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C. Matuschek[1] · E. Bölke[1] · S.L. Roth[1] · K. Orth[1] · I. Lang[1] · H. Bojar[2] · J.W. Janni[3] · W. Audretsch[4] · C. Nestle-Kraemling[5] · G. Lammering[1,7] · V. Speer[1] · S. Gripp[1] · P.A. Gerber[1] · B.A. Buhren[1] · R. Sauer[6] · M. Peiper[8] · M. Schauer[8] · M. Dommach[9] · K. Struse-Soll[9] · W. Budach[1]

[1] Medical Faculty, Department of Radiation Oncology, Heinrich Heine University of Duesseldorf
[2] European Institute for Molecular Oncology, Heinrich Heine University of Duesseldorf
[3] Department of Gynaecology, Heinrich Heine University of Duesseldorf
[4] Department of Senology and Breast Surgery, Marien Hospital Duesseldorf – MHD, Duesseldorf
[5] Department of Gynaecology, Sanaklinik, Krankenhaus Gerresheim, Duesseldorf
[6] Department of Radiation Oncology, University of Erlangen
[7] MAASTRO Clinic (Radiation Oncology), Maastricht
[8] Department of Surgery, Heinrich Heine University of Duesseldorf
[9] Medizinisches Versorgungszentrum, Sana Krankenhaus Gerresheim, Duesseldorf

Long-term outcome after neoadjuvant radiochemotherapy in locally advanced noninflammatory breast cancer and predictive factors for a pathologic complete remission

Results of a multivariate analysis

Breast cancer is a morbid disease associated with a high incidence of recurrence. Besides surgery, adjuvant chemotherapy in treating breast cancer is well accepted. Neoadjuvant chemotherapy applied to breast cancer patients has been effective in downstaging the primary tumor, as confirmed by studies, and neoadjuvant treatments have allowed for breast-conserving surgery instead of mastectomy [1]. In addition to neoadjuvant chemotherapy, preoperative radiochemotherapy is a new concept aiming to improve the downstaging in primary advanced cancers. An earlier published series of neoadjuvant radiochemotherapy (NRT-CHX) in locally advanced noninflammatory breast cancer (LABC) has now been updated to include a follow-up of more than 15 years [1]. This study reviews the prognostic factors for assessing pathologic complete remission (pCR) after neoadjuvant radiochemotherapy in LABC [2, 3, 4, 5].

Patients, material and methods

This retrospectively evaluated cohort study included 315 LABC patients (cT1-cT4/cN0-N1). They were treated during 1991–1998, with a recent update in follow-up up to November 2011. The study criteria included untreated, histologically confirmed, invasive adenocarcinoma of the breast not amenable to breast-conserving surgery (tumor size relative to breast volume, unfavorable location of the tumor bed, or multifocal T1 disease, and extended intraductal component [EIC]), in stages IIA–IIIC according to the International Union Against Cancer (ICRU). Preoperative examinations included chest radiography, liver ultrasonography, and bone scanning. Patients with bilateral breast disease, inflammation, or systemic metastasis were excluded from this study. Institutionally approved written informed consent was obtained from all patients.

Radiotherapy

External-beam radiotherapy

Preoperative external-beam radiotherapy (EBRT) was applied with 50 Gy (ICRU) to the breast and the supra-/infraclavicular lymph nodes, using 5×2.0 Gy/week via tangential fields. The energy depended on the breast size: 6- to 10-MVX photons in large breasts (n=161) versus 60 Co in small breasts (n=154). In cases of medial primaries, a mammary chain field (combination of photons and electrons) was added. In addition, the supraclavicular region was irradiated in 255 of 315 patients on neoadjuvant treatment.

This work was presented in the form of a talk at DEGRO 2012 in Wiesbaden, Germany.

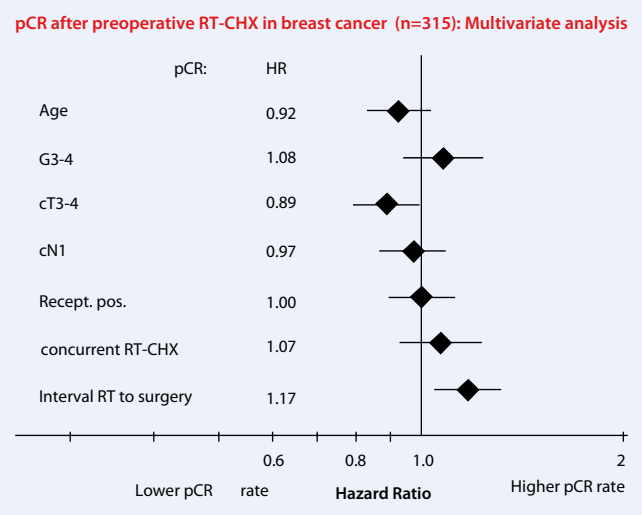

Fig. 1 ▲ Multivariate analysis after preoperative radiochemotherapy in breast cancer

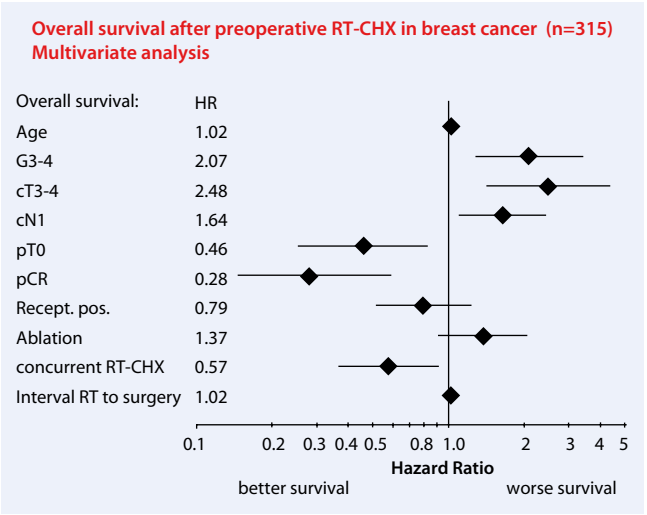

Fig. 2 ▲ Overall survival after preoperative radiochemotherapy in breast cancer. Multivariate analysis

Boost radiotherapy

In total, 101 patients were treated upfront with an interstitial ^{192}Ir high-dose rate (HDR) boost of 10 Gy. Generally, patients with interstitial implants had more advanced primary tumors. Initially, local hyperthermia was delivered with 43.5–44.5°C over 60 min immediately before interstitial radiotherapy. Details of treatment have been described previously [1]. The other 214 neoadjuvant patients (82/100 patients with cT1–T2 tumors, 84/137 patients with cT3 tumors, and 48/78 patients with cT4 tumors) received an electron boost with 10 Gy after EBRT and no interstitial boost.

Chemotherapy

The neoadjuvant chemotherapy consisted of 4× EC (epirubicin, cyclophosphamide) in 53%, mitoxantrone in 35.6%, 4× AC (adriamycin, cyclophosphamide) in 6.6%, 3× CMF (cyclophosphamide, methotrexate, 5-fluorouracil) in 0.6%, 6× CMF in 0.6%, and 6× EC in 0.6% of patients. Preoperative chemotherapy was applied before radiotherapy in 192 cases, simultaneously in 113 cases, and 10 patients (3.2%) had no chemotherapy.

Hormonal therapy

In all, 241 neoadjuvant-treated patients received additional hormonal treatment with tamoxifen or a luteinizing hormone-releasing hormone (LHRH) agonist, while 74 patients had no antihormonal treatment.

Postradiation surgery

Patients without distant metastases underwent surgical resection irrespective of the primary tumor response as assessed by palpation, ultrasound, or magnetic resonance imaging. The extent of the resection depended on the relative volume of the tumor and of the breast–tumor relationship after radiochemotherapy. In most cases, oncoplastic surgery with latissimus or TRAM was performed [23, 24]. Today, advanced oncoplastic surgery allows for personalized tailoring and sequencing of partial or total immediate breast reconstruction, according to the order or radiotherapy with regard to breast-conserving surgery or mastectomy in breast cancer treatment [6].

Tumor response

An in-breast pCR was defined as being an epithelial malignant residual component strictly in situ or representing less than 5% of the breast tumor mass without any mitosis according to the concept of a "total or near total therapeutic effect" proposed by Sataloff et al. [7] in 1995. Since nodal status is also taken into account for pCR, patients with pCR after neoadjuvant RT-CHX had to have no positive breast tumor cells and no axillary lymph nodes at surgery (ypT0, ypN0).

Age, tumor grade, nodal status, hormone receptor status, simultaneous vs. sequential CHX, and the time period up to surgery were examined by multivariate analysis for pCR and overall survival.

The clinical responses after neoadjuvant treatment were evaluated by comparing bidimensional measurements of the tumor after radiochemotherapy. Consecutive mammography and ultrasonography were also carried out. Clinical responses were characterized by using the classification system of the World Health Organization (WHO). The largest perpendicular diameters of the primary tumor were calculated and their products were analyzed before and after the administration of chemotherapy. Patients were categorized as being in complete remission if there was no clinical sign of tumor remaining in the breast. A partial response was defined as a reduction in the diameter product of more than 50%. If there was an increase of more than 25% in the diameter product, the patient was considered to have progressive disease. Patients whose tumor response did not meet the definitions of complete remission, partial response, or progressive disease were considered to have stable disease. Patients were evaluated after three cycles of chemotherapy had been administered. Patients were advised to undergo

Abstract · Zusammenfassung

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Long-term outcome after neoadjuvant radiochemotherapy in locally advanced noninflammatory breast cancer and predictive factors for a pathologic complete remission. Results of a multivariate analysis

Abstract

Background. An earlier published series of neoadjuvant radiochemotherapy (NRT-CHX) in locally advanced noninflammatory breast cancer (LABC) has now been updated with a follow-up of more than 15 years. Long-term outcome data and predictive factors for pathologic complete response (pCR) were analyzed.

Patients and methods. During 1991–1998, 315 LABC patients (cT1-cT4/cN0-N1) were treated with NRT-CHX. Preoperative radiotherapy (RT) consisted of external beam radiation therapy (EBRT) of 50 Gy (5×2 Gy/week) to the breast and the supra-/infraclavicular lymph nodes combined with an electron boost in 214 cases afterwards or—in case of breast conservation—a 10-Gy interstitial boost with ^{192}Ir afterloading before EBRT. Chemotherapy was administered prior to RT in 192 patients, and concomitantly in 113; 10 patients received no chemotherapy. The update of all follow-up ended in November 2011. Age, tumor grade, nodal status, hormone receptor status, simultaneous vs. sequential CHX, and the time interval between end of RT and surgery were examined in multivariate terms with pCR and overall survival as end point.

Results. The total pCR rate after neoadjuvant RT-CHX reached 29.2%, with LABC breast conservation becoming possible in 50.8% of cases. In initially node-positive cases (cN+), a complete nodal response (pN0) after NRT-CHX was observed in 56% (89/159). The multivariate analysis revealed that a longer time interval to surgery increased the probability for a pCR (HR 1.17 [95% CI 1.05–1.31], p<0.01). However, in large tumors (T3–T4) a significantly reduced pCR rate (HR 0.89 [95% CI 0.80–0.99], p=0.03) was obtained. Importantly, pCR was the strongest prognostic factor for long-term survival (HR 0.28 [95% CI 0.19–0.56], p<0.001).

Conclusion. pCR identifies patients with a significantly better prognosis for long-term survival. However, a long time interval to surgery (>2 months) increases the probability of pCR after NRT-CHX.

Keywords

Brustkrebs · Prognostische Marker
Neoadjuvante Radiochemotherapie · Pathologisch komplette Remission · Langzeitverlauf

Langzeitergebnisse nach neoadjuvanter Radiochemotherapie beim lokal fortgeschrittenen nichtinflammatorischen Mammakarzinom und prädiktive Faktoren für eine pathologisch komplette Remission. Ergebnisse einer multivariaten Analyse

Zusammenfassung

Hintergrund. Eine früher publizierte Studie zur neoadjuvanten Radiochemotherapie (NRT-CHX) beim lokal fortgeschrittenen nichtinflammatorischen Mammakarzinom wurde nun mit einer Nachbeobachtungszeit von über 15 Jahren aktualisiert. Langzeitergebnisse und prädiktive Faktoren für eine pathologisch komplette Remission (pCR) wurden untersucht.

Methodik. Zwischen 1991 und 1998 erhielten 315 Patienten mit Mammakarzinom im Stadium cT1–cT4/cN0–N1 eine NRT-CHX und wurden bis November 2011 nachbeobachtet. Die Brust und die supra-/infraklavikulären Lymphabflusswege wurden präoperativ mit 50 Gy (5×2 Gy/Woche) bestrahlt, in 214 Fällen danach mit einem Elektronenboost kombiniert bzw. in 101 Fällen von brusterhaltender Therapie mit einem interstitiellen Boost von 10 Gy und ^{192}Ir-Afterloading davor. Die Chemotherapie (CMF, EC oder Mitotraxon) wurde bei 192 Patienten vor der Bestrahlung verabreicht und bei 113 gleichzeitig appliziert; 10 Patienten erhielten keine Chemotherapie. Alter, Grading, Tumorgröße, N-Status, Hormonrezeptorstatus, simultane vs. sequenzielle CHX und der Zeitraum von NRT-CHX bis zur Op. wurden multivariat in Bezug auf das Erreichen einer pCR und auf das Gesamtüberleben untersucht.

Ergebnisse. Die pCR-Rate nach NRT-CHX zum Zeitpunkt der Op. betrug 29,2%, dabei wurde in 50,8% der Fälle der Brusterhalt möglich. Bei Patienten mit initialem Lymphknotenbefall (cN+) wurde in 56% der Fälle (89/159) eine komplette nodale Response (pN0) nach NRT-CHX festgestellt. In der multivariaten Analyse erhöhte ein längeres Intervall bis zur Op. die Wahrscheinlichkeit einer pCR [Hazard Ratio (HR): 1,17; 95%-Konfidenzintervall (95%-KI): 1,05–1,31; p<0,01]. Bei großen Tumoren wurde eine signifikant niedrigere pCR beobachtet (HR: 0,89; 95%-KI: 0,80–0,99; p=0,03). In Bezug auf das Gesamtüberleben war das Erreichen einer pCR der stärkste Prädiktor für ein langes Überleben (HR: 0,28; 95%-KI: 0,19–0,56; p<0,001).

Schlussfolgerung. Ein langes Intervall bis zur Op. (>2 Monate) verbessert die Wahrscheinlichkeit eine pCR nach NRT-CHX. Wie nach neoadjuvanter alleiniger CHX ist auch nach NRT-CHX das Erreichen einer pCR der wichtigste Prognosefaktor.

Schlüsselwörter

Breast cancer · Prognostic markers · Neoadjuvant radiochemotherapy · Pathologic complete response · Long-term outcome

breast-conserving surgery if the tumor diameter decreased to 2 cm or less. Otherwise, modified radical mastectomy was executed. Specimens were sent to the pathology department for complete evaluation.

Statistical analysis

Multivariate survival analyses were performed using Kaplan–Meier survival curves. The hazard ratios (HRs) and comparisons of HRs (Cox) were computed by appropriate Cox regression models [8]. For all calculations, the statistical analysis system SAS version 9.2 (SAS Institute Inc. Cary, NC, USA) was used.

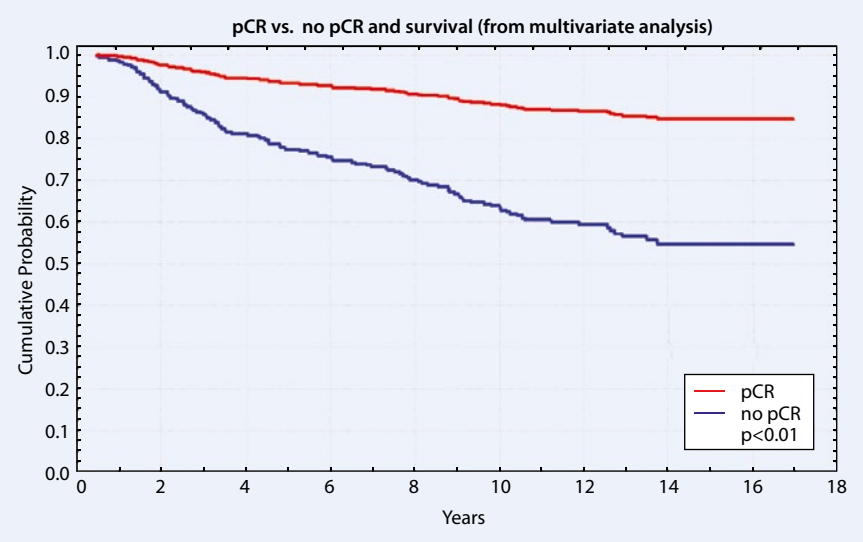

Fig. 3 ▲ pCR versus non-pCR and survival Kaplan–Meier plots. Results from a multivariate analysis are shown. The ordinate shows the cumulative survival proportions and the abscissa the time duration in years

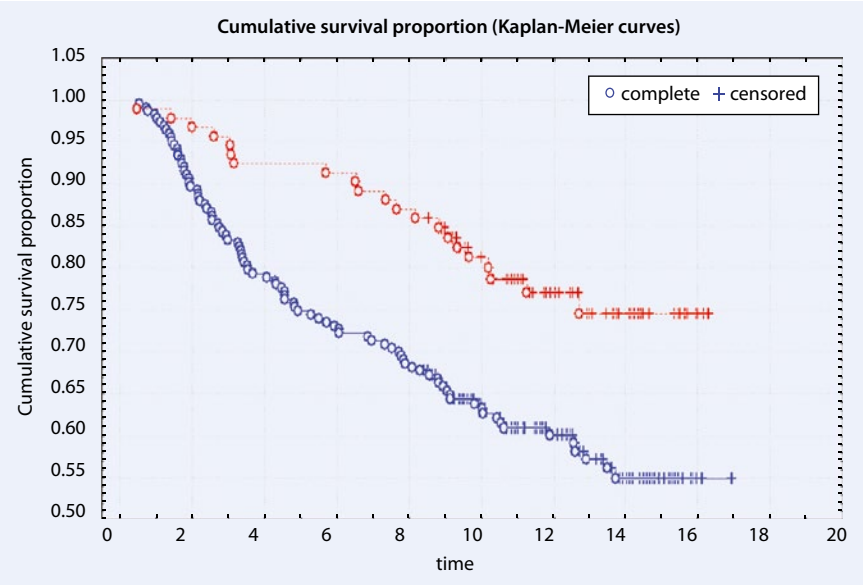

Fig. 4 ▲ Cumulative survival proportions. The ordinate shows the cumulative survival proportions and the abscissa the time duration in years

Results

After neoadjuvant RT-CHT, 116/315 (36.8%) primary tumors presented with a pathohistologic complete tumor remission, pT0: 67% (2/3) of cT1, 42.27% (41/97) of cT2, 37.96% (52/137) of cT3, and 26.92% (21/78) of cT4 tumors. The incidence of negative axillary nodes increased from 49.5% (156/315) cN0 to 68.9% (217/315) pN0. Breast-conserving surgery could be performed with immediate reconstruction in 160 of 315 patients (50.8%). A pathologic complete tumor and nodal remission rate (pCR = pT0+pN0) at surgery was found in 29.2% (92/315) of patients: 67% (2/3) of cT1, 36% (35/97) of cT2, 28% (39/137) of cT3, and 20% (16/78) of cT4 tumors.

The results of multivariate analysis after neoadjuvant radiochemotherapy in breast cancer regarding age, grading, tumor stage, nodal involvement, receptor status, concurrent radiochemotherapy, and the time sequence from radiation therapy to surgery are shown in **Fig. 1.** In the multivariate analysis, a long time interval to surgery increased the probability of pCR (HR 1.17 [95% CI 1.05–1.31], p<0.01). Age and progressive tumors seem to suffer from NRT-CHX (HR 0.92 and 0.89, respectively). The results of multivariate analysis for overall survival after preoperative radiochemotherapy in breast cancer regarding age, grading, tumor stage, nodal involvement, receptor status, concurrent radiochemotherapy, and the time sequence from radiation therapy to surgery are shown in **Fig. 2.** A pCR was identified as the strongest prognostic factor for long-term survival (HR 0.28 [95% CI 0.19–0.56], p<0.001). Also, pT0 (HR 0.46) and positive receptor status (HR 0.79) predicted a significantly better survival.

Fig. 3 and Fig. 4 present the Kaplan–Meier survival plots regarding pCR versus non-pCR after multivariate analysis. Here, the survival function shows a better clinical outcome for patients with pCR than patients without pCR.

Discussion

The application of neoadjuvant chemotherapy to breast cancer patient has the theoretical advantage of providing early treatment of micrometastases, probably leading to an increased survival rate compared to conventional treatment [9]. However, no difference in the relapse-free survival rate was found [10]. Other studies have shown no survival benefit from using neoadjuvant chemotherapy [11, 12].

In the National Surgical Adjuvant Breast and Bowel Project B-18.2, an objective response was seen in 80% of 747 patients after they received neoadjuvant chemotherapy of doxorubicin and cyclophosphamide [1]. Especially tumors larger than 5 cm in diameter shrank so that lumpectomy was possible, which experienced an increase of 175%. In general, there was an increase in lumpectomy of 12%.

After neoadjuvant RT-CHT, we observed a complete tumor remission in 37% of patients (116/315). Shanta et al. [13] reported a tumor downstaging rate of 45% after neoadjuvant simultaneous RCT with CMF or EC or AC. A pathologic nodal remission (pN0) after neoadjuvant RCT could be observed in 56% of our node-

positive (cN+) patients (89/156). Shanta et al. [13] published a nodal downstaging rate of 57% in 1,117 consecutive cases of LABC. pN0 probates had a 50% better prognosis compared to patients with N+, irrespective of primary tumor sterility. Lerouge et al. [14] as well as Shanta et al. [13] emphasize the importance of pN0. In their opinion, a nodal downstaging from cN+ to pN0 has the same prognosis as that in patients who presented with cN0 and had pN0 postoperatively.

Of our neoadjuvant-treated patients, 29.2% (92/315) presented a complete histopathologic response to neoadjuvant radiochemotherapy (**Fig. 1, 2, 3, 4**). These probates had a better outcome than patients who showed no response. This was similar to the effects of neoadjuvant chemotherapy alone, which reached a pCR rate of 5.9% [1/17] in advanced cancers [2]. Multivariate analysis showed a longer time interval to surgery increased the probability of pCR. The latter can be explained by a further growth of the advanced tumors after initial local inhibition. In our series, preoperative RT-CHT with 60 Gy was less effective in cT3 and cT4 tumors than in cT2 tumors [1]. The probability of occult axillary and distant metastases exceeds 50% in breast tumors reaching a size of 2–3 cm [15, 16]. Neoadjuvant radiotherapy may destroy occult stem cell metastases if the radiotherapy field includes the whole primary tumor and the occult regional nodal disease [17].

In terms of overall survival, the achievement of pCR was the strongest predictor for long-term survival (**Fig. 3, 4**). This implies that a better control of the primary tumor and regional metastases in the radiation field may lead to better survival rate. Low tumor status (HR 0.46) and positive receptor status (HR 0.79) predicted better survival. This is in accordance with earlier studies that compared the efficacy of neoadjuvant and adjuvant chemotherapy depending on tumor size [18, 19, 20]. Better survival rates could be shown for neoadjuvant chemotherapy in cases of tumors between 2.1 and 5 cm in diameter. The advantage of combined neoadjuvant RT-CHT is presumed to be due to the high tumoricidal effect against the stem and progenitor cells in the mammary gland [21, 22].

Conclusion

A long time interval to surgery (>2 months) increased the probability of pCR after NRT-CHX. However, in large tumors (T3–T4) a significantly more frequent pCR rate could be obtained. Low tumor status and positive receptor status predicted better survival. As in neoadjuvant CHX, the achievement of a pCR is an important prognostic factor for long-term survival.

Corresponding address

PD Dr. E. Bölke
Medical Faculty, Department of Radiation Oncology, Heinrich Heine University of Duesseldorf
Moorenstr. 5, 40225 Duesseldorf
Germany
boelke@med.uni-duesseldorf.de

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Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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