TIME TRENDS OF NEOADJUVANT CHEMOTHERAPY FOR EARLY BREAST CANCER

Fabian Riedel1 | Ann Sophie Hoffmann1 | Mareike Moderow2 | Sabine Heublein1 | Thomas M. Deutsch1 | Michael Golatta1 | Markus Wallwiener1 | Andreas Schneeweiss1,3 | Joerg Heil1 | André Hennigs1

1Department of Gynecology and Obstetrics, Heidelberg University Hospital, Heidelberg, Germany
2West German Breast Center (WBC), Düsseldorf, Germany
3National Center for Tumor Diseases Heidelberg, Heidelberg, Germany

Correspondence
André Hennigs, Department of Gynecology and Obstetrics, Heidelberg University Hospital, Im Neuenheimer Feld 440, 69120 Heidelberg, Germany.
Email: andre.hennigs@med.uni-heidelberg.de

Abstract
Neoadjuvant chemotherapy (NACT) in early breast cancer (EBC) enables in vivo sensitivity testing and less radical surgery as compared to primary surgery and adjuvant chemotherapy (ACT). The aim of our study is to illustrate trends of systemic treatment of EBC. The study analyzed chemotherapy usage and time trends for patients with EBC treated at 104 German breast units between January 2008 and December 2017. The data were obtained through a quality-controlled benchmarking process. Altogether, 124 084 patients were included, of whom 46 279 (37.3%) received chemotherapy. For 44 765 of these cases, detailed information on systemic treatment and surgery were available. Overall use of chemotherapy declined from 42.0% in 2008 to 32.0% in 2017. During that same time, the proportion of NACT increased from 20.0% to 57.7%, irrespective of tumor subtype. The pathological complete response (pCR) rate (defined as ypT0 ypN0) at surgery after NACT increased from 15.0% to 34.2%. The results from this large cohort from the clinical routine reflect the refined indications for chemotherapy in EBC.

KEYWORDS
early breast cancer, pathological complete response, neoadjuvant chemotherapy, adjuvant chemotherapy

INTRODUCTION
The understanding of early breast cancer (EBC) as a systemic disease that is determined by specific molecular genetic factors was one of the fundamental breakthroughs in breast cancer research and constitutes the basis for therapeutic decision-making. Subsequently, adjuvant systemic therapy additional to surgery gained in importance for EBC treatment. In particular, the evolution of chemotherapy has contributed substantially to the improved outcome of EBC patients today, especially for patients with a high risk of local or distant recurrence.

Currently, preoperative (neoadjuvant) administration of chemotherapy is standard approach when cytotoxic therapy is indicated according to risk assessment for a specific patient. Several large trials have already demonstrated equivalent survival for adjuvant chemotherapy (ACT) and neoadjuvant chemotherapy (NACT). A recent Early...
Breast Cancer Trialists’ Collaborative Group meta-analysis including 10 randomized NACT trials with a median of 15 years showed equivalent distant disease-free and overall survival in comparison to adjuvant chemotherapy.\textsuperscript{5}

The decision for systemic therapy in general remains made primarily based on a risk stratification by tumor load and differentiating EBC subtypes defined by immunochemistry.\textsuperscript{6} As an additional decision aid, multigene signature testing has become more widely available in initial therapy management, but it is not yet standard in international and national guidelines. Multigene signature testing remains restricted to cases in which a clear therapy decision cannot be made based on all other criteria.\textsuperscript{7,8}

NACT was used initially to enable or improve the operability of breast tumors that were large, inflammatory, or locally advanced. This approach offers several benefits compared to ACT. Although the improvement in the rate of breast-conserving surgery (BCT) due to NACT is not as important now as it was in the prescreening era, NACT can decrease the need for completing axillary lymph node dissection (cALND), thereby reducing surgical morbidity.\textsuperscript{9,10} NACT also provides important prognostic information and enables in vivo testing for drug sensitivity that facilitates postneoadjuvant escalation and de-

**What’s new?**

During the last decade, neoadjuvant chemotherapy of early breast cancer evolved from a therapy intended to enable operability to a standard treatment option enabling \textit{in vivo} sensitivity testing. To date, there is only limited data on the use of chemotherapy in routine cohorts, however. Here, the authors analyze recent time trends on chemotherapy indications and applications as well as pathological complete response rates based on 124,084 patients treated at 104 breast care centers in Germany between 2008 and 2017. These results reflect today’s refined, more individualized indications for chemotherapy in routine clinical practice and its preferred application as neoadjuvant chemotherapy.

---

**FIGURE 1** Flow chart of subject inclusion and categorization in this database analysis

| Clinical Parameters | N   |
|--------------------|-----|
| All female patients with primary (non-metastasized), invasive breast cancer treated at 104 German centers 2008-2017 | 124,084 |
| Primary cases with chemotherapy | 46,274 |
| Primary cases with completed chemotherapy and information on chemotherapy / surgery date | 44,765 |

**Pat. with completed neoadjuvant chemotherapy (NACT)**

- n = 14,783

**Subtype distribution due to pre-surgical biopsy**

- HR+ HER2-: n = 5,257; 36.7%
- HR+ HER2+: n = 2,650; 19.5%
- HR- HER2+: n = 1,550; 11.4%
- HR- HER2-: n = 4,125; 30.4%
- no distribution possible: n = 1,201

**Pat. with completed adjuvant chemotherapy (ACT)**

- n = 29,982

**Subtype distribution due to post-surgical histology**

- HR+ HER2-: n = 17,895; 63.2%
- HR+ HER2+: n = 3,909; 13.8%
- HR- HER2+: n = 1,851; 6.5%
- HR- HER2-: n = 4,646; 16.4%
- no distribution possible: n = 1,681

---
TABLE 1  Patient and tumor characteristics of female cases with primary, nonmetastatic breast cancer who were diagnosed and treated at 104 German Breast Cancer Units between January 1, 2008 and December 31, 2017, and underwent chemotherapy (n = 44 765)

|                          | Total CHT (n) | Total CHT (%) | ACT (n) | ACT (%) | NACT (n) | NACT (%) |
|--------------------------|---------------|---------------|---------|---------|----------|----------|
| **Age (in years)**       |               |               |         |         |          |          |
| ≤29                      | 354           | 0.8           | 117     | 0.4     | 237      | 1.6      |
| 30-39                    | 2978          | 6.7           | 1309    | 4.4     | 1669     | 11.3     |
| 40-49                    | 10 056        | 22.5          | 6019    | 20.1    | 4037     | 27.3     |
| 50-59                    | 13 029        | 29.1          | 8679    | 28.9    | 4350     | 29.4     |
| 60-69                    | 11 458        | 25.6          | 8540    | 28.5    | 2918     | 19.7     |
| ≥70                      | 6890          | 15.4          | 5318    | 17.7    | 1572     | 10.6     |
| **Total**                | 44 765        | 100.0         | 29 982  | 100.0   | 14 783   | 100.0    |
| **Menopausal status**    |               |               |         |         |          |          |
| Pre                      | 14 008        | 31.6          | 8142    | 27.4    | 5866     | 40.2     |
| Peri                     | 2658          | 6.0           | 1582    | 5.3     | 1076     | 7.4      |
| Post                     | 27 616        | 62.4          | 19 972  | 67.3    | 7644     | 52.4     |
| **Total**                | 44 282        | 100.0         | 29 696  | 100.0   | 14 586   | 100.0    |
| **Missing**              | 483           |               | 286     |         | 197      |          |
| **(y)pT stage**          |               |               |         |         |          |          |
| (y)pT0                   | 4042          | 9.6           | 0       | 0       | 4042     | 30.6     |
| (y)pTis                  | 4467          | 10.6          | 3260    | 11.3    | 1207     | 9.1      |
| (y)pT1                   | 16 000        | 38.1          | 11 647  | 40.5    | 4353     | 33.0     |
| (y)pT1mic                | 129           | 0.3           | 32      | 0.1     | 97       | 0.7      |
| (y)pT2                   | 14 348        | 34.2          | 11 727  | 40.8    | 2621     | 19.8     |
| (y)pT3                   | 2104          | 5.0           | 1532    | 5.3     | 572      | 4.3      |
| (y)pT4                   | 884           | 2.1           | 569     | 2.0     | 315      | 2.4      |
| **Total**                | 41 974        | 100.0         | 28 767  | 100.0   | 13 207   | 100.0    |
| **Missing**              | 2791          |               | 1215    |         | 1576     |          |
| **(y)pN stage**          |               |               |         |         |          |          |
| (y)pN0                   | 22 205        | 53.2          | 14 017  | 49.2    | 8188     | 61.9     |
| (y)pN1                   | 11 359        | 27.2          | 8410    | 29.5    | 2949     | 22.3     |
| (y)pN1mi                 | 1361          | 3.3           | 975     | 3.4     | 386      | 2.9      |
| (y)pN2                   | 4333          | 10.4          | 3169    | 11.1    | 1164     | 8.8      |
| (y)pN3                   | 2488          | 6.0           | 1940    | 6.8     | 548      | 4.1      |
| **Total**                | 41 746        | 100.0         | 28 511  | 100.0   | 13 235   | 100.0    |
| **Missing**              | 3019          |               | 1471    |         | 1548     |          |
| **Grading**              |               |               |         |         |          |          |
| G1                       | 1538          | 3.9           | 1209    | 4.2     | 329      | 3.0      |
| G2                       | 20 315        | 51.2          | 15 650  | 54.7    | 4665     | 42.2     |
| G3                       | 17 828        | 44.9          | 11 767  | 41.1    | 6061     | 54.8     |
| **Total**                | 39 681        | 100.0         | 28 626  | 100.0   | 11 055   | 100.0    |
| **Missing**              | 5084          |               | 1356    |         | 3728     |          |
| **Estrogen receptor status** |             |               |         |         |          |          |
| Positive                 | 29 347        | 68.8          | 21 705  | 75.3    | 7642     | 55.3     |
| Negative                 | 13 292        | 31.2          | 7108    | 24.7    | 6184     | 44.7     |
| **Total**                | 42 639        | 100.0         | 28 813  | 100.0   | 13 826   | 100.0    |
| **Missing**              | 2126          |               | 1169    |         | 957      |          |
| **Progesterone receptor status** |         |               |         |         |          |          |
| Positive                 | 25 081        | 58.8          | 18 710  | 65.0    | 6371     | 46.1     |
| Negative                 | 17 546        | 41.2          | 10 096  | 35.0    | 7450     | 53.9     |

(Continues)
after NACT (ypT0/is ypN0). Reaching pCR is associated with improved disease-free survival (DFS) and overall survival (OS), with the strongest correlation in aggressive breast cancer subtypes such as HER2 positive or triple-negative (TN) breast cancer. At the patient level, this has recently been confirmed again by a large pooled analysis. In addition, NACT also offers the potential for rapidly testing regimens that may improve the response rate and therefore may be likely to improve outcomes in patients.

In our study, we analyzed chemotherapy use in the routine clinical care of a prospective cohort of 124,084 female patients with primary, nonmetastatic, EBC treated at 104 German BCUs between January 2008 and December 2017.

### 2 | METHODS

#### 2.1 | Database

Data were obtained from a voluntary benchmarking database in Germany. The participating BCUs contributed clinical, surgical, and pathological data from their patients with EBC to the West German Breast Center (WBC) in Düsseldorf, Germany. The WBC is an institution that provides quality control through an annual benchmarking report. The data are also used for the German Cancer Society’s periodical re-certification process for certified BCUs. Collaborating BCUs collected the data prospectively. Thus, this is a post hoc analysis of a prospectively maintained database. For this analysis, anonymized data from all patients with EBC treated between January 1, 2008 and December 31, 2017 were extracted from the WBC database. The final dataset comprised n = 124,084 female patients. From these patients included 11.6% were treated at university hospitals, 63.1% at academic hospitals and 25.3% at nonacademic hospitals.

The validity and quality of the data registered in the WBC tumor documentation system are assessed through a detailed benchmarking system. Comparative quality assessment through benchmarking requires accurate recording of treatment data. The credibility of the tumor documentation is reviewed for validation purposes. Besides the statistical data-check procedures, in-house data monitoring by clinical research associates is performed twice per year in the participating BCUs. Random verification of original data is also performed. After addressing documentation discrepancies, the results are used to optimize documentation processes to enhance the validity of quality indicators.

#### 2.2 | Definitions of tumor histology and stages

Tumor histology was defined according to the World Health Organization criteria, and grading was performed according to the most recent TNM classification. The expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 was assessed using formalin-fixed paraffin-embedded tumor tissue according to international standards. Positivity for ER and PR was defined as an immunoreactive score (IRS) of Remmele and Stegner of 1 out of 12 or as a total score (TS) of Allred of 1 out of 8. Moreover, any positive staining (ie, ≥1%) was defined as positive in accordance with the recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommendations. HER2 status was defined as positive in case of a semiquantitative score of 3+ by immunohistochemistry (IHC) or in case of a positive FISH/CISH assay as per ASCO/CAP guideline recommendations. Based on ER, PR and HER2 ± FISH/CISH, four EBC subtypes were defined: (a) hormone receptor (HR)-positive (defined as a
positive ER or a positive PR status) along with a negative HER2 (HR+ HER2−); (b) positive HR and positive HER2 (HR+ HER2+); (c) negative ER and PR but positive HER2 (HR− HER2+); (d) negative ER, PR and HER2 status, corresponding to triple negative (TN; HR− HER−).

Immunohistochemical information was based on the pretreatment biopsy (if available) for patients with NACT and on the final post-surgery pathological sample for patients with ACT (Figure 1).

2.3 | Statistical analysis

Data were analyzed descriptively using SPSS software version 25 (IBM; Armonk, New York). Annual percentages of chemotherapy use were calculated and presented as a longitudinal time trend analysis for the period from 2008 to 2017. All cases were assigned to a year (2008-2017) according to the date of first histopathological documentation of the disease.

3 | RESULTS

3.1 | Patient and tumor characteristics

The cohort comprised 124 084 EBC patients, of whom 46 279 (37.3%) received chemotherapy. From these 46 279 patients with chemotherapy, complete information on the timing of chemotherapy...
relative to surgery was available for 44,765 cases. In that subsample, chemotherapy was administered as NACT in 14,783 patients (33.0%) and as ACT in 29,982 (67.0%) patients (Figure 1). Demographic and tumor characteristics are presented in Table 1. In the ACT subgroup, the largest portion patients were 50 to 59 years old (28.9%) closely followed by 60 to 69 years (28.5%). More than half of the women

**FIGURE 4** Portion of the chemotherapy-receiving patients (within each of four subtypes of breast cancer) who received their chemotherapy neoadjuvant (n = 41,883; missing n = 2,882)

**FIGURE 5** Rates of pathological complete remission according to different definitions (ypT0 ypN0 vs ypT0/is ypN0) after neoadjuvant chemotherapy (n = 12,056; missing n = 2,727)
were postmenopausal (67.3%) and 41.1% had a G3 tumor. Slightly more than half of the patients had a tumor <2 cm (51.9%) and almost half were node-negative (49.2%). Patients in the NACT subgroup tended to be younger and had a higher proportion of G3 tumors (54.8%) than patients who received ACT. In the NACT subgroup, the largest age group was also 50 to 59 years with 29.4%, while the second largest group was patients aged 40 to 49 years with 27.3%. More women were premenopausal or perimenopausal (40.2% and 7.4%, respectively) than in the ACT group (27.4% and 5.3%). As expected, the tumor size distribution after NACT was shifted to smaller tumors with a relevant percentage of ypT0 stage (30.6%) and lower proportions of (yp)T1 and (yp)T2 tumors than in the ACT group. In the NACT cohort, 38.7% of patients had a HR− HER2−, 19.5% HR+ HER2+, 11.4% HR− HER2+ and 30.4% a TN subtype as compared to the ACT cohort with 63.5% HR+ HER2−, 13.8% HR+ HER2+, 6.5% HR− HER2+ and 16.2% TN.

Distribution of tumor characteristics remained stable over the whole study period, shown exemplarily for tumor and lymph node stage as well as tumor subtype in the Figures S1–S3.

3.2 | Chemotherapy usage

Use of chemotherapy declined over time from 42.0% (2008) to 32.0% (2017) (Figure 2). NACT gradually replaced ACT during this time period (Figure 3). This replacement of ACT with NACT was seen regardless of breast cancer subtype: The relative proportion of NACT by breast cancer subtype in 2017 was highest in HR− HER2+ and HR− HER2+ tumors with 79.0% and 77.6%, respectively. This rate is closely followed by TN tumors with 76.2% and lowest in HR+ HER2− tumors with 39.3% (Figure 4).

3.3 | Response to neoadjuvant chemotherapy

The overall pCR rate (according to the most common definition ypT0 ypN0) rose from 15.0% (2008) to 34.2% (2017; Figure 5). The most prominent effect in the increasing pCR rate was seen in tumors of the HER2+ HR− subtype with the pCR rate rising from 27.3% in 2008 to 54.8% in 2017 and the HR+ HER2+ subtype rising from 20.9% in 2008 to 41.0% in 2017. For TN, a rise of 17.2% between 2008 (25.3%) and 2017 (42.5%) was seen. On a lower level but with almost a tripled rate, an increase in pCR was also seen in HR+ HER2− tumors with an increase from 5.6% to 16.3% (Figure 6).

4 | DISCUSSION

Our results reflect developments in the use of chemotherapy in EBC patients. Since the advent of molecular classification systems, it has become evident that systemic therapy of EBC needs to be tailored according to individual risk factors, in particular tumor load, as reflected by stage and intrinsic subtype. Modern microarray-based gene expression profiles mirror the heterogeneity of breast cancer. These have been implemented in clinical routine for cases when all other criteria do not allow an adequate treatment recommendation.
regarding chemotherapy. While systemic treatment indications for HER2+ TN and high-risk HR+ HER2 EBC are based on their comparably poor prognosis, the benefit from chemotherapy for intermediate-risk HR+ HER2 EBC is not clear. Several trials have been set up to enable a better adjuvant risk stratification for these patients through multigene signatures, with recent results, for example, from the MINDACT the PlanB and the TAILORx trials. While the MINDACT trial (using Mammaprint) identified 46% of EBC patients at high clinical risk that might not require chemotherapy, PlanB (using Oncotype DX) showed excellent 5-year DFS of 94% for clinically high-risk, genomically low-risk (i.e., recurrence score ≤ 11) pN0-1 patients without ACT. In the TAILORx trial (also using Oncotype DX) omission of chemotherapy was associated with similar 9-year invasive DFS (83.3% vs 84.3%). The intention of these trials was to identify patients that can be spared chemotherapy without comprising outcome. Thus, it is reassuring that these developments are an important factor that lead to a substantial reduction of overall chemotherapy use in EBC over time in daily practice in Germany as was already shown for the US.

In addition, study results from surgical trials might have had an influence on ACT usage. In recent years, it has been possible to reduce surgical radicality, especially in the axilla, because the need for cALND in cases of affected sentinel lymph nodes (LN) has been put into question. The ACOSOG Z0011 trial showed no difference in outcome in patients with pT1-T2 cN0 breast cancer and involvement of up to two sentinel lymph nodes after breast-conserving surgery and whole-breast irradiation who did not receive cALND. This comparable outcome was achieved despite the fact that a high rate of additional nonsentinel metastases (NSM) can be assumed to be left behind when cALND is omitted. This high prevalence of occult tumor burden was also confirmed in a German study. Although tumor biology is undoubtedly the most important factor in clinical decision making for ACT, pathological LN status still represents a strong prognostic factor, so lack of this information could reduce the usefulness of stratification for ACT. Nonetheless, post hoc studies trying to estimate the impact of information gained from cALND in these situations have shown inconclusive results.

In EBC, chemotherapy is currently used more often neoadjuvantly for several reasons. First, NACT is used for in vivo sensitivity testing and enabling postneoadjuvant therapy escalation in cases of residual disease, to improve prognosis. This was first reported for HER2 negative tumors in the CREATE-X trial in 2017, with the addition of oral capecitabine leading to better disease-free survival (74.1% vs. 67.6%) and overall survival (89.2% vs 83.6%) at 5 years, in comparison to standard adjuvant therapy only. The same was shown for HER2 positive breast cancer and non-pCR after neoadjuvant chemotherapy plus anti-HER2 treatment in the KATHERINE trial. Adjuvant treatment with TDM-1 as compared to trastuzumab resulted in significantly better 3-year disease-free survival (88.3% vs 77.0%). Both trials changed the standard of practice and have already found their way into recent guideline recommendations for patients with non-pCR after NACT.

Second, beside these aspects of postneoadjuvant systemic risk-stratification, NACT often reduces the degree of surgical radicality needed. In clinically node-negative patients, SLNB performed after neoadjuvant therapy has the potential to downstage microscopic nodal disease and avoid ALND. For example, the NSABP B-27 trial reported significant reductions in lymph node involvement in women receiving preoperative docetaxel and doxorubicin (adriamycin) and cyclophosphamide (AC) compared to those receiving neoadjuvant AC alone (40% vs 49%, P < .001). In patients with initial node-positive lymph nodes that convert during NACT from cN+ to ycN0, targeted axillary dissection offers a new treatment option in biopsy-proven node-positive patients and implies the combined removal of the SLN and the target lymph node. This concept leads to an acceptably low false-negative rate and lower axillary morbidity and is therefore also recommended in recent guidelines.

There is only sparse comparable data on the use of neoadjuvant chemotherapy in recent years. Some reports showed rising rates of NACT of 39.7% in 2014 in China and 35.2% for 2009 to 2011 in South Africa. The use of NACT is also rising in the US but remains at a comparative low level with 23.5% in 2012 or 24.0% in 2011. Finally, achieving pCR is associated with a better prognosis for the individual patient, particularly for those with aggressive breast cancer subtypes such as HR− G3, HER2+ and TN, as a large pooled analysis has shown. That study from 2014 reported pCR rates of 34% for TN, 31% for HR+ HER2+ and 50% for HR− HER2+ treated with trastuzumab, and 16% for HR+ HER2− G3 based on a less conservative pCR definition (ypT0/is ypN0). Our study reports routine clinical data that are comparable for HR+ HER2− (16.3%) and HR− HER2+ (51.4%) but higher for HR+ HER2+ (41.0%) and TN (42.5%) (Figure 5). These rates are consistent with recent data reported for TN and HER2 positive subtypes. For those subtypes, increasing pCR rates have been achieved in routine clinical practice during the past decade, based on results from randomized trials (e.g., on carboplatin for TN tumors, on trastuzumab in the neoadjuvant setting for HER2 positive tumors, and on additional pertuzumab for dual blockade). Unfortunately, we cannot provide detailed information about the systemic therapy regimens that were used for the individual cases. It is unlikely that the changes in pCR rates can be explained by major changes in the choice of chemotherapy regimens. In 2008, standard regimens for NACT were already anthracycline and taxane-based as they were still in 2017 along with recent guideline recommendations. In the future, higher pCR rates can be expected through more individualized treatment options, as it has already been demonstrated in recent results from clinical trials for TN, for example, through adding anti-PD1 drugs (duralumab) or anti-PD1 drugs (pembrolizumab) to standard chemotherapy.

Although the present study reported on a large dataset, some limitations must be considered. First, we cannot exclude a possible selection bias due to the fact that only half of the breast cancer units in Germany participated in the voluntary benchmarking. Second, we cannot guarantee the representativeness of all breast cancer patients, as there is no nationwide clinical cancer registry to which our study sample can be compared. Third, due to legal data privacy protection reasons, we know neither the geographic locations within Germany of the participating institutions nor their annual caseload volumes. Fourth, the dataset lacks information about oncological outcomes, so
no analyses could be performed about how the changes in chemotherapy usage over time affected outcomes.

5 | CONCLUSIONS

The results from this large, nationwide sample from routine clinical practice reflect the refined, more individualized indications for chemotherapy in EBC and its preferred application as NACT.

ACKNOWLEDGEMENTS

The authors would like to thank all clinical research associates from the participating breast units for documentation and data management and the WBC for providing the data. We would also like to thank Michael Hanna, PhD (Mercury Medical Research & Writing) for proof-reading the manuscript prior to submission to the journal. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

S. H. reports grants from the following organizations/companies: FöFoLe LMU Munich Medical Faculty, FERRING, Novartis Oncology, Astra Zeneca, Apethc, Heuer Stiftung, Deutsche Forschungsgemeinschaft. She further reports personal fees from Roche and nonfinancial support from Addex. All the support listed here has been received outside the submitted work. A. S. reports grants from Celgene, grants from Roche, grants from AbbVie, grants from Molecular Partner, personal fees from Roche, personal fees from AstraZeneca, personal fees from Celgene, personal fees from Roche, personal fees from Roche, personal fees from Celgene, personal fees from Pfizer, personal fees from AstraZeneca, personal fees from Novartis, personal fees from MSD, personal fees from Tesaro, personal fees from Lilly, personal fees from Pfizer, other from Roche. All the support listed here has been received outside the submitted work. F. R., A. S. H., M. M., T. M. D., M. G., M. W., J. H. and A. H. have nothing to declare.

DATA ACCESSIBILITY

The data that support the findings of our study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the ethics committee of the University of Heidelberg and was conducted in accordance with the Declaration of Helsinki. The study was deemed to be without risk, including only anonymized analysis of routinely collected data; consequently, the ethics committee of the University of Heidelberg did not request approval for consent for this designated analysis. Informed consent was obtained from all individual participants within the data acquisition of the benchmarking process to analyze the anonymized data.

ORCID

Fabian Riedel https://orcid.org/0000-0002-9693-2667

REFERENCES

1. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA. Molecular portraits of human breast tumours. Nature. 2000;406: 747-752.
2. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001;98:10869-10874.
3. Hennigs A, Riedel F, Gondos A, et al. Prognosis of breast cancer molecular subtypes in routine clinical care: a large prospective cohort study. BMC Cancer. 2016;16:1-9.
4. Wockel A, Festl J, Stubler T, et al. Interdisciplinary screening, diagnosis, therapy and follow-up of breast cancer. Guideline of the DGGG and the DKG (S3-level, AWMF registry number 032/045OL, December 2017)—part 1 with recommendations for the screening, diagnosis and therapy of breast cancer. Geburtshilfe Frauenheilkd. 2018;78: 927-948.
5. Early Breast Cancer Trialsist's 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;19:27-39.
6. Burstein HJ, Curigliano G, Loibl S, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen international consensus guidelines for the primary therapy of early breast cancer 2019. Ann Oncol. 2019;30:1541-1557.
7. Ditsch N, Untch M, Thill M, et al. AGO recommendations for the diagnosis and treatment of patients with early breast cancer: update 2019. Breast Care (Basel). 2019;14:224-245.
8. Wockel A, Festl J, Stubler T, et al. Interdisciplinary screening, diagnosis, therapy and follow-up of breast cancer. Guideline of the DGGG and the DKG (S3-level, AWMF registry number 032/045OL, December 2017)—part 2 with recommendations for the therapy of primary, recurrent and advanced breast cancer. Geburtshilfe Frauenheilkd. 2018;78:1056-1088.
9. Hunt KK, Yi M, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. Ann Surg. 2009;250: 558-566.
10. Mamounas EP, Brown A, Anderson S, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and bowel project protocol B-27. J Clin Oncol. 2005;23:2694-2702.
11. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376: 2147-2159.
12. von Minckwitz G, Untch M, Blommer 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;30:1796-1804.
13. Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. Eur J Cancer. 2012;48:3342-3354.
14. 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;384:164-172.
15. Neuschwander E, Elsner G, Hettenbach A, Becker G. Überblick der Therapie der Mammakarzinome: Eine Bewertung aus der Sicht des Klinikners. Senol Z Mammadign Ther. 2007;4:77-84.
16. Brucker SY, Bamberg M, Jonat W, et al. Certification of breast centres in Germany: proof of concept for a prototypical example of quality assurance in multidisciplinary cancer care. BMC Cancer. 2009;9:228.
17. Tavassoli FA, ed. World Health Organization classification of Tumours. Pathology and genetics of tumours of the breast and female genital organs. Lyon, France: IARC Press; 2003.
18. Sobin LH, Gospodarowicz MK, Wittekind C, UICCInternational Union Against Cancer. TNM classification of malignant tumours. Vol 7. New York, NY: Wiley-Blackwell; 2009.
19. Remmele W, Stegner HE. Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue. Pathologe. 1987; 8:138-140.
20. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med. 2010;134:e48-e72.
21. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31:3997-4013.
22. Goldhirsch A, Wood WC, Coates AS, et al. Worldwide inconsistencies in the treatment of early breast cancer: highlights of the St. Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol. 2011;22: 1736-1747.
23. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med. 2016;375:717-729.
24. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk P0N0 and P1N1 early breast cancer patients: five-year data from the prospective, randomised phase 3 west German study group (WSG) PlanB trial. Breast Cancer Res Treat. 2017;165:573-583.
25. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018;379:111-121.
26. Reyes SA, De La Cruz LM, Ru M, Pisapati KV, Port E. Practice changing vignettes from the clinical practice guideline update. J Clin Oncol. 2013;31:3997-4013.
27. Giuliani AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons oncology group Z0011 randomized trial. Ann Surg Oncol. 2010;27; 252:426-432. discussion 32.
28. Riedel F, Heil J, Feisst M, et al. Non-sentinel axillary tumor burden of residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380:617-628.
33. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and bowel project protocol B-27. J Clin Oncol. 2003;21:4165-4174.
34. Manguso N, Gangi A, Giuliano AE. Neoadjuvant chemotherapy and surgical Management of the Axilla in breast cancer: a review of current data. Oncology (Williston Park). 2015;29:733-738.
35. Bao X, Sun K, Tian X, et al. Present and changing trends in surgical modalities and neoadjuvant chemotherapy administration for female breast cancer in Beijing, China: a 10-year (2006-2015) retrospective hospitalization summary report-based study. Thorac Cancer. 2018;9: 707-717.
36. Ruff P, Cubasch H, Joffe M, et al. Neoadjuvant chemotherapy among patients treated for nonmetastatic breast cancer in a population with a high HIV prevalence in Johannesburg, South Africa. Cancer Manag Res. 2018;10:279-286.
37. Puig CA, Hoskin TL, Day CN, Habermann EB, Boughey JC. National Trends in the use of neoadjuvant chemotherapy for hormone receptor-negative breast cancer: a National Cancer Data Base Study. Ann Surg Oncol. 2017;24:1242-1250.
38. Mougallan SS, Souls PR, Killelea BK, et al. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. Cancer. 2015;121:2544-2552.
39. Pandy JGP, Balolong-Garcia JC, Cruz-Ordinario MVB, Que FV. Triple negative breast cancer and platinum-based systemic treatment: a meta-analysis and systematic review. BMC Cancer. 2019;19:1065.
40. Wuerstlein R, Harbeck N. Neoadjuvant therapy for HER2-positive breast cancer. Rev Recent Clin Trials. 2017;12:81-92.
41. von Minckwitz G, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy among women with early triple-negative breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol. 2014;15:747-756.
42. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neo-adjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010; 375:377-384.
43. Gianni L, Oienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13:25-32.
44. Loibl S, Untch M, Burchardi N, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple negative breast cancer - clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30:1279-1288.
45. Nanda R, Liu MC, Yau C, et al. Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): results from I-SPY 2. J Clin Oncol. 2017;35(15_suppl):506.