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Pathologic Response to Neoadjuvant Chemotherapy and Survival Outcomes amongst Breast Cancer Patients in Yaounde

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Abstract

Introduction: The rising incidence of breast cancer is a concern globally and 70% of cancer patients present at advanced stages in Cameroon. Neoadjuvant chemotherapy (NACT) has been shown to offer clinical benefits and objective pathologic response (OPR) to NACT is a potential surrogate marker of survival in some breast cancer subtypes. The prognostic value of OPR is unknown in Cameroon. We therefore sought to investigate the relationship between pathologic response to NACT and survival outcomes in breast cancer patients in Yaounde. **Methodology:** This was a historical cohort study from January 2019 to December 2023 at the Yaounde General and Central Hospitals of non-metastatic breast cancer patients with post-NACT pathological evaluation. Bivariate analysis and logistic regression were used to identify factors associated with OPR. Event-free and overall survival (EFS/OS) were compared using the Kaplan-Meier method and log-rank test. The association between pathologic response and survival outcomes was evaluated using Cox regression analysis and the likelihood ratio test. **Results:** This study included 119 female participants. Triple-negative breast cancer was the most common subtype (42.31%), and Doxorubicin/Cyclophosphamide plus a taxane (AC+taxane) was the most frequently used NACT protocol (53.78%). Good responders (complete/> 50% partial response) comprised 25.21% of the cohort, with a significantly better EFS compared to poor responders (41.91 ± 2.43 versus 19.86 ± 5.26 months, p = 0.01). Pathological response to NACT was not significantly associated to EFS (p = 0.79) or OS (p = 0.37). However, the use of AC plus taxane was in-

dependently associated with a longer EFS (HR: 0.23, p = 0.01) and OS (HR: 0.10, p = 0.00). **Conclusion:** The study reveals that pathologic response is not independently associated with survival outcomes. Instead, the use of a complete NACT by the AC + taxane protocol emerged as being independently associated to survival outcomes, informing treatment decisions and potentially improving patient outcomes.

Keywords

Breast Cancer, Neoadjuvant Chemotherapy, Pathologic Response, Survival, Yaounde

1. Introduction

Breast cancer represents the most common malignancy globally, with 2.3 million new cases and 665,000 deaths reported in 2022. In the same year in Africa, a previously predicted steeply rising incidence was observed with over 198,000 new breast cancer cases, and above 90,000 deaths [1]. Cameroon reported 4,207 new breast cancer cases and 2,285 deaths in 2022 [1], and breast cancer is characterized by an earlier onset of disease, more aggressive subtypes, and notably higher mortality rates [2]-[4].

Locally advanced breast cancer encompasses a diverse group of tumours characterized by extensive locoregional spread, which may be operable or inoperable without clinical or radiological evidence of metastasis [5]. Some Cameroonian studies have revealed that over 70% of breast cancer patients presented with locally advanced and metastatic disease (stages 3 and 4) [6]-[8].

Neoadjuvant chemotherapy (NACT) has shown significant clinical benefits for locally advanced and inoperable breast cancers. It can transform previously inoperable tumours into operable ones and, in largely operable tumours, down staging leads to a modest increase (7% to 12%) in breast conservation rates [9]. Some studies have shown that patients achieving pathologic complete response (pCR) to NACT experience significantly improved overall survival (OS) and disease-free survival (DFS), particularly in triple-negative and HER2+ breast cancers [10]. This has led to the consideration of objective pathologic response (OPR) to NACT as potential surrogate marker for DFS and OS. However, chemotherapy responses are influenced by various factors, such as stage, grade, and biological markers.

The impact of OPR achievement on survival outcomes in different breast cancer subtypes across several studies is divergent, and varies with the NACT regimen used [11]. The impact of lymph node OPR on survival has been shown in Cameroon [8]; however, the prognostic value of the overall OPR and its associated factors are not known and may vary from that in the literature given the differences in Cameroonian breast cancer genomics [12]. In a resource-limited setting like ours, it is crucial to identify patients most likely to benefit from NACT and to

understand the relationship between OPR and patient and treatment characteristics and its long-term advantages in our specific context.

2. Methods

2.1. Study Design and Setting

This study employed a historical cohort design to investigate the differences between two patient groups based on their response to treatment. This study was carried out at two oncology treatment centres in Cameroon: the Yaounde General Hospital (YGH) and the Yaounde Central Hospital (YCH). Both are referral hospitals in Cameroon, located in the administrative capital and serve as teaching hospitals.

2.2. Study Duration and Period

This cohort study included patients who were followed up at both study sites from the 1st of January 2019 to the 31st of December 2023; spanning 5 years. Data were collected retrospectively for a duration of 3 months from the 1st of June to the 31st of August 2024.

2.3. Study Population

The target population of the present study was all patients with breast cancer in Yaounde. This study evaluated breast cancer patients with initially non-metastatic breast cancer and who received NACT at the YGH and YCH between the 1st of January 2019 and the 31st of December 2023. Inclusion criteria for good responders were all patients with histologically-confirmed breast cancer, who had staging information, had indication for NACT, and with available data on therapeutic response showing complete, near total or >50% pathological response. For poor responders, all patients with histologically-confirmed breast cancer, who had staging information, had indication for NACT, and with available data on therapeutic response showing <50% pathological response or no response were included. Exclusion criteria included patients with relative or absolute contraindications to standard chemotherapy including pregnant patients and those with heart conditions contraindicating the use of anthracyclines.

2.4. Sample Size Calculation

Using the Fleiss formula [13] for comparing two proportions, assuming an expected proportion of good responders of 80% and poor responders of 20%, with 80% power and 95% confidence, the calculated minimum sample size was 110 patients.

2.5. Procedure

The Ethical Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I approved this study. Questionnaires were coded leaving

no link between the patient's record and the questionnaire. The identity and personal details of participants of the study were kept strictly confidential. Moreover, all patient files were examined within the archive of this institution without any tampering or modification of their contents. This study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013) [14].

Patient demographics including age, sex, marital status, profession, and gynecological history were collected. The diagnosis of cancer was based on the pathological confirmation from the files either written and signed by the consultant oncologist or from the histopathological report. Histopathological characteristics including tumour grade, hormone receptor status, Ki67, and human epidermal growth factor receptor 2 (HER2) were noted where available. Staging was noted based on imaging including chest and abdominopelvic CT scan or on chest radiography and abdominopelvic ultrasound; these were done using the Tumour Node Metastasis (TNM) staging method. The chemotherapy regimen used prior to surgery was also recorded, with details of the number of cycles received. The post-operative pathological reports were examined for pathological response using the Sataloff and margin status. The occurrence of an event (progression, relapse, or death) was noted and the dates of these events were recorded. The date of last contact was noted from the files. Data from validated questionnaires was entered into Microsoft excel 2013 spread sheets.

2.6. Assessment of Response

Clinical response was assessed using the response evaluation criteria in solid tumors (RECIST) criteria [15] by measuring tumour size and node size after neoadjuvant chemotherapy. The Sataloff Classification was used to evaluate the pathologic response based on the response of the primary carcinoma and the lymph nodes. The Sataloff classification was used for pathologic response assessment as it is the routine reporting system adopted in our pathology services. Residual Cancer Burden (RCB) and Miller-Payne grading are not systematically implemented in our setting due to limited availability of standardized quantitative tumor bed measurement and dedicated pathology infrastructure. Thus, the Sataloff system was selected for consistency with existing institutional protocols. Those classified as pCR and pPR1 were placed into the good responders' group and those with pPR2 and pNR were placed in the poor responders' group (**Table 1**).

Table 1. Pathologic response category according to Sataloff criteria.

AJCC Response Category	Sataloff criteria T and N
pCR	TANA
pPR1	TANB, TBNA, TBNB
pPR2	TCNA, TCNB, TANC, TBNC, TCNC, TDNA, TDNB, TDNC, TAND, TBND, TCND
pNR	TDND

AJCC, American Joint Committee on Cancer; pCR, pathologic complete response; pPR1, pathologic partial response > 50%, pPR2, pathologic response < 50%, pNR, pathologic no response.

2.7. Analysis

Descriptive statistics were employed to summarize demographic, clinical, and pathological characteristics of the study participants. Chi-square tests and Fisher's exact tests were conducted to compare categorical variables between patients with OPR and those without. The independent samples t-test was used to compare continuous variables between these groups. Kaplan-Meier curves were used to estimate OS and EFS for the entire cohort. The log-rank tests were employed to compare survival curves between different response groups. Multivariate Cox regression analysis was performed to assess whether pathologic response to NACT significantly was independently associated with survival outcomes (EFS and OS), adjusting for potential confounding variables. The multivariate Cox regression models included age at diagnosis, civil Status, professional status, menopausal status, histological type, histological grade, molecular subtype, AJCC Stage, surgical technique, surgical margin status, and chemotherapy regimen. For molecular subtype analysis, patients with missing immunohistochemical data were excluded from subtype-specific analyses but retained in overall survival analyses. No imputation method was applied due to the retrospective nature of data collection. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient Characteristics

Our study included 119 female participants: 30 (25.21%) in the good responders' group (pCR: 10, 8.40% and pPR1: 20, 16.81%) and 89 (74.79%) in the poor responders' group (pPR2: 82, 68.91% and NR 7, 5.88%). The median age of the overall participants was 47.00 ± 11.44 years (range 28 to 80) years (Table 2). When the mean age was compared between subgroups, good responders were averagely one year older than poor responders, albeit without statistical significance (48 ± 12 versus 47 ± 11.26, $p = 0.75$). The average age at menarche was 13.34 ± 2.17 (range 9 to 18) years, while that at menopause was 50.41 ± 3.72 (range 42 to 59) years.

Table 2. Sociodemographic characteristics of the participants per subgroup.

Characteristic	Overall		Good responders		Poor responders		p-value
	frequency	%	frequency	%	frequency	%	
Age, years (n = 119)							0.98
<40	31	26.05	8	26.67	23	25.84	
40 - 64	79	66.39	20	66.67	59	66.29	
≥65	9	7.56	2	6.67	7	7.87	
Civil Status (n = 102)							0.82
Married	63	61.67	18	69.23	45	59.21	
Single	33	32.35	7	29.92	26	34.21	
Widowed	6	5.88	1	3.85	5	6.58	

Continued

Professional Status (n = 80)							0.51
Employed/Student	48	60.00	9	47.37	39	63.93	
Unemployed	32	40.00	10	52.63	22	36.07	
Menopausal status (n = 119)							0.81
Pre-menopausal	75	63.03	18	60.00	57	64.04	
Post-menopausal	44	36.97	12	40.00	32	35.96	
No	16	20.00	3	15.79	13	21.31	

Percentages show distribution of characteristics within good and poor responders.

Triple-negative breast cancer was the most common subtype (33, 42.31%), while non-luminal HER2+ was the least represented (3, 3.85%). The majority (60, 61.22%) had grade 2 tumours. Poor responders had a higher proportion of histological grade III than good responders (26.58% versus 15.79%, p = 0.01, Table 3).

Table 3. Clinical and pathobiologic characteristics of the study participants.

Characteristic	Overall		Good responders		Poor responders		p-value
	frequency	%	frequency	%	frequency	%	
Histological type (n = 119)							0.30
Invasive ductal carcinoma	79	66.39	23	76.67	56	62.92	
Mucinous carcinoma	7	5.88	–	–	7	7.87	
Others	33	27.73	7	23.33	26	29.21	
Histological grade (n = 98)							**0.01**
I	14	14.29	5	26.32	9	11.39	
II	60	61.22	11	57.89	49	62.03	
III	24	24.49	3	15.79	21	26.58	
IHC subtype (n = 78)							0.81
Triple negative	33	42.31	7	36.84	26	44.07	
Luminal A	25	32.05	8	42.11	17	28.81	
Luminal B	17	21.79	3	15.79	14	23.73	
HER2+	3	3.85	1	5.26	2	3.39	
Stage (n = 119)							0.08
Local	37	31.09	13	43.33	24	26.97	
Locally advanced	82	68.91	17	56.67	65	73.03	

IHC, Immunohistochemistry; HER2+, human epidermal growth factor receptor 2 positive.

3.2. Treatment Profile

All participants received at least one line of chemotherapy, while 76 (63.87%) received an additional cycle (NACT cycle 2). The AC plus taxane combination was the most common NACT protocol used (64, 53.78%), and most (114, 95.80%) underwent a radical surgical procedure (mastectomy) (Table 4).

Table 4. Treatment modalities observed in the study population.

Treatment Modality	Overall		Good responders		Poor responders		p-value
	frequency	%	frequency	%	frequency	%	
NACT Protocol (n = 119)							0.44
AC alone	17	14.29	9	30.00	33	37.08	
AC + TAXANE	64	53.78	19	63.33	45	50.56	
Others	38	31.93	2	6.67	11	12.36	
Surgical technique (n = 119)							0.78
Radical surgery	114	95.80	29	96.67	85	95.51	
Conservative surgery	5	4.20	1	3.33	4	4.49	

AC, Doxorubicin plus Cyclophosphamide; NACT, neoadjuvant chemotherapy.

3.3. Clinical and Pathologic Response

The clinical response after NACT showed that a majority of the participants had a partial clinical response (69, 57.98%) followed by complete response (32, 26.89%). Notably, a higher proportion of good responders had complete clinical response albeit without statistical significance (33.33 % versus 24.72 %, p = 0.61). Good responders had a significantly higher proportion of negative surgical margins than poor responders (83.33% versus 56.18%, p = 0.01).

3.4. Survival Outcomes

The median follow-up period was 27 months. At the end of the study, 31 (26.05%) participants had died and up to 47 (39.5%) participants had disease progression.

The comparison of EFS between the two groups revealed a significantly better median EFS in the good responders; 41.91 ± 2.43 months (95% CI: 35.64 - 45.15) versus 19.86 ± 5.26 months (95% CI: 9.49 - 30.11), p = 0.00 (Figure 1).

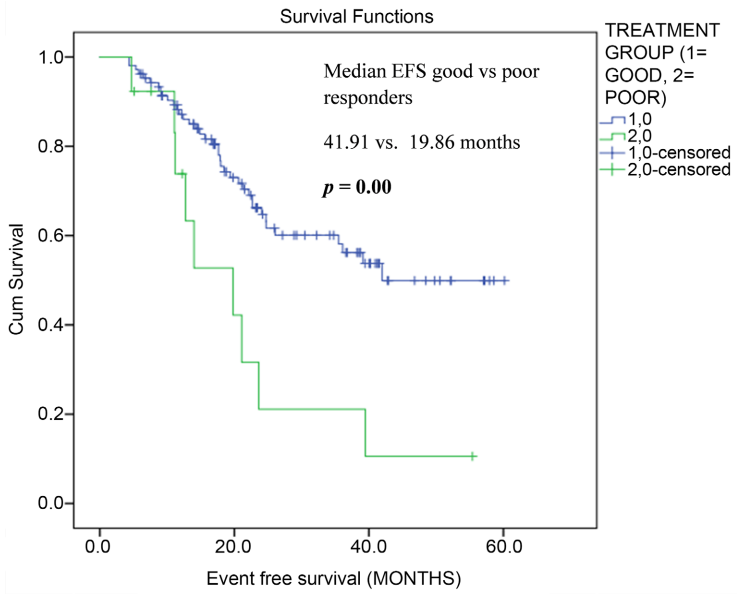

Figure 1. Event-free survival with respect to treatment-response subgroups.

When overall survival was compared between the two groups, the good responders had a better median overall survival; 6.20 ± 0.27 years (95% CI: 4.10 - 8.15) versus 3.26 ± 0.47 years (95% CI: 2.34 - 4.18), p = 0.12, albeit without statistical significance, as shown in Figure 2.

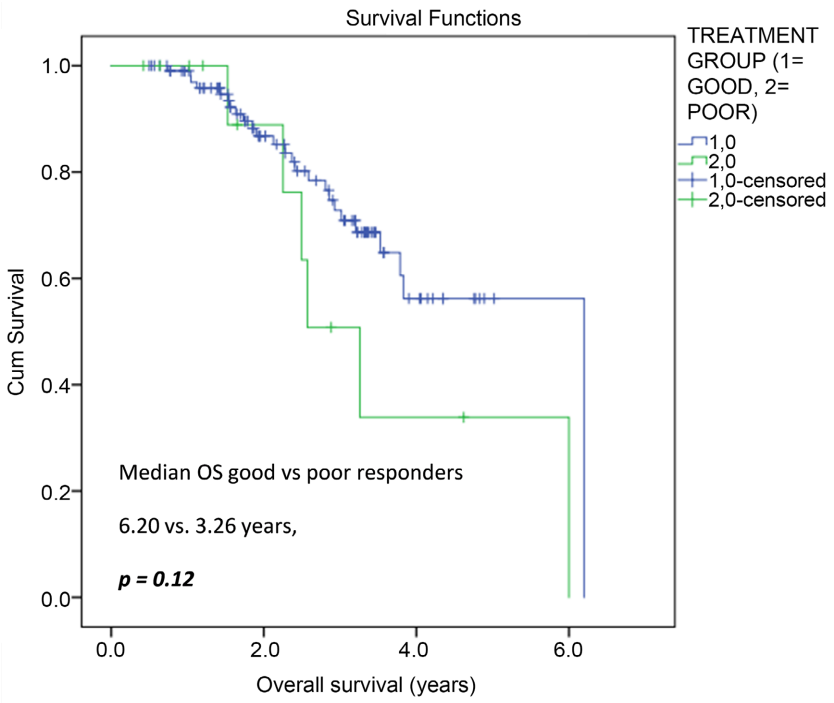

Figure 2. Overall survival with respect to treatment response groups.

3.5. Association between Response and Survival

In the multivariate Cox regression analysis investigating the association of pathologic response to NACT and survival duration, pathological response to NACT was not significantly associated to EFS (p = 0.79) or OS (p = 0.37) (Table 5). However, the use of AC plus taxane was independently associated with a longer EFS (HR: 0.23, p = 0.01) and OS (HR: 0.10, p = 0.00). A positive surgical margin was associated with shorter OS (HR: 1.81, p = 0.03).

Table 5. Cox regression model of pathological response and survival.

Variable	Hazard ratio	95% Confidence Interval	p-value
Pathological response and EFS	1.11	0.49 - 2.52	0.80
Pathological response and OS	0.57	0.16 - 1.10	0.38

EFS, Event-free survival; OS, Overall survival.

4. Discussion

This retrospective cohort study investigated the relationship between post-NACT pathological response and survival outcomes in breast cancer patients treated in Yaounde. Our findings offer intriguing insights when compared to both devel-

oped country and other African cohorts.

The predominance of triple-negative breast cancer (42.31%) in our cohort corroborates the findings in recent studies in Cameroon [16] [17]. This however differs markedly from patterns in developed countries where luminal breast cancer is most frequent. This difference could be explained by the higher prevalence of genetic factors like BRCA1/2 mutations in Africans [18], which has been linked to higher prevalence of triple-negative breast cancer and increased aggressivity [4].

Our pCR rate of 8.40% is consistent with previously reported lymph node pCR rates in Cameroon [8], but falls below the 10% - 35% range found in other African countries and significantly below rates in high-resource settings [19]. This lower rate could be linked to the high rate of treatment abandonment in our setting and because the pathologic response is not systematically recorded in the different centers where patients do their pathology evaluations [6]. McFarland *et al*. evaluated the evolution of pCR across a period in time. They had an overall complete response rate of 26.5%, similar to our findings. However, they described an increase from a pCR rates of 14% to 43% that was significantly associated to the transitioning of targeted therapies and personalized care to the neoadjuvant setting [20].

Moreover, IHC data that could guide targeted neoadjuvant treatment is often available late in treatment or not at all due to financial challenges, limited patient knowledge about breast cancer [6], and scarcity of adapted molecular testing centres [21].

The mortality rate of 26.05% observed by the end of the follow-up period falls between rates reported in U.S. (21%) and Nigerian (25.3%) cohorts [22], although slightly higher than both studies. Our findings regarding event-free survival in good versus poor responders align with recent international and African studies, with good responders showing significantly better median EFS [22] [23].

Importantly, our study did not find a significant independent association between pathologic response and survival outcomes, similar to multiple previous studies [23]. A recent meta-analysis cautioned against the reliability of pathological complete response (pCR) as a surrogate marker for long-term patient outcomes in breast cancer, demonstrating its limitations at the trial level [24]. The findings suggest that pCR should not be relied upon as a definitive predictor of long-term outcomes across all breast cancer subtypes [24].

However, this study found that using anthracycline (AC) plus taxane chemotherapy was independently associated with longer event-free survival and overall survival in breast cancer patients. The independent association between AC plus taxane regimen and improved survival must be interpreted cautiously. Patients who completed the full sequential regimen may have had better baseline performance status, fewer comorbidities, or improved financial capacity to afford complete treatment. Although multivariate analysis adjusted for major clinicopathologic variables, residual confounding cannot be excluded. The retrospective de-

sign did not allow full assessment of treatment adherence versus treatment intention [25].

5. Limitations

The retrospective nature of our study limited control over the accuracy of recorded information, resulting in incomplete medical records and missing vital information. Despite these limitations, this study provides the first comprehensive data on overall pathological response to NACT and survival outcomes in our context.

The median follow-up duration of 27 months limits the interpretation of overall survival outcomes, as breast cancer-specific mortality often occurs beyond 5 years. Longer follow-up is required to draw definitive conclusions regarding long-term survival patterns.

6. Conclusions

This retrospective cohort study reveals that while good responders had significantly better event-free survival, pathologic response to NACT was not independently associated with event-free survival or overall survival. The findings emphasize the complexity of breast cancer treatment outcomes, highlighting the need for personalized approaches and continued research.

The study reveals that pathologic response to NACT may not reliably predict survival outcomes, suggesting that relying solely on pathologic complete response may not accurately predict treatment efficacy or patient prognosis. Instead, the use of AC plus taxane emerged as being independently associated with longer survival duration, supporting the use of complete neoadjuvant chemotherapy protocols.

This study provides valuable insights into the effectiveness of NACT in treating breast cancer patients in Yaounde, contributing to the growing body of evidence highlighting the complexities of breast cancer treatment outcomes in sub-Saharan Africa. The findings draw attention to the need for continued research, personalized treatment approaches, and tailored interventions to address the unique challenges faced by breast cancer patients in Cameroon.

The high proportion of triple-negative breast cancer underscores the need for targeted therapies and intensified research efforts to address the unique challenges faced by patients with aggressive breast cancer subtypes. Furthermore, the advanced disease presentation in the Cameroonian population highlights the need for improved early detection strategies, access to care, and culturally tailored interventions.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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List of Abbreviations Used

Abbreviation	Full Term
AC	Doxorubicin plus Cyclophosphamide
AJCC	American Joint Committee on Cancer
EFS	Event-Free Survival
HER2+	Human Epidermal Growth Factor Receptor 2 Positive
NACT	Neoadjuvant Chemotherapy
OPR	Objective Pathologic Response
OS	Overall Survival
pCR	Pathological Complete Response
RECIST	Response Evaluation Criteria in Solid Tumours
YCH	Yaounde Central Hospital
YGH	Yaounde General Hospital