



Post-Mastectomy Radiotherapy After Neoadjuvant Chemotherapy in Breast Cancer: A Pooled Retrospective Analysis of Three Prospective Randomized Trials

David Krug, MD^{1,2,21}, Bianca Lederer, PhD³, Fenja Seither, MSc³, Valentina Nekljudova, PhD³, Beyhan Ataseven, MD⁴, Jens-Uwe Blohmer, MD⁵, Serban Dan Costa, MD⁶, Carsten Denkert, MD⁷, Nina Ditsch, MD⁸, Bernd Gerber, MD⁹, Claus Hanusch, MD¹⁰, Joerg Heil, MD¹¹, Jörn Hilfrich, MD¹², Jens B. Huober, MD¹³, Christian Jackisch, MD¹⁴, Sherko Kümmel, MD¹⁵, Stefan Paepke, MD¹⁶, Christian Schem, MD¹⁷, Andreas Schneeweiss, MD¹⁸, Michael Untch, MD¹⁹, Jürgen Debus, MD, PhD^{1,2}, Gunter von Minckwitz, MD³, Thorsten Kühn, MD²⁰, and Sibylle Loibl, MD³

¹Department of Radiation Oncology, University Hospital Heidelberg, Heidelberg, Germany; ²National Center for Radiation Oncology (NCRO), Heidelberg Institute for Radiation Oncology (HIRO), Heidelberg, Germany; ³German Breast Group, Neu-Isenburg, Germany; ⁴Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany; ⁵Charité, Klinik für Gynäkologie, Berlin, Germany; ⁶Universitätsklinikum Magdeburg, Universitätsfrauenklinik, Magdeburg, Germany; ⁷Institute for Pathology, Philipps-University Marburg, Marburg, Germany; ⁸Department of Obstetrics and Gynecology, Ludwig-Maximilians-University of Munich, Munich, Germany; ⁹Department of Gynecology and Obstetrics, University Hospital, Rostock, Germany; ¹⁰Rotkreuzklinikum München, Frauenklinik, Munich, Germany; ¹¹Breast Unit, University Hospital, University of Heidelberg, Heidelberg, Germany; ¹²Frauenklinik Henriettenstiftung, Hannover, Germany; ¹³Universitätsklinikum Ulm, Universitätsfrauenklinik, Ulm, Germany; ¹⁴Sana Klinikum Offenbach, Klinik für Gynäkologie und Geburtshilfe, Offenbach, Germany; ¹⁵Breast Unit, Kliniken Essen-Mitte, Essen, Germany; ¹⁶Klinikum rechts der Isar TU München, Frauenklinik und Poliklinik, Munich, Germany; ¹⁷Mammazentrum Hamburg, Hamburg, Germany; ¹⁸National Center for Tumor Diseases, Heidelberg, Germany; ¹⁹Helios Klinikum Berlin-Buch, Klinik für Gynäkologie und Geburtshilfe, Berlin, Germany; ²⁰Department for Gynecology and Obstetrics, Interdisciplinary Breast Center, Esslingen, Germany; ²¹Present Address: Department of Radiation Oncology, University Hospital Schleswig-Holstein, Kiel, Germany

ABSTRACT

Background. The impact of locoregional radiotherapy (RT) after neoadjuvant chemotherapy (NACT) and mastectomy in breast cancer patients is currently unclear. Several publications have suggested that patients with a

favorable response to NACT might not benefit from RT after mastectomy.

Methods. A retrospective analysis of three prospective randomized NACT trials was performed. Information on the use of RT was available for 817 breast cancer patients with non-inflammatory breast cancer who underwent mastectomy after NACT within the GeparTrio, GeparQuattro, and GeparQuinto-trials. RT was administered to 676 of these patients (82.7%).

Results. The 5-year cumulative incidence of locoregional recurrence (LRR) was 15.2% (95% confidence interval [CI] 9.0–22.8%) in patients treated without RT and 11.3% in patients treated with RT (95% CI 8.7–14.3%). In the multivariate analysis, RT was associated with a lower risk of LRR (hazard ratio 0.51, 95% CI 0.27–1.0; $p = 0.05$). This effect was shown especially in patients with cT3/4 tumors, as well as in patients who were cN+ before

Electronic supplementary material The online version of this article (<https://doi.org/10.1245/s10434-019-07635-x>) contains supplementary material, which is available to authorized users.

© Society of Surgical Oncology 2019

First Received: 16 October 2018;
Published Online: 26 July 2019

D. Krug, MD
e-mail: david.krug@uksh.de

neoadjuvant therapy, including those who converted to ypN0 after neoadjuvant therapy. In the bivariate analysis, disease-free survival was significantly worse in patients who received RT, however this was not confirmed in the multivariate analysis.

Conclusions. Our results suggest that RT reduces the LRR rates in breast cancer patients who receive a mastectomy after NACT without an improvement in DFS. Prospective randomized controlled trials such as the National Surgical Adjuvant Breast and Bowel Project B-51/RTOG 1304 trial will analyze whether RT has any benefit in patients who have a favorable response after NACT.

Neoadjuvant chemotherapy (NACT) for breast cancer has enjoyed increasing popularity during the last decade.¹ The outcome after NACT is at least equivalent to postoperative administration in terms of survival.^{2,3} Treatment response to NACT, especially pathological complete response (pCR) is a strong prognostic factor in individual patients, especially those with triple-negative or human epidermal growth factor receptor 2 (HER2)-overexpressing tumors.^{4,5}

There is a clear effect of systemic therapy on the risk of locoregional recurrence (LRR).⁶ Although the absolute benefit of adjuvant post-mastectomy radiotherapy (PMRT) on LRR likely decreases when an effective systemic therapy regimen is administered, its effect on survival is thought to be largest in this context.^{7,8} The question remains as to what extent PMRT improves locoregional control and survival with contemporary systemic therapy since the trials included in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis on PMRT used outdated systemic therapy regimens.^{9,10} Furthermore, we need additional evidence as to whether

PMRT improves results in patients with response to NACT, especially with a pCR or conversion from clinically involved lymph nodes (cN+) to pathologically negative lymph nodes (ypN0).^{11,12}

We pooled information on the use of PMRT from three prospective randomized controlled trials¹³⁻¹⁹ investigating different NACT regimens, to analyze the impact of adjuvant PMRT on LRR and survival.

PATIENTS AND METHODS

A pooled analysis of three prospective randomized controlled trials testing different regimens of NACT in breast cancer patients was performed; the results of these trials (GeparTrio, GeparQuattro, and GeparQuinto) have been published elsewhere.¹³⁻¹⁹

A total of 6139 patients were treated in these trials from September 2002 to July 2010. Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram for patients included in this analysis. We excluded patients with progression or death before surgery, patients with missing surgery data, patients without further randomization after two initial cycles of TAC (docetaxel, doxorubicin, and cyclophosphamide) in GeparTrio, patients with inflammatory breast cancer, and those who did not receive radiotherapy (RT) due to early progression before surgery. Information on the administration of RT was collected prospectively. Clinical data and follow-up were available from 817 of 1569 patients who had a mastectomy. Details on treatment regarding systemic therapy in GeparTrio, GeparQuattro, and GeparQuinto are available in "Electronic supplementary material".

The study protocols for all three trials provided recommendations regarding the use of RT after NACT and surgery (electronic supplementary Table 1). The choice

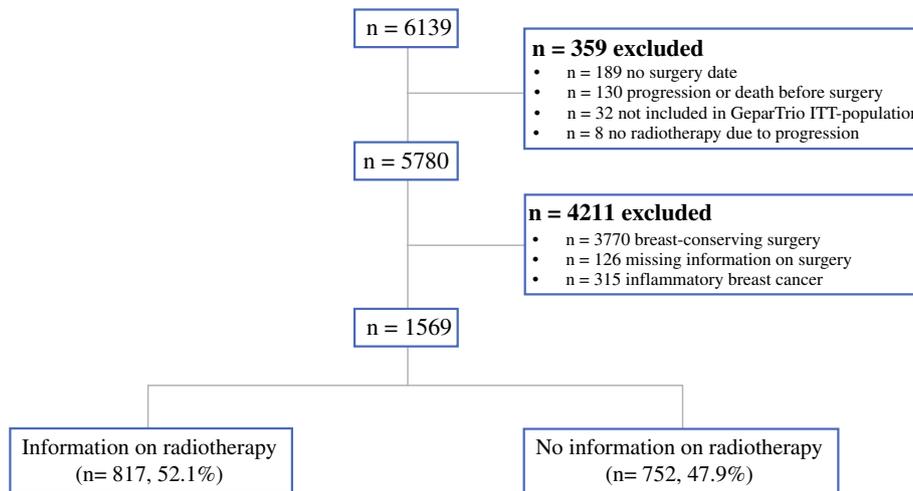


FIG. 1 Overview of patients included in the current analysis. *ITT* intention to treat

TABLE 1 Patient characteristics

Parameter	All patients (<i>n</i> = 817)	RT (<i>n</i> = 676)	No RT (<i>n</i> = 141)	<i>p</i> value (RT vs. no RT)
Age, years [median (min–max)]	49 (21–78)	49 (21–78)	48 (23–68)	
Age group (years)				0.004
< 40	123 (15.1)	89 (13.2)	34 (24.1)	
40–49	303 (37.1)	258 (38.2)	45 (31.9)	
≥ 50	391 (47.9)	329 (48.7)	62 (44.0)	
Histology				0.371
Ductal invasive	623 (76.3)	511 (75.6)	112 (79.4)	
Lobular invasive	145 (17.7)	121 (17.9)	24 (17.0)	
Other	49 (6.0)	44 (6.5)	5 (3.5)	
Grading				0.115
G1	31 (3.8)	30 (4.4)	1 (0.7)	
G2	483 (59.1)	398 (58.9)	85 (60.3)	
G3	271 (33.2)	224 (33.1)	47 (33.3)	
Missing	32 (3.9)	24 (3.6)	8 (5.7)	
ER status				0.921
ER-positive	556 (68.1)	459 (67.9)	97 (68.8)	
ER-negative	258 (31.6)	214 (31.7)	44 (31.2)	
Missing	3 (0.4)	3 (0.4)	0	
PR status				0.926
PR-positive	464 (56.8)	384 (56.8)	80 (56.7)	
PR-negative	349 (42.7)	288 (42.6)	61 (43.3)	
Missing	4 (0.5)	4 (0.6)	0	
HER2 status				0.746
HER2-positive	207 (25.3)	170 (25.1)	37 (26.2)	
HER2-negative	564 (69.0)	470 (69.5)	94 (66.7)	
Missing	46 (5.6)	36 (5.3)	10 (7.1)	
Breast cancer subtype				0.816
HR+/HER2–/G1–2	323 (39.5)	272 (40.2)	51 (36.2)	
HR+/HER2–/G3	103 (12.6)	87 (12.9)	16 (11.3)	
HR+/HER2+	116 (14.2)	93 (13.8)	23 (16.3)	
HR–/HER2+	90 (11.0)	76 (11.2)	14 (9.9)	
TNBC	128 (15.7)	104 (15.4)	24 (17.0)	
Missing	57 (7.0)	44 (6.5)	13 (9.2)	
Clinical tumor stage				< 0.001
cT1	38 (4.7)	28 (4.1)	10 (7.1)	
cT2	403 (49.3)	315 (46.6)	88 (62.4)	
cT3	253 (31.0)	222 (32.8)	31 (22.0)	
cT4a–c	119 (14.6)	108 (16.0)	11 (7.8)	
Missing	4 (0.5)	3 (0.4)	1 (0.7)	
Clinical nodal stage				0.001
cN0	309 (37.8)	238 (35.2)	71 (50.4)	
cN+	501 (61.3)	432 (63.9)	69 (48.9)	
Missing	7 (0.9)	6 (0.9)	1 (0.7)	
Initial SLNB				0.484
Yes	74 (9.1)	61 (9.0)	13 (9.2)	
No	448 (54.8)	383 (56.7)	65 (46.1)	
Missing	295 (36.1)	232 (34.3)	63 (44.7)	

TABLE 1 continued

Parameter	All patients (n = 817)	RT (n = 676)	No RT (n = 141)	p value (RT vs. no RT)
SLNB-positive (valid %)	43 (61.4)	40 (69.0)	3 (25.0)	< 0.001
Pathological tumor stage				0.001
ypT0	78 (9.5)	58 (8.6)	20 (14.2)	
ypT1	207 (25.3)	158 (23.4)	49 (34.8)	
ypT2	173 (21.2)	151 (22.3)	22 (15.6)	
ypT3	115 (14.1)	109 (16.1)	6 (4.3)	
ypT4a-c	25 (3.1)	24 (3.6)	1 (0.7)	
ypT4d	5 (0.6)	5 (0.7)	0	
> ypT0	172 (21.1)	139 (20.7)	33 (23.4)	
ypTis	37 (4.5)	28 (4.2)	9 (6.4)	
Missing	5 (0.6)	4 (0.6)	1 (0.7)	
Pathological nodal stage				< 0.001
ypN0	335 (41.0)	241 (35.7)	94 (66.7)	
ypN+	464 (56.8)	421 (62.3)	43 (30.5)	
Missing	18 (2.2)	14 (2.1)	4 (2.8)	
Axillary surgical procedure				< 0.001
Axillary dissection	694 (84.9)	586 (86.7)	108 (76.6)	
SLNB alone	26 (3.2)	14 (2.1)	12 (8.5)	
None	13 (1.6)	9 (1.3)	4 (2.8)	
Missing	84 (10.3)	67 (9.9)	17 (12.1)	
Median number of removed lymph nodes (IQR)	15 (11–19)	15 (12–20)	13 (10–18)	
ypT0 ypN0				0.089
Yes	67 (8.2)	50 (7.4)	17 (12.1)	
No	750 (91.8)	626 (92.6)	124 (87.9)	
ypT0/Tis ypN0				0.020
Yes	95 (11.6)	70 (10.4)	25 (17.7)	
No	722 (88.4)	606 (89.6)	116 (82.3)	

Data are expressed as *n* (%) unless otherwise specified

RT radiotherapy, SLNB sentinel lymph node biopsy, IQR interquartile range, *min* minimum, *max* maximum, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor, HR hormone receptor, TNBC triple-negative breast cancer

between breast-conserving surgery and mastectomy after NACT was left to the discretion of the local investigator. Surgery was scheduled 1–14 days after completion of the last cycle of chemotherapy or at least 28 days after the last infusion of bevacizumab for patients in the GeparQuinto trial.

Endocrine therapy for a duration of at least 5 years was recommended to all patients with estrogen and/or progesterone receptor-positive breast cancer. One year of trastuzumab was administered to patients with HER2-overexpressing tumors in the GeparQuattro and GeparQuinto trials, while no trastuzumab was administered to patients in the GeparTrio trial.

Information on the use of RT was prospectively collected from the case report forms (CRFs), however the impact of RT was not a predefined endpoint in any of the included trials. The CRF design differed between the three

trials and only contained limited information regarding target volume, RT dose, and fractionation. Thus, the original RT reports were requested from the study centers and reviewed by the first author.

Endpoints and Covariates

All endpoints and covariates were assessed by local investigators, while histopathological reports were assessed by an experienced pathologist. Follow-up was performed according to local guidelines and was monitored at least every 6 months for 5 years after diagnosis.

pCR was defined as the absence of both invasive and non-invasive residual tumor in the breast and ipsilateral axillary lymph nodes (ypT0 ypN0). Patients were grouped according to their clinical lymph node status at first diagnosis (cN+ vs. cN0) and their pathological lymph node

status after NACT (ypN+ vs. ypN0). LRR included chest wall relapses and regional lymph node metastases, and was calculated from the date of surgery until the occurrence of an LRR. Only LRR events occurring before or simultaneously with distant recurrence were evaluated. Disease-free survival (DFS) was defined as the time from surgery until the occurrence of a locoregional or distant recurrence, or death from any cause.

All three trials were approved by the local Ethics Committees, and written informed consent was obtained from all patients before registration.

Statistics

Statistical analysis was performed using SPSS software version 22.0 (IBM Corporation, Armonk, NY, USA) and SAS version 9.4 (SAS Institute, Cary, NC, USA). Baseline patient characteristics were compared using the two-sided Pearson Chi square test, and Cox regression analysis was used for univariate and multivariate analyses regarding DFS.

The cumulative incidence functions of LRR using distant recurrence as the competing event were compared using Gray's test, with $\alpha = 0.05$ stratified for study. Bivariate analyses adjusted for the trial were used for LRR and DFS.

Multivariate competing risk analysis of LRR using distant recurrence as the competing event was performed using the Fine–Gray model. Hazard ratios (HRs) and 95% confidence intervals (CIs) are given.

Multivariate analysis was adjusted for known prognostic factors, i.e. clinical tumor and lymph node stage, age, hormone receptor and HER2 receptor status, histologic subtype, grading, response to chemotherapy, and trial. A two-sided p value of 0.05 was used as the alpha error for consideration of statistical significance.

RESULTS

The CONSORT diagram according to the use of RT is depicted in Fig. 1. Median follow-up was 51.5 months from surgery. Of the 817 patients included in this analysis, 676 (82.7%) received adjuvant RT to the chest wall and/or the regional lymph nodes (Fig. 1). Baseline and post-therapeutic patient characteristics for patients with information on RT are listed in Table 1. Detailed reports were available from 318 patients (46.4%) treated with RT; 313 of these patients (98.7%) received RT to the thoracic wall. RT to the regional lymph nodes was delivered to 243 of 318 patients (76.7%) and included the supraclavicular/infraclavicular lymph nodes in 237 of 318 patients (74.5%), the parasternal (internal mammary) lymph nodes in 49

patients (15.4%), and the axillary lymph nodes in 58 patients (18.2%). Seventy-two patients (22.6%) were treated with an additional boost irradiation to the mastectomy scar. Electronic supplementary Table 2 shows the patient and tumor characteristics for the 817 patients with available CRF information regarding RT, and the 752 patients without information on RT.

Patients who did not receive RT were significantly younger than patients who received RT. In addition, patients who received RT had significantly more advanced tumor and nodal stages before and after NACT and were more likely to have an axillary dissection. There was a significantly lower rate of pCR in the group who received RT when non-invasive residual disease in the breast was also considered (ypT0/is ypN0, 17.7% with RT vs. 10.4% without RT; $p = 0.02$).

Locoregional Recurrence

The 5-year cumulative incidence of LRR was 15.2% (95% CI 9.0–22.8%) in patients treated without RT and 11.3% in patients treated with adjuvant RT (95% CI 8.7–14.3). The cumulative incidence functions are shown in Fig. 2. Using multivariate competing risk analysis, there was no statistically significant difference between patients who had or had not received adjuvant RT ($p = 0.23$). Table 2 lists the 5-year cumulative incidence of LRR and the results of the bivariate competing risk analysis. LRR in patients with cT3/4 tumors was significantly lower after locoregional RT. There was a borderline significant result for patients with cN+ and patients who converted from cN+ to ypN0, and a trend towards lower LRR in patients with ypN0. In patients who had a pCR after NACT, there was no significant difference whether locoregional RT was used or not.

In the multivariate analysis, estrogen receptor, progesterone receptor, and baseline nodal status were significant prognostic factors for LRR, while the use of adjuvant RT was of borderline significance, with a p value of 0.05 (Table 3).

We carried out multivariate analyses according to baseline tumor and nodal stage, pCR, and nodal stage after NACT. No significant effect of RT was found in patients who did or did not achieve a pCR. Adjuvant RT did not result in improved outcomes for patients with cT1/2 tumors, but did improve results for patients with cT3/4 tumors (HR 0.4, 95% CI 0.17–0.94; $p = 0.04$). Similar results were found according to baseline nodal status, where patients with cN+ had a significantly better outcome when treated with RT (HR 0.39, 95% CI 0.19–0.83; $p = 0.01$), whereas patients with cN0 showed similar results with or without RT. Patients with ypN0 did significantly benefit from RT (HR 0.2, 95% CI 0.06–0.62;

TABLE 2 Cumulative incidence of locoregional recurrence and bivariate competing risk analysis adjusted for trial in relation to pCR, clinical lymph node status before neoadjuvant chemotherapy (cN+/cN0), and pathological lymph node status after neoadjuvant chemotherapy (ypN+/ypN0)

Parameter	5-Year locoregional recurrence rate			
	Radiotherapy (95% CI) [n = 676]	No radiotherapy (95% CI) [n = 141]	HR (95% CI)	p value
pCR [n = 67]	5.8% (0.3–24.0%) [n = 50]	13.8% (2.0–36.6%) [n = 17]	0.2 (0.02–2.39)	0.21
No pCR [n = 750]	11.8% (9.1–15.0%) [n = 626]	15.4% (8.8–23.7%) [n = 124]	0.74 (0.42–1.30)	0.3
cT1/2 [n = 441]	10.3% (7.2–14.0%) [n = 343]	10.5% (4.8–18.8%) [n = 98]	0.94 (0.45–1.95)	0.86
cT3/4 [n = 372]	12.2% (8.3–16.9%) [n = 330]	24.9% (11.8–40.6%) [n = 42]	0.43 (0.19–0.95)	0.04
cN0 [n = 309]	8.1% (4.3–13.4%) [n = 238]	8.9% (3.2–18.4%) [n = 71]	0.89 (0.28–2.83)	0.84
cN+ [n = 501]	13.3% (9.9–17.2%) [n = 432]	22.9% (11.6–36.5%) [n = 69]	0.54 (0.29–0.99)	0.05
ypN0 [n = 335]	7.5% (4.0–12.4%) [n = 241]	13.7% (6.8–23.1%) [n = 94]	0.44 (0.19–1.02)	0.06
ypN+ [n = 464]	13.6% (10.1–17.6%) [n = 421]	17.0% (6.7–31.2%) [n = 43]	0.81 (0.34–1.95)	0.64
cN+ → ypN0 [n = 158]	9.3% (4.4–16.4%) [n = 121]	22.2% (7.9–40.9%) [n = 37]	0.37 (0.14–0.99)	0.05

pCR pathological complete response, HR hazard ratio, CI confidence interval

$p = 0.01$), while patients with ypN+ did not. In the subgroup of patients who converted from cN+ to ypN0, RT was associated with a lower risk of LRR (HR 0.19, 95% CI 0.04–0.97; $p = 0.05$).

Disease-Free Survival

Overall, DFS was significantly worse for patients who received RT compared with patients who did not receive RT in the bivariate analysis (HR 1.48, 95% CI 1.01–2.18; $p = 0.04$). However, RT was not associated with an inferior DFS upon multivariate analysis (HR 1.14, 95% CI 0.75–1.73; $p = 0.55$), as shown in Table 3. Patients who were clinically node negative at diagnosis and received RT had a significantly worse DFS upon multivariate analysis

(HR 3.4, 95% CI 1.46–7.91; $p = 0.01$). In all other multivariate subgroup analyses, RT was not significantly associated with DFS.

DISCUSSION

Our results from this retrospective explorative analysis of three large prospective randomized phase III trials suggest that RT decreases the risk of LRR in breast cancer patients who have a mastectomy after NACT without an improvement in DFS.

The positive impact of RT on LRR and survival has been shown in large meta-analyses, both after breast-conserving surgery and after mastectomy in the adjuvant setting.²⁰ However, most of the randomized trials included

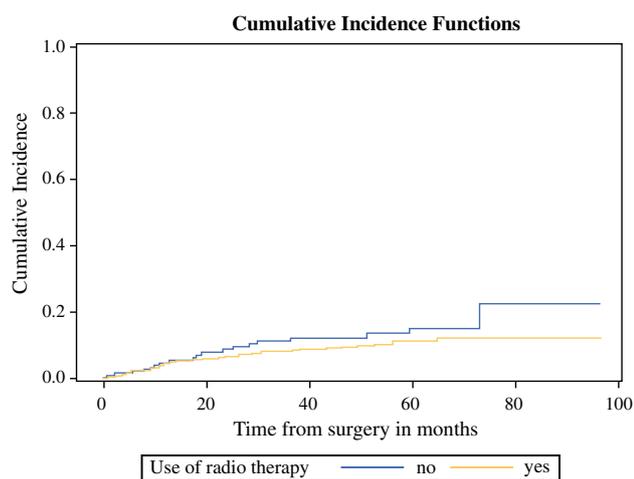


FIG. 2 Kaplan–Meier plot for cumulative incidence of locoregional recurrence

in these meta-analyses used adjuvant systemic therapy regimens considered suboptimal according to contemporary standards.

While two meta-analyses based on published data found no increased risk of LRR with NACT compared with adjuvant chemotherapy when trials with suboptimal local treatment were excluded,^{2,3} the recently published EBCTCG meta-analysis based on individual patient data showed an increase in local recurrence, even in this context.²¹

Several studies showed that a favorable treatment response, e.g. pCR or ypN0, correlates with a decreased risk of locoregional failure, while the overall risk of LRR is influenced by both pre- and post-therapeutic tumor and nodal stage.^{9,10}

Evidence on the role of RT after NACT followed by mastectomy is limited. A systematic review on post-mastectomy RT identified 24 publications, of which 23 were single-center, retrospective reports.²² While some of those studies implied that the omission of RT is possible in selected patients after NACT and mastectomy without compromising locoregional control or survival,^{23–25} other researchers have shown that RT improved both endpoints, even in subgroups of patients with a pCR.²⁶ A recent systematic review of publications studying the possibility of RT treatment individualization based on treatment response yielded 13 retrospective studies, mostly from single institutions.²⁷

In our analysis, the incidence of LRR was higher than in the NSABP B18/27 analysis and the I-SPY 1 trial.^{25,28} This is most likely related to negative patient selection in the present analysis, with > 45% of patients presenting with cT3/4 disease and > 60% presenting with clinically involved lymph nodes. Although the great majority of

patients received RT and the absolute numbers of recurrences were low, we were able to demonstrate that RT is associated with a decreased risk of LRR without a DFS benefit. The most intriguing finding is that patients with negative axillary lymph nodes at surgery (ypN0) had a significantly lower risk of LRR when treated with RT (HR 0.2, 95% CI 0.06–0.62; $p = 0.01$). However, it should be mentioned that 61.3% of included patients had clinically involved lymph nodes and 45.6% had cT3–4 tumors. Both subgroups had a significantly lower risk of LRR when treated with RT in the absence of a DFS benefit, while patients with cN0 had no benefit from RT and showed a worse DFS (HR 3.4, 95% CI 1.46–7.91; $p = 0.01$). Interestingly, age was not associated with LRR on multivariate analysis, which is line with findings from the NSABP B18/27 analysis.²⁵

Other groups have addressed the question as to whether patients with ypN0 would benefit from RT after mastectomy. Two retrospective studies showed no benefit of RT on LRR or survival, however these studies included a substantial amount of cN0 patients.^{24,29} Several other publications suggest that the benefit from RT is highly dependent on the pretherapeutic tumor and nodal stage, and that selected subgroups with advanced disease can derive a significant advantage both in terms of LRR and survival.^{23,26,30}

The finding that patients with cN0 had a significantly worse DFS on multivariate analysis might be related to the presence of a negative selection bias and is not supported by the current evidence.²⁷

This study has several limitations. Due to the non-randomized retrospective comparison and the complex interaction between clinical and pathological parameters and the response to NACT, the presence of underlying confounding factors cannot be excluded. Since only patients after mastectomy were included, our study population mostly contained patients with high-risk features such as advanced tumor stage at diagnosis and unfavorable treatment response, which is illustrated by the relatively low pCR rate and high number of patients with pathologically involved lymph nodes after NACT. The treatment regimens were heterogeneous among the three trials and included a response-adapted treatment schedule without anti-HER2 medication in GeparTrio, and a second randomization for non-responders in GeparQuinto. In addition, the RT recommendations differed between GeparTrio and GeparQuattro/GeparQuinto. A detailed analysis of target volume, radiation dose, and fractionation, all of which might impact patient outcome, was not possible due to missing information.

Since the included trials were conducted before publication of several prospective trials supporting its use,^{31,32} irradiation of the internal mammary lymph nodes was

TABLE 3 Results of the multivariate Cox regression analysis for locoregional recurrence and disease-free survival

Parameter	LRR [HR (95% CI)]	LRR <i>p</i> value	DFS [HR (95% CI)]	DFS <i>p</i> value
Age (years)		0.34		0.42
≥ 50	1.0 (Ref)		1.0 (Ref)	
40–49	0.7 (0.4–1.21)	0.2	1.22 (0.90–1.67)	0.21
< 40	1.08 (0.54–2.15)	0.82	1.19 (0.79–1.80)	0.41
Histology		0.31		0.39
Ductal invasive	1.0 (Ref)		1.0 (Ref)	
Lobular invasive	0.64 (0.28–1.43)	0.28	0.73 (0.47–1.15)	0.18
Other	0.42 (0.09–1.88)	0.26	0.88 (0.49–1.61)	0.68
Grading		0.51		0.13
G1	1.0 (Ref)		1.0 (Ref)	
G2	0.93 (0.23–3.79)	0.91	1.80 (0.66–4.93)	0.25
G3	1.25 (0.3–5.17)	0.76	2.27 (0.82–6.28)	0.11
ER-negative	4.5 (2.42–8.37)	< 0.01	1.93 (1.33–2.80)	< 0.01
PR-negative	0.52 (0.29–0.96)	0.04	1.45 (1.01–2.08)	0.05
HER2/neu-positive	0.58 (0.32–1.06)	0.08	0.66 (0.47–0.93)	0.02
cT		0.71		< 0.01
cT1	1.0 (Ref)		1.0 (Ref)	
cT2	1.59 (0.39–6.57)	0.52	3.07 (0.96–9.84)	0.06
cT3	1.45 (0.35–6.04)	0.61	4.04 (1.26–13.00)	0.02
cT4a–c	2.13 (0.45–10.11)	0.34	5.98 (1.81–19.75)	< 0.01
cN+	2.14 (1.19–3.87)	0.01	1.87 (1.35–2.60)	< 0.01
Study number		0.53		0.64
GeparQuinto	1.0 (Ref)		1.0 (Ref)	
GeparTrio	0.78 (0.43–1.41)	0.41	0.98 (0.70–1.37)	0.89
GeparQuattro	0.7 (0.36–1.36)	0.29	0.85 (0.58–1.23)	0.38
pCR [ypT0 ypN0]	0.38 (0.11–1.29)	0.12	0.38 (0.2–0.71)	< 0.01
Radiotherapy	0.51 (0.27–1.0)	0.05	1.14 (0.75–1.73)	0.55

*p*CR pathological complete response, *HR* hazard ratio, *CI* confidence interval, *LRR* locoregional recurrence, *DFS* disease-free survival, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor

infrequently used. Since irradiation to the internal mammary lymph nodes has also been shown to significantly improve outcome in patients treated with NACT,^{33,34} its infrequent use might have negatively influenced the outcome of patients who received RT in this analysis.

Despite these limitations, the results of this explorative analysis provide insight into the role of RT after NACT followed by mastectomy, and suggest that RT delivered to the chest wall ± supraclavicular nodes decreases LRR without a benefit in terms of DFS.

CONCLUSIONS

While individualization of locoregional RT based on treatment response is a concept worth pursuing, results from prospective randomized controlled trials including meticulous quality assurance, such as the NSABP B-51/RTOG 1304 trial (NCT01872975), are needed to guide

clinical practice. In the absence of those data, there is currently insufficient evidence for routine omission of adjuvant RT in patients with cT3/4 tumors or clinically involved lymph nodes.^{11,27,35} In patients with cT1–2 cN+ who become ypN0 or have pCR after NACT, the benefit and risk of RT should be discussed based on the individual recurrence risk for each patient.

ACKNOWLEDGMENT The authors thank all participating centers for providing radiotherapy reports. This work was previously presented in part at the 51st Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, USA, 29 May–2 June 2015.

FUNDING Financial support for the original trials was provided by Amgen, Chugai, GlaxoSmithKline, Roche, and Sanofi-Aventis.

DISCLOSURE David Krug, Bianca Lederer, Fenja Seither, Valentina Nekljudova, Beyhan Ataseven, Jens-Uwe Blohmer, Serban

Dan Costa, Carsten Denkert, Nina Ditsch, Bernd Gerber, Claus Hanusch, Joerg Heil, Jörn Hilfrich, Jens B. Huober, Christian Jackisch, Sherko Kümmel, Stefan Paepke, Christian Schem, Andreas Schneeweiss, Michael Untch, Jürgen Debus, Gunter von Minckwitz, Thorsten Kühn, and Sibylle Loibl have no conflicts of interest relevant to this study.

REFERENCES

- Mougalian SS, Soulos PR, Killelea BK, et al. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. *Cancer*. 2015;121(15):2544–52.
- Mauri D, Pavlidis N, Ioannidis JPA. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst*. 2005;97(3):188–94.
- Mieog JSD, van der Hage JA, van de Velde CJH. Neoadjuvant chemotherapy for operable breast cancer. *Br J Surg*. 2007;94(10):1189–200.
- Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164–72.
- von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30(15):1796–804.
- Mamounas EP, Tang G, Liu Q. The importance of systemic therapy in minimizing local recurrence after breast-conserving surgery: the NSABP experience. *J Surg Oncol*. 2014;110(1):45–50.
- Poortmans P. Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. *Lancet*. 2014;383(9935):2104–6.
- Punglia RS, Morrow M, Winer EP, Harris JR. Local therapy and survival in breast cancer. *N Engl J Med*. 2007;356(23):2399–405.
- Buchholz TA, Tucker SL, Masullo L, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. *J Clin Oncol*. 2002;20(1):17–23.
- Chen AM, Meric-Bernstam F, Hunt KK, et al. Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. *J Clin Oncol*. 2004;22(12):2303–12.
- Marks LB, Prosnitz LR. Reducing local therapy in patients responding to preoperative systemic therapy: Are we outsmarting ourselves? *J Clin Oncol*. 2014;32(6):491–3.
- White J, Mamounas E. Locoregional radiotherapy in patients with breast cancer responding to neoadjuvant chemotherapy: a paradigm for treatment individualization. *J Clin Oncol*. 2014;32(6):494–5.
- Huober J, Fasching PA, Hanusch C, et al. Neoadjuvant chemotherapy with paclitaxel and everolimus in breast cancer patients with non-responsive tumours to epirubicin/cyclophosphamide (EC) ± bevacizumab—results of the randomised GeparQuinto study (GBG 44). *Eur J Cancer*. 2013;49(10):2284–293.
- Untch M, Loibl S, Bischoff J, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline–taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol*. 2012;13(2):135–44.
- Gerber B, Loibl S, Eidtmann H, et al. Neoadjuvant bevacizumab and anthracycline–taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). *Ann Oncol*. 2013;24(12):2978–84.
- Untch M, Rezai M, Loibl S, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol*. 2010;28(12):2024–31.
- von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med*. 2012;366(4):299–309.
- von Minckwitz G, Blohmer JU, Costa SD, et al. Response-guided neoadjuvant chemotherapy for breast cancer. *J Clin Oncol*. 2013;31(29):3623–30.
- von Minckwitz G, Rezai M, Fasching PA, et al. Survival after adding capecitabine and trastuzumab to neoadjuvant anthracycline-taxane-based chemotherapy for primary breast cancer (GBG 40–GeparQuattro). *Ann Oncol*. 2013;25(1):81–9.
- EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014;383(9935):2127–35.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. 2018;19(1):27–39.
- Fowble BL, Einck JP, Kim DN, et al. Role of postmastectomy radiation after neoadjuvant chemotherapy in stage II–III breast cancer. *Int J Radiat Oncol Biol Phys*. 2012;83(2):494–503.
- Garg AK, Strom EA, McNeese MD, et al. T3 disease at presentation or pathologic involvement of four or more lymph nodes predict for locoregional recurrence in stage II breast cancer treated with neoadjuvant chemotherapy and mastectomy without radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004;59(1):138–45.
- Le Scodan R, Selz J, Stevens D, et al. Radiotherapy for stage II and stage III breast cancer patients with negative lymph nodes after preoperative chemotherapy and mastectomy. *Int J Radiat Oncol Biol Phys*. 2012;82(1):e1–7.
- Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of national surgical adjuvant breast and bowel project B-18 and B-27. *J Clin Oncol*. 2012;30(32):3960–6.
- McGuire SE, Gonzalez-Angulo AM, Huang EH, et al. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. *Int J Radiat Oncol Biol Phys*. 2007;68(4):1004–9.
- Krug D, Baumann R, Budach W, et al. Individualization of post-mastectomy radiotherapy and regional nodal irradiation based on treatment response after neoadjuvant chemotherapy for breast cancer: a systematic review. *Strahlenther Onkol*. 2018;21:2600–12.
- Cureton EL, Yau C, Alvarado MD, et al. Local recurrence rates are low in high-risk neoadjuvant breast cancer in the I-SPY 1 Trial (CALGB 150007/150012; ACRIN 6657). *Ann Surg Oncol*. 2014;21(9):2889–96.
- Shim SJ, Park W, Huh SJ, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II–III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). *Int J Radiat Oncol Biol Phys*. 2014;88(1):65–72.
- Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. *J Clin Oncol*. 2004;22(23):4691–9.
- Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med*. 2015; 373:317–27.

32. Whelan TJ, Olivetto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med*. 2015;373:307–16.
33. Kim KH, Noh JM, Kim YB, et al. Does internal mammary node irradiation affect treatment outcome in clinical stage II–III breast cancer patients receiving neoadjuvant chemotherapy? *Breast Cancer Res Treat*. 2015;152:589–99.
34. Luo J, Jin K, Chen X, et al. Internal Mammary Node Irradiation (IMNI) improves survival outcome for patients with clinical stage II–III breast cancer after preoperative systemic therapy. *Int J Radiat Oncol Biol Phys*. 2019;103:895–904.
35. Recht A, Comen EA, Fine RE, et al. Postmastectomy radiotherapy: an American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. *J Clin Oncol*. 2016;34(36):4431–42.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.