Concurrent Radiotherapy and Taxane Chemotherapy in Patients with Locoregional Recurrence of Breast Cancer

A Retrospective Analysis

Sabine Semrau[1], Bernd Gerber[2], Toralf Reimer[2], Gunther Klautke[1], Rainer Fietkau[1]

Background and Purpose: Locoregional breast cancer recurrence is characterized by a high rate of systemic and local re-recurrence. Data on concurrent radiochemotherapy (RCT) in these cases are scarce. The purpose of this study was to evaluate feasibility, toxicity and efficacy of local control of a radiotherapy combined with a chemotherapy containing a taxane.
Patients and Methods: Between May 1999 and November 2004, 36 women referred to the authors' clinic because of locoregional breast cancer recurrence that was either inoperable (n = 29) or resected (n = 7) received concurrent irradiation and taxane monotherapy weekly (TAX/RT; n = 28: paclitaxel 90 mg/m^2, n = 24, or docetaxel 35 mg/m^2, n = 4) or taxane + cisplatin therapy (TAX/CIS/RT; n = 8; paclitaxel 135 mg/m^2 d1 and cisplatin 20 mg/m^2 d1–5 q28).
Results: Comparing TAX/RT with TAX/CIS/RT, the complete remission rate in patients with macroscopic tumor prior to RCT was significantly higher for TAX/RT than for TAX/CIS/RT (7/19 vs. 0/8; p = 0.046), but overall remission rates were comparable, i.e., partial remission: 11/20 versus 6/8 cases, stable disease (no change): 1/20 versus 2/8 cases, and response rate: 95% versus 75%, respectively. The cumulative local recurrence-free survival rate at 1 and 2 years post-treatment was 83% and 68% and that of systemic recurrence-free survival 56% and 29%, respectively. The main toxic reactions of third-degree and higher were dermatitis in TAX/RT (57% vs. 11% for TAX/CIS/RT) and leukocytopenia in TAX/CIS/RT (62% vs. 7% for TAX/RT).
Conclusion: Concurrent irradiation and taxane chemotherapy weekly, in particular with paclitaxel, is recommended due to response and acceptable side effects for treatment of inoperable locoregional breast cancer recurrence.

Key Words: Locoregional recurrent breast cancer · Radiochemotherapy · Taxane · Cisplatin

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Simultane Radiochemotherapie mit einem Taxan bei Patientinnen mit lokoregionär rezidivierendem Mammakarzinom. Eine retrospektive Analyse

Hintergrund und Ziel: Lokoregionäre Mammakarzinomrezidive sind durch eine hohe systemische und lokale Rezidivneigung gekennzeichnet. Daten zur simultanen Radiochemotherapie liegen kaum vor. Ziel der Studie ist es, die Durchführbarkeit, Toxizität und Wirksamkeit bezüglich lokaler Kontrolle durch eine Radiotherapie in Kombination mit einer taxanhaltigen Chemotherapie zu untersuchen.
Patienten und Methodik: Zwischen Mai 1999 und November 2004 wurden 36 Frauen mit inoperablem lokoregionärem Rezidiv (n = 29) oder nach Resektion (n = 7) an der Klinik der Autoren mit einer simultanen Bestrahlung und taxanhaltigen wöchentlichen Monotherapie (TAX/RT; n = 28: Paclitaxel 90 mg/m^2, n = 24, oder Docetaxel 35 mg/m^2, n = 4) oder einem Taxan + Cisplatin (TAX/CIS/RT, n = 8; Paclitaxel 135 mg/m^2 d1, Cisplatin 20 mg/m^2 d1–5 q28) behandelt.
Ergebnisse: Bei inoperablen Tumoren lag nach TAX/RT die Rate kompletter Remissionen signifikant höher als nach TAX/CIS/RT (7/20 vs. 0/8; p = 0,046). Die übrigen Remissionsraten waren vergleichbar, d.h. partielle Remissionen 11/20 versus 6/8 Patientinnen, unveränderter Tumor: 1/20 versus 2/8 Patientinnen, entsprechend einer Responserate von 95% versus 75%. Das kumulative lokalrezidivfreie Überleben nach 1 und 2 Jahren betrug 83% und 68%, die 1- und 2-Jahres-Rate des systemisch progressionsfreien Überlebens 56% und 29%. Die dominant auftretende Nebenwirkung Grad 3 und 4 war die Dermatitis bei TAX/RT (57% vs. 11% bei TAX/CIS/RT) und die Leukozytopenie bei TAX/CIS/RT (62% vs. 7% bei TAX/RT).
Schlussfolgerung: Bei inoperablem lokoregionärem Mammakarzinomrezidiv wird eine Radiotherapie in Kombination mit einer wöchentlichen taxanhaltigen Chemotherapie, insbesondere mit Paclitaxel, aufgrund des Tumoransprechens und der akzeptablen Nebenwirkungen empfohlen.

Schlüsselwörter: Lokoregionäres Mammakarzinomrezidiv · Radiochemotherapie · Taxan · Cisplatin

[1] Department of Radiotherapy, University of Rostock, Germany,
[2] Department of Gynecology and Obstetrics, University of Rostock, Südstadt Hospital – Rostock, Germany.

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Introduction

The treatment of inoperable local recurrences of breast cancer with the aim of achieving local tumor control is a demanding and variegated task. The use of a multimodal strategy is prudent in almost all cases. Readily visible and palpable growths are perceived as stigmatizing. Hence, the removal of such tumors not only helps to improve the patient's emotional well-being, but also serves to prevent systemic tumor spread in patients without distant metastases. Retrospective studies show that overall survival is better in cases with local control [7, 15, 32]. This means that even women with local recurrence have a chance of cure.

Treatment of locoregional breast cancer recurrence should generally include surgery, whenever microscopically complete tumor resection can be achieved [6, 20]. Radiation therapy is indicated, if the tumor is inoperable.

Systemic cytostatic therapy supplementary to local treatment is sound practice for several reasons. First of all, one can assume that micrometastasis is more frequent after recurrence than after primary tumor occurrence, since roughly 50% of all women with isolated locoregional recurrence of breast cancer develop distant metastases [12, 13, 27]. Second, the therapeutic radiation reserve of the normal tissue may be reduced due to prior radiotherapy in some individuals, and the dose normally administered for tumor control (60–70 Gy) may be inadequate because of the tumor size in others. Concurrent radiochemotherapy (RCT) can be an attractive option in such cases. However, the scarcity of data on the potential side effects and therapeutic benefits of systemically effective doses of the cytostatic agents used in concurrent RCT is perceived as an obstacle to the implementation of such treatment.

In recent years, certain drugs, in particular taxanes, were shown to be potent cytostatic agents for systemic treatment of breast cancer [1, 23, 29] as well as radiosensitizers for treatment of other tumor entities [8, 18, 19, 31]. We have compiled the largest amount of data ever published regarding toxicity and efficacy with high-dose radiotherapy plus chemotherapy with a taxane alone (paclitaxel or docetaxel; TAX/RT) or in combination with cisplatin (paclitaxel plus cisplatin; TAX/CIS/RT) in recurrent breast cancer.

Patients and Methods

From May 1999 to November 2004, 36 women referred to the Department of Radiotherapy of the University of Rostock, Germany, received concurrent RCT as an integral part of a multimodal strategy for treatment of locoregional recurrence of breast cancer with skin metastases or lymph node metastases classified as distant metastases according to the TNM classification (e.g., cervical, contralateral supraclavic-ular, and contralateral axillary lymphomas). The closing date for inclusion in the data analysis was December 15, 2004.

The patients' median age was 52 years (range: 28–72 years). The event was a first recurrence in 26 cases, a second recurrence in nine cases, and a third recurrence in one case. The present recurrence was treated a median 39 months after first-time therapy (minimum 2 months, maximum 13 years).

At the time of concurrent RCT, 20/36 patients had tumor manifestations corresponding to distant metastases. Seven of them had cervical, contralateral supraclavicular or contralateral axillary lymph node metastases, which were targeted in radiation therapy.

In 14/36 patients (39%), the current treatment represented the repeat irradiation of a previous target volume. The median dose was 54 Gy (minimum 48 Gy, maximum 66 Gy) in patients receiving radiation therapy for the first time. Further characteristics of the patient population are shown in Table 1.

As described in Table 2, the present recurrences had been treated by various methods before the patients were referred for RCT.

Before the start of concurrent RCT, a clinically or radiologically detectable tumor recurrence was present in the target volume in 28/36 patients. In the other eight patients, radia-

Table 1. Patients characteristics for the total group, TAX/RT group, and TAX/CIS/RT group. CIS: cisplatin; RT: radiotherapy; TAX: taxane.

Tabelle 1. Patientencharakteristika der Gesamtgruppe und unterteilt nach beiden Therapieschemata TAX/RT und TAX/CIS/RT. CIS: Cisplatin; RT: Radiotherapie; TAX: Taxan.

	Total n (%)	TAX/RT n (%)	TAX/CIS/RT n (%)
Number	36	28	8
Age (range)	52 years	54 (28–72) years	50 (35–63) years
Tumor status			
Chest wall recurrence			
• Yes	20 (57)	14 (50)	6 (75)
• No	16 (43)	14 (50)	2 (25)
Regional lymph node recurrence (N)			
• Yes	17 (49)	15 (54)	2 (25)
• No	19 (51)	13 (46)	6 (75)
Distant metastases (M)			
• Total	20 (57)	17 (61)	3 (38)
• Nodal M1	7 (20)	6 (21)	1 (12)
• Not nodal M1	17 (49)	14 (50)	3 (38)
Prior adjuvant treatments			
Chemotherapy	30 (83)	25 (89)	5 (62)
Hormone therapy	23 (64)	19 (68)	4 (50)
Surgery	36 (100)	28 (100)	8 (100)
Irradiation	14 (39)	11 (39)	3 (38)

Table 2. Treatment of recurrences. CIS: cisplatin; RCT: radiochemotherapy; RT: radiotherapy; TAX: taxane.

Tabelle 2. Therapie des Rezidivs. CIS: Cisplatin; RCT: Radiochemotherapie; RT: Radiotherapie; TAX: Taxan.

	Total (n)	TAX/RT (n)	TAX/CIS/RT (n)
Resection			
Biopsy/R2 resection	21	16	5
R1 resection	1	1	0
R0 resection	6	6	0
None	8	5	3
Chemotherapy	13	11 (1× complete remission before RCT)	2
Hormone therapy	Could not be assessed due to extremely variable beginning		

tion therapy was indicated because of incomplete resection (R1) of an axillary lymph node recurrence (n = 1), after tumor excision with a narrow safety margin and/or repeat surgery (n = 5), serial recurrences (n = 1), and in case of complete remission of tumor after chemotherapy in an otherwise tumor-free patient (n = 1). Tumor spread was generally assessed by computed tomography (CT) or ultrasound of the neck and axilla, chest X-ray, abdominal ultrasound (or CT), and whole-body bone scintigraphy.

All patients consented to treatment in writing after being informed individually and in detail of the potential risks and expected benefits of concurrent RCT.

Chemotherapy

Two chemotherapy strategies were used (see Figure 1). The first, taxane monotherapy (within TAX/RT), consisted of weekly doses of either paclitaxel 90 mg/m^2 body surface area or docetaxel 35 mg/m^2, which was administered as a 1-h infusion immediately prior to irradiation. Chemotherapy, including four to seven weekly courses per patient, extended throughout the entire irradiation period. The patients generally had a 2- to 3-week treatment break between the RCT and subsequent cycles of chemotherapy. The second regimen, taxane plus cisplatin (within TAX/CIS/RT), consisted of a 1-h infusion of 120–135 mg paclitaxel/m^2 on day 1, and 20 mg cisplatin/m^2 on days 1–5 and was repeated once after 28 days. The patients were premedicated with intravenous dexamethasone (8 mg), cimetidine (200 mg) and ondansetron (8 mg) 20 min before the infusion.

Chemotherapy was generally possible as long as the patient had sufficient bone marrow function (white blood cells [WBCs] > 3,000/µl, platelets > 100,000/µl, and hemoglobin 6.0 mmol/l). Before receiving the cytostatic drugs, each patient was assessed by echocardiography and ECG; creatinine clearance (minimum: 60 ml/min) was additionally determined in patients scheduled to receive cisplatin. The intravenous fluid volume (2 l/day) should be handled by cardiac compensation mechanisms. If peripheral cytopenia developed, taxane administration was delayed for a few days and cisplatin administration was delayed for 1 week until WBCs were not < 3,000/µl or platelets not < 100,000/µl. Chemotherapy was suspended, if third-degree dermatitis (confluent areas of moist epitheliolysis on the skin, Radiation Therapy Oncology Group [RTOG] criteria) and/or third-degree dysphagia (Common Toxicity Criteria [CTC]) developed.

The specific chemotherapy regimen for a given patient was chosen with due consideration to both the dynamics of tumor progression and the expected effects of the tumor outside the target volume. High tumor mass and rapid tumor progression were important criteria for selecting the more densely dosed, weekly taxane monotherapy schedule. Taxane plus cisplatin was generally used to treat recurrences involving the chest wall or isolated (focal) lymph nodes. The drug used for taxane monotherapy was selected in agreement with the oncologic gynecologist in consideration of all prior or planned treatments. Ultimately, paclitaxel was used in 24, docetaxel in four, and paclitaxel + cisplatin in eight patients.

Radiation Therapy

The target volume and target dose were calculated according to the following criteria:

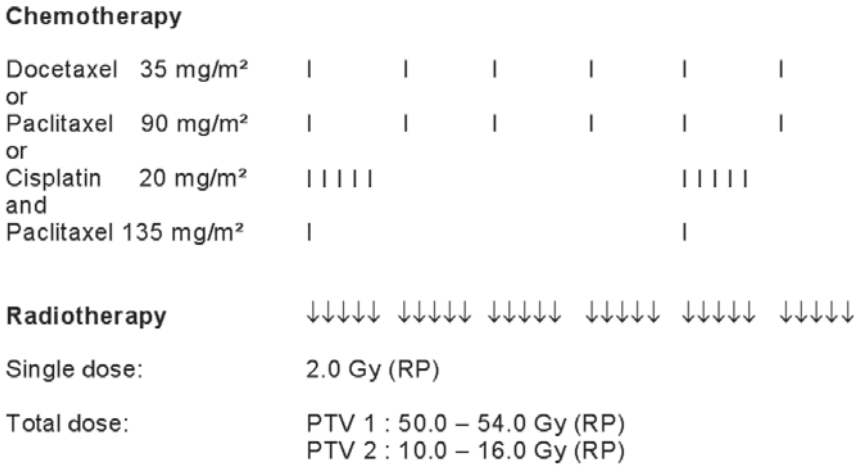


Figure 1. Treatment protocol. PTV 1/PTV 2: planning target volume 1 and 2 according to specified criteria; RP: reference point.

Abbildung 1. Behandlungsprotokoll. PTV 1/PTV 2: Planungszielvolumen 1 und 2 gemäß den formulierten Kriterien; RP: Referenzpunkt.

- Chest wall recurrence without prior radiotherapy: irradiation of chest wall (5 cm safety margin) and locoregional lymph nodes except those in the axilla.
- Recurrence limited to supra- und infraclavicular lymph nodes: irradiation of affected nodes with a safety margin of roughly 3–5 cm.
- Axillary lymph node recurrence: irradiation of axillary, supraclavicular and parasternal lymph nodes as well as chest wall.
- Lymphoma in M1 regions: irradiation of lymphoma and adjacent lymph node regions.
- All clinically visible and/or symptomatic recurrences were irradiated whenever possible.
- Dose: large-volume dose of 50–54 Gy supplemented by a booster dose of 10–16 Gy.
- In case of repeat radiotherapy, the target volume included the tumor or tumor bed plus a safety margin of roughly 3–5 cm. The maximum dose was 50 Gy; saturation with small doses of up to 10 Gy was permissible.
- Method: conventional fractionated radiation therapy.
- Radiation treatment planning: generally three-dimensional.
- If third-degree dermatitis occurred in cases where more than three dose fractions had yet to be delivered, the series of radiation treatments was temporarily interrupted and continued after the symptoms had subsided.

Classification of Side Effects and Tumor Response

The CTC were used to grade the severity of acute radiation side effects, and the severity of dermatitis was graded according to the criteria of the RTOG. Using the WHO criteria, tumor response was rated as either complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD). The success of concurrent RCT was first assessed as a response within the radiation volume, and the remission rates (CR, PR, SD) refer to this. Systemic progression during RCT and thereafter was also evaluated. Tumor response was assessed clinically upon completion of RCT in 13 patients, and 3–4 weeks after completion of RCT in 16 patients. CT and/or magnetic resonance imaging (MRI) were used in individual cases: CT conducted for boost irradiation planning in three cases, and CT/MRI scans obtained 3–4 weeks after completion of RCT in three patients. In one case there was no information available.

Statistical Analysis

The descriptive statistics, frequency distributions, survival and tumor progression data were computed as Kaplan-Meier analyses using SPSS software. The criterion for treatment failure, apart from symptomatic systemic tumor progression, was progression in the treatment field and/or field margin. The time between the start of treatment and treatment failure was measured in months. Survival time was also measured in months, beginning from the start of treatment.

Results

Feasibility of Concurrent Radiochemotherapy

Radiation Therapy

It was possible to administer the planned dose of radiation in 35/36 patients (95%). One patient died on the 10th irradiation-free day of a treatment break implemented because of third-degree dermatitis. The cause of death (intermittent atrial fibrillation) was unrelated to treatment. Radiation therapy had to be interrupted for a median 10 days (minimum 2 days, maximum 20 days) due to toxic side effects in seven cases.

The median dose in the target volume was 62 Gy (± 6 Gy) in patients without prior radiation therapy and 51 Gy (± 5 Gy) in those with prior radiation therapy.

Chemotherapy

In all, 147/166 (89%) planned taxane monotherapy cycles were actually administered. Half of the patients (50%) required a dose reduction; the dose had to be reduced to < 75% of the planned chemotherapy dose in 18% (5/28) of patients (see Table 3).

16 of 18 (88%) planned paclitaxel + cisplatin cycles were administered.

Supplementary chemotherapy, which normally consisted of two further cycles of six paclitaxel or docetaxel doses each, was carried out in 18/36 patients.

Toxicity

Local side effects in the treatment field were most prominent in patients in weekly paclitaxel or docetaxel monotherapy and radiotherapy. Third-degree dermatitis with confluent moist epitheliolysis occurred in 16/28 cases (57%), and second-degree dermatitis in three (11%). Third-degree dermatitis was noted in only one patient on paclitaxel + cisplatin + radiotherapy (12%); the worst side effect in the rest of the group was mild (first-degree) erythema. Cutaneous side effects led to third-degree infections in 6/16 women. Severe dermatitis occurred in all patients, regardless of the total radiation dose or field size. Marked dermatitis developed toward the end of concurrent RCT (4th–5th week of treatment) in most cases, but only after completion of therapy in others.

Table 3. Feasibility of chemotherapy. Percentage of patients in the different dose levels of the taxane monotherapy group on paclitaxel or docetaxel (n = 28).

Tabelle 3. Durchführbarkeit der Chemotherapie. Anteil der Patientinnen in verschiedenen Dosisstufen der Monotherapie mit Paclitaxel oder Docetaxel (n = 28).

Chemotherapy dose density (%)	Patients (n)	Percentage
< 75	5	18
75–95	9	32
95–100	14	50

Mucositis with dysphagia occurred more frequently in the TAX/RT group (21%; second- and third-degree in three cases each) than in the TAX/CIS/RT group (12%; third-degree in one case). One of the 36 patients (3%) developed third-degree pneumonitis.

Hematotoxic side effects only occurred in the TAX/CIS/RT group, where third-degree leukocytopenia was observed in 5/8 patients, and third-degree thrombocytopenia in 1/8. TAX/RT led to third- (1/28 patients) and fourth-degree leukocytopenia (1/28 patients), but not to more severe thrombocytopenia. Higher-grade anemia did not occur.

Data on 18 patients were available for assessment of chronic treatment sequelae: 7/18 developed chronic lymphedema in the arm region, and the axillary lymph drainage area had been irradiated in each of these cases. Radiodermatosis (ranging from pigmentation disorders to fibrosis) occurred in 4/18 patients. 10/18 women did not develop any major cosmetic problems related to treatment.

Deaths causally related to treatment did not occur. However, one patient developed unilateral jugular/subclavian vein thrombosis in the former treatment field and died of pulmonary embolism 11 months after completion of therapy. In this case, the causal relationship was unclear.

Tumor Response

We were able to assess tumor response in 27/28 patients with macroscopic tumors immediately after completion of RCT. The TAX/RT and TAX/CIS/RT groups differed significantly with respect to the frequency of CR ($p = 0.046$). The response rate in the TAX/RT group was 95% compared to 75% for TAX/CIS/RT (Table 4). In eight patients without macroscopically detectable tumors prior to RCT (R0, R1, CR after induction chemotherapy), the treatment field remained tumor-free for at least 6 months after TAX/RT.

Analysis of Recurrence and Survival

Local Control (in the Treatment Field)

By a median 25 months of follow-up, 8/35 patients (23%) had developed recurrences in the treatment field or field margins (median time to new recurrence: 24 months). As calculated by Kaplan-Meier analysis, the cumulative local recurrence-free survival rate was 83% (± 7%) 1 year and 68% (± 10%) 2 years after treatment (see Figure 2a). All eight patients affected also had a new occurrence or progression of distant metastases (prior to local recurrence in 1/8 cases, at the time the local recurrence was diagnosed in 4/8 cases, and thereafter in 3/8 cases).

Distant Control

Progression or a first occurrence of distant metastases during follow-up occurred in 13/36 (36%) of the women treated. The median time to progression and/or a new occurrence of distant metastases was 14 months (95% confidence interval [95% CI]: 10–18 months; see Figure 2b). The percentage (± standard deviation) of women without progression of distant metastases was 73% (± 7%) at 6 months, 56% (± 9%) at 1 year, 29% (± 9%) at 2 years, and 23% (± 9%) at 3 years.

Table 4. Remission rates in the treatment field in the TAX/RT group and TAX/CIS/RT group. CIS: cisplatin; RT: radiotherapy; TAX: taxane.

Tabelle 4. Remissionsraten innerhalb des Bestrahlungsvolumens in der Gruppe TAX/RT und der Gruppe TAX/CIS/RT. CIS: Cisplatin; RT: Radiotherapie; TAX: Taxan.

	Total (n)	TAX/RT (n)	TAX/CIS/RT (n)
Patients	28	20	8
Data sets available	27	19	8
Complete remission	7	7 (37%)	0 (0%)
Partial remission	17	11	6
Response rate	24/27 (89%)	18/19 (95%)	6/8 (75%)
Stable disease	3	1	2
Progressive disease	0	0	0

Survival

19 of the 36 women treated have died so far; 17 of these deaths were cancer-related. The median survival time was 25 months (95% CI: 7–43 months). The total survival statistics (± standard deviation) were as follows: 1 year: 81% (± 7%), 2 years: 57% (± 9%), 3 years: 41% (± 9%), and 4 years: 30% (± 10%; see Figure 2c).

Univariate Analysis of Prognostic Factors

Because of the heterogeneity of the data, the univariate analysis of potentially prognostic factors has to be interpreted with caution; the findings are suggestive at most (see Table 5).

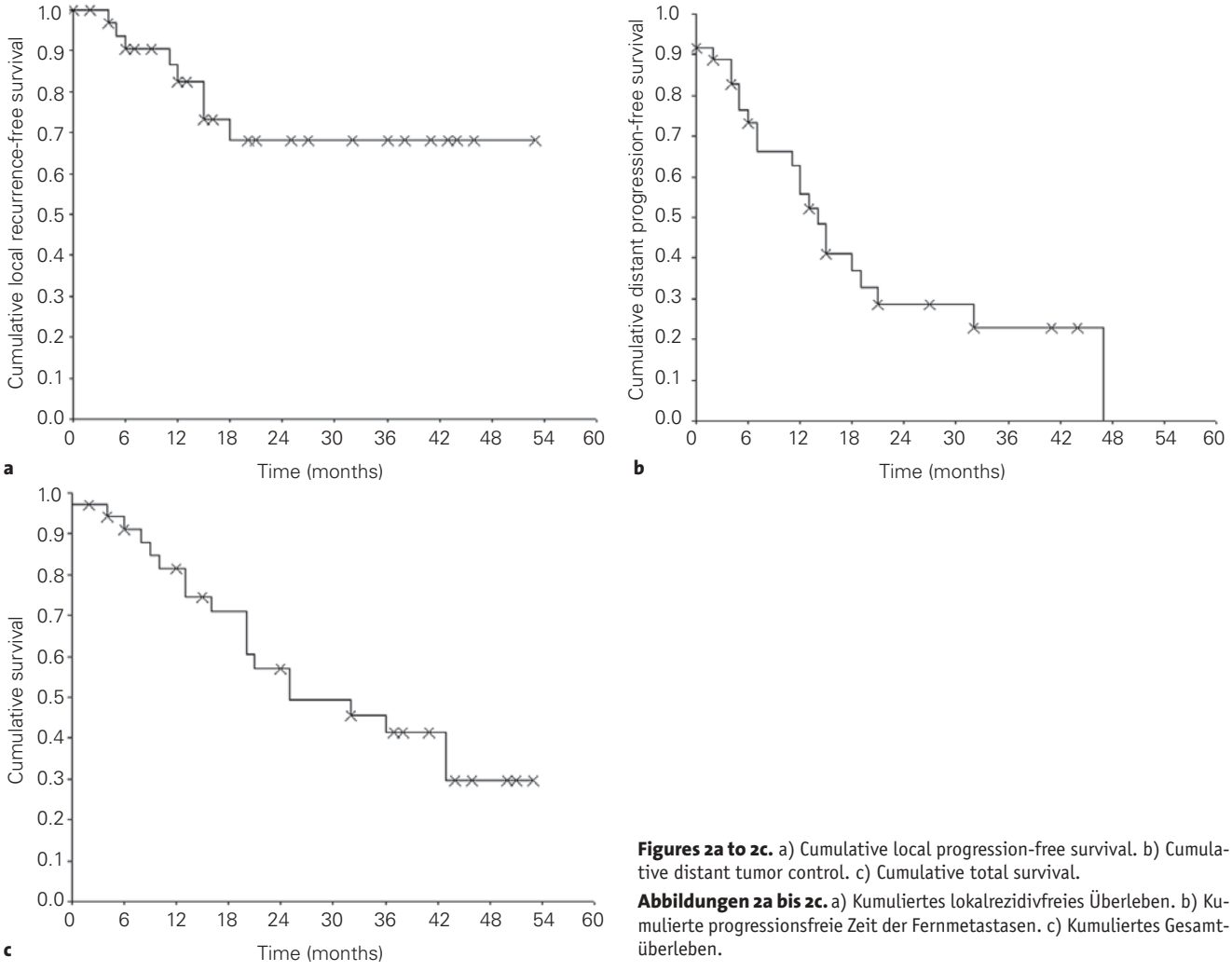
Age and absence of macroscopic tumor prior to RCT had a significant impact on local control within the treatment field. The onset of recurrence > 5 years after primary tumor occurrence, the absence of distant metastases at the time of concurrent TAX/RT showed a favorable tendency. The number of recurrences and prior radiotherapy had no effect on local prognosis.

Systemic progression most often occurred in cases where distant metastases were already present at the time of concurrent RCT. 44% of the women without distant metastases at the time of treatment remained so for the next 2 years. Inversely, almost all patients with distant metastases present at the time of treatment underwent progression. The other parameters studied were not found to be influential.

The factors that most strongly influenced 2-year total survival were the time of recurrence onset and the absence of macroscopic tumor prior to RCT.

Discussion

This is the first report at all describing the feasibility and results of treatment of locoregional recurrence of breast cancer by means of concurrent TAX/RT. On the whole, the available



Figures 2a to 2c. a) Cumulative local progression-free survival. b) Cumulative distant tumor control. c) Cumulative total survival.

Abbildungen 2a bis 2c. a) Kumuliertes lokalrezidivfreies Überleben. b) Kumulierte progressionsfreie Zeit der Fernmetastasen. c) Kumuliertes Gesamtüberleben.

data on the use of concurrent RCT for treatment of this tumor entity is insufficient, although this treatment modality would appear to be useful with respect to local and distant tumor control. Our treatment concept was developed in pursuit of this goal. Concurrent RCT was thereby conceived as part of a multimodal treatment strategy permitting the subsequent continuation of chemotherapy. For the cancer patient, maintaining an unmarred physical appearance is extremely important, even if the treatment is only palliative. Therefore, remission should preferably be complete and last until the end of the patient's lifetime, which is usually a median 2 years in these cases.

Surgery and irradiation are the available options for local tumor treatment. However, surgical resection generally is possible only, if the tumor is relatively small and located on the chest wall. The long-term outcome of radiation therapy is unsatisfactory with regard to local control [2, 7, 17, 28]. Hyperthermia or neutron radiotherapy is available at only a few centers, and the moulage technique is suitable only for irradiation of superficial tumors with infiltration depths of only a few millimeters [22]. In agreement with reports in the literature, our data show that R0/1 resection and, accordingly, relatively small tumor size correlate with better long-term control following radiation therapy [6, 20].

We found published data on two concurrent RCT trials for treatment of breast cancer recurrence. Renner & van Kampen [26], who used concurrent radiation and cyclophosphamide/methotrexate/5-fluorouracil (CMF) in 71 patients, achieved an 89% remission rate. Plasswilm & Sauer [25] achieved comparable remission rates (82% and 87%, respectively) with concurrent irradiation and 5-fluorouracil/mitomycin C in 20 or CMF in 28 patients.

Concurrent RCT has also been used for primary treatment of breast cancer. A limited amount of toxicity data are available for analysis [3, 9–11, 16, 30]. A remission rate of 91% [11] was achieved with taxane chemotherapy, and of 71% with 5-fluorouracil [10].

As in all previous studies, local progression did not occur in any of our patients during concurrent RCT. Local con-

Table 5. Univariate analysis of 2-year local re-recurrence-free rate, 2-year distant metastasis progression-free rate, and 2-year survival rate, including p-values, corresponding to a log-rank analysis. CIS: cisplatin; CR: complete remission; TAX: taxane.

Tabelle 5. Univariate Analyse bezüglich der 2-Jahres-Rate der lokalen Re-Rezidivfreiheit, der 2-Jahres-Rate der Progressionsfreiheit der Fernmetastasen und der 2-Jahres-Überlebensrate, einschließlich p-Werten entsprechend Log-Rank-Analyse. CIS: Cisplatin; CR: komplette Remission; TAX: Taxan.

Parameter	2-year local control rate	2-year distant control rate	2-year survival rate
Age at time of recurrence			
• ≤ 50 years	91 ± 8%	30 ± 12%	47 ± 14%
• > 50 years	50 ± 14%	27 ± 12%	65 ± 12%
• p-value	0.046	0.91	0.71
Time of recurrence after primary therapy			
• ≤ 5 years	58 ± 14%	22 ± 10%	45 ± 12%
• > 5 years	80 ± 13%	39 ± 15%	75 ± 12%
• p-value	0.18	0.26	0.02
Frequency of recurrence			
• First recurrence	64 ± 12%	19 ± 9%	52 ± 11%
• Second or third recurrence	77 ± 14%	36 ± 16%	67 ± 16%
• p-value	0.59	0.71	0.16
Absence of macroscopic local tumor before radiochemotherapy (R0, R1, CR)			
• Yes	100 ± 0%	38 ± 20%	100 ± 0%
• No	56 ± 12%	25 ± 9%	46 ± 10%
• p-value	0.058	0.49	0.02
M-status before radiochemotherapy			
• M0	76 ± 12%	44 ± 13%	62 ± 14%
• M1	59 ± 15%	9 ± 9%	51 ± 12%
• p-value	0.43	0.008	0.21
Type of chemotherapy			
• TAX	74 ± 10%	30 ± 11%	59 ± 10%
• TAX/CIS	51 ± 20%	25 ± 15%	50 ± 18%
• p-value	0.32	0.82	0.98
Irradiation of target volume			
• Second time	73 ± 13%	45 ± 16%	63 ± 15%
• First time	63 ± 14%	18 ± 9%	53 ± 11%
• p-value	0.81	0.72	0.19

trol 2 years post-treatment was 68% and, to our knowledge, no comparable results have been reported. Our rationale for including taxanes in the treatment protocol was as follows:

- Taxanes have a proven radiosensitizing effect [5, 21, 33].
- Since these drugs are a standard part of palliative breast cancer treatment, taxanes can easily be integrated into multimodal treatment strategies.
- At the time the study was conducted, the epirubicin/cyclophosphamide scheme was the standard for adjuvant treatment; CMF was rarely used. Therefore, the use of taxanes as a new class of drugs for treatment of breast cancer recurrence seemed prudent.
- The weekly taxane schedule was adopted because this reportedly achieves good control of hematotoxicity [4, 14, 24], as was ultimately confirmed in our patients. Because of the proven systemic efficacy of weekly taxane administration, we anticipated that it would also act on existing or potential distant metastases.
- Cisplatin, a drug with a known radiosensitizing effect on other types of organ tumors [2, 5, 8, 18, 19, 31], was also added to the chemotherapy protocol for patients with locally advanced tumors.

The toxicity data show that early integration of irradiation into a chemotherapy regimen is possible in treatment of breast cancer recurrence. Hematologic side effects were not a problem, and it was possible to continue chemotherapy after concurrent RCT in many cases. Pneumonitis (0–4%), an often feared complication of concurrent RCT, was only a minor factor in cases where there was adequate radiation treatment planning and careful avoidance of lung exposure. However, there are conflicting reports in the literature [3, 9, 11, 16].

The potential effects of concurrent RCT on the skin and mucosal linings deserve particular attention. Dermatitis was more frequent and more severe in the taxane monotherapy group. However, these patients received higher average radiation and chemotherapy doses than others on neoadjuvant or adjuvant therapy [3, 11]. Since the observed toxic skin reactions occurred near or after the end of radiation therapy, omitting the taxanes from the treatment protocol is hardly likely to influence the occurrence of these side effects in isolated patients, even in the case of weekly taxane administration. Roughly 40% of our patients had to be hospitalized for intensive antibiotic/ointment treatment of dermatitis/mucositis-related problems. The larger the target volume, the more frequent the need for treatment of these complications. Therefore, patients on this schedule must be monitored carefully for timely initiation of supportive treatment or hospitalization as needed.

Since it provides better local control, concurrent RCT has established itself as a modality for treatment of other organ tumors. The present data show that concurrent RCT is also suitable for treatment of breast cancer. Apart from taxanes, other drugs that can be used for concurrent RCT include 5-fluorouracil, oral capecitabine, vinca alkaloids, and cisplatin. Since taxanes will presumably be used more often for primary tumor treatment in the future, further studies should be performed to assess the role of these cytostatic drugs in the treatment of tumor recurrence. The good remission rates achieved in the present study also suggest that the efficacy of taxanes in improving the operability of locally advanced breast cancer

should also be investigated. In this respect, the present work represents a first step in the early integration of concurrent RCT in multimodal breast cancer treatment.

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Address for Correspondence
Prof. Dr. Rainer Fietkau
Klinik und Poliklinik für Strahlentherapie
der Universität Rostock
Südring 75
18059 Rostock
Germany
Phone (+49/381) 494-9000, Fax -9002
e-mail: rainer.fietkau@med.uni-rostock.de