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Survivors of primary breast cancer 5 years after surgery: follow-up care, long-term problems, and treatment regrets. Results of the prospective BRENDA II-study

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Abstract

Purpose This study aims to answer the questions where breast cancer patients in Germany receive follow-up care (with what types of doctors) and what are the long-term problems and treatment regrets of breast cancer patients.

Methods In the prospective multicenter cohort study BRENDA II ("Breast Cancer under Evidence-Based Guidelines"), 456 patients with primary breast cancer were sampled consecutively over a period of 4 years (2009–2012) and contacted again 5 years after surgery. Long-term problems were elicited on a 4-point Likert scale ranging from 0 ('not at all') to 3 ('very much').

Results 82% of the patients receive follow-up (FU) at the private practice gynecologist. In 22%, the initial treating hospital is involved in the FU, and in 20% the general practitioner does this (multiple answers possible). Long-term problems attributed to the treatment were most often related to endocrine therapy (mean 1.29) and to chemotherapy (mean 0.94).
Most of the patients were happy to have had radiotherapy (95%). For chemotherapy, endocrine therapy, and antibody therapy, the satisfaction for the treatment decision was 87%, 87%, and 84% respectively. Among patients who reported they regretted having undergone a recommended treatment, it was most often for endocrine therapy (5%) and chemotherapy (4%).

Conclusion In Germany, different specialists are involved in the patients' FU care for BC. The detection of long-term problems due to BC treatment is an essential part of FU care.

Keywords Breast cancer · Breast cancer survivors · Follow-up · Long-term problems · Treatment regrets

Introduction

Breast cancer (BC) is the most frequent cancer among women [1]. Due to early detection of BC and improvements in the available treatment strategies, more than 80% of the patients will be long-term survivors [2–4]. After curative BC treatment, patients move on to follow-up care, which marks the shift from curative care to survivorship. FU in BC care involves periodic visits for history and physical examination and annual surveillance mammograms [5, 6]. Detection of recurrent and new primary BC is the main goal of the FU program [7, 8].

In Germany, BC is commonly treated by a gynecologic oncologist, and, hence, they are usually involved in the patient's FU care. However, general practitioners, medical oncologist, radio-oncologist, or other doctors also perform FU care for BC. To date, it is not known to which doctors BC patients go for FU care and to what extent. Thus, this

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paper addresses the question as to where (to a private practice or hospital) and from what types of doctors patients receive FU care. Moreover, we were interested in whether there are differences between patients with and without metastatic disease.

Besides monitoring for cancer recurrence, the objectives of FU care also include the improvement of quality of life and physical performance as well as the reduction of therapy-related side effects. Identifying long-term problems and the patient's opinions related to the different treatment strategies of the adjuvant setting such as surgery, chemotherapy, radiotherapy, endocrine therapy, and antibody therapy are essential for example to understand treatment discontinuation that prevents patients from undergoing guideline-adherent adjuvant treatment in primary BC care [9, 10]. Therefore, the aim of the prospective BRENDA II study is to assess these patient-related factors to promote guideline adherence, which may be associated with improved survival parameters in BC.

This study aims to answer the following questions:

1. Where do patients receive FU care (with what types of doctors)? Are there differences between patients who have metastases and those that do not?
2. What are the patients' current complaints related to the treatment they have received?
3. In hindsight, what are the patients' attitudes regarding the treatment they have received?

Methods

Data collection

In the prospective multicenter cohort study BRENDA II ("Breast Cancer under Evidence-Based Guidelines"), patients with primary BC were sampled consecutively over a period of 4 years (2009–2012). Patients were approached before surgery (t1), before initiation of adjuvant treatment (t2), after completion of adjuvant radio- and/or chemotherapy (t3), and contacted again 5 years after surgery (t4). Patients were eligible for this study if they had been diagnosed with primary histologically confirmed BC. Exclusion criteria were: metastatic or recurrent disease at baseline, bilateral BC, primary occult disease and phylloides tumor, inability to complete a questionnaire, and no written informed consent. Following a consultation, each patient was informed about the study by her doctor and asked to participate. If she agreed, the doctor handed over the first series of questionnaires and interviewed the patient. FU interviews were performed by trained study nurses. We collected data at the University Medical Center in Ulm, Kempten Hospital, Memmingen Hospital, and Esslingen Hospital, all of which are breast cancer centers certified by the German Cancer Society. Ethical approval was obtained from the Ethics Committee of Ulm University.

Instruments

Clinical data were obtained from the medical records by trained data managers. The patients' individual risk was defined according to the Nottingham Prognostic Index based on the size of the lesion, number of lymph nodes involved, and tumor grade and then consequently grouped into risk groups [11]. Missing values for any of the three parameters were imputed using the mean. The occurrence of distant metastases was reported by the patients at t4.

Socio-demographic data such as age, marital status, and employment were provided by the patient.

We elicited long-term problems by asking: 'If there are any current problems, how much are they, in your opinion, related to the following treatments: breast surgery, axillary lymph node dissection, radiotherapy, chemotherapy, endocrine therapy, antibody therapy?' Responses were collected on a 4-point Likert scale ranging from 0 ('not at all') to 3 ('very much'). Patients could also tick 'I did not receive this treatment'. Potential *treatment regrets* were elicited by asking 'Are you happy/sorry about having done radiotherapy/chemotherapy/endocrine therapy/antibody therapy?' and accordingly 'Are you happy/sorry about having refused to do radiotherapy/chemotherapy/endocrine therapy/antibody therapy?'

Statistical analysis

Absolute and relative frequencies were calculated for categorical variables and mean scores for continuous variables to describe the sample. Non-participants at t4 were compared to participants regarding age at baseline and risk group (according to Nottingham Prognostic Index) using analysis of variance and Chi^2 tests.

We defined the proportion of patients in the various types of FU care (the kind of doctor the participants are receiving FU care from) and compared the patients with and without metastases and in different educational groups using $2 \times k$ tables and Chi^2 tests.

Statistical analyses were performed using STATA 12.1 (StataCorp LP, College Station, TX, USA).

Results

Sample

857 patients with primary BC were treated at the collaborating clinics during the study enrollment period and 759

patients participated in the BRENDA II study. At t4, 456 (60%) patients participated again, and these data were used for analysis. 101 (13%) other patients declined (51 of them had participated at t3 but declined now at t4, the remaining 50 had already declined before t4 during the course of the study), 60 (8%) were known to be deceased, 1 had moved to an unknown address abroad, and 141 (19%) did not reply for unknown reasons.

The participants were on average 63 years old at t4 (SD 11, minimum 31, maximum 93 years). They were at baseline on average younger than those who declined (+7 years) and those who were deceased (+8 years). Patients with an unknown reason for non-participation had the same age as the participants. Also, the participants had a better prognostic outlook at baseline according to the Nottingham Prognostic Index than those who were deceased at t4 ($p < 0.001$).

Baseline clinical and socio-demographic data are displayed in Tables 1 and 2.

Treatment

All patients received surgical care, 86% breast-conserving surgery, and 14% mastectomy (Table 2). 31% of the patients received axillary lymph node dissection. The time since surgery was on average 5.5 years (median 5.3, minimum 4.3, maximum 7.3 years). 46% of the patients were treated with chemotherapy, and 12% with additional antibody therapy. The majority of the patients received adjuvant radiotherapy (91%) and endocrine therapy (82%). Regarding the type of endocrine therapy, more than half of the patients (55%) were exposed to tamoxifen, and 59% of the patients were treated with some type of aromatase inhibitor (Table 3).

Table 1 Socio-demographic characteristics of the sample ($n = 456$)

	N	Percent (%)
Marital status (at t4)		
Unmarried	42	9
Married	314	69
Divorced	47	10
Widowed	52	11
Unknown	1	0
Cohabitation (at t4)		
Lives with partner in same household	290	64
Lives with partner in different households	23	5
No partner	89	20
Unknown	54	12
Employment		
Yes, full time, ≥ 35 h/week	72	16
Yes, half time, 15–35 h/week	83	18
Yes, minor employment, < 15 h/week	37	8
No, housewife	51	11
No, seeking employment	3	1
No, reduced-earning-capacity pension	13	3
No, retirement pension	181	40
Unemployment (other reasons)	14	3
Unknown	2	0

Table 2 Clinical characteristics of the sample ($n = 465$)

	N	Percent (%)
Nottingham Prognostic Index (at baseline)		
Low risk	45	10
Medium risk	212	46
High risk	149	33
Very high risk	50	11
Risk according to St. Gallen (at baseline)		
Low risk	39	9
Intermediate risk	344	75
High risk	70	15
Unknown	3	0
Recurrence (at t4)		
No	437	96
Yes	15	4
Unknown	4	1
Distant metastases (at t4)		
No	436	96
Yes	13	3
Unknown	7	2
Type of surgery		
Breast-conserving surgery	392	86
Mastectomy	64	14
Axillary lymph node removal		
No	31	7
Sentinel node biopsy (only)	284	62
Axillary lymph node dissection Level 1	11	2
Axillary lymph node dissection Level 1–2	123	27
Axillary lymph node dissection Level 1–3	7	2
Radiation therapy		
No	40	9
Yes	416	91
Chemotherapy		
No	247	54
Yes	209	46
Antibody therapy		
No	403	88
Yes	53	12
Endocrine therapy		
No	84	18
Yes	372	82

Table 3 Type of endocrine therapy received (multiple answers possible)

	N	Percent (%)
Tamoxifen	203	55
Arimidex	85	23
Femara	89	24
Aromasin	45	12
Faslodex	1	0.3
Zoladex	29	8

Follow-up care

In the majority of the patients, the private practice gynecologist performs their FU care (82%) (Table 4). In 22%, the initial treating hospital is involved in the FU, and in 20% the general practitioner (GP) does this. Other hospitals, private practice medical oncologists, private practice radio-oncologist, or others are rarely consulted for FU care. Fifteen of the patients reported they did not attend any doctor for FU care.

13 patients had distant metastases at t4, and they visited at least one doctor for FU care. In the metastatic setting, patients go less often to a private practice gynecologist ($p = 0.007$) and more often to a private practice medical oncologist ($p = 0.06$) compared to patients without distant metastases. No statistically significant differences were found for FU care in the initial treating hospital, with the GP, or in a private practice radio-oncologist. There was no evidence for an effect of education on which doctor was visited for FU care (Table 4).

Long-term problems

Long-term problems attributed to the treatment by the patients were most often related to endocrine therapy (mean 1.29) and to chemotherapy (mean 0.94). Thereafter, problems are associated with surgery (axillary lymph node dissection > surgery of the breast). Rarely, patients report long-term problems due to radiation therapy (0.54) or antibody therapy (0.28) (Fig. 1).

Treatment regret

In general, many patients were happy to have had the curative treatment possibilities listed in Table 5a. In 41% of patients, chemotherapy was not recommended, and in 19% endocrine therapy was not recommended. Regarding only those patients who had had a doctor's recommendation for a particular therapy (Table 5b), most of the patients were happy to have had radiotherapy (95%). For chemotherapy, endocrine therapy, and antibody therapy, the satisfaction for the treatment decision was 87%, 87%, and 84% respectively. Among patients who reported they regretted having undergone a recommended treatment, it was in descending order for endocrine therapy (5%), chemotherapy (4%), radiotherapy (3%), and antibody therapy (1%).

On the other hand, patients almost never regretted having refused a recommended treatment. Among patients who indicated they were happy they had decided against a treatment recommendation, it was most often for antibody therapy (13%), followed by chemotherapy (10%), endocrine therapy (8%), and radiotherapy (2%).

Discussion

Based on BC statistics, there are millions of women alive who have been diagnosed with BC in the past [12]. A steady increase in this number underlines the importance of FU care to provide optimal treatment and improve BC outcomes. In Germany, different specialized doctors such as gynecologists (in private practice or hospital), medical oncologist, or radio-oncologist are involved in the patient's FU care.

Table 4 Type of doctor the patients receive FU care from (multiple answers possible) in the total sample, among patients with and without metastatic disease, and in patients with different educational levels

	Total	Metastases			Education			
		Without metastases $n = 436$ (%)	With metastases $n = 13$ (%)	*p*	< 10 years $n = 195$ (%)	10 years $n = 162$ (%)	> 10 years $n = 94$ (%)	*p*
Hospital where surgery was performed	101 (22%)	22	38	*0.15*	19	25	24	*0.43*
Other hospital	14 (3%)	3	0	*0.51*	3	3	4	*0.74*
Private practice gynecologist	374 (82%)	83	54	*0.007*	80	86	79	*0.19*
General practicioner	92 (20%)	20	31	*0.34*	19	20	22	*0.84*
Private practice medical oncologist	38 (8%)	8	23	*0.06*	8	7	12	*0.44*
Private practice radio-oncologist	26 (6%)	6	15	*0.13*	7	6	3	*0.39*
Other doctor	22 (5%)	5	0	*0.4*	4	5	7	*0.36*

The *p* values are based on diffrences between the reference groups using Chi^2 test

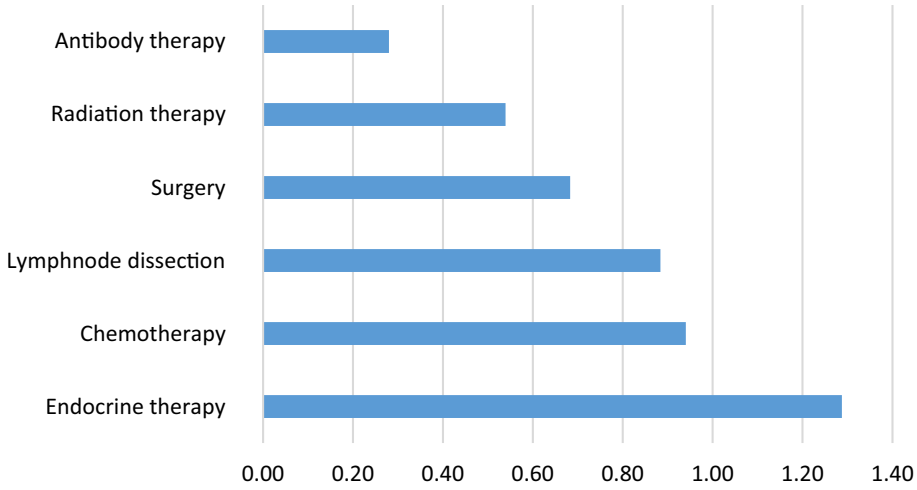

Fig. 1 Long-term problems due to treatment (0 = not at all, 3 = very much)

Table 5 (a) Treatment regret and (b) treatment regret (if treatment was recommended and patients responded)

	Radiotherapy		Chemotherapy		Endocrine therapy		Antibodies	
	N	Percent (%)	*N*	Percent (%)	*N*	Percent (%)	*N*	Percent (%)
(a)								
Not recommended by the doctor	28	6	187	41	87	19	315	69
I am happy to have done…	394	86	195	43	287	63	56	12
I regret having done…	12	3	8	2	16	4	1	0
I regret having decided against…	0	0	0	0	2	0	1	0
I am happy to have decided against…	10	2	22	5	25	5	9	2
No answer	12	3	44	10	39	9	74	16
(b)								
I am happy to have done…	394	95	195	87	287	87	56	84
I regret having done…	12	3	8	4	16	5	1	1
I regret having decided against…	0	0	0	0	2	1	1	1
I am happy to have decided against…	10	2	22	10	25	8	9	13

Thus, it would also be important that clinical cancer registries document where patients receive their FU. To ensure standardized FU, national guidelines are well established [6, 7]. Therefore, in Germany, several specialists of each sector are also members of the national guideline panels for BC. On the other hand, a considerable number of patients receive FU at their GP, which is confirmed by our data. GPs are well positioned to provide cancer care FU because of their knowledge of the personal history, social background, and comorbidities of the patients [13, 14]. BC is the most common cancer in women, and many GPs will have several BC patients in their practice who are currently undergoing treatment or were affected in the past. Furthermore, as many BC patients are elderly, FU care and the management of comorbidities is becoming increasingly essential [15]. As previous studies have demonstrated, FU care for BC patients provided by their GP is a safe and acceptable alternative to specialist FU care [16]. In our study cohort, the GP was even more involved in the patient's care if she had metastatic disease. Previous studies confirm that the GP also plays an important role in palliative care for cancer patients [17].

In addition to detecting recurrent BC, a main goal of FU is the management of treatment-related side effects and the improvement of quality of life. Thus, the prospective BRENDA study sets out to better understand BC patients' long-term problems and treatment regrets. We found that patients in the BRENDA study in general did not report a high level of long-term problems. Indeed, the risk of serious side effects in early stage BC treatment is small [18]. In the BRENDA cohort, patients' current complaints were most often related to endocrine therapy, and, for the patients who regretted having undergone a certain treatment, it was most often concerning endocrine therapy. This underlines the importance in daily clinical practice to detect current problems and to provide supportive care especially for the long treatment period of endocrine

treatment. Surprisingly, in our cohort, chemotherapy is reported only in second position regarding long-term problems or treatment regrets. This is contrary to other studies which have demonstrated that chemotherapy is often associated with decreased quality of life, both short and long term [19–21]. On the other hand, the data for this analyses were collected at t4, which is on average 5 years after surgery. Hence, the majority of the patients who had a recommendation for endocrine therapy are still undergoing this treatment because most patients start it after radiation [22] and especially because extended adjuvant endocrine treatment is nowadays standard in high-risk primary BC [23, 24]. Therefore, current problems due to endocrine therapy are more present to the patient than chemotherapy-related problems, as chemotherapy lays further back in time. Furthermore, patients participating in the BRENDA II study were younger than patients who declined. As was demonstrated in a previous study, younger age was associated with a more negative perception of endocrine treatment, presumably because side effects are more detrimental for premenopausal women [19].

After long-term problems caused by endocrine treatment and chemotherapy, patients reported long-term problems associated with surgery, especially axillary lymph node dissection. Patients who had axillary lymph node dissection have a higher rate of morbidity, mainly caused by lymphedema compared to patients with sentinel node biopsy alone [25]. Furthermore, lymphedema of the arm presents one of the most important long-term sources of distress following surgery for BC [26]. This underlines the significance of the lower radicalness in axillary surgery in recent times also from the patient's point of view [27, 28]. There were rarely long-term problems and treatment regrets concerning radiotherapy. Nowadays, due to modern radio-oncology techniques, the side effects of radiotherapy have been considerably reduced [29, 30]. This has translated into decreased fear toward radiotherapy [19] and to a basically positive perception in our study cohort.

In the BRENDA cohort, 12% of the patients received antibody therapy, in particular trastuzumab, which was the standard in Her2-positive primary BC in combination with adjuvant chemotherapy at the time [31–33]. Patients in the BRENDA cohort rarely associated long-term problems with antibody therapy, and there were almost no patients with treatment regrets toward antibody therapy. Thus, our findings underline the results of previous trials which have demonstrated a good tolerance to adjuvant trastuzumab [34, 35]. On the other hand, 13% of the patients in the BRENDA cohort indicated they were happy to have refused a recommended antibody therapy. It is very likely that patients of this group overestimated the side effects of trastuzumab.

While interpreting the results of our study, its limitations should be taken into account.

First, the extent to which patients discontinued their treatment because of side effects or long-term problems was not analyzed. Thus, we can only assume that a higher level of long-term problems might cause treatment discontinuation and accordingly guideline violation in BC treatment. Because of the short follow-up in the BRENDA II study, we cannot demonstrate outcome results, but there is retrospective evidence from the BRENDA I study demonstrating that non-adherence to guidelines is associated with worse outcome parameters [10]. Further limitations are that problems and treatment regrets were only evaluated at one time point 5 years after surgery, due to limited financial resources; whether the patients who indicated problems concerning endocrine therapy have already finished their treatment or are still undergoing endocrine treatment was also not evaluated. A longer follow-up period or an evaluation at several time points would be interesting, as the results concerning long-term problems and treatment regrets may further change over time.

In conclusion, this study shows that, in Germany, different specialist are involved in the patients' FU care for BC. This underlines the importance of national guidelines to ensure standardized treatment. The detection of long-term problems due to BC treatment is an essential part of FU care. Further studies are required to analyze the effect of long-term problems and treatment regrets on treatment discontinuation and consequently on BC outcomes.

Author contributions EL: manuscript writing. RK: funding acquisition, conceptualization. AW: funding acquisition, conceptualization, data collection. TK: data collection. FF: data collection. RF: data collection. WJ: data collection. KT: manuscript writing. SS: conceptualization, methodology, manuscript writing. LS: conceptualization, manuscript writing.

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Compliance with ethical standards

Conflict of interest Susanne Singer has received a research grant from Pfizer, the quality of life prize from Lilly, travel grants from Genzyme, and lecture fees from Astra Zeneca, Pfizer, Bristol-Myers Squibb, and Boehringer Ingelheim. The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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