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GYNECOLOGIC ONCOLOGY

Therapy of isolated locoregional recurrent carcinoma of the breast

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Abstract

Purpose There is widespread consent that isolated locoregional recurrence (ILRR) in breast cancer should be treated surgically. On searching literature and guidelines most studies include ipsilateral recurrence in breast tissue or on thoracic wall post-mastectomy, recurrence in scar tissue as well as in ipsilateral axillary lymph nodes. Some studies discuss metachronous contralateral breast cancer as ILRR. About 10–35% of women with primary breast cancer suffer from ILRR. The existing data concerning the role of systemic therapy in the treatment of ILRR are insufficient. We investigated the influence of chemotherapy on disease-free- (DFS) and overall-survival (OS).

Methods Retrospective analysis of all patients with ILRR and without distant metastasis was done, which were treated at the Department of Gynecology, Obstetrics and Reproductive Medicine, Saarland University between 2005 and 2013. Data collection used patients' database system and was followed via patient questionnaires.

Results In total, we collected data of 93 patients with locally recurrent breast cancer and observed a 72.6% questionnaire response rate. Average timeline accounted for 99 months between primary diagnosis and local recurrence; average age of patients at diagnosis of local recurrence was 60.6 years. After a median follow-up of 63 months DFS reached 76% with and 73% without chemotherapy, and after 74 months overall survival amounted to 94% and 70%, respectively.

Conclusion Almost all patients with ILRR were operated. Especially patients with hormone receptor-negative recurrent breast cancer seemed to show a benefit having been treated with chemotherapy. Most patients were without recurrence after their particular therapies.

Keywords Local recurrence · Breast cancer · Chemotherapy · Estrogen receptor

Background

Breast cancer is the most common malignant disease in women. The prevalence of breast cancer in Germany is > 71,000/year. The median 5-year-overall survival time adds up to 88% [26].

About 10–35% of women with primary breast cancer suffer from isolated locoregional recurrence (ILRR) after ending primary treatment [21]). Regarding primary therapy, 5–10% of patients after breast-conserving surgery followed by adjuvant whole breast irradiation suffer from recurrent carcinoma of the breast after 10 years, about 4% of patients suffer from local recurrence post-mastectomy [2] and 1% of patients suffer from axillary local recurrence. Differences are not observed concerning progress of disease or biological performance between local recurrence of breast cancer in glandular tissue after breast-conserving therapy or in scar tissue of the thoracic wall after mastectomy [26].

There is no exact definition of local recurrence of breast cancer. Searching literature, most studies include ipsilateral recurrence in breast tissue or on thoracic wall post-mastectomy as well as recurrence in scar tissue and in ipsilateral axillary and infraclavicular lymph nodes [18]. Some include even recurrent carcinoma of the contralateral breast tissue and in cervical lymphnodes [6]. "Early" contralateral breast carcinoma (CBC) up to a 2 years' interval is regarded as

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recurrence, whereas "late" CBC behave like second primary carcinoma. The probability of secondary CBC is in between 4% and 10%. The 5-, 10-, 15-, and 20-year rates of CBC were 7.1, 10.5, 12.8, and 14.7%, respectively [22].

Median 5-year-OS of patients with ILRR after breast-conserving surgery followed by radiotherapy and after mastectomy is 65% and 50–55%, respectively. Valid main prognostic factors are local recurrence-free interval, size of recurrent tumor, primary tumor staging and the time interval to distant metastasis. Further prognostic factors are age, nodal involvement [12], tumor grading and hormone receptor as well as her2neu status. Surprisingly the question of free margins at primary surgery seems to be of minor importance [29]. Commonly there is a differentiation made in so-called "early" and "late" recurrence of breast cancer, depending on appearance of local recurrence within or after 2 years after primary disease. These "early" locally recurrent carcinoma of the breast are linked with an adverse prognosis, as they are more likely to cause distant metastasis [14].

Following current guidelines of breast cancer the cornerstone treating ILRR is surgery and includes secondary mastectomy or repeated breast conserving surgery followed by (re-) irradiation. Mastectomy should be preferred as standard. Thoracic wall and scar as well as axillary lymph node metastases should be excised radically.

After surgery of ILRR most of the patients will be in a "post-adjuvant" situation, and the experienced relapse signalises tumor aggressiveness. But the use of systemic post-adjuvant therapy is still unclear. American patient guidelines suggest that it may be "considered" after surgery [16]. An additional endocrine therapy may be offered if indicated as it might increase disease-free survival time. An increase of overall survival by post-adjuvant endocrine therapy is yet to be proven [23].

In case of recurrent disease without prior whole or partial breast irradiation during first-line treatment, radiotherapy should be performed especially after breast conserving surgery or secondary mastectomy with risk factors. Published data suggest that a combined strategy with breast conserving surgery and adjuvant re-irradiation could be a reasonable option [10, 12]. In case of inoperable local recurrent carcinoma of the breast, radiation, chemotherapy or endocrine therapy are established therapeutic options, either individually or in combined regime [26]. Due to the experiences with neo-adjuvant therapies, systemic treatment is recommended as first choice [4]. The existing data concerning the role of systemic therapy in the treatment of locally recurrent carcinoma of the breast are insufficient and further information is needed.

Materials and methods

Based on our own patient database, we investigated the influence of different particular therapies, especially the role of chemotherapy, on disease-free survival and overall survival. To meet the equivocal definitions in literature we defined ILRR as ipsilateral recurrence in breast tissue, thoracic wall and lymphatic drainage region as well as recurrence in contralateral breast tissue.

This study has a retrospective design und included an analysis of all women with locally recurrent carcinoma of the breast between 2005/01/01 and 2013/09/30, which were treated in our Department of Gynecology, Obstetrics and Reproductive Medicine at the Saarland University Medical School. Patients with co-existent distant metastasis were excluded. The data were collected via the hospital's electronic patient data base system (SAP) and a specially designed patient questionnaire, which was sent by post to all of our patients.

Following data were collected concerning primary and recurrent breast tumor, respectively:

- time of primary diagnosis and time of recurrence
- patient's age at diagnosis
- TNM-status of the primary tumor
- hormone receptor status/her2neu status of primary and recurrent tumor
- therapeutic strategies: operation, chemotherapy, radiation therapy, and her2-therapy

In addition, patients were contacted by phone and—after ensuring their consent—requested to answer a specially designed questionnaire. Besides the questionnaire the patients also received a letter with a declaration of consent, contact details of our department and a return-to-sender envelope.

Following data were collected via questionnaire:

- regular preventive and aftertreatment care
- diagnosis of locally recurrent breast cancer (palpation vs. mammography vs. ultrasound vs. MRI/CT-scan)
- therapeutic strategy (single vs. combined therapy, patient's compliance)
- incidence of multiple and isolated locally recurrent carcinoma of the breast
- occurence of distant metastasis

The data were collected, elaborated and analyzed for descriptive statistics via Microsoft Excel. SPSS was used for statistical comparisons and survival curves of the entire patients' data and in patients' subgroups. These subgroups were selected with regard to individual therapies (applied

vs. not applied): chemotherapy in general, chemotherapy in estrogen receptor-negative ILRR and radiation therapy. Points of interest were disease-free survival DFS) and overall survival (OS), displayed in Kaplan–Meier survivorship curves. Statistical significance was tested with Log rank (Mantel–Cox) Chi square and p value. A p value of < 0.05 was statistically significant.

Results

In total, data of $n = 93$ female patients with local recurrence of carcinoma of the breast were included. The questionnaire response rate was 72.6%. The average age of patients at time of primary diagnosis with local breast cancer was 54.5 years, the median age of patients at time of diagnosis with local recurrence was 60.6 years.

There was an average timeline of 73.7 months between primary diagnosis and local recurrence. Median follow-up was 37 months. At the time of latest follow-up, $n = 68$ (73.1%) of patients were alive, $n = 9$ (9.7%) died, $n = 11$ (11.8%) suffered from progressive disease and in $n = 13$ (14%) no information was found.

Diagnosis of locally recurrent breast cancer was found clinically in $n = 24$ (25.9%) patients, in $n = 21$ (22.6%) by mammography, in $n = 10$ (10.8%) by ultrasound, in $n = 4$ (4.5%) by MRI and in $n = 2$ (2.2%) patients by CT-scan. In $n = 32$ (34.4%) patients, information was missing.

A comparison between primary breast cancer and locally recurrent breast cancer was made regarding TNM stage, grading, hormone-receptor and her2neu status (see Table 1). Unfortunately a classification regarding molecular subtypes showed little satisfactory results. Most of the patients had their primary breast cancer diagnosis before 2003, the time when the her2neu-test was included in the pathological routine program. Her2neu data were not available (NA) in 64 cases (68.8%). The smaller part of our cohort ($n = 29$) showed 19 Luminal A, 4 Luminal B, one her2neu and 5 triple-negative (basal-like) subtypes. A re-classification of the corresponding ILRR-tumours revealed 21 NA-cases (22.6%). 72 patients with complete analysis of prognostic factors showed 41 Luminal A (56.9%), 8 Luminal B (11.1%), 7 her2neu (9.7%) and 16 triple-negative (basal-like, 22.2%) subtypes.

In addition we matched the event of locally recurrent breast cancer with second relapse (see Table 2).

Potential changes in hormone receptor status were analyzed comparing primary breast cancer and locally recurrent breast cancer. In 30% of the patients no receptor switch could be found, whereas in 22% of the patients there was a switch in hormone receptor status from positive-to-negative and in 6% of patients from negative-to-positive. In the remaining 42% of the patients there were no comparable data to be evaluated.

Table 3 shows therapeutic strategies in primary breast cancer and locally recurrent breast cancer.

An operation was performed on $n = 88$ (94.6%) primary and on $n = 90$ (96.8%) secondary occasions, respectively. Chemotherapy was applied in $n = 42$ (45.2%) primary cases and in $n = 38$ (40.9%) ILRR, endocrine therapy was used in $n = 43$ (46.2%) and $n = 54$ (58.1%), and radiation therapy was performed in $n = 50$ (53.8%) primary and $n = 40$ (43.0%) secondary indications, respectively. During follow-up we found five patients with a second lLRR, two others with local recurrence and synchronous distant metastasis and further five with distant metastasis but no local relapse. The relation of second recurrences and/or distant metastasis and the particular therapies is given in Table 3.

Altogether 12 out of 93 patients suffered from further relapse of breast cancer. We observed no significant switch with regard to hormone receptors. There was only one out of 27 patients (3.7%) treated with breast-conserving operation and adjuvant radiotherapy at initial diagnosis and the same treatment at ILRR who experienced a second recurrence of breast cancer. Four second local recurrences were documented in 52 patients after mastectomy for ILRR and/or without radiotherapy (7.7%).

As mentioned before, the leading question of this study was to evaluate the role of systemic therapy in the treatment of locally recurrent carcinoma of the breast. Chemotherapy was applied in $n = 38$ (40.9%) of the patients, whereas $n = 55$ (59.1%) of the patients did not receive chemotherapy. The oncologic course of disease concerning disease-free and overall survival in dependence of chemotherapy is presented in Fig. 1a, b.

After 63 months of follow-up (FU), disease-free survival (DFS) of patients with or without chemotherapy is 76% and 73%, respectively ($p = 0.772$). Overall survival (OS) amounts to 94% and 70% after 74 months FU with or without chemotherapy, respectively ($p = 0.748$).

Furthermore the patient population was subanalyzed with regard to the role of chemotherapy applied in estrogen receptor-negative or estrogen receptor-positive recurrent carcinoma (see Fig. 2a–d).

A total number of $n = 34$ patients showed estrogen receptor-negative recurrent carcinoma of the breast. 18 patients were treated with chemotherapy, 16 patients were not. After 73 months FU, DFS reached 83% with and 86% without chemotherapy ($p = 0.473$), and OS was 100% and 62% after 63 months, respectively ($p = 0.160$).

A total number of $n = 53$ patients showed estrogen receptor-positive recurrent carcinoma of the breast. 18 patients were treated with chemotherapy, 35 patients were not. DFS was 80% and 66% after 69 months FU ($p = 0.651$). After

Table 1 Comparison between primary breast cancer (initial disease) and locally recurrent breast cancer (ILRR)

	Number (*n*) of initial disease	Percentage (%) initial disease	Number (*n*) of ILRR	Percentage (%) ILRR
In total	93	100	93	100
Tumor stage				
Tis	8	8.6	19	20.4
T1	33	35.5	42	45.2
T2	23	24.7	17	18.3
T3	1	1.1	0	0
T4	1	1.1	4	4.3
Unavailable	25	26.9	11	11.8
Phyllodes tumor	2	2.1		
Lymph node status				
N0	43	46.2	41	44.1
N1	13	14	9	9.7
N2	2	2.1	2	2.2
N3	1	1.1	1	1.1
Unavailable	34	36.6	40	43.0
Metastasis				
M0	93	100	93	100
M1	0	0	0	0
Grading				
G1	3	3.2	0	0
G2	37	39.8	44	47.3
G3	14	15.1	23	24.7
Unavailable	39	41.9	26	28.0
ER				
Positive	40	43.0	53	57.0
Negative	16	17.2	34	36.6
Unavailable	37	39.8	6	6.5
PR				
Positive	38	40.9	46	49.5
Negative	18	19.4	41	44.1
Unavailable	37	39.8	6	6.5
Her2				
Positive	5	5.1	15	16.1
Negative	24	25.8	57	61.3
Unavailable	64	68.8	21	22.6
Average of Ki 67		25.7% (known of 6 patients)		2.4% (known of 57 patients)
Average age at diagnosis	52.1 years		60.6 years	
Average time between initial disease and ILRR	99 months			

76 months FU, OS of all patients with or without chemotherapy was 92% and 75%, respectively ($p = 0.402$).

An analysis of patients, who received chemotherapy alone ($n = 19$), endocrine therapy alone ($n = 35$), or a combination of chemo- and endocrine therapy ($n = 18$) did not render statistically significant differences either regarding disease-free or overall survival.

Another point of interest was the effect of radiation therapy. A total number of $n = 40$ patients received post-operative radiation therapy, $n = 53$ patients did not. DFS after

Table 2 Comparison between primary breast cancer, locally recurrent breast cancer and further relapse ($n=12$)

Number (n)	12		
Average age at initial disease	48.9 years	Average age at ILRR	58.4 years
Time from initial disease to ILRR	115 months	Time from ILLR to further relapse; known of 10 patients	28 months
Tumor stage at initial disease		Tumor stage at ILRR	
Tis	0	Tis	1
T1	3	T1	4
T2	4	T2	1
T3	1	T3	0
T4	0	T4	1
Unavailable	3	Unavailable	5
Phyllodes tumor	1		
Lymph node status initial disease		Lymph node status ILRR	
N0	4	N0	4
N1	2	N1	1
N2	0	N2	0
N3	1	N3	1
Unavailable	5	Unavailable	6
Metastasis of initial disease		Metastasis of ILRR	
M0	12	M0	12
M1	0	M1	0
Grading of initial disease		Grading of ILRR	
G1	1	G1	0
G2	3	G2	3
G3	1	G3	3
Unavailable	7	Unavailable	6
ER of initial disease		ER of ILRR	
Positive	6	Positive	7
Negative	0	Negative	2
Unavailable	6	Unavailable	3
PR status of initial disease		PR of ILRR	
Positive	6	Positive	6
Negative	0	Negative	3
Unavailable	6	Unavailable	3
Her2 status of initial disease		Her2 status of ILRR	
Positive	2	Positive	3
Negative	3	Negative	5
Unavailable	7	Unavailable	4
		Average Ki67 of ILRR, known of 6 patients	19%

63 months FU was 77% and 70%, respectively ($p=0.493$), and overall survival was 83 and 58% after 99 months FU ($p=0.379$) (see Fig. 3a, b).

Discussion

This single-center study was accomplished by retrospective data analysis, including patient questionnaires. The affinity and compliance of our patients are reflected by the high response rate of returned questionnaires (72.6%).

Retrospectively designed studies are associated with well-known disadvantages, e.g., loss of data due to insufficient documentation. Data acquisition via questionnaires is also known to be limited by, e.g., (non-) response-bias or misreading/misinterpretation by patients. Nevertheless this study possesses a representative patient population with full access to histopathological findings. As all patients were treated in the Department of Gynecology, Saarland University Medical School in a certified center for breast diseases, each patient has been thoroughly discussed by the same interdisciplinary tumor conference, and therapeutic decisions are driven by the actual guidelines. Patients were

Table 3 Therapeutic strategies at first diagnosis, after isolated locoregional recurrence (ILRR; $n=93$) and outcome: second ILRR and/or distant metastasis ($n=5+2+5=12$)

	First diagnosis	ILRR	Second ILRR	ILRR + metastasis	Metastasis
Operation					
None	5	3			1
Breast conserving	71	27	1		
Mastectomy	17	52	3	1	3
Lymphnode		5			1
Chest wall		5	1	1	
Not available		1			
Chemotherapy					
No	51	55	4	1	3
Yes	42	38	1	1	2
Radiotherapy					
No	43	53	3	2	2
Yes	50	40	2		3
Endocrine therapy					
No	50	39	2	1	3
Yes	43	54	3	1	2

enrolled into this study chronologically, representing the spectrum of daily routine at a university hospital center.

Local recurrence was defined as an ipsilateral or contralateral recurrence in breast tissue or thoracic wall as well as involvement of ipsilateral locoregional lymphatic drainage regions [22]. This has to be taken in account when comparing and discussing the data presented here with literature data [18].

Our patient population should be regarded as representative as we observed similar histopathological findings and patient data compared to already published literature. The average age of our patients at diagnosis of locally recurrent breast cancer was 60.5 years. Insa et al. as well as Gräßer describe a median age of 58 years and 58.5 years, respectively, of their patient populations at time of diagnosis with local recurrence of breast cancer [8, 11]. An even younger patient population with a median age of 56 years at diagnosis is characterized in the CALOR trial [1]. Not only the median age of our patients, but also the histopathological details line up with already existing data. Similar to our study, Gräßer and Bayerl et al. report the pTNM status of their patients to be at T1 or T2/N0 stage in most cases. Likewise to our study, histopathological grading was mainly G2 [2, 8].

About 10–35% of women with primary local breast cancer suffer from ILRR after ending primary therapy [21] and they are at high risk of facing distant metastasis and death [5]. Therefore, choosing an optimal therapeutic strategy is highly important.

Appropriate surgery is the first and major step of ILRR treatment. Guidelines recommend histological proof by core- or punch biopsy of the lesion before surgery, and the prognostic factors grading, hormone receptors, her2neu-antigen and ki 67 should be examined [19]. The lesion should be removed with clear margins. After breast conserving therapy, secondary mastectomy is the method of choice [4]. Repeated breast conserving surgery is an option if desired by the patient. Combined with a second radiotherapy we experienced only one second ILRR (see below).

Regardless of the operative strategies, patients with ILRR might benefit from an additional adjuvant local radiotherapy treatment, despite prior irradiation, especially in case of breast conserving surgery. Recent publication shows feasible and safe results regarding toxicity for reirradiation after secondary breast recurrence [9, 12].

A second breast conserving therapy needs meticulous pre-operative imaging, discussion of the prognostic factors and consideration about repeated adjuvant radiotherapeutic treatment approaches. Several strategies are reported like secondary fractionated external beam whole breast [12], intraoperative or accelerated partial breast irradiation by intrabeam [13], interstitial multicatheter brachytherapy or external beam partial breast irradiation [9, 17]. Secondary radiation strategy should be planned with respect of the particular individual situation before or during ILRR surgery.

In this study it has been possible to add irradiation in 40 patients (43.0%). 77% of these patients are free of recurrence after a 5-year interval, whereas patients without irradiation in case of recurrent breast cancer show a recurrence-free rate of 70%. Though these results are not significant we observed that patients with a second breast conserving surgery combined with repeated radiotherapy own the smallest risk of second local recurrence ($1/27=3.7\%$, see Table 3). Furthermore the application of radiotherapy halved the amount of second ILRR (2/40 with vs. 5/53 without radiotherapy). No doubt that the majority of ILRR patients have a history of breast, thoracic

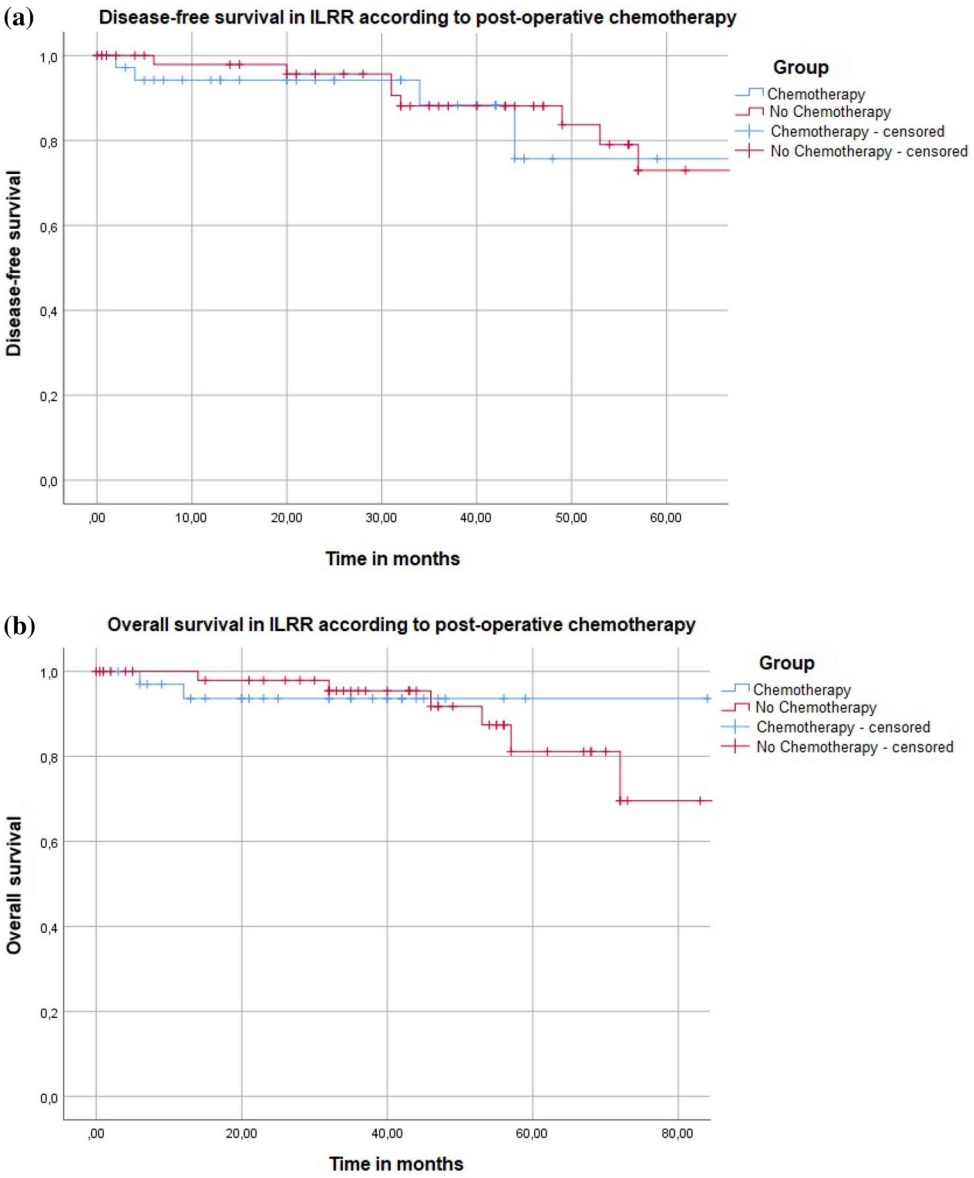

Fig. 1 **a** Disease-free survival in ILRR according to post-operative chemotherapy; chemotherapy yes $n=38$ (events $n=4$), chemotherapy no $n=55$ (events $n=8$), log rank (Mantel–Cox) Chi square = 0.084; $p=0.772$. **b** Overall survival in ILRR according to post-operative chemotherapy. Chemotherapy yes $n=38$ (events $n=2$), chemotherapy no $n=55$ (events $n=6$), log rank (Mantel–Cox) Chi square = 0.103; $p=0.748$

wall and/or axillary lymph node irradiation, and appraisal of possible side effects will hamper a second irradiation attempt.

All the more there is a need for systemic therapy strategies whether endocrinological, chemotherapeutical, targeted anti-her2 or anti-neoangiogenetic. Upcoming strategies like cyclin-kinase inhibitors (anti CDK4/CDK6) should be incorporated [4].

Up to now there are rather poor results of placebo-controlled endocrine therapy studies [23] showing significant improvement in disease-free survival (DFS) with tamoxifen, which did not translate into prolonged overall survival (OAS). Studies with the aromatase inhibitor exemestan [7] do not focus on ILRR or report a second-line setting [28]. Other endocrine studies are not placebo-controlled, anticipating that to do something is better than nothing.

In our study all 53 patients with positive ER- or PR-status had an endocrine treatment.

Analyzing our findings concerning a potential switch of hormone receptor status in primary and recurrent tumor cells we observed a higher shift rate in progesterone receptors than in estrogen receptors (27% vs. 16% of patients). In their study Mavrova et al. investigated the hormone receptor status of locally recurrent breast cancer compared to the status at primary diagnosis. They reported comparable results, as the switch in progesterone receptors was significantly higher than in estrogen receptors (34% vs. 23.5%). Yang et al. and Bogina et al. described similar observations, even more prominent when comparing receptor status of distant metastasis [3, 15, 27]. Yang et al. suggested a poorer prognosis when a switch in estrogen receptor occurs. Mavrova et al. found no correlation between the different therapeutic

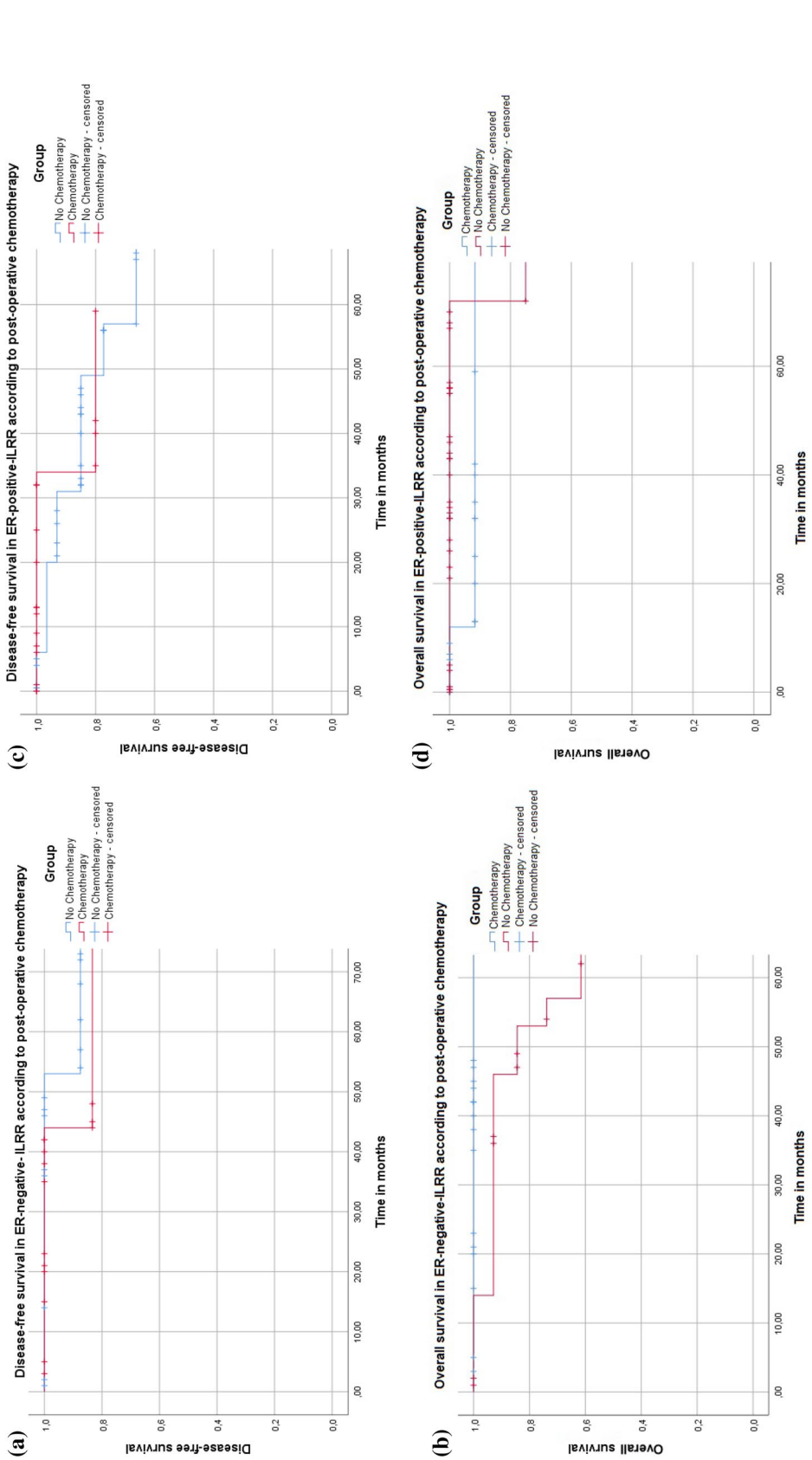

Fig. 2 **a** Disease-free survival in ER-negative-ILRR according to post-operative chemotherapy; chemotherapy yes $n = 18$ (events $n = 1$), chemotherapy no $n = 16$ (events $n = 1$), log rank (Mantel–Cox) Chi square = 0.515; $p = 0.473$. **b** Overall survival in ER-negative-ILRR according to post-operative chemotherapy; chemotherapy yes $n = 18$ (events $n = 0$), chemotherapy no $n = 16$ (events $n = 4$), Log rank (Mantel–Cox) Chi square = 1.973; $p = 0.160$. **c** Disease-free survival in ER-positive-ILRR according to post-operative chemotherapy; chemotherapy yes $n = 18$ (events $n = 1$), chemotherapy no $n = 35$ (events $n = 6$), log rank (Mantel–Cox) Chi square = 0.205; $p = 0.651$. **d** Overall survival in ER-positive-ILRR according to post-operative chemotherapy; chemotherapy yes $n = 18$ (events $n = 1$), chemotherapy no $n = 35$ (events $n = 1$), Log rank (Mantel–Cox) Chi square = 0.701; $p = 0.402$

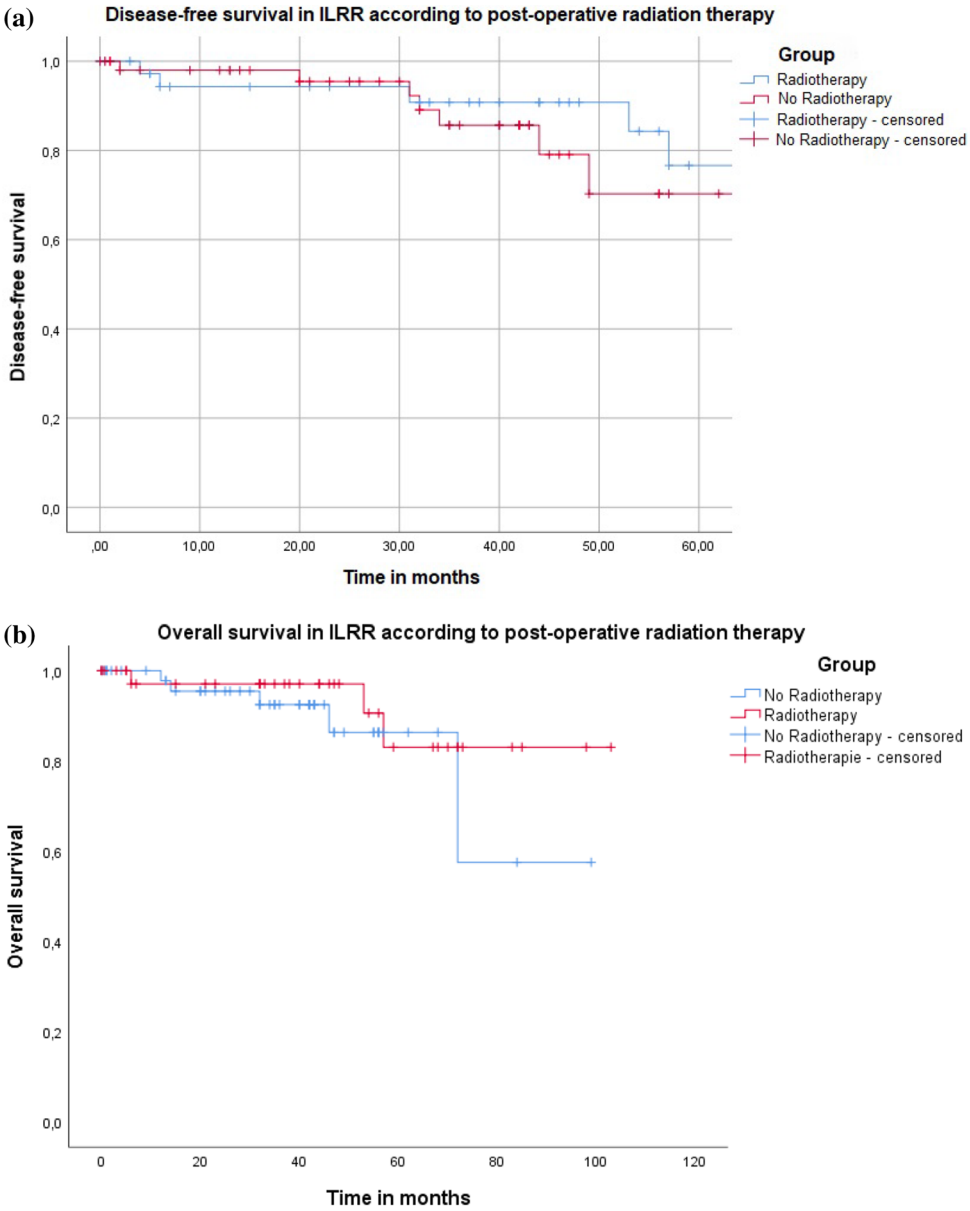

Fig. 3 **a** Disease-free survival in ILRR according to post-operative radiation therapy; radiation yes $n=40$ (events $n=5$), radiation no $n=53$ (events $n=7$), log rank (Mantel–Cox) Chi square = 0.470; $p=0.493$. **b** Overall survival in ILRR according to post-operative radiation therapy; radiation yes $n=40$ (events $n=3$), radiation no $n=53$ (events $n=5$), log rank (Mantel–Cox) Chi square = 0.773; $p=0.379$

pathways and the incidence of hormone receptor switch. What is to cause these shifts in hormone receptors is still topic of ongoing research. Side effects of therapies, co-existing heterogeneity in tumor cells as well as inconsistent assay methods might be possible explanations [20].

Regarding the effects of chemotherapy in ILRR treatment, the CALOR (= Chemotherapy as Adjuvant for LOcally Recurrent breast cancer) -study was published 2014 after intermediate analysis [1]. CALOR was planned as a prospective randomised multi-centered trial to determine whether chemotherapy improves the outcome of the patients. Differing to our patient population, only ipsilateral relapse of breast cancer was defined as ILRR. Patients with distant metastasis were excluded as well. During an accrual time of 78 months 162 patients with ILRR were included into the CALOR trial, with 58 ER-negative and 104 ER-positive ILRRs. ER-positive patients received endocrine treatment following doctor's discretion. Her2-positive patients had optional trastuzumab therapy; some patients with insufficient resection margins had post-operative radiotherapy. 85 patients were allocated to chemotherapy and 77 patients were not. Primary endpoint was disease-free survival.

The median time interval between primary diagnosis and local recurrence in our study is 99 months. The CALOR trial reported a recurrence-free interval of 5–6.2 years, which is considerably lower than in our study. With a median age of 56 years, patients in the CALOR trial were a little bit younger compared to our study when diagnosed with locally recurrent breast cancer. There was a notable switch in hormone receptor status as well: 15%

in estrogen receptors and 26% in progesterone receptors, both very similar values compared to our study.

Meanwhile CALOR has been published with final results [25]. Analysis in respect of receptor status after observation of 27 recurrences in ER- and 40 events in ER + -patients was calculated to a disease-free hazard ratio of HR 0.29 (95% CI 0.13–0.67; 10-year DFS, 70% vs 34%, CT vs no CT, respectively) in ER-negative patients.

In ER-positive patients the corresponding data were reported HR 1.07 (95% CI 0.57–2.00; 10-year DFS, 50% vs. 59%, respectively). So chemotherapy has been effective in regard of DFS in the receptor-negative group, but not in the receptor-positive patients. Prolonged DFS did not translate into prolonged OS.

A comparison of the CALOR results with our study should only be drawn very carefully. We conducted a retrospective analysis of data collected over almost 13 years, double as long as the recruiting time of CALOR. Distribution of the patients' receptor-status (ER-negative 39%, ER-positive 61%) equals the CALOR-study. Relapse-free time was longer and the average age at ILRR was higher compared to CALOR, which may be caused by a less-aggressive tumor biology. After 6 years observation time we experienced only 12 events of relapse (12.9%) compared to 67/162 (41.4%) events within 9 years in the CALOR-study. Eight of our patients died (8.6%), 26 (16%) in the CALOR-study [24].

These low relapse and death figures make it understandable that none of the Kaplan–Meier diagram curves in our study cross the 50%-line and none of them show significant differences between the study samples, respectively. This underlines that an even longer follow-up time is needed to observe statistically relevant differences.

Nevertheless we realized that the amount of relapses and deaths is halved by chemotherapy of ILRR (four second ILRR and two deaths with and eight second ILRR/four deaths without chemotherapy). Apparently similar to the CALOR-study, we were able to observe an effect of chemotherapy especially in the ER-negative group.

The observations of the CALOR-study and in our sample support the demand of a prospectively designed study with fixed chemotherapy in this subgroup, bigger sample size and longer observation time. Our actual knowledge of the effect of anti-her2-therapy in the primary or adjuvant situation and of bevacizumab in adjuvant and palliative indications suggest the use of these options in combination with chemotherapy and compared to chemotherapy alone.

Being aware of the poor evidence of endocrine treatment in ER-positive ILRR a concise study design of endocrine therapy alternatives (tamoxifen vs. aromatase inhibitors supplemented with anti-resorptive therapy like denosumab) is warranted. As long as the effect of an endocrine therapy has not been proven, addition of anti-her2- or antineoangiogenetic therapies as well as checkpoint-blockers does not seem meaningful.

Conclusion

When patients suffer from a relapse of breast cancer, individual counseling and shared decision-making are most important. Obviously surgical complete removal is the basic therapy. As most of the patients have a radiotherapeutic history, this therapeutic tool will be matter of individual decision. It has been possible to add radiation therapy to nearly half of our patients, and in those a 77% DFS rate was observed after 5 years. Actually the concept of accelerated partial breast irradiation in ILRR after breast conserving surgery and previous breast irradiation is under investigation and seems to be promising.

Almost reflexively patients with positive hormone-receptor status will receive endocrine treatment as part of the ILRR treatment concept, though the evidence out of clinical studies is lacking. Future endocrine treatment protocols are mandatory, perhaps in the future including innovative targeted and immunological concepts.

There is some evidence that patients should be offered systemic therapy based on biological prognostic factors like in the primary breast cancer situation. In our study we observed a statistically not significant advantage for ER-negative patients by adding chemotherapy. Comparing these results to analogous findings of the CALOR trial, we consent that chemotherapy should be recommended, especially to patients with locally recurrent estrogen receptor-negative breast cancer.

To provide more information for an optimized therapy strategy, the goal should be a novel multi-center study of systemic therapy options in ILRR of breast cancer after complete surgical resection. This study should include endocrine and chemotherapeutic approaches in combination with modern targeted and immunological therapies.

Author contributions LG: data analysis, manuscript writing. MS: data collection and analysis, manuscript writing. SJ-B: protocol development and data collection. PM: radiotherapeutic protocol development, data analysis, manuscript review. AvH: surgical data collection. G Schmidt: surgical data collection. NK: systemic therapy data collection and analysis. EFS: manuscript editing. IJ-B: project development, data analysis, manuscript review and editing. GPB: data analysis, manuscript writing, review and editing.

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Compliance with ethical standards

Conflict of interest Authors Lena Gabriel, Marina Schmidt, Stephanie Juhasz-Böss, Patrick Melchior, Anika von Heesen, Gilda Schmidt,

Nicole Kranzhöfer, Erich-Franz Solomayer, Ingolf Juhasz-Böss and Georg-Peter Breitbach declare that he/she has no conflict of interest.

Ethical approval All procedures performed in the study 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. This article does not contain any studies with animals performed by any of the authors.

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

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