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ORIGINAL RESEARCH

Neoadjuvant Doxorubicin-Paclitaxel Combined Chemotherapy in Patients with Inoperable Stage III Breast Cancer: A Retrospective Cohort Study with 10 Years of Follow-Up in Vietnam

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ABSTRACT

Introduction: The combination of doxorubicin and paclitaxel (AP) is widely used in our country for the neoadjuvant treatment of breast cancer as well as metastatic breast cancer. The AP regimen has shown promise as a neoadjuvant therapy for breast cancer that improves pathological complete response (pCR), increases the rate of conservative surgery, and improves the survival of patients. However, up to now, no research has evaluated the response of this regimen for the neoadjuvant treatment of advanced breast cancer, especially with a 10-year period of follow-up.

Methods: This retrospective analysis reviewed 126 patients with inoperable stage III breast cancer who received neoadjuvant chemotherapy with doxorubicin 50 mg/m^2 plus paclitaxel 175 mg/m^2 every 3 weeks for a maximum of six courses followed by surgery. pCR was evaluated. Survival was analyzed for all breast cancer patients using Kaplan–Meier and log-rank models.

Results: Of 126 women treated with neoadjuvant chemotherapy (NAC), the overall pCR rate was 25.4% and was significantly higher in patients with tumor stage cT1–T2, hormone receptor-negative (HR-negative), and human epidermal growth factor receptor 2 (HER2)-positive disease. Patients achieving pCR had significantly longer disease-free survival (DFS) and overall survival (OS). Ten-year DFS rates were 43.8% vs. 25.0% ($p = 0.030$) and 10-year OS rates were 59.4% vs. 28.9% ($p = 0.003$) for patients with pCR and non-pCR, respectively. The cumulative 10-year DFS was 19.6% for patients with HR-negative disease and 37.3% for those with HR-positive disease. Achieving pCR was associated with improved 10-year OS and DFS. Several clinicopathological features were closely associated with pCR in the inoperable

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stage III breast cancer patients who were treated by neoadjuvant chemotherapy.
Conclusion: Achieving pCR was associated with improved 10-year OS and DFS. Patients with advanced breast cancer with HR-negative and HER2-positive status who benefited from the AP neoadjuvant therapy regimen were significantly more likely to achieve pCR.

Keywords: Doxorubicin-paclitaxel regimen; Advanced breast cancer; Neoadjuvant chemotherapy; Pathological complete response

Key Summary Points

The addition of a taxane to neoadjuvant chemotherapy regimens has been shown to increase the rate of pathological complete response (pCR) and overall survival (OS).

However, up to now, no research has evaluated the response with a combination of doxorubicin and paclitaxel (AP) regimen for the neoadjuvant chemotherapy (NAC) of advanced breast cancer, especially with a 10-year period of follow-up.

The aim of this study was to evaluate treatment efficacy and identify reliable long-term prognostic factors in stage III breast cancer patients who were treated with a neoadjuvant AP regimen in Vietnam.

This study demonstrated that achieving pCR was associated with improved 10-year OS and disease-free survival (DFS).

We found that advanced breast cancer patients with hormone receptor-negative (HR-negative) and human epidermal growth factor receptor 2 (HER2)-positive disease benefited from neoadjuvant therapy, achieving higher pCR.

INTRODUCTION

Breast cancer (BC) incidence in Vietnam has more than doubled over the last two decades. Many breast cancer patients in our country are diagnosed at advanced stage, making treatment more difficult and expensive [1]. Lack of awareness of signs and symptoms, economic insufficiency, less intention to undergo screening, and weak referral systems contribute to the late diagnosis among Vietnamese cancer patients [2]. Neoadjuvant chemotherapy (NAC) is currently the standard of care widely administrated to patients with locally advanced breast cancer [3, 4]. NAC is commonly employed to reduce the size of the primary tumor, downstage cancer, improve the chance of undergoing surgery, and increase the rate of breast-conserving surgery [5]. In addition, NAC assesses the sensitivity and effectiveness of systemic treatments to guide strategies for the patient [6]. Anthracyclines and taxanes are known to be highly effective in the treatment of breast cancer and are therefore used in the neoadjuvant setting. The addition of a taxane to NAC regimens was shown to increase the rate of pathological complete response (pCR) and overall survival (OS). The results of many studies strongly support the use of anthracyclines plus taxanes as neoadjuvant therapy for the treatment of breast cancer [4, 7, 8]. Some studies have demonstrated the effectiveness of using taxanes concurrently with anthracyclines. From 2009 to 2011, the combination of doxorubicin and paclitaxel (AP) was widely used in our country for the neoadjuvant treatment of breast cancer, as well as metastatic breast cancer. The AP regimen has shown promise as a neoadjuvant therapy for breast cancer that improves pCR rates, increases the rate of conservative surgery, and improves the survival of patients [3, 8, 9]. In addition to pCR, several clinical and biological factors are associated with patient survival, among which hormone receptor (HR) status and human epidermal growth factor receptor 2 (HER2) status are widely accepted as predictive markers [3, 4, 7]. Prognostic factors such as molecular type, risk category, and androgen/estrogen receptor ratio are important

for making clinical decisions to treat and monitor individual cancer patients, and have been investigated in Vietnam [10–12]. However, few studies have been established to evaluate the effectiveness and prognostic factors of an AP regimen for locally advanced breast cancer patients. Therefore, to comprehensively decipher the role of NAC with an AP regimen in advanced BC, the current retrospective study aimed to evaluate treatment efficacy and identify reliable long-term prognostic factors in stage III breast cancer patients who underwent neoadjuvant doxorubicin-paclitaxel combination chemotherapy. To our knowledge, the follow-up in this study is the longest reported to date for breast cancer patients receiving neoadjuvant chemotherapy with an AP regimen.

METHODS

Study Design

This retrospective study included all eligible patients (126 women with BC) treated at the Vietnam National Cancer Hospital from February 2009 to August 2012.

Patient Selection and Study Process

Eligible patients were women between the ages of 26 and 65 years with histologically confirmed inoperable stage III breast cancer and who were considered candidates for NAC. The staging was based on the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, seventh edition. Patients in our study had the following characteristics: tumors with cT4, metastasis in ipsilateral axillary lymph nodes with invasion of surrounding tissue, metastasis in ipsilateral internal mammary lymph nodes, and ipsilateral supraclavicular or supraclavicular lymph nodes. All patients were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and received neoadjuvant therapy with an AP regimen. They had a baseline left ventricular ejection fraction (LVEF) $\geq$ 50%, adequate renal function (serum creatinine level $\leq$ 1.5 $\times$ upper normal limits), and adequate hepatic function (aspartate aminotransferase, alanine aminotransferase, and bilirubin $\leq$ 1.5 $\times$ upper normal limits). Exclusion criteria were as follows: bilateral breast cancer or metastatic breast disease; any previous treatment for breast cancer including surgery, radiation, or cytotoxic or endocrine therapy; any prior malignancy other than breast cancer; history of atrial or ventricular arrhythmias and/or congestive heart failure; pregnant or lactating women.

Most patients underwent immunohistochemistry (IHC). According to College of American Pathologists (CAP)/American Society of Clinical Oncology (ASCO) guidelines, the definition of estrogen receptor (ER)- or progesterone receptor (PgR)-positive was changed to 1% [13]. The United Kingdom recommendations were used for the assessment of HER2 expression [14]. A HER2 score of 3+ was considered HER2-positive. Patients who had an IHC HER2 score of 2+ were unknown for the amplification of the HER2 gene. All patients in this study received neoadjuvant chemotherapy every 21 days. Treatment consisted of doxorubicin 50 mg/m^2 administered intravenously (IV) for 5–30 min followed by paclitaxel 175 mg/m^2 as a 3-h infusion. After the completion of neoadjuvant treatment, breast surgery with axillary intervention was performed within 6 weeks after the final dose of chemotherapy. Patients were treated for at least three cycles and continued in the absence of unacceptable toxicity or disease progression for a maximum of six courses. Following surgery, adjuvant endocrine therapy and radiotherapy were administered if indicated. However, none of the patients received adjuvant anti-HER2 therapy. This was due to the limited availability of anti-HER2 drugs in our country at the time of treatment. In addition, patients had limited access to the drugs due to financial constraints. pCR was defined as the absence of invasive cancer in the breast and axillary lymph nodes (ypT0/is ypN0) as per the pathological evaluation. After NAC, all patients underwent tumor removal by modified radical mastectomy, or conservative surgery, combined with axillary lymph node dissection. Tumors or tumor beds were defined to measure their maximum diameter. Resected tumor and nodal samples were assessed via

pathological tests. Disease-free survival (DFS) was defined as the time from the date of surgery to the date of disease relapse. OS was defined as the time from disease diagnosis until death from any cause. The cutoff date for follow-up was July 1, 2022. This study was approved by the research committee of the Vietnam National Cancer Hospital in 2009 (number 940/QD-BVK). All patients provided written informed consent before they were enrolled in the study. Participants could withdraw from the study at any time without any threats or disadvantages, and for no stated reasons. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Statistical Analysis

All collected data were analyzed and measured using SPSS 20.0 software. Factors associated with pCR were assessed by univariable and multivariable logistic regression modeling. The Kaplan–Meier method was used to estimate the survival outcomes of patients by subgroup. Subgroups were compared using the log-rank statistic. A p-value < 0.05 was recognized as statistically significant. All statistical tests were two-sided.

RESULTS

Patient Characteristics and Associations with pCR

Between January 2009 and August 2012, approximately 2000 breast cancer patients were examined and treated at the Vietnam National Cancer Hospital. Among them, 188 patients were diagnosed with inoperable stage III breast cancer. Of this group, 132 patients received treatment with the AP regimen, which was commonly used in our hospital during that time period. Six patients did not meet the inclusion criteria and were excluded from the study. As a result, 126 patients were enrolled in our study. The main characteristics of the patients are shown in Table 1. The median age

Table 1 Clinicopathological characteristics of 126 patients with inoperable invasive BC

Features	*n*	%
Age, years		
Median (range)	46.0 (25–65)	
< 50	83	65.9
≥ 50	43	34.1
Performance status		
0	112	88.9
1	14	11.1
Menopausal status		
Premenopausal	92	73.0
Postmenopausal	34	27.0
Histopathological type		
Invasive ductal carcinoma, NOS	92	73.0
Invasive lobular carcinoma	12	9.5
Invasive mucinous carcinoma	6	4.8
Invasive anaplastic carcinoma	1	0.8
Unknown	15	11.9
Histological grade		
1	9	5.6
2	83	69.5
3	13	10.3
Unknown	21	24.6
Clinical tumor stage		
T1	1	0.8
T2	22	17.5
T3	42	33.3
T4	61	48.4
Clinical nodal stage		
N0	3	2.4
N1	22	17.5
N2	82	65.1
N3	19	15.1
Clinical stage		

Table 1 continued

Features	*n*	%
IIIA	58	46.0
IIIB	49	38.9
IIIC	19	15.1
HER2 status		
Positive	45	35.7
Negative	52	41.3
Unknown	29	23.0
HR status		
Positive	71	56.3
Negative	51	40.5
Unknown	4	3.2

BC breast cancer, *NOS* not otherwise specified, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor

was 46.0 (range 25–65) years. The median pretreatment tumor size was 60 mm (range 15–180 mm). Ninety-two (73.0%) patients were classified as having invasive ductal carcinoma, not otherwise specified (NOS) type, and 12 (9.5%) patients were classified as having invasive lobular carcinoma. There were six inflammatory breast cancer cases, accounting for 4.8%. Twenty-three (18.3%) patients had clinical stage T1 or T2 disease, while 42 (33.3%) and 61 (48.4%) had stage T3 and T4 disease, respectively. Most patients (80.1%) had cN2 or cN3 nodal status before NAC. Stages IIIA, IIIB, and IIIC accounted for 46.0, 38.9, and 15.1% of all patients, respectively; 56.3% of patients had positive hormone receptor (HR) status (defined as ER and/or PgR > 1%). The level of HER2 expression was assessed by IHC. We did not perform fluorescence in situ hybridization (FISH) testing to determine HER2 status due to the high cost, as many patients in our study were economically disadvantaged. Therefore, we only considered cases where HER2 (3+) was positive and HER2 (1+) or HER2 (−) was negative. Of 126 patients, 45 (35.7%) patients were HER2-positive, 52 (41.3%) patients were HER2-negative, and 29 (23.0%) patients with IHC HER2 2+ had unknown HER2 amplification status. The majority of patients (95.2%) received six cycles of the AP regimen, and only three patients (2.4%) received three cycles.

Based on the RECIST (response evaluation criteria in solid tumors) criteria, complete response (CR) and partial response (PR) rates were 29.4% and 65.1%, respectively, which corresponded to an overall response rate (ORR) of 94.5%. Stable disease was observed in four patients (3.2%), while disease progression occurred in three patients (2.4%). Three (2.4%) patients underwent breast-conserving surgery. For other patients, mastectomy was performed because of a large amount of residual disease or

Table 2 Response, operation type, and adjuvant therapy in patients with BC

Features	*n*	%
Operation type		
Mastectomy	123	97.6
Lumpectomy	3	2.4
Clinical response		
CR	37	29.4
PR	82	65.1
SD	4	3.2
PD	3	2.4
Pathological response		
pCR	32	25.4
RD	94	74.6
Adjuvant radiation therapy		
Yes	122	96.8
No	4	3.2
Adjuvant hormone therapy		
Yes	75	59.5
No	51	40.5

BC breast cancer, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *pCR* pathological complete response, *RD* residual disease

Table 3 Factors associated with pCR in patients

Factors	pCR	Univariable analysis			Multivariable analysis		
	%	OR	95% CI	*p*	OR	95% CI	*p*
Age, years							
< 50	26.5						
≥ 50	23.3	1.119	0.504–2.810	0.691	1.329	0.160–11.019	0.792
Menopausal status							
Premenopausal	25.0						
Postmenopausal	26.5	0.926	0.378–2.269	0.866	0.330	0.050–5.649	0.601
Histological grade							
1 or 2	18.5						
3	46.2	0.264	0.079–0.888	0.031	0.272	0.051–2.439	0.126
Tumor stage							
T1–T2	43.5						
T3–T4	21.4	2.832	1.096–7.320	0.032	4.922	1.143–21.203	0.032
Clinical nodal stage							
N0/N1/N2	27.1						
N3	15.8	1.983	0.538–7.310	0.304	0.518	0.082–3.276	0.485
HER2 status							
Negative	19.2						
Positive	40.0	0.357	0.144–0.889	0.027	0.330	0.094–1.159	0.084
HR status							
Negative	35.3						
Positive	18.3	2.434	1.059–5.590	0.036	1.317	0.362–4.783	0.676
Clinical stage							
IIIA	32.8						
IIIB	20.4	0.385	0.100–1.484	0.166			0.721
IIIC	15.8	0.731	0.178–3.011	0.665			
Clinical response							
CR	37.8						
PR + SD + PD	20.2	2.401	1.034–5.573	0.041	3.375	0.934–12.187	0.063

HR hormone receptor, *OR* odds ratio, *CI* confidence interval, *HER2* human epidermal growth factor receptor type 2, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *pCR* pathological complete response

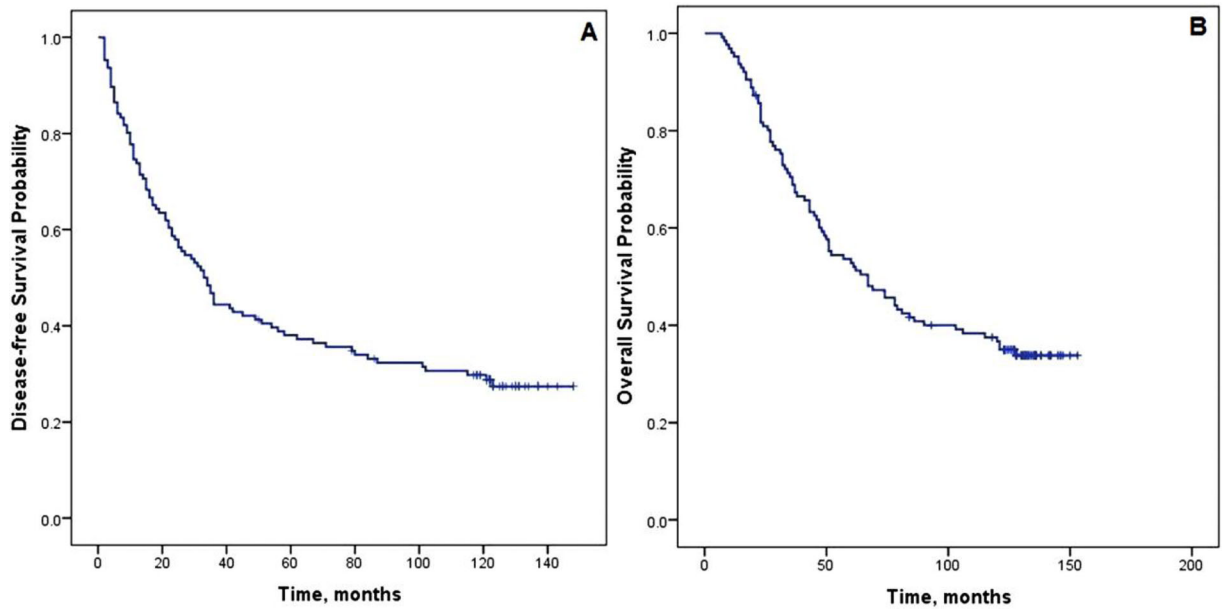

Fig. 1 Survival curves for all patients with inoperable invasive BC. **A** Disease-free survival. **B** Overall survival. *BC* breast cancer

because the patients did not want breast-conserving surgery. Pathological complete response (ypT0/is ypN0) was achieved in 32 (25.4%) patients (Table 2). Conventional clinical and histopathological parameters for pCR prediction were evaluated using univariable and multivariable binary logistic regression analyses (Table 3). In the univariable analysis, the clinical tumor stage was significantly associated with response to chemotherapy. Patients with clinical tumor stages cT3–4 were significantly less likely to achieve pCR than those with stages cT1–2 (21.4% vs. 43.5%, $p = 0.032$, respectively). pCR was significantly lower in patients with HR-positive than in those with HR-negative disease (18.3% vs. 35.3%, $p = 0.036$, respectively). Of patients whose tumors were HER2-positive, 40.0% achieved pCR, while only 19.2% of patients with HER2-negative breast cancer achieved pCR ($p = 0.027$). The other factors associated with pCR were clinical response and histological grade ($p < 0.05$), while age group, menopausal status, clinical lymph node stage, and clinical stage had no significant effect ($p > 0.05$). Multivariable analysis revealed that only tumor stage was significantly associated with pathological response to chemotherapy ($p = 0.032$), although HER2 status and clinical response as a continuous variable almost reached significance ($p = 0.084$ and $p = 0.063$, respectively). Most patients (96.7%) underwent adjuvant radiation, and 59.5% received adjuvant endocrine therapy. None received adjuvant anti-HER2 therapy.

Survival Estimates

The mean (range) follow-up time was 75 (7–-153) months. At the time of this analysis, 65.1% of the women had died. After treatment, recurrence or death was reported in 71.4% of patients. Kaplan–Meier survival curves for DFS and OS for all patients are shown in Fig. 1A, B. The median DFS and OS were 33.0 months (95% CI 25.1–40.9 months) and 67.0 months (95% CI 45.9–88.1 months), respectively. Five-year and 10-year DFS were 38.0% and 29.7%, while 5-year and 10-year OS were 52.9% and 36.7%, respectively. The analysis of factors affecting DFS and OS is detailed in Table 4. The analysis showed that the factors affecting DFS and OS were clinical tumor stage, clinical nodal stage, clinical tumor node metastasis (cTNM)

Table 4 Factors affecting disease-free survival (DFS) and overall survival (OS)

Factors	No. of patients	DFS			OS		
		5-Year %	10-Year %	*p*	5-Year %	10-Year %	*p*
Age, years				0.890			0.674
< 50	83	38.6	29.8		55.0	37.6	
≥ 50	43	37.1	29.7		48.8	34.9	
Menopausal status				0.383			0.274
Premenopausal	92	36.9	28.8		50.7	33.9	
Postmenopausal	34	41.2	32.4		58..8	44.1	
Histological grade				0.293			0.669
1 or 2	92	41.3	29.8		52.8	36.0	
3	13	23.1	23.1		46.2	30.8	
Clinical tumor stage				0.047			0.017
T1–T2	23	52.2	43.5		69.6	56.5	
T3–T4	103	34.9	26.6		49.1	32.2	
Clinical nodal stage				0.041			0.036
N0/N1/N2	107	42.0	34.2		55.1	40.0	
N3	19	15.8	5.3		39.1	8.4	
Clinical stage				0.086			0.026
IIIA	58	43.0	37.5		60.3	48.2	
IIIB	49	40.8	30.4		49.0	32.4	
IIIC	19	15.8	5.3		39.1	8.4	
HER2 status				0.020			0.031
Negative	52	47.9	37.7		67.3	45.8	
Positive	45	28.9	22.2		46.7	31.1	
HR status				0.004			0.004
Negative	51	23.5	19.6		37.3	25.5	
Positive	71	49.2	37.3		65.8	45.6	
Pathological response				0.030			0.003
pCR	32	53.1	43.8		75.0	59.4	
Non-pCR	94	32.9	25.0		45.2	28.9	

HR hormone receptor, *pCR* pathological complete response, *HER2* human epidermal growth factor receptor 2

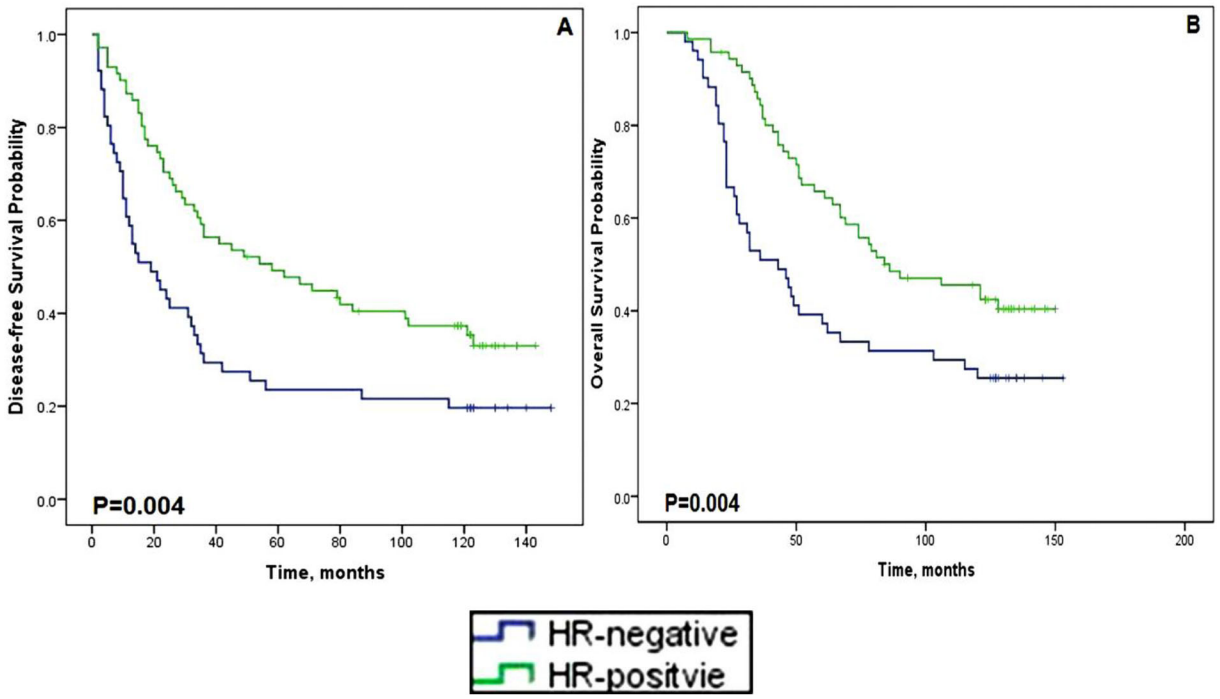

Fig. 2 DFS and OS according to HR status in patients with inoperable invasive BC. **A** Disease-free survival. **B** Overall survival. *DFS* disease-free survival, *OS* overall survival, *HR* hormone receptor, *BC* breast cancer

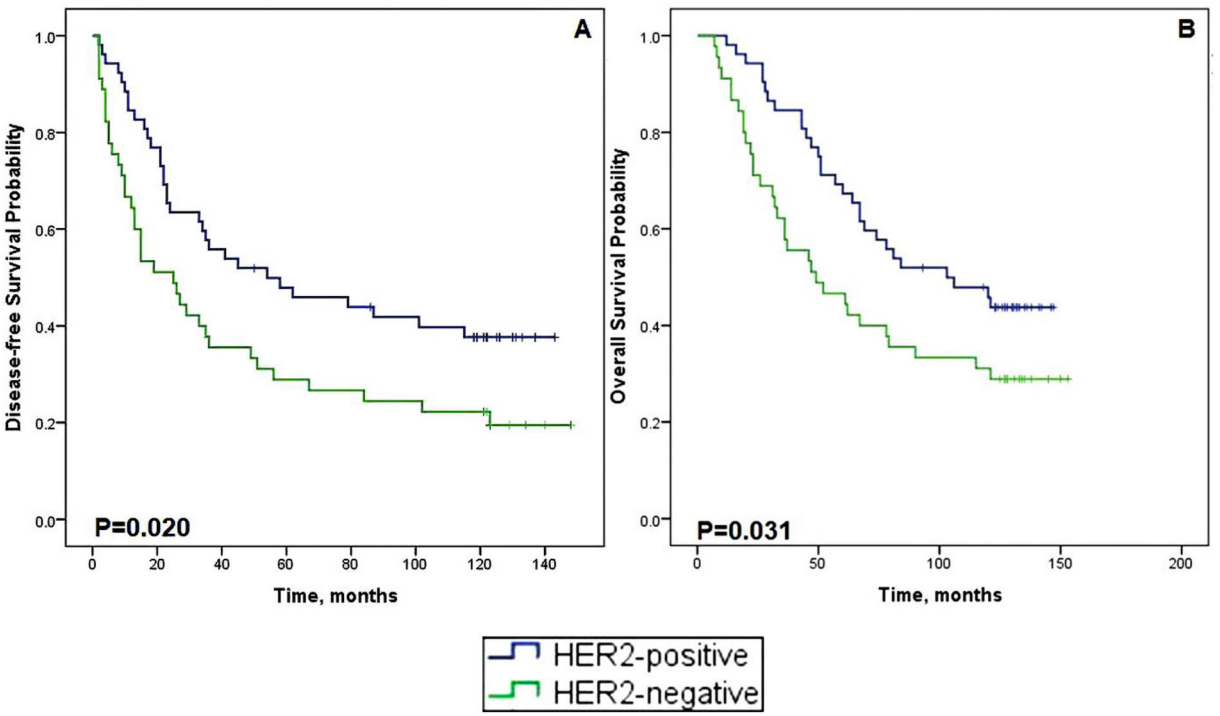

Fig. 3 DFS and OS according to HER2 status in patients with inoperable invasive BC. **A** Disease-free survival. **B** Overall survival. *DFS* disease-free survival, *OS* overall survival, *HER2* human epidermal growth factor receptor 2, *BC* breast cancer

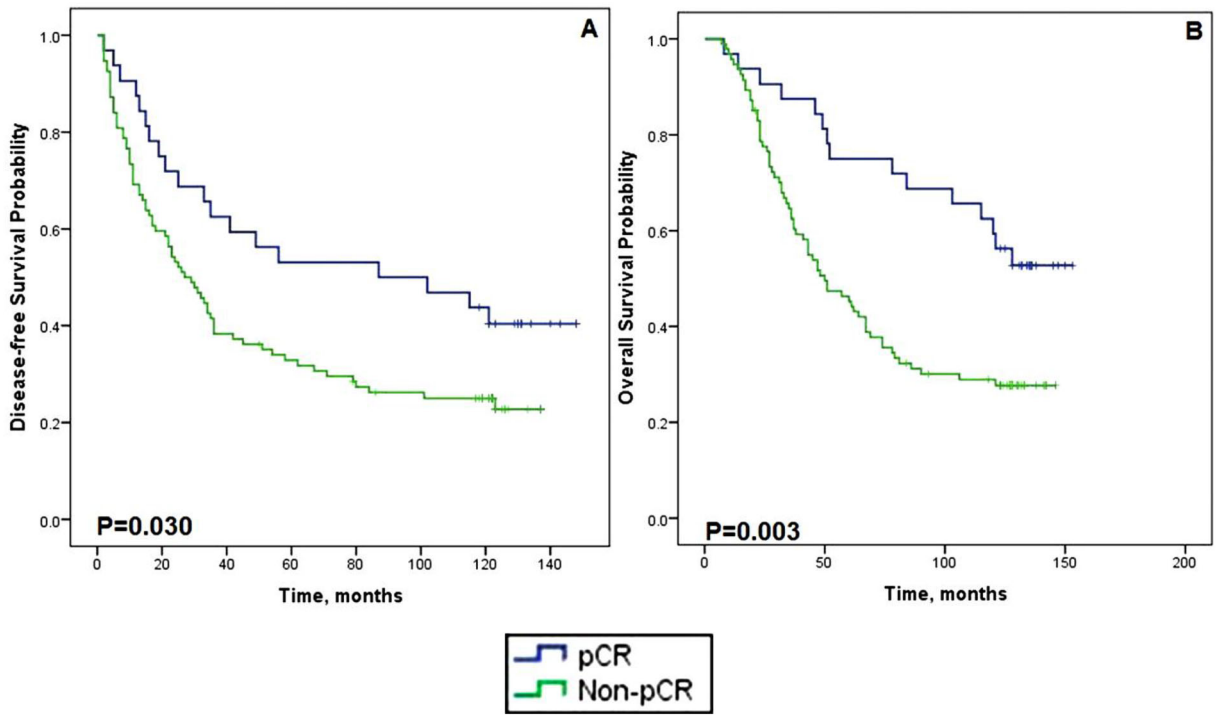

Fig. 4 DFS and OS according to pCR status in patients with inoperable invasive BC. **A** Disease-free survival. **B** Overall survival. *DFS* disease-free survival, *OS* overall survival, *pCR* pathological complete response, *BC* breast cancer

stage, HR status, HER2 status, and pathological response ($p < 0.05$).

Survival curves (DFS and OS) for patients according to HER2 status and HR status are shown in Figs. 2A, B and 3A, B. At 10-year follow-up, patients with HER2-positive breast cancer had a worse prognosis than those with HER2-negative breast cancer. Ten-year OS rates were 45.8% and 31.1%, respectively, for patients with HER2-positive tumors and HER2-negative tumors ($p = 0.031$), while 10-year DFS rates were 37.7% and 22.2%, respectively ($p = 0.020$). Survival rates were higher for patients with HR-negative disease than for those with HR-positive disease, with 10-year OS of 45.6% and 25.5%, respectively, and 10-year DFS of 37.3% and 19.6%, respectively. These differences were statistically significance ($p = 0.004$).

Figure 4A, B shows DFS and OS according to achievement of pCR to NAC. Among the patients, 25.4% (32 patients) achieved pCR while 74.6% (94 patients) did not. As expected, patients with pCR had significantly longer DFS ($p = 0.030$) and OS ($p = 0.003$) than those without pCR. The 10-year DFS rates were 43.8% vs. 25.0%, respectively, and the 10-year OS rates were 59.4% vs. 28.9%, respectively

DISCUSSION

Doxorubicin and paclitaxel are well known as the most effective neoadjuvant and adjuvant treatments for breast cancer [4, 8]. Our analysis is one of the few studies reporting 10-year outcomes for patients treated with the AP regimen. This study presents a Vietnamese experience of neoadjuvant treatment for stage III breast cancer with a combination of paclitaxel and doxorubicin. It demonstrates the effectiveness of this regimen and identifies reliable long-term prognostic factors affecting patient outcomes. These predictive factors will be a valuable tool to inform oncologists in similar contexts to help them in adjusting management and follow-up plans. Our study demonstrates that the AP regimen is a promising neoadjuvant chemotherapy regimen for patients with stage III breast cancer.

Neoadjuvant chemotherapy in this study achieved high clinical responses, with clinical CR and PR rates of 29.4 and 65.1%, respectively. The overall response rate was 94.5%. Stable disease was observed in four patients (3.2%), while disease progression was observed in three patients (2.4%). Other neoadjuvant chemotherapy studies have consistently shown a low risk of progressive disease during chemotherapy (less than 5%) [4, 5, 8]. Of 37 patients with a clinical CR, 15 breast cancer patients (40.5%) achieved pCR.

Many studies around the world have determined that the main goal of neoadjuvant chemotherapy is the pCR rate. pCR is a predictor for disease free-survival and overall survival [9]. In this study, 25.4% (32 of 126 patients) achieved pCR. Diéras et al. studied 200 patients who received neoadjuvant chemotherapy with an AP regimen or doxorubicin plus cyclophosphamide (AC) regimen. The pCR rates were 16% and 10% of patients in the AP and AC arms, respectively [8]. Malhotra et al. [15] reported a pCR rate of 15%, while other studies have reported rates in the range of 3–46% [9, 16]. The rate of pCR can vary depending on the definition of pCR as well as the clinicopathological characteristics. In our study, pCR was defined as the absence of invasive cancer in breast and axillary lymph nodes (ypT0/is ypN0).

Several studies have investigated the factors predicting pCR. Our study found significant associations between pCR and histological grade, clinical tumor stage, HER2 status, HR status, and clinical response. Our results are consistent with those of other studies. We found that higher cT-stages were associated with significantly lower pCR rates than lower cT-stages (cT3–4 vs. cT1-2; $p < 0.05$). Goorts et al. ($n = 2366$) reported that pCR rates for cT1, cT2, cT3, and cT4 were 31, 22, 18, and 17%, respectively. A significant finding from the study was that patients with a lower cT-stage (cT1-2) had a higher pCR rate than those with a higher cT-stage (cT3–4), and this was found to be an independent predictor (OR 3.15, $p < 0.001$) [17]. Furthermore, previous meta-analyses demonstrated a higher pCR rate in HR-negative or HER2-positive patients than in HR-positive or HER2-positive patients. Von Minkwitz et al. analyzed 6377 breast cancer patients receiving preoperative anthracycline-taxane chemotherapy in seven clinical trials. The results showed that the CR rate was 7.6% in the group of ER-positive patients, 26% in ER-negative patients, 7.4% in PgR-positive patients, and 22.9% in PgR-negative patients ($p < 0.001$) [18]. Yanli et al. studied 261 patients with operable primary breast cancer receiving neoadjuvant chemotherapy, with a pCR rate of 29.1%. The factors related to the pCR rates were as follows: ER (negative: 57.9% vs. positive: 42.1%), PgR (negative: 65.8% vs. positive: 34.2%), and HER2 status (positive: 54.7% vs. negative: 45.3%) [19]. Hong et al. reported that the pCR rate in the breast was higher in HER2-positive patients (HER2 positive: 33.3% vs. negative: 10.0%, $p = 0.002$) [20]. Cortazar et al. analyzed 12 studies on neoadjuvant therapy and found that the HER2-positive patients had higher pCR than those with HER2-negative disease [9].

In this retrospective study of 126 patients with stage III breast cancer treated with a neoadjuvant AP regimen, the mean follow-up was 75 months. The median DFS and OS were 33 months and 67 months, respectively. The 5-year and 10-year DFS were 38.0% and 29.7%, while the 5-year and 10-year OS rates were 52.9% and 36.7%, respectively. The study by Diéras et al. included 200 patients with stage II and III breast cancer who received doxorubicin and paclitaxel-based chemotherapy. The 5-year and 10-year event-free survival were 69.5% and 60.5%, while the 5-year and 10-year OS rates were 85.0% and 70.0%, respectively [8]. Another study involving 634 nonmetastatic cT4 breast cancer patients treated with neoadjuvant therapy had 10-year results of 52.3% for OS, 37.0% for invasive disease-free survival (IDFS), and 49.8% for distant disease-free survival [21]. Additionally, a retrospective cohort study of 1600 women treated with neoadjuvant therapy recorded 5-year OS and recurrence-free survival (RFS) rates of 79% and 67%, respectively; the 10-year OS and RFS rates were 64% and 58%, respectively [22]. Survival results in our study were lower than those in other studies, for several reasons. Firstly, the patients in our study were at a later stage, with more than half

(54.0%) having stage IIIB or IIIC. Secondly, many patients were HER2-positive and did not have access to targeted therapy, especially trastuzumab. Finally, triple-negative breast cancer patients with residual disease after NAC did not receive capecitabine maintenance therapy after surgery.

In our study, the HR status was found to be a factor affecting DFS and OS. Patients with HR-positive breast cancer had longer DFS and OS than those with HR-negative breast cancer ($p < 0.05$). The 10-year OS rates were 45.6% and 25.5%, respectively ($p = 0.004$), and the 10-year DFS rates were 37.3% and 19.6%, respectively ($p = 0.004$). El-Sayed et al. studied 95 patients with locally advanced breast cancer who received neoadjuvant taxane-based treatment. The results showed that the DFS rates at 5 years were 82.3% and 26.5% for breast cancer patients with positive and negative HR, respectively ($p < 0.0001$, HR 21.48), and the OS rates were 84% and 35.7%, respectively ($p = 0.0001$, HR 11.59) [23]. Our results also confirmed that HER2 overexpression or amplification impacts the prognosis of stage III breast cancer patients. El-Sayed et al. reported that the 5-year DFS rates were 33.8% and 81.8% for patients with HER2-positive and HER2-negative breast cancer, respectively ($p < 0.0001$, HR 12.27), and the 5-year OS rates were 41.7% and 83.2%, respectively ($p = 0.001$, HR 7.14) [23].

In our study, we found that patients with pCR had better OS and DFS than patients with residual disease. Achievement of pCR in our cohort was significantly associated with survival outcomes. These findings are in concordance with a recently published large meta-analysis by Spring et al., which included more than 27,000 patients who were evaluated from 52 studies. The study found that patients who had pCR, as compared to the absence of pCR, had significantly better event-free survival and overall survival (HR 0.31, $n = 26{,}378$, and HR 0.22, $n = 23{,}329$, respectively) [24]. Diéras et al. studied patients with T2-3, N0-1, M0 disease who received preoperative chemotherapy with the AP regimen. At a median follow-up of 31 months, DFS was higher in patients who reached pCR than in those without pCR (91% vs. 70%) [8]. This result is similar to the findings of Cortazar et al. [9]. However, in our country, there are still many patients who come to the hospital when the disease is already in an advanced stage. Over the years, thanks to increased awareness campaigns, education, and screening, this rate has gradually decreased. In addition, FISH testing is now much more common than it was in the 2010s. Now, many patients have the opportunity to be treated with anti-HER2, CDK4/6 inhibitors, and immunotherapy, which improves the survival time of breast cancer patients.

The limitations of our study should be acknowledged. Firstly, the retrospective nature of the study may have limited our ability to control for all possible confounding variables, and therefore our findings should be interpreted with caution. Additionally, the small sample size and missing data, particularly regarding HR and HER2 status, may have impacted the accuracy of our results. FISH/chromogenic in situ hybridization (CISH) testing for HER2 is also beyond affordability for the reported population, so HER2 IHC (2+) patients were not evaluated by CISH or FISH. Furthermore, we did not have specific data on the use of endocrine therapy in our patients. This was due to the conditions at our hospital between 2009 and 2012, which prevented many patients from receiving consistent hormone therapy. Some patients started on aromatase inhibitors and then switched to tamoxifen, while others did the opposite. Finally, the primary aim of our study was to evaluate the response to treatment and survival outcomes. We did not focus on analyzing the toxicity or dose reductions related to the treatment. Future studies with larger sample sizes and more complete data collection would be necessary to confirm our findings and address these limitations.

CONCLUSIONS

Our study has provided evidence that clinicopathological characteristics including histopathological grade, tumor stage, clinical response, HER2 status, and HR status were closely related to pCR in patients with stage III breast cancer who were treated by neoadjuvant

chemotherapy. We also found that HER2 status, HR status, and pCR were predictors of long-term clinical outcomes in these patients.

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Compliance with Ethics Guidelines. The Scientific and Ethical Committee of the National Cancer Hospital, Vietnam, approved this study (number 940/QD-BVK). All of the patients provided written informed consent before they were enrolled in the study. Participants could withdraw from the study at any time without any threats or disadvantages, and for no stated reason. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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