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# Lymph node response after neoadjuvant chemotherapy and correlation with relapse free survival in breast cancer at Yaoundé General Hospital

## Réponse ganglionnaire après chimiothérapie néo-adjuvante et corrélation avec la survie sans rechute dans le cancer du sein à l'Hôpital Général de Yaoundé

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**Article original**

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**Mots clés :** Cancer du sein, Chimiothérapie néo - adjuvante, Réponse ganglionnaire, Survie sans rechute, Cameroun.

## ABSTRACT

**Background:** Breast cancer is the first cancer all sexes considered, in Cameroon. Neoadjuvant chemotherapy is the recommended treatment strategy in patients presenting with node positive breast cancer. Axillary lymph node involvement is the most important prognostic factor in breast cancer. Pathological lymph node response was found to be a prognostic factor for relapse-free survival. In this study we evaluated the impact of lymph node response after neoadjuvant chemotherapy and its relationship to relapse free survival (RFS) in our oncologic unit.
**Method:** We carried out a cross-sectional study with retrospective data collection from January 2013 to December 2019. In our study, records of patients with histologically and cytologically confirmed breast cancer started on NACT, and whose anatomopathological reports of the surgical specimen were found and exploitable for an analysis of the therapeutic response were included.
**Results:** A total of 67 patients were recruited: 66 (98.5%) female and 1(1.5%) male. The peak frequency was noted in the age group 50 to 65 years. The most used protocol was FAC50 (43.28%). 55.2% of patients presented with axillary lymph nodes with breast nodules being the most common sign found (97.1%). More than half of the patients (59.71%) presented with at least a clinical N1 according to TNM staging system. In patients who had a total therapeutic effect or a 50% effect or more, we obtained a median of 36.27 months [95%CI: 30.26-42.27] of RFS. In contrast, we had a median of 19.08 months [95% CI: 5.65-32.52] for patients with less than 50% lymph node response (p=0.016).
**Conclusion:** Lymph node response after NACT is a potential marker for RFS and a potential marker for disease overall survival.

## RESUME

**Introduction :** Le cancer du sein est le premier cancer au Cameroun. La chimiothérapie néo-adjuvante est la stratégie de traitement recommandée chez les patientes présentant un cancer du sein à ganglions positifs. Le but de l'étude était d'évaluer l'impact de la réponse ganglionnaire après une chimiothérapie néo-adjuvante et sa relation avec la survie sans rechute.
**Méthode :** Il s'agissait d'une étude transversale avec recueil de données rétrospectives de janvier 2013 à décembre 2019. Etaient inclus les dossiers des patientes atteintes d'un cancer du sein confirmé histologiquement et cytologiquement débutant une chimiothérapie néo-adjuvante et dont les rapports anatomopathologiques de la pièce opératoire étaient retrouvés et exploitables.
**Résultats :** Au total, 67 patients étaient recrutés : 66 femmes (98,5 %) et 1 homme (1,5 %). Le pic de fréquence était la tranche d'âge de 50 à 65 ans. Le protocole le plus utilisé était le FAC50 (43,28%). Les ganglions lymphatiques axillaires étaient présents (55,2 %). Les nodules mammaires étant le signe le plus fréquent (97,1 %). Plus de la moitié des patientes (59,71 %) présentaient au moins un stade clinique N1 selon le système de stadification TNM. Chez les patients qui ont eu un effet thérapeutique total ou un effet de 50 % ou plus, une médiane de 36,27 mois [IC 95 % : 30,26-42,27] de survie sans récidive était obtenue. En revanche, une médiane de 19,08 mois [IC 95 % : 5,65-32,52] était obtenue pour les patients ayant eu une réponse ganglionnaire inférieure à 50 % (p=0,016).
**Conclusion :** La réponse ganglionnaire après une chimiothérapie néo-adjuvante est un marqueur potentiel de la survie sans rechute.





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## Introduction

Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world.[1] The most commonly diagnosed cancer in the world is breast cancer all sexes considered, with GLOBOCAN statistics showing an incidence of 2 261 419 (11.7%) in 2020.[2] and the same trend is seen in Africa with breast cancer being the leading malignancy in African females.[3] Although more than half of all new cases of breast cancer are diagnosed in the industrialized world (North America excluding Mexico and Western Europe), more than three quarters of breast cancer related deaths occur in the developing countries.[4]

Up to 80% of women with breast cancer in Sub-Saharan Africa (SSA) are diagnosed with late stage (stage III or IV) disease, compared with 15% of women in high-income countries.[5] This situation is reflected in breast cancer 5-year survival outcomes, which are 40–60% in low and medium income counties (LMICs) versus 84% in North America.[6] Most patients present with at least nodal involvement or locally advanced disease in Africa hence the need for neoadjuvant chemotherapy (NACT) to be considered not only to downstage disease, improve operability, but also to evaluate chemotherapy responsiveness. There is now sufficient evidence that if neoadjuvant chemotherapy leads to complete pathologic response, the patient will enjoy a better outcome.

Therefore, assessment of the degree of response to neoadjuvant chemotherapy has a major impact on patient selection and the follow-up management of each patient and defines patient outcome.[7] Axillary lymph node involvement is the most important prognostic factor in breast cancer and pathological lymph node response was found to be a prognostic factor for relapse-free survival.[8] We therefore carried out a study to evaluate the impact of lymph node response after neoadjuvant chemotherapy and its relationship to relapse free survival (RFS) in our oncologic unit.

## Methodology

We carried out a cross-sectional study with retrospective data collection at the Yaoundé General Hospital (YGH) and more precisely in the medical oncology department. The choice was justified by the fact that it is a specialized and reference service in the management of cancerous pathologies. Our recruitment concerned patients with breast cancer diagnosed and put on NACT between January 2013 and December 2019. Our target population was breast cancer patients requiring NACT and who have undergone surgery. Included in the study were records of patients with histologically and cytologically confirmed breast cancer, records of patients put on NACT between January 2013 and December 2019, records of patients with an indication for NACT and patients whose anatomopathological reports of the surgical specimen were found and exploitable for an analysis of the therapeutic response. Patients with a contraindication to NACT were excluded from the study. We used consecutive and non-probability sampling. Patients were identified using registries. Records containing a pathology report were considered, pathologic report with no indication of the pathologic response was excluded to the analysis.

We performed an exhaustive sampling with systematic inclusion of all patients meeting the inclusion criteria. Studied variable where the date of diagnosis, as recorded in the pathologic report of the diagnostic biopsy. We also recorded the clinical features of the breast cancer, the date and type of chemotherapy regimen and the date of surgery. Response evaluation was done by a pathologic analysis of the surgery specimen, using Sataloff criteria. Patient with a therapeutic effect upper than 50% were considered “node responders” (NODR) other was “no node responder” (NO NODR).

Data were collected and analyzed with Microsoft Excel software. Qualitative data were represented in frequency and proportions. Survival curve was determined by the Kaplan Meier method and the comparison of survival curve by the Log Rank test. A p-value < 0.05 was considered statistically significant.

## Results

We collected 190 cases but only 67 files were exploitable. Of those 67 cases, 66 (98.5%) were female and there was 1 male patient. Peak age at presentation was between 50 – 65 years with a mean age of 46.32 ± 12.48. Most of our sample size had at least a secondary level education (41.79% of the 67 cases), 41.79% were married, and mostly housewives (71.64% of the 67 cases). Stage $T_3$ (35.82% of the 67 cases) was the most represented and the majority of our study population was classified $N_1$ (59.71% of the 67 cases) as seen on **table I and II.**



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**Table I:** Population distribution according to TNM classification (classification T)

| | Frequency | Percentage |
|---|---|---|
| **T1** | 3 | 4.48% |
| **T2** | 20 | 29.85% |
| **T3** | 24 | 35.82% |
| **T4** | 20 | 29.85% |
| **Total** | 67 | 100.00% |

52.3 % of the 67 cases, presented at a stage III AJCC. Most of the patients had a clinical lymph node invasion, according to **table II**, the total frequency of patients with at least one lymph node involvement is 59,7% of the 67 cases.

The most frequently chemotherapy regimen used was FAC 50 (5-Fluorouracil, Adriblastine and Cyclophos-phamide) with 43,28% of the 67 cases. The distribution of chemotherapy regimens is given on **table III**.

**Table II:** Population distribution according to TNM classification (classification N)

| | Frequency | Percentage |
|---|---|---|
| **N0** | 27 | 40.30% |
| **N1** | 22 | 32.83% |
| **N2** | 15 | 22.39% |
| **N3** | 3 | 04.48% |
| **Total** | 67 | 100.00% |

**Table III:** Regimen used according to frequency

| | Frequency | Percentage |
|---|---|---|
| **FAC 50** | 29 | 43.28% |
| **AC-TXT** | 19 | 28.36% |
| **AC 60** | 12 | 17.91% |
| **AC-TXL** | 7 | 10.45% |
| **Total** | 67 | Regimen |

***FAC :*** *5 Fluorouracile-Doxorubicine-Cyclophosphamide;*
***AC-TXT :*** *Doxorubicine-Cyclophosphamide then Docetaxel;*
***AC-TXL :*** *Doxorubicine-Cyclophosphamide then Paclitaxel*

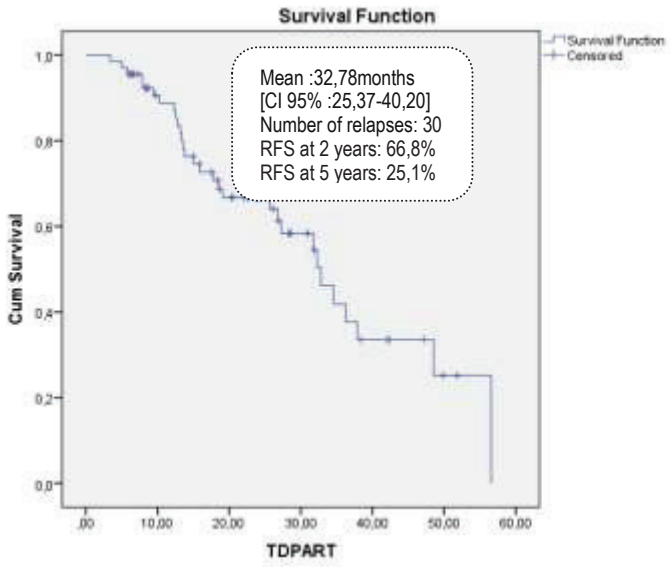


**Figure 1:** Relapse-free survival curve for the Overall population

The complete pathological response in our population was 8.96 %. Relapse free survival (RFS) was 66.8% at 2 years and 25.1 % at 5 years (figure 1). In patients who had a nodal pathological response (NODR), the RFS at 2 years was 81.8% versus 45,4% in patients with no nodal pathologic response (NO NODR) *(p=0.016*) (figure 2).

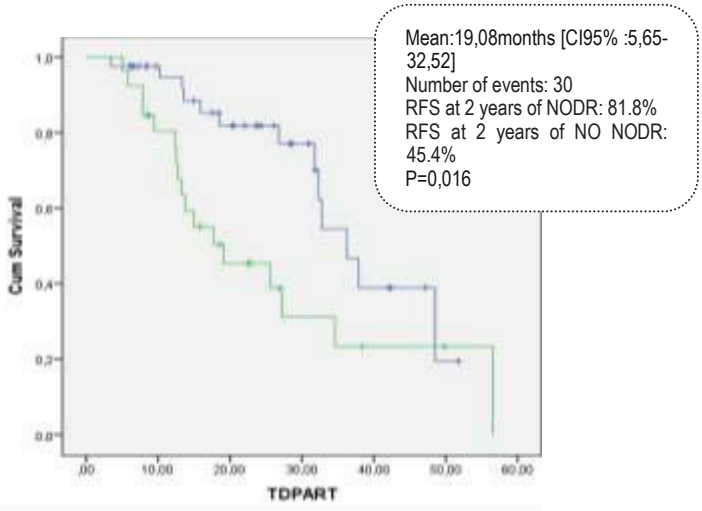


**Figure 2**: Relapse free survival curve according to lymph node response in the overall population

In our study, most patients were female, and this can be explained by the fact that, less than 1% of all breast cancers occur in men.9 the mean age at presentation was 46.32 ± 12.48. Our result was comparable to a study done in Ibadan Nigeria on the characteristics and determinants of patient's



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discontinuation of breast cancer follow-up care where a mean age of 47.7 years was obtained.10 Hence in relationship with studies that show that breast cancer occurs in younger African women.

Stage at diagnosis is a major determinant of survival from breast cancer with early-stage disease being associated with a better prognosis than late-stage disease.11,12,13 In our study, most patients presented with at least a locally advanced breast cancer (nodal involvement). This is like a study done by Olaogun GJ et al in Ekiti Nigeria where 74.4% of their sample size presented at locally advanced stages.14 Neoadjuvant chemotherapy is increasingly used in breast cancer, especially for downstaging the primary tumour in the breast and the metastatic axillary lymph node. Furthermore, pathologic complete response is a validated and valuable surrogate prognostic factor of survival after therapy.15 The majority of the patients in our study sample (43.28%) received FAC 50 as first line treatment. This contrasts with a study done by Sandra Esperanza and al. in a Latin American population in which the most frequent regimen used for NACT was Adriblastine, cyclophosphamide and a taxane.16 Complete pathological response (pCR) in our sample size was 8.96%, unlike a study done in Latin America and India with a pCR of 15.2% and 16.2% respectively.[16,17] This may be due to a difference in molecular subtypes and their frequency in the different regions. These molecular subtypes respond differently to chemotherapy.

In our population, the relapse free survival period after NACT had a median of 32.78 months [95% CI: 25.37-40.2]. Response to chemotherapy is a major prognostic factor particularly the nodal response. The impact of lymph node response after NACT, was a median of 36.27 months [CI95%: 30.26-42.27] for patients who had a total therapeutic effect and greater than or equal to 50% (NODR). While patients with less than 50% therapeutic effect (NO NODR) had a median of 19.08 months [CI95%: 5.65-32.52 p = 0.016]. these results corroborate those of Hennesy and al who showed better relapse free survival but with a complete pathological response (pCR) of the axillary lymph nodes.[18]

Our study provides a broader view of patients with lymph node response. the results obtained in this work could indicate a prognostic impact of a therapeutic response, whether partial or complete. A prospective, larger trial is needed to demonstrate this hypothesis. The main limitation was the retrospective nature of our sampling. It had the effect of restricting the size of the sample as well as exposing itself to classification biases. To lower the impact of those limits, we excluded the missing data from analysis.

## Conclusion

Lymph node response after NACT is a potential biomarker for RFS and for disease overall survival. Further studies are needed to demonstrate this hypothesis.

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### Author's contribution

Atenguena OE **designed the study.** Penda Nded, Atenguena OE, Glenda Nkeng and Ebenda OA **collected and analysed data.** Atenguena OE, Glenda Nkeng and Ebenda OA **drafted the manuscript.** Atenguena OE, Mapenya R, Tabola FL, Douanla MP, Montheu EL, Hadidja Garba and Nsangou Moun AN **revised the manuscript.** Ndom P, Meka JE and Atenguena OE **rigorously revised the manuscript.** All authors **have read and approved the final manuscript.**

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