TREATMENT PATTERNS AND OUTCOME OF HER2-POSITIVE BREAST CANCER PATIENTS IN TANZANIA

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TREATMENT PATTERNS AND OUTCOMES OF HER2-POSITIVE BREAST CANCER PATIENTS IN TANZANIA

By

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A Dissertation Submitted in Partial Fulfilment of the Requirements for

The Degree of Master Medicine in Clinical Oncology of

Muhimbili University of Health and Allied Sciences

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CERTIFICATION

These undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Science this research project titled ***"Treatment Patterns and Outcome of Her2+ Breast Cancer Patients in Tanzania"*** in partial fulfilment of the requirement for the degree of Master of Medicine in Obstetrics and Gynecology of the Muhimbili University of Health and allied sciences.

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(Co-Supervisor)

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Date

DECLARATION

I**, Lemi Zinga,** declare that this dissertation is my original work and that it has not been Presented and will not be presented to any other university for a similar or any other degree Award.

Signature: ……..… Date……..…

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DEDICATION

This study is a testament to the unwavering love and support of my family, who have been my rock throughout this journey. I am deeply indebted to them for their physical and spiritual presence in my life and eternally grateful for their prayers and encouragement.

ABSTRACT

Background: Breast cancer is the second leading cause of death among women globally, with an approximately 20% rate of the HER2-positive (HER2+) subtype. This subtype is linked to poorer outcomes and higher mortality rates. Despite trastuzumab being the preferred treatment, many patients, especially in developing countries like Tanzania, are unable to access it due to financial constraints. Therefore, there is a need for local data on the survival outcomes and treatment patterns of HER2-positive breast cancer patients in resource-limited settings to guide optimal management strategies.

Objective: to assess the treatment and survival outcomes of Tanzanian patients diagnosed with HER2—-positive (HER2+) breast cancer at Ocean Road Cancer Institute (ORCI) and Muhimbili National Hospital (MNH).

Materials and Methods: This hospital-based retrospective study was conducted at ORCI and MNH from January 2018 to May 2021 by enrolling patients with HER2+ non-metastatic breast cancer. The dependent variable was a three-year overall survival rate. The independent variables were social demographics and clinic pathological characteristics such as hypertension, diabetes mellitus, histology, HIV, ER/PR status, stage at diagnosis, laterality, ECOG, age, marital status, occupation, menopause status, parity, education level, smoking, alcohol, and payment mode and treatment pattern. Survival analysis was done by using the Kaplan-Meier method. Cox regression analysis was used in the multivariate analysis.

Results: In this study, 169 patients with HER2-positive breast cancer had a median age of 50. The majority had ductal carcinoma (92.3%), were estrogen receptor-positive (50.3%), and had stage III cancer (58.6%). Approximately 70.4% of the patients received Trastuzumab, 24.3% had neoadjuvant chemotherapy, and 95.9% underwent surgical treatment. Trastuzumab was commonly used in the adjuvant setting compared to the neoadjuvant setting and was more accessible to patients with higher socioeconomic status. The 3-year overall survival rate was 57%, with a median survival time of 72 months. Trastuzumab was associated with a 74% lower risk of mortality. Extended therapy with Trastuzumab was more beneficial in hormone negative HER2+ breast cancer compared to hormonal receptor-positive. Advanced-stage disease

increased the likelihood of death, while not smoking and premenopausal status were linked to lower mortality. An ECOG score of more than one was associated with a higher mortality risk.

Conclusion: The study found that trastuzumab improved overall patient outcomes in breast cancer care. Extended trastuzumab therapy was associated with better survival rates, particularly in hormone receptor-negative HER2+ patients. The study also highlighted the significant role of socioeconomic factors in treatment accessibility and outcomes, including the impact of health insurance on survival rates. It also showed the association between a higher mortality rate and advanced cancer stage, ECOG, smoking, and menopausal status.

Keywords: HER2-positive, breast cancer, trastuzumab, treatment outcome, treatment pattern

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LIST OF ABBREVIATIONS

BC	Breast Cancer
PI	Principal investigator
BCS	Breast conservative Surgery
CT	Computerized tomography
DALYs	Disability-Adjusted Life-Years
DCIS	Ductal carcinoma in situ
DFS	Disease-Free Survival
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen Receptors
FISH	Fluorescence in Situ Hybridization
HER2	Human Epidermal Growth Factor Receptor-2
IHC	Immunohistochemistry
ISHI	In Situ Hybridization
LIC	Low Income
LMICs	Low and Middle-Income Countries
MNH	Muhimbili National Hospital
MRM	Modified Radical Mastectomy
ORCI	Ocean Road Cancer Institute
OS	Overall Survival
PET	Positron emission tomography
PR	Progesterone Receptors
RT	Radiotherapy
SPSS	Statistical Package in Social Science
SSA	Sub-Saharan Africa
WHO	World Health Organization
CHR	Crude hazard ratio

OPERATIONAL DEFINITIONS

HER 2+ breast cancer- is a breast cancer that tests positive for a protein called human epidermal growth factor receptor 2 (*HER2*).

Overall Survival (OS)-Described as duration from the date of medical diagnosis of cancer to the time of death/last follow-up.

Predictors of Survival (PS)- Defined as social demographics, clinical pathological factors, and treatment modalities that impact the treatment outcome.

Disease Free Survival (DFS)- Defined as the time a patient survives without experiencing a disease relapse following the conclusion of their primary cancer treatment.

Chemotherapy - is the kind of cancer treatment that employs anti-cancer drugs to either kill cancer cells or prevent them from spreading.

Induction chemotherapy - is giving drug therapy as the primary treatment for patients who have advanced cancer, whereby there is no alternative treatment.

Radiotherapy - is a treatment that uses ionizing radiation to kill cancer cells. A cobalt 60 machine or linear accelerator can be used to deliver radiation.

Neoadjuvant chemotherapy is chemo given to patients with locally advanced cancer when other treatments like radiation or surgery are less effective.

Hormonal therapy- *is* a type of cancer treatment that removes, blocks, or adds specific hormones to the body.

HER 2-target therapy- a class of medicines used to treat HER2-positive breast cancer, inhibits the HER2 protein's aberrant activity, which promotes the growth of breast cancer cells.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Breast cancer (BC) makes up 25% of all cancer cases and 15% of cancer-related mortality in women worldwide, making it the primary cause of cancer-related deaths in this population (1,2). The cancer burden globally is expected to increase by 47% from 2020 to 2040 (3), and the prevalence in sub-Saharan Africa (SSA) is expected to double by 2050 (3). Despite bearing almost 80% of the burden as measured by disability-adjusted life-years (DALYs), lower and middle-income countries (LMICs) have approximately less than 5% share of the global resources allocated to the fight against cancer (4).

Breast cancer is the leading malignancy that causes high mortality rates among females globally(5). It is genetically and clinically heterogeneous with multiple subtypes. As per routine immunohistochemically (IHI) parameters for clinical pathologic management, breast cancer is classified into four molecular subtypes based on the immunohistochemical expression of hormone receptors: estrogen receptor-positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor positive (HER2+), and triple-negative (TNBC), which is characterized by the lack of expression of any of the above receptors (6,7). The subtypes include luminal A (ER- and/or PR-positive/HER2-negative/low Ki-67), luminal B (ER- and/or PR-positive/HER2-negative/high Ki-67), HER2-positive luminal B (ER- and/or PR-positive/HER2 overexpression/any Ki-67), non-luminal HER2-positive (ER and PR absent/HER2 overexpression), and triple-negative (ER and PR absent/HER2-negative) (6,7)

Human epidermal growth factor 2-positive (HER2+) BC is a highly aggressive and fast-growing associated with high mortality rates and poor response to conventional chemotherapy regimens; it accounts for about 15% to 20% of breast cancers worldwide, and its status is mainly relevant in the choice of appropriate treatment(8,9). Anti-HER2-directed therapies, such as trastuzumab, have drastically altered patients' treatment paradigms and improved outcomes (1). Trastuzumab significantly increases the cure rate in patients with localized HER2+ BC. It also has survival benefits in locally advanced disease and metastatic HER2+ BC(10–14).

Trastuzumab, in combination with chemotherapy, is included in Tanzania's national guidelines and international guidelines as a recommended frontline treatment option for patients with HER2+ BC and has been included in the WHO's essential medicine list since 2015(15). Based on Tanzania's national cancer treatment guidelines, patients with Hormone Receptor Positive (ER+ and/or PR+) AND Her2 + are recommended to receive Adjuvant endocrine therapy ± adjuvant chemotherapy + trastuzumab (if available). In contrast, those with Hormone Receptor Negative (ER- and PR-) AND Her2 + are recommended to receive Adjuvant chemotherapy with trastuzumab(if available(16). The most commonly used chemotherapy is the AC-T regimen, which comprises Doxorubicin, cyclophosphamide, and Taxane (Docetaxel/Paclitaxel) given in eight cycles. Trastuzumab (if available; may be administered concurrently with radiation therapy, as well as with endocrine therapy if indicated) is given intravenously (8 mg/kg for 90 minutes), followed by 6 mg/kg for 30 minutes Q3W for a total of 52 weeks(16). Endocrine Therapy recommended is Tamoxifen (pre-menopausal) and anastrozole (post-menopausal) (typically given after completion of chemotherapy(16).

However, access to trastuzumab and its biosimilars remains highly variable in LMICs (15). This has impacted the treatment pattern of many patients with HER2+BC. According to a technical report published by the World Health Organization (WHO), low- and middle-income countries (LMICs) had less access to anti-cancer medications or had to pay more out-of-pocket for them, particularly for more expensive medicines like targeted therapies. (4).

A majority of patients in LMICs come from low-income households and can't afford expensive treatment; hence, the majority of patients, especially cancer patients, cannot afford to buy costly drugs (17,18). Out of over 60 million Tanzanian inhabitants, only about 15% are fully covered by a health insurance scheme (HIS) (19). If a medication is prescribed to the patient without private insurance, the patient has to pay, causing him/her to choose or receive a more affordable treatment than the recommended first-line treatment, which has better survival benefits, which will, in turn, impact treatment outcome.

Although there is data on disease outcome and survival rates when a patient uses adjuvant treatment of HER2+ BC, most of them are based on well-controlled clinical trials from high-

income countries (10,20,21). There is minimal data on the epidemiology, treatment pattern, and clinical outcomes of HER2+ BC patients in our local setting in Tanzania. This study aims to evaluate and understand different treatment patterns used in our settings to treat HER 2+ BC patients and treatment outcomes for this group of patients as a whole based on the treatment received with or without targeted HER2 therapy.

1.2 Problem Statement

HER2 overexpression in breast cancer (BC) is linked to an aggressive clinical phenotype, resulting in high tumor grade, rapid progression, and reduced disease-free and overall survival rates (22,23). While trastuzumab combined with chemotherapy has established itself as the standard treatment for HER2+ BC in many countries (9,13,20,24), including Tanzania, a significant number of patients in this region receive alternative drug combinations. This inconsistency raises concerns regarding the effectiveness of current treatment patterns and their impact on clinical outcomes

Moreover, confounding factors such as treatment-related toxicities and limited access to optimal therapies further complicate patient management in resource-limited settings. Despite the critical need for comprehensive data on treatment practices and outcomes for HER2+ BC in Tanzania, there remains a lack of research addressing these issues. Therefore, this study aims to investigate the association between treatment patterns and clinical outcomes in patients with HER2+ BC to inform better clinical practices and policies in the management of this patient population.

1.3 Conceptual Framework

This study's conceptual framework examines the relationship between independent and dependent variables and their influence on treatment modality of choice and outcome. The dependent variables are the treatment outcomes of interest, including OS and DFS of HER 2+ BC patients. Factors like socio-demographic, clinic-pathological characteristics and treatment-related factors have been known to influence treatment outcome(25–27).

Socio-demographic factors like family history of cancer, education level, and economic status have been shown to impact health-seeking behavior, early BC detection, and early treatment (14,26,27). Factors like menopausal status and age have been known to have an impact on treatment modality used for patients as well as treatment outcome(28,29). Pathologic characteristics like HER 2-receptor status, BC stage, grade, and HIV status have prognostic and therapeutic implications(30,31)**.**

These factors(exposures) will consequently influence the trends of HER 2+ BC treatment modalities and survival(outcomes). Higher survival rates and better treatment results can result by taking into account all these factors. Patients' treatment modality and prognosis can be determined by factors influencing treatment access, like insurance coverage and financial status, as well as by the accessibility or affordability of treatment of choice like trastuzumab (15,16,32). Understanding treatment patterns and outcomes of HER 2+ BC in Tanzania will require collection and analysis of all these various variables that influence each other and consequently influence the treatment of choice and its outcome for HER 2+ BC patients.

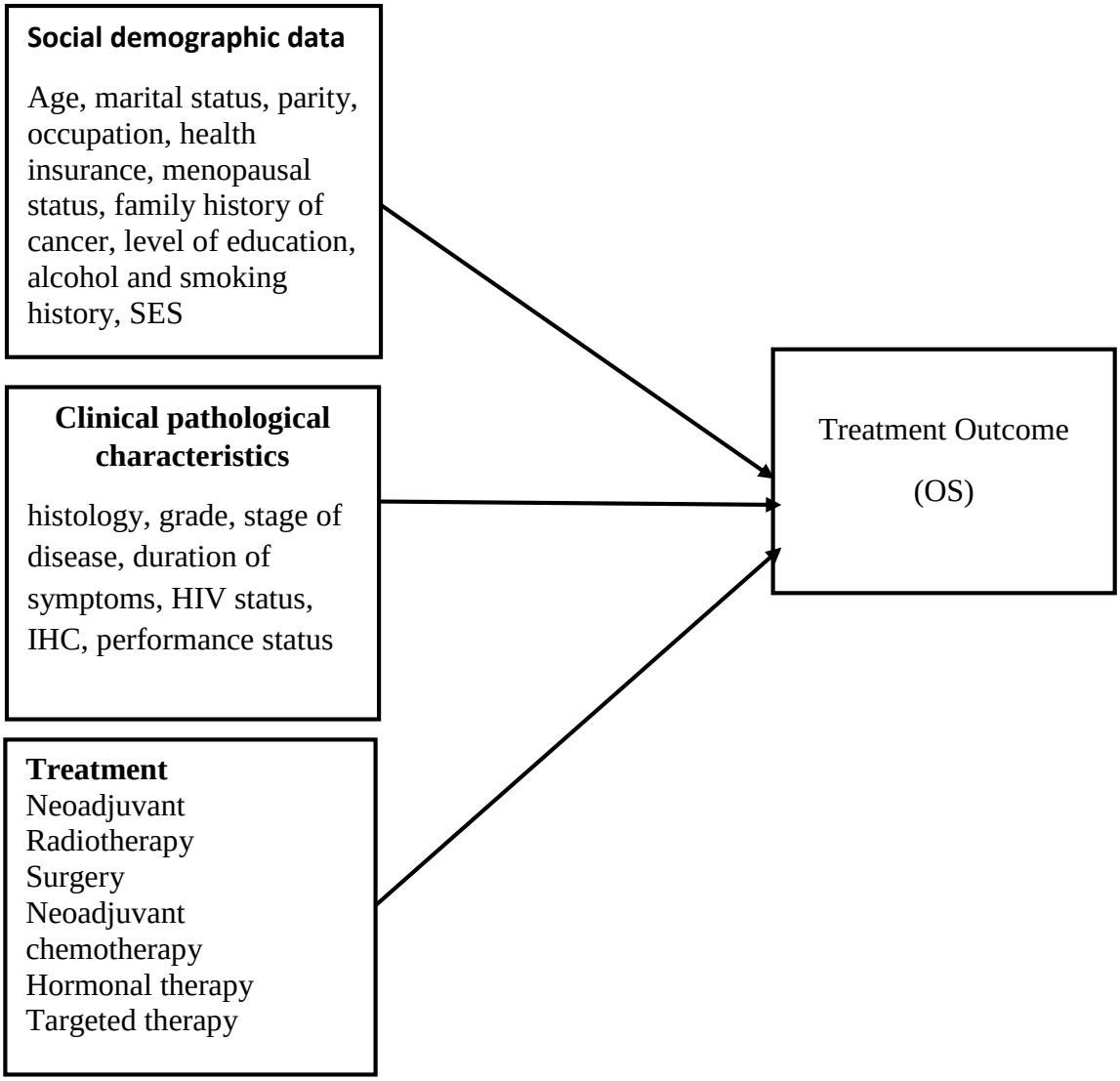


Figure 1: Conceptual framework

Source: Developed from the literature

1.4 Rationale of the study

Although research on treatment outcomes with HER2 target therapy have been done in developed nations (12,32–34), data in Tanzania is limited.

The findings from this study will provide important information on the treatment patterns and the factors that influence the survival of HER 2+ BC in a resource-limited country like Tanzania. The study emphasizes the impact of socioeconomic factors on cancer care and treatment outcomes. It highlights disparities in treatment access based on employment, education, health insurance coverage, and socioeconomic status. The findings call for interventions to address these barriers, reduce disparities, ensure equal access to therapies, and implement personalized cancer care plans.

1.5 Research Question

1.5.1 Broad research question

What are the treatment patterns and factors influencing treatment outcomes of HER2+ breast cancer patients in Tanzania from January 2018 to May 2020?

1.5.2 Specific Research Questions

1. What are the socio-demographic and clinical-pathological characteristics of patients diagnosed with HER2+ breast cancer in Tanzania from January 2018 to May 2020?
2. What are the prevailing treatment patterns for HER2+ breast cancer patients in Tanzania from January 2018 to May 2020?
3. What is the 3-year survival rate among patients diagnosed with HER2+ breast cancer in Tanzania from January 2018 to May 2020?
4. What factors are predictive of the overall 3-year survival rate among patients diagnosed with HER2+ breast cancer in Tanzania?

1.6 Objective

1.6.1 Broad objective

To identify and analyze the factors influencing the clinical practice and outcomes of HER2+ breast cancer patients in Tanzania from January 2018 to May 2020.

1.6.2 Specific objectives

1. To analyze the socio-demographic and clinical-pathological characteristics of patients diagnosed with HER2+ breast cancer in Tanzania between January 2018 and May 2020.
2. To examine the treatment patterns and regimens utilized for HER2+ breast cancer patients in Tanzania from January 2018 to May 2020.
3. To determine the 3-year survival rate of patients with HER2+ breast cancer in Tanzania diagnosed between January 2018 and May 2020.
4. To identify the predictors of overall 3-year survival among patients with HER2+ breast cancer in Tanzania during the period from January 2018 to May 2020.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Breast cancer

Breast cancer is continuing to be a public health problem in SSA, with a projection of doubling in prevalence by 2050 (2,5,35). The lack of a disease registry in most SSA countries compounds the problem of understanding the true burden of the disease, hindering prioritization and effective allocation of available resources for effective control and management of the disease (36).

One of the main causes of cancer-related mortality in women is breast cancer (5). About 685000 breast cancer-related mortality were recorded worldwide, with SSA accounting for most of these deaths. (5). Majority of cancer cases by 2025 and 2030 will be from SSA (37).

There is a need to have local data that show geographic diversity and risk factors among different cultures and economic backgrounds. This will help to put forward the necessary tools for early diagnostic strategies aiming at reducing barriers to care and improving access to treatment, hence improving treatment outcomes and survival rate(35,38).

2.2 HER 2+ breast cancer

There are various breast cancer subtypes, each with unique traits that affect how they react to various treatments. Worldwide, 20–25% of breast cancer cases are associated with overexpression of the human epidermal growth factor receptor 2 (HER2). (22). It has been demonstrated that the HER2 oncogene is crucial to the development and progression of breast cancer. (23).

For clinic pathologic management, breast cancer is categorized into four molecular subtypes using immunohistochemical (IHC) parameters, which include HER2-positive luminal B (ER and/or PR-positive/HER2 overexpression/any Ki-67), triple negative (ER and PR absent/HER2-negative), luminal A (ER-and/or PR-positive/HER2-negative/low Ki-67), luminal B (ER and/or

PR-positive/HER2-negative/high Ki-67) and non-luminal HER2-positive (ER and PR absent/HER2 overexpression) (7).

HER2 oncogenes (HER2, HER2/neu, and c-erbB-2) are found on chromosome 17.HER2 oncogene's main role is to encode transmembrane receptor tyrosine kinase (39). HER2-positive BC is an aggressive subtype that differs from HER2-negative tumors in terms of epidemiology, clinical features, and prognosis. It also responds poorly to conventional chemotherapy regimens. (22).

The risk of disease progression and distant metastases is associated with tumor cell multiplication and invasion (23). The amplification of HER2 genes result in the growth and progression of certain aggressive breast cells, and the activation of the Ras/Raf/MEK/MAPK and PI3K/AKT pathways mediates signal transduction, which leads to unfavorable biological traits and clinical outcomes in patients with breast cancer(39–42).HER2 gene amplification stands as an independent adverse prognostic factor that has an impact on all other prognostic variables (43,44).

There is a need for regular data and updates on the management outcome and clinical mechanisms of HER2-positive breast cancer from resource-limited countries, including Tanzania, where the burden of the disease is high. This will help in the renewal of clinical practice strategies using effective and recommended therapeutics and establish the framework for the daily clinical treatment of HER2+ BC patients for better management and outcomes.

2.3 HER 2+ breast cancer diagnosis and testing.

Accurate diagnosis and assessment of HER2 status are crucial for informing treatment strategies and enhancing patient prognosis. The primary methodologies employed for evaluating HER2 status include immunohistochemistry (IHC), in situ hybridization (ISH), and fluorescence in situ hybridization (FISH) (45,46).

Immunohistochemistry (IHC) serves as the standard initial diagnostic test for assessing HER2 protein expression in breast cancer tissue(45–47). This technique utilizes specific antibodies to detect the presence of HER2 proteins on the surface of malignant cells, with results categorized

on a scale from 0 to 3+. Scores of 0 and 1+ indicate a HER2-negative status, while a score of 3+ confirms HER2 positivity(46,48). A score of 2+ is classified as equivocal, warranting further investigation to determine HER2 status definitively.

In instances where IHC results yield an equivocal score, fluorescence in situ hybridization (FISH) is utilized to quantify the number of copies of the HER2 gene within tumor cells through the application of fluorescent DNA probes. A positive FISH result corroborates HER2 positivity, whereas a negative result indicates a HER2-negative classification(46). Additionally, the INFORM HER2 Dual in situ hybridization (ISH) test may be employed as an alternative, allowing for concurrent assessment of both HER2 gene amplification and protein expression, thereby providing a comprehensive diagnostic perspective(46,47). Furthermore, it is recommended that patients experiencing recurrence or metastasis undergo retesting for HER2 status, given that alterations in receptor expression may occur over time. The accurate determination of HER2 status is imperative as it directly impacts treatment protocols.

In Tanzania, immunohistochemistry remains the primary method for assessing receptor status in breast cancer. IHC testing is performed at major hospitals like Muhimbili National Hospital (MNH), but access can be limited, particularly in rural areas(49,50). As of recent studies, testing is not routinely available and often depends on specific hospital resources with challenges in proper handling of tissue samples based on standard operating procedures (SOPs)(49–51). This contributes to many patients who are referred for treatment having histopathology results with no IHC status, which delays effective treatment, a significant number of patients also can't afford to do IHC even if the test is available once they reach a tertiary center for treatment. FISH and ISH are also not routinely performed in Tanzania due to cost and availability, which poses a challenge for patients with equivocal results; the only place where FISH and ISHI are done is at Lancer laboratories. All this leads to a significant number of patients in our community missing appropriate receptor status stratification and treatment, impacting their outcomes. Enhanced efforts are needed to establish standardized testing protocols across healthcare facilities and increase access to improve patient treatment and outcomes.

2.4 Treatment pattern of HER 2+ breast cancer patients with HER 2-target therapy.

Molecular studies on the HER2 gene have paved the way for scientists to develop strategies to inhibit pathways associated with HER2+ breast cancer (42). One of the life-changing therapies is trastuzumab, which is a monoclonal IgG1 class humanized murine antibody that binds to the ECD of HER2 transmembrane receptor (52) thereby inhibiting the pathway. It was authorized for use in breast cancer treatment directed against HER2 (33)When it binds to the ECD of the HER2 receptor, it blocks ligand-independent HER2 receptor dimerization and causes antibody-dependent cell-mediated cytotoxicity (ADCC). (53). This inhibits angiogenesis as well as downstream signal transduction pathways, causing cell-cycle arrest and apoptosis and interference with DNA repair (54).

Trastuzumab is recommended for patients with advanced HER2-positive breast cancer to improve survival endpoints and quality of life (1,32,55). It has been approved for use in combination with cytotoxic agents like Taxane for early-stage HER2 breast cancer patients following the conclusion of doxorubicin therapy. (56). The combination with other agents resulted in a reduced 1-year death rate, a longer duration of disease-free progression, a longer survival duration, and a longer response duration (20,24,30,34).

Research carried out in various African nations has demonstrated that despite trastuzumab being the recommended treatment for HER2+ breast cancer, less than five percent of patients were able to afford it. (57). They showed that many patients ended up being treated with tamoxifen regardless of their receptor status (58). In one multicenter study on challenges of the patients with breast cancer in Africa, among the subset of patients receiving HER2-targeted therapy, the study shows the average number of cycles was 5 for patients paying Out of Pocket only compared with 14 for patients with some level of healthcare insurance coverage. Given that approximately 15%–22% of breast cancers are observed to be HER2 positive, a lower-than-expected proportion of patients received HER2-targeted therapy (5%–8%); this is suggestive of poor/absent healthcare insurance coverage with limited access to treatment and influence the type of treatment a patient gets. Furthermore, access to trastuzumab is severely limited in low-resource settings due to financial constraints and disparities in healthcare infrastructure(58).

Trastuzumab, as a therapy for HER 2 + BC, is not cost-effective in many African countries, impacting its incorporation in adjuvant treatment(57). A comprehensive analysis across African countries revealed that the incremental cost-effectiveness ratios (ICERs) for trastuzumab ranged from approximately $19,534 to $21,697 per Quality-Adjusted Life Year (QALY), exceeding the World Health Organization's recommended thresholds for cost-effectiveness. While the treatment offers notable survival benefits, with life year gains between 0.92 and 1.07 years, these advantages do not justify the high costs when compared to GDP per capital(57).

In Tanzania, patient treatment is variable due to socioeconomic factors, access, and our health infrastructures(49). Still, due to minimal data availability, there is very scant evidence regarding actual treatment patterns in Tanzania, which are important to guide our treatment guidelines. There is very limited real data on the characteristics and clinical outcomes of patients with Her2+ in our setting, Tanzania. Our study will reflect on the actual treatment patterns and outcomes of HER2+ patients who received treatment at ORC or MNH, and a comparison will be made between those who received trastuzumab and those who didn’t.

2.5 Factors associated with treatment outcome among HER 2+ breast cancer patients

Improvement of patient care due to early detection and treatment has resulted in improved overall survival, disease-free survival, complete remission, and reduced mortality and morbidity. These have been achieved due to the availability of various treatment modalities to manage breast cancer based on biology and the tumor stage (58,59).

Due to different factors, results of breast cancer treatment are poor in SSA (3,36,59). Some of the factors include few healthcare resources and inequality in treatment and healthcare facilities (51). Late diagnosis and management of patients have also been shown to be associated with diagnosis at an advanced stage, which reduces the overall survival (60). The chance of survival is almost non-existent with palliative care in metastatic breast cancer. Research indicates that most patients with breast cancer receive an advanced diagnosis despite the Tanzania National Cancer Screening Guideline's promotion of early detection (51).

Delays in diagnosis are attributed to patient factors and health system factors. Patient factors include a lack of awareness of cancer symptoms, seeking traditional medicine first, and poverty (3,61,62). Factors associated with the health care system include providers' knowledge of breast cancer diagnosis and treatment and the ability to provide care for breast cancer patients, which includes long waiting times for referral to appropriate hospitals that provide cancer treatment (51). The delay in the patient, as well as the health care system, are associated with late-stage disease, and long total delay to proper treatment increases the risk of late-stage disease (59,60).

Patients with breast cancer have a higher chance of survival when they receive treatment and diagnosis early on; delayed diagnosis and treatment are associated with worse clinical outcomes. (63,64). Understanding the treatment patterns and associated factors among HER 2 breast cancer patients from our institution is, therefore, of uttermost importance to improve patient outcomes. Also, understanding the factors that are associated with patients' outcomes is therefore vital to inform policy and program development to improve patient care and their outcomes.

The single biggest reason why treatment is not pursued has been shown to be a lack of financial resources (51). Even though trastuzumab is on the essential drug list for the treatment of patients with 2+ BC, it is not being offered for free or at a discounted price in Tanzania and other hospitals in SSA (18,57–59). Tackling this problem necessitates systemic modifications to enhance access to financial assistance programs and to ensure that life-saving therapies are both affordable and accessible to all patients, irrespective of their socioeconomic status.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study design

This retrospective cohort-designed study was conducted amongst Her 2+ breast cancer patients treated in public tertiary hospitals in Ilala Municipality, Ocean Road Cancer Institute, and Muhimbili National Hospital, Dar es Salaam, from January 2018 to May 2020.

3.2 Study setting

This study was conducted at Ocean Road Cancer Institute and Muhimbili National Hospital. Muhimbili National Hospital (MNH) is the largest referral hospital in Tanzania, located in Dar es Salaam. It is a teaching hospital at Muhimbili University of Health and Allied Sciences. The hospital provides a wide range of medical services and is an essential center for healthcare and medical education in the country. MNH has a dedicated oncology unit that offers services such as chemotherapy, hormonal therapy, and targeted therapy. Also, through the Department of Surgery, MNH performs surgery for all cancer cases with indications of surgery. It receives approximately 1000 BC patients annually; some are treated at MNH, and others are referred to ORCI and other hospitals for cancer treatment., MNH relies on ORCI for cases that require radiotherapy.

The Ocean Road Cancer Institute (ORCI) is a specialized cancer treatment and research center in Dar es Salaam, Tanzania. Established in 1996, it provides comprehensive cancer care services with a multidisciplinary team. The institute offers chemotherapy, radiotherapy, surgical oncology, and palliative care, handling a monthly attendance of approximately 41 cases. ORCI focuses on breast cancer care, including tailored management for Her2+ cases, utilizing targeted therapies like Herceptin.

These two sites have been selected because they received the majority of cancer patients from different parts of Tanzania; as a result, the patients are a representative group, and the study results can reflect the actual situation in Tanzania.

3.3 Study population

All eligible patients aged more than 18 years who received care at ORCI or MNH for HER2+ BC stage II and III from January 2018 to May 2020 (with a minimum of 3 years follow-up for each respondent). Groups were analyzed according to whether or not they received anti-HER2 treatment in addition to standard treatment. Patients were identified through electronic and medical records.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

Patients more than 18 years of age with HER2+ BC stage II and III, diagnosis confirmed by histology and immunohistochemistry ((HER2/neu immunohistochemistry (IHC) 3+)), FISH or ISH who were treated from Jan 2018 to May 2020 at ORCI or MNH**.**

3.4.2 Exclusion criteria

BC not being the primary cancer.

Patients with undocumented treatment regimens.

Patient with distant metastatic disease at diagnosis.

Patients with a cardiac contraindication to Her2 therapy.

3.5 Sample size

The PI included all eligible patients treated between 2018 and 2020.

3.6 Sampling process

The principal investigator (PI) conducted consecutive sampling to enroll 169 Her 2+ breast cancer cases treated at a public tertiary hospital in Ilala municipality, Dar es Salaam, between 2018 and 2020. The PI systematically reviewed medical records from ORCI and MNH to identify individuals diagnosed with HER2+ BC. The selection process adhered to the study's stringent eligibility criteria to ensure the participant cohort's relevance and integrity.

All relevant information related to social demographics, clinical characteristics, treatment completion, discharge, follow-up dates, and investigation reports was obtained from both medical files and the Inaya systems in both institutions.

3.7 Study variables

3.7.1 Dependent variable

The study's dependent variable was the overall survival over three years. The PI checked the records for documentation of events such as survival status, death, and loss to follow-up.

For those who experienced events before the end of the follow-up period, the PI recorded the time at which the events occurred. After the follow-up period, the PI assessed the outcome and recorded it as either deceased, alive, or lost to follow-up.

3.7.2 Independent variables.

Social demographic characteristics: age, menopause status, marital status, parity, education level, occupation, smoking, alcohol, and payment mode.

Clinicopathological characteristics: hypertension, diabetes mellitus, histology, HIV, ER/PR status, stage, laterality, ECOG, and ECHO.

***Treatment Received*:** Trastuzumab, surgery, neoadjuvant chemo, adjuvant chemo, hormonal therapy, and radiotherapy.

3.8 Data collection

During data collection, the PI recruited and trained four research assistants and two research assistants for each study site. These researchers were doctors and medical record personnel familiar with the medical records in their respective sites. Data collection was conducted within two months.

Data collection started by identification of the study population, Her2+ breast cancer, from all records of breast cancer cases treated in each study unit between 2018 and 2020. At ORCI, the research assistant identified the medical files of all breast cancer patients, and those who were

Her2+ were isolated from the rest of the breast cancer cases during the year 2018 to 2020. At MNH, the research assistants used the filter option, thereby isolating breast cancer cases treated during the time of 2018 to 2020 and then isolating those who were Her2+.

In each study unit, the research assistants consecutively selected the study participants by removing those who were not eligible. After selection, all relevant information related to social demographics, clinical characteristics, treatment completion, discharge, follow-up dates, and investigation reports was obtained from both medical files and the Inaya systems in both institutions.

The vital status of the patients was abstracted from medical charts to determine the OS of patients in the study. The study involved calling patients or next of kin for those who have had documentation of the recent vital status of the patient or loss to follow-up.

For those who were found to have passed away after a telephone call, the date of death was inquired, and those who were not reached out through telephone contact were considered lost to follow-up.

3.9 Data collection tool

This study used a data abstraction form developed by the principal investigator after a thorough literature review. The form had four sections: social demographic characteristics, clinicopathological profiles of participants, and follow-up summary information for survival analysis. Before data collection, the form was piloted to ensure it accurately captured the necessary information. Following the pilot, the researcher identified the need to add information about subsequent follow-up for examining relapses.

3.10 Validity and Reliability

After being developed by the principal researcher, the study's supervisor and co-supervisor reviewed this data abstraction tool for its comprehensiveness. Additionally, the principal investigator (PI) piloted this tool to ensure that all necessary information to answer the research

questions was accurately captured and to identify any missing information in the data system that might require additional questions.

3.11 Data management

Research assistants were trained to abstract data and gather information during subsequent follow-ups, and the principal researcher was responsible for calling participants for outcome assessments.

After data collection, the principal researcher reviewed all completed study data collection forms for completeness and accuracy. Participants requiring outcome ascertainment through telephone calls were isolated for further assessment, ensuring thorough and complete data collection.

The data collection forms underwent rigorous clinical oncology review by supervisors and experts to ensure information validity. Additionally, ethical issues were reviewed by the Muhimbili University of Health and Allied Sciences, adding to the study tool's construct and logical validity.

All filled data collection forms were stored in a secure location accessible only to the principal researcher. At the same time, the digital data in SPSS was accessible only to the principal researcher and study supervisor. These measures ensured proper data handling and security.

3.12 Data analysis

Data analysis was done using SPSS version 29.0 (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp) for analysis. Raw data collected from the field were entered into the SPSS.

Categorical variables were summarized in percentages and frequencies, while continuous variables were summarized using median and range. Data presentation was done using texts, graphs, and tables.

The study participants' social demographics and clinicopathological characteristics were summarized in frequency and percentage form and presented in a table.

Patterns of treatment received by the studied sample were summarized by frequency and percentage and presented in the table.

The Kaplan-Meier method illustrated the comparison of survival status among different groups. The univariate analysis explored the relationship between individual independent variables and survival.

Following the univariate analysis, a Cox regression analysis was performed to further investigate the influence of multiple independent variables on survival outcomes while accounting for potential confounding factors. This method provided hazard ratios (HRs), p-values, and 95% confidence intervals, enabling a more comprehensive understanding of the variables' association with survival.

3.13 Ethical consideration

The ethical clearance was sought from the institutional review board of the MUHAS. The permission to conduct the study at MNH and ORCI was requested from the MNH ethical clearance committee and the ORCI Institutional Review Board. As a medical review study, it inflicted minimum risk; therefore, the waiver of the informed consent was obtained from MUHAS IRB. No patient identification was revealed. Verbal consent was sought for those who were called through telephone calls to determine the patient's current state.

3.14 Publication and dissemination of results

The study's findings will count toward the partial fulfillment of MUHAS's Masters of Medicine in Clinical Oncology program. After its successful completion and acceptance, the dissertation will be distributed to the institute management. With support from my mentor team, the study will be submitted for publication in a peer-reviewed journal.

CHAPTER FOUR

4.0 RESULTS

Out of 1831 patients, 169 patients with HER2+BC who met the eligibility criteria were included in this study.

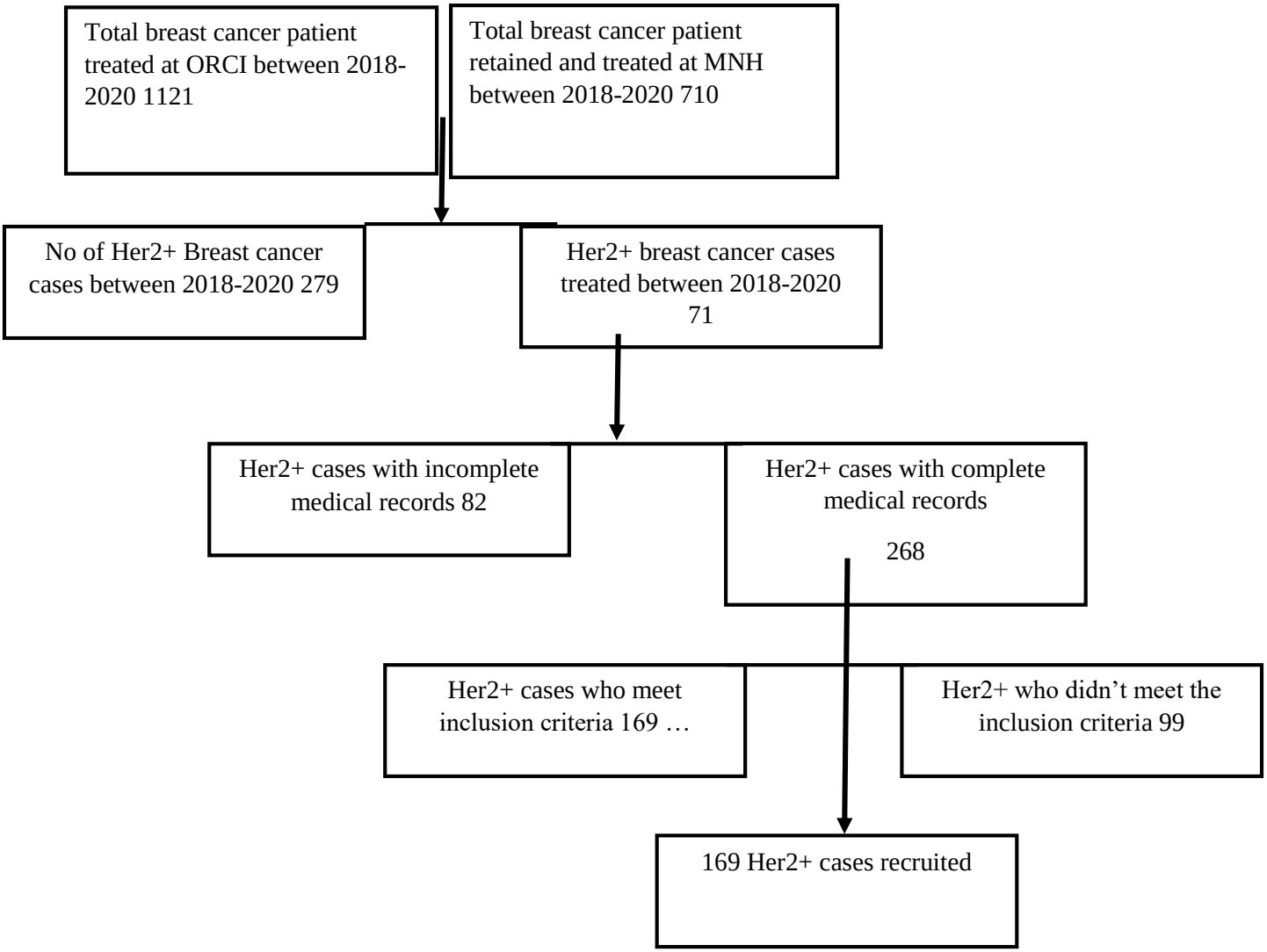


Figure 2: Recruitment of the study participants

4.1 Socio-demographic and clinical-pathological characteristics of patients with HER2+ BC in Tanzania from Jan 2018-May 2020

4.1.1 Social Demographic Descriptions.

The demographic characteristics of the study participants are presented in Table 1. Participants had a median age of 51 years, with an age range of 56 years (minimum age of 27 years and maximum age of 83 years). Most participants were married (69.2%) and postmenopausal (63%). The median number of pregnancies (parity) reported was 4, with a range of 10 (minimum of 0 and maximum of 10 pregnancies). Regarding educational attainment, most participants had not completed secondary school (79.3%). However, of those with an education level above secondary school, a substantial proportion (85.7%) received Trastuzumab treatment. The occupation status of the participants indicated that a large majority were peasants or unemployed (76.9%), while among those who were employed or retired, a high percentage (89.7%) received Trastuzumab. Additionally, a significant majority of participants with health insurance (86.7%) were administered Trastuzumab.

Table 1: Sociodemographic characteristics of the patients according to their Trastuzumab treatment status

	WHOLE COHORT	TRASTUZUMAB GIVEN		
		YES	NO	P-Value
VARIABLES	**N (%)**	**N (%)**	**N (%)**	
Age (Years)				
≤50	82 (48.5)	52(63.4)	30(36.6)	0.66
>50	87 (51.5)	58(66.7)	29(33.3)	
Menopause status				
Premenopausal	62 (36.7)	38(61.3)	24(38.7)	0.43
Postmenopausal	107 (63.3)	72(67.3)	35(32.7)	
Marital status				
Married	117(69.2)	80(68.4)	37(31.6)	0.18
Single/divorced/widow	52 (30.8)	30(57.7)	22(42.3)	
Parity				
≤4	126 (74.6)	87(69.0)	39(31.0)	
>4	43(25.4)	23(53.5)	20(46.5)	0.07
Education level				
Below the secondary	134 (79.3)	80(59.7)	54(40.3)	**0.04**
Beyond secondary	35 (20.7)	30(85.7)	5(14.3.)	
Occupation				
Retired/ employed	39 (23.1)	35(89.7)	4(10.3)	**0.00**
Peasant/unemployed/self-employed	130(76.9)	75(57.7)	55(42.3)	
Smoking				
Yes	2(1.2)	1(50.1)	1(50.0)	0.65
No	126(98.2)	109(65.3)	58(34.7)	
Alcohol				
Yes	48(28.4)	35(72.9)	13(27.1)	0.18
No	121 (71.6)	75 (62.0)	46 (38.)	
Payment mode				
Health Insurance	83(49.1)	72(86.7)	11(13.3)	
Cash private/Cost sharing	86 (50.6)	38(44.2)	48(55.8)	**0.00**

4.1.2 Clinical pathological characteristics of the patients

In the examined cohort, the incidence of hypertension was found to be 36.9%, while HIV prevalence was reported at 8.3%. The predominant histological finding was invasive ductal carcinoma, which constituted 92.3% of cases. Estrogen receptor-positive breast cancer (ER+ BC) was observed in approximately 50% of the patients. Trastuzumab administration was significantly more common among patients with an ECOG of less than 1, with 81.7% receiving the treatment compared to 55% of those with a higher ECOG score, denoting a statistically significant difference (p=0.00). Cellular differentiation levels were documented for 37 patients, representing 21.9% of the total cohort. A minority of patients, 5(3%), were reported to have Ki-67. Lymph vascular invasion was present in 29.6% of participants, with 19 (38%) of this subset experiencing lymphatic vascular invasion. Axillary node dissection was part of the clinical history for 79(46.7%) patients, and the mean number of nodes removed was 7 (Table 2).

Table 2: Clinical pathological characteristics of the patients according to their Trastuzumab treatment status.

VARIABLES	ENTIRE COHORT	TRASTUZUMAB GIVEN		P VALUE
		YES	NO	
Hypertension				
Yes	61 (36.1)	41 (62.7)	20 (32.8)	0.66
No	108 (63.9)	69 (63.9)	39 (36.1)	
Diabetes Mellitus				
Yes	15 (8.9)	13 (86.7)		0.06
No	154 (91.1)	97 (63.0)	2 (13.3) 57(37.0)	
Histology				
Ductal carcinoma	156(92.3)	103(66.0)	53(34.0)	0.39
Lobular carcinoma	13 (7.7)	7(53.8)	6(46.2)	
HIV				
Yes	14 (8.3)	8(57.1)	6 (42.9)	0.52
No	155 (91.7)	102 (65.8)	53 (34.2)	
ER/PR status				
ER+	85 (50.3)	55(64.7)	130(35.3)	0.92
ER-	84 (49.5)	55(65.5)	29(34.5)	
Stage				
II	70 (41.4)	49(70.0)	12(30.0)	0.26
III	99 (58.6)	61(61.6)	38(38.4)	
Laterality				
Left	107 (63.3)	69(64.5)	38(35.5)	0.76
Right	62 (36.7)	41(66.1)	21(33.9)	
ECOG				
0	60 (35.5	49(81.7)	11(18.3)	**0.00**
≥1	109 (64.5)	61(55.9)	48(44.0)	
ECHO				
Yes	41 (24.3)	30(73.2)	11(26.8)	
No	125 (75.7)	80(62.5)	48(37.5)	0.21

4.2 Treatment pattern of HER 2+ BC patients in Tanzania from Jan 2018-May 2020

In this study, 119 patients with HER2+ BC (70.4%) underwent at least one cycle of Trastuzumab treatment. The average number of cycles administered was 10.2 (SD = 5.6), with a median of 9 cycles (range 1-18). Neoadjuvant chemotherapy (NACT) was administered to 41 participants (24.3%), with 13 (31.0%) receiving AC-T, 12 (28.5%) receiving TAC (docetaxel, doxorubicin, and cyclophosphamide), and another 12 (28.5%) receiving AC (Adriamycin and cyclophosphamide). Additional NACT regimens included Taxane and Carboplatin, Epirubicin, cyclophosphamide and paclitaxel, Docetaxel and Cisplatin, as well as FEC-T (5 fluorouracil, Epirubicin, cyclophosphamide then docetaxel), each received by 1 (2.4%), 1 (2.4%), 2 (4.8%), and 1 (2.4%) patient respectively. The median number of NACT cycles was 4 (range 2-8). A higher proportion of patients who did not undergo NACT (69.5%) received Trastuzumab compared to those who did (51.2%).

About 162 participants (95.9%) underwent surgical intervention, and 115 (68.1%) underwent radiotherapy. All patients receiving radiotherapy were treated with 3DCRT to the chest wall, breast, and supraclavicular nodes. Patients who underwent conventional fractionation (88.9%) were more likely to receive Trastuzumab than those who underwent hypofractionation (50.8%), $p = 0.009$.

Adjuvant chemotherapy was administered to 145 patients (85.8%), with AC-T (Adriamycin, cyclophosphamide followed by paclitaxel (Taxol)) being the most common regimen, received by 101 patients (69.2%). Other regimens included Taxane (10.3%), docetaxel, doxorubicin and cyclophosphamide (6.8%), Epirubicin, and cyclophosphamide, followed by docetaxel (6.8%), TCH (Taxol, carboplatin and Herceptin) (2.1%), and Docetaxel (1.4%). Single patients (0.7%) received TC (docetaxel and cyclophosphamide), CAF (cyclophosphamide, doxorubicin, fluorouracil), Gemcitabine, Platinum, Capecitabine, and AC (Adriamycin and cyclophosphamide). Trastuzumab was more frequently administered to patients who had adjuvant chemotherapy (69.0%) compared to those who did not (41.7%), $p < 0.001$.

72 patients (42.6%) received hormonal therapy. The results are detailed in Table 3.

Table 3: Treatment pattern of HER2+ BC according to their Trastuzumab treatment status

VARIABLES	ENTIRE COHORT N (%)	TRASTUZUMAB GIVEN		P-Value
		YES N (%)	NO N (%)	
Neoadjuvant chemotherapy				
Yes	41 (24.3)	21 (51.2)	20(48.8)	
No	128 (75.7)	69(58.9)	39 (30.5)	0.03
Surgical treatment				
MRM	146 (86.4)	96(65.8)	50(34.2)	
BCS	16(9.5)	12(75.0)	4(25.0)	
None	7 (4.1)	2(28.6)	5(71.4)	0.47
Radiotherapy				
Hypo fractionation	61 (36.1)	31(50.8)	30(49.2)	
Conventional fraction	54 (32.0)	48(88.9)	6(11.1)	
Not received	54 (32.0)	31(57.4)	23(42.6)	**0.00**
Adjuvant chemo				
Yes	145(85.8)	100(69.0)	45(31.0)	
No	24 (14.2)	10(41.7)	14(58.3)	**0.009**
Hormonal therapy				
Yes	72 (42.6)	51(70.8)	21(29.2)	
No	97 (57.4)	59(60.8)	38(39.2)	0.12

4.3 Predictors of three years OS among HER2+ BC patients in Tanzania from Jan 2018-May 2020

4.3.1 Survival analysis

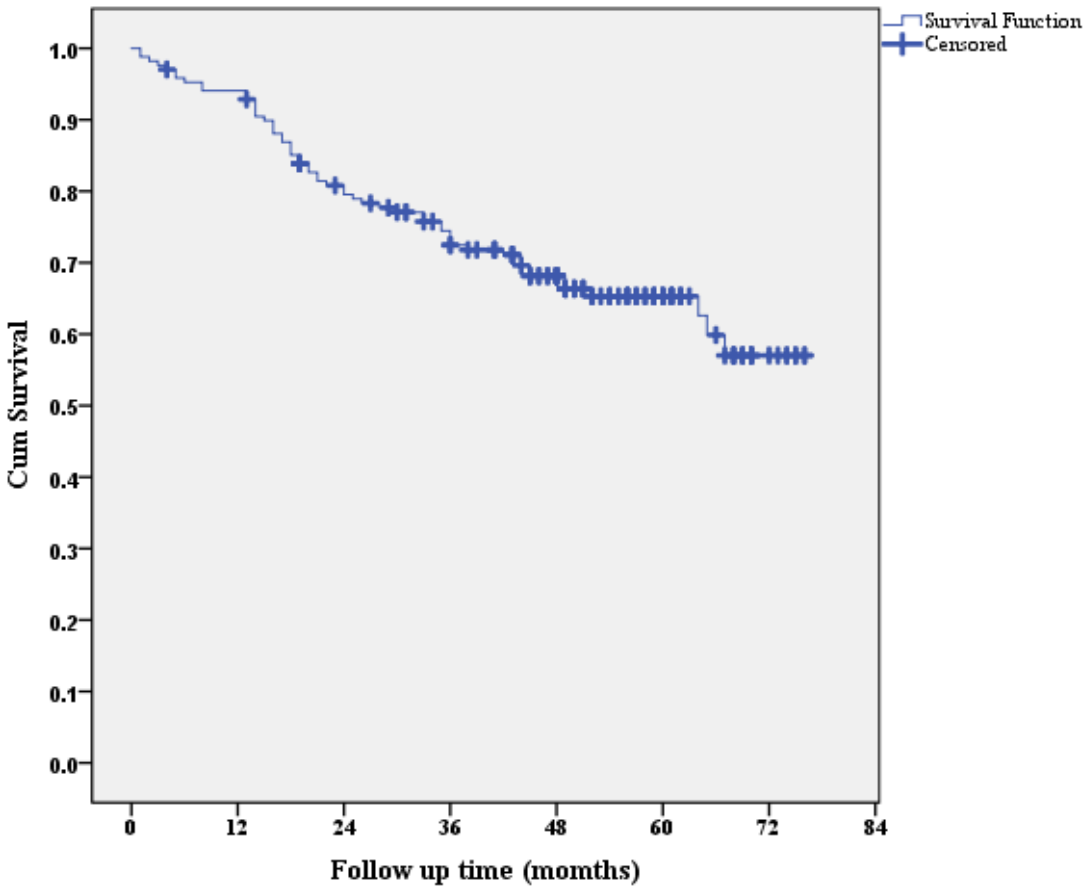


Figure 3: The Kaplan Meir overall survival curve for HER2+ BC treated at ORCI and MNH from January 2018 -May 2020

The 5-year OS rate was 57%, and the median survival time was 72 months (Figure 1).

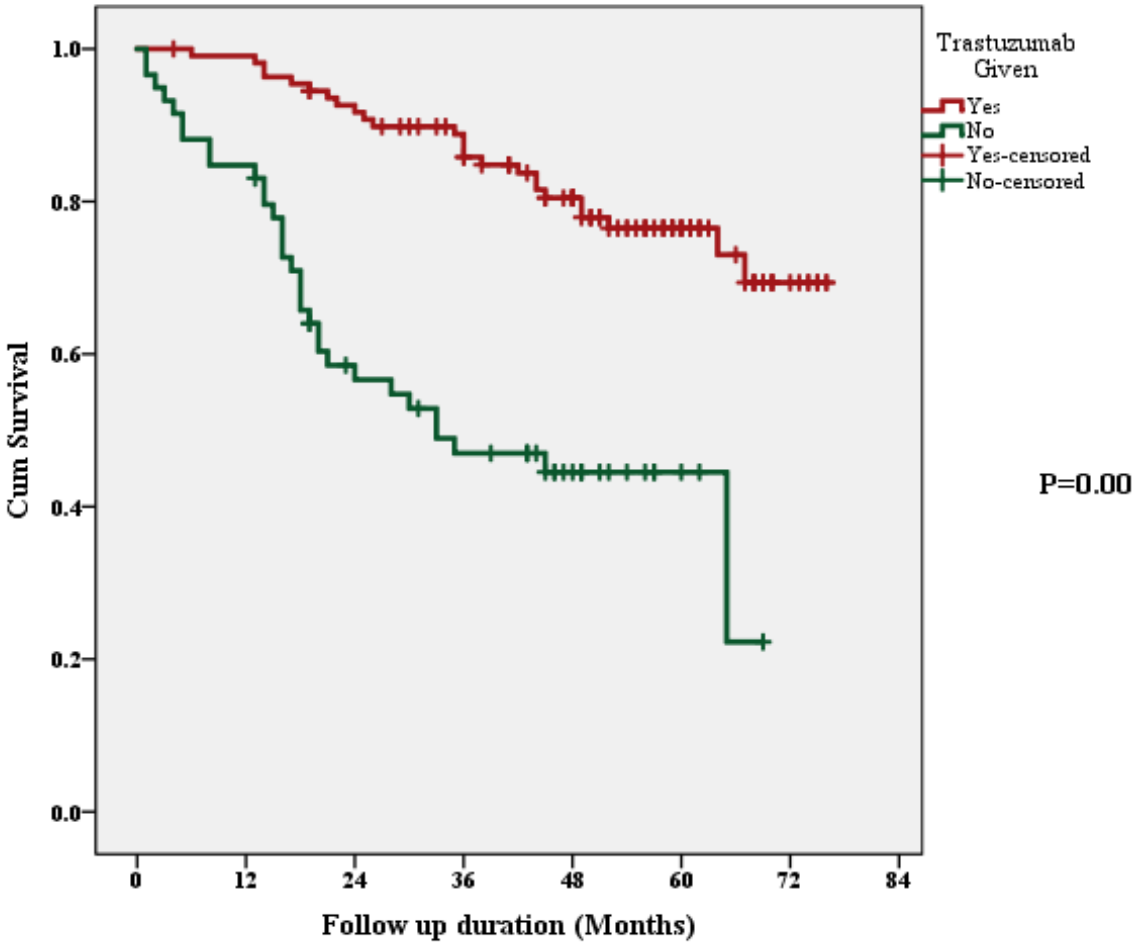


Figure 2: Kaplan-Meier Survival Curve for HER2+ Breast cancer patients who received and who didn't receive trastuzumab

The median survival time was higher for patients who received Trastuzumab than those who did not (p=0.00) (Figure 2).

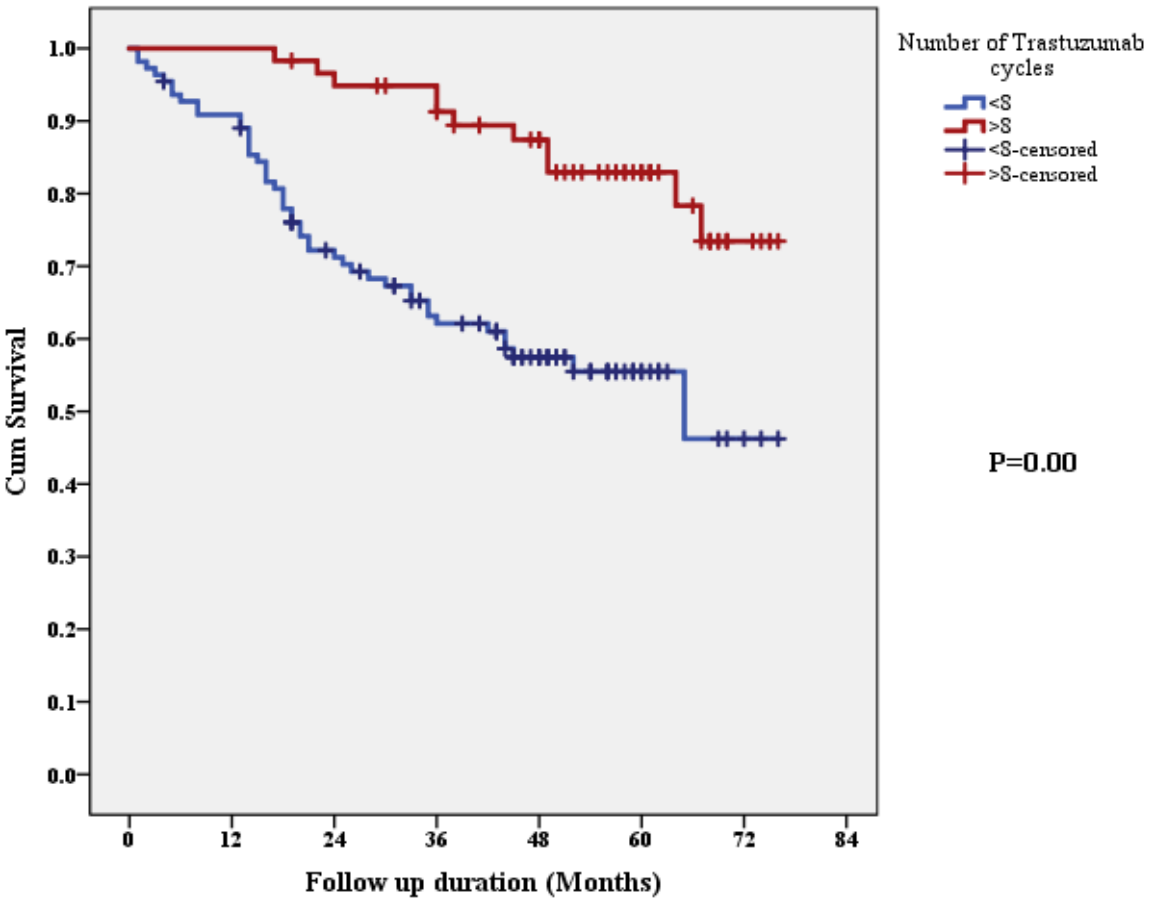


Figure 3: Kaplan-Meier Survival Curve for HER2+ Breast cancer patients who received more than eight cycles of trastuzumab and those who received less than eight cycles of trastuzumab.

The median survival time of patients receiving Trastuzumab for more than eight cycles was significantly longer than that of patients who received less than eight cycles (p=0.00) (Figure 3).

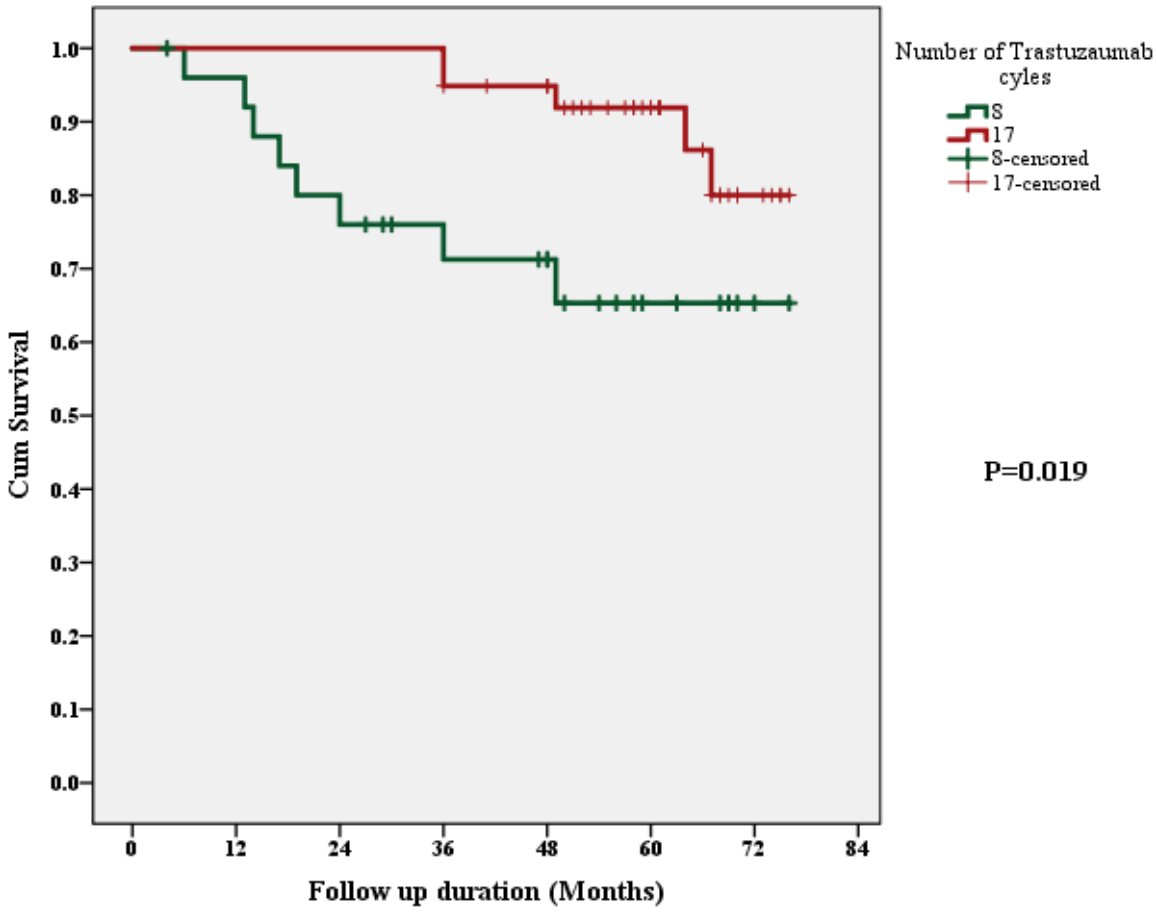


Figure 4: Subgroup analysis comparing patients who received eight cycles of Trastuzumab and those who received 17 cycles

The median survival time was increased for patients who received 17 cycles of Trastuzumab compared to those who received eight cycles (p=0.019) (Figure 4).

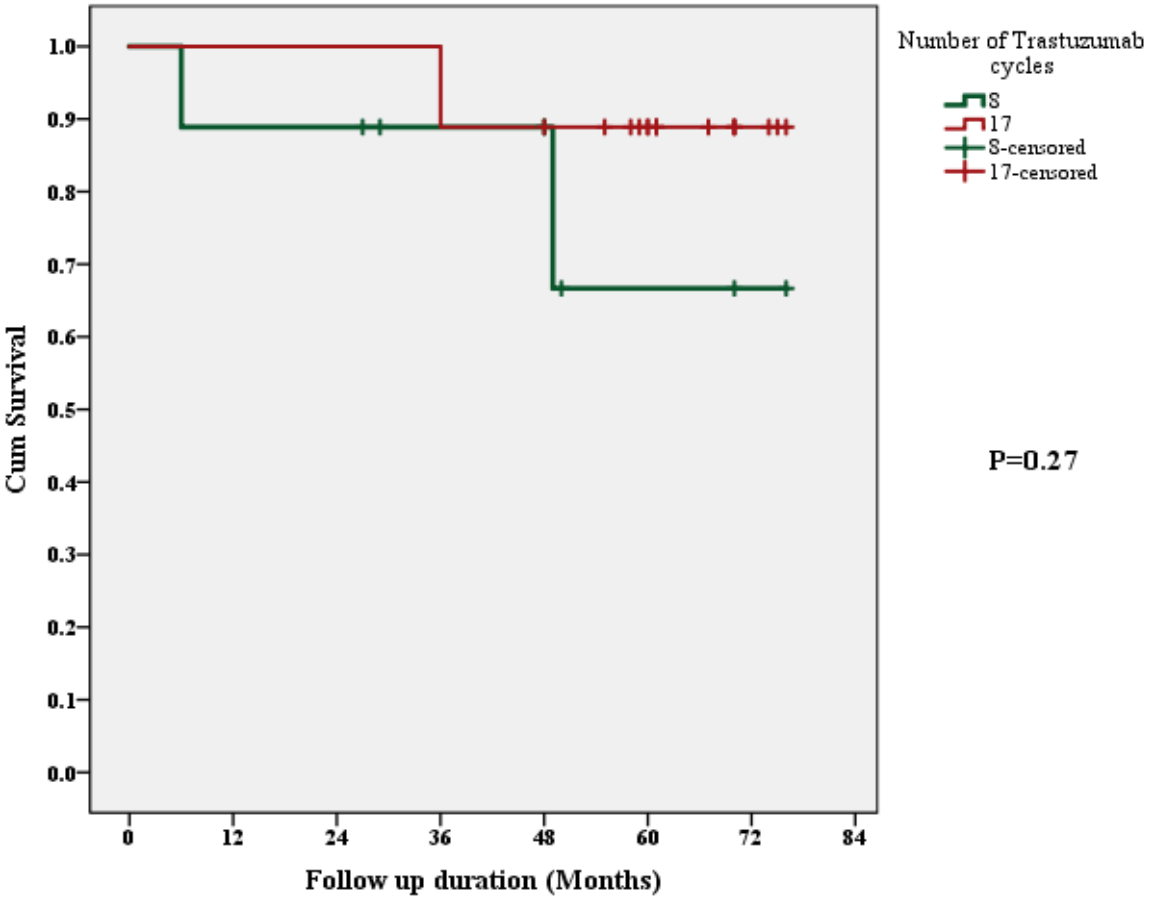


Figure 5: Subgroup analysis comparing patients with ER+ BC HER2+ who received eight cycles of Trastuzumab and those who received 17 cycles

For ER+ HER2+ BC, patients who received 17 Trastuzumab cycles had a median survival similar to those who received eight cycles (p=0.27) (Figure 5).

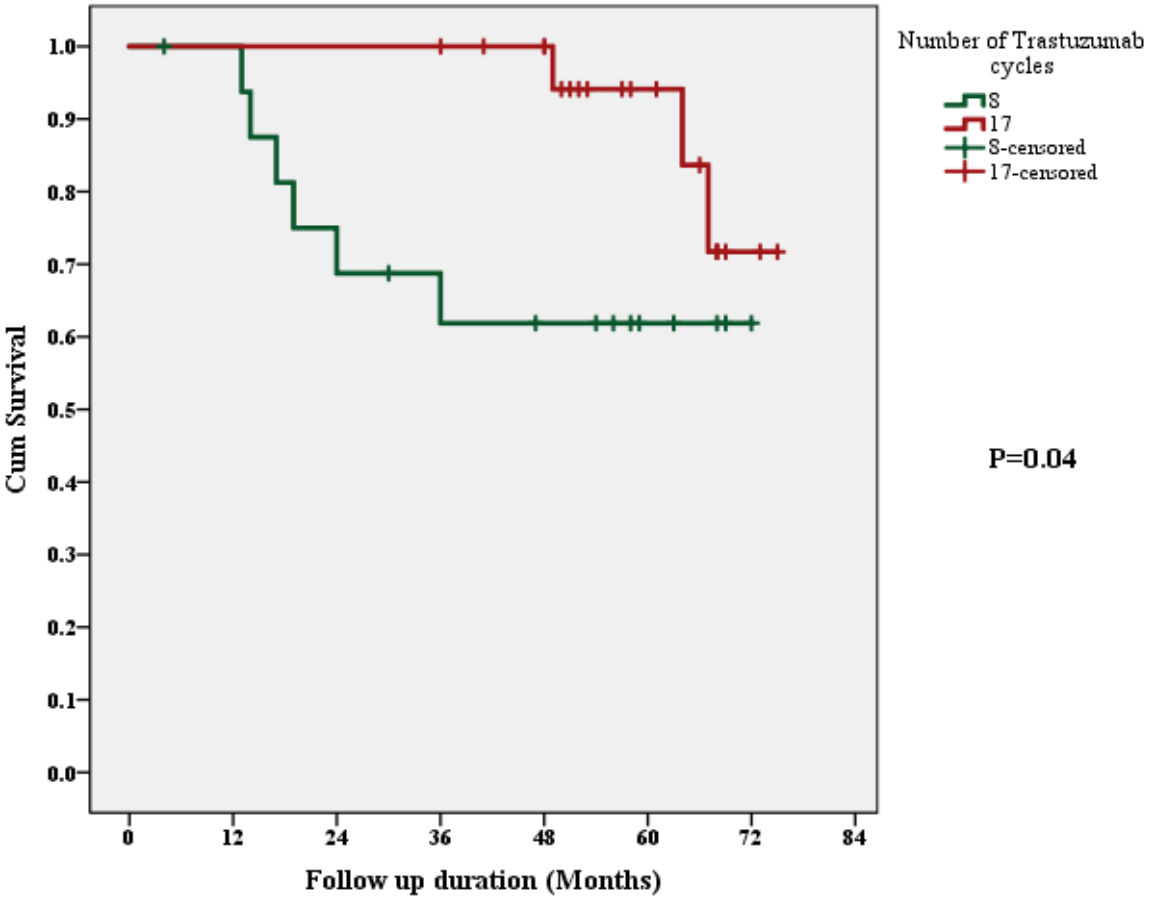


Figure 6: Subgroup analysis comparing patients with ER- BC HER2+ who received eight cycles of Trastuzumab and those who received 17 cycles

For ER-HER2+ BC, patients who received 17 cycles of Trastuzumab had a longer median survival time than those who received eight cycles (p=0.04) (Figure 6).

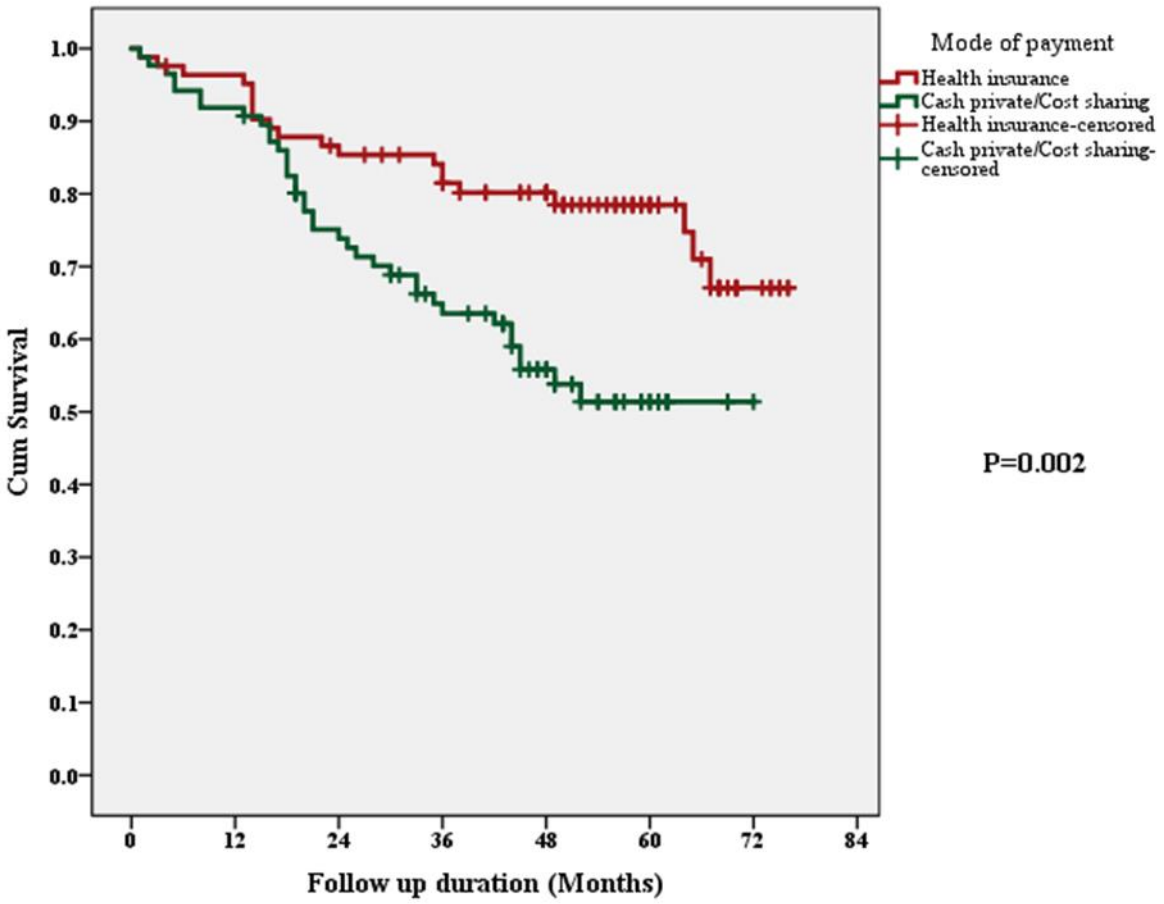


Figure 7: Kaplan-Meier Survival Curves for HER2+ BC patients according to mode of payment/insurance status

The median survival time for patients with health insurance was longer than those who paid out of pocket (p=0.002) (Figure 7).

4.3.2 Univariate analysis of the factors associated with mortality among HER2+ breast cancer patients treated between 2018 and 2020

The univariate analysis presented in Table 4 elucidates several independent factors correlating with HER2+ breast cancer (BC) outcomes. Notably, premenopausal patients exhibited a significantly higher mortality rate, being 2.43 times more likely to succumb to the disease than their post-menopausal counterparts ($p = .006$). Conversely, those who didn't receive adjuvant chemotherapy had a higher mortality rate, being 2.1 times more likely to die compare to their counterpart ($p = .04$). The absence of relapse emerged as a strong indicator of survival, with patients experiencing no relapse demonstrating an 80% decreased risk of mortality compared to those with relapse events ($p < .001$).

Furthermore, a history of hypertension was identified as a risk factor, doubling the likelihood of mortality ($p = .002$). The stage of cancer at diagnosis also played a critical role; patients diagnosed at advanced stages had a quadrupled risk of death relative to those diagnosed at early stages ($p < .001$). The ECOG performance status served as another prognostic indicator, where patients with a score equal to or greater than 1 had a 2.5-fold increased risk of mortality compared to patients with a score of less than 1 ($p < .001$). Receiving Trastuzumab also played a critical role on survival; patients who did not received Trastuzumab had a quadrupled risk of death relative to those who received it ($p < .001$). People who had insurance to cover treatment cost had a substantial reduction in mortality risk by 57% ($p = .003$).

Lastly, lifestyle factors such as smoking history were significant, with non-smokers having an 88% reduced risk of dying from HER2+ BC compared to smokers ($p < .001$). These findings underscore the multifaceted nature of cancer prognosis and highlight the importance of considering a broad range of patient characteristics when evaluating treatment outcomes and survival probabilities.

Table 4: A summary of univariate analysis

VARIABLES	95.0% CI for CHR (Lower—Upper)	P value
Menopausal status		
Postmenopausal	REFERENCE	
Pre-menopausal	2.43(1.26—4.57)	.006
Relapse		
Yes	REFERENCE	
No	0.20 (0.11—0.37)	.00
Parity		
≤4	REFERENCE	
>4	0.52 (0.27—1.02)	.058
HT		
Yes	REFERENCE	
No	1.992 (1.09—3.65)	.02
ECOG		
0	REFERENCE	
≥1	2.54(1.43—4.81)	.00
Smoking		
No	REFERENCE	
Yes	0.12 (0.02—0.50)	.00
Trastuzumab		
Yes	REFERENCE	
No	3.909 (2.291—6.671)	.000
Adjuvant chemo		
Yes	REFERENCE	
No	2.17 (1.06—4.48)	.04
Hormonal therapy		
Yes	REFERENCE	
No	1.85 (0.94—2.89)	.08
Stage		
II	REFERENCE	
III	4.06(2.05-8.05)	.00
Payment method		
Insurance	REFERENCE	
Cash private/cost sharing	.429 (.246—.748)	.003

4.3.2 Multivariate Cox regression analysis of the factors associated with mortality among HER2+ breast cancer patients treated between 2018 and 2020

Table 5 shows the Cox regression analysis results for the adjustment of stage, smoking status, menopausal status, ECOG score, and mode of payment. The use of Trastuzumab was associated with a 74% lower risk of mortality compared to those who were not given Trastuzumab (p=0.00).

After adjusting for the use of Trastuzumab, smoking status, menopausal status, ECOG score, and mode of payment, patients with advanced staged disease were 2.8 times more likely to die compared to those with early disease stages (p=0.003).

After adjusting for stage, the use of trastuzumab, menopausal status, ECOG score, and mode of payment, not smoking, was associated with a 63% lower risk of mortality compared to smoking (p=0.00).

After adjusting for stage, smoking status, trastuzumab use, ECOG score, and mode of payment, mortality risk was decreased by 74% when stratified by postmenopausal status (p=0.001).

After adjusting for stage, smoking status, menopausal status, the use of Trastuzumab, and mode of payment, patients with ECOG score of equal to or more than 1 were 2.3 more likely to die in comparison to those with an ECOG score of less than 1 (p=0.015).

Table 5: Cox regression analysis

VARIABLES	95.0% CI for AOR (Lower —Upper)	P value
Use of Trastuzumab	.264 (.143—.487)	.000
Stage	2.863 (1.427—5.746)	.003
Smoking status	.37 (.007—.192)	.000
Menopause status	.366 (.206—.652)	.001
ECOG	2.306 (1.173—4.532)	.015
Payment mode	.864 (.451—1.655)	.659

CHAPTER FIVE

5.0 DISCUSSION

The cohort in this study was notably characterized by a high rate of unemployment, with 77% of individuals reporting limited employment opportunities. Furthermore, nearly 80% of the cohort had education levels at or below the primary school level. The distribution of health insurance coverage was evenly split, with half of the participants being health-insured. The most prevalent histological diagnosis was ductal carcinoma, identified in over 92% of cases. Hormone receptor status was equally divided, with half of the cohort presenting an ER+ status. The majority of participants (59%) presented with locally advanced disease at the time of diagnosis.

The prevalence of high unemployment and low education levels among the cohort indicates that socioeconomic factors may influence access to cancer care and treatment options. The association between employment, education, and the likelihood of receiving trastuzumab suggests that individuals with higher socioeconomic status have better access to this essential therapy. Similar findings were observed in a study by Pragya Singh et al. done in northern India, whereby the majority of trastuzumab recipients were well-educated, from high-income strata, and belonged to upper/middle socioeconomic status as compared to the non-recipient group(65)The study underscores the potential impact of socioeconomic status on treatment access and outcomes, highlighting the gravity of the situation. It is clear that interventions are urgently needed to address these disparities. A study exploring the cost-effectiveness and affordability of adjuvant trastuzumab in 11 African countries found that it is not cost-effective, with 94% of respondents citing drug costs as a barrier to prescribing it. Significant discounts on the cost of trastuzumab would be needed to make it affordable in low-resource settings where the majority of patients are from low-income households.(57)Increased health technology assessment and policy decisions to expand access to essential cancer medicines in public health systems also seem important.

Regarding treatment, there was a notable trend in the administration of trastuzumab; 90% of employed individuals received this therapy, compared to a lower percentage among the unemployed. A higher receipt rate of trastuzumab was also observed in individuals with secondary-level education or above (86%). Stable ECOG scores were reported in over 81% of the cohort, with a majority receiving trastuzumab. The treatment pattern also included neoadjuvant chemotherapy (NACT) for nearly a quarter of the cohort, with half of these patients also receiving trastuzumab. Adjuvant chemotherapy (ACT) was administered to over 85% of the cohort, with two-thirds receiving trastuzumab as part of their treatment regimen. It has been well demonstrated that in HER2-positive BC, adding trastuzumab to neoadjuvant chemotherapy greatly increases pathologic complete response (pCR) rates and event-free survival when compared to chemotherapy alone(66,67). However, the overall survival (OS) benefits of initiating trastuzumab in the neoadjuvant setting compared to the adjuvant setting are still being investigated; 5 years follow-up of the NOAH trial showed a trend towards OS with (HR 0.66, 95 % CI 0.43−1.01; $p = 0.055$)(12). The lack of solid evidence of superior overall survival benefits in neoadjuvant settings and insurance coverage limitations, considering how expensive the treatment is, maybe why many doctors prefer to give it in adjuvant settings at ORCI. Also, many patients receiving neoadjuvant treatment at ORCI have advanced tumor stage and low KPS, adding to the potential of getting side effects like cardiotoxicity before surgery due to trastuzumab and chemotherapy; many would prefer to add trastuzumab in an adjuvant setting rather than neoadjuvant.

The disparity in treatment access between insured and uninsured patients underscores the impact of health insurance on patient care outcomes. A study by Michael Addo Kwabeng et al. from Ghana also demonstrated that insurance status was significantly associated with survival in breast cancer patients (p-values= 0.036) (68). Additionally, the observation that adding trastuzumab is inconsistent across different demographics emphasizes the potential impact on survival rates and quality of life. These findings highlight the necessity for policies and interventions aimed at reducing socioeconomic barriers to cancer treatment and ensuring equal access to life-saving therapies like trastuzumab, ultimately improving overall patient outcomes in breast cancer care. One such intervention that can enhance access and affordability of these

life-saving medications is the introduction of biosimilars, which are very comparable versions of biologic pharmaceuticals like trastuzumab. Biosimilars could improve overall results in breast cancer care by boosting competition, bringing down costs, and giving patients more treatment alternatives(69,70). A study by Annie Alexander et al. also showed that the availability of biosimilar drugs significantly improved its affordability among breast cancer patients in LMIC countries like India; the cost of treatment went down from $30,600 for Herceptin to $11,300 for biosimilars, with some patients managing to complete the treatment despite not being covered by health insurance(71). There is, however, a lack of studies comparing the cost-effectiveness of biosimilars in African countries; this can be an area for future research. Another solution is expanding insurance coverage and reimbursement, and Policymakers should work to expand insurance coverage and reimbursement for trastuzumab treatment to reduce financial barriers for patients. A study in China by Yiqin Xia et al. found that the health insurance policy in China has improved access for breast cancer patients who require trastuzumab; patients with medical insurance were 3.909 times more likely to use trastuzumab compared to those without insurance with insurance coverage greatly reducing the out-of-pocket costs for patients(72). Other studies have also found that lack of drug funding and reimbursement is a major barrier to trastuzumab use, especially in low- and middle-income countries (73,74). The cost of 58% of essential cancer medications is borne by the patient, compared to just 1.8% in upper-middle-income countries(74). High prices are a significant reason hindering patient access to cancer medications like trastuzumab. Also, with a proper diagnosis of HER 2 positivity, we could cut down treatment costs by avoiding unnecessary costs to patients by adhering to guidelines and giving target therapy only to patients with IHC results of 3+.

The 3-year survival rate of 57% and median survival of 72 months highlight the variable prognosis in this patient population. Trastuzumab significantly improves outcomes, with extended median survival times correlating with the duration of therapy. Notably, patients receiving more than eight cycles of trastuzumab exhibited better survival rates, suggesting a dose-response relationship (75,76). This trend was further substantiated by the increased median survival observed in patients undergoing 17 cycles compared to eight. However, the benefit of

extended trastuzumab therapy was not uniform across all biomarker subgroups; ER+/HER2+ patients did not show a significant difference in median survival between eight and 17 cycles, unlike their ER-/HER2+ counterparts. This discrepancy may indicate the influence of estrogen receptor status on the efficacy of HER2-targeted therapies (77). The PERSEPHONE trial found that six months of adjuvant trastuzumab was non-inferior to 12 months for early breast cancer, with similar disease-free survival. At the 4-year mark, the absolute difference in overall survival (OS) between the two treatment cohorts was 1%, demonstrating non-inferiority. From a safety standpoint, the incidence of severe adverse events was significantly lower in the 6-month treatment regimen compared to the longer duration regimen, with fewer patients stopping treatment due to cardiotoxicity. However, subgroup analyses from the trial suggested that for higher-risk patients, such as those with ER-negative disease, the 12-month regimen has better survival and may still be preferred if affordable in these patients (78).This has important implications for resource-limited settings like Tanzania, where drug affordability is a major issue. Based on results from our study and Persephone trial, a shorter 6-month trastuzumab regimen can be offered to ER-positive patients, significantly reducing costs, treatment toxicity and improving access to this targeted therapy. On the other hand, ER-negative patients should get the full 12-month course of Trastuzumab therapy.

In an effort to enhance accessibility while simultaneously decreasing both costs and toxicity, other countries like South Africa have also utilized data from clinical trials like the PERSEPHONE study(79). Consequently, the National Essential Medicines List Committee (NEMLC) has revised its clinical criteria document to reduce the recommended duration of trastuzumab therapy from 12 months to 6 months for adjuvant treatment of early HER 2+ BC (79). A cost-effectiveness analysis done in Iran; a middle-in-come country indicates that a 6-month trastuzumab regimen may be the most economically advantageous option(80). This study found that the shorter treatment duration optimizes healthcare resource utilization while maintaining effective patient outcomes, yielding favorable cost-effectiveness ratios compared to longer regimens. This further solidifies the fact that shorter treatment regimens, and tailored economic evaluations is crucial to improving access to effective cancer therapies in MLICs like Tanzania.

The disparity in median survival times between HER 2+ BC with health insurance and those paying out-of-pocket highlights the significant role of socioeconomic factors in treatment accessibility and outcomes. This is supported by literature indicating that insurance coverage is strongly associated with the quality of cancer care and survival rates (81,82)**.** Research has shown that uninsured patients and those covered by Medicaid experience worse survival outcomes compared to privately insured individuals(82).A Study by Naomi Y. Ko et al highlights that inadequate health insurance is linked to disparities in breast cancer survival ; The research indicates that women without insurance are more likely to be diagnosed at later stages, which adversely affects their survival rates(83). These data and our study findings point to the fact that Patients possessing health insurance are more likely to access timely and appropriate interventions, including targeted therapies such as trastuzumab, which are essential for managing HER 2+ BC. In contrasts uninsured populations may delay or forgo treatment due to cost concerns leading to poor treatment options and outcomes. As of late 2021, around 15% of the Tanzanian population had health insurance, with approximately 8% enrolled in the National Health Insurance Fund (NHIF). This indicates that over 75% of individuals in Tanzania remain uninsured, reflecting considerable disparities in health coverage(19). To enhance health insurance coverage in Tanzania, the government should implement a mandatory scheme for the informal sector and consider a tax-funded model while providing financial support to low-income households. Additionally, improving public awareness of insurance benefits and strengthening healthcare infrastructure will help address barriers and improve health outcomes nationwide.

The advanced stage of cancer being associated with a higher mortality rate is consistent with established knowledge that early detection and treatment are crucial for improving survival (81,84) The stage at which breast cancer is diagnosed is a significant predictor of survival, with earlier stages correlating with much higher survival rates(85,86). Cancer stage also influences the type of treatment a patient receives whether its palliative or curative. In Tanzania, a considerable number of breast cancer patients are diagnosed at advanced stages of the disease;

Research indicates that approximately 80% of breast cancer cases are identified at stage III or IV, which significantly restricts treatment options and exacerbates patient outcomes (49,62,87,88). Contributing factors have been preference for traditional healing ,poor health seeking behavior , lack of awareness, economical and geographical barriers resulting in poorer outcomes(49,61,62,89). To tackle the high rates of late-stage breast cancer in Tanzania, a comprehensive approach is essential. This includes boosting public awareness through community outreach, improving healthcare access via better referral systems and financial support, enhancing healthcare infrastructure with expanded diagnostic services and trained personnel, developing national cancer control guidelines, and collaborating with international partners for funding and expertise.

The increased mortality rate in premenopausal women could be attributed to the aggressive nature of cancers in younger patients, which has been observed in other studies as well (90–92)**.** A study by Jennifer L Gnerlich et al found women less than 40 years of age had a significantly higher risk of mortality compared to older women, even after controlling for variables like race, treatment and cancer stage(92). This finding indicates that menopausal status is a critical factor in breast cancer prognosis. Consequently, treatment strategies may need to consider menopausal status more thoroughly, as premenopausal women might require different therapeutic approaches or closer monitoring due to their elevated risk.

The ECOG performance status is a reliable predictor of patient outcomes, with higher scores correlating with increased mortality risk. This emphasizes the need for individualized treatment plans based on patient health status. This finding is similar to others in the literature, which have found that lower performance status is often associated with higher levels of fatigue, weakness, and other symptoms that can make it difficult for patients to engage in and benefit from intensive treatments (93,94).

Based on our data, smoking has been identified as an independent risk factor that affects breast cancer survival. The association between non-smoking and a significant reduction in the risk of death is in line with a wealth of evidence showing the detrimental effects of smoking on cancer prognosis and overall survival (95–97). Based on a study by Akshara Singareeka Raghavendra

et al., quitting smoking after a breast cancer diagnosis is linked to substantially improved survival outcomes(95). Smoking has been shown to undermine cancer treatment effectiveness by influencing the immune tumor microenvironment, which in turn impacts how the body responds to chemotherapy(98). It elevates risks of late side effects post-therapy, increases the risk of distant metastasis and recurrence, and drives up healthcare costs (80,81). Interestingly, the benefits of smoking cessation hold regardless of other prognostic factors. Conversely, continuing to smoke post-diagnosis significantly increases both overall mortality and breast cancer-specific mortality(95,97).These findings highlight the critical importance of smoking cessation support as part of comprehensive breast cancer care**.** Integrating comprehensive tobacco treatment programs into cancer care will enable high quit rates and better survival for patients. Oncologists should routinely screen for smoking and connect patients to these impactful cessation services.

These findings collectively underscore the multifaceted nature of cancer survival, influenced by treatment regimens, socioeconomic status, stage at diagnosis, hormonal status, performance scores, and lifestyle factors such as smoking. They call for a multidisciplinary approach to cancer care that includes targeted therapies, early detection programs, socioeconomic support, personalized treatment plans, and lifestyle interventions to improve patient outcomes holistically. There is also a need to add trastuzumab into national and health scheme programs in Tanzania. The government should recognize the significance of medications that significantly affect survival, particularly in cases of cancer that are prevalent in the populace and must make every effort to ensure that patients have easy access to these treatments.

The study's strength lies in its thorough analysis of the impact of socioeconomic factors on cancer care and treatment outcomes. It provides detailed insights into the association between employment, education, health insurance coverage, and access to essential therapies like trastuzumab. The emphasis on individualized treatment plans based on patient health status and lifestyle factors further enhances the validity of the findings. Overall, the study's comprehensive approach strengthens its significance in oncology.

LIMITATIONS

A retrospective design was used in our study, which might have limitations. The accuracy of our conclusions could be impacted by the dependence on already-existing medical records and data, which could have incomplete information. An excellent example of such a limitation was how hard it was for us to assess the economic status of our cohort due to data limitations. The sample size was limited with only 169 patients included, this was due to strict inclusion criteria which excluded a significant number of patients with metastatic disease or lacking crucial information for the study. Ki 67 could not be assessed since majority of patients didn't have it done due to the lack of the test in past years and financial constraints. Finally, the study represents a cohort from only two institutions and mainly represents the population treated at these centers.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

This study reveals a significant connection between socioeconomic factors and access to cancer care, particularly regarding trastuzumab treatment for breast cancer. The study cohort predominantly comprised individuals with constrained employment prospects and lower educational attainment, many of whom were diagnosed with ductal carcinoma, with nearly half exhibiting estrogen receptor-positive (ER+) status. The results indicate that individuals with employment and higher educational levels were more likely to receive trastuzumab, whereas uninsured patients encountered considerable barriers to access. The study found that trastuzumab improved overall patient outcomes in breast cancer care. Extended trastuzumab therapy was associated with better survival rates, particularly in ER-negative HER2+ BC patients.

The findings of this study also reveal a significant association between higher mortality rates and several critical factors, including advanced cancer stage, an Eastern Cooperative Oncology Group (ECOG) performance status greater than 1, smoking, and pre-menopausal status. Advanced cancer stages are linked to increased tumor burden and metastasis, while a higher ECOG score indicates diminished functional capacity, both contributing to poorer survival outcomes. Additionally, smoking exacerbates disease progression and negatively impacts prognosis. Pre-menopausal status may also influence cancer biology and treatment efficacy. These results underscore the necessity for comprehensive patient evaluations to inform clinical decision-making and improve survival strategies in oncology.

6.2 Recommendations

1. Develop personalized treatment plans for HER2+ BC patients by incorporating proper receptor status analysis to guide therapy duration. The goal is to minimize side effects and reduce costs.
2. Conduct qualitative research to understand the barriers and facilitators to accessing Trastuzumab in Tanzania, which will help create an implementation strategy to address access disparities.
3. Strengthen early detection and diagnosis initiatives by offering community-based screening programs and increasing awareness through educational campaigns highlighting the importance of early intervention.
4. Design treatment strategies for premenopausal women that include hormone therapy evaluation and addressing specific risks and concerns of this demographic.
5. . Enhance smoking cessation efforts within the cancer care plan. High cessation rates and improved patient survival will be made possible by the integration of comprehensive tobacco treatment programs into cancer care. Regular smoking screening and referral to these cessation therapies should be provided by oncologists to their patients.
6. This study was done when most patients without health insurance were exempt from paying. A similar study needs to be conducted after the introduction of user fees for patients without health insurance to assess changes in access to Trastuzumab in Tanzania

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APPENDENCES

Appendix 1: Data Extraction Form

Patient Identification

The Patient's study number ……

The hospital registration number ……

The initial attendance date (dd/mo/yr)……...

Part 1

Social-demographic traits (patient related factors)

Date of birth:

Gender:

1) Female
2) Male

Menopause status:

1) Pre
2) Post
3) Not documented

marital status:

1. Married
2. Single
3. Not documented

Highest level of education

1. Not attend school
2. Primary education
3. Secondary education
4. College/university degree
5. Post graduate
6. Not documented

Health insurance coverage

a) Yes
b) No

If Yes, which insurance type

a) Government health insurance
b) Private health insurance

Does your insurance package cover target therapy treatment

a) Yes
b) no

Parity……

Occupation:

a) Peasant
b) Retired
c) Degree holder employee in a government or private sector
d) Self-employed
e) Unknown

Level of income

a) <100,000/=
b) 100,000- 1,000,000/=
c) 1,000,000-4,000,000/=
d) >4,000,0000
e) Could not be determined

History of First-degree relative diagnosed with breast cancer:

1) Yes
2) No
3) Unknown

Family history of other cancers:

4) Yes
5) No

6) Unknown

Alcohol consumption

1) Current
2) Former
3) unknown
4) Never

Smoking

1) Current
2) Former
3) unknown
4) Never

Part 2

Clinical/Pathological characteristics (disease related factors)

Date of diagnosis

Type of Histology found: -

1) Infiltrating lobular ca
2) Infiltrating ductal carcinoma
3) Other

Level of differentiation:

1) Moderately
2) Poorly
3) Well
4) Not documented

Test for ki 67

a) Yes
b) No

Ki 67 percentage……

Lymph vascular invasion: -

1) Yes

2) No
3) Not documented

immunohistochemistry:

ER

1. Positive
2. Negative
3. Not documented

PR

1. Positive
2. Negative
3. Not documented

Her2

1. Positive
2. Negative
3. Not documented

If HER 2 positive, is it

1. +1
2. +2
3. +3
4. Not documented

Breast affected:

1) Left
2) Right
3) Both
4) Not documented

Axillary node status:

1) Yes
2) No
3) Not documented

HIV status:

a) Positive
b) Negative
c) Not documented

ECOG of patient at diagnosis……...

Staging: Clinical:

T: N: M: Tumor size:

MANAGEMENT

Treatment start date…….

Treatment Modality Recommended

1. Neoadjuvant Chemotherapy, then Surgery, then Adjuvant RT
2. Surgery, then Adjuvant chemotherapy, then RT
3. Neoadjuvant chemotherapy – Surgery
4. Surgery – Adjuvant Chemotherapy

Neoadjuvant chemotherapy given:

1) Yes
2) No

Regimen of Neoadjuvant chemotherapy given …….

Number of neoadjuvant cycles received……

Initial Regimen:

1) AC-T (doxorubicin and cyclophosphamide followed by Taxane-paclitaxel)
2) TAC (Taxotere, Adriamycin, and Cyclophosphamide)
3) TC (Taxotere and cyclophosphamide)
4) CMF (cyclophosphamide, methotrexate & fluorouracil)
5) Taxane & Capecitabine
6) CAF (cyclophosphamide, Adriamycin & fluorouracil)
7) Taxane and carboplatin
8) Gemcitabine and Platinum
9) Taxane & Gemcitabine

10) Gemcitabine alone
11) Taxane alone
12) Capecitabine alone

Date for receiving first cycle…….

No of cycles: ……...

Did the patient have Surgery?

1) No
2) Yes

Date the surgery was conducted……...

Type of surgery done

1) MRM
2) BSC
3) Others…. describe

Was trastuzumab prescribed?

1) Yes
2) No

If yes, was trastuzumab received?

If yes, date of initiation initiated……

Duration of trastuzumab (no of doses received) …….

Did the patient receive radiation:

1) Yes
2) No

The type of radiation

1) Received hypofractionation
2) Received conventional fractionation

Radiation Therapy technique

1. 2D
2. 3D

Did the patient receive adjuvant chemotherapy?

1) No
2) Yes
3) Unknown

The regimen of adjuvant chemotherapy given.

Number of cycles given…….

Date of completing treatment……...

Was hormonal therapy given?

1) Yes
2) No

Type of hormonal therapy given to the patient:

1) Tamoxifen
2) Anastrozole

For how long did the patient take hormonal therapy……

Outcome measurement

Did the the patient have a relapse?

1) No
2) Yes

Date of relapse: …….

The duration of follow-up till relapse in months…….

The type of relapse that occurred

1) Distant
2) Local

Site that relapses occurred

1) Brain
2) Chest wall
3) Bone
4) liver
5) lung

6) Others

SURVIVAL DATA

Date at last follow up:…….

Status of the patient at the end of follow-up

1) Dead
2) Alive
3) Loss to follow up

Active cancer at last follow-up

Yes

No

Duration of follow-up in months…….

STUDY TELEPHONIC FOLLOW-UP

Appendix II: Verbal Informed Consent Document

Hello Ms./Mr.……....., my name is Dr Lemi Zinga. I am a master's student in the Clinical Oncology (MMED Clinical Oncology) department at Muhimbili University of Health and Allied Sciences (MUHAS). I am doing research as a partial fulfilment of my degree. The study aims at determining Barriers and Facilitators of Accessing Trastuzumab and Treatment Outcomes for Patients with Human Epidermal Growth Factor Receptor 2-positive Breast Cancer in the Real World. Data for the study is collected from files of patients with breast cancer who were treated at ORCI, and those missing clinic follow-up notes are contacted. The aim of this call is to find out what has happened to patients since their last follow up. Your involvement will help us get important data that is needed for the study outcome. This study has received ethical approval, and if you choose to participate, your identity will remain anonymous, and you will be asked various health-related questions.

Patients care and management during clinic visit will not change whether you choose to participate, answer questions or not.

Are you willing to proceed and participate in this study? and are you aware of the goal and consequences of participating?

Yes /No

QUESTIONNAIRE

Date…. Time: …….

Verbal consent obtained: Yes /No

Patient identity verified…… DOB …….

- Address of patient ……...
- Diagnosis of patient ……

Questions:

How are you?.....

Have you had a disease recurrence on your breast? Yes /No

If yes

when?..... Where?.....

Did you receive treatment?

When?.....where(hospital)?

Can you tell me the kind of treatment you received?

How is your health currently?.....

Were you ever diagnosed with any cancer other than breast cancer after treatment completion?

Yes/No

If yes – where?

If the patient is dead, the date of death and cause will be asked (if known).

If you have any more questions, please feel free to contact us through.

DR. LEMI ZINGA

EMAIL: wabuxis@gmail.com

CELL: 0654231568

Dr. Emmanuel Lugina

CELL;0713306408

MUHAS

P.O. Box 65015,

Dar es Salaam.

Swahili Version

RIDHAA YA MANENO

Habari Bi/Bw……. naitwa Lemi Zinga mimi ni mwanafunzi wa shahada ya uzamili ninaye soma katika chou kikuu cha muhimbili, Dar es salaam, inasomea udaktari bingwa wa saratani. Ninafanya utafiti kama sehemu ya kutimiliza masomo yangu.Utafiti huu unahusu sababu zinazosaidia na zinazoleta vikwazo katika upatikanaji wa trastuzumab na matokeo ya matibabu kwa wanawake walio na saratani ya matiti zenye vipokezi chanya vya HER2.Taarifa zinazotumika katika utafiti huu zinatolewa kwenye mafaili ya wagonjwa wa kansa ya matiti waliotibiwa katika hospitali ya saratani ya ocean road.Taarifa za karibuni za kliniki ambazo hazipo kwenye mfumo zitatafutwa kwa kupigia simu wagonjwa husika. Dhumuni la simu hii ni kuulizia maendeleo ya mgonjwa tokea siku ya mwisho aliyokuja kliniki, ushiriki wako katika utafiti huu utatusaidia kupata taarifa muhimu zitakazotumika kupata matokeo ya utafiti huu.Tumepata ruhusa kufanya utafiti huu kwa vyombo husika na kama ukiamua kushiriki jina lako litabaki kuwa siri.Pia kuna maswali utaulizwa kama sehemu ya ushiriki wako katika utafiti huu.

Usimamizi wako wa tiba ukija kliniki hautabadilika ikiwa utachagua kushiriki au kutoshiriki katika utafiti huu.

Je, unaelewa madhumuni ya utafiti huu, nini tunataka kwako na ungependa kuendelea au hapana?

Jibu - Hapana/ndio

DODOSO

Tarehe…… Saa……...

Idhini ya maneno inayoruhusu kuuliza maswali imepatikana? Hapana/ndio

Utambulisho wa mgonjwa umethibitishwa: Tarehe ya kuzaliwa…….

- Anwani …….
- Aina ya kansa ya mgonjwa

Maswali:

Je, unaendeleaje?

Je, saratani yako ya matiti imewahi kujirudia?

Ndio/hapana

Kama ndiyo

lini? Wapi?

Je,Ulipata tiba?Ndio/hapana

Kama ndiyo

Ulipata tiba hospitali gani na lini?

Unaweza niambia aina ya matibabu uliyopata?

Sasa hivi unaendeleaje?

Je, baada ya kumaliza matibabu yako ya awali umegunduliwa kuwa na saratani yeyote isipokuwa saratani ya matiti?

Hapana/ndio

kama ndio - wapi?

Kama mgonjwa amefariki, siku ya kifo na sababu vitaulizwa (kama inajulikana)

Kama una maswali Zaidi unaweza uliza kupitia

Dr. lemi zinga

MUHAS S.L.P 65015,

Dar es Salaam.

Namba ya simu: 0654231568

Barua pepe wabuxis@gmail.com

Au

Dr. Emmanuel Lugina,

Namba ya simu;0713306408

MUHAS

S.L.P 65015,dar-es-salaam

Appendix III: Ethical clearance

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION

Ref. No.DA.282/298/01.C/2037 Date: 14/02/2024

MUHAS-REC-02-2024-2037
LEMI NDUGUMBI ZINGA
COLLEGE OF MEDICINE MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: TREATMENT PATTERNS AND OUTCOME OF HER2-POSITIVE BREAST CANCER PATIENTS IN TANZANIA

Reference is made to the above heading,

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 14/02/2024
EXPIRATION DATE OF APPROVAL: 14/02/2025

STUDY DESCRIPTION:
Purpose:

The purpose of this Retrospective cohort study is to determine treatment patterns and outcomes for HER 2 positive breast cancer patients in Tanzania.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided: https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2014554.pdf and in the MUHAS archives.

The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain Data Transfer Agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain Material Transfer Agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country.
8. Apply for and obtain permission to publish the results from National Institute for Medical Research. The application should be before submitting to a publisher and not concurrently through the email publications@nimr.or.tz.
9. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
10. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
11. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.



Dr. Nahya Salim Masoud,
CHAIRPERSON, MUHAS RESEARCH AND ETHICS COMMITTEE

Appendix IV: Introduction Letter

UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote;
Ref. No. HD/MUH/T.33/2021

26th February, 2024

The Executive Director,
Ocean Road Cancer Institute,
P.O. Box 3592,
DAR ES SALAAM

Re: INTRODUCTION LETTER

We would like to inform you that the bearer of this letter is Lemi Ndugumbi Zinga with Reg. No. HD/MUH/T.33/2021 is a student at Muhimbili University of Health and Allied Sciences (MUHAS) pursuing MMed. Clinical Oncology.

As part of her studies, she will be doing an elective research titled: **"TREATMENT PATTERNS AND OUTCOME OF HER2-POSITIVE BREAST CANCER PATIENTS IN TANZANIA"**
She is being supervised by Dr. Mamsau Ngoma from MUHAS and Dr. Emanuel Lugina from ORCI.

The research has been approved by the Chairman of University Senate.

Kindly provide her with the necessary assistance to facilitate the conduct of her research.

We thank you for your cooperation.

Ms. Victoria Mwanilwa
For: DIRECTOR, POSTGRADUATE STUDIES
c.c. Lemi Ndugumbi Zinga

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam. Tel. G/Line: +255-22-2150302/6; Ext. 1015, Direct Line:+255-22-2151378;Telefax:+255-22-2150465;E-mail:dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz