



Do hospital type or caseload make a difference in chemotherapy treatment patterns for early breast cancer? Results from 104 German institutions, 2008–2017



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ABSTRACT

Background: Over the past decade, chemotherapy has been used more selectively in early breast cancer (EBC) due to better risk stratification. Neoadjuvant chemotherapy (NACT) has evolved to the primary treatment option. The type and size of hospitals is known to have a substantial influence on the kinds of treatment they provide, and therefore on patient outcomes (e.g. rates for pathological complete response, pCR), but it is not yet known how this has affected delivery of chemotherapy for EBC in Germany.

Methods: This study analyzed chemotherapy use and pCR rates after NACT for EBC patients treated at 104 German institutions 2008–2017. Institutions were separated into associated hospital type (university hospital; teaching hospital; community hospital) and annual caseload (≤ 100 ; 101–250; >250 cases/year).

Results: Overall, 124,084 patients were included, of whom 11.6% were treated at university hospitals, 63.1% at teaching hospitals, and 25.3% at community hospitals. In total, 46,274 (37.3%) received chemotherapy, of whom 44,765 had information available about systemic treatment and surgery. From 2008 to 2017, chemotherapy use declined from 48.3% to 36.4% for university hospitals, from 40.7% to 30.3% for teaching hospitals, and from 42.4% to 33.7% for community hospitals. Furthermore, the proportion of NACT increased the most in university hospitals (from 32.0% to 68.1%); whereas, the rate of pCR (defined as ypT0 ypN0) increased irrespective of institutional type. Analyses regarding annual caseload did not show any differences.

Conclusions: The results from this large, nationwide cohort reflect a more selective use of chemotherapy in Germany, irrespective of institutional type or case load.

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1. Introduction

Mortality in early breast cancer (EBC) has declined over the past decade in most developed countries including Germany, due to new developments in screening, diagnostics, surgery, radiotherapy, and (neo)adjuvant systemic therapy, as well as structural

improvements (multidisciplinary, specialized breast centers) and quality improvement measures [1]. A better molecular understanding [2] suggests that systemic therapy for EBC needs to be tailored according to individual risk factors and intrinsic subtype [3]. In the past decade, this process has led to a substantial decline of overall chemotherapy use, due to more individualized treatment decisions [4]. On the other hand, the rising application of neoadjuvant chemotherapy (NACT) (in proportion to adjuvant chemotherapy, ACT) has led to a rising number of patients with pathological complete response (pCR) [5] which can be regarded as a surrogate for better outcomes (in comparison to non-pCR). These

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developments been shown in previous analyses for Germany [6].

Most patients in Germany are treated in specialized breast cancer units (BCU) [7], but they differ in annual caseload and affiliation with a local oncology network. Some BCUs are affiliated with a university hospital or a teaching hospital, some are part of a community hospital, and some are independent. Collaborations or networks between different BCUs are also possible [8].

The impact of the hospital type and local affiliation on treatment patterns and outcome for EBC within the German health care system is unclear. Although study participation [9] in connection with guideline adherence [10] leads to better outcomes, the impact of being treated in an academic versus non-academic setting has not yet been analyzed. In general, the quality of care for EBC in Germany is assumed to be quite high [11].

The type and size of hospitals is known to have a substantial influence on the kinds of treatment they provide, and therefore on patient outcomes, but it is not yet known how this has affected delivery of chemotherapy for EBC in Germany. The aim of the analysis was to evaluate the routine use of systemic therapy in Germany (including outcome data with pCR rates after NACT), depending on the type of institution and annual caseload.

2. Methods

2.1. Database

The study used data from the West German Breast Center Ltd (WBC), in Düsseldorf, Germany [12]. In this database, the participating hospitals/BCUs contributed clinical, surgical, and pathological data from their patients with EBC. The collaborating institutions collected the data prospectively. Thus, this is a post hoc analysis of a prospectively collected database. The dataset does not include follow-up information on oncological outcome.

For this analysis, anonymized data from all female patients with invasive EBC treated between 1 January 2008 and 31 December 2017 were extracted from the WBC database. The final dataset comprised 124,084 patients. EBC was defined as primary (non-metastasized) breast cancer treated in curative intention. All patients underwent breast surgery. The division in ACT and NACT was defined by the date of surgery. Patients having received both neoadjuvant and adjuvant (=postneoadjuvant) chemotherapy were subsumed as neoadjuvant (because NACT was the primary therapy intention in these cases).

The study was approved by the Ethics Committee of the University of Heidelberg and was conducted in accordance with the Declaration of Helsinki. As the study is based on analyses of routinely collected anonymized data, the ethics committee did not request approval for consent for this designated analysis. Informed consent to analyze the anonymized data was obtained from all individual participants for the data acquisition of the benchmarking process.

2.2. Categorization of participating institutions

All participating institutions were labeled before the beginning of the analyses either as university hospitals, teaching hospitals (i.e. associated to a university hospital), community hospitals. For annual caseload, three groups were pre-defined: ≤ 100 ; 101–250; > 250 cases/year. Rationale for this caseload categorization were two aspects: First, the minimum required caseload for a certified BCU in Germany are 100 cases/year which can be regarded as a minimum quality threshold [7]. Second, to differentiate intermediate from large BCUs, another threshold was set at 250 cases/year. This number is based on health economic analyses by Pagano et al. who could show a peak at 250 cases/year in marginal cost analyses

for BCUs which has been interpreted that over this number disproportionately higher surgical resources are necessary to provide adequate care [13].

2.3. Definitions of tumor histology, stages and subtypes

Tumor histology was defined according to the World Health Organization criteria [14]. Postoperative pathological staging was done along the recent TNM classification [15]. Response to NACT was determined from the postoperative specimens along international standards; pCR after NACT was defined as ypT0 ypN0, i.e. absence of invasive cancer in breast and axillary lymph nodes. The expression of the immunohistochemical (IHC) parameters 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. For patients receiving NACT, IHC was based on the pretreatment biopsy (if available); whereas, for patients with ACT, IHC was based on the final postoperative pathological sample. The detailed criteria for positivity of the hormone receptors (HR), i.e. ER and PR, and the HER2 status have been described before [16]. HR was defined as negative if both ER/PR were negative, and as positive if ER or PR were positive. We then defined four subtypes: 1) HR positive and HER2 negative (HR+ HER2-), 2) HR positive and HER2 positive (HR+ HER2+), 3) HR negative and HER2 positive (HR- HER2+), or 4) HR negative and HER2 negative (HR- HER-, i.e. “triple negative”, TN).

2.4. Statistical analysis

Data were analyzed descriptively using SPSS software version 25 (IBM; Armonk, NY; USA). Annual percentages of chemotherapy use were calculated and presented as a longitudinal time trend analysis for the period from 2008 to 2017 (in %). Rates for pCR were calculated from patients that have received NACT. All cases were assigned to a year (2008–2017) according to the date of first histopathological documentation. Comparisons of patient characteristics between different hospital types were performed with chi-square tests. Multivariable logistic regression was used to identify factors associated with the application of chemotherapy and for the decision between adjuvant and neoadjuvant chemotherapy use. In both, p-values of < 0.001 were considered as statistically significant in a descriptive sense. Missing data were not imputed. These analyses were performed with R, version 3.5.1.

3. Results

3.1. Patient and tumor characteristics

In total, 104 institutions provided a final dataset of 124,084 patients with EBC, of whom, 14,397 (11.6%) were treated at university hospitals, 78,336 (63.1%) were treated at teaching hospitals, and 31,351 (25.3%) were treated at community hospitals. Fig. 1 shows a consort diagram with an overview of the patients included in the analyses. Patients at university hospitals were younger, were more often premenopausal and more often had a HR- HER2- subtype. No relevant differences were obtained concerning tumor characteristics; most cases had T1 tumors without nodal involvement and were HR+ HER2- (Table 1).

3.2. Chemotherapy use

In total, 46,274 (37.3%) patients received chemotherapy. Of these 46,274 chemotherapy patients, complete information was available for 44,765 of them; 1509 (3.3%) had missing data on treatment. Out

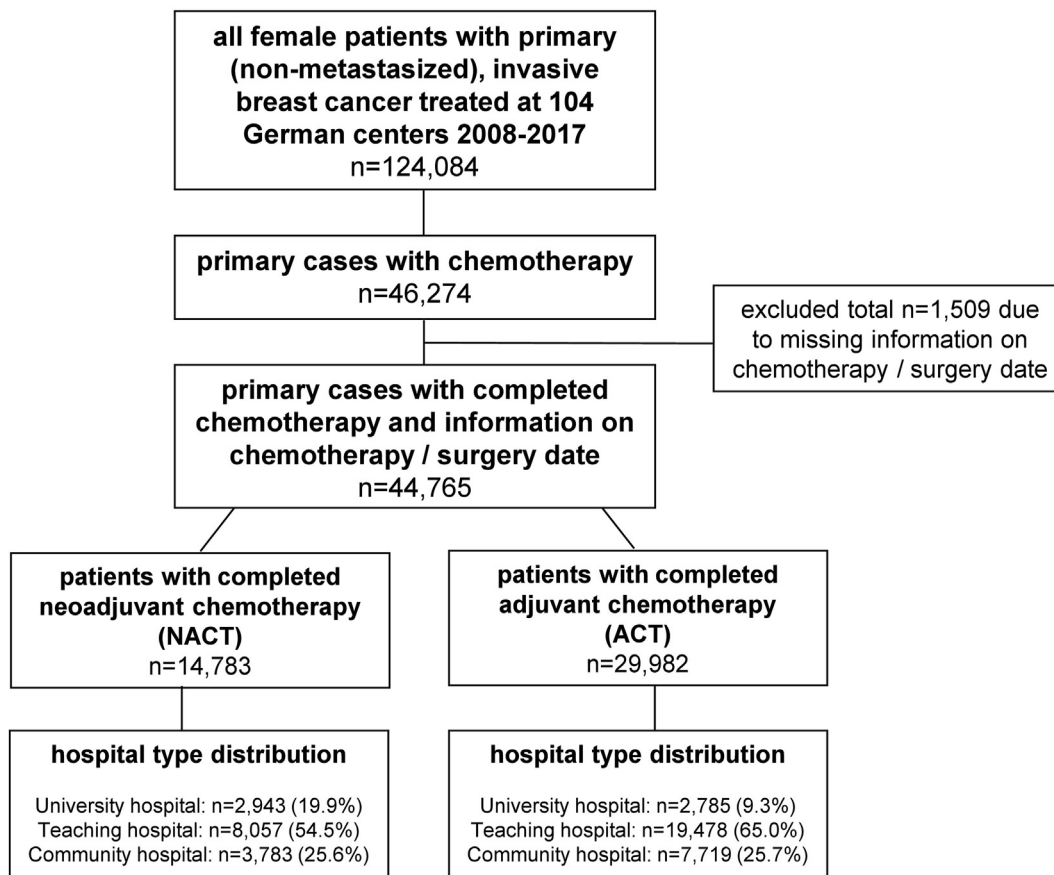


Fig. 1. Consort diagram.

of the patients with complete information, 29,982 (67.0%) received chemotherapy as ACT and 14,783 (33.0%) received it as NACT. In total 1367 patients received both neoadjuvant and adjuvant chemotherapy. The overall chemotherapy rate was 41.4% in university hospitals, 36.3% in teaching hospitals, and 37.8% in community hospitals. Fig. 1 shows this rate separated for ACT and NACT. Chemotherapy treatments in university hospital and community hospital settings were conducted predominately in institutions with >250 cases/year, while most patients in teaching hospitals were treated in institutions with 101–250 cases/year (Supplemental Fig. S1).

From 2008 to 2017, chemotherapy use increased slightly in HER2+ patients, decreased slightly in HR+ HER2– patients, and remained about the same in HR– HER– patients (Fig. 2). An overall decrease of chemotherapy was observed irrespective of hospital type: In 2008, university hospitals had the highest rate of chemotherapy (48.3%) in comparison to teaching hospitals or community hospitals, the rate declined to 36.4% in 2017. While the decline in overall chemotherapy was less pronounced in teaching hospitals and community hospitals, these groups had lower rates of chemotherapy rate in 2017: 30.3% and 33.7% respectively (Fig. 3). NACT rates have risen substantially during over the study period in all three types of hospitals, but most in university hospitals (from 32.0% to 68.1%) (Fig. 4). Separated for tumor subtype, NACT use was higher in HR+ HER2– cases in university hospitals than in teaching or community hospitals (Supplemental Fig. S2).

In multivariable analyses including hospital type and case load, age, HR negative as well as HER2 positive subtype had significant influence on chemotherapy indication and the decision between neoadjuvant vs. adjuvant application in EBC patients. Table 2

presents detailed results.

3.3. Response to neoadjuvant chemotherapy

The overall rate of pCR (ypT0 ypN0) rose from 2008 to 2017 in all three hospital types (Fig. 5), and, university hospitals lost their preeminence in this regards. The pCR rate increased more in the HR– HER2+ subtype than in the other three subtypes, irrespective of institutional setting. From 2016 to 2017 in university hospitals there was a decrease of pCR for both HER2+ subtypes; whereas, the pCR rates continued increasing in the other two hospital types. In university hospitals, the pCR rate in HR+ HER2– remained consistent over the observation period (Supplemental Fig. S3).

3.4. Annual caseload

Regarding annual caseload, no relevant trends were seen between hospitals with ≤100, 101–250, or >250 cases/year. NACT use did not differ significantly (Fig. 6), and pCR rates were also congruent (Supplemental Fig. S4).

4. Discussion

The overall use of chemotherapy decreased substantially in the study period, while NACT use increased. These trends confirm results from an earlier German single-center analysis [6].

Since the emergence of molecular classification systems [17], it has become evident that systemic therapy of EBC needs to be tailored according to individual risk factors, such as tumor stage and subtype. Gene expression profiles have been implemented in

Table 1

Patient and tumor characteristics of all cases with early breast cancer and separated for hospital type (university hospital, teaching hospital, community hospital; total n = 124,084).

Patient Characteristics									
	University Hospital (n = 14,397)		Teaching Hospital (n = 78,336)		Community Hospital (n = 31,351)			Total (n = 124,084)	
	n	%	n	%	n	%	p value	n	%
Age (years)									
≤29	140	1.0	249	0.3	100	0.3	<0.001	489	0.4
30–39	929	6.5	2304	2.9	1016	3.2		4249	3.4
40–49	2622	18.2	10,260	13.1	4384	14.0		17,266	13.9
50–59	3574	24.8	17,849	22.8	6971	22.2		28,394	22.9
60–69	3557	24.7	20,244	25.8	7819	24.9		31,620	25.5
≥70	3575	24.8	27,430	35.0	11,061	35.3		42,066	33.9
Menopause status									
Pre	3827	27.0	14,493	18.7	5913	19.3	<0.001	24,233	19.8
Peri	797	5.6	3215	4.2	1846	6.0		5858	4.8
Post	9542	67.4	59,688	77.1	22,842	74.6		92,072	75.4
missing	231	–	940	–	750	–		1921	–
ypT stage									
ypT0	854	32.8	2134	29.4	1054	31.5	<0.001	4042	30.6
ypTis	219	8.4	747	10.3	241	7.2		1207	9.1
ypT1	852	32.7	2332	32.1	1170	34.9		4354	33.0
ypT1mic	21	0.8	57	0.8	19	0.6		97	0.7
ypT2	481	18.5	1491	20.6	650	19.4		2622	19.9
ypT3	137	5.3	300	4.1	135	4.0		572	4.3
ypT4	42	1.6	194	2.7	79	2.4		315	2.4
missing	337	–	802	–	435	–		1574	–
pT stage									
pT0	0	–	0	–	0	–	<0.001	0	–
pTis	0	–	0	–	0	–		0	–
pT1	5007	59.8	31,495	56.2	13,200	56.1		49,702	56.5
pT1mic	25	0.3	106	0.2	57	0.2		188	0.2
pT2	2741	32.7	20,117	35.9	8722	37.0		31,580	35.9
pT3	424	5.1	2641	4.7	859	3.6		3924	4.5
pT4	181	2.2	1675	3.0	710	3.0		2566	2.9
missing	3076	–	14245	–	4020	–		21,341	–
ypN stage									
ypN0	1706	65.3	4436	61.1	2046	60.8	<0.001	8188	61.9
ypN1	542	20.7	1639	22.6	768	22.8		2949	22.3
ypN1mi	78	3.0	201	2.8	107	3.2		386	2.9
ypN2	207	7.9	650	9.0	307	9.1		1164	8.8
ypN3	81	3.1	329	4.5	138	4.1		548	4.1
missing	329	–	802	–	417	–		1548	–
pN stage									
pN0	6347	69.3	42,190	68.6	16,366	68.7	<0.001	64,903	68.7
pN1	1757	19.2	11,549	18.8	4543	19.1		17,849	18.9
pN1mi	288	3.1	1654	2.7	648	2.7		2590	2.7
pN2	493	5.4	3770	6.1	1441	6.0		5704	6.0
pN3	280	3.1	2379	3.9	834	3.5		3493	3.7
missing	2289	–	8737	–	3736	–		14,762	–
Grading									
G1	1598	14.3	9897	14.3	3666	13.1	<0.001	15,161	14.0
G2	6694	60.0	41,284	59.8	16,556	59.2		64,534	59.7
G3	2863	25.7	17,849	25.9	7735	27.7		28,447	26.3
missing	3242	–	9306	–	3394	–		15,942	–
Estrogen receptor status									
positive	11,006	80.7	59,201	83.8	24,290	82.5	<0.001	94,497	83.1
negative	2625	19.3	11,414	16.2	5140	17.5		19,179	16.9
missing	766	–	7721	–	1921	–		10,408	–
Progesterone receptor status									
positive	9786	71.8	51,692	73.2	21,133	71.8	<0.001	82,611	72.7
negative	3838	28.2	18,907	26.8	8293	28.2		31,038	27.3
missing	773	–	7737	–	1925	–		10,435	–
HER2 receptor status									
positive	1792	13.4	8602	12.4	3959	13.8	<0.001	14,353	12.9
negative	11,585	86.6	60,891	87.6	24,667	86.2		97,143	87.1
missing	1020	–	8843	–	2725	–		12,588	–
Subtype distribution									
HR+ HER2–	9844	73.7	53,067	76.5	21,296	74.5	<0.001	84,207	75.7
HR+ HER2+	1181	8.8	5916	8.5	2700	9.5		9797	8.8
HR– HER2+	599	4.5	2772	4.0	1282	4.5		4653	4.2
HR– HER2–	1730	13.0	7578	10.9	3291	11.5		12,599	11.3
missing	1043	–	9003	–	2782	–		12,828	–

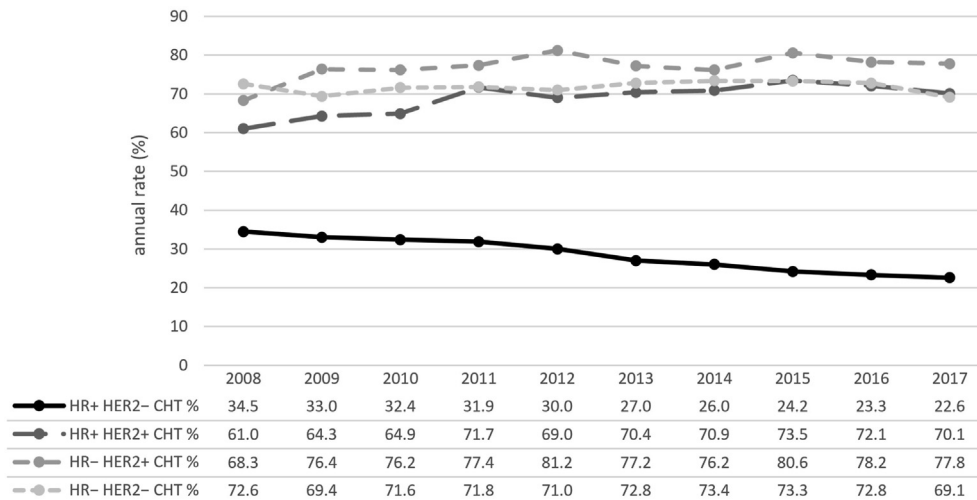


Fig. 2. Overall portion of patients receiving chemotherapy (CHT), separated according to the four tumor subtypes (HR+ HER2-, HR+ HER2+, HR- HER2+ HR- HER2-; total n = 124,084).

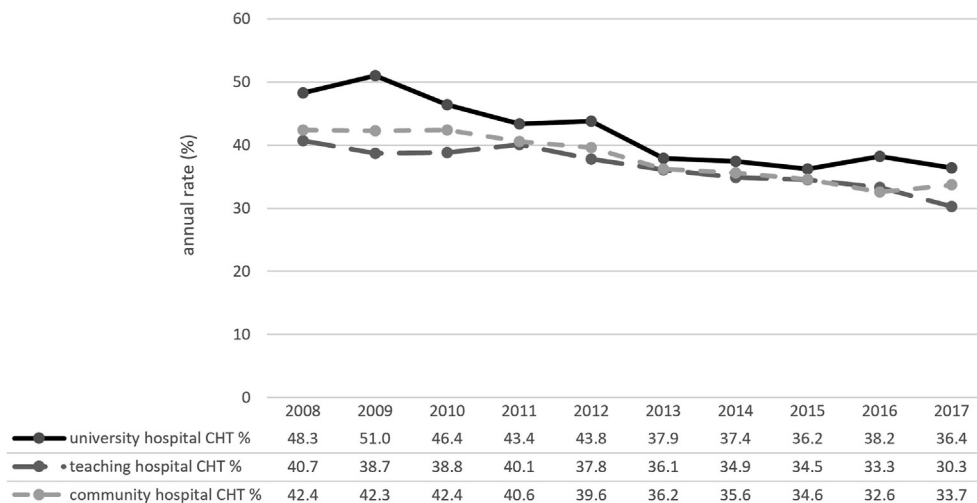


Fig. 3. Overall portion of patients receiving chemotherapy (CHT), separated according to the type of hospital (university hospital, teaching hospital, community hospital; total n = 124,084).

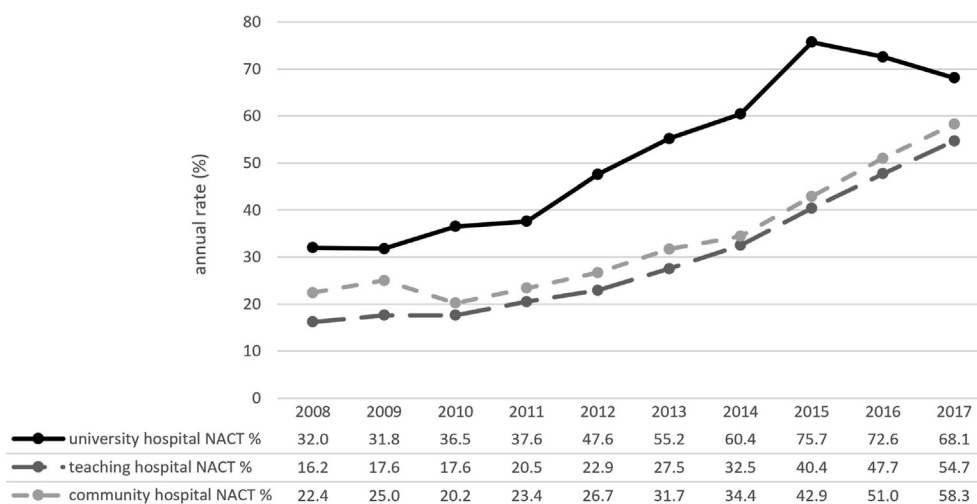


Fig. 4. Relative portion of neoadjuvant chemotherapy (NACT) use (of all patients with chemotherapy), separated according to the type of hospital (university hospital, teaching hospital, community hospital; total n = 44,765; missing n = 1509).

Table 2
Multivariable analyses of factors influencing the decision to perform chemotherapy (vs. no chemotherapy) and the decision to perform neoadjuvant chemotherapy (vs. adjuvant chemotherapy).

Variable	Chemotherapy (vs. no chemotherapy)		Neoadjuvant chemotherapy (vs. adjuvant chemotherapy)	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age				
≤29 years	Reference		Reference	
30–39 years	0.730 (0.477–1.118)	0.148	0.567 (0.393–0.817)	0.002
40–49 years	0.520 (0.344–0.786)	0.002	0.399 (0.281–0.568)	<0.001
50–59 years	0.344 (0.228–0.519)	<0.001	0.280 (0.197–0.398)	<0.001
60–69 years	0.246 (0.163–0.372)	<0.001	0.191 (0.134–0.272)	<0.001
≥70 years	0.052 (0.034–0.078)	<0.001	0.138 (0.097–0.198)	<0.001
Grading				
G1	Reference		Reference	
G2	3.505 (3.276–3.749)	<0.001	0.897 (0.758–1.061)	0.203
G3	9.096 (8.429–9.816)	<0.001	1.070 (0.902–1.271)	0.438
Subtype				
HR+ HER2–	Reference		Reference	
HR+ HER2+	5.602 (5.228–6.003)	<0.001	1.628 (1.481–1.789)	<0.001
HR– HER2+	6.778 (6.052–7.592)	<0.001	1.545 (1.355–1.762)	<0.001
HR– HER2–	4.826 (4.507–5.167)	<0.001	1.908 (1.741–2.090)	<0.001
Hospital type				
University	Reference		Reference	
Teaching	1.127 (1.054–1.205)	<0.001	0.461 (0.415–0.513)	<0.001
Community	1.209 (1.126–1.298)	<0.001	0.585 (0.522–0.655)	<0.001
Annual caseload				
≤100	Reference		Reference	
101–250	1.088 (1.025–1.156)	0.006	0.962 (0.859–1.076)	0.493
>250	1.191 (1.120–1.267)	<0.001	1.060 (0.945–1.188)	0.321

multigene test in the adjuvant setting has become clinical routine in Germany [18]. Their findings explain the declining use of chemotherapy use in our cohort, especially for the HR+ HER– cases in recent years (Fig. 2).

In contrast to these general trends, our results regarding institutional setting show only minor differences in chemotherapy use between university, teaching and community hospitals (Fig. 3). Furthermore, annual caseload of the treating facilities also did not reveal difference in the use of NACT (Fig. 6) or pCR rates (Supplemental Fig. S4). These are reassuring results suggesting comparable nationwide EBC care, regardless of institutional setting. In the management of EBC, there have been multiple initiatives on the institutional level in Germany to ensure high-quality treatment, such as a certification process started in 2003. This also comprises benchmarking with quality indicators of the certified BCUs [22,23]. The adherence of treatments to evidence-based guidelines was demonstrated through benchmarking, and this adherence had positive effects on clinical outcomes, as shown in several national [24,25] and international [26] studies. In Germany, the effect of BCU certification on clinical outcomes has been mixed, with studies both showing [10] and not showing [27] a benefit.

Minor differences between hospital types might be explained by differences of the patients, regarding demographics, oncological characteristics, and treatment strategies. First, overall chemotherapy use is slightly higher at university hospitals in our analyses when comparing crude time trends (Fig. 3). This might be related to a higher portion of younger, premenopausal patients with more

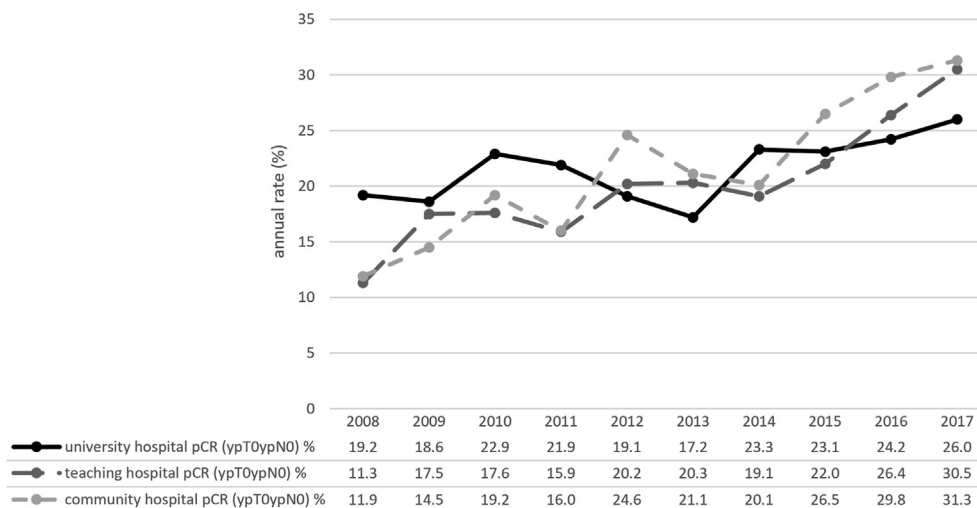


Fig. 5. Rates for pathological complete response (pCR: ypT0 ypN0) after neoadjuvant chemotherapy, according to the type of hospital (university hospital, teaching hospital, community hospital; total n = 14,783).

the clinical routine for cases when all other criteria do not allow an adequate adjuvant chemotherapy treatment recommendation as recommended by the German AGO guidelines [18]. While systemic treatment indications for HER2+, TN, and high-risk HR+ HER2– EBC are based on their comparably poor prognosis (and they receive preferably neoadjuvant therapy), the benefit of chemotherapy for intermediate risk HR+ HER2– EBC is not apparent and these patients normally undergo surgery first. Trials have been set up for these patients groups to enable a better adjuvant risk stratification through multigene signatures, with recent results e.g. from the MINDACT [19], the PlanB [20], and the TAILORx trials [21]. These trials were able to identify groups with HR+ HER2– EBC that can be spared ACT without compromising outcome. The use of

aggressive tumor subtypes (Table 1). Because EBC in these patients (i.e. young patients with aggressive tumor subtypes) is more likely to have a hereditary background, these patients are often treated and counseled at centers that belong to the German Consortium for Hereditary Breast and Ovarian Cancer [28]. These centers normally have affiliations to university hospitals, which might explain this effect of a higher overall chemotherapy use in these patient subgroups. This explanation is supported by multivariate analyses presenting significant higher odds for overall chemotherapy indication in community hospitals (in comparison to university hospitals) after adjusting for age and tumor characteristics (Table 2).

Second, our data also show a higher rate of NACT at university hospitals comparing to the other types of hospitals (Fig. 4), which is

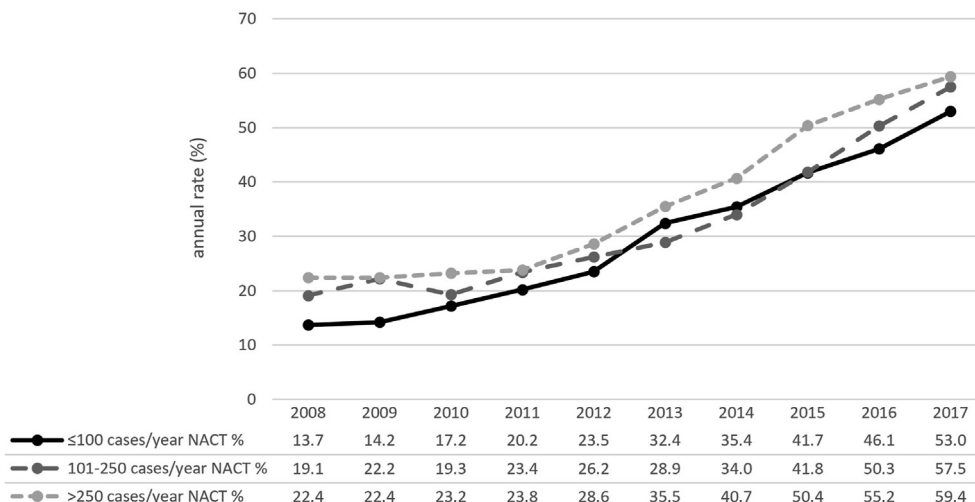


Fig. 6. Relative portion of neoadjuvant chemotherapy (NACT) use (of all patients with chemotherapy), separated according to annual caseload (≤100; 101–250; >250 cases/year; total n = 44,765; missing n = 1509).

also consistent with the multivariate analyses presenting significantly higher odds for NACT use in university hospital settings (Table 2). This might be related to an earlier adoption of study results and guideline recommendations into clinical practice. Furthermore, a higher portion of patients in university hospitals participate in clinical trials, especially for NACT. In the network of the German Breast Group (GBG), several practice-changing trials were recruiting in Germany during this period [29–31]. It has previously been shown in a German cohort that participation in adjuvant clinical trials is associated with higher survival rates, but only if guideline-adherent treatment was applied [9]. Patients taking part in NACT clinical trials have a higher pCR rate and a lower mastectomy risk than patients receiving treatment outside of clinical trials [32]. On the other hand, only a small portion of EBC patients are treated within randomized clinical trials, so the generalizability of results from trials could be questioned [33]. Therefore, it is important to compare results from cancer trials with routine data [34]. Our results reveal a higher portion of NACT use in university hospitals, especially for HR+ HER2– cases, which might be one explanation for their lower overall pCR rate. In this context the importance of NACT used for in vivo sensitivity testing and providing postneoadjuvant therapy escalation in cases of non-pCR must be considered [35].

Until now, there has been no comparable analysis between different hospital types for the systematic treatment of EBC patients regarding chemotherapy use and pCR rates after NACT in Germany. Previous German studies have not shown any difference in outcomes between treatment in urban versus rural areas for patients with EBC [36] or other tumor diseases [37].

There are limited data from other countries concerning chemotherapy use depending on the type of hospital, and the results have been inconsistent. For Dutch EBC cohorts, the use of ACT [38] as well as NACT [39] was not influenced by the hospital type. But for a nationwide US cohort, patients treated in academic centers were more likely to receive NACT [40]. Two studies have shown better survival among patients being treated in teaching hospitals compared to community hospitals in the US [41] and Canada [42]. It must be emphasized that these results are difficult to compare with the German healthcare landscape, because insurance status plays a more important role in treatment allocation in the US [43]. Beyond

EBC, other studies have demonstrated better patient outcomes in teaching versus non-teaching hospitals, e.g. for rectal cancer patients in the UK [44] or generally in patients with non-oncologic diseases [45]. On the other hand, there was no difference between different hospital types for the outcomes of systemic therapy in a Dutch cohort with various gynecological cancers [46]. A large review has shown that the overall beneficial effect of hospital type on cancer survival is small [47]. Nonetheless comparing different institutions, the rates for the application of systemic therapies varied widely between hospitals after adjusting for case-mix across all ages as a study from England has shown [48].

In our cohort, annual case load did not influence NACT use or pCR rates. This suggests that also smaller institutions do not differ from large-scale centers regarding chemotherapy use or NACT recommendations for their patients. As one study has been able to show a beneficial effect of higher caseload on the surgical aspects of EBC [49], similar analyses for systemic treatment have not been made until now. Treatment for EBC at high-volume BCUs seems to be connected with improved outcome in the US [50]; whereas, this effect is unclear for European hospitals [51].

This study has a few limitations that should be kept in mind. Although this German registry is large and nationwide, it is still only a sample, not a comprehensive mandatory registry, so the results may not exactly represent all institutions. Unfortunately, as we have a benchmarking database individual patient status information (concerning performance status, comorbidities, etc.) and clinical tumor stage are not available. Thus, we could not adjust our data for these baseline patient characteristics.

Due to legal restrictions on data privacy protection, we also do not know details about the individual caseloads of the participating institutions nor their geographical distribution within Germany. Also, the portion of certified BCUs from all contributing centers is unknown; the cohort comprises patients from BCUs with and without certification. Therefore, it is not possible to speculate on the association of BCU certification with our findings. As already stated, the data for Germany concerning the influence of certification itself on outcome on patients with EBC were inconclusive [10,27]. On the other hand, the proportion of patients treated at university hospitals in our cohort reflects the average portion of all in-patients cases treated at university hospitals in Germany that is

reported by the German Federal Statistics Bureau [52].

5. Conclusion

The results from this large, nationwide cohort reflect a decreasing use of chemotherapy in Germany, irrespective of hospital type or annual case load. The highest portions of NACT have been in university hospitals. Nonetheless, over the past decade, rising pCR rates were observed in all hospital settings, concordant with previous analyses for this database [16].

Declaration of competing interest

Fabian Riedel declares that he has no conflict of interest. Ann Sophie Hoffmann declares that she has no conflict of interest. Mareike Moderow declares that she has no conflict of interest. Manuel Feisst declares that he has no conflict of interest. Sabine Heublein declares that she has no conflict of interest. Thomas Maximilian Deutsch declares that he has no conflict of interest. Benedikt Schäfergen declares that he has no conflict of interest. Michael Golatta declares that he has no conflict of interest. Christoph Domschke declares that he has no conflict of interest. Markus Wallwiener declares that he has no conflict of interest. Jörg Heil declares that that he has no conflict of interest. André Hennigs declares that he has no conflict of interest.

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Compliance with ethical standards

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethics committee of Heidelberg University Medical School did not request approval for consent for this designated analysis. Informed consent to analyze the anonymized data was obtained from all individual participants for the data acquisition of the benchmarking process.

Data accessibility

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2021.04.006>.

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