Retrospective Study of Neoadjuvant Versus Adjuvant Radiochemotherapy in Locally Advanced Noninflammatory Breast Cancer

Survival Advantage in cT2 Category by Neoadjuvant Radiochemotherapy*

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Purpose: This retrospective study compares patients treated between 1991 and 1998 with neoadjuvant radiotherapy ± chemotherapy (RCT) or adjuvant RCT for locally advanced noninflammatory breast cancers (LABC) in terms of pathologic complete response (pCR), 10-year relapse-free (RFS), and overall survival (OS).
Patients and Methods: Preoperative RCT in 315 and adjuvant RCT in 329 cases consisted in 50 Gy (5 × 2 Gy/week) to the breast and the supra-/infraclavicular lymph nodes. 101 neoadjuvant patients received – in case of breast conservation – a 10-Gy interstitial boost with ^{192}Ir afterloading before and 214 neoadjuvant patients a preoperative electron boost after external-beam radiotherapy. In the neoadjuvant RCT group, chemotherapy was applied prior to radiotherapy in 192 patients, and simultaneously in 113; ten had no chemotherapy. In the adjuvant RCT group, chemotherapy was applied to 44 patients before surgery and to 166 after surgery; 119 had no chemotherapy.
Results: Breast conservation became possible in 50.8% after neoadjuvant RCT for LABC with a pCR rate at surgery of 29.2%. A complete nodal remission (pN0) after RCT was observed in 56% (89/159) of the cN+ (clinically node-positive) neoadjuvant patients. There were trends in favor of preoperative RCT for RFS and OS (hazard ratio [HR] = 0.85; p = 0.09 for RFS; HR = 0.8130; p = 0.1037 for OS). For patients with cT2 tumors the RFS and OS were statistically significantly better (HR = 0.5090; p = 0.0130 for RFS; HR = 0.4390; p = 0.0026 for OS) after neoadjuvant compared to adjuvant RCT.
Conclusion: Neoadjuvant RCT achieved a pCR rate of 29.2% and a statistically significantly better RFS and OS in patients with cT2-category breast cancer.

Key Words: Breast cancer · Neoadjuvant · Radiotherapy · Chemotherapy · Retrospective study

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Retrospektive Studie einer neoadjuvanten versus adjuvanten Radiochemotherapie beim lokal fortgeschrittenen Mammakarzinom. Überlebensvorteil für die cT2-Kategorie durch eine neoadjuvante Radiochemotherapie

Ziel: Die Studie untersucht retrospektiv die Daten von Patientinnen, die in den Jahren 1991–1998 wegen eines lokal fortgeschrittenen, nichtinflammatorischen Mammakarzinoms (LABC) behandelt wurden. Verglichen werden eine neoadjuvante Strahlentherapie ± Chemotherapie (RCT) mit einer adjuvanten RCT hinsichtlich der pathologisch kompletten Remission (pCR), der 10-Jahres-Erkrankungsfreiheit (RFS) und des Gesamtüberlebens (OS).
Patienten und Methodik: Bei 315 Patientinnen mit einer präoperativen RCT und bei 329 Patientinnen mit einer adjuvanten RCT wurden 50 Gy (5 × 2 Gy/Woche) auf die Brust und die supra-/infraklavikulären Lymphknoten appliziert. 101 neoadjuvante Patientinnen erhielten im Fall einer Brusterhaltung einen interstitiellen 10-Gy-Boost mit ^{192}Ir-Afterloading vor und 214 neoadjuvante Patientinnen einen 10-Gy-Elektronenboost nach externer Strahlentherapie. Die Chemotherapie wurde in der neoadjuvanten

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RCT-Gruppe bei 192 Patientinnen vor der Strahlentherapie und bei 113 simultan appliziert. Zehn Patientinnen erhielten keine Chemotherapie. In der adjuvanten RCT-Gruppe wurde die Chemotherapie vor der Operation bei 44 und nach der Operation bei 166 Patientinnen appliziert. 119 Patientinnen erhielten keine Chemotherapie.

Ergebnisse: Die neoadjuvante RCT ermöglichte bei 50,8% der Patientinnen eine Brusterhaltung. Die lokale und gleichzeitig auch regionale komplette Remissionsrate (pCR) betrug 29,2%. Durch die neoadjuvante RCT konnte bei 56% (89/159) der cN+ neoadjuvanten Patienten ein pN0 erzielt werden. Im Gesamtkollektiv war zwar die neoadjuvante der adjuvanten Therapie hinsichtlich RFS und OS nur tendenziell überlegen (Hazard-Ratio [HR] = 0,85; p = 0,09 für RFS; HR = 0,8130; p = 0,1037 für OS), bei Patientinnen mit einer cT2-Kategorie erwiesen sich jedoch RFS und OS nach einer neoadjuvant RCT als signifikant besser als nach einer adjuvanten RCT (HR = 0,5090; p = 0,0130 für RFS; HR = 0,4390; p = 0,0026 für OS).

Schlussfolgerung: Eine neoadjuvante RCT erzielte eine Brusterhaltung bei 50,8% der LABC, eine pCR-Rate von 29,2% und bei cN+ eine pN0-Rate von 56%. Bei Patientinnen mit einer cT2-Kategorie waren RFS und OS nach einer neoadjuvanten versus einer adjuvanten RCT statistisch signifikant überlegen.

Schlüsselwörter: Mammakarzinom · Neoadjuvant · Radiotherapie · Chemotherapie · Retrospektive Studie

Introduction

Interdisciplinary guidelines for the treatment of breast cancer recommend neoadjuvant radiotherapy, possibly in combination with systemic therapy, only for inoperable stage III, if the disease remains inoperable following systemic therapy [11, 19, 28, 30]. Neoadjuvant chemotherapy alone is recommended in these indications, because patients, who achieve a pathologic complete remission (pCR), have a superior chance of survival as compared to patients without pCR [3, 6, 8, 9, 14, 22, 25, 31, 34].

The aim of the current retrospective, nonrandomized, monocenter study was to present the 10-year results of neoadjuvant radiotherapy plus chemotherapy (RCT) in locally advanced noninflammatory breast cancers (LABC).

Patients and Methods

Patients

Between 1991 and 1998, 315 LABC patients without distant metastases received neoadjuvant RCT at the University Hospital of Düsseldorf and the Interdisciplinary Breast Center – IBC, Sana Hospital, Düsseldorf, Germany. They were compared with 329 patients subjected to adjuvant radiotherapy ± chemotherapy during the same period. The retrospective study started with the selection of neoadjuvant-treated patients. Afterwards, patients showing similar categories and stages were chosen for comparison. Eligibility 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, and extended intraductal component [EIC]), stages IIA–IIIC according to the International Union Against Cancer (ICRU) criteria. Patients with inflammatory or bilateral breast disease were excluded from the protocol. Institutionally approved written consent was obtained from all the well-informed patients. Patient characteristics are outlined in Table 1. Stage distribution was comparable in neoadjuvant versus adjuvant patients: stage 2: n = 160 versus 155; stage 3: n = 155 versus 174.

Treatment

Systemic Treatment

Chemotherapy

In the neoadjuvant RCT group, chemotherapy consisted of 4 × EC (epirubicin, cyclophosphamide) in 53%, mitoxantrone in 35.6%, 4 × AC (adriamycin, cyclophosphamide) in 6.7%, no chemotherapy in 3.2%, 3 × CMF (cyclophosphamide, methotrexate, 5-fluorouracil) in 0.3%, 6 × CMF in 0.3%, and 6 × EC in 0.3%. In neoadjuvant RCT patients chemotherapy was applied before radiotherapy in 192 cases, simultaneously in 113, and 10 had no chemotherapy.

In the adjuvant RCT group, 37% received no chemotherapy, 27% 4 × EC, 16% mitoxantrone, 9% 3 × CMF, 5% 6 × CMF,

Table 1. Patient characteristics of 644 retrospective breast cancer cases from Düsseldorf, Germany.

Tabelle 1. Patientencharakteristika von 644 retrospektiv ausgewerteten Brustkrebspatienten aus Düsseldorf, Deutschland.

	Neoadjuvant radiotherapy ± chemotherapy	Adjuvant radiotherapy ± chemotherapy
Patients (n)	315	329
≤ 50 years	117	82
> 50 years	198	247
cT-categories		
cT1	3	1
cT2	97	180
cT1 + cT2	100	181
cT3	137	62
cT4	78	86
cN-categories		
cN0	156	117
cN+	159	212
Pathologic T-categories		
pT0	116	4
pT1	138	13
pT2	46	182
pT3	4	51
pT4	11	79

4% 4 × CMF, 1% 4 × AC, 0.3% 3 × EC, 0.3% 3 × adriamycin, and 0.3% 4 × taxane. Chemotherapy was applied before surgery in 44 cases, and after surgery in 166. 119 patients had no chemotherapy.

Hormonal Therapy

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

In the adjuvant group, 213 patients received additional hormonal treatment with tamoxifen or an LHRH agonist. 116 patients had no antihormonal treatment.

Radiotherapy

External-Beam Radiotherapy

Dose and energy. Preoperative radiotherapy consisted of one course of external-beam radiotherapy of 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 case of medial primaries, a mammary chain field (combination of photons and electrons) was added. The supraclavicular field was irradiated in 255/315 neoadjuvant patients.

Adjuvant radiotherapy after primary surgery consisted of 50 Gy (6- to 10-MVX X-rays [n = 160] or ^{60}Co [n = 169]) plus a 10-Gy electron boost in case of breast conservation. The supraclavicular field was irradiated in 188/329 adjuvant patients.

Interstitial Therapy

101 patients received an interstitial boost of 10 Gy ^{192}Ir afterloading therapy. Generally, patients with interstitial implants had more advanced primary tumors. 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, 15, 16]. 214 neoadjuvant patients (82/100 patients with cT1–T2 tumors, 84/137 patients with cT3 tumors, and 48/78 patients with cT4 tumors) received only an electron boost after external-beam radiotherapy and no interstitial boost.

Surgery

The original tumor location was marked with ink and documented by photographs prior to treatment. Surgery was performed on every patient without distant metastases irrespective of the primary tumor response as assessed by palpation, ultrasound, or magnetic resonance. The extent of the resection depended on the relative volume of the tumor prior to RCT and of the breast-tumor relationship.

Pathology – Tumor Response

Pathologic tumors with an epithelial malignant residual component strictly in situ or representing < 5% of the breast tumor mass without any mitosis were classified in the group of in-breast pCR. This definition followed the concept of a "total or near total therapeutic effect" proposed by Sataloff et al. in 1995 [27]. Since pCR did take histological nodal status into account, patients with pCR after neoadjuvant RCT had no positive breast tumor cells and no axillary lymph nodes at surgery.

Statistical Analysis

For all patients with neoadjuvant RCT, the preoperative cT-category and cN-category were known. For patients with adjuvant RCT, the pT-category was used for comparison, if the cT-value was not stated. Primary endpoint were the pCR, pT0 and pN0 rates, as well as the 10-year overall (OS) and relapse-free survival (RFS) rates of patients with neoadjuvant versus adjuvant RCT. The OS period was defined as the elapsed interval between the start of treatment and the date of death regardless of etiology, and the date of end of follow-up, respectively. Circumstances for the calculations of RFS included all local, regional, or distant recurrences, whereas occurrences of contralateral breast cancer, other second primary cancer, and deaths without recurrence were treated as censoring circumstances.

The survival probability was estimated by the actuarial method [18]. The results are given with standard error (SE) and patients at risk in parentheses. Univariate survival analysis was performed by log-rank test and Kaplan-Meier survival curves. The hazard ratios (HRs) and comparisons of HRs [10] were computed by appropriate Cox regression models. For all computation, the statistical analysis system SAS version 9.2 (SAS Institute Inc. Cary, NC, USA) was used.

Results

Effect of Neoadjuvant Therapy

Breast Conservation

Breast-conserving surgery was performed with a tumor-specific immediate reconstruction on 160/315 patients (50.8%) from the neoadjuvant group in spite of surgically difficult primary tumors.

Tumor Remission (pT0)

After neoadjuvant RCT, 116/315 (36.8%) primary tumors showed 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 (Figure 1).

Nodal Remission (pN0)

Due to neoadjuvant radiochemotherapy, the incidence of negative axillary nodes increased from 49.5% (156/315) cN0 to 68.9% (217/315) pN0. In patients with postoperative RCT, the incidence of negative axillary nodes did not change: 35.6% (117/329) cN0 versus 36.2% (119/329) pN0 (p = < 0.0001). A complete nodal remission (pN0) was observed after RCT in 56% (89/159) of the cN+ (clinically node-positive) neoadjuvant patients (Figure 2).

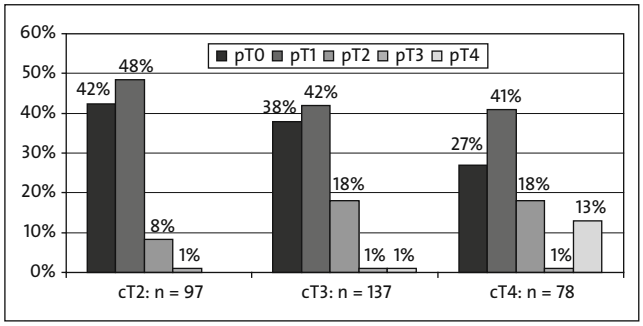


Figure 1. Complete tumor remission after neoadjuvant RCT was observed in 42% of the cT2, 38% of the cT3, and 27% of the cT4 categories.

Abbildung 1. Komplette Tumorrückbildung nach neoadjuvanter RCT wurde bei 42% der cT2-, 38% der cT3- und 27% der cT4-Kategorien beobachtet.

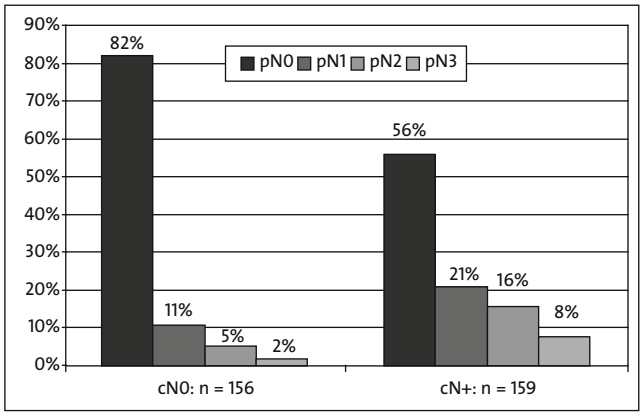


Figure 2. Complete axillary node remission after neoadjuvant RCT was observed in 56% of the cN+ patients.

Abbildung 2. Bei 56% der cN+ Patienten zeigte sich nach einer neoadjuvanten RCT bei der Operation pathohistologisch ein pN0.

Simultaneous Pathologic Complete Tumor and Nodal Response (pCR) After Neoadjuvant RCT

In the preoperative RCT group, a pathologic simultaneous complete tumor and nodal remission rate (= pT0 + pN0) at surgery was found in 29.2% (92/315): 67% (2/3) of cT1, 36% (35/97) of cT2, 28% (39/137) of cT3, and 20% (16/78) of cT4 tumors.

Survival

Relapse-Free Survival of Neoadjuvant Versus Adjuvant Patients

The 10-year RFS of patients after preoperative radiochemotherapy (n = 315) was not significantly better (67.96%) than that of patients (n = 329) after adjuvant RCT (66.31%; p = 0.2367; HR 0.857; standard error [SE] lower limit 0.663; SE upper limit 1.108; Figures 3a and 4a).

Overall Survival of Neoadjuvant Versus Adjuvant Patients

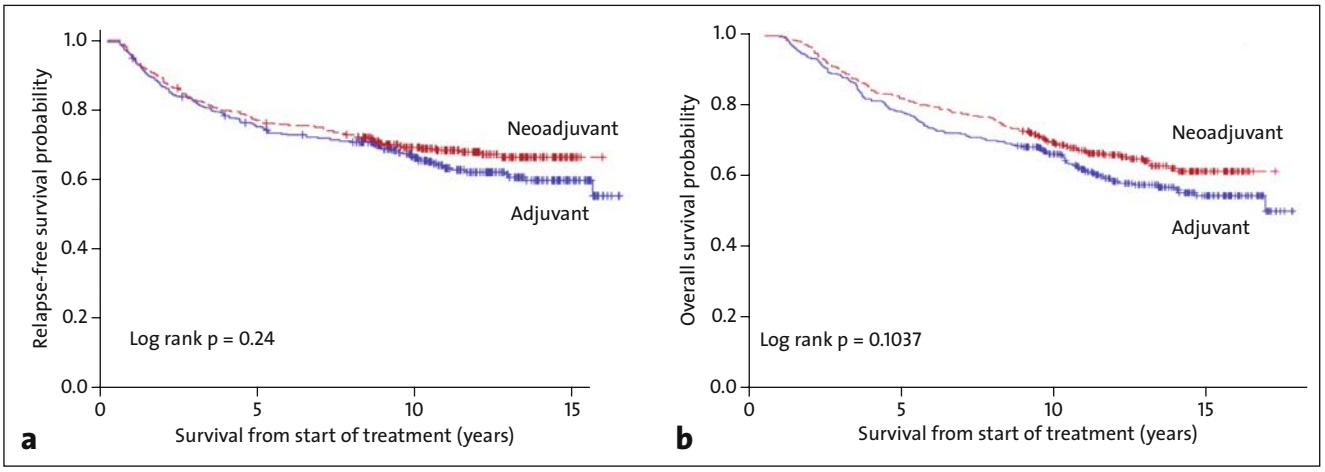
The patients with neoadjuvant RCT (n = 315) showed a nonsignificant trend toward better 10-year OS (68.59%) as compared to the patients receiving adjuvant treatment (n = 329; than 64.96%, p = 0.1037; HR 0.813; SE 0.632 and 1.043; Figures 3b and 4b).

Prognostic Factors for Survival

cT-Categories

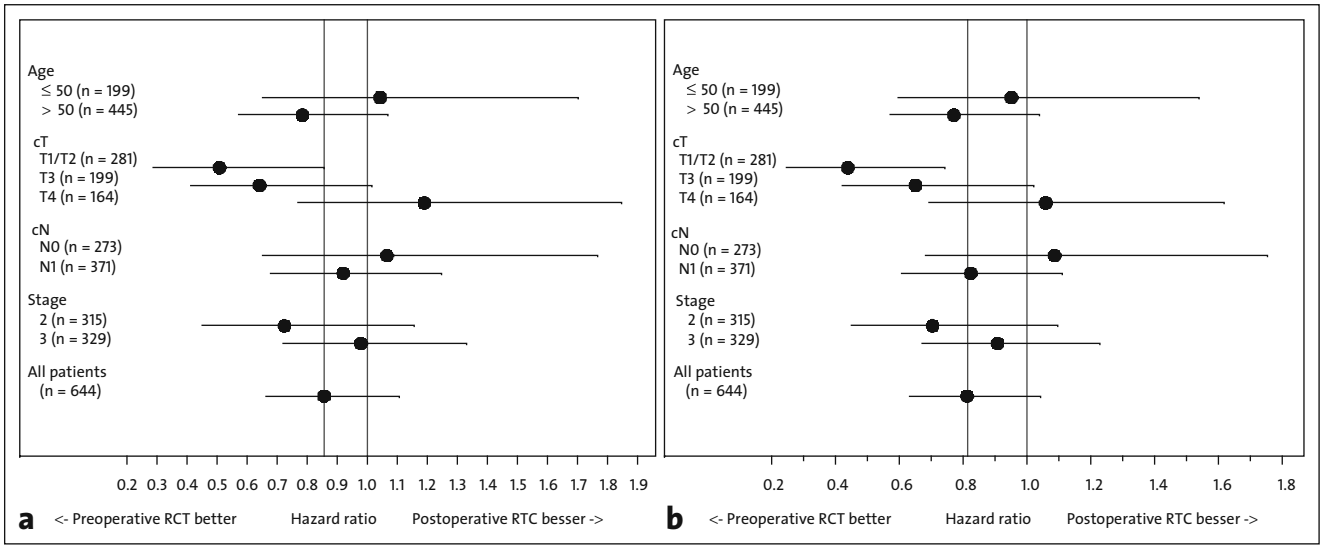
The main result of this retrospective study was the statistically significantly better 10-year RFS rate of 84.84% after neoadjuvant RCT in patients with cT1 and cT2 disease, which means an improvement by 11.6% compared to 73.27% after adjuvant RCT (p = 0.0130; HR 0.5090; lower confidence limit [CL] 0.2870; upper CL 0.8560).

After neoadjuvant RCT, the 10-year OS in patients with cT1 (n = 3) and cT2 (n = 97) tumors of 85.76% was better (by



Figures 3a and 3b. No significant difference after neoadjuvant versus adjuvant RCT in relapse-free survival (p = 0.24; a) and overall survival (p = 0.1037; b) was found in 644 patients with locally advanced noninflammatory breast cancer.

Abbildungen 3a und 3b. Nach einer neoadjuvanten RCT zeigte sich hinsichtlich des rezidivfreien Überlebens (p = 0,24; a) und des Gesamtüberlebens (p = 0,1037; b) kein signifikanter Unterschied bei 644 Patientinnen mit einem lokal fortgeschrittenen Brustkrebs.



Figures 4a and 4b. The hazard ratio (HR) of prognostic factors in 644 patients with neoadjuvant versus adjuvant RCT indicates that a preoperative RCT is better, especially for cT2 breast cancer, concerning relapse-free survival (HR 0.5090; a) and overall survival (HR 0.4390; b).

Abbildungen 4a und 4b. Die Hazard Ratio (HR) der prognostischen Faktoren bei 644 Patientinnen mit einer neoadjuvanten vs. einer adjuvanten RCT zeigt, dass eine präoperative RCT speziell beim cT2- Brustkrebs hinsichtlich des rezidivfreien Überlebens (HR 0,5090; a) und des Gesamtüberlebens (HR 0,4390; b) besser ist.

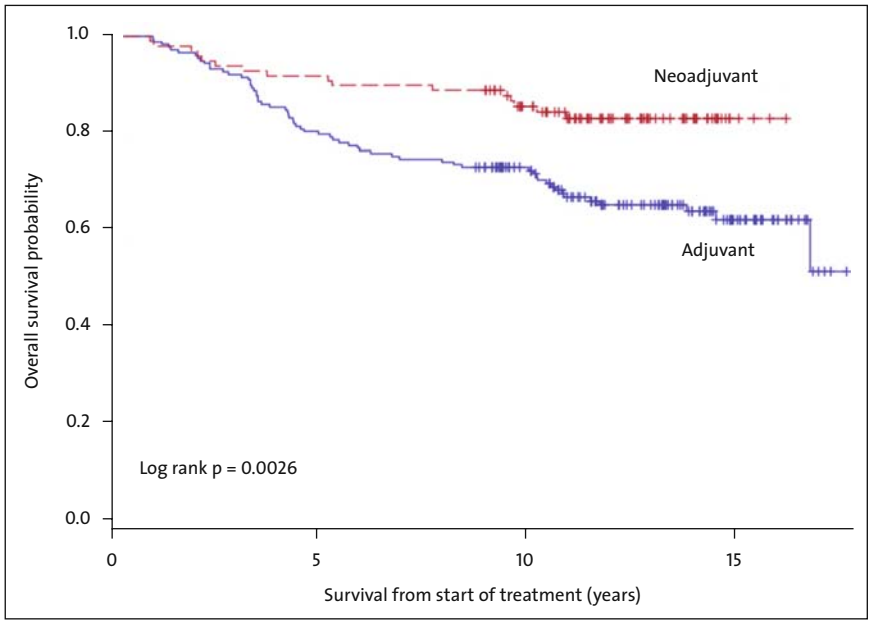


Figure 5. 10-year overall survival in the cT2 category was better (by 13.6%) after neoadjuvant than after adjuvant RCT.

Abbildung 5. Die 10-Jahres-Überlebensrate betrug in der cT2-Kategorie nach einer neoadjuvanten RCT 13,6% mehr als nach einer adjuvanten.

13.6%) compared to 72.19% in patients with cT1 (n = 1) and cT2 (n = 180) tumors receiving adjuvant treatment (p = 0.0026; Figure 5).

This advantage in 10-year OS was less evident for cT3 (66.80% after neoadjuvant therapy vs. 54.31% after adjuvant treatment; p = 0.0535; HR 0.651; HR lower CL 0.422; HR upper CL 1.020) and cT4 tumors (49.78% after neoadjuvant therapy vs. 57.54% after adjuvant treatment; p = 0.789; HR 1.059; HR lower CL 0.694; HR upper CL 1.616).

Nodal Involvement

The difference between neoadjuvant and adjuvant RCT regarding RFS in cN+ and cN0 patients was HR 0.92 (lower PLCL 0.676; upper PLCL 1.246) and HR 1.066 (lower PLCL 0.652; upper PLCL 1.768), respectively.

The difference between neoadjuvant and adjuvant RCT regarding OS in N+ and cN0 patients was HR 0.824 (lower PLCL 0.607; upper PLCL 1.111) and HR 1.087 (lower PLCL 0.683; upper PLCL 1.752), respectively.

Stage

The difference between neoadjuvant and adjuvant RCT regarding OS in stage 2 and stage 3 patients was HR 0.704 (lower PLCL 0.448; upper PLCL 1.096) and HR 0.908 (lower PLCL 0.67; upper PLCL 1.227), respectively.

Discussion

Breast Conservation

Although, in general, the patients suffered from LABC, breast-conserving surgery could be performed on 160/315 neoadjuvant patients (50.8%) with tumor-specific reconstruction [2, 24].

Tumor Remission Rates

In our series, complete tumor remission after neoadjuvant RCT was observed in 37% of patients (116/315). Shanta et al. [29] reported an even higher primary tumor downstaging of 45% after neoadjuvant simultaneous RCT with CMF or EC or AC.

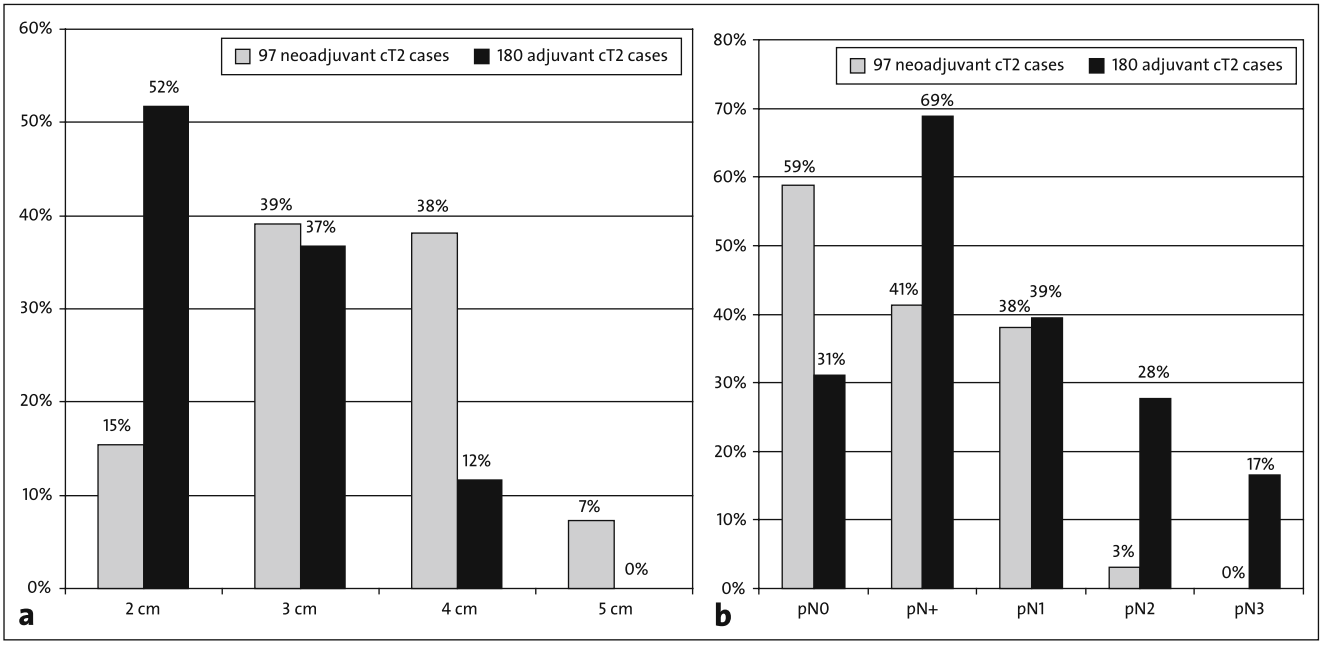
Nodal Remission Rates

A complete nodal remission (pN0) after neoadjuvant RCT was observed in 56% of our node-positive (cN+) patients (89/156). Shanta et al. [29] reported a similar nodal downstaging in 57% of 1,117 consecutive cases of LABC. Patients with pN0 had a 50% better prognosis compared to patients with N+, irrespective of primary tumor sterility. Shanta et al. [29] as well as Lerouge et al. [21] proved, that patients with nodal downstaging from cN+ to pN0 had the same good prognosis as patients, who presented with cN0 and had pN0 at axillary dissection.

29.2% of our neoadjuvant cases (92/315) presented a pathohistologic primary tumor and simultaneous axillary node sterility. This implies that achieving a better degree of control of the primary tumor and of regional metastases in the radiation field may ultimately lead to better survival rates.

Relapse-Free Survival and Overall Survival Advantage After Neoadjuvant Versus Adjuvant Radiotherapy

This series is the first in the literature to compare long term RFS and OS after neoadjuvant RCT and adjuvant RCT in LABC or surgically unfavorable breast cancer. This comparison is, however, compromised because of the retrospective and nonrandomized study design. Patients selected underwent treatment in the same period from 1991 to 1998 and showed comparable stages of disease. 10-year RFS was not significantly better in the neoadjuvant RCT arm (n = 315) as compared to the adjuvant RCT arm (n = 329; 67.96% vs. 66.31%; p = 0.2367; HR 0.857 [0.663–1.108]), and also the OS rate in the neoadjuvant group only tended to compare favorably with that of the adjuvant arm (p = 0.1037; HR 0.813 [0.632–1.043]; Figure 3). According to the internal protocol of our radiotherapy department, patients with more advanced disease or planned flaps commonly receive neoadjuvant RCT. This is one reason, why the number of patients with larger tumors is smaller in the postoperative group of this retrospective study



Figures 6a and 6b. The clinical tumor diameter in cT2 patients was larger in the group receiving neoadjuvant RCT than in the adjuvant RCT arm (a). Nethertheless 59% of the cT2 cases were pN0 after neoadjuvant RCT versus only 31% after adjuvant RCT (b).

Abbildungen 6a und 6b. Obwohl der klinische Tumordurchmesser bei den Patientinnen mit einer pT2-Kategorie bei den neoadjuvant Behandelten größer war, konnte trotzdem durch eine neoadjuvante RCT in 59% pN0 erzielt werden vs. nur 31% bei den adjuvanten Patientinnen (b).

and may explain the statistically not significant difference in survival rates.

Efficacy of Neoadjuvant Compared to Adjuvant Radiochemotherapy Depends on the Tumor Size

The main result of this retrospective study was the statistically significantly better (by 13.6%) 10-year OS after neoadjuvant RCT in patients with cT1 (n = 3) and cT2 (n = 97) tumors of 85.76% compared to 72.04% in patients with cT1 (n = 1) and cT2 (n = 180) tumors receiving adjuvant treatment (p = 0.0026). 85% of the patients in the neoadjuvant group showed large T2 tumors ≥ 3 cm as compared to only 48% in the adjuvant group. Yet 59% of the 97 neoadjuvant cT2 cases were pathologically node-negative after RCT versus 31% of the 180 cT2 cases in the adjuvant group (Figure 6).

According to Bonadonna et al. and the Early Breast Cancer Trialists' Collaborative Group [4, 13], primary tumors < 5 cm seem to respond well to neoadjuvant chemotherapy. The National Surgical Adjuvant Breast and Bowel Project Protocol B-18 compared the efficacy of neoadjuvant and adjuvant chemotherapy depending on tumor size [3, 14, 25]: forest plots by clinical tumor size showed better 15 year OS and RFS rates for neoadjuvant chemotherapy in case of a tumor size between 2.1 and 5 cm (HR 0.90 and 0.93), whereas T1 tumors ≤ 2 cm (HR 1.1 and 1.15) and T3 tumors >5 cm (HR 1.18 and 1.05) benefitted more from adjuvant chemotherapy.

Radiation Dose and Tumor Control Probability

In our series, preoperative RCT with 60 Gy was less effective in cT3 and cT4 tumors than in cT2 tumors. In 1980, Withers & Peters [33] reported complete regression in only 30% of T3 tumors, if 70–80 Gy are given. For a tumor control probability of 75%, 80–100 Gy must be applied [23, 33].

The advantage of combined RCT compared to chemotherapy alone is presumed to be due to the higher tumoricidal effect against the stem and progenitor cells in the mammary gland [12, 17]. The risk of occult axillary and distant metastases exceeds 50% in breast tumors reaching a size of 2–3 cm [7, 20]. If the disease is limited to the breast and the regional nodes, the radiotherapy field may include the whole primary tumor and the occult regional nodal disease and radiation field may destroy more occult stem cell metastases [5, 32].

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