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RESEARCH ARTICLE

Long-term Effectiveness of Adjuvant TAC and AC Chemotherapy Regimens in Patients with Stage II–IIIA Breast Cancer: 15-Year Follow-up Results from K Hospital, Hanoi

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Abstract

Introduction: Adjuvant chemotherapy with TAC or AC regimens is widely used in stage II–IIIA breast cancer, but their long-term comparative effectiveness and late toxicity profiles remain unclear. This study aimed to compare long-term outcomes of TAC versus AC regimens in patients with stage II–IIIA breast cancer, focusing on disease-free survival (DFS), time to recurrence (TTR), overall survival (OS), and late adverse events. **Materials and Methods:** In this retrospective-prospective cohort study, 94 patients treated with TAC (n = 31) or AC (n = 63) between 2008 and 2011 were followed prospectively through October 2025. Kaplan–Meier analysis and log-rank tests estimated survival, and Cox proportional hazards models assessed mortality risk. Of the 94 patients, 23 (74%) in the TAC group and 42 (67%) in the AC group completed 15-year follow-up; others were censored for loss to follow-up or competing mortality. **Results:** Adverse events varied over time but were similar between regimens. During year 1, hot flashes (32.3% vs. 22.2%) and menstrual disturbances (25.8% vs. 17.5%) were most common, while arthralgia increased during years 1–5 (31.0% vs. 22.4%). Late toxicities after 5 years, including osteoporosis/fractures (21.7% vs. 20.0%) and persistent sexual dysfunction (26.1% vs. 24.4%), were comparable. Over 15 years, DFS events occurred less frequently with TAC (38.7% vs. 58.7%), with lower distant recurrence (32.3% vs. 52.4%, p = 0.043) and longer median TTR (88.5 vs. 71.2 months). TAC was associated with lower recurrence and a trend toward longer median OS (162 vs. 112 months; HR = 0.73, 95% CI: 0.56–0.95, p = 0.018), though log-rank test was not significant (p = 0.163). **Conclusion:** TAC was linked to lower recurrence and longer OS without significantly increased adverse events. Observations are exploratory and cannot establish causality; larger prospective studies are needed to confirm these findings.

Keywords: Breast cancer, adjuvant chemotherapy, TAC, AC, survival, recurrence, late toxicity, long-term follow-up

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Introduction

Breast cancer is currently the most common malignancy among women worldwide, with approximately 2.26–2.30 million new cases and more than 680,000 deaths reported globally in 2020 [1]. In Vietnam, according to GLOBOCAN 2020, breast cancer accounts for approximately 21,000 new cases annually, ranking first among cancers in women and continuing to show an increasing trend [2]. Although multimodal treatment strategies have substantially improved survival outcomes in many countries, long-term post-treatment follow-up data in Vietnam, particularly from specialized oncology centers remain limited.

Beyond its growing disease burden, breast cancer poses significant challenges in selecting optimal treatment strategies for different risk groups, especially in stage II–IIIA disease, where adjuvant therapy plays a pivotal role in controlling micrometastatic disease and improving long-term prognosis. In this context, adjuvant chemotherapy aims not only to prolong disease-free survival (DFS) but also to reduce the risk of recurrence (TTR) over an extended period.

The AC regimen (doxorubicin plus cyclophosphamide), based on an anthracycline backbone, has been widely used for several decades and has become a standard

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adjuvant chemotherapy regimen in many countries, including Vietnam. The introduction of taxanes and their incorporation into adjuvant chemotherapy, forming the TAC regimen (docetaxel, doxorubicin, and cyclophosphamide), represents a major advancement in the treatment of breast cancer, particularly for patients at high risk of recurrence. However, the incremental benefits of TAC compared with AC must be carefully weighed against cumulative toxicities and late adverse events, especially in the context of prolonged patient survival.

Several studies have demonstrated the survival benefits of TAC in clinical trials. A phase III study by Martin et al. (2005) showed that the TAC regimen significantly improved disease-free survival and overall survival compared with the FAC regimen [3]. A systematic review by De Laurentiis et al. further confirmed that the addition of taxanes reduces the risk of recurrence to a clinically meaningful extent [4]. Most available evidence derives from short- to medium-term follow-up. However, late recurrence, particularly among patients with hormone receptor–positive breast cancer, may occur 10–15 years after treatment.

Clinical practice indicates that breast cancer is a disease with a prolonged natural history, with recurrence risk not confined to the first five years after treatment but persisting over many subsequent years. Late events such as distant recurrence, secondary malignancies, anthracycline-related cardiotoxicity, and long-term taxane-associated toxicities have attracted increasing attention but remain insufficiently reported in studies with limited follow-up durations. Therefore, evaluating both the effectiveness and safety of adjuvant chemotherapy regimens over long-term follow-up is essential to provide more comprehensive evidence for clinical decision-making.

In Vietnam, several small-scale studies have described short-term treatment responses to adjuvant chemotherapy regimens [5]; however, robust long-term follow-up evidence (≥10–15 years) directly comparing TAC and AC in real-world clinical practice remains scarce. With a large patient database and extended follow-up at K Hospital, analysis of 15-year follow-up data allows for a more in-depth assessment of recurrence rates, TTR, and late adverse events, factors that are critically important in guiding the selection of appropriate adjuvant chemotherapy regimens.

Therefore, this study was conducted with the following objectives: 1) to compare the long-term effectiveness of TAC and AC regimens in terms of recurrence rates, TTR, and 15-year survival outcomes among patients with stage II–IIIA breast cancer; and 2) to evaluate and compare late adverse events between the two treatment regimens.

Materials and Methods

Study design and participants

This study was designed as a retrospective–prospective cohort study. All consecutive patients with stage II–IIIA breast cancer who underwent surgical treatment at Vietnam National Cancer hospital (K Hospital) between January 2008 and December 2011 were retrospectively identified from institutional medical records and hospital registries. Patients were subsequently followed longitudinally until October 2025.

Inclusion criteria: Patients were eligible if they met all of the following criteria:

(i) histopathologically confirmed diagnosis of primary breast cancer at K Hospital between January 2008 and December 2011;

(ii) age ≤70 years at the time of diagnosis;

(iii) stage II–IIIA disease as defined by the UICC/AJCC staging system, included the following substages: T2N0, T2N1, T3N0, T3N1, and T1–3N2;

(iv) treatment with modified radical mastectomy (Patey procedure);

(v) histological diagnosis of invasive carcinoma;

(vi) performance status >70%;

(vii) no history of other malignancies and no severe acute or chronic comorbidities;

(viii) adequate bone marrow function (peripheral blood cell counts within normal limits) and preserved renal function;

(ix) completion of the prescribed adjuvant chemotherapy regimen; and

(x) availability for regular follow-up and successful contact throughout the entire follow-up period up to 2025.

Exclusion criteria: Patients were excluded if they had:

(i) primary breast cancer at stages other than II–IIIA or secondary breast cancer; patients with T4 tumors or N3 nodal involvement were excluded.

(ii) received other cancer-specific treatments prior to surgery; or

(iii) incomplete follow-up data, failure to attend scheduled follow-up visits, or inability to be contacted after hospital discharge.

A total of 153 patients treated during the study period were initially screened. After applying the predefined inclusion and exclusion criteria, 94 eligible patients were included in the final analysis, comprising 31 patients treated with TAC and 63 patients treated with AC (Figure 1).

Sample size and grouping

As this was a retrospective–prospective cohort study, the final sample size and group distribution were determined by the actual number of eligible patients treated during the study period.

To assess whether the available sample size was sufficient for meaningful comparison, a theoretical sample size calculation was performed using the formula for comparing two proportions, assuming a two-sided significance level (α) of 0.05 and a statistical power of 80%. The calculation indicated that a minimum of 31 patients per group would be required.

During the study period, 31 patients received TAC and 63 patients received AC, reflecting routine clinical practice at the hospital. The TAC group met the minimum required sample size, while the larger AC group was retained to maximize statistical efficiency and improve precision of effect estimates.

No matching, stratification, or selective inclusion was

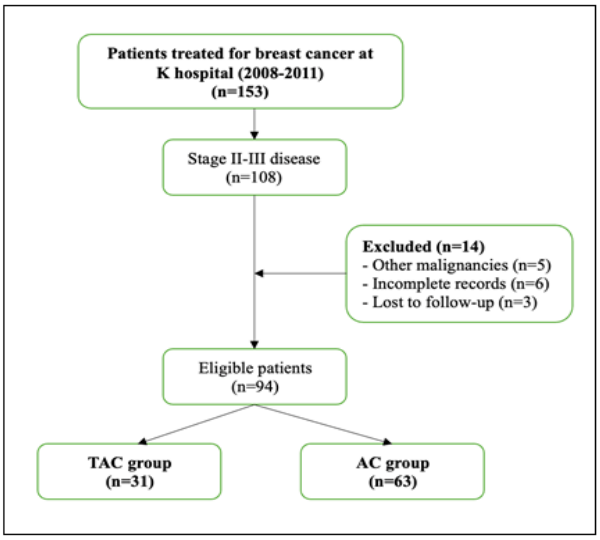

Figure 1. Participant Selection Process

performed to achieve balance between treatment groups. Treatment allocation reflected routine clinical practice during the study period, and baseline characteristics were compared descriptively to assess group comparability. The imbalance in group size reflects real-world treatment utilization during the study period rather than selective inclusion or post hoc sampling.

The primary outcome used for the theoretical sample size calculation was overall disease-free survival (DFS). Given the observed event rates in the study (38.7% TAC vs. 58.7% AC), a post-hoc power analysis indicated that the study had approximately 65–70% power to detect this difference at $\alpha = 0.05$. Power for secondary outcomes, including adverse events and subgroup analyses, was lower, and null findings should be interpreted cautiously as they may reflect limited sample size rather than true equivalence.

Chemotherapy regimens

Patients in the TAC group received: docetaxel 75 mg/m² + doxorubicin 50 mg/m² + cyclophosphamide 500 mg/m² IV on day 1, repeated every 3 weeks for 6 cycles.

Patients in the AC group received: doxorubicin 50 mg/m² + cyclophosphamide 500 mg/m² IV on day 1, repeated every 3 weeks for 4 cycles.

All chemotherapy drugs were administered intravenously. Dose adjustments were performed according to institutional protocols for renal or hepatic impairment or for treatment-related toxicity. Supportive care included antiemetics as standard, and granulocyte-colony stimulating factor (G-CSF) was used as clinically indicated to prevent neutropenia. No routine prophylactic cardioprotective agents (e.g., dexrazoxane) were used (Table 1).

Treatment procedures and long-term follow-up

During the study period (2008–2011), adjuvant chemotherapy regimens at K Hospital were not assigned through randomization. Treatment selection was guided by prevailing institutional practice and national guidelines at the time, in which both TAC and AC were considered acceptable adjuvant options for patients with stage II–IIIA breast cancer.

The choice between TAC and AC was primarily determined by the treating oncologist based on overall clinical assessment, including patient age, performance status, perceived ability to tolerate chemotherapy-related toxicity, and patient preference after counseling. There was no formal institutional protocol mandating preferential assignment of TAC or AC based on tumor stage, nodal status, or receptor subtype.

During this period, TAC was less frequently prescribed due to concerns regarding higher toxicity, need for more intensive supportive care, and higher treatment cost compared with AC. Consequently, AC remained the more commonly used regimen in routine practice, resulting in an imbalanced group size.

Importantly, no retrospective selection or exclusion of patients was performed based on treatment regimen or baseline characteristics. All eligible patients who received TAC or AC during the study period were included consecutively.

Patients with stage II–IIIA breast cancer who met the predefined inclusion and exclusion criteria were enrolled, and baseline clinical data were collected. All patients underwent modified radical mastectomy with axillary lymph node dissection (Patey procedure). Postoperatively, patients received adjuvant chemotherapy according to the assigned treatment regimen: the TAC group was treated with docetaxel, doxorubicin, and cyclophosphamide, whereas the AC group received doxorubicin and cyclophosphamide. Subsequent standard adjuvant treatments were administered as clinically indicated according to prevailing institutional practice at the time.

Information regarding the use of HER2-targeted therapy (e.g., trastuzumab) in HER2-positive patients was not consistently available in the retrospective medical records and therefore could not be systematically documented or analyzed. Similarly, detailed data on adjuvant endocrine therapy, including agent selection

Table 1. Chemotherapy regimens and treatment characteristics of the TAC and AC groups

Regimen	Drug	Dose (mg/m²)	Route	Day	Cycle interval	Number of cycles	Supportive care
TAC	Docetaxel	75	IV	1	q3w	6	Antiemetics, G-CSF if needed
	Doxorubicin	50	IV	1	q3w	6	
	Cyclophosphamide	500	IV	1	q3w	6	
AC	Doxorubicin	50	IV	1	q3w	4	
	Cyclophosphamide	500	IV	1	q3w	4	

Table 2. Baseline Clinical and Histopathological Characteristics of Patients Treated with TAC and AC Regimens

Contents		Chemotherapy regimens				p
		TAC (n=31)		AC (n=63)		
		n	%	n	%	
Age group (years)	30 – 39	8	25.8	13	20.6	0.202
	40 – 49	16	51.6	23	36.5	
	50 - 60	7	22.6	23	36.5	
	>60	0	0	4	6.4	
Menopausal status	Premenopausal	21	67.7	31	49.2	0.089
	Postmenopausal	10	32.3	32	50.8	
Tumor laterality	Left breast	18	58.1	35	55.6	0.541
	Right breast	13	41.9	28	44.4	
Tumor size (AJCC/UICC T stage)	T2 (2–5 cm)	27	87.1	54	85.7	0.553
	T3 (>5 cm)	4	12.9	9	14.3	
Lymph node involvement	Yes	28	90.3	54	85.7	0.674
	No	3	9.7	9	12.8	
Histological type	Invasive ductal carcinoma	24	77.4	57	90.5	0.371
	Invasive lobular carcinoma	7	25.6	6	9.5	
Histological grade (n=24 for TAC; n=57 for AC)	1 and 2	20	83.4	53	93	0.831
	3	4	16.6	4	7	1
	4	0	0	0	0	1
Hormone receptor status	Positive	20	64.5	41	65.1	0.554
	Negative	11	35.5	22	34.9	
Hormone receptor subtype	ER+/PR+	15	48.4	30	47.6	0.94
	ER+/PR−	3	9.7	7	11.1	
	ER−/PR+	2	6.5	4	6.3	
	ER−/PR−	11	35.4	22	34.9	
HER2 status	Positive	7	22.6	20	31.8	0.186
	Negative	24	77.4	43	68.3	
Karnofsky performance status (KPS)	71 – 80	5	16.1	13	20.6	0.484
	81 - 90	8	25.8	23	26.5	
	91 - 100	18	58.1	27	42.9	

ER: Estrogen receptor; PR: Progesterone receptor; +positive; -negative. Stage II–IIIA includes T2N0, T2N1, T3N0, T3N1, and T1–3N2 according to AJCC/UICC 7th edition. Percentages calculated from available data; missing values noted where applicable. Histological grade data were available for 24/31 TAC patients and 57/63 AC patients; 100% of patients had stage II–IIIA breast cancer according to UICC/AJCC staging, and all patients had a Karnofsky Performance Status (KPS) >70%, consistent with inclusion criteria (iii) and (vi). Other inclusion criteria, including age ≤70 years, completion of the prescribed adjuvant chemotherapy regimen, and availability for follow-up, were also met in all cases.

(tamoxifen versus aromatase inhibitors), treatment duration, and sequencing strategies were incomplete and were not incorporated into the comparative analysis. Data on radiotherapy utilization and techniques were also not uniformly recorded and thus were not evaluated in this study.

Endocrine therapy: patients with hormone receptor–positive tumors received adjuvant endocrine therapy according to institutional guidelines at the time of treatment. Endocrine therapy was initiated after completion of chemotherapy and consisted primarily of tamoxifen or aromatase inhibitors, depending on menopausal status. The standard planned duration was 5 years, with extended therapy considered in selected high-risk patients. Endocrine therapy was not administered to hormone receptor–negative patients.

Treatment effectiveness and treatment-related adverse events were systematically assessed throughout a long-term follow-up period of up to 15 years. Follow-up evaluations were conducted at regular intervals: every 3 months during the first 2 years, every 6 months during years 3–5, and annually from the fifth year onward. During each follow-up visit, patients were evaluated for disease DFS, survival outcomes, and both early and late complications, allowing comprehensive assessment of long-term efficacy and cumulative treatment-related toxicities.

Definition of adverse events and late complications

Adverse events were defined as any unfavorable and unintended signs, symptoms, or diseases temporally associated with adjuvant chemotherapy, whether or not considered related to treatment. Adverse events were classified as early complications (occurring during treatment or within the first 12 months after completion of chemotherapy) and late complications (occurring more

than 12 months after treatment completion). Adverse events documented during follow-up were classified using CTCAE criteria during retrospective chart review.

Late complications of interest included, but were not limited to, cardiotoxicity associated with anthracycline use, long-term neurotoxicity related to taxanes, secondary malignancies, and other clinically significant chronic conditions potentially attributable to systemic chemotherapy. All adverse events were prospectively recorded at each follow-up visit throughout the entire 15-year follow-up period, allowing for assessment of cumulative and delayed toxicities.

Follow-up outcomes and definitions

The primary and secondary outcomes were defined as follows:

Disease-free survival (DFS): was analyzed as a primary endpoint, defined as the time from surgery to the first documented event of local recurrence, regional recurrence, distant metastasis, second primary malignancy, or death from any cause. DFS includes TTR as well as second primary malignancy and death from any cause; TTR is specifically the time from surgery to first documented breast cancer recurrence. Recurrence was ascertained through a combination of systematic clinical examination and imaging according to institutional follow-up protocols: breast ultrasound and/or mammography at each visit, with additional imaging (CT, MRI, bone scan, or PET) performed as clinically indicated. Pathologic confirmation was obtained whenever feasible. Surveillance schedules and ascertainment methods were applied uniformly to both TAC and AC groups to minimize detection bias. Sensitivity analyses were planned to assess the impact of asymptomatic recurrences detected only by routine imaging.

Overall survival (OS): defined as the time from the date of surgery to death from any cause or the last known date of follow-up.

Time to recurrence (TTR): defined as the time from the date of surgery to the first documented breast cancer recurrence (local, regional, or distant), with patients without recurrence censored at the last follow-up.

All outcomes were assessed over a maximum follow-up duration of 15 years, enabling evaluation of both early and late disease events, particularly late recurrences.

Patients were followed according to a standardized postoperative surveillance protocol applied uniformly to both treatment groups. Follow-up visits were scheduled every 3 - 6 months during the first 2 years after surgery, every 6 - 12 months from years 3 to 5, and annually thereafter.

Surveillance assessments included clinical examination and routine imaging studies in accordance with institutional guidelines, including breast ultrasound and/or mammography, with additional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), bone scan, or positron emission tomography (PET) performed when clinically indicated.

Disease recurrence was identified based on radiological findings, pathological confirmation when available, or unequivocal clinical evidence. Both symptomatic recurrences and asymptomatic recurrences detected during routine surveillance imaging were included. The timing and intensity of follow-up were comparable between the TAC and AC groups, minimizing potential bias in recurrence detection and timing.

Handling of missing data and loss to follow-up

Missing data were assessed prior to analysis. Given the long-term follow-up design, missing values primarily arose from incomplete clinical documentation or loss of specific variables at certain follow-up time points. No imputation was performed for missing data. Analyses were conducted using a complete-case approach, including only patients with available data for the variables of interest.

For survival analyses, patients with incomplete follow-up information were right-censored at the date of last confirmed contact, assuming they were alive and recurrence-free at that time. Loss to follow-up was explicitly quantified at predefined intervals (5, 10, and 15 years) and stratified by treatment group. Sensitivity analyses were performed to evaluate the potential impact of unobserved events, assuming that 10–20% of patients lost to follow-up may have experienced death or disease recurrence. The extent of missing data was limited and not expected to substantially bias the results.

Data analysis

All statistical analyses were performed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize baseline demographic, clinical, and pathological characteristics. Categorical variables were presented as frequencies and percentages. Comparisons between the TAC and AC groups were performed using the Chi-square test or Fisher's exact test, as appropriate.

Survival outcomes, including disease-free survival (DFS) and overall survival (OS), were estimated using the Kaplan–Meier method, and differences between groups were assessed using the log-rank test. Cox proportional hazards regression in SPSS used the Efron method to handle tied event times (hazard ratios (HRs) and 95% confidence intervals (CIs).

The proportional hazards assumption was evaluated using log-minus-log survival plots and tests based on time-dependent covariates. Evidence suggestive of non-proportional hazards for chemotherapy regimen was observed, consistent with delayed separation of Kaplan–Meier curves. Therefore, Cox regression results should be interpreted as average effects over the follow-up period.

A multivariable Cox proportional hazards model was constructed a priori including chemotherapy regimen (TAC vs. AC), disease stage (II vs. IIIA), lymph node involvement (yes vs. no), hormone receptor status (positive vs. negative), and HER2 status (positive vs. negative). The number of covariates was restricted to preserve an adequate events-per-variable ratio and reduce the risk of overfitting.

Patients without events were censored at the date of last follow-up. All statistical tests were two-sided, and a

p-value < 0.05 was considered statistically significant. No data transformations were performed. Patients with missing data for a given variable were excluded from analyses involving that variable (complete-case analysis).

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki. The study protocol was reviewed and approved by the Biomedical Research Ethics Committee of K Hospital (approval number: KH-IRB-2008-045; approval date: Dec 21, 2008). All participants were fully informed about the objectives and procedures of the study, and written informed consent was obtained prior to inclusion. Patient confidentiality was strictly maintained, and all data were anonymized and used solely for research purposes. As this was an observational study, no intervention was performed, and standard clinical management was not affected.

Results

By 15 years, 23 patients in the TAC group (74% of original cohort) and 42 patients in the AC group (67% of original cohort) remained under observation. The remaining patients were lost to follow-up due to relocation, withdrawal, or death unrelated to cancer recurrence. Loss to follow-up was similar between treatment groups (p = 0.42). Sensitivity analyses assuming 10 - 20% of lost-to-follow-up patients experienced unobserved events did not materially change survival estimates. The last confirmed contact for each patient was determined via medical records and telephone follow-up; sensitivity analyses assuming 10–20% of lost-to-follow-up patients had unobserved events showed no meaningful impact on survival estimates, supporting the robustness of our findings.

Baseline clinical and histopathological characteristics of patients treated with TAC and AC regimens

Baseline clinical and histopathological characteristics were well balanced between the TAC and AC groups, with no statistically significant differences observed in age, menopausal status, tumor location, tumor size, lymph node involvement, histological type, histological grade, hormone receptor status, HER2 status, or performance status according to the AJCC/UICC staging system (all p > 0.05), as shown in Table 2. When hormone receptor status was further stratified, the distribution of ER/PR subtypes, particularly ER+/PR+ tumors, which are associated with distinct late DFS patterns, was comparable between the TAC and AC groups (p = 0.94).

As shown in Table 3, chemotherapy completion was high and comparable between the TAC and AC groups (83.9% vs. 87.3%, p = 0.64). Rates of dose reduction (22.6% vs. 14.3%) and treatment delay ≥7 days (19.4% vs. 15.9%) were also similar. Discontinuations were mainly due to toxicity, patient refusal, or disease progression. Among hormone receptor–positive patients, most received adjuvant endocrine therapy (TAC 22/31, 71%; AC 41/63, 65%) after chemotherapy, with a median duration of 5 years in both groups. Hormone receptor subtype distribution (ER/PR status) was comparable (Table 2).

Recurrence and adverse events in patients with stage II–IIIA breast cancer treated with TAC and AC over 15 years

Table 4 shows that the incidence of acute grade 3-4 chemotherapy-related toxicities was low and did not differ significantly between the TAC and AC groups. Grade 3-4 neutropenia occurred in 12.9% of patients receiving TAC compared with 4.8% in the AC group (p = 0.19), while febrile neutropenia was observed in 6.5% versus 3.2%, respectively (p = 0.58). The use of supportive care measures was comparable between regimens, including

Table 3. Chemotherapy Completion, Dose Modification, and Endocrine Therapy Use

Variable	TAC (n=31)		AC (n=63)		p-value
	n	%	n	%	
Chemotherapy					
Completed planned cycles	26	83.9	55	87.3	0.64
Discontinuation	5	16.1	8	12.7	
Due to toxicity	3	9.7	4	6.3	
Patient refusal	1	3.2	2	3.2	
Disease progression	1	3.2	2	3.2	
Dose reduction ≥1 cycle	7	22.6	9	14.3	0.31
Treatment delay ≥7 days	6	19.4	10	15.9	0.65
Relative dose intensity (%)	92.5 ± 6.8		94.1 ± 5.9		0.28
Endocrine therapy (HR+ patients)					
Number receiving therapy	22	71	41	65	0.56
Tamoxifen	15	48	28	44	-
Aromatase inhibitors	7	23	13	21	-
Median duration (years)	5 (3-7)		5 (2-7)		-
≥4 years completed	19		35		-

Table 4. Acute Grade 3-4 Chemotherapy-related Toxicities (CTCAE) and Hematologic Management

Toxicity	TAC (n=31)		AC (n=63)		p-value
	n	%	n	%	
I. Acute grade 3-4 chemotherapy-related toxicities (CTCAE)					
Neutropenia	4	12.9	3	4.8	0.19
Febrile neutropenia	2	6.5	2	3.2	0.58
Anemia	0	0	1	1.6	1
Thrombocytopenia	0	0	0	0	-
Nausea/vomiting	1	3.2	2	3.2	1
Hepatotoxicity (AST/ALT increase)	1	3.2	2	3.2	1
Hospitalization due to toxicity	2	6.5	3	4.8	0.72
II. Supportive care and hematologic management					
Primary G-CSF prophylaxis	12	38.7	18	28.6	0.33
Secondary G-CSF use	6	19.4	9	14.3	0.52
Blood transfusion	3	9.7	5	7.9	0.72
Hospital admission	2	6.5	3	4.8	0.72

Table 5. Adverse Events Following Chemotherapy and Endocrine Therapy Across Different Follow-up Periods Over 15 Years

Adverse event	<1 year (n;%)	p	1–5 years (n;%)	p	>5 years (n;%)	p
Hot flashes	TAC 10/31 (32.3) AC 14/63 (22.2)	0.291	TAC 7/29 (24.1) AC 10/58 (17.2)	0.413	–	–
Menstrual disturbances	TAC 8/31 (25.8) AC 11/63 (17.5)	0.343	–	–	–	–
Deep vein thrombosis	TAC 1/31 (3.2) AC 1/63 (1.6)	0.612	TAC 2/29 (6.9) AC 3/58 (5.2)	0.731	–	–
Arthralgia	TAC 6/31 (19.4) AC 9/63 (14.3)	0.493	TAC 9/29 (31.0) AC 13/58 (22.4)	0.361	TAC 4/23 (17.4) AC 8/42 (17.8)	0.652
Vaginal dryness	TAC 5/31 (16.1) AC 8/63 (12.7)	0.64	TAC 6/29 (19.4) AC 6/58 (10.3)	0.089	–	–
Decreased libido	TAC 4/31 (12.9) AC 7/63 (11.1)	0.79	TAC 7/29 (24.1) AC 12/58 (20.7)	0.7	–	–
Endometrial cancer	–	–	TAC 1/29 (3.4) AC 2/58 (3.4)	1	TAC 1/23 (4.3) AC 3/42 (6.7)	0.861
Osteopenia/ osteoporosis or fracture	–	–	–	–	TAC 5/23 (21.7) AC 9/42 (20.0)	0.445
Persistent sexual dysfunction	–	–	–	–	TAC 6/23 (26.1) AC 11/42 (24.4)	0.47

p-values calculated using Chi-square test or Fisher's exact test. Dashes indicate that the adverse event was not evaluated or not applicable during that follow-up period

primary G-CSF prophylaxis (38.7% vs. 28.6%, p = 0.33), secondary G-CSF use (19.4% vs. 14.3%, p = 0.52), blood transfusion (9.7% vs. 7.9%, p = 0.72), and hospitalization due to toxicity (6.5% vs. 4.8%, p = 0.72).

Adverse events were mostly mild to moderate and occurred at similar rates in the TAC and AC groups across all follow-up periods, with no significant between-group differences (all $p > 0.05$). Cardiac monitoring showed comparable baseline and follow-up left ventricular ejection fraction between regimens, with LVEF decline ≥10% observed in 9.7% of patients receiving TAC and 11.1% receiving AC; congestive heart failure was uncommon in both groups (3.2% each). Peripheral neuropathy was generally mild, with most patients experiencing no neuropathy (58.1% in TAC vs. 71.4% in AC) and severe neuropathy (grade ≥3) being rare (3.2% vs. 0%). Late and severe adverse events, including osteopenia/ osteoporosis, persistent sexual dysfunction, and secondary hematologic malignancies, were uncommon and comparably distributed between groups (Table 5).

Table 6. Patterns of Breast Cancer Recurrence and Timing of Recurrence over a 15-year Follow-up Period

DFS events	TAC (n=31)		AC (n=63)		p-value
	n	%	n	%	
Local recurrence	2	6.5	4	6.3	1
Distant metastasis	10	32.3	33	52.4	0.043
Bone	5	16.1	20	31.8	0.143
Lung	3	9.7	7	11.1	1
Liver	1	3.2	4	6.3	1
Brain	1	3.2	2	3.2	1
Overall recurrence	12	38.7	37	58.7	0.081
Timing of TTR (in accordance with AJCC/UICC conventions)					
Early (≤5 years)	7	22.6	22	34.9	0.254
Late (5-10 years)	3	9.7	8	12.7	1
Very late (>10 years)	2	6.5	7	11.1	0.712
Median TTR, months (95% CI)	88.5 (95% CI: 72.4–104.6)		71.2 (95% CI: 60.1–82.3)		-

Median DFS was estimated using the Kaplan–Meier method; Early: TTR within 5 years; Late: TTR between 5 and 10 years; Very late: TTR after 10 years, according to AJCC/UICC classification; Local DFS event refers to ipsilateral breast recurrence only; isolated chest wall DFS event is categorized as regional recurrence.

As shown in Table 6, local DFS rates were comparable between the TAC and AC groups (6.5% vs. 6.3%). DFS events occurred less frequently in the TAC group than in the AC group (38.7% vs. 58.7%), although this difference did not reach statistical significance. Distant metastasis was observed less often with TAC compared with AC (32.3% vs. 52.4%, p = 0.043), with bone being the most common metastatic site in both groups, while other metastatic sites were infrequent. The median TTR was longer in the TAC group than in the AC group (88.5 vs. 71.2 months); however, this observation should be interpreted cautiously given the limited number of events and the exploratory nature of this analysis.

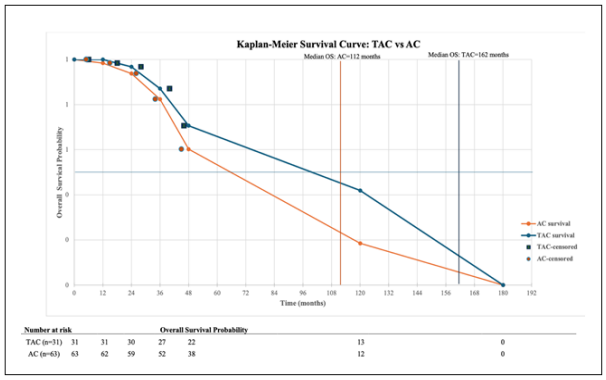

Figure 2. Cumulative Overall Survival Over 15 Years

Overall survival and mortality in patients with stage II–IIIA breast cancer treated with TAC versus AC after 15 years of follow-up

Patients receiving TAC showed numerically higher overall survival than those receiving AC over 15 years (15-year OS: 58.1% vs. 42.9%; Table 7). Disease-free survival (DFS) analyses, including death as an event, demonstrated a similar pattern, with higher 15-year DFS rates in the TAC group (54.8% vs. 39.7%; log-rank p = 0.038; Figure 2). Notably, separation of the survival curves became apparent only after approximately 4 - 5 years, suggesting a potential delayed effect of TAC. This delayed pattern was further supported by the time-stratified Cox regression analysis (Table 8), which represents the key finding. No significant difference in mortality was observed between TAC and AC during the first 0 - 5 years of follow-up (HR = 0.95, p = 0.85). In contrast, during the 5 - 15 year period, TAC was associated with a significantly lower risk of death compared with AC (HR = 0.60, p = 0.045). Sensitivity analyses excluding asymptomatic DFS events detected by routine imaging yielded consistent results.

Sensitivity analysis in HR-positive/HER2-negative patients

In a sensitivity analysis restricted to patients with hormone receptor–positive and HER2-negative tumors (n = 43), survival trends were directionally consistent with the overall cohort. Patients treated with TAC showed numerically higher 15-year DFS (60.2% vs. 45.1%) and OS (64.8% vs. 49.5%) compared with AC, although these differences were not statistically significant. Time-stratified Cox analysis again showed no difference in mortality during the first 0–5 years (HR = 0.98), with a trend toward lower mortality with TAC during the 5–15 year period (HR = 0.62), supporting a delayed treatment effect (Supplementary Table S1).

Analyses stratified by enrollment period (2008 - 2009 vs. 2010 - 2011) showed similar TAC and AC distributions, with consistent TAC survival benefit in both strata. Adjustment for enrollment period minimally changed the hazard ratio, indicating that temporal treatment differences did not materially affect OS (Supplementary Tables S2–S4).

Kaplan–Meier curves illustrating cumulative overall survival in patients with stage II–IIIA breast cancer treated

Table 7. Cumulative Overall Survival Time and Cumulative Mortality According to Adjuvant Chemotherapy Regimen

Follow-up time	Cumulative OS rate (%)		Cumulative number of deaths	
	TAC (n = 31)	AC (n = 63)	TAC (n = 31)	AC (n = 63)
Baseline	0	0	0	0
12 months	100	98.4	0	1
24 months	96.7	95.2	1	3
36 months	93.5	88.9	2	7
48 months	90.3	74.6	5*	14
60 months	80.7	68.5		21
10 years	71	57.1	9	27
15 years	58.1	42.9	18	45

* No additional deaths occurred between 48–60 months

Table 8. Time-stratified Cox Proportional Hazards Regression for Overall Mortality

Follow-up period	Chemotherapy regimen	Events (n)	HR (95% CI)	p-value
0–5 years	AC (reference)	14	1	–
	TAC	5	0.95 (0.56–1.62)	0.85
>5–15 years	AC (reference)	31	1	–
	TAC	13	0.60 (0.36–0.99)	0.045
Median overall survival (months)	AC	162±13.6 (95% CI: 140-185)		
		(Min=48; Max=240)		
	TAC	112±9.3 (95% CI: 96-129)		
		(Min=36; Max=220)		

with adjuvant TAC or AC chemotherapy over a 15-year follow-up period. Differences between survival curves were assessed using the log-rank test.

In unadjusted analysis, TAC was associated with lower overall mortality compared with AC; however, this association was attenuated and no longer statistically significant after multivariable adjustment. Advanced stage (IIIA) remained the only independent predictor of mortality (Table 9).

Discussion

DFS and adverse events in patients with stage II–IIIA breast cancer treated with TAC and AC regimens over 15 years of follow-up

Our findings of low and comparable rates of acute grade 3–4 chemotherapy-related toxicities with TAC and AC align with prior clinical evidence suggesting that, with appropriate supportive care, severe toxicities are manageable in taxane- and anthracycline-containing regimens. In the large BCIRG-005 trial, TAC was associated with higher febrile neutropenia compared with sequential TAC, yet the overall acute toxicity profile was considered acceptable, particularly with prophylactic G-CSF support [6]. Similarly, network meta-analyses have shown that while TAC may carry a higher odds of febrile neutropenia, overall grade ≥3 adverse events are not markedly different from other regimens when supportive measures are applied [7]. These observations suggest that the acute toxicity burden in our real-world cohort is consistent with published experience and supports the feasibility of both regimens under routine clinical practice.

The present study demonstrates that treatment-related adverse events in patients with stage II–IIIA breast cancer vary across follow-up periods, reflecting the biological effects and cumulative toxicity of adjuvant chemotherapy and endocrine therapy. Early neuroendocrine symptoms, such as hot flashes and menstrual disturbances, were predominantly observed within the first year, consistent with ovarian suppression and acute chemotherapy-related effects reported in anthracycline–taxane trials [3, 8-9]. The higher, though non-significant, frequency of these symptoms in the TAC group aligns with the known neuroendocrine toxicity profile of taxanes. In the intermediate period (1–5 years), arthralgia increased in both groups, likely associated with prolonged endocrine therapy, particularly aromatase inhibitors, as previously reported in long-term analyses by Sparano et al. and Pan et al. [9-10]. Late adverse events, including osteopenia/osteoporosis and persistent sexual dysfunction, mainly occurred after 5 years, reflecting sustained estrogen deprivation and mirroring findings from survivorship studies in breast cancer populations [10-11]. Importantly, no statistically significant differences in adverse event rates were observed between TAC and AC, consistent with meta-analyses showing that taxane-containing regimens increase toxicity to an acceptable extent relative to their clinical benefit [4], and in line with reports from Vietnamese cohorts evaluating TAC or AC/T regimens [5, 12]. In addition, the observed comparable baseline and follow-up LVEF between TAC and AC regimens, with only 10% of patients experiencing a ≥10% decline in LVEF and rare clinically overt heart failure, aligns with recent cardiotoxicity data in modern chemotherapy settings

Table 9. Unadjusted and Adjusted Cox Proportional Hazards Regression for Overall Mortality

Variable	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Chemotherapy regimen				
AC	1.00 (reference)	–	1.00 (reference)	–
TAC	0.73 (0.56–0.95)	0.018	0.78 (0.59–1.04)	0.09
Stage				
II	1.00 (reference)	–	1.00 (reference)	–
IIIA	1.82 (1.25–2.66)	0.002	1.69 (1.14–2.52)	0.009
Lymph node involvement				
No	1.00 (reference)	–	1.00 (reference)	–
Yes	1.54 (0.92–2.58)	0.1	1.42 (0.84–2.41)	0.19
Hormone receptor status				
Negative	1.00 (reference)	–	1.00 (reference)	–
Positive	0.62 (0.41–0.93)	0.021	0.68 (0.44–1.05)	0.08
HER2 status				
Negative	1.00 (reference)	–	1.00 (reference)	–
Positive	0.89 (0.58–1.36)	0.59	0.94 (0.60–1.47)	0.78

HR: hazard ratio; CI: confidence interval. Adjusted model includes all variables shown. Due to the large number of comparisons, some statistically significant findings beyond the pre-specified primary outcomes (overall survival and overall recurrence) should be interpreted as exploratory and may reflect false positives from multiple testing.

showing modest average LVEF reductions and low rates of symptomatic heart failure after anthracycline-based treatment [13]. Peripheral neuropathy being mostly mild and severe cases uncommon is consistent with taxane-associated neuropathy profiles reported in clinical cohorts. While anthracycline cardiotoxicity remains a concern, current evidence suggests that significant cardiac dysfunction and severe neuropathy events are relatively infrequent with contemporary dosing and monitoring strategies [13].

Regarding disease control, DFS events over 15-year was higher in the AC group than in the TAC group (58.7% vs. 38.7%), although this difference did not reach statistical significance, likely due to limited sample size. Nevertheless, the lower incidence of distant recurrence and the significantly longer median TTR observed in the TAC group suggest more durable disease control with taxane-based chemotherapy. This pattern is biologically plausible and consistent with evidence that anthracycline-only regimens may be less effective in suppressing micrometastatic disease, particularly skeletal metastases. While the phase III trial by Martin et al. reported no significant differences in recurrence or survival between TAC and AC after 10 years of follow-up in a broad population [8], subsequent subgroup and retrospective analyses have suggested that the benefit of TAC may be more pronounced in patients with higher-risk disease or unfavorable tumor biology [9]. Our findings support this nuanced interpretation, indicating that the long-term effectiveness of TAC may depend on patient and tumor characteristics.

Late and very late recurrence remained evident beyond 10 years in both treatment groups, occurring more frequently in the AC group. This observation is consistent with long-term studies demonstrating persistent recurrence risk in breast cancer, particularly in hormone receptor–positive disease [10-11]. The significantly longer median TTR in the TAC group (88.5 vs. 71.2 months) further supports the notion that taxane-containing regimens may delay disease relapse rather than eliminate late recurrence risk. From a clinical perspective, these results underscore the importance of prolonged follow-up and survivorship care, as well as individualized selection of adjuvant chemotherapy. In the Vietnamese context, TAC appears to offer a favorable balance between long-term disease control and acceptable toxicity in appropriately selected patients, while reinforcing the need for risk-adapted treatment strategies and extended post-treatment. The reduction in distant recurrence observed with TAC was primarily attributable to fewer bone metastases. As bone relapse is strongly influenced by hormone receptor biology and endocrine treatment, residual confounding cannot be excluded. Moreover, multiple recurrence endpoints were analyzed without formal adjustment for multiple comparisons. Therefore, these findings should be interpreted cautiously and viewed as hypothesis-generating rather than definitive. Accordingly, these findings should be interpreted cautiously and confirmed in adequately powered prospective studies.

Overall survival and mortality according to TAC and AC regimens over 15 years of follow-up

Our findings indicate that the TAC regimen was associated with more favorable cumulative overall survival and lower cumulative mortality compared with AC in patients with stage II–IIIA breast cancer. Specifically, cumulative survival at 48 months was 90.3% in the TAC group versus 74.6% in the AC group; at 10 years, 71.0% versus 51.1%; and at 15 years, 58.1% versus 42.9%, respectively. These results suggest a potential OS benefit of TAC in our study population.

The discrepancy between the non-significant log-rank

test and the statistically significant Cox regression may reflect differences in the timing of survival effects between treatment groups. Visual inspection of the Kaplan–Meier curves suggests that survival differences between TAC and AC became more apparent after approximately 4–5 years of follow-up, indicating a potential delayed treatment effect. In such situations, the log-rank test, which weights events equally over time, may have limited power, whereas the Cox proportional hazards model captures the average hazard reduction across the entire follow-up period. These findings suggest that the survival benefit associated with TAC may emerge predominantly in the later phase of follow-up rather than early after treatment.

In comparison with international randomized trials, our results are partially concordant in terms of overall survival trends but differ in magnitude. Large trials such as BCIRG-001 and BCIRG-005 did not demonstrate a significant OS advantage of TAC over AC at 10 years of follow-up. It should be noted, however, that these trials reported outcomes at earlier time points and were conducted in highly selected trial populations, whereas our analysis reflects a real-world cohort with extended 15-year follow-up [6, 14]. Moreover, the 15-year overall survival rates observed in our cohort should be interpreted cautiously when compared with 10-year trial data. Kaplan–Meier estimates at later time points are influenced by decreasing numbers at risk and may reflect differences in population characteristics, treatment completion, and post-treatment surveillance rather than a direct treatment effect. Therefore, our findings do not suggest superiority of TAC beyond randomized evidence but rather highlight potential OS differences in a real-world clinical setting. In contrast, several retrospective studies have reported superior DFS and OS with TAC compared with AC, particularly among patients at higher risk of recurrence [15]. Although detailed data on chemotherapy dose intensity, treatment delays, and grade 3–4 toxicities were not available, patients in this cohort were managed within a standardized institutional protocol with regular follow-up. Differences in patient characteristics, treatment adherence, and post-chemotherapy supportive care within the Vietnamese clinical setting may partly explain the discrepancy between our findings and those reported by Mackey et al. [8]. The use of a more intensive combination regimen together with careful monitoring may have contributed to favorable long-term outcomes in this real-world cohort. Nevertheless, the absence of detailed treatment adherence and toxicity data, along with the relatively small sample size, limits definitive conclusions regarding the role of treatment intensity and supportive care. Larger, multicenter studies are therefore warranted to validate the OS impact of TAC versus AC under real-world conditions in Vietnam.

Our findings should also be interpreted in the context of broader international evidence. Large randomized trials, including BCIRG-005, did not demonstrate significant differences in 10-year DFS or OS between TAC and sequential AC to T regimens, although toxicity profiles varied [6]. Meta-analyses of multiple adjuvant chemotherapy regimens similarly indicate comparable OS outcomes between TAC and other anthracycline–taxane regimens, despite somewhat increased febrile neutropenia risk [7]. Conversely, some retrospective and subgroup analyses suggest that TAC may confer greater benefit in higher-risk populations, such as patients with triple-negative or node-positive disease [15]. These findings highlight that the long-term effectiveness of TAC may vary according to patient and tumor characteristics, supporting our observation that the survival and recurrence advantages in our cohort may reflect real-world treatment effects in a selected patient population.

However, the lack of detailed data on HER2-targeted therapy, endocrine treatment strategies, and radiotherapy represents an important source of residual confounding. These unmeasured factors may have influenced long-term outcomes and therefore limit causal interpretation of the observed survival differences between chemotherapy regimens. In addition, incomplete data on HER2-targeted therapy constitutes a key source of residual confounding. During the study period, trastuzumab use was limited and differed between groups, with a higher proportion of HER2-positive patients in the AC group receiving HER2-targeted therapy compared with the TAC group (31.8% vs. 22.6%). This imbalance may have biased survival comparisons between regimens and contributed to attenuation of treatment effects after adjustment, thereby limiting causal interpretation. Importantly, sensitivity analyses restricted to HR-positive/HER2-negative patients, who did not receive HER2-targeted therapy showed survival trends consistent with the main analysis, supporting the robustness of the observed delayed benefit of TAC and suggesting that differential use of HER2-targeted therapy alone is unlikely to fully explain the findings.

Consistent with our findings, studies conducted in Vietnam have shown that the adoption of modern adjuvant chemotherapy regimens, including TAC, has led to meaningful improvements in 5-year survival rates compared with earlier treatment eras [5, 12], supporting the continued optimization and risk-adapted use of taxane-containing regimens in clinical practice. While our study demonstrates a clear long-term benefit of TAC over AC in terms of recurrence and survival, it is important to recognize that these data were generated between 2008 and 2011, before the widespread adoption of genomic risk stratification and HER2-targeted therapies. Contemporary adjuvant therapy now incorporates tools such as Oncotype Dx or MammaPrint, dose-dense anthracycline-taxane regimens, extended endocrine therapy, and HER2-directed treatments, which may modify both absolute and relative benefits of TAC versus AC. Therefore, the applicability of our findings should be interpreted with caution, particularly in settings where modern therapeutic options are available, while acknowledging that in resource-limited environments, the balance of efficacy, toxicity, and cost remains a critical consideration.

Despite careful cohort definition and assessment of baseline comparability, residual confounding by indication

cannot be fully excluded. Unmeasured factors such as patient frailty, subtle comorbidities not captured in medical records, clinician treatment preference, and differences in supportive care may have influenced treatment selection. If TAC was preferentially administered to younger and fitter patients more likely to tolerate an intensive regimen, the observed survival benefit associated with TAC may be partially overestimated. Conversely, if TAC was selected for patients perceived to have higher-risk disease, any observed benefit would represent a conservative estimate. A qualitative sensitivity analysis suggests that a moderate unmeasured confounder associated with both treatment selection and outcome (with a relative risk in the range of 1.5–2.0) would attenuate but is unlikely to fully negate the observed treatment effect, supporting the robustness of the main findings.

This study is limited by its retrospective, single-center design and relatively small sample size, particularly in the TAC group, which may reduce statistical power and limit generalizability. Second, the unequal distribution between the TAC and AC groups, reflecting real-world treatment patterns, may also have reduced the precision of effect estimates and limited the ability to detect rare outcomes, especially late adverse events. Third, potential residual confounding related to treatment adherence, supportive care, and unmeasured clinical factors cannot be excluded. In addition, incomplete availability of detailed molecular subtyping restricted subgroup analyses. Changes in adjuvant treatment practices over the long follow-up period may also have influenced long-term outcomes. Fouth, the pooling of stage II and IIIA patients and various receptor subtypes is a limitation of our study. Although exploratory analyses suggest that the observed benefit of TAC is largely consistent across subgroups, the greatest absolute benefit may occur in hormone receptor-positive, node-positive patients. Future studies with larger cohorts and prospective stratification are warranted to clarify whether specific subgroups derive differential benefit from TAC versus AC. These findings highlight the importance of integrating stage and receptor status into treatment decision-making, particularly when applying historical trial results to contemporary clinical practice. Moreover, as a single-center study in Vietnam, findings may not be fully generalizable to other settings or countries. Treatment practices, supportive care, and patient characteristics from 2008–2011 may differ substantially from contemporary clinical practice, which should be considered when interpreting these results. Finally, detailed data on specific endocrine therapy agents and duration were not uniformly available due to changes in treatment standards over time and the retrospective design. In addition, incomplete data on HER2-targeted therapy constitutes a key source of residual confounding. During the study period, trastuzumab use was limited and differed between groups, with a higher proportion of HER2-positive patients in the AC group receiving HER2-targeted therapy compared with the TAC group (31.8% vs. 22.6%). This imbalance may have biased survival comparisons between regimens and contributed to attenuation of treatment effects after adjustment, thereby limiting causal interpretation.

Although these findings suggest a potential late-term benefit of TAC in selected patients with stage II–IIIA breast cancer, particularly beyond 5 years of follow-up, the substantial attenuation of treatment effects after adjustment underscores the important role of confounding by disease stage, receptor status, and concurrent therapies. The retrospective design, limited sample size, and incomplete documentation of HER2-targeted and endocrine treatments preclude causal inference regarding chemotherapy regimen effects. Taken together, these results should be interpreted as hypothesis-generating and highlight the need for larger, prospective, risk-adapted studies with comprehensive treatment documentation to clarify the long-term clinical benefit of TAC in contemporary practice.

In conclusion, over 15 years of follow-up, adjuvant TAC chemotherapy in patients with stage II–IIIA breast cancer was associated with lower unadjusted recurrence rates, reduced distant metastasis, and a trend toward improved overall survival compared with AC. However, these apparent benefits were substantially attenuated and no longer statistically significant after adjustment for disease stage and receptor status, suggesting that the observed differences were largely driven by imbalances in baseline disease characteristics rather than an independent treatment effect. Acute and late adverse events, including cardiotoxicity, neuropathy, and endocrine-related effects, were generally mild and comparable between regimens. Given the retrospective design, limited sample size, and historical treatment context, causal inferences cannot be made. Prospective, adequately powered, risk-adapted studies are needed to clarify the true long-term benefit of TAC in the modern treatment era.

Acknowledgments

Statement of Transparency and Principles

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

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