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DEPARTEMENT OF INTERNAL MEDICINE AND SPECIALTIES

DEPARTEMENT DE MEDECINE INTERNE ET SPECIALITES

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

Dissertation submitted in partial fulfilment of the requirements for the award of a Specialist Diploma in Medical Oncology by:

KENN CHI NDI

Matricule: 12M063

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Academic year 2023-2024

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DEDICATION

This piece of work is dedicated to my wife Venessa, and our two children, Talia and Keren. To my devoted parents and thoughtful siblings

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ABSTRACT

Introduction: The rising incidence of breast cancer is a concern globally and 70 % present at advanced stages in Cameroon. Neoadjuvant chemotherapy (NACT) offers 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 from 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). Although a potential inverse relationship between pathologic response and a positive surgical margin status and higher histological grade seemed to be suggested, the 95 % confidence intervals included 1, indicating no statistically significant association. 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 independently 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.

Key words: breast cancer, survival, pathologic response Yaounde

RESUME

Introduction : L'incidence croissante du cancer du sein est une préoccupation mondiale, et 70 % des patientes camerounaises présentent des stades avancés. La chimiothérapie néoadjuvante (NACT) offre des bénéfices cliniques, et la réponse pathologique objective (RPO) à la NACT pourrait être un marqueur substitut de survie pour certains sous-types de cancer du sein. Cependant, la valeur pronostique de la RPO est inconnue au Cameroun. Nous avons donc cherché à étudier la relation entre la réponse pathologique à la NACT et les issues de survie chez les patientes atteintes de cancer du sein à Yaoundé.

Méthodologie : Cette étude de cohorte historique (janvier 2019-décembre 2023) a inclus des patientes atteintes de cancer du sein non métastatique des hôpitaux général et central de Yaoundé ayant subi une évaluation pathologique post-NACT. L'analyse bivariée et la régression logistique ont permis d'identifier les facteurs associés à la RPO. Les méthodes de Kaplan-Meier et le test de log-rank ont comparé la survie sans événement (SSE) et la survie globale (SG). L'analyse de régression de Cox et le test de ratio de vraisemblance ont évalué l'association entre la réponse pathologique et les issues de survie.

Résultats : Cette étude a inclus 119 participantes féminines. Le cancer du sein triple négatif était le sous-type le plus courant (42,31 %), et la combinaison Doxorubicine/Cyclophosphamide plus taxane (AC+taxane) était le protocole NACT le plus fréquemment utilisé (53,78 %). Les bonnes répondeuses (réponse complète ou > 50 % de réponse partielle) représentaient 25,21 % de la cohorte, avec une SSE significativement meilleure comparée aux mauvaises répondeuses (41,91 ± 2,43 contre 19,86 ± 5,26 mois, p = 0,01). Bien qu'une relation inverse potentielle entre la réponse pathologique et un statut de marge chirurgicale positive et un grade histologique élevé ait été suggérée, les intervalles de confiance à 95 % incluaient 1, indiquant aucune association statistiquement significative. La réponse pathologique à la NACT n'était pas significativement associée à la SSE (p = 0,79) ou à la SG (p = 0,37). Cependant, l'utilisation du protocole AC+taxane était indépendamment associée à une SSE plus longue (HR : 0,23, p = 0,01) et à une SG plus longue (HR : 0,10, p = 0,00).

Conclusion : Cette étude révèle que la réponse pathologique à la NACT n'est pas indépendamment associée aux issues de survie. En revanche, l'utilisation d'un protocole NACT complet par AC+taxane est émergée comme étant indépendamment associée aux issues de survie, informant les décisions thérapeutiques et améliorant potentiellement les issues des patientes.

Mots-clés : cancer du sein, marqueur substitut, survie, réponse pathologique, Yaoundé, Cameroun.

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LIST OF ABBREVIATIONS AND ACRONYMS

AJCC	American Joint Committee on Cancer
BRCA1	Breast Cancer Gene 1
BRCA2	Breast Cancer Gene 2
CR	Complete Response
DCIS	Ductal Carcinoma In Situ
DFS	Disease-Free Survival
EFS	Event-Free Survival
HER2+	Human Epidermal Growth Factor Receptor 2 Positive
IBC	Inflammatory Breast Cancer
IBCs	Inflammatory Breast Cancers
IDC	Invasive Ductal Carcinoma
ILC	Invasive Lobular Carcinoma
MRI	Magnetic Resonance Imaging
NACT	Neoadjuvant Chemotherapy
OPR	Objective pathologic response
ORR	Objective Response Rate
OS	Overall Survival
pCR	Pathological Complete Response
PD	Progressive Disease
PR	Partial Response
RECIST	Response evaluation criteria in solid tumours
SCLNs	Supraclavicular Lymph Nodes
SD	Stable Disease
YCH	Yaounde Central Hospital
YGH	Yaounde General Hospital

CHAPTER I: INTRODUCTION

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I.1 BACKGROUND AND PROBLEM STATEMENT

Breast cancer is the commonest cancer globally, with 2.3 million new cases and 665,000 deaths 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 [1,2]. 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 [3], more aggressive subtypes, and notably higher mortality rates [4–6].

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 [7]. Some Cameroonian studies have revealed that over 70% of breast cancer patients presented with locally advanced and metastatic disease (stages 3 and 4) [8–10].

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 [11]. 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 [12]. 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 [13]. The impact of lymph node OPR on survival has been shown in Cameroon [10]; 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 [14]. 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. This study will likewise add to the global body of knowledge on NACT effectiveness across different populations and cancer subtypes.

I.2 RESEARCH QUESTION

What is the pathologic response to neoadjuvant chemotherapy and survival outcomes amongst breast cancer patients in Yaounde?

I.3 RESEARCH HYPOTHESIS

Null hypothesis (H0): There is no difference in the association between pathologic response to neoadjuvant chemotherapy and overall survival outcomes among breast cancer patients in Yaounde.

Alternative hypothesis (H1): There is a difference in the association between pathologic response to neoadjuvant chemotherapy and overall survival outcomes among breast cancer patients in Yaounde.

I.4 OBJECTIVES

I.4.1 General Objective

To determine whether there is an association between pathologic response to neoadjuvant chemotherapy and survival outcomes in breast cancer patients in Yaounde, Cameroon

I.4.2 Specific Objectives

1. To determine the distribution of therapeutic responses to neoadjuvant chemotherapy in breast cancer patients
2. To investigate the factors associated to the therapeutic response
3. To assess overall survival and event-free survival rates in the study population
4. To analyse the relationship between therapeutic response categories to NACT and survival outcomes

I.5 DEFINITION OF OPERATIONAL TERMS

Locally advanced breast cancer was defined as T3 tumours (>5 cm), with or without skin or chest wall involvement, alone or together, inflammatory breast cancers (IBCs), matted ipsilateral and/or

fixed axillary lymph nodes, ipsilateral supraclavicular lymph nodes (SCLNs), and/or internal mammary lymph nodes without distant metastases according to the eighth edition of the American Joint Committee on Cancer (AJCC) cancer staging manual [7].

Neoadjuvant chemotherapy (NACT) is a type of cancer treatment that involves administering chemotherapy before the main treatment, usually surgery. It usually reduce the size of a tumour or cancer cells, making it easier to remove surgically, reducing the risk of cancer cells spreading to other parts of the body, and improves treatment outcomes and survival rates [15].

Objective Response Rate (ORR) is a metric used to quantify the effectiveness of a given treatment in reducing tumour size in patients with solid tumour malignancies, representing the percentage of patients who experience either a partial or complete reduction in tumour burden following therapy. ORR serves as a valuable indicator of a treatment's capacity to combat tumour growth, and over time, researchers and clinicians have developed and employed various criteria to evaluate and determine ORR in clinical settings [16].

There is no consensus definition of ***objective pathologic response (OPR)*** across several studies [17]. Similar to other previous studies that had similar designs and settings to ours [10,18], OPR in the present study was defined as a significant reduction in tumour size, typically defined as a pCR or PR > 50%. That is, those who had an association of a TA/TB and NA/NB Sataloff classification [19].

Therapeutic response is defined as the change in tumour size and characteristics following neoadjuvant chemotherapy, categorized as follows: complete response (CR), where there is no detectable residual tumour; partial response (PR), with a ≥ 30 % reduction in tumour size; stable disease (SD), with < 30 % reduction or < 20 % increase in tumour size; and progressive disease (PD), with a ≥ 20 % increase in tumour size or if there are new lesions [20].

Overall survival (OS) can be defined as a probability function, specifically a survival function, which represents the probability of a patient surviving beyond a certain point in time, while ***event-free survival*** (EFS) the probability of a patient not experiencing disease progression, disease recurrence, or death up to a certain point in time [21].

Good responders to breast cancer NACT in the current study were defined as patients who achieve a significant reduction in tumour size, typically defined as a pCR or PR > 50% (OPR). ***Poor***

responders, on the other hand, were defined as patients who exhibit little to no reduction in tumour size, typically defined as a PR < 50 % and no response (no OPR) [16,20].

CHAPTER II: LITERATURE REVIEW

CHAPTER II: LITERATURE REVIEW

II.1 KNOWLEDGE RECALL

II.1.1 INTRODUCTION

Breast cancer is a complex and multifaceted disease that affects millions of individuals worldwide, making it one of the most prevalent and devastating cancers globally. Accounting for approximately 15% of all cancer-related deaths, breast cancer claims the lives of hundreds of thousands of people annually, with an estimated 2.3 million new cases diagnosed worldwide each year [1,22].

Despite advancements in medical research and treatment options, breast cancer remains a leading cause of cancer-related mortality among women, with a staggering one in eight women expected to develop the disease in their lifetime. The impact of breast cancer extends beyond the individual, affecting families, communities, and societies as a whole [23].

II.1.2 GENERALITIES

Breast cancer is not a single disease, but rather a heterogeneous group of diseases characterized by distinct molecular subtypes, each with unique biological features and clinical behaviours. The most common types of breast cancer include ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and inflammatory breast cancer (IBC) [22,23].

The aetiology of breast cancer is multifactorial, involving a complex interplay between genetic, environmental, and lifestyle factors. Established risk factors include family history, BRCA1 and BRCA2 mutations, radiation exposure, hormone replacement therapy, and obesity [23].

Fortunately, advances in screening, diagnosis, and treatment have improved breast cancer outcomes significantly. Early detection through mammography, ultrasound, and magnetic resonance imaging (MRI) has increased survival rates, while targeted therapies, immunotherapies, and precision medicine have revolutionized treatment approaches [24].

II.1.2.1 DEFINITION

Breast cancer is a malignant neoplasm that originates in the breast tissue, typically in the ducts or lobules, and is characterized by the uncontrolled growth and proliferation of abnormal cells. It is a heterogeneous group of diseases, encompassing various histological and molecular subtypes, each with distinct biological features and clinical behaviours [23]. Breast cancer can arise in different cell types, including epithelial, stromal, and hematopoietic cells, and can manifest as non-invasive (in situ) or invasive (infiltrating) disease. The invasive form can further spread to surrounding tissues and distant organs, such as lymph nodes, bones, liver, and lungs, through lymphatic or haematogenous dissemination. Breast cancer is often classified into several subtypes based on molecular characteristics, including hormone receptor-positive (oestrogen and/or progesterone receptor-positive), human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative breast cancer, each with different treatment approaches and prognostic implications [25].

The breast consists of 15-20 glandular lobes, each draining into the nipple, surrounded by fibrous connective tissue and adipose tissue (Figure 1, [26]). This complex anatomy supports the breast's primary function of milk production and secretion. The axillary lymph nodes, located in the axillary fat pad between the pectoralis minor and latissimus dorsi muscles, play a crucial role in lymphatic drainage. There are 20-30 nodes, divided into three levels: Level 1 (lateral to pectoralis minor), Level 2 (posterior to pectoralis minor), and Level 3 (medial to pectoralis minor), and grouped into anterior (pectoral), posterior (subscapular), lateral, central, and apical categories. The breast lymphatic vessels primarily drain into axillary lymph nodes (70-80%), with the remaining drainage occurring through parasternal lymph nodes (10-20%) and infraclavicular lymph nodes (5-10%) [26–28].

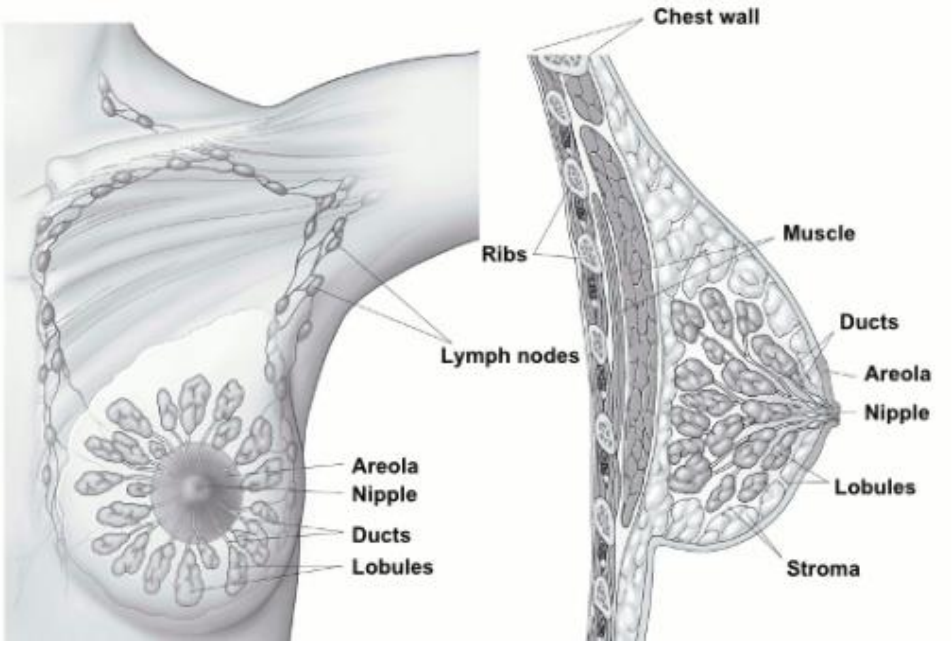

Figure 1: a brief review of breast anatomy

II.1.2.2 RELEVANCE

Studying breast cancer is crucial due to its significant impact on global health, economic burden, and societal implications. As the most common cancer affecting women worldwide, breast cancer accounts for approximately 15% of all cancer-related deaths, with an estimated 2.3 million new cases diagnosed annually. Understanding the complex biology, molecular mechanisms, and clinical behaviours of breast cancer is essential to improve early detection, diagnosis, and treatment outcomes. Moreover, breast cancer research has far-reaching implications for developing effective prevention strategies, targeted therapies, and personalized medicine approaches. By investigating breast cancer, scientists can also gain insights into the underlying causes of cancer development and progression, ultimately informing strategies for other types of cancer. Furthermore, advancements in breast cancer research have already led to improved survival rates, reduced mortality, and enhanced quality of life for patients. Continued research efforts are vital to address the remaining challenges, disparities, and unmet needs in breast cancer management, ultimately aiming to reduce the burden of this devastating disease on individuals, families, and communities worldwide.

II.1.3 EPIDEMIOLOGY

II.1.3.1 DESCRIPTIVE EPIDEMIOLOGY

In 2022, female breast cancer was the second most common type of cancer globally, accounting for 11.6% of all cancer cases, with approximately 2.3 million new cases diagnosed. It was also the fourth leading cause of cancer-related deaths worldwide, resulting in 666,000 fatalities, which represents 6.9% of all cancer deaths [1]. Breast cancer was the most frequently diagnosed cancer among women, and it was the leading cause of cancer deaths globally and in 157 countries and 112 countries, respectively. Globally, breast cancer accounted for nearly one-quarter of cancer cases and one-sixth of cancer deaths in women [1,23]. The highest incidence rates were observed in France, Australia/New Zealand, Northern America, and Northern Europe, where rates were four times higher than in South-Central Asia and Middle Africa. Notably, women in transitioned countries had higher incidence rates (54.1 per 100,000) compared to those in transitioning countries (30.8 per 100,000), but lower mortality rates (11.3 vs. 15.3 per 100,000, respectively). The highest mortality rates were found in Melanesia, with Fiji having the world's highest mortality rate, followed by Western Africa and Micronesia/Polynesia [1].

II.1.3.1 ANALYTICAL EPIDEMIOLOGY

The higher incidence of breast cancer in transitioned countries compared to transitioning countries is attributed to a higher prevalence of various reproductive and lifestyle risk factors, including early menarche, late menopause, delayed first birth, fewer children, less breastfeeding, hormone replacement therapy, oral contraceptives, alcohol consumption, excess body weight, and physical inactivity [4,29]. These factors, along with increased detection through mammographic screening, have driven the rising trends in breast cancer incidence over time. In high-income regions, such as Northern America, Oceania, and Europe, incidence rates rose uniformly from 1980 to 2000, followed by stable or declining trends in the early 2000s, linked to reduced hormone replacement therapy use and plateauing screening participation [1]. However, since 2007, some high-income countries have reported rising incidence rates for premenopausal and postmenopausal breast cancer. In contrast, mortality rates have decreased in many high-income countries since the early 1990s, reflecting improvements in treatment and early detection [1].

The unambiguous cause of carcinogenesis has not yet been established, but several risk factors conducive to the development of breast cancer are known. One of the most important, as also indicated by the epidemiological data described above, are the gender, age, and degree of economic development of a given country. No less important are hormonal factors, mainly related to the time of exposure to oestrogens, procreative factors, including the number of children born, the age of birth of the first child, or breastfeeding. Great importance in the development of breast cancer is attributed to genetic factors, the use of hormone replacement therapy, improper diet, and the resulting obesity. Among the significant risk factors for the development of breast cancer, hormonal contraception, alcohol consumption and exposure to ionizing radiation at a young age are also mentioned [30].

II.1.4 AETIOLOGY

The aetiology of breast cancer is attributed to a complex interaction between various modifiable and non-modifiable factors. This aetiology is determined by genetics, environmental, nutritional, hormonal, and heritable elements that contribute to the development of this disease. Risk factors include prior history of breast cancer, positive family history, obesity, tall stature, smoking, alcohol consumption, early menarche, late menopause, sedentary lifestyle, nulliparity and hormone replacement therapy. Factors associated with decreased risk of breast cancer include multiparity, history of breastfeeding, physical activity, weight loss, and prophylactic surgical and medical interventions. In the United States, approximately one in eight women will be diagnosed with breast cancer in her lifetime. This disease is more common in white, post-menopausal females. Risk increases with older age with about 80% of breast cancer patients being older than 50 years. Analysing the aetiology of breast cancer allows for the development of improved screening and treatment interventions [31]. The aetiology of breast cancer is multi-factorial, and several factors have been implicated, which may act independently or in combination, especially in high risk individuals. It is important to understand the aetio-pathogenesis of this common disease, which is associated with high morbidity and mortality, especially if not detected early. Furthermore, TNBC poses special diagnostic, treatment and prognostic challenges, because of the absence of the commonly identified receptors, as well as associated poor survival in this group of patients [32].

II.1.6 PATHOMORPHOLOGY AND MOLECULAR PATHOLOGY

Breast cancer originates in the epithelial cells lining the ducts and lobules of the breast, with the majority (80-90%) being carcinomas derived from epithelial cells. The main types of breast cancer include Ductal Carcinoma In Situ (DCIS), a non-invasive cancer confined to the ducts, and invasive cancers such as Invasive Ductal Carcinoma (IDC) and Invasive Lobular Carcinoma (ILC), which invade surrounding tissue. Less common types include Medullary Carcinoma, Tubular Carcinoma, Mucinous Carcinoma, Papillary Carcinoma, and Inflammatory Breast Cancer (IBC), an aggressive cancer with skin inflammation.

Molecularly, breast cancer is a heterogeneous disease characterized by distinct subtypes, including Luminal A, Luminal B, HER2-enriched, Basal-like (Triple-Negative), and Claudin-low. Genetic alterations such as BRCA1 and BRCA2 mutations increase the risk of breast and ovarian cancer, while TP53 mutations and PIK3CA mutations activate the phosphatidylinositol 3-kinase (PI3K) pathway. HER2 amplification and ESR1 mutations also contribute to breast cancer development. Epigenetic alterations, including DNA methylation, histone modification, and microRNA dysregulation, further influence gene expression.

Key signalling pathways involved in breast cancer include the PI3K/AKT pathway, promoting cell survival and proliferation, the MAPK/ERK pathway, regulating cell proliferation and differentiation, and the oestrogen receptor pathway, driving hormone-dependent growth. HER2 signalling also plays a crucial role in cell proliferation and survival. Biomarkers such as ER, PR, and HER2 status, Ki-67 proliferation index, p53 protein expression, and BRCA1 and BRCA2 mutation status guide targeted therapies and personalized medicine approaches.

Breast cancer progression is influenced by various molecular mechanisms, including angiogenesis, invasion, and metastasis. Tumour microenvironment factors, including immune cells, fibroblasts, and extracellular matrix components, also contribute to disease progression. Understanding these complex pathological and molecular pathological features enables the development of effective treatment strategies and improved patient outcomes.

II.1.7 IMMUNOHISTOCHEMISTRY SUBTYPES

Routinely determined elements of the pathomorphological examination seem insufficient to predict the clinical course of breast cancer, which makes it difficult to make appropriate therapeutic decisions. The diverse clinical course of cancers with similar morphological characteristics is due to their different gene profile [22].

The study of gene expression allowed the identification of five molecular subtypes of breast cancer, such as: luminal A, luminal B, HER-2 positive non-"luminal", basal-like and special histological types. These surrogates correspond to the immunophenotypes of cancer cells determined according to pathological criteria [33].

The luminal type A is characterized by high expression of genes associated with the activity of oestrogen receptors and at the same time low expression of genes associated with proliferation and genes associated with expressed by the HER2 receptor [34].

Luminal type B is characterized by a positive ER status associated with low expression of genes associated with this receptor and higher than in type A expression of genes associated with the assessed proliferation by marking Ki-67 [33]. A panel of panellists in St. Gallen recognized the meltdown and expression of the Ki-67 as factors that could be used to differentiate between tumours of luminal type A and subtype B. This is important in the prognostic assessment, which is better in type A [33].

The next type is basal-like breast carcinoma, also called triple negative cancer due to the absence of oestrogen and progesterone receptors and the lack of expression of the HER2 receptor- consequently, there is no expression of genes associated with these receptors. The group of patients with this type of cancer with metastases to the cerebellum is particularly interesting, in their case the use of biological markers (CK 5/6, HER1, c-KIT) can help in the restoration of the basal subtype similar and dissimilar, nevertheless, their clinical usefulness is ambiguous [34].

The molecular subtype of breast cancer HER2- positive is characterized by overexpression of *HER2* combined with the absence of ER and PR [34].

Breast cancer is the most common cancer in women. Every year, the results of many clinical trials are published, only some of which cause a change in the standard of conduct. Treatment rules for patients with early breast cancer are updated every two years as part of a consensus set by experts

St. Gallen International Breast Cancer Conference. Similarly, the European Society for Medical Oncology (ESMO) is developing its recommendations for the treatment of patients with breast cancer at an early stage. Recent Recommendations from St. Gallen (2019) highlight the progress that has been made, particularly in the management of HER2-positive and triple-negative breast cancers with residual disease after preoperative treatment [33–36].

II.1.7 CLINICAL PRESENTATION

Breast cancer can manifest in various ways, and its clinical presentation can vary depending on the type, location, and stage of the disease. A painless, firm, and non-tender mass or lump in the breast or axilla is the most common symptom, accounting for approximately 80% of breast cancer diagnoses. Changes in breast size or shape, such as uneven breast size, swelling, or shrinkage, may also occur. Skin changes, including dimpling, puckering, or scaliness of the skin overlying the tumour, can be present. Nipple retraction or inversion, where the nipple becomes inverted or retracts into the breast, and spontaneous, unilateral, and bloody nipple discharge are additional symptoms [22].

In some cases, breast cancer presents with inflammatory symptoms, characterized by rapid onset of redness, swelling, warmth, and tenderness, often mistaken for infection. Paget's disease, an eczematous change in the nipple-areolar complex, can also occur, often accompanied by an underlying ductal carcinoma. Metastatic disease symptoms related to distant spread, such as bone pain, respiratory distress, or neurological deficits, may be present. Advanced disease can cause weight loss, fatigue, and general decline, as well as lymphedema, swelling of the arm or hand due to axillary lymph node dissection or radiation, and skin metastases, nodules or ulcers on the skin [23].

Approximately 5-10% of breast cancers are detected through screening mammography in asymptomatic women. However, symptoms such as breast pain, while often benign, persistent or severe pain warrants evaluation. Axillary lymphadenopathy, enlarged or tender lymph nodes, changes in nipple sensation, itching, burning, or numbness, should also be noted. Early recognition of these symptoms and signs is crucial for prompt diagnosis and treatment [22].

II.1.8 TREATMENT

Breast cancer treatment is a complex and multifaceted approach that has evolved significantly over the years. The goal of treatment is to eliminate the cancer, prevent its recurrence, and maintain the best possible quality of life for the patient. Treatment plans are highly individualized, taking into account factors such as the cancer's stage, type, and molecular characteristics, as well as the patient's overall health, age, and personal preferences [23,37].

Surgery remains the primary treatment for most breast cancers. There are two main types of surgery: breast-conserving surgery (also known as lumpectomy or partial mastectomy) and mastectomy. In breast-conserving surgery, only the tumor and some surrounding tissue are removed, preserving most of the breast. This is often followed by radiation therapy to eliminate any remaining cancer cells. Mastectomy involves removing the entire breast and is sometimes recommended for larger tumors or when cancer is found in multiple areas of the breast. In some cases, women may opt for a double mastectomy, removing both breasts, especially if they have a high genetic risk of developing cancer in the other breast [13,38–40].

Reconstruction surgery is an option for many women who undergo mastectomy. This can be done immediately after the mastectomy or at a later date. Reconstruction may use artificial implants or the patient's own tissue from another part of the body, such as the abdomen or back [38,41].

Radiation therapy is a common treatment that uses high-energy rays to kill cancer cells. It's typically used after breast-conserving surgery and sometimes after mastectomy, depending on the cancer's characteristics. External beam radiation is the most common type, delivered from a machine outside the body. Newer techniques like intensity-modulated radiation therapy (IMRT) and proton therapy can target the radiation more precisely, reducing damage to healthy tissue. Brachytherapy, where radioactive material is placed directly into the breast tissue, is sometimes used for early-stage cancers [42,43].

Chemotherapy uses drugs to kill cancer cells throughout the body. It can be given before surgery (neoadjuvant chemotherapy) to shrink tumours, making them easier to remove, or after surgery (adjuvant chemotherapy) to kill any remaining cancer cells. Chemotherapy is often recommended for larger tumours, cancers that have spread to the lymph nodes, or aggressive types of breast cancer. Common chemotherapy drugs include anthracyclines (like doxorubicin), taxanes (like paclitaxel),

and cyclophosphamide. While effective, chemotherapy can have significant side effects, including hair loss, nausea, fatigue, and an increased risk of infections [44–46].

Hormone therapy is a crucial treatment for hormone receptor-positive breast cancers, which make up about 70% of all breast cancers. These cancers have receptors for oestrogen and/or progesterone, which stimulate their growth. Hormone therapy works by either lowering hormone levels or blocking their effects on cancer cells. For premenopausal women, tamoxifen is often used to block oestrogen receptors. Postmenopausal women may be treated with aromatase inhibitors like letrozole or anastrozole, which lower oestrogen levels. In some cases, ovarian suppression (using drugs or surgery to stop the ovaries from producing hormones) may be recommended for premenopausal women [15,47,48].

Targeted therapies are drugs that attack specific features of cancer cells. The most well-known targeted therapy for breast cancer is trastuzumab (Herceptin), used for HER2-positive breast cancers. HER2 is a protein that promotes cancer cell growth, and it's overexpressed in about 20% of breast cancers. Other HER2-targeted drugs include pertuzumab, T-DM1, and neratinib. For certain types of advanced breast cancers, drugs targeting other molecular features, such as CDK4/6 inhibitors (like palbociclib) or PARP inhibitors (like olaparib), have shown promising results [34,36,49–52].

Immunotherapy, which stimulates the body's immune system to fight cancer, is an emerging field in breast cancer treatment. While not yet as widely used as in some other cancers, drugs like atezolizumab and pembrolizumab have shown effectiveness in treating certain types of triple-negative breast cancer, a particularly aggressive form of the disease [35].

Neoadjuvant therapy, or treatment given before surgery, is increasingly used in breast cancer care. This approach can shrink tumours, potentially allowing for less extensive surgery. It also provides valuable information about the cancer's response to treatment, which can guide further treatment decisions [53].

Palliative care, which focuses on managing symptoms and improving quality of life, is an important component of breast cancer treatment, especially for advanced stages. This can include pain management, emotional support, and treatments to alleviate side effects of cancer or its treatments [54].

Clinical trials are ongoing to develop new treatments and improve existing ones. These may include novel targeted therapies, immunotherapies, or combinations of existing treatments. Participating in a clinical trial can give patients access to cutting-edge treatments not yet widely available. The future of breast cancer treatment is moving towards more personalized approaches. Genomic testing of tumours can provide detailed information about a cancer's characteristics, allowing for more tailored treatment plans. This may help some patients avoid unnecessary treatments while ensuring others receive the most effective therapies for their specific type of cancer [55].

Supportive care throughout treatment is crucial. This includes managing side effects, providing nutritional support, and addressing the psychological impact of cancer diagnosis and treatment. Many cancer centres now offer integrative medicine programs that may include acupuncture, massage, meditation, and other complementary therapies to help manage symptoms and improve overall well-being [56].

In conclusion, breast cancer treatment is a rapidly evolving field that combines multiple approaches to provide the best possible outcomes for patients. The choice of treatments depends on many factors, and decisions are made collaboratively between the patient and a multidisciplinary team of healthcare providers. As research continues, we can expect even more effective and personalized treatment options in the future, offering hope to breast cancer patients and their families [36,49,50].

II.2 CURRENT STATE OF KNOWLEDGE ON THE SUBJECT

II.2.1. Introduction

Breast cancer remains a significant global health concern, with increasing incidence in many parts of the world, including Africa. Neoadjuvant chemotherapy (NAC) has emerged as a crucial treatment strategy, particularly for locally advanced or inflammatory breast cancer [1,57]. This section focuses on the current state of knowledge regarding the use of therapeutic response to NAC as a surrogate marker for survival in breast cancer, with special attention to studies in Yaounde and Africa.

II.2.2. Global Studies and Meta-analyses

Recent global studies have provided substantial evidence supporting the relationship between NAC response and survival outcomes

II.2.2.1 Pathological Complete Response and survival outcomes

Cortazar et al. conducted a landmark meta-analysis of 12 international trials involving 11,955 patients. Their findings demonstrated a strong association between pCR and improved event-free survival (EFS) and overall survival (OS). This association was particularly pronounced in aggressive breast cancer subtypes, such as triple-negative breast cancer (TNBC) and HER2-positive tumors [53].

Spring et al. further corroborated these findings in a comprehensive meta-analysis of 52 studies, including 27,895 patients. They confirmed the robust association between pCR and improved long-term outcomes, especially in HER2-positive and triple-negative breast cancers. Their analysis showed that patients achieving pCR had a 69% reduction in the risk of recurrence or death compared to those who did not achieve pCR [58].

However, several large clinical trials have shown that pCR is not a reliable surrogate endpoint of survival despite its association to improved outcomes [53]. This has only been shown in some breast cancer subtypes in some trial-level and patient-level studies [58].

II.2.2.2 Subtype-Specific Outcomes

Masuda et al. focused specifically on TNBC in a Japanese cohort. Their study of 130 patients demonstrated that achieving pCR after NAC was associated with significantly better disease-free survival (DFS) and OS. Patients who achieved pCR had a 3-year DFS rate of 86% compared to 70% in non-pCR patients [59].

II.2.2.3 Residual Cancer Burden as a Prognostic Tool

Symmans et al. introduced and validated the Residual Cancer Burden (RCB) index as a prognostic tool. Their study, involving 5,160 patients from 12 cancer centers, showed that RCB was an independent predictor of distant relapse-free survival (DRFS) across all breast cancer subtypes [60].

II.2.3. African Studies

While research specific to Yaounde is limited, several studies from other African countries have explored this topic, providing valuable insights into the regional context.

II.2.3.1 NACT Use in Sub-Saharan Africa

Vanderpuye et al. reviewed the use of NAC in sub-Saharan Africa, analyzing data from multiple countries. Their review highlighted the effectiveness of NAC in downstaging tumors and improving surgical outcomes. However, they noted significant challenges in delivering optimal NAC regimens due to resource constraints and emphasized the need for more research on long-term survival benefits in African populations [42].

II.2.3.2 Nigerian Study on NAC Response and Survival

Adisa et al. conducted a prospective study of 99 patients with locally advanced breast cancer in Nigeria. They found that both clinical and pathological responses to NAC were significantly associated with improved overall survival. Patients who achieved clinical complete response had a 5-year OS of 81% compared to 46% for non-responders [61].

II.2.4. Yaounde-Specific Research

While direct studies on NAC response and survival outcomes in Yaounde are scarce, some related research has been conducted, providing a foundation for future studies. Ngowa et al. conducted a

retrospective study of 531 breast cancer patients in Yaounde. They found that the majority of patients (95.5%) presented with locally advanced or metastatic disease, underscoring the potential importance of NAC in this population. The study provided valuable baseline data on patient characteristics, treatment patterns, and outcomes, which could inform future research on NAC response and survival [8].

Sando et al. investigated treatment patterns and outcomes of 117 breast cancer patients in Yaounde. They reported that 23.9% of patients received NAC, highlighting its use in the local context. While the study did not specifically address NAC response as a surrogate marker, it provided important insights into the feasibility of NAC use and follow-up in this setting [9].

Mapoko *et al* analysed the determinants of prolonged survival of patients diagnosed with breast cancer at the Yaounde General Hospital. Notably, chemotherapy was identified as a significant factor improving survival. The study's emphasis on early-stage diagnosis and multimodal treatments, including chemotherapy, underscores the importance of effective neoadjuvant strategies [62].

In 2024, Atenguena *et al.* investigated the impact of lymph node response after neoadjuvant chemotherapy and its relationship to relapse free survival in a tertiary hospital in Yaounde, one of the major cancer treatment centres in the country. Patients with a lymph node pCR had a significantly higher disease-free interval compared to those without. They concluded that lymph node pCR could be a potential predictor of disease-free survival [10].

Conclusion

While global evidence strongly supports the use of NAC response as a surrogate marker for survival in breast cancer, more research is needed in the African context, particularly in Yaounde. The unique challenges and characteristics of breast cancer presentation and treatment in this region necessitate targeted studies to validate the applicability of global findings to local populations.

Future studies should focus on long-term follow-up, standardized assessment methods, and consideration of local genetic and environmental factors to establish the validity of this surrogate marker in the local population. Such research has the potential to significantly improve breast cancer management and outcomes in Yaounde and similar settings across Africa.

CHAPTER THREE: METHODOLOGY

CHAPTER III: METHODOLOGY

III.1 STUDY DESIGN

This study employed a historical cohort design to investigate the differences between two patient groups based on their response to treatment. Data from patients who had previously undergone NACT were retrospectively analysed and categorized into two cohorts: good responders and poor responders. Good responders were defined as patients who exhibited an objective pathologic response to the treatment, while poor responders were those who did not show such a response.

III.2 STUDY SITE

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.

The YGH was created in 1987 and is a first category health service in the health Pyramid of Cameroon. The YGH is found in a quarter called Ngousso which is at the north-east of the political capital. The YGH is bordered to the North by 'la pharmacie bleue', and the Mvog Ebanda quarter, to the south by Ngousso Government primary school, to the east by HGOPY and to the west by CHRACERH. The YGH has several health departments which are internal medicine and specialties, gynaecology, surgery and specialties, paediatrics, radiology, intensive care and radiotherapy. The Internal medicine department has several services: infectious diseases, medical oncology, hepato-gastroenterology, cardiology, neurology, endocrinology, rheumatology, dermatology and nephrology. The radiotherapy service has not been functional for several years. The hospital has a capacity of 302 beds.

The oncology unit was created in 1997 and runs services from screening to diagnosis, management, and surveillance. It is the first oncology service in the country and one of the reference centres in Cameroon for the management of cancers. It's comprised of a team of 03medical oncologists, 01 radiation oncologist, 21 residents, a general practitioner, two Majors (conventional hospitalization unit and the day hospital), certified nurses, state registered nurses, nurse aids, auxiliary staff and a secretary. The service is very well structured with a big office shared by the head nurse and the resident doctors, a nurse's station, a kitchen and 08 wards of 03 different categories each with a restroom. There are 05 general wards with 06 beds per ward, 01 semi private ward with 03 beds and

02 private wards with 01 bed each, making a total of 35 hospital beds. The first general ward is designated as the hospitalization day hospital and set aside for chemotherapy sessions that warrant an overnight stay at the hospital, when it's the very first cycle of treatment or the first time a patient receives a new protocol. There is a day hospital with 11beds for patients whose chemotherapy sessions last just for few hours and they return home. The beds in both the day hospital and conventional hospitalization are fully occupied 80% of the time. The service has 02 functional computers and a printer to enable patients to have personalized and typed chemotherapy prescriptions and protocols, transfer letters, medical certificates and other documents like estimated cost of treatment when the need arises.

The team runs a daily out-patient department (OPD) consultation clinic which has a patient turnover of about 120 patients a week and averagely 700 new patients yearly. In 2022, the service realized a total of 6824 consultations and 4570 chemotherapy sessions. Cytotoxic preparations and administration of cancer related treatment is carried out by nurses. The radiotherapy unit is non-functional since 2012.

The YCH equally serves as a teaching hospital. It was created in 1993 and initially intended for outpatient consultation. Over the years it has undergone several changes and is now considered a second category hospital with good quality technical facilities. It has several health departments among which is the internal medicine and specialties department with 152 hospital beds. This department includes the following specialties gastroenterology, cardiology, haematology, nephrology, neurology, endocrinology, infectious diseases, dermatology, rheumatology, geriatrics and oncology. The oncology service is newly created. There is 01 medical oncologist, 01 oncologic surgeon, a head nurse who also serves as the head nurse for gastroenterology and haematology services as all three services share same space, several state registered nurses and nurse assistants. Outpatient consultations are done on Tuesdays and Thursdays with a patient turnover of about 35patients weekly. Chemotherapy sessions are prepared and administered by the nurses daily.

These two centres have an experienced health care team that provides comprehensive cancer care. The centres also have a high volume of diverse cancer patients with an acceptable medical record system. For these reasons, these two treatment centres were chosen as our study site to maximize and diversify the number of cases received and to improve on generalizability.

III.3 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.

III.4 STUDY POPULATION

The target population of the present study was all patients with breast cancer in Yaounde. The source population were the medical oncology departments of the YGH and YCH. 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 group responders: 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.

Exclusion criterion

Patients with relative or absolute contraindications to standard chemotherapy including pregnant patients and those with heart conditions contraindicating the use of anthracyclines

Study Entry Date: The date of breast cancer diagnosis confirmed by histopathology. This marks the beginning of each patient's participation in the study cohort.

Study Exit Date: Defined as either:

a) The date of death (from any cause) for patients who died during the follow-up period

b) The date of last known follow-up for patients lost to follow-up

c) The study end date (December 31, 2023) for patients still alive and under follow-up at the end of the study period

SAMPLE SIZE

To determine the required sample size, we used the Fleiss formula, which is suitable for comparing two proportions [63]. This formula accounts for the variability in both good and poor responder groups, providing a robust estimate of sample size. Given the comparison of two independent groups, the Fleiss formula is an appropriate choice for our study.

Assuming an expected proportion of good responders of 80% and poor responders of 20% [13], with 80% power and 95% confidence, we calculated the sample size as follows:

$n = [Z\alpha/2 + Z\beta]^2 * [p1(1-p1) + p2(1-p2)] / (p1 - p2)^2$

where:

Significance level (α) = 0.05 ($Z\alpha/2 = 1.96$)

Power ($1-\beta$) = 80% ($Z\beta = 0.84$)

Expected proportion of good responders (p1) = 80% = 0.80

Expected proportion of poor responders (p2) = 20% = 0.20

$n = [1.96 + 0.84]^2 * [0.80(1-0.80) + 0.20(1-0.20)] / (0.80 - 0.20)^2$

n = 55 for each group

This gives a total minimum sample size of 110 patients for the present study.

III.5 PROCEDURE

When the protocol and the questionnaire form were completed, the data collection tools were pretested and validated. All these were submitted to the Ethical Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I, for ethical evaluation. Also, administrative authorizations was obtained from the administration of all two study sites.

Data collection procedure

All qualifying patients' files were explored by the investigator. Patient demographics including age, sex, marital status, profession, and region of origin will be collected. The date of first symptoms

and date of diagnosis were noted from the history of the patients. 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. Mode of presentation and tumour location were also gotten from the records. Patient comorbidities, gynaecologic history, smoking and drinking history, were also be obtained. Details on pre-treatment CA 15-3 levels, were collected where available. The chemotherapy regimen used prior to surgery was also recorded, with details of the number of cycles received, side effects noted, and the dose intensity (treatment dose and schedule adherence). 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) were noted and the date of this events noted equally. The date of last contact was noted from the files. Data from validated questionnaires was entered into Microsoft excel 2013 spread sheets.

Assessment of response

Clinical response was assessed using the response evaluation criteria in solid tumors (RECIST) criteria by measuring tumour size and node size after neoadjuvant chemotherapy. RECIST utilizes the following classifications for therapeutic response: complete response (CR), primary tumour disappearance; partial response (PR), 30% or greater decrease in the longest diameter of the primary tumour; progressive disease (PD), 20% or greater increase in longest diameter of the primary tumour; stable disease (SD), tumours that did not show either sufficient shrinkage to be classified as PR or sufficient increase to be classified as PD [64].

The Sataloff Classification was used to evaluate the pathologic response. The Sataloff classification is based on the response of the primary carcinoma and the lymph nodes. The Sataloff tumor (T) and Sataloff nodal (N) classification were used as follows: T-A was total or near total therapeutic effect, T-B for > 50 % effect, T-C for < 50 % effect, T-D for no therapeutic effect. For Sataloff (N): N-A represented node negative with evidence of therapeutic effect, N-B for node negative without evidence of effect, N-C for node positive with evidence of effect, and N-D for node positive with

no evidence of therapeutic effect [11]. cPR was defined by a Sataloff TA and NA. pPR was set into two groups pPR >50% (pPR_1) and pPR <50% (pPR_2),

Table I.

Table I: 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

Those classified as pCR and pPR1 were then put into the good responders group and those with pPR2 and pNR were placed in the poor responders group.

III.6 DATA ANALYSIS

Visual checking for obvious errors and inconsistencies in the excel data was done. Initially, descriptive statistics were employed to summarize demographic characteristics (age, marital status, profession, breastfeeding status and menopausal status), clinical characteristics (stage, and subtype), and pathological characteristics (receptor status and histological grade) of the study participants. Means, medians, and standard deviations were calculated for continuous variables, while frequencies and percentages were calculated for categorical variables.

Inferential statistics were then applied to examine relationships between variables and test hypotheses. Chi-square tests and Fisher's exact tests were conducted to compare categorical variables, such as tumor subtype and receptor status, between patients with OPR and those without. The independent samples t-test was used to compare continuous variables, including age, CA 15-3 and Ki67 levels, between these groups. The results were presented in figures and tables, generated by Microsoft Excel 2013.

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. Bivariate correlation and logistic regression analyses were performed to assess the relationship between therapeutic response and survival outcomes (OS and DFS). Adjustments were made for potential confounding factors such as age, tumour stage, grade, hormone receptor status, HER2 status, and Ki67 levels. Spearman's rank correlation coefficient was used to evaluate the relationship between the patient clinicopathologic and treatment characteristics and therapeutic response.

To assess whether pathologic response to NACT significantly was independently associated with survival outcomes (EFS and OS) in breast cancer patients, multivariate Cox regression analysis was then performed to adjust for potential confounding variables. The statistical software IBM SPSS version 23 for analysis and a two-sided p-value < 0.05 was used to infer statistical significance.

MATERIAL FOR DATA COLLECTION AND WRITEUPS

For our study we used a laptop computer for the entry and analysis of the data. A USB flash disk of 2 GB was used for transferring of information. We then printed the forms with a printer and a ream of papers. We equally used ball point pens and pencils to record the information into the forms. A mobile phone was used to contact the parents of patients.

III.7 ETHICAL AND ADMINISTRATIVE CONSIDERATION

Protocol and the questionnaire forms were submitted to the Ethical Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I for ethical evaluation and approval. Authorization was obtained from the administration of the study sites, and the questionnaire was 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. Only the investigator was able to decipher these codes. Information collected was used for the sole purpose of the study. Moreover, all patient files were examined within the archive of this institution without any tempering or modification of their contents. This study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013) [65].

CHAPTER IV: RESULTS

CHAPTER IV: RESULTS

Our study was carried out from the cases in the registers and medical records starting from January 1st, 2019 to December 31st, 2023. During this 5-year period, there were 1 061 cases of breast cancer identified. Participants with metastatic disease at diagnosis (21.21 %), without staging data (10.65 %), who underwent upfront surgery (12.44 %), who had no surgery (27.52 %), and who has contraindications to anthracyclines (1.13 %) were not included. Moreover, those whose surgical specimen histology report had no therapeutic effect analysis (16.02 %) were excluded, leaving a total of 119 retained participants (11.34 %) for the final analysis.

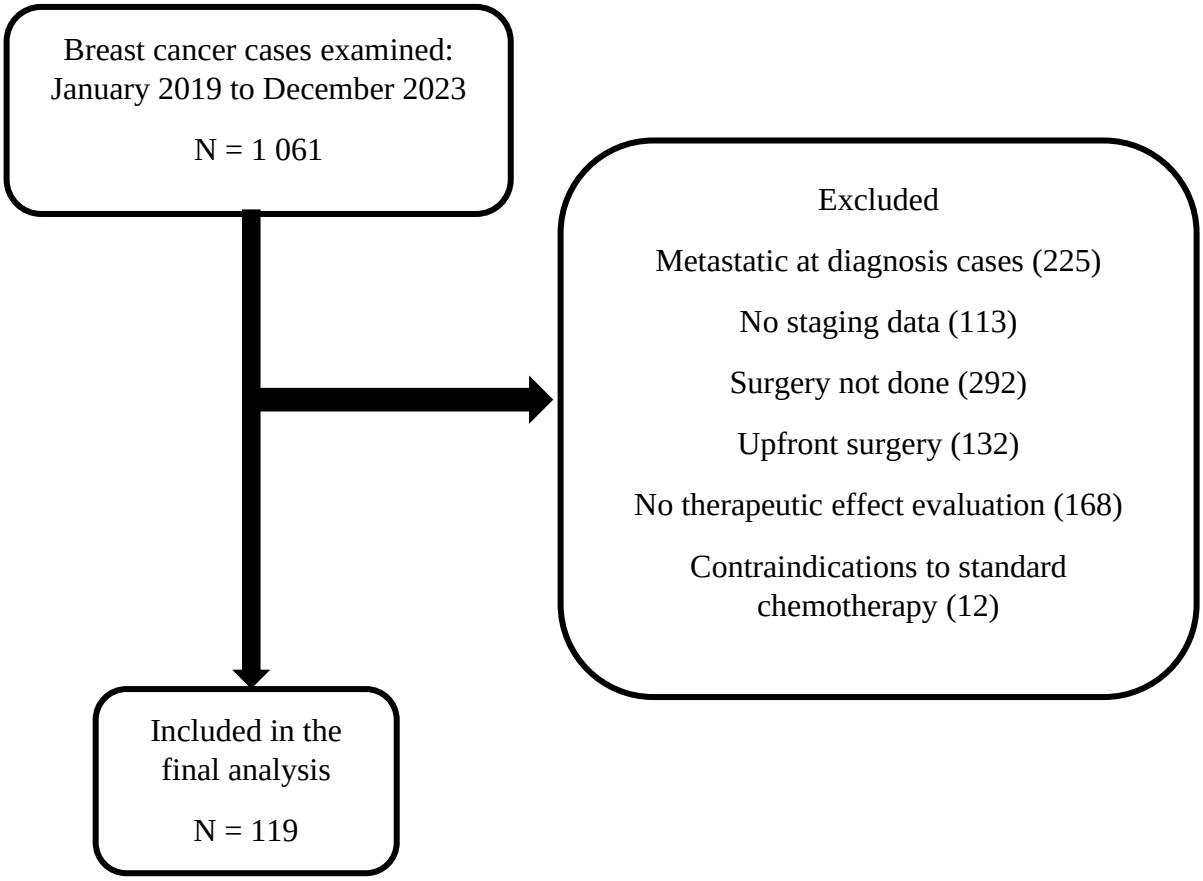

Figure 2: flow chart showing the recruitment procedure

IV.1 CHARACTERISTICS OF THE STUDY POPULATION

IV.1.1 SOCIODEMOGRAPHIC CHARECTERISTICS

This study retained 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 sociodemographic characteristics of the study population are shown in **Error! Reference source not found.**.

Table II: 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	
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	
Breastfed (n = 80)							0.60
Yes	64	80.00	16	84.21	48	78.69	
No	16	20.00	3	15.79	13	21.31	

Percentages show distribution of characteristics within good and poor responders

The median age of the overall participants was 47.00 ± 11.44 (range 28 to 80) years. The peak age group was 45 to 54 years (32.77 %). 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.

IV.1.2 COMORBIDITIES AND RISK FACTORS

Thirty-nine (32.77 %) of the study participants had a family history of cancer. Most participants (88, 73.94 %) had at least 1 comorbidity. Details of the comorbidities are detailed in

Table III.

Table III: comorbidities/risk factors in the study population

Comorbidities (n = 83)	Overall		Good responders		Poor responders		*p*-value
	frequency	%	frequency	%	frequency	%	
Use of OCP	35	21.08	8	20.51	27	21.26	0.82
Smoking	3	1.81	1	2.56	2	1.57	0.74
Alcohol	54	32.53	14	35.90	40	31.50	0.87
HIV	7	4.22	2	5.13	5	3.94	0.83
Diabetes	6	3.61	–	–	6	4.72	0.14
HTA	27	16.27	4	10.26	23	18.11	0.16
Hepatitis	2	1.20	1	2.56	1	0.79	0.42
Obesity	32	19.28	9	23.08	23	18.11	0.65

HIV, Human Immunodeficiency Virus; HTA, hypertension; OCP, oral contraceptive pills

IV.1.3 CLINICAL AND PATHOBIOLOGIC CHARACTERISTICS

IV.1.3.2 PATHOBIOLOGIC CHARACTERISTICS

The biologic marker Carbohydrate antigen 15-3 (CA 15-3) was available in 69 cases, with a mean value of 41.44 ± 66.47 UI/L (range 1.00 to 406.00 UI/L) and median of 16.30 UI/L. When the mean CA 15-3 level was compared between subgroups, good responders had a significantly lower level than poor responders (Figure 3).

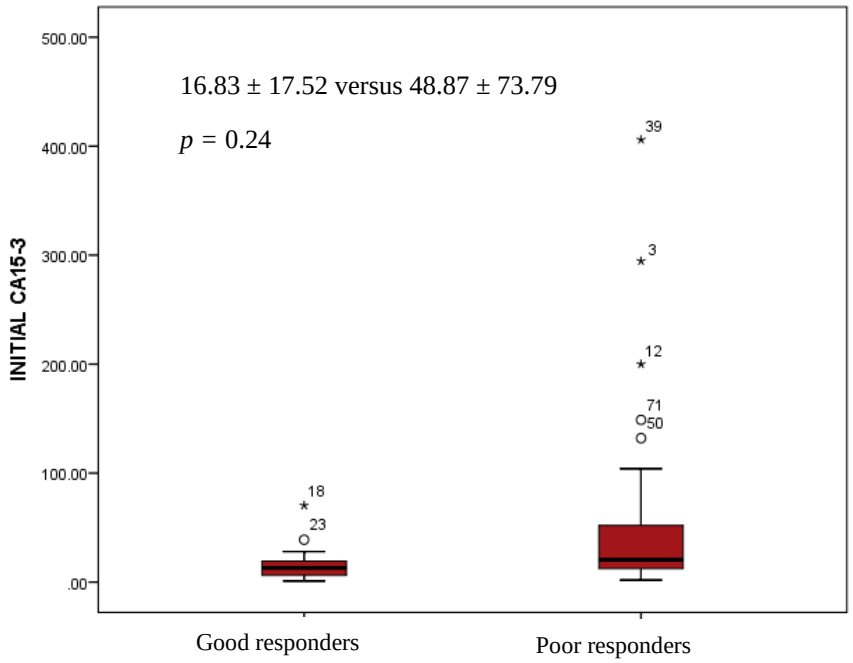

Figure 3: comparison of the initial CA 15-3 levels between both groups

The most common subtype was invasive ductal carcinoma at 79 (66.39 %) cases. The tumour grade was equally evaluated in our study population. Data on the histological grade was available in 98 (82.35 %), precisely by the Nottingham criteria. Of these 98 participants, the majority (60, 61.22 %) had grade 2. Of note, poor responders had a higher proportion of histological grade III than good responders (26.58 % versus 15.79 %, $p = 0.01$). Further details are provided in Table IV.

The immunohistochemistry profile of the study participants was assessed. Of the 119 subjects, IHC analysis was performed in 78 (65.55 %) and not done in 36 (30.25 %) cases. IHC

analysis was inconclusive in 5 (4.20 %) cases reportedly due to issues with sample preservation and preparation. The most represented molecular subtype was triple negative (33, 42.31 %), while non-luminal HER 2+ was the least represented (3, 3.85 %). It is worth noting that most of the triple negatives had a low Ki67 (34.62 % low versus 7.69 % high) (Table IV). The mean Ki67 level was compared between subgroups; good responders had a lower level than poor responders; however, without statistical significance (Figure 4).

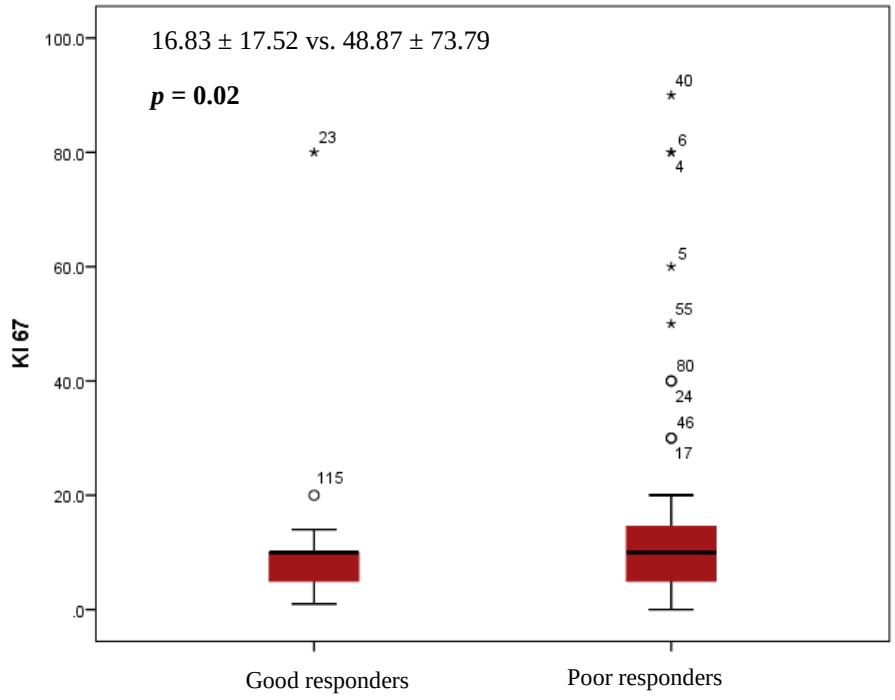

Figure 4: **comparison of the Ki67 levels between both groups**

Table IV: 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	
Ki67 (n = 78)							0.15
≤ 14	61	78.21	17	89.47	44	74.58	
> 14	17	21.79	2	10.53	15	25.42	

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

IV.1.5 TREATMENT PROFILE

All participants received at least one line of chemotherapy, while 76 (63.87 %) received an additional cycle (NACT cycle 2) and 1 (0.84 %) received up to 4 cycles of NACT. 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 V.

Table V: 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

IV.2 THE THERAPEUTIC RESPONSES TO NEOADJUVANT CHEMOTHERAPY IN THE STUDY POPULATION

IV.2 THE CLINICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY

The clinical response after NACT was analysed using the RECIST criteria. A majority of the participants had a partial clinical response (69, 57.98 %) followed by complete response (32, 26.89 %), as shown in Table VI. Notably, a higher proportion of good responders had complete clinical response albeit without statistical significance (33.33 % versus 24.72 %, $p = 0.61$).

Table VI: clinical response to neoadjuvant chemotherapy using the RECIST criteria

Treatment Modality	Overall		Good responders		Poor responders		*p*-value
	frequency	%	frequency	%	frequency	%	
Clinical response (n = 119)							0.61
Complete response	32	26.89	10	33.33	22	24.72	
Partial response	69	57.98	15	50.00	54	60.67	
Stable disease	10	8.40	2	6.67	8	8.99	
Progressive disease	8	6.72	3	10.00	5	5.62	

IV.2.2 PATHOLOGIC RESPONSE TO NEOADJUVANT CHEMOTHERAPY

The reports of the surgical specimen were analysed. The histopathological reports did not give any information on the surgical margin in 20 (16.81) cases. A majority (75, 63.03 %) had a negative margin while 24 (20.17 %) had a positive margin. Good responders had a significantly higher proportion of negative surgical margins than poor responders (83.33 % versus 56.18 %, $p = 0.01$), and the margin status was always specified in good responders (Table VII).

Table VII: surgical margin status in the study population

Treatment Modality	Overall		Good responders		Poor responders		*p*-value
	frequency	%	frequency	%	frequency	%	
Surgical margin							**0.01**
Negative	75	63.03	25	83.33	50	56.18	
Positive	20	16.81	5	16.67	15	16.85	
Unspecified	24	20.17	–	–	24	26.97	

IV.3 FACTORS ASSOCIATED TO THE THERAPEUTIC RESPONSE NEOADJUVANT CHEMOTHERAPY IN THE STUDY POPULATION

The factors associated to the therapeutic response were investigated. The correlation between the clininopathologic and therapeutic characteristics of the study participants and the pathologic response to NACT was analysed using Spearman's correlation coefficient, rho (ρ). Although the proportional odds ratio suggested a potential inverse relationship between pathologic response and a positive surgical margin status and higher histological grade, the 95 % confidence intervals included 1, indicating no statistically significant association. Increasing age, HER2+ status, the use of AC and a taxane were correlated with a better pathological response, although these were not statistically significant (Table VIII).

Table VIII: association between patient characteristics and pathologic response

Variable	Bivariate correlation analysis		Ordinal logistic regression analysis			
	Spearman's rho	***p - value***	**aPOR**	**Standard error**	**95 % CI**	***p - value***
Age at diagnosis	-0.01	0.89	-0.01	0.31	-0.06 – 0.04	0.63
Histological grade	0.37	**0.00**	0.87	0.29	0.30 – 1.45	0.00
Initial AJCC stage	0.09	0.32	0.53	0.24	-0.44 – 0.49	0.92
HER2+	-0.03	0.75	-1.135	1.697	-4.46 – 2.19	0.50
Triple Negative	0.06	054	0.37	0.76	-1.13 – 1.86	0.63
AC alone	0.06	0.49	-3.38	2.18	-7.66 – 0.90	0.12
AC + Taxane	-0.11	0.23	-2.68	2.18	-6.95 – 1.60	0.22
Others	0.08	0.0.39	-4.18	2.21	-8.51 – 0.15	0.06
Surgical margin status	0.28	**0.00**	0.88	0.35	0.20 – 1.56	0.01

95 % CI, 95 % confidence interval; AC, Doxorubicin + Cyclophosphamide; AJCC, American Joint Committee on Cancer; aPOR, adjusted proportional odds ratio; NACT, neoadjuvant chemotherapy, HER2+, human epidermal growth factor receptor 2 positive

IV.4 SURVIVAL OUTCOMES OF THE STUDY POPULATION

IV.4.1 TREATMENT OUTCOME

The median follow-up up period was 27 months. At the end of the study, 31 (26.05%) participants had died. Up to 47 (39.5 %) participants had disease progression (17, 14.3 %).

IV.4.2 EVENT FREE SURVIVAL

The comparison of EFS between the two groups (good versus poor responders), 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 years (95 % CI: 9.49 – 30.11), p = 0.00 (Figure 5).

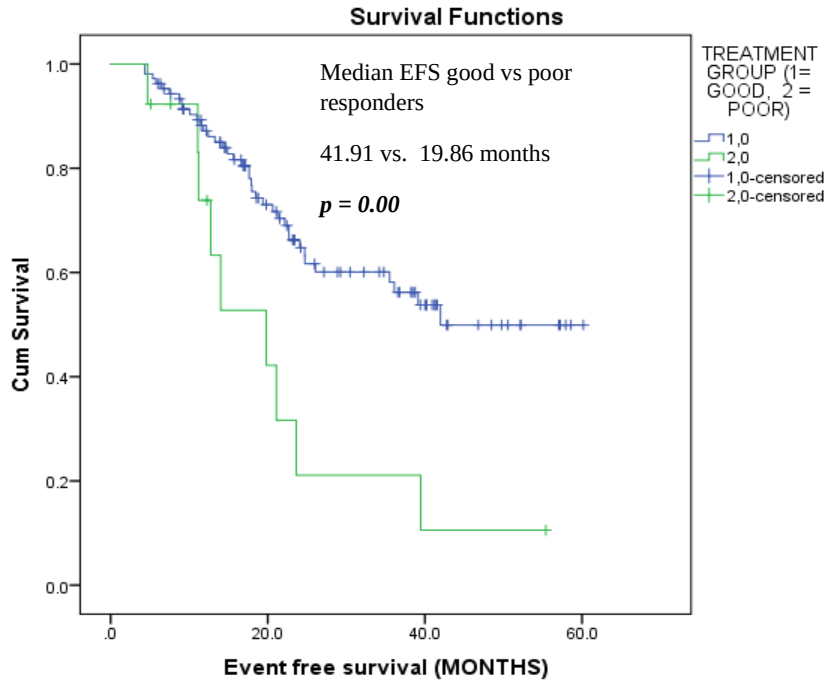

Figure 5: event-free survival with respect to treatment-response subgroups

IV.3.3 OVERALL SURVIVAL

When overall survival was compared between the two groups (good versus poor responders), 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 (Figure 6).

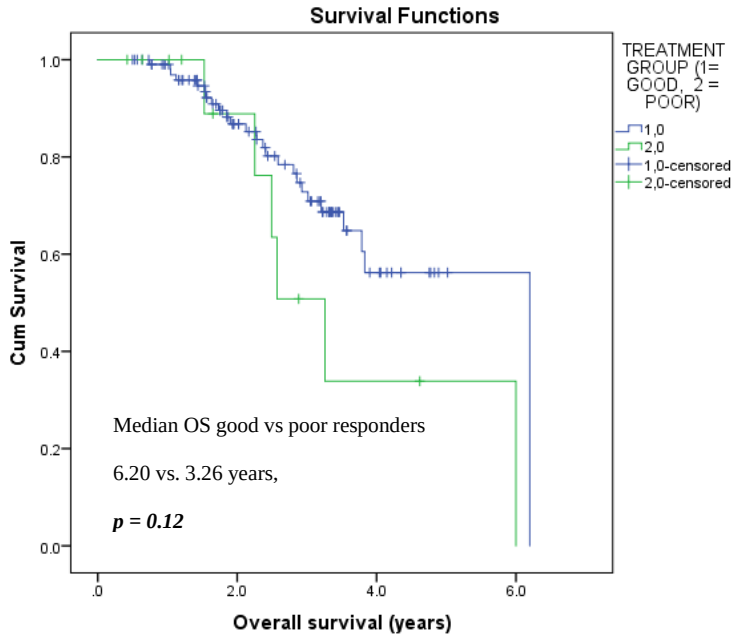

Figure 6: overall survival with respect to treatment response groups

IV.5 THE ASSOCIATION BETWEEN THERAPEUTIC RESPONSE AND SURVIVAL OUTCOMES

In this study, we investigated the association of pathologic response to NACT and survival (EFS and OS) duration in breast cancer patients using a multivariate Cox regression analysis. From the Cox regression analysis, only the use of AC plus taxane was significantly associated to a longer EFS (Table IX).

Table IX: Cox regression model of patient characteristics and event free survival

Variable	Hazard ratio	95% Confidence Interval	*p*-value
Age	1.01	0.98 – 1.04	0.47
Histological grade	0.86	0.58 – 1.27	0.45
HER2+	0.83	0.10 – 7.20	0.86
Triple negative	2.30	0.91 – 5.82	0.08
Initial AJCC stage	1.17	0.85 – 1.61	0.34
Initial nodal status	0.67	0.42 – 1.07	0.82
Surgical margin status	1.64	1.08 – 2.49	0.02
AC alone	0.15	0.05 – 0.49	0.06
AC + Taxane	0.23	0.08 – 0.67	**0.01**
Pathological response	1.11	0.49 – 2.52	0.80

AC, Doxorubicin + Cyclophosphamide; AJCC, American Joint Committee on Cancer; HER2+, human epidermal growth factor receptor 2 positive

The same Cox regression analysis was applied for OS. AC with taxane protocol alone remained significantly associated increased OS, while a positive surgical margin seemed to associated with a shorter OS, however the 95 % confidence interval included 1 suggesting no difference between the groups (Table X).

Table X: Cox regression of patient characteristics and overall survival

Variable	Hazard ratio	95% Confidence Interval	*p*-value
Age	1.01	0.97 – 1.05	0.73
Histological grade	0.71	0.43 – 1.18	0.19
HER2+	0.64	0.06 – 7.01	0.72
Triple negative	1.23	0.32 – 4.75	0.76
Initial AJCC stage	1.08	0.66 – 1.78	0.75
Initial nodal status	1.01	0.52 – 1.97	0.97
Surgical margin status	1.81	1.07 – 3.07	0.03
AC alone	0.10	0.02 – 0.45	0.09
AC + Taxane	0.10	0.02 – 0.46	**0.00**
Pathological response	0.57	0.16 – 1.10	0.38

AC, Doxorubicin + Cyclophosphamide; AJCC, American Joint Committee on Cancer; HER2+, human epidermal growth factor receptor 2 positive

CHAPTER FIVE: DISCUSSION

CHAPTER 5: DISCUSSION

The present study sought to evaluate the relationship between post-NACT pathologic response and survival outcomes in breast cancer patients treated in Yaounde. This was a historical cohort study from January 2019 to December 2023 from the YGH and YCH of 119 female non-metastatic breast cancer patients who received NACT and had an available post-operative pathology report detailing the pathologic effect. There were 30 (25.21 %) good and 89 (74.79 %) poor responders. Although a potential inverse relationship between pathologic response and a positive surgical margin status and higher histological grade seemed to be suggested, the 95 % confidence intervals included 1, indicating no statistically significant association. At the end of the study 31 (26.05%) participants had died and up to 47 (39.5 %) participants had disease progression. Good responders had a significantly better median EFS than poor responders (41.91 ± 2.43 months versus 19.86 ± 5.26 years, 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 independently associated with a longer EFS (HR: 0.23, p = 0.01) and OS (HR: 0.10, p = 0.00).

LIMITATIONS AND DIFFICULTIES ENCOUNTERED

We were confronted with certain limitations. The retrospective nature of our study implied we could not exercise control over the accuracy with which information concerning the patients were collected and recorded. Consequently, a good number of medical records were incomplete and lacked vital information. To handle these limitations, we excluded patients with incomplete data from our analysis. In those with unsure result, laboratory records were retraced where possible from the photocopy versions that are usually archived with the patient files.

Despite this limitations, this study for the first time in our context provides data on the overall pathological response to NACT and survival outcome. We showed that there was no significant difference in survival outcomes between good and poor responder breast cancer patients in Yaounde.

V.1 CHARACTERISTICS OF THE STUDY POPULATION

The present study found a mean age of 47 years for breast cancer patients, aligning with regional trends, such as the 48 years found by Noa *et al.* in their recent study in Cameroon, and global trends (47 – 48 years) [66,67]. This highlights that our sample population may be representative of the general breast cancer population.

Triple negative breast cancer was the most common IHC subtype corroborating the findings of Ekono *et al.* in Cameroon 2023 [68]. This however differs from the findings from the USA where luminal breast cancer is the most frequent. This difference could be explained by the higher prevalence of genetic factors like BRCA1/2 mutations in Africans [69], which has been linked to a higher prevalence of triple negative breast cancer and higher aggressivity [2].

The treatment sequence usually consisted of anthracycline-based combinations with or without the association of taxanes prior to surgery following international guidelines, which recommend sequential treatment by adding taxanes to the anthracycline protocol combining doxorubicin with cyclophosphamide [70].

V.2 THE THERAPEUTIC RESPONSES TO NEOADJUVANT CHEMOTHERAPY IN THE STUDY POPULATION

The clinical evaluation in the present study found a complete response rate of 27 % and partial response rate of 58% after NACT. These are similar to those of Adjade *et al.* in Morocco, who had a complete response rate of 33 % and partial response rate of 61% [71]. This is probably owing to the similarities in the patient population, as they analysed just non-metastatic breast cancer in patients of African ancestry as in the present study. Mapoko *et al.* in Cameroon had slightly different findings (complete response, 38% and partial response, 43%) [72]. This better clinical complete response rate may be due to the fact that they included all groups of breast cancer including those with early breast cancer and those with upfront surgery, in whom NACT has been shown to eradicate the local tumour [70], and the absence of an evaluable target lesion following upfront surgery. Similarly, their inclusion of metastatic breast cancer could explain their lower rates of partial response.

The pCR rate found in the present study was 8.40 %. This adds to local data and is similar to the previously reported lymph node pCR rates of 8.96 % reported in Cameroon [10]. It should be noted that our pCR rates may have been different if the pathologic response was always noted, hence enlarging the sample size. Our values however do not fall far away from the range of 10 – 35 % found in other small studies in other African countries [42]. 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 [73]. Their increase to 43 % is not yet represented in our study population probably due the fact that targeted therapies are scarcely used in the neoadjuvant setting in Cameroon [8,68,72,74]. IHC data that could have guided targeted neoadjuvant treatment is also usually available late into treatment or not at all due to financial challenges and low patient knowledge about breast cancer [8], and equally due to the scarcity of adapted molecular testing centres leading to a long time interval from sample collection to molecular profile availability [75]. In brief, our study found a pathologic complete response (pCR) rate of 8.4% in Cameroonian breast cancer patients, consistent with local and some African studies, but lower than global rates, likely due to limited access to targeted therapies and molecular testing. This highlights the needs for nation-wide efforts to increase access to molecular testing and targeted therapies.

V.3 SURVIVAL OUTCOMES OF THE STUDY POPULATION

In the present study population, a mortality rate of 26.05 % was observed by the end of the follow-up period. The present study's findings offer intriguing insights when compared to both U.S. and Nigerian cohorts, revealing noteworthy similarities and differences in survival outcomes among breast cancer patients. The mortality rate we found falls between the rates reported in the U.S. (21%) and Nigerian (25.3 %) cohorts, although slightly higher than those of both studies [77].

Our study's findings regarding event-free survival (EFS) in good versus poor responders to neoadjuvant chemotherapy align with and further support the trends observed in recent international and African studies. We found a significantly better median EFS in good responders (41.91 ± 19.86 months) compared to poor responders (19.86 ± 4.60 months), with a statistically significant difference ($p = 0.00$). This substantial difference of approximately 20 months in EFS is consistent

with recent literature. Our findings reflect the disparities observed in the study of Anya *et al.* where those with better pathological response had a better EFS (60.9 % vs 48.4 %) [77]. Reshu *et al.* equally showed better EFS in the good responders (73.4 vs. 46.1%, log rank p = 0.032) [80]. This could be explained by the fact that a good pathologic response has been linked to clearance of systemic disease, hence leading to a better EFS [58].

V.4 FACTORS ASSOCIATED TO THE THERAPEUTIC RESPONSE NEOADJUVANT CHEMOTHERAPY IN THE STUDY POPULATION

Our analysis did not identify significant correlations between clinicopathologic and therapeutic characteristics and pathologic response to NACT in breast cancer patients. Although a potential inverse relationship between pathologic response and a positive surgical margin status and higher histological grade seemed to be suggested, the 95 % confidence intervals included 1, indicating no statistically significant association. These findings are limited by the retrospective nature of our study which could not gather complete data on all possible associated factors in other to provide a clearer understanding of the factors associated to pathological response in our setting. Increasing tumour grade has often been associated with a higher pCR rate in several studies, contrary to that which our study seemed to suggest [13,53,81]. Nevertheless, some other studies identified increasing tumour histological grade as a predictor of poorer pathologic complete response in some breast cancer subtypes [17]. This divergent findings could in part be due to the inconsistent performance of IHC and in our setting and the imbalance in the different IHC subtype populations in our study sample which may have been the origin of some bias. Larger studies with more inclusive grade and IHC reporting may clarify this issue.

Our results diverge from Zhang *et al.*'s finding on HER2 status as an independent predictor of pCR [81]. This discrepancy may be attributed to the low rate of the HER2+ non-luminal subtype in our study population, as well as the limited access to targeted treatment for patients with luminal B HER2+ tumours due to high costs and limited access [75]. Consequently, the potential associations between HER2 status and pCR may not have been detectable in our study.

V.5 THE ASSOCIATION BETWEEN THERAPEUTIC RESPONSE AND SURVIVAL OUTCOMES

Similar to multiple previous studies, our study did not a significant independent association between pathologic response and survival outcomes. The single-center study of Reshu *et al.* demonstrated minimal association between the effect of the treatment on pCR and the effect on EFS and OS. They found that the R2 values for pCR as a surrogate for EFS and OS were extremely low [80]. This limits the applicability of their findings. There is wide divergence in the literature on this issue. By combining the evidence on the trial-level association between pCR and EFS with the individual-level association as shown by prior studies, a recent meta-analysis concluded that pCR is significantly associated with survival outcomes and can be considered a reasonable surrogate endpoint for EFS in the setting of the neoadjuvant treatment of TNBC [83].

A recent meta-analysis sounded a cautionary note on the reliability of pathological complete response (pCR) as a surrogate marker for long-term patient outcomes in breast cancer, conclusively demonstrating its limitations at the trial level. The findings unequivocally suggest that pCR should not be relied upon as a definitive predictor of long-term outcomes across all breast cancer subtypes. Instead, its utility is primarily confined to assessing individual patients' residual risk of relapse and guiding adjuvant treatment decisions. The use of pCR as a surrogate endpoint in neoadjuvant clinical trials is strongly discouraged, highlighting the need for more robust and reliable markers of treatment efficacy [84].

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 in Yaounde. The research adds value by focusing on a specific population, contributing to evidence on breast cancer treatment strategies in diverse settings. These findings align with external literature recommending AC plus taxane before surgery [70]. The study supports using AC plus taxane neoadjuvant chemotherapy for breast cancer patients in Yaounde, showing significant improvements in survival outcomes. Future research could include larger multi-center studies, investigation of genetic or environmental factors affecting treatment efficacy, and strategies to improve access to effective chemotherapy regimens in resource-limited settings.

CONCLUSION

CONCLUSION

This retrospective cohort study aimed to investigate the relationship between post-neoadjuvant chemotherapy (NACT) pathological response and survival outcomes in breast cancer patients treated in Yaounde. The findings suggest 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.

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, ultimately aiming to improve patient outcomes and reduce breast cancer-related mortality in this region.

RECOMMENDATIONS

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. Future research should prioritize identifying robust surrogate markers or combinations of markers to accurately predict treatment efficacy and patient prognosis, exploring innovative treatment strategies, addressing disparities in breast cancer outcomes, and investigating the molecular mechanisms underlying breast cancer subtypes to inform personalized treatment approaches. Based on the findings and conclusions of this study, we therefore make the following recommendations.

TO THE MINISTRY OF PUBLIC HEALTH

- To establish histopathology and molecular biology units and laboratories in the health institutions especially at the regional level.
- To emphasize on sensitization campaigns to raise awareness the general public on breast cancer and its presentation to increase early diagnosis
- To ensure the availability of chemotherapy and targeted which have been shown to increase survival at subsidized prices to facilitate the access to full treatment. This will greatly improve on the prognosis.

TO THE FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES

- To train more oncologists for better diagnosis and management of breast cancer.

TO RESEARCH INSTITUTIONS AND CLINICIANS

- To systematically keep a robust record of patient data to aid future research
- To further investigate and evaluate the factors associated to the pathologic response in a prospective setting
- To further investigate whether using a more complete protocol of AC plus taxane does offer better survival outcomes

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APPENDICES

APPENDICES

APPENDIX 1: DATA COLLECTION FORM

Topic: **Pathologic Response to Neoadjuvant Chemotherapy as a Surrogate Marker of Survival amongst Breast Cancer Patients in Yaounde.**

Questionnaire code ……. Date……./……./……

Hospital recruited from……..

Number	Variables	Response
	IDENTIFICATION	
1	**Age (Years)**	
2	**Sex:** 1=Male 2=Female	
3	**Profession:** 1=Public-sector 2=Private-sector 3=Trader 4=Semi-independent 5=Unemployed 6=Peasant 7=Housewife 8=Retired 9=Student 10=Priest	
4	**Matrimonial status:** 1=Married 2=Divorced 3=Widow 4=widower 5=Single	
	COMORBIDITIES/RISK FACTORS	
5	**Past Medical History**: 1= HTN 2= DT2 3=HIV 4= HEPATITIS 5=OTHERS	
6	**Family History of Cancer** 1= Yes 2= No	
7	**Smoking History** 1= Yes 2= No	
8	**Alcohol**: 1= Yes 2= No	
9	**Menopausal Status**: 1= Pre 2= Post	
10	**Breastfed**: 1= Yes 2= No	

	Cumulative duration:	
11	Height: Weight: BMI:	
CLINICAL, BIOLOGIC AND PATHOLOGIC CHARACTERISTICS		
12	Histological Type	
13	Histological grade 1=1, 2=2, 3=3	
14	**IHC** PR:_____% OR____% ki67____ HER2 1+____, 2+____ 3+____	
15	**Initial stage** T_____ N_____ M_____	
16	Pre-treatment CA 15-3 _____	
TREATMENT CHARACTERISTICS		
17	Chemotherapy Protocol:	
18	Surgery Type:	
OUTCOMES		
19	**Clinical Response:** 1=CR 2=PR 3=SD 4=PD	
20	**Surgical Margin Status:** 1= Negative 2= Positive 3=Unspecified	
21	**Sataloff Classification**: T____ N____	
22	**Event:** 1=Locoregional PD 2= Biologic PD 3= Metastatic PD	
23	**Date of Event:**	
24	**Last Date of Follow up:**	
25	**State at last contact: 1=Dead 0= Alive**	

Appendix 2: ETHICAL APPLICATION

KENN CHI NDI
Fourth Year Resident in Medical Oncology
Email kenn2809@gmail.com
Tel: +237 670 012 691

The President,
Institutional Ethics and Research
Committee, Faculty of Medicine and
Biomedical Sciences, University of
Yaounde 1.
Sir,

AN APPLICATION FOR ETHICAL CLEARANCE

I am most honoured to write you in view of obtaining and ethical clearance.

I am a fourth year resident in medical oncology at the Faculty of Medicine and Biomedical Sciences, University of Yaounde 1 and for my end of specialization memoire I intend working on "Pathologic Response to Neoadjuvant Chemotherapy and Survival Outcomes amongst Breast Cancer Patients in Yaounde" under the supervision of Professor NDOM PAUL.

We believe that understanding the patterns of neoadjuvant chemotherapy for breast cancer in our setting will lead to better prognosis and good outcomes.

For this study, ethical considerations shall be of utmost importance and obtaining an ethical clearance is indispensable.

While waiting for a favourable response, accept Sir, my best regards.

Sincerely,

KENN CHI NDI

Attached:

Copy of research protocol
Copy of receipt of school fees

Appendix 3: Research Authorization

REPUBLIQUE DU CAMEROUN
Paix - Travail - Patrie

MINISTERE DE LA SANTE PUBLIQUE

HOPITAL GENERAL DE YAOUNDE

DIRECTION GENERALE

BP 5408 YAOUNDÉ - CAMEROUN
TÉL : (237) 22 21 31 81 FAX : (237) 22 21 20 15.

REPUBLIC OF CAMEROON
Peace - Work - Fatherland

MINISTRY OF PUBLIC HEALTH

YAOUNDE GENERAL HOSPITAL

GENERAL MANAGEMENT DEPARTMENT

N/Ref : 806-24 /HGY/DG/DPM/APM-AS.

Yaoundé, le 26 AOUT 2024

Le Directeur Général

A/TO

Monsieur KENN CHI NDI
Oncologue Médicale
Tel : (237) 670 012 691 Matricule : 12M063
FACULTE DE MEDECINE ET DES SCIENCES BIOMEDICALES – UNIVERSITE DE YAOUNDE I

Objet/subject :
V/Demande d'autorisation de recherches.

Monsieur,

En réponse à votre correspondance du 08 aout 2024 dont l'objet est porté en marge,

Nous avons l'honneur de marquer notre accord pour que vous effectuiez vos travaux de recherches au Service ONCOLOGIE, dans le cadre votre étude intitulée : « *Patterns of the therapeutic response of Neoadjuvant Chemotherapy amongst breast cancer molecular subtypes in Yaoundé* ».

Cette étude sera dirigée par le Docteur ATENGUENA, Oncologue.

Vous observerez la réglementation en vigueur à l'Hôpital Général de Yaoundé pendant la durée des recherches. Toutefois, les publications se rapportant à ce travail devraient inclure les personnels de l'Hôpital Général de Yaoundé.

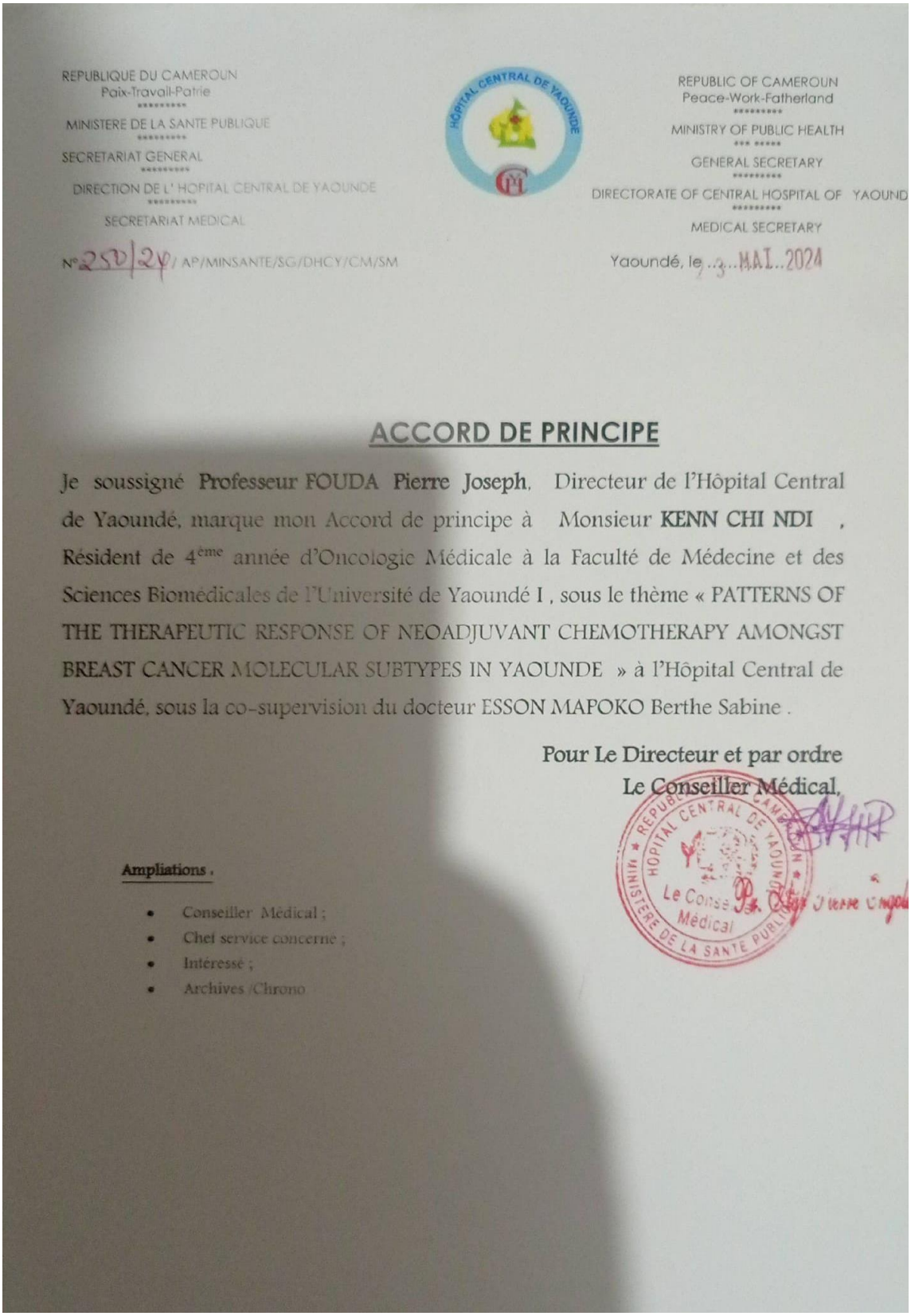
Recevez, Monsieur, nos salutations distinguées. /-

Le Directeur Général,

Ampliations :
- DPM
- Service Oncologie
- Chrono/archives.

H.G.Y Le Directeur Général Adjoint

Prof. EYENGA Victor



REPUBLIQUE DU CAMEROUN
Paix-Travail-Patrie
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MINISTERE DE LA SANTE PUBLIQUE
****
SECRETARIAT GENERAL
****
DIRECTION DE L' HOPITAL CENTRAL DE YAOUNDE
****
SECRETARIAT MEDICAL

N°250/24/ AP/MINSANTE/SG/DHCY/CM/SM

REPUBLIC OF CAMEROUN
Peace-Work-Fatherland
****
MINISTRY OF PUBLIC HEALTH
*** *****
GENERAL SECRETARY
****
DIRECTORATE OF CENTRAL HOSPITAL OF YAOUND
****
MEDICAL SECRETARY

Yaoundé, le 13 MAI 2024

ACCORD DE PRINCIPE

Je soussigné **Professeur FOUDA Pierre Joseph**, Directeur de l'Hôpital Central de Yaoundé, marque mon Accord de principe à Monsieur **KENN CHI NDI** , Résident de 4ème année d'Oncologie Médicale à la Faculté de Médecine et des Sciences Biomédicales de l'Université de Yaoundé I , sous le thème « PATTERNS OF THE THERAPEUTIC RESPONSE OF NEOADJUVANT CHEMOTHERAPY AMONGST BREAST CANCER MOLECULAR SUBTYPES IN YAOUNDE » à l'Hôpital Central de Yaoundé, sous la co-supervision du docteur ESSON MAPOKO Berthe Sabine .

Pour Le Directeur et par ordre
Le Conseiller Médical,

Ampliations :

- Conseiller Médical ;
- Chef service concerné ;
- Intéressé ;
- Archives /Chrono