They compared their data with age-adjusted QoL scores from a general female population ($n = 949$). In addition, multiple factors (demographic, personality traits, involvement in treatment decision making, satisfaction with information provided and medical characteristics) were simultaneously investigated in a multivariate model to determine which variables have the strongest association with QoL one year after surgery. QoL was also evaluated using the EORTC QLQ-C30 at the time of diagnosis, 3 and 12 months postoperatively. Women with breast cancer scored significantly lower on emotional, cognitive and social functioning items at the time of diagnosis compared to the general female population and continued to score lower on

cognitive and social functioning one year after surgery. In addition to initial QoL, breast-conserving surgery was predictive of better physical functioning and body image, while chemotherapy was predictive of poorer role functioning one year after surgery. These results are similar to ours, where fear of treatment (particularly related to chemotherapy) and mastectomy as a surgical procedure were major predictors of a deterioration in global QoL during therapy. In the study by Schou et al., dispositional optimism was predictive of better emotional and social functioning one year after surgery. At diagnosis and throughout the post-diagnosis period, dispositional optimism was associated with better QoL and fewer symptoms.

One limitation of our study was that QoL was measured using a generic instrument only, while the breast-cancer-specific EORTC module was not administered. Since the problem of multiple testing would have been increased with additional QoL domains from the breast-cancer-specific module, we restricted our analyses to four pre-defined QoL domains in order to avoid multiple testing. Here, we may have overlooked important impacts on the course of QoL relevant to patients with primary breast cancer. For example, young women forced to undergo menopause prematurely due to chemotherapy may suffer from various physical and mental problems which are not (explicitly) covered in the EORTC QLQ-C30. We only surveyed more general aspects of QoL, assuming that those potential QoL problems eventually would transfer into general QoL impairments.

Another limitation is that follow-up was restricted to the time of primary and adjuvant treatment. Our findings cannot be extrapolated to the course of QoL after this period. A final limitation is that mental health was measured with a self-administered questionnaire. This is usually a reliable and valid method, since that there truly are no “objective” measurand for feelings of sadness, depression or anxiety. However, many mental health problems, especially drug or alcohol dependency, tend to be underreported because of denial or social desirability. We therefore might have underestimated the rate of mental health disorders in our sample.

Conclusions

Overall, the global QoL in patients with primary breast cancer improved over the course of therapy from the pre-operative diagnosis phase to the post-adjuvant, conclusion of treatment phase. On average, however, physical functioning, emotional functioning and fatigue deteriorated. Younger age and comorbid mental health condition were predictors of poor QoL before surgery. Global QoL deteriorated more often in women who had received

chemotherapy. Consistently poor QoL was reported mainly by women who suffered from an intense fear of treatment and who received chemotherapy and/or mastectomy.

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