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Omission of anthracyclines in HER2-positive Breast Cancer: A Retrospective Cohort Study

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Abstract

Purpose

The role of anthracyclines (ANT) in HER2-positive breast cancer treatment is increasingly questioned because of their toxicity. We compared ANT-containing versus ANT-free systemic therapies regarding pathological complete response (pCR) and survival in a real-world cohort.

Methods

In this retrospective population-based study, female patients with primary invasive HER2-positive breast cancer (UICC I–III) diagnosed between 2010 and 2020 were identified from the Tumor Center Regensburg. Patients were analyzed separately in the neoadjuvant and adjuvant settings. Primary endpoints were overall survival (OS), recurrence-free survival (RFS), and pCR.

Results

A total of 701 patients were included (328 neoadjuvant, 373 adjuvant). PCR rates were comparable between ANT-containing and ANT-free regimens (40.7% vs. 50.0%; OR 0.601, p = 0.088). ANT-free regimens were associated with significantly improved OS in both the neoadjuvant (HR 6.905, p = 0.019) and adjuvant settings (HR 4.291, p = 0.006). In a sub-analysis comparing the ANT-containing regimen epirubicin/cyclophosphamide followed by paclitaxel plus trastuzumab and pertuzumab (EC-T-TP) with the ANT-free regimen docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP), pCR rates were similar (54.0% vs. 54.3%). The TCHP arm showed 100% 5-year OS.

Conclusion

ANT-free therapies demonstrated high efficacy without compromising pCR or survival. These findings support ANT-free de-escalation strategies as standards of care for early HER2-positive breast cancer.

Introduction

Breast cancer remains the most common malignancy among women worldwide and is the leading cause of cancer-related death in the female population. In Germany alone, approximately 75,000 new cases are diagnosed annually, meaning that about one in eight women will develop breast cancer in her lifetime [1]. Among these, approximately 15–20% of cases are characterized by the overexpression or amplification of the Human Epidermal Growth Factor Receptor 2 (HER2), a tyrosine kinase receptor encoded by the c-erbB-2 gene on chromosome 17 [2–4]. Historically, HER2-positive breast cancer was associated with an aggressive tumor biology, early metastasis, and a poor prognosis. However, the introduction of HER2-targeted therapies has revolutionized the treatment landscape. Consequently, HER2 status has established itself as a critical biomarker for therapeutic decision-making [4–7]. Based on the current evidence, HER2 status should be regarded as a predictive biomarker for HER2-targeted chemotherapy [8, 9]. Despite these well-known advances, the optimal chemotherapy backbone remains a subject of debate. Guidelines used to recommend a neoadjuvant or adjuvant regimen containing a taxane and an anthracycline, combined with HER2-targeted therapy [8]. Anthracyclines are highly effective cytotoxic agents that are associated with significant long-term toxicity. Most notably, anthracycline exposure is linked to an increased risk of cardiotoxicity and secondary malignancies, particularly acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) [5, 10–15]. The Alliance A151511 study showed a significant more than 5-fold increase in the risk of developing AML/MDS in patients treated with anthracyclines compared to those who were not [16]. The TRAIN-2, a multicenter, open-label, randomized phase III trial in patients with stage II–III HER2-positive breast cancer comparing anthracycline-containing versus anthracycline-free neoadjuvant chemotherapy with dual HER2 blockade, showed that patients receiving anthracycline-containing neoadjuvant therapy with dual HER2 blockade had a more than twofold higher risk of clinically significant cardiac

events, including declines in left ventricular ejection fraction, compared to those treated with anthracycline-free regimens [10, 11].

Further, anthracyclines carry a dose-dependent risk of cumulative cardiotoxicity, which can lead to irreversible heart failure [17–21]. This effect is especially observed in combination with HER2-targeted substances and when compared with anthracycline-free protocols, as shown in the BCIRG-006 study. In this trial, the non-anthracycline regimen consisting of docetaxel, carboplatin, and trastuzumab (TCH) demonstrated similar disease-free and overall survival compared to the anthracycline-containing regimen doxorubicin and cyclophosphamide followed by paclitaxel (AC-T) plus trastuzumab, while showing significantly lower rates of congestive heart failure and cardiac dysfunction [22]. Given these risks, de-escalation strategies aiming to omit anthracyclines without compromising oncological efficacy have gained traction in the current evidence landscape [20, 21]. In the era of dual HER2-blockade with trastuzumab and pertuzumab that have improved survival drastically compared to the pre-targeted therapy, the necessity of aggressive chemotherapy with anthracyclines is further questioned. Landmark trials such as the single-arm APT trial demonstrated excellent outcomes with 10-year invasive disease-free survival (DFS) of 91.3% (95%-CI 88.3–94.4), 10-year OS of 94.3% (95%-CI 91.8–96.8), and 10-year breast cancer-specific survival of 98.8% (95%-CI 97.6–100) with the anthracycline-free regimen of paclitaxel and trastuzumab in patients with small, node-negative tumors [5, 23–25].

Supporting these findings, the phase III TRAIN-2 study compared anthracycline-containing vs. anthracycline-free regimens in the presence of dual blockade and found no significant difference in pCR or event-free survival, but significantly lower toxicity in the anthracycline-free arm. They concluded that omitting anthracyclines from neoadjuvant treatment regimens may be a preferred approach in the presence of dual HER2 blockade in patients with early HER2-positive breast cancer [10].

This study seeks to evaluate the extent to which outcomes observed in controlled clinical trials are reproducible in a real-world context. Leveraging data from a large, population-based cancer registry, we systematically assess the impact of anthracycline-containing versus anthracycline-free systemic regimens on pCR, RFS and OS among patients with early-stage HER2-positive breast cancer. Analyses are conducted across both neoadjuvant and adjuvant treatment settings.

A specific subgroup analysis was performed on patients receiving neoadjuvant dual blockage with protocols containing trastuzumab and pertuzumab but different chemotherapy protocols (anthracycline-containing EC-T-TP vs. anthracycline-free TCHP) to analyze the impact of anthracyclines in survival outcomes and pCR while controlling confounding effects attributable to the targeted therapy itself.

Methods

Study population and variables

This retrospective cohort study analyzes clinical cancer registry data from the Tumor Center Regensburg, a regional clinical cancer registry in Bavaria, Germany. The registry covers a population of over 2.2 million people and documents diagnosis, treatment, and follow-up data for all cancer patients in its catchment area (Upper Palatinate and Lower Bavaria). Data collection and management adhere to the stringent requirements of the German Cancer Early Detection and Cancer Registry Law (KFRG), ensuring high-quality, standardized, and continuously updated population-based data. Vital status is regularly updated through death certificates and linkage with residents' registration offices, allowing for comprehensive long-term follow-up. The study cohort comprised female patients diagnosed with primary, non-metastatic, invasive HER2-positive breast cancer (UICC stages I–III) between January 1, 2010, and December 31, 2020. HER2 positivity was defined according to standard guidelines as an immunohistochemistry (IHC) score of 3 + or a positive in-situ hybridization (ISH) test (HER2/CEP17 ratio ≥ 2.0). Patients with a prior or synchronous secondary malignancy at the time of diagnosis were excluded to ensure that survival outcomes were attributable to the index breast cancer. From the Registry we obtained the following patient and tumor characteristics: age at diagnosis, menopausal status, histological tumor type, TNM stage (clinical and pathological), grading, hormone receptor status (ER/PR), and Ki-67 proliferation index. Furthermore, we collected treatment details as of type of

surgery (breast conserving therapy vs. mastectomy), radiation therapy, dates and types of systemic therapy (chemotherapy, targeted therapy, endocrine therapy).

Treatment Cohorts

The analysis focuses on patients who received systemic therapy. Patients were stratified into two primary collectives based on the timing of systemic therapy: The first group contains patients in the neoadjuvant setting who received preoperative systemic therapy (328 patients). The second group contains patients in the adjuvant setting who received postoperative systemic therapy (373 patients). Within these collectives, patients were categorized based on whether their chemotherapy regimen included an anthracycline (ANT) or not (ANT-free). Furthermore, a subcohort was analyzed nested within the neoadjuvant setting to compare two contemporary standard-of-care regimens both utilizing dual HER2-blockade (trastuzumab + pertuzumab) with one containing anthracycline (EC-T-TP) and the other one being anthracycline-free (TCHP). The EC-T-TP protocol contains epirubicin and cyclophosphamide followed by paclitaxel plus trastuzumab and pertuzumab (anthracycline-containing). The TCHP protocol contains docetaxel and carboplatin plus trastuzumab and pertuzumab (anthracycline-free). Figure 1 illustrates the inclusion and exclusion criteria of the study cohort.

Statistical analysis

The primary endpoints were the following: OS, defined as the time from the date of diagnosis to death from any cause. RFS, defined as the time from diagnosis to the first locoregional or distant recurrence or death. PCR, defined as the absence of invasive tumor residues in the breast and axillary lymph nodes (ypT0yN0) after neoadjuvant therapy. Continuous variables were summarized using means, medians, and standard deviations. Categorical variables were described using absolute frequencies and percentages. Differences between groups were assessed using the Chi-square test or Fisher's exact test for categorical variables. For continuous variables, the Student’s t-test was used for normally distributed data, and the Mann-Whitney U test for non-normally distributed data. Survival analyses were performed using the Kaplan-Meier method, and differences between survival curves were compared using the Log-Rank (Mantel-Cox) test. Follow-up time was calculated using the reverse Kaplan-Meier method. To adjust for potential confounders, univariable and multivariable Cox proportional hazards regression models were estimated. The Hazard Ratios (HR) are reported with 95% Confidence Intervals (CI). Covariates included in the models were age at diagnosis, histological type, grading, hormone receptor status, significant Ki-67 index (> 25% vs < 25%), and UICC stage. The proportional hazards assumption was verified by visual inspection of Kaplan-Meier curves. For the analysis of pCR, univariable and multivariable binary logistic regression models were employed to estimate OR. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics, Version 28.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 975 patients with HER2-positive breast cancer were identified in the registry period. Patients who did not receive chemotherapy or had incomplete or missing treatment data were excluded. The final study cohort included 701 patients, of which 328 received neoadjuvant chemotherapy and 373 patients received adjuvant chemotherapy. Table 1 demonstrates clinical and histopathological characteristics of patients in the analyzed chemotherapy groups. Table 2 summarizes the results of the three analyzed groups across the end points pCR (for neoadjuvant settings), OS and RFS.

Table 1
Clinical and histopathological characteristics of patients in chemotherapy groups

		Neoadjuvant group						Adjuvant group					
		ANT		ANT-free		Total		ANT		ANT-free		Total	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Age at diagnosis	< 50	100	40,3	18	22,5	118	36,0	95	33,1	15	17,4	110	29,5
	50–59	83	33,5	24	30,0	107	32,6	101	35,2	15	17,4	116	31,1
	60–69	52	21,0	20	25,0	72	22,0	57	19,9	22	25,6	79	21,2
	> 70	13	5,2	18	22,5	31	9,5	34	11,8	34	39,5	68	18,2
Menopausal status	Pre	105	42,3	19	23,8	124	37,8	97	33,8	16	18,6	113	30,3
	Post	143	57,7	61	76,3	204	62,2	190	66,2	70	81,4	260	69,7
Histological type	IDC	226	91,1	74	92,5	300	91,5	251	87,5	75	87,2	326	87,4
	ILC	13	5,2	5	6,3	18	5,5	18	6,3	9	10,5	27	7,2
	Unspecified	9	3,6	1	1,3	10	3,0	18	6,3	2	2,3	20	5,4
Grading	G1	3	1,2	0	0,0	3	0,9	14	4,9	1	1,2	15	4,0
	G2	89	35,9	34	42,5	123	37,5	158	55,1	43	50,0	201	53,9
	G3	65	26,2	30	37,5	95	29,0	111	38,7	42	48,8	153	41,0
	NR	91	36,7	16	20,0	107	32,6	4	1,4	0	0,0	4	1,1
Hormone receptor status	Positive	164	66,1	56	70,0	220	67,1	204	71,1	60	69,8	264	70,8
	Negative	75	30,2	22	27,5	97	29,6	75	26,1	24	27,9	99	26,5
	NR	0	0,0	0	0,0	0	0,0	8	2,8	2	2,3	10	2,7
Ki67	< 25	113	45,6	20	25,0	133	40,5	120	41,8	34	39,5	154	41,3
	> 25	117	47,2	54	67,5	171	52,1	133	46,3	45	52,3	178	47,7
	NR	18	7,3	6	7,5	24	7,3	34	11,8	7	8,1	41	11,0
UICC Stage	I	78	31,5	20	25,0	98	29,9	107	37,3	37	43,0	144	38,6
	II	135	54,4	44	55,0	179	54,6	123	42,9	28	32,6	151	40,5
	III	32	12,9	15	18,8	47	14,3	57	19,9	21	24,4	78	20,9
	NR	3	1,2	1	1,3	4	1,2	0	0,0	0	0,0	0	0,0
PCR	PCR no/NR	147	59,3	40	50,0	187	57,0	147	-	-	-	-	-
	PCR yes	101	40,7	40	50,0	141	43,0	101	-	-	-	-	-
Surgery	BCT	191	77,0	60	75,0	251	76,5	212	73,9	61	70,9	273	73,2
	Mastectomy	48	19,4	19	23,8	67	20,4	55	19,2	18	20,9	73	19,6
	Mastectomy after BCT	5	2,0	1	1,3	6	1,8	17	5,9	6	7,0	23	6,2
	Surgery (unspecified)	4	1,6	0	0,0	4	1,2	3	1,0	1	1,2	4	1,1
Local Residual	R0	225	90,7	70	87,5	295	89,9	-	-	-	-	-	-

		Neoadjuvant group						Adjuvant group					
		ANT		ANT-free		Total		ANT		ANT-free		Total	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
tumor	R1/2	4	1,6	1	1,3	5	1,5	-	-	-	-	-	-
	NR	19	7,7	9	11,3	28	8,5	-	-	-	-	-	-
	Total	248	100,0	80	100,0	328	100,0	287	100,0	86	100,0	373	100,0

BCT = Breast conserving treatment

IDC = Invasive ductal carcinoma

ILC = Invasive lobular carcinoma

NR = not reported

Neoadjuvant Setting

In the neoadjuvant setting with 328 patients, 248 patients (75.6%) received an anthracycline-containing regimen, while 80 patients (24.4%) received an anthracycline-free regimen. Patients receiving anthracycline-free therapy were significantly older, with a mean age of 58.7 years compared to 52.6 years in the anthracycline group ($p < 0.001$). With 67.5% the anthracycline-free group had a significantly higher proportion of tumors with a high proliferation index (Ki-67 > 25%) than the anthracycline group with 47.2% ($p = 0.004$). This data suggests that anthracycline-free regimens were not solely reserved for "low-risk" or indolent tumors but were frequently used in biologically aggressive disease in real world setting, possibly due to the older age of these patients prohibiting anthracycline use.

pCR The pCR rate was 40.7% (101 out of 248) in the anthracycline-containing group and 50.0% (40 out of 80) in the anthracycline-free group (Fig. 3). In univariable analysis, this difference was not statistically significant ($p = 0.145$). In the multivariable logistic regression adjusted for confounders, no significant independent effect of anthracyclines on pCR was observed (OR 0.601; 95% CI 0.335–1.078; $p = 0.088$). Significant predictors of pCR in the overall cohort included hormone receptor status and proliferation index. Patients with hormone receptor-negative tumors had a more than 4-fold higher chance of achieving pCR compared to hormone receptor-positive patients (OR 4.108; $p < 0.001$). Similarly, high Ki-67 (> 25%) was associated with a higher likelihood of pCR (OR 2.335; $p = 0.004$).

OS The median follow-up was 3.9 years. The 5-year OS rate was 92.1% for the anthracycline-containing group and 97.8% for the anthracycline-free group (Fig. 2). Multivariable Cox regression analysis revealed a statistically significant disadvantage for the anthracycline-containing group (HR 6.905; 95% CI 1.378–34.606; $p = 0.019$), indicating an increased risk of mortality compared to the anthracycline-free group.

RFS The 5-year RFS rate was 87.3% for the anthracycline-containing group and 85.3% for the anthracycline-free group. Multivariable analysis showed no significant difference regarding RFS (HR 1.991; 95% CI 0.784–5.060; $p = 0.148$).

Adjuvant Setting

In the adjuvant setting (N = 373), 287 patients (76.9%) were treated with anthracyclines, and 86 patients (23.1%) received anthracycline-free regimens.

OS The median follow-up was 7.9 years. The 5-year OS rate was 94.3% for the anthracycline-containing group versus 95.8% for the anthracycline-free group. Multivariable analysis demonstrated a significantly higher risk of death for patients treated with anthracyclines (HR 4.291; 95% CI 1.506–12.228; $p = 0.006$).

RFS The 5-year RFS rate was 91.2% for the anthracycline-containing group and 94.5% for the anthracycline-free group. In the multivariable model, anthracycline-containing therapy was associated with a significantly increased risk of recurrence or death (HR 4.181; 95% CI 1.643–10.643; p = 0.003).

Subcohort with Dual Blockade

To better isolate the effect of anthracyclines from the variability of modern HER2-targeted therapies, a specific subgroup analysis (subcohort with N = 135) was performed on patients receiving neoadjuvant dual blockade with protocols containing trastuzumab and pertuzumab. We compared the anthracycline-containing EC-T-TP regimen (N = 100) to the anthracycline-free TCHP regimen (N = 35) in the presence of dual blockage in both groups. This analysis was performed following the design of the initially described TRAIN-2 study and aims to better compare the effect of anthracyclines while muting effects of the targeted therapy in the comparison.

pCR The pCR rates were similar between the two groups: 54.0% for EC-T-TP and 54.3% for TCHP (Fig. 4). Multivariable analysis confirmed no significant difference (OR 1.486; 95% CI 0.547–4.037; p = 0.437). This emphasizes that in the presence of dual blockade, the addition of anthracyclines does not appear to increase the rate of complete tumor eradication.

OS There were 3 deaths (3.0%) in the EC-T-TP group and 0 deaths in the TCHP group within the observation period. The 5-year OS was 93.6% for EC-T-TP vs. 100% for TCHP. Due to the lack of events in the TCHP arm, a Hazard Ratio could not be computed.

RFS Recurrence or death occurred in 3.5% of EC-T-TP patients and 6.7% of TCHP patients. No significant difference was found in multivariable analysis (HR 0.136; 95% CI 0.007–2.728; p = 0.192).

Table 2
End points in the three analyzed cohorts

		Univariable regression analysis[a]				Multivariable regression analysis[a]			
		p	OR/HR[b]	Upper 95%-CI	Lower 95%-CI	p	OR/HR[b]	Upper 95%-CI	Lower 95%-CI
Neoadjuvant cohort[c]	pCR	.146	.687	.414	1.140	.088	.601	.335	1.078
	OS(R0)	.202	2.590	.600	11.187	.019	6.905	1.378	34.606
	RFS(R0)	.734	1.154	.504	2.644	.148	1.991	.784	5.060
Adjuvant cohort[c]	OS	.857	.925	.397	2.159	.006	4.291	1.506	12.228
	RFS	.307	1.527	.678	3.436	.003	4.181	1.643	10.643
Subcohort[d]	pCR	.977	1.012	.467	2.190	.437	1.486	.547	4.037
	OS(R0)	.999	.000	.000	-	.999	.000	.000	-
	RFS(R0)	.783	1.288	.213	7.787	.192	.136	.007	2.728

[a] Logistic regression analysis for pCR; Cox regression analysis for OS, OS (R0)

[b] OR for pCR; HR for OS, OS (all), OS (R0), RFS, RFS(R0)

[c] Exposure group = ANT-containing; reference group = ANT-free

[d] Exposure group = TCHP; reference group = EC-T-TP

Discussion

This retrospective population-based study provides comprehensive real-world evidence regarding the efficacy of anthracycline-free versus anthracycline-containing systemic therapies in HER2-positive breast cancer. More recently, the current body of evidence containing some findings of the studies mentioned in this paper have been reflected in the updated clinical guideline, in which anthracycline-free treatment strategies are assigned a substantially greater role than in the previous guideline version, that recommended anthracyclines plus taxane therapy for primary HER2-positive breast cancer [5, 8, 15, 20, 26].

Our findings challenge the historical dogma that anthracyclines are an indispensable component of curative chemotherapy for this subtype as well. A noticeable finding of our analysis is that anthracycline-free regimens were associated with non-inferior or even superior survival outcomes compared to anthracycline-containing regimens. This held true in both the neoadjuvant and adjuvant settings. In the neoadjuvant setting, patients receiving anthracycline-free therapy had significantly better OS with an HR of 6.905 ($p = 0.019$). PCR and RFS were comparable. In the adjuvant setting, anthracycline use was associated with significantly worse OS with an HR of 4.291 ($p = 0.006$) and RFS with an HR of 4.181 ($p = 0.003$). Critically, patient characteristic analysis revealed that the anthracycline-free cohort was not simply a "low-risk" group. The anthracycline-free cohort was both older with a mean age of 58.7 years compared to 52.6 years in the anthracycline group ($p < 0.001$) and had a significantly higher portion of high-proliferation tumors with 67.6% compared to the anthracycline group with 47.2% ($p = 0.004$). Despite this biological aggressiveness, they achieved higher pCR rates (50% vs. 40.7%) and better survival. In the presence of strong indicators of current studies, the robust performance of anthracycline-free regimens in this study suggests that taxane-based regimens combined with HER2-blockade are sufficient to treat HER2-positive disease. These results align with and extend the findings of major clinical trials.

The phase II APT trial conducted by Tolaney et al. demonstrated excellent survival rates in small (≤ 3 cm), node-negative, HER2-positive breast cancer treated with an anthracycline-free adjuvant therapy consisting of paclitaxel and trastuzumab. This trial established the efficacy of anthracycline-free regimens in low-risk patients [5, 23–25]. The initially described TRAIN-2 study compared anthracycline-containing vs. anthracycline-free regimens in the presence of dual blockade and found no significant difference in pCR or event-free survival, but significantly lower toxicity in the anthracycline-free arm [10, 11]. The subcohort analysis (EC-T-TP vs. TCHP) reproduces the TRAIN-2 design in a real-world-setting, showing similar pCR rates of the two groups and 100% 5-year survival in the THCP arm. These findings indicate that anthracycline-free regimens are not inferior when differences in HER2-targeted therapies are controlled. Moreover, the incremental benefit of anthracyclines appears negligible in the setting of potent dual HER2 blockade. Critically, the potential drivers for the inferior survival in the anthracycline-containing group warrant discussion. Since breast cancer-specific mortality was low in both groups, the survival disadvantage for anthracycline-treated patients might reflect non-breast cancer mortality, potentially driven by long-term toxicities by anthracyclines. In our real-world population, these competing risks may outweigh the previously believed oncological benefit of anthracyclines.

The primary strength of the present study lies in its utilization of a large population-based regional cancer registry comprising a substantial cohort of 701 patients with HER2-positive breast cancer and comprehensive longitudinal data on diagnosis, therapy, and disease progression in a population of over 2.2 million people. This provides a robust real-world dataset addressing a clinically highly relevant question regarding the role of anthracyclines in HER2-positive breast cancer treatment. The registry-based design ensures that the data reflects routine clinical practice, including older patients and those with comorbidities who are often underrepresented or excluded from randomized clinical trials. The high follow-up rate further enables reliable survival analyses and outcome estimates. Another major strength is the separate evaluation of neoadjuvant and adjuvant treatment settings, allowing for a more differentiated assessment of treatment effects across clinical scenarios. In addition, the dedicated sub-analysis of dual HER2 blockade regimens provides clinically meaningful insights into contemporary treatment strategies. Furthermore, the study employs rigorous statistical methods, including Kaplan–Meier analyses and regression models, to comprehensively evaluate the impact of anthracyclines in the chemotherapy of HER2-positive breast cancer.

However, there were several limitations in the study design that need to be acknowledged. These include the retrospective, non-randomized design. Treatment allocation was at the discretion of the treating physician, introducing selection bias. Anthracyclines were more likely given to younger patients, while older patients received anthracycline-free regimens. However,

we attempted to control for this using multivariable regression models adjusting for personal and histopathological parameters like age, stage, and biology. Nevertheless, the retrospective nature of registry-based studies and the use of statistical models to adjust for risk factors might not have accounted for all biases. The sample size of the specific TCHP subcohort with 35 patients was relatively small, limiting statistical power for rare events.

Conclusion

In conclusion, our real-world data suggest that anthracycline-free systemic therapies are a highly effective and safe treatment option for early HER2-positive breast cancer. In our cohort, omitting anthracyclines did not compromise pathological complete response rates or survival outcomes. In fact, anthracycline-free regimens were associated with favorable survival statistics, even in patients with high-proliferation tumors. Given the well-established toxicity profile of anthracyclines, particularly regarding cardiotoxicity and secondary malignancies, these findings support the shift towards anthracycline-free regimens as a standard of care.

Declarations

Data Availability

All relevant data supporting the findings of this study are available within the article. Additional datasets containing potentially identifiable patient information that were collected and analyzed during the current study are not publicly available due to data protection. Anonymized data are available from the corresponding author on reasonable request.

Author contribution statement

All authors contributed to the study. The study conception, design and research question were developed by Stephan Seitz in cooperation with Naomi Harman. Material preparation, data collection and analysis were performed by Michael Gerken and Naomi Harman. The first draft of the manuscript was written by Naomi Harman and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Additional Information

Competing Interests

Jonas Roth received travel grants from Menarini Stemline and MSD as well as honoraria from Novartis, Medizinwelten, AstraZeneca and Gilead. Sara Plavic-Radeka is serving on the advisory board of AwoGyn. Maria Hatzipanagiotou received speaking and lecture fees from Novartis, Lilly, Roche, Pfizer, RG Ärztefortbildung and AstraZeneca within the past three years. Olaf Ortmann has received honoraria for lectures, advisory board participation, chairing educational events, and scientific leadership activities from Astellas Pharma, AstraZeneca, Eisai, iOMEDICO AG, Novartis Pharma, Med Update, Forum für medizinische Fortbildung (FomF GmbH), Aurikamed, RG Ärztefortbildung, and other medical education organizations. He has also received travel support related to some of these activities. Stephan Seitz reports consulting fees from AstraZeneca, Daiichi Sankyo, Gilead, GSK, Lilly, MSD, Novartis, Pfizer, Roche and Stemline Menarini as well as honoraria for lectures from AstraZeneca, Daiichi Sankyo, GE HealthCare, Gilead, Lilly, MSD, Novartis, Pfizer, Roche, and Stemline Menarini and conferences or meetings with AstraZeneca, GE HealthCare, Gilead, Lilly, Pfizer, and Stemline Menarini within the past 3 years.Naomi Harman, Michael Gerken, Monika Klinikhammer-Schalke and Miriam Fernandenz-Pacheco declare to have no conflicts of interest in relation to this study.

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Ethical statement

This retrospective cohort study was conducted using anonymized data from the clinical cancer registry of the Tumor Center Regensburg, a regional clinical cancer registry in Bavaria, Germany. All methods were carried out in accordance with the relevant guidelines and regulations governing the use of clinical cancer registry data. The Ethics Committee of the University of Regensburg confirmed that there are no ethical concerns regarding the publication of this study. As the data collection is based on Section 65c of the German Social Code Book V (SGB V), patient information and informed consent from the participants and/or their legal guardians were not required.

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Figures

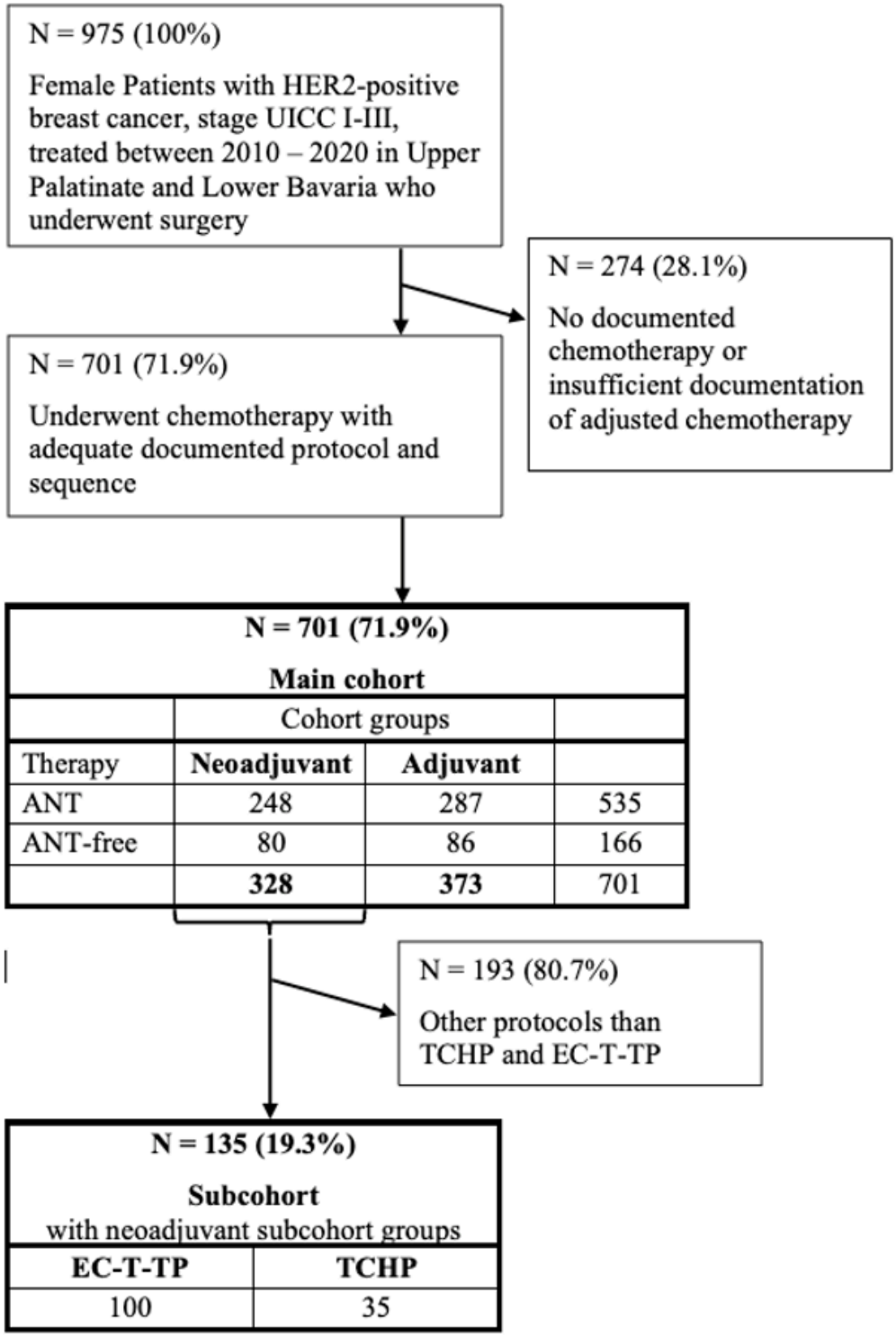


Figure 1

Depiction of the study collective

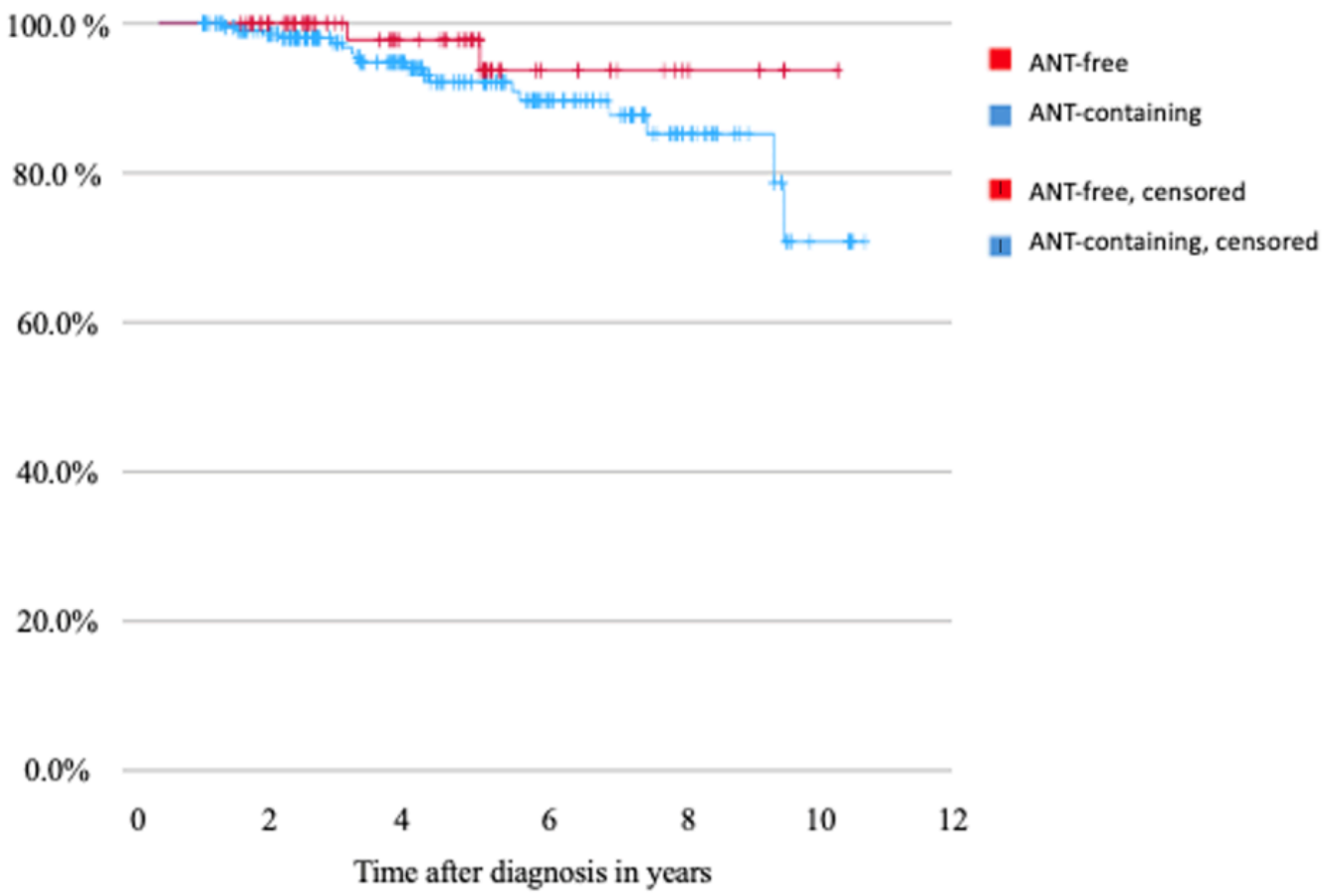


Figure 2

Kaplan Meier analysis of overall survival in neoadjuvant group

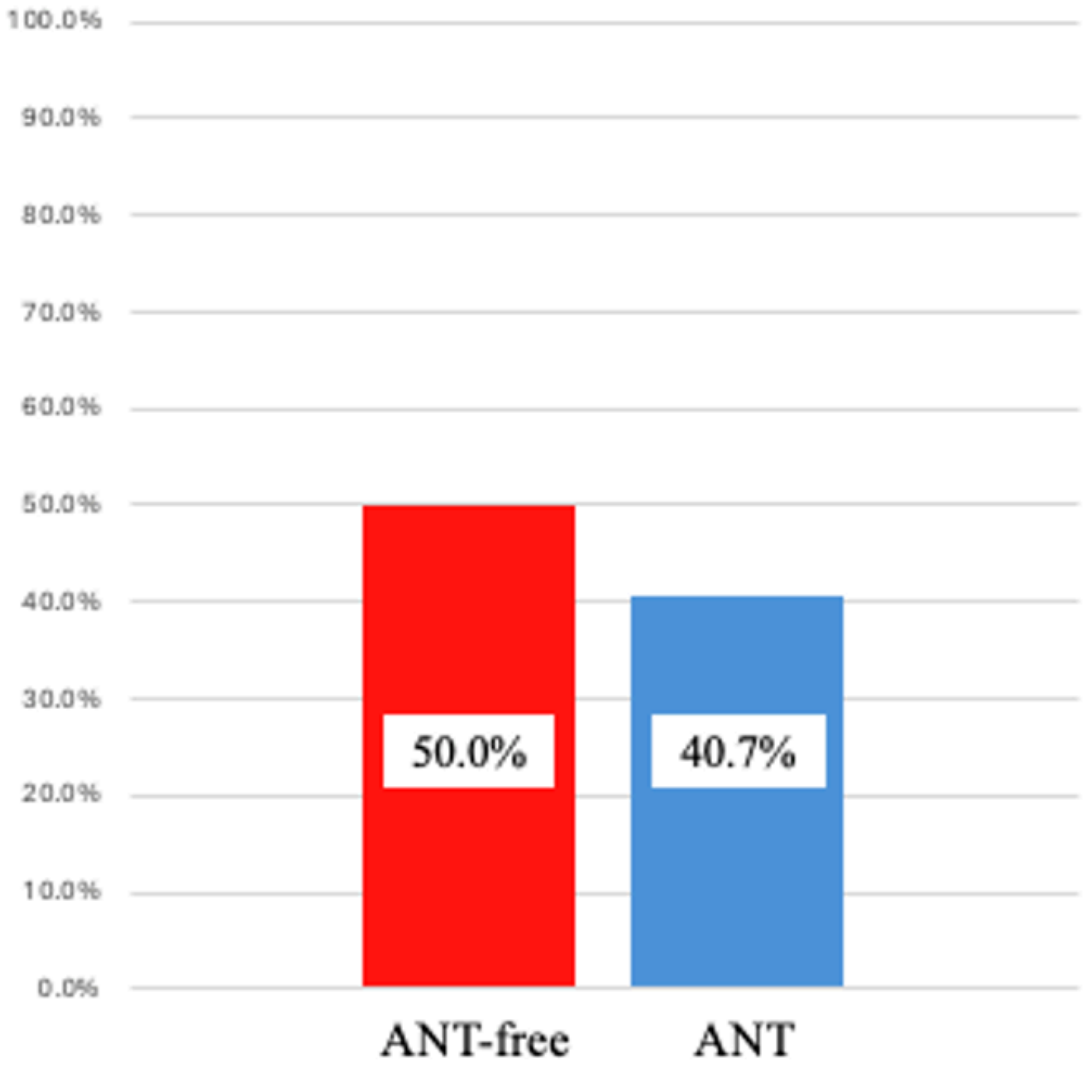


Figure 3

pCR-rates in neoadjuvant group in ANT-free vs. ANT-containing therapy groups

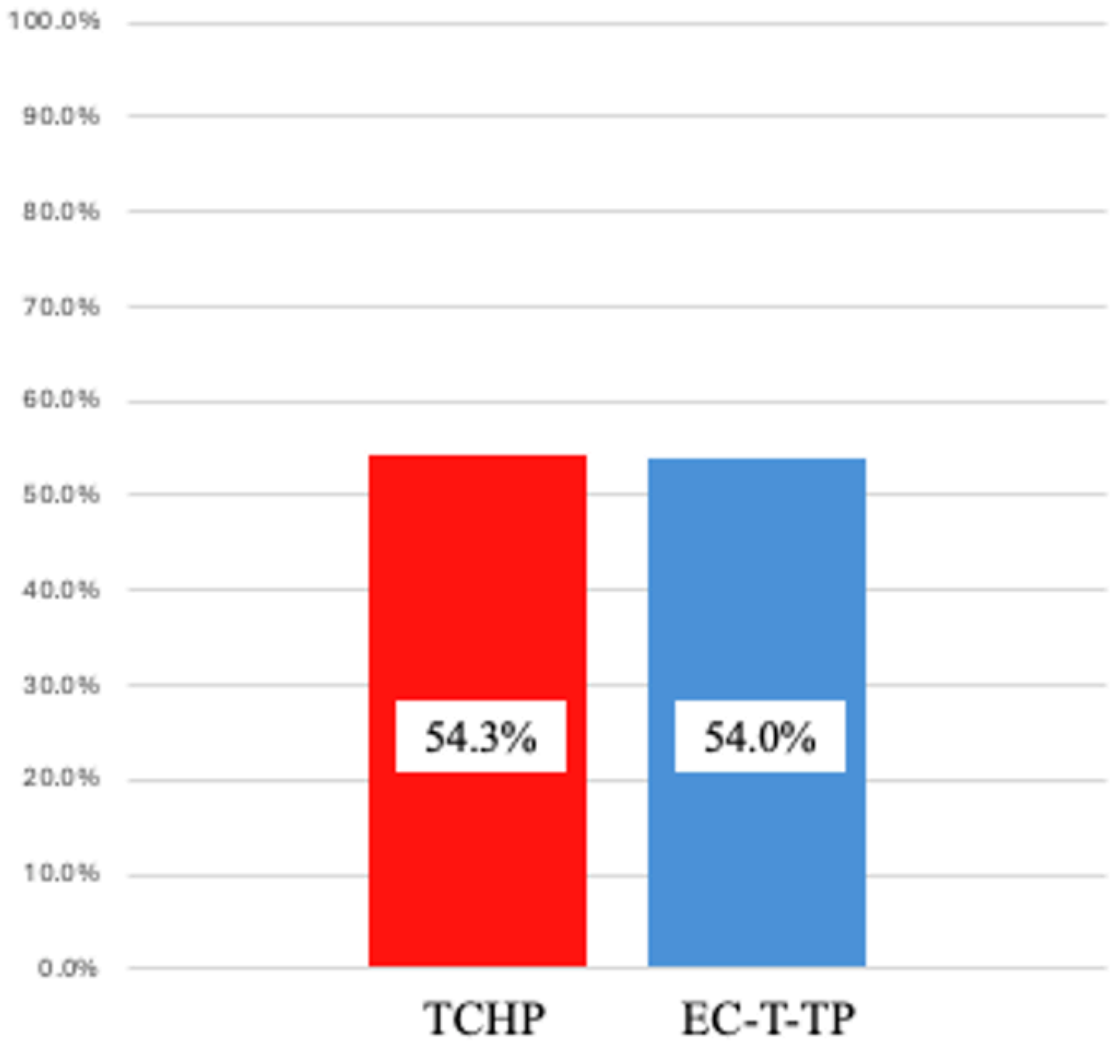


Figure 4

pCR-rates in dual blockage subcohort with ANT-free TCHP group vs. ANT-containing EC-T-TP group