Neoadjuvant Interstitial High-Dose-Rate (HDR) Brachytherapy Combined with Systemic Chemotherapy in Patients with Breast Cancer

Sandra J. Roddiger[1], Christos Kolotas[2], Ineza Filipowicz[1], Ralf Kurek[1], Ralph Paul Kuner[3], Thomas Martin[4], Dimos Baltas[1], Bernd Rogge[1], Marina Kontova[1], Gerald Hoffmann[3], Bettina Pollow[3], Nikolaos Zamboglou[1]

Background and Purpose: This is the first study investigating neoadjuvant interstitial high-dose-rate (HDR) brachytherapy combined with chemotherapy in patients with breast cancer. The goal was to evaluate the type of surgical treatment, histopathologic response, side effects, local control, and survival.

Patients and Methods: 53 patients, who could not be treated with breast-conserving surgery due to initial tumor size (36/53) or due to an unfavorable breast-tumor ratio (17/53), were analyzed retrospectively. All but one were in an intermediate/high-risk group (St. Gallen criteria). The patients received a neoadjuvant protocol consisting of systemic chemotherapy combined with fractionated HDR brachytherapy (2 × 5 Gy/day, total dose 30 Gy). In cases, where breast-conserving surgery was performed, patients received additional external-beam radiotherapy (EBRT, 1.8 Gy/day, total dose 50.4 Gy). In patients, who underwent mastectomy but showed an initial tumor size of T3/T4 and/or more than three infiltrated lymph nodes, EBRT was also performed.

Results: In 30/53 patients (56.6%) breast-conserving surgery could be performed. The overall histopathologic response rate was 96.2% with a complete remission in 28.3% of patients. 49/53 patients were evaluable for follow-up. After a median of 58 months (45–72 months), one patient showed a mild fibrosis of the breast tissue, three patients had mild to moderate lymphatic edema of the arm. 6/49 (12.2%) patients died of distant metastases, 4/49 (8.2%) were alive with disease, and 39/49 (79.6%) were free from disease. Local recurrence was observed in only one case (2%) 40 months after primary therapy. After mastectomy, this patient is currently free from disease.

Conclusion: The combination of interstitial HDR brachytherapy and chemotherapy is a well-tolerated and effective neoadjuvant treatment in patients with breast cancer. Compared to EBRT, treatment time is short. Postoperative EBRT of the whole breast – if necessary – is still possible after neoadjuvant brachytherapy. Even though the number of patients does not permit definite conclusions, the results are promising regarding survival and the very low rate of local recurrences.

Key Words: Interstitial HDR brachytherapy · Neoadjuvant treatment · Breast cancer

Strahlenther Onkol 2006;182:22–9
DOI 10.1007/s00066-006-1454-7

Neoadjuvante interstitielle HDR-Brachytherapie in Kombination mit Chemotherapie bei Patientinnen mit Mammakarzinom

Hintergrund und Ziel: Dies ist die erste Studie, welche den neoadjuvanten Einsatz einer Kombination aus interstitieller High-Dose-Rate-(HDR-)Brachytherapie und Chemotherapie bei Patientinnen mit Mammakarzinom untersucht. Ziel war es, die Art des chirurgischen Eingriffs, das histopathologische Ansprechen wie auch Nebenwirkungen, lokale Kontrolle und Überleben zu evaluieren.

Patienten und Methodik: Es wurden retrospektiv 53 Patientinnen ausgewertet, bei welchen eine primäre brusterhaltende Therapie nicht möglich war (36/53 wegen initialer Tumorausdehnung, 17/53 wegen ungünstigen Tumor-Brust-Verhältnisses). 52/53 Patientinnen zählten gemäß den St.-Gallen-Kriterien zur Gruppe mit intermediärem bzw. hohem Risiko. Alle erhielten eine neoadjuvante systemische Chemotherapie, kombiniert mit fraktionierter interstitieller HDR-Brachytherapie (2 × 5 Gy/Tag, Summendosis 30 Gy). Nach brusterhaltender Therapie wurde eine perkutane Radiatio der Brust (1,8 Gy/Tag, Summendosis 50,4 Gy) durchgeführt, ebenso bei Patientinnen nach Mastektomie mit initialem Tumorstadium T3/T4 und/oder mehr als drei befallenen Lymphknoten.

[1] Radiation Department, Klinikum Offenbach, Germany,
[2] Radiation Department, Kantonsspital Bern, Switzerland,
[3] Department of Gynecology and Obstetrics, St. Josefs Hospital, Wiesbaden, Germany,
[4] Radiation Department, Klinikum Bremen-Mitte, Germany.

Received: April 12, 2005; accepted: November 2, 2005

Ergebnisse: Bei 30/53 (56,6%) der Patientinnen konnte eine brusterhaltende Therapie durchgeführt werden. Das histopathologische Gesamtansprechen lag bei 96,2%, eine Komplettremission fand sich in 28,3% der Fälle. Von 49/53 Patientinnen konnten Daten für eine Nachuntersuchung erhoben werden. Nach einer medianen Nachbeobachtungszeit von im Mittel 58 Monaten (45–72 Monate) zeigte sich bei einer Patientin eine geringe Fibrose der Brust, bei drei Patientinnen ein gering bis mäßig ausgeprägtes Lymphödem des Arms. 6/49 (12,2%) der Patientinnen starben an Fernmetastasen, 4/49 (8,2%) lebten mit manifester Fernmetastasierung, 39/49 (79,6%) waren tumorfrei. Ein Lokalrezidiv trat bei einer Patientin (2%) 40 Monate nach Primärtherapie auf. Nach Mastektomie ist sie gegenwärtig tumorfrei.

Schlussfolgerung: Die Kombination von interstitieller HDR-Brachytherapie und Chemotherapie erweist sich als gut verträgliche und effektive neoadjuvante Therapie für Patientinnen mit Mammakarzinom. Ein Vorteil gegenüber der perkutanen Radiatio ist die kurze Behandlungszeit. Ferner bleibt die Option einer adjuvanten perkutanen Radiatio – falls nötig – bestehen. Obwohl die Anzahl der Patientinnen noch keine definitiven Schlussfolgerungen erlaubt, sind die Ergebnisse hinsichtlich des Überlebens sowie der niedrigen Lokalrezidivrate erfolgversprechend.

Schlüsselwörter: Interstitielle HDR-Brachytherapie · Neoadjuvante Therapie · Mammakarzinom

Introduction

Chemotherapy as well as radiation therapy are effectively used as neoadjuvant treatment modalities for different tumors. A recent study, e.g., showing improved local control and reduced toxicity of neoadjuvant versus adjuvant radiochemotherapy, has changed the therapeutic approach in locally advanced rectal cancer [35].

Previous management approaches in patients with locally advanced breast cancer (LABC) included primary mastectomy alone or followed by radiotherapy, as well as radiotherapy alone or followed by surgery. All of these strategies resulted in unacceptably high local recurrence rates and disappointing survival rates [27]. The use of neoadjuvant chemotherapy finally changed the treatment schedule and became the standard of care for patients with LABC. Even breast-conserving surgery can be offered to a selected group of patients after downstaging by induction chemotherapy [6, 7, 11, 14, 19, 24, 36, 42]. Also in patients with large tumors or an unfavorable breast-tumor ratio, breast preservation is a feasible treatment option after induction chemotherapy.

In patients with stage I and II breast cancer the NSABP B-18 report showed no significant difference concerning overall survival after neoadjuvant versus adjuvant chemotherapy. However, in the subgroup of patients, who reached a pathologic complete remission (pCR) after neoadjuvant chemotherapy, statistically significantly higher rates of lumpectomy and relapse-free survival were observed [12].

Only few studies investigated the combination of chemotherapy and radiotherapy in the neoadjuvant setting [2, 8, 15, 38–40]. Interestingly, Gerlach et al. were able to show significantly higher rates of pCR after radiochemotherapy compared to chemotherapy alone [15]. However, neoadjuvant radiotherapy in these studies is based on external-beam radiotherapy (EBRT) of the whole breast to a total dose of 45–50 Gy, followed by a boost of 6–11 Gy. Thus, an adjuvant EBRT after surgery is strictly limited regarding the dose or not possible at all.

Using interstitial brachytherapy, a high dose can be achieved within the tumor area while minimizing the dose in the normal tissue [20, 29]. A downstaging of the tumor – and breast conservation – could be reached without spoiling the option for an adjuvant EBRT, if necessary.

To date, interstitial brachytherapy is used as a boost to the tumor bed in addition to EBRT after breast-conserving surgery in patients with early-stage breast cancer [26, 30–32]. Interstitial low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy of the tumor bed as the sole adjuvant treatment after breast-conserving surgery is currently under investigation with very promising results [3, 18, 28, 34, 41, 45, 46].

The aim of our study was to evaluate the impact of a neoadjuvant combined-modality treatment consisting of systemic chemotherapy and interstitial HDR brachytherapy on type of surgical treatment and histopathologic response. Our goal was to induce an inactivation and downstaging of the tumor and – if possible – to perform breast-conserving surgery. Furthermore, the follow-up would show the influence of neoadjuvant HDR brachytherapy on side effects, local control, and survival.

Patients and Methods

Between 1997 and 2000, 53 patients were included in our study, who could not be treated with breast-conserving sur-

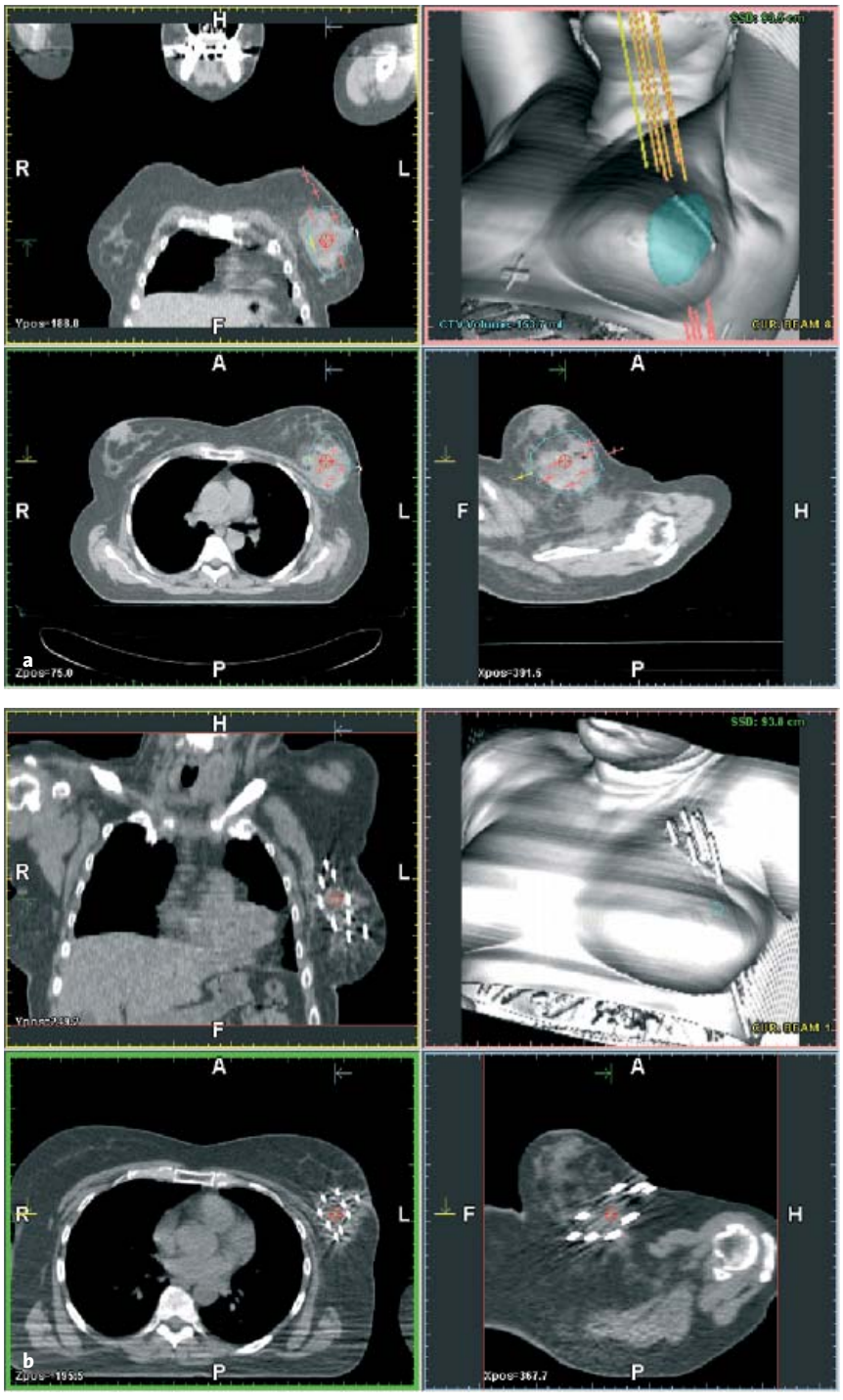
Table 1. Overview of tumor stage, typing and grading.

Tabelle 1. Überblick über Tumorstadium, Typing und Grading.

Tumor size		Nodal status		Typing		Grading	
T1c	2 (3.8%)	N0	38 (71.7%)	Ductal	37 (69.8%)	GI	2 (3.8%)
T2							
> 3cm	33 (62.3%)	N1	12 (22.6%)	Lobular	8 (15.1%)	GII	32 (60.4%)
T3	10 (18.9%)	N2	3 (5.7%)	Other	8 (15.1%)	GIII	16 (30.2%)
T4	8[a] (15.0%)					GIV	3 (5.6%)

[a] including one patient with inflammatory breast cancer

gery due to initial tumor size (36/53) or due to an unfavorable breast-tumor ratio (17/53). Treatment was approved by the institutional review board. Informed consent was obtained from every patient. Median age was 47.5 years (range 27–66 years), hormonal status was premenopausal in 31 (58.4%) and postmenopausal in 22 patients (41.6%). In 28 patients (52.8%) the tumor was located in the left, in 25 (47.2%) in the right breast. Diagnosis was made by punch biopsy of the suspicious region. In 31 patients (58.4%) the tumor cells were tested positive for both estrogen and progesterone receptors by immunohistological examination, in 20 patients (37.8%) the tumor cells were negative for both receptors, in one patient positive for the estrogen receptor, and in one patient positive for the progesterone receptor only. All patients had no distant metastases in bone scan and chest X-ray at initial diagnosis. Tumor size and nodal involvement were determined by clinical examination, ultrasound and – if available – MRI before and after neoadjuvant treatment. Results were compared to histological examination after surgery. Initial tumor size and nodal involvement as well as typing and grading are listed in Table 1.



Figures 1a and 1b. Preplanning of brachytherapy using the ProSoma system (a). Postimplantation CT scan with steel needles before replacement with plastic tubes (b).

Abbildungen 1a und 1b. Brachytherapieplanung mittels ProSoma (a). CT nach Sondenimplantation mit Stahlnadeln, vor dem Einführen der Plastiksonden (b).

Two courses of neoadjuvant chemotherapy were given before and two courses after interstitial brachytherapy. 39 of the patients received an epirubicin/cyclophosphamide-based chemotherapy, 13 patients underwent a chemotherapy consisting of docetaxel (Taxotere)/doxorubicin, and one patient was treated with CMF.

2–3 weeks after the first two courses of chemotherapy, brachytherapy was performed.

For brachytherapy, preplanning was done using CT images (Somatom plus 4, Siemens, Pforzheim, Germany) with 3- to 5-mm contiguous slices and ProSoma 3-D-planning system (Medcom, Darmstadt, Germany) to visualize shape and size of the tumor and preplan possible implant configurations. The gross tumor volume (GTV) was defined as planning target volume (PTV). If the extent of the tumor was unclear in the preplanning CT, 100 ml of contrast dye were given and/or an additional MRI and image fusion with the CT scan was performed. An example of a preplan and the corresponding postimplant CT scan is given in Figure 1.

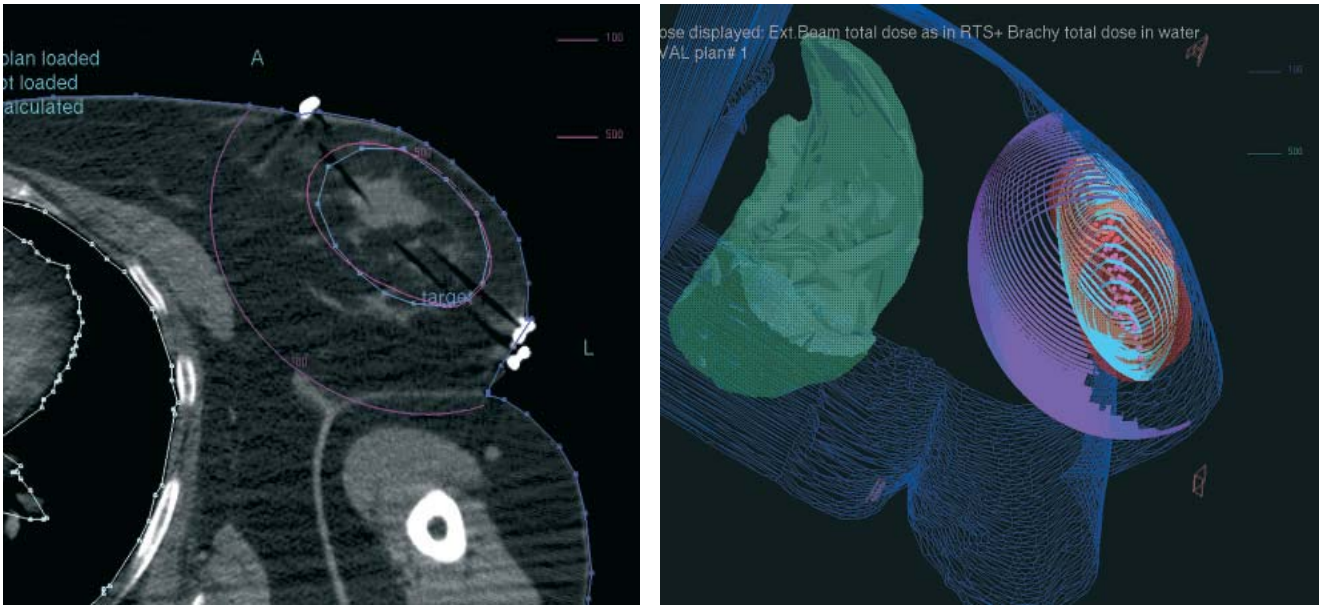


Figure 2. Evaluation after 3-D planning: 3-D reconstruction showing target (red), dwell positions (pink), isodoses (1 Gy = purple, 5 Gy = light blue), lung (green), and skin (blue).

Abbildung 2. Evaluation nach 3-D-Brachytherapieplanung: 3-D-Rekonstruktion von Target (rot), Haltepunkten der Quelle (pink), Isodosen (1 Gy = violett, 5 Gy = hellblau), Lunge (grün) und Haut (blau).

After sedoanalgesia with 5 mg midazolam and 50 mg pethidine, local anesthesia was applied and flexible plastic tubes were inserted into the tumor. Implantation of plastic tubes was performed "freehand" using CT guidance. Contrast dye was given, if necessary.

CT-based 3-D brachytherapy planning was performed, allowing 3-D reconstruction of implants and target as well as 3-D dose optimization to the surface of the PTV (Plato BPS, Nucletron, Venendaal, The Netherlands) and calculation of the PTV coverage. The PTV coverage was defined as the proportion of the PTV recieving 100% of the prescribed dose. An example of the isodose distribution is given in Figure 2.

HDR brachytherapy was performed using iridium-192 and an afterloading device (microSelectron, Nucletron). A fractional dose of 5 Gy was given twice a day for 3 days to a total dose of 30 Gy. Minimum time between each fraction was 6 h.

The combined neoadjuvant treatment was followed by surgery. In addition, patients received three cycles of CMF chemotherapy. In cases, where breast-conserving surgery was performed, patients received additional EBRT (1.8 Gy/day, total dose 50.4 Gy) using a linear accelerator (Siemens, Erlangen, Germany). In patients, who underwent mastectomy but showed an initial tumor size of T3/T4 and/or more than three infiltrated lymph nodes, EBRT was also performed.

All patients with positive hormone receptor status received tamoxifen 20–30 mg/day after initial treatment for 5 years.

For statistical analysis Winstat and SPSS were used. The χ^2-test was used to compare type of surgery and histopathologic response in different subgroups of patients. A $p = 0.05$ was considered to be significant.

Results

Brachytherapy

The mean number of implanted plastic tubes was nine (three to 15) per implant, mean target volume was 102.0 cm^3 (13.7–368.0 cm^3). The mean PTV coverage was 90.77% (73.8–95.4%). The treatment was well tolerated. A mild to moderate skin erythema was found in 14 patients, which was reversible within 2 weeks after completion of treatment.

Surgery Technique

In the majority of patients mastectomy could be avoided after neoadjuvant radiochemotherapy. The decision for mastectomy or breast conservation was based on initial tumor stage and clinical findings after neoadjuvant chemo-brachytherapy. 30 patients (56.6%) underwent breast-conserving surgery; in six cases additional reconstruction using a latissimus dorsi (LAT) flap was necessary; in two patients a transversus abdominis (TRAM) flap was used. In 23/53 patients (43.4%) a mastectomy was performed. One of those patients underwent a mastectomy including resection of pectoralis major muscle due to intraoperative suspicion of tumor infiltration, which was not confirmed by the pathology report. Nine patients received a primary reconstruction, in two cases using a LAT flap and in seven cases a TRAM flap.

When comparing subgroups of patients, the probability of performing breast-conserving surgery after neoadjuvant

chemo-brachytherapy correlated significantly with the initial tumor size. 25 (71.4%) of 35 patients with initial stage T1 or T2 where able to undergo breast-conserving surgery compared to five (27.8%) of 18 patients with a T3 or T4 tumor at initial diagnosis ($p < 0.01$). No statistically significant difference was seen when comparing patients with a T3 tumor to patients with a T4 tumor ($p = 0.25$).

Histopathologic Response

In all patients immunohistopathologic examination was accessible. Overall response rate was 96.2% (51/53). In 15/53 patients (28.3%) the histopathologic report showed a complete remission. In seven (46.7%) of those 15 cases a second immunohistopathologic examination found focal residual – but heavily damaged – tumor cells. In 51/53 patients a reduction of tumor size and an alteration and damage of the tumor cells were visible. 1/53 patients was found to be „no change". In 1/53 the initial extension of the tumor was underestimated. It was initially staged as a T2 tumor, but histopathologic examination after surgery revealed an infiltration of fat and connective tissue, which "upgraded" the tumor stage to T4. In eight patients with stage T2 tumors initial tumor size was reduced but not significant for the lower staging group. Three of those eight patients showed fibrosis within the tumor area with only few spots of vital tumor tissue. However, the whole fibrotic area was measured as "tumor area" by the pathologist and, therefore, no downstaging was reached.

In Table 2 an overview of the initial and histopathologic tumor size is given.

Table 2. Comparison of initial clinical tumor size and pathologic tumor size after neoadjuvant therapy.

Tabelle 2. Vergleich von initialer klinischer Tumorgröße und pathologischer Tumorgröße nach neoadjuvanter Therapie.

Initial tumor size (before neoadjuvant treatment)	Histopathologic tumor size (after surgery)
T1c n = 2	CR n = 1 T1b n = 1
T2 n = 33	CR n = 10 T1a n = 1 T1c n = 13 T2 n = 8 T4 n = 1[a]
T3 n = 10	CR n = 2 T1a n = 1 T1b n = 1 T1c n = 3 T2 n = 2 T3 n = 1
T4 n = 8	CR n = 3 T1b n = 1 T1c n = 3 T3 n = 1

[a] initially underestimated

Comparing subgroups of different initial tumor size concerning histopathologic response (ypCR vs. ypPR), no statistically significant difference could be found ($p = 0.39$ for T2 vs. T4; $p = 0.14$ for T2 vs. T4; $p = 0.62$ for T1c + T2 vs. T3 + T4). 26/53 patients (49.1%) were staged as ypN0, 12/53 (22.6%) were ypN1b, 4/53 (7.5%) ypN1bi, and 7/53 (13.3%) ypN1biii. 4/53 patients (7.5%) were postoperatively staged as ypN2.

At first restaging after completion of the initial treatment, 51/53 patients (96.2%) remained to be free from metastatic disease. In two patients newly developed bone metastases were found, both patients had had local complete remission. These two patients had unfavorable prognostic markers: both were GIII, one was negative for estrogen and progesterone receptors, the other was found to have positive lymph nodes in level II and a positive HER2/neu status.

Follow-up

After a median of 58 months (45–72 months), only four patients were lost to follow-up, six of the remaining 49 patients (12.2%) died of distant metastases, four patients were alive with disease (8.2%) and 39 patients were free from disease (79.6%). Overall and disease-specific survival were equivalent (87.8%). All four patients, who were alive with disease, suffered from distant metastases and were currently treated with chemo- and/or radiotherapy. One of 39 patients without disease was found to have contralateral breast cancer 2 years after primary therapy, which was treated by breast-conserving surgery followed by EBRT. Local recurrence was observed in only one case (2%) 40 months after primary therapy and was treated by mastectomy. The patient is currently free from disease.

One patient showed a mild fibrosis of the breast tissue, three patients had mild to moderate lymphatic edema of the arm.

Discussion

We will compare breast conservation rate, histopathologic findings, survival and rate of local recurrence of our study with the results of neoadjuvant chemotherapy and combined radiochemotherapy presented by other authors.

In our study 56.6% of patients were able to undergo breast-conserving surgery after neoadjuvant treatment. Breast conservation correlated significantly with initial tumor size: in patients with large T2 tumors or with T1 tumors with unfavorable breast-tumor ratio, breast-conserving surgery could be performed more often compared to patients with T3 and T4 tumors.

Also in other studies, breast conservation rate is strongly dependent upon the patient selection. As already mentioned in the introduction, authors like Bonadonna et al. and Veronesi et al. were able to report a breast conservation rate of up to 90% after neoadjuvant chemotherapy. Included were only patients with large (> 3 cm) T2 tumors [5, 44].

Not only the selection of patients does influence the breast conservation rate but also the choice of chemotherapeutic agents. Erol et al., for example, used three cycles of CMF in the neoadjuvant treatment of patients with LABC. Toxicity was mild, but only 4% of patients were eligible for breast-conserving surgery [10]. Amat et al. reported a breast conservation rate of 72.4% in patients with primary operable stage II–III tumors after six cycles of docetaxel 100 mg/m^2 every 21st day. Unfortunately, the side effects were impressive as well: 70.5% of patients developed a grade 3–4 neutropenia and 13.6% suffered from neutropenic sepsis [1].

In general, one must distinguish between studies including patients with primary inoperable LABC and studies including patients with primary operable large breast tumors. Of course, the first report a lower rate of breast conservation, e.g., 36% and 44% [7, 36], while the latter reach breast conservation therapy in 48–90% of cases [1, 5, 9, 13, 21, 25, 33, 44].

Over the last few years, the addition of other chemotherapeutic agents such as docetaxel to a standard anthracycline-based neoadjuvant treatment schedule has led to further improvement in breast conservation. The Aberdeen Breast Group investigated patients with large or locally advanced tumors and found a breast conservation rate of 67% after a combination of both substances versus 48% after an anthracycline-based schedule [17].

Only few authors investigated the combination of chemotherapy and irradiation. An interesting study was presented by Aryus et al. in 2000 [2]. The authors compared the effect of an epirubicin- and cyclophosphamide-based neoadjuvant chemotherapy to neoadjuvant chemotherapy (same schedule) combined with EBRT to a total dose of 50 Gy plus an additional boost of 6–11 Gy. Like in our study, patients with large tumors and an unfavorable breast-tumor ratio as well as patients with LABC were included. 61% of patients were able to undergo breast-conserving surgery; no differences could be detected between the chemotherapy and the radiochemotherapy group. A follow-up study by the same group published in 2003 found a breast conservation rate of 41% in patients treated with chemotherapy and of 55% in patients treated with radiochemotherapy – but again no significant difference [15].

Some authors partly excluded surgery from the treatment schedule: in the studies of Mauriac et al., Toubol et al. and Merajver et al., decision about further therapeutic management after neoadjuvant treatment was based upon clinical findings or punch biopsy [23, 24, 43]. Patients with a clinical complete remission received no surgical treatment at all and were given an additional EBRT boost to the tumor bed or – if EBRT was not included in the neoadjuvant schedule – they received EBRT to a total dose of 50 Gy.

In our opinion, it may be dangerous to stage patients after a neoadjuvant treatment by clinical examination only. Swain et al. performed a second punch biopsy after neoadjuvant treatment. They were able to show residual tumor cells in 38% of patients clinically staged as having complete remission [42]. Finally, the meta-analysis by Mauri et al. clearly shows the dangerous inefficiency of treatment schedules without surgery. Neoadjuvant therapy, compared with adjuvant therapy, was associated with a significantly increased risk of locoregional recurrence when radiotherapy without surgery was performed [22].

In our study the overall histopathologic response rate was 96.2%. In 15/53 patients (28.3%) the first histopathologic report showed a complete remission. In seven (46.7%) of those 15 cases a second immunohistopathologic examination found focal residual – but heavily damaged – tumor cells within the former tumor area. Therefore, a complete remission was found in 8/53 (15%) of our patients.

In studies using neoadjuvant chemotherapy, rates of histopathologic complete remission ranged from 0% to 34% [1, 4, 5, 11, 16, 17, 19, 25, 26, 44].

Again, comparison of the studies is complicated by the use of different chemotherapeutic schedules and different patient selection. A variety of chemotherapeutic schedules – some without anthracyclines – were analyzed in the study by Bonadonna in 1990. The patients had breast cancer too large for breast-conserving surgery and a relatively low pCR of 4.2% was found [5]. In an even older study presented by Hortobagyi in 1988, patient characteristics were the same, but an anthracycline-based regimen (FAC) was used and pCR was 16.7% [16]. A study with patients suffering from inflammatory breast cancer published in 2004 by Baldini et al. showed a pCR of 6% only after three cycles of an anthracycline-based regimen (FAC or FEC) [4]. Macchiavelli et al., investigating patients with LABC after three cycles of FAC and surgery, found no pCR at all, minimal microscopic disease in 18% and gross residual tumor in 82% of their patients [19]. The addition of docetaxel to an anthracycline-based schedule seems to increase the number of patients achieving pCR. Hutcheon et al. presented the data of patients with large or primary unresectable tumors: in patients treated with four cycles of docetaxel after four cycles of CVAP, a pCR was reached in 34%, which was significantly higher than the pCR rate of 16% in patients after eight cycles of CVAP [17].

In studies using neoadjuvant combined radiochemotherapy, rates of histopathologic complete remission ranged from 8.6% to 43% [2, 8, 15, 38–40].

In 1997, Skinner et al. reported a pCR of 17% in patients with LABC after neoadjuvant treatment with 5-fluorouracil (5-FU) and EBRT of the whole breast up to 50 Gy [39]. A study published in 1999 by the same authors showed an increased pCR rate of 26% after neoadjuvant treatment with paclitaxel and EBRT of the whole breast up to 45 Gy [40]. In the study by Aryus et al. comparing combined neoadjuvant radiochemotherapy to chemotherapy alone, the authors were able to show a significant difference between the two groups: patients treated with radiochemotherapy had a pCR rate of 43%, compared to only 6% of patients in the chemotherapy

group. Median tumor diameter in the chemotherapy group was 3 cm, and four cycles of an anthracycline-based regimen (EC) were administered. In contrast to other chemotherapy studies with a comparable patient selection and chemotherapy schedule, the pCR rate was relatively low. Also in the follow-up study published in 2003, the pCR rate in the chemotherapy group was low (3%), however, the significant difference between chemotherapy and radiochemotherapy was found again [2, 15].

The relatively low pCR rate in our study may be explained by our policy of performing a second histopathologic examination in all cases with a pCR as the first result. Furthermore, the median time interval (9 weeks) between completion of radiochemotherapy and surgery in our study was lower than in the study by Aryus et al. (16 weeks) [2].

In our study, the survival rate was 87.8% with only 2% of local recurrences.

In studies using neoadjuvant chemotherapy the 5-year overall survival rate for patients with LABC ranges from 44% for stage IIIB to 84% for stage IIIA [16, 26]. The rate of local recurrences after 5 years ranges from 5.9% for patients with large-size but primary operable tumors [44] to 14% for patients with LABC including also patients with inflammatory cancer [6]. Cance et al. found that the pathologic response of the primary tumor and the ability of performing breast-conserving surgery had a marked prognostic significance and influenced long-term outcome of patients. The authors were able to show a 5-year survival of 96% for those patients, who had a sufficient downstaging allowing breast-conserving surgery [6].

Unfortunately, only one of the studies with combined radiochemotherapy reported a follow-up. After a median of 53 months the estimated 5-year overall survival rate in the study of Semiglazov et al. is 86.1% [38].

Comparing EBRT and interstitial HDR brachytherapy in the neoadjuvant setting, the interstitial treatment shows three advantages. First of all, it can be delivered in a very short time interval, which was usually not longer than 3 days in our study. The short treatment time helps to increase our patients' quality of life [37]. Second, the treatment can be tailored to the tumor area while sparing healthy breast tissue. Furthermore, in patients with breast-conserving surgery, adjuvant EBRT of the whole breast up to 45–50 Gy is still possible after neoadjuvant HDR brachytherapy but not after neoadjuvant EBRT.

Conclusion

In patients with large or locally advanced breast cancer, neoadjuvant brachytherapy in combination with chemotherapy is a safe and feasible treatment option with a low rate of side effects. Although all but one of our patients were in an intermediate/high-risk group (according to the criteria defined by the St. Gallen consensus conference), we achieved a high rate of overall survival and the lowest rate of local recurrences so far.

References

1. Amat S, Bougnoux P, Penault-Llorca F, et al. Neoadjuvant docetaxel for operable breast cancer induces a high pathological response and breast-conservation rate. Br J Cancer 2003;88:1339–45.
2. Aryus B, Audretsch W, Gogolin F, et al. Remission rates following preoperative chemotherapy and radiation therapy in patients with breast cancer. Strahlenther Onkol 2000;176:411–5.
3. Baglan KL, Martinez AA, Frazier RC, et al. The use of high-dose-rate brachytherapy alone after lumpectomy in patients with early-stage breast cancer treated with breast conserving surgery. Int J Radiat Oncol Biol Phys 2001; 50:1003–11.
4. Baldini E, Gardin G, Evangelista G, et al. Long-term results of combined-modality therapy for inflammatory breast carcinoma. Clin Breast Cancer 2004; 5:358–63.
5. Bonadonna G, Veronesi U, Brambilla C, et al. Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst 1990;82:1539–45.
6. Cance WG, Carey LA, Calvo BF, et al. Long-term outcome of neoadjuvant therapy for LABC: effective clinical downstaging allows breast preservation and predicts outstanding local control and survival. Ann Surg 2002;236:295–302.
7. Clark J, Roseman J, Cance W, et al. Extending the indication for breast conserving treatment to patients with locally advanced breast cancer. Int J Radiat Oncol Biol Phys 1998;42:345–50.
8. Colleoni M, Nole F, Minchella I, et al. Pre-operative chemotherapy and radiotherapy in breast cancer. Eur J Cancer 1998;34:641–5.
9. De Lena M, Varini M, Zucali R, et al. Multimodal treatment for locally advanced breast cancer. Results of chemotherapy-radiotherapy versus chemotherapy-surgery. Cancer Clin Trials 1981;4:229–36.
10. Erol K, Baltali E, Altundag K, et al. Neoadjuvant chemotherapy with cyclophosphamide, mitoxantrone, and 5 FU in LABC. Onkologie 2005;28:81–5.
11. Ezzat AA, Ibrahim EM, Ajarim DS. High complete pathological response in locally advanced breast cancer using paclitaxel and cisplatin. Breast Cancer Res Treat 2000;62:237–44.
12. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project – B18. J Clin Oncol 1997;15:2483–93.
13. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16:2672–85.
14. Fornasiero A, Ghiotto C, Daniele O, et al. Neoadjuvant moderatly high-dose chemotherapy with rh-G-CSF in locally advanced breast carcinoma. Tumori 2001;87:223–8.
15. Gerlach B, Audretsch W, Gogolin F, et al. Remission rates in breast cancer with preoperative chemotherapy and radiotherapy. Strahlenther Onkol 2003;179:306–11.
16. Hortobagyi GN, Ames FC, Buzdar AU, et al. Management of stage III primary breast cancer with primary chemotherapy, surgery and radiation therapy. Cancer 1988;62:2507–16.
17. Hutcheon AW, Heys SD, Sarkar TK, and the Aberdeen Breast Group. Neoadjuvant docetaxel in locally advanced breast cancer. Breast Cancer Res Treat 2003;79:Suppl 1:19–24.
18. Kolotas C, Zamboglou N. Role of interstitial brachytherapy in the treatment of malignant disease. Onkologie 2001;24:222–8.
19. Macchiavelli MR, Romero AO, Perez JE, et al. Prognostic significance of pathological response of primary tumor and metastatic axillary lymph nodes after neoadjuvant chemotherapy for locally advanced breast carcinoma. Cancer J Sci Am 1998;4:125–31.
20. Major T, Fodor J, Takacsi-Nagy Z et al. Evaluation of HDR interstitial breast implants planned by conventional and optimized CT-based dosimetry systems with respect to dose homogeneity and conformality. Strahlenther Onkol 2005;181:89–96.
21. Makris A, Powles TJ, Ashley SE, et al. A reduction in the requirements for mastectomy in a randomised trial of neoadjuvant chemoendocrine therapy in primary breast cancer. Ann Oncol 1998;9:1151–4.
22. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005;97:188–94.
23. Mauriac L, Durand M, Avril A, et al. Effects of primary chemotherapy in conservative treatment of breast cancer patients with operable tumors larger than 3 cm. Ann Oncol 1991;2:347–54.

24. Merajver SD, Weber BL, Cody R, et al. Breast conservation and prolonged chemotherapy for locally advanced breast cancer: the University of Michigan experience. J Clin Oncol 1997;15:2873–81.
25. Minckwitz G von, Raab G, Schuette M, et al. Dose-dense versus sequential adriamycin/docetaxel combination as preoperative chemotherapy in operable breast cancer (T2–3,N0–2,M0) – primary endpoint analysis of the GEPARDUO-study. Proc Am Soc Clin Oncol 2002;21:43a.abstract 168.
26. Morell LE, Lee YJ, Hurley J, et al. A phase II trial of neoadjuvant methothrexate, vinblastine, doxorubicine and cisplatin in the treatment of patients with locally advanced breast carcinoma. Cancer 1998;82:503–11.
27. Newman LA. Management of patients with locally advanced breast cancer. Curr Oncol Rep 2004;6:53–61.
28. Ott OJ, Potter R, Hammer J, et al. Accelerated partial breast irradiation with iridium-192 multicatheter PDR/HDR brachytherapy: preliminary results of the German-Austrian multicenter trial. Strahlenther Onkol 2004; 180:642–9.
29. Ott OJ, Schulz-Wendtland R, Uter W, et al. Fat necrosis after conserving surgery and interstitial brachytherapy and/or external-beam irradiation in women with breast cancer. Strahlenther Onkol 2005;181:638–44.
30. Polgar C, Fodor J, Major T, et al. The role of boost irradiation in the conservative treatment of stage I–II breast cancer. Pathol Oncol Res 2001; 7:241–50.
31. Polgar C, Fodor J, Major T, et al. Is boost irradiation with interstitial brachytherapy less favourable than with teletherapy after breast conserving surgery? Eur J Obstet Gynecol Reprod Biol 2002;94:255–6.
32. Polgar C, Fodor J, Orosz Z, et al. Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I–II breast cancer. Strahlenther Onkol 2002;178:615–23.
33. Rouzier R, Mathieu MC, Sideris L, et al. Breast conserving surgery after neoadjuvant anthracycline-based chemotherapy for large breast tumors. Cancer 2004;101:918–25.
34. Sauer G, Strnad V, Kurzeder C, et al. Partial breast irradiation after breast-conserving surgery. Strahlenther Onkol 2005;181:1–8.
35. Sauer R, Becker H, Hohenberger W, et al., German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40.
36. Schwartz GF, Birchansky CA, Karmanicky LT, et al. Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. Cancer 1994;73:362–9.
37. Sehlen S, Hollenhorst H, Schymura B, et al. Psychosocial stress in cancer patients during and after radiotherapy. Strahlenther Onkol 2003;179:175–80.
38. Semiglazov VF, Topuzov EE, Bavli JL, et al. Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb–IIIa breast cancer. Ann Oncol 1994;5:591–5.
39. Skinner KA, Dunnington G, Silberman H, et al. Preoperative 5-fluorouracil and radiation therapy for locally advanced breast cancer. Am J Surg 1997; 174:705–8.
40. Skinner KA, Silberman H, Florentine B, et al. Preoperative paclitaxel and radiotherapy for locally advanced breast cancer: surgical aspects. Ann Surg Oncol 1999;7:145–9.
41. Strnad V, Ott O, Potter R, et al. Interstitial brachytherapy alone after breast conserving surgery: interim results of a German-Austrian multicenter phase II trial. Brachytherapy 2004;3:115–9.
42. Swain SM, Sorace RA, Bagley M, et al. Neoadjuvant chemotherapy in the combined modality approach of locally advanced nonmetastatic breast cancer. Cancer Res 1987;47:3889–94.
43. Toubol E, Buffat L, LeFranc JP, et al. Possibility of conservative local treatment after combined chemotherapy and preoperative irradiation for locally advanced noninflammatory breast cancer. Int J Radiat Oncol Biol Phys 1996;34:1175–7.
44. Veronesi U, Bonadonna G, Zurrida S, et al. Conservation surgery after primary chemotherapy in large carcinomas of the breast. Ann Surg 1995;222: 612–8.
45. Vicini F, Kini VR, Chen P, et al. Irradiation of the tumor bed alone after lumpectomy in selected patients with early stage breast cancer treated with breast conserving therapy. J Surg Oncol 1999;70:33–40.
46. Vicini FA, Chen PY, Fraile M, et al. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early stage breast cancer treated with breast conserving therapy: preliminary results of a pilot trial. Int J Radiat Oncol Biol Phys 1997;38:301–10.

Address for Correspondence
Prof. Dr. Dr. N. Zamboglou
Klinikum Offenbach
Strahlenklinik
Starkenburgring 66
63069 Offenbach
Germany
Phone (+49/69) 8405-3335, Fax -3334
e-mail: nzamboglou@klinikum-offenbach.de