FIVE-YEAR SURVIVAL AMONG POST MASTECTOMY BREAST CANCER PATIENTS MANAGED AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM

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By

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A dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Master of Medicine (General Surgery) of Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation titled: **"Five-year survival among post mastectomy breast cancer patients managed at Muhimbili National Hospital, Dar es Salaam"**, in (partial) fulfillment of the requirement for the degree of Master of Medicine (General Surgery) of the Muhimbili University of Health and Allied Sciences

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Date

DECLARATION
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I, **Adelaida Mghase,** declare that this **dissertation** is my own original work and that it has not yet been presented and will not be presented to any other University for the similar or any other degree award.

Signature:…… **Date**:……

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DEDICATION

This dissertation is dedicated to my beloved husband Ernest Mchihiyo, my mother for their encouragement and our children for their love and patience.

ABSTRACT

Background

Breast cancer is the most common cancer among women, with more than 1.1 million women newly diagnosed globally every year. Death from breast cancer accounts for 1.6% of female deaths every year worldwide. In Tanzania, 90.7% of patients with breast cancer present with advanced disease by the time they reach a tertiary care institution. There is no documented data on breast cancer survival following surgical treatment in Tanzania.

Objective

The main objective was to determine the five-year survival among patients who underwent mastectomy at Muhimbili National Hospital during the period January 2007 to June 2010.

Methods

A hospital-based retrospective cohort study conducted in Dar es Salaam. A structured checklist was used to collect data from 337 patient's case files and theatre operation register books, from Muhimbili National Hospital as well as medical records of Ocean Road Cancer Institute. All patients' records, irrespective of their co-morbidities, performance status, breast cancer stage, histological type, grade and treatment modalities were included. Survival at 5 years was estimated by using Kaplan Meier method. Factors associated with survival were examined using Cox proportional Hazards model. Ethical clearance was sought from the MUHAS review board and ORCI ethical committee.

Results

A total of 337 patients who underwent mastectomy were analyzed. One hundred thirty nine (41.2%) of the participants were aged between 46-60 years. The overall five-year breast cancer survival for the entire cohort of 204 stage II and III patients after excluding stage IV patients was 66% (95% CI=54% to 75%). The five year breast cancer survival for stage II patients was 84% and stage III was 65%. The common surgical treatments performed were MRM (modified radical mastectomy) and Toilet mastectomy. The most frequently used adjuvant therapy was chemotherapy (43.4%) followed by hormonal therapy (36.0%) and

radiotherapy (18.5%). The least used adjuvant treatment was immunotherapy (2.1%). Factors such as age, pathological grade and stage of the disease were found to be significant predictors of breast cancer survival post mastectomy.

Conclusion

Good survival rate is achieved for patients with early disease i.e. stage II. Age and pathological grade of the tumor influence survival rate in breast cancer patients. The common surgical treatments performed were MRM (modified radical mastectomy) and Toilet mastectomy followed by adjuvant therapies; chemotherapy, hormonal, radiotherapy and immunotherapy respectively.

Recommendation

These findings call for strengthening health education and promote early health seeking behavior and advocate on screening for early detection of breast cancer for good survival rate.

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LIST OF ABBREVIATIONS

ABC	Advanced breast cancer
ALN	Axillary lymph nodes
AJCC	American Joint Committee on Cancer.
BCS	Breast conserving surgery
BRCA 1	Breast cancer -Tumor suppressor gene 1
BRCA 2	Breast cancer -Tumor suppressor gene 2
CT	Computerized Tomography
ER	Estrogen receptor
HER	Human Epidermal Growth Factor Receptor
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
MRM	Modified radical mastectomy
ORCI	Ocean Road Cancer Institute
PR	Progesterone receptor
PTEN	Phosphatase and tensin homolog
P53	Tumor Protein p53
SLN	Sentinel lymph node
TNM	Tumor, Nodes, Metastases

DEFINITION OF KEY TERMS

Breast Conserving Surgery (BCS), is a surgical removal of the cancerous breast tissue and a portion of the breast tissue around the cancerous lump with lymph nodes dissection. Resection of the primary breast cancer is alternatively called segmental mastectomy, lumpectomy, partial mastectomy, wide local excision, and tylectomy. However, radiation therapy is often given after breast-conserving surgery to destroy cancer cells that may not have been removed during surgery.

Modified Radical Mastectomy (MRM): A modified radical mastectomy is a procedure in which the entire breast is removed, including the skin, areola, nipple, and most axillary lymph nodes; the pectorals' major muscle is spared.

Adjuvant therapy Adjuvant therapy for breast cancer is designed to treat micro metastatic disease, or breast cancer cells that have escaped the breast and regional lymph nodes but have not yet established, identifiable metastasis i.e. Include chemotherapy, hormonal therapy, immunotherapy (herceptin) radiation therapy, biological therapy or a combination of treatments.

Neo-adjuvant therapy is the administration of therapeutic agents before a main treatment. Neoadjuvant therapy aims to reduce the size or extent of the cancer before using radical treatment intervention, thus making procedures easier and more likely to succeed, and reducing the consequences of a more extensive treatment technique that would be required if the tumor wasn't reduced in size or extent.

Cancer survival was defined as the percentage of people still alive after a specified amount of time (often 1, 5 or 10 years) subsequent to a diagnosis of cancer at a specific time

Kaplan Meier method is a non-parametric used to estimate the probability of survival past a given time point.

CHAPTER ONE

1.0 INTRODUCTION

Breast cancer is the most common cancer among women, with more than 1.1 million women newly diagnosed globally every year. Death from breast cancer accounts for 1.6% of female deaths every year worldwide (1,2). Age standardized incidence rates vary greatly worldwide from 19.3 per 100,000 women in Eastern Africa to 89 per 100,000 women in Western Europe. In most of the developing regions the incidence rates are below 40 per 100,000 (3),(4). The lowest incidence rates are found in most African countries but here breast cancer incidence rates are also increasing. Breast cancer not only affects women but also men do get breast cancer though their incidence is low compared to women(1). Studies done in Tanzania showed that few breast cancer patients had early stage i.e. stage I and II but the vast majority of cases (90.73%) are diagnosed as advanced stage 3 and 4 cases. These late stage (LS) cases presented with tumor size greater than 5 cm ulceration, pain, nipple retraction, erythema or peaud'orange(5).

There are various factors that place women at increased risk for breast cancer. The etiological or risk factors for breast cancer are both endogenous and exogenous. Endogenous factors such as hormone levels and breast cancer risk, levels of multiple sex steroids – including total estradiol, free estradiol, estrone, and estrone sulfate increase risk of breast cancer. Exogenous factors i.e.; radiation, hormone replacement therapy, age at menarche, nulliparity, first birth at late age, the absence of lactation, and, postmenopausal obesity/weight gain and alcohol consumption are found to be associated with breast cancer(6). These factors include increasing woman age, mutations in tumor suppressor genes (including BRCA1 and BRCA2, PTEN, and p53) and other factors related to a family history of breast cancer (1,2,3,6). Environmental factors include diet, cigarette smoking, alcohol consumption and the lifestyle characteristic of developed Western countries, certain pathologic findings within breast tissue e.g. previous breast cancer, various premalignant lesions: cervical, ovarian and endometrial cancers are the risk factors for breast cancer etiology.

It is now recognized that mutations in some tumor suppressor genes, such as p53, BRCA1, BRCA2, PTEN, or ATM, or epigenetic functional inactivation of other tumor suppressor genes, such as SYK and NES1, appear to play important early roles in the formation of some breast cancers. In addition, alterations in proto-oncogenesis, such as HER2/neu, may contribute to the development of some breast cancer (2, 3).

There are different staging systems such as TNM(Tumor/Node/Metastases) system, of the American Joint Committee on Cancer staging and endoscopic reporting(7). However TNM is the most commonly accepted staging system worldwide including Tanzania. Used in Muhimbili Hospital is T- primary Tumor size- N-secondary metastasis to the nodes. M - Distant metastasis(7).

Histologically ductal carcinoma is the commonest type of breast cancer among women in Africa including Tanzania. This resembles the histological pattern of breast cancer in other parts of the world (1). Medullary and mucinous carcinomas are found more in Africa than Europe . In addition; women have more grade 3 tumors' in Africa than Europe. In Tanzania, a study has shown that 56.4% of patients had tumor with histological grade 3 ductal carcinoma, one patient had in-situ ductal carcinoma(8). This reflects that patient with breast cancer in African societies present late with the disease(1).

Radiologically breast cancer can be detected by Mammography, breast ultrasound, other metastatic work up such as chest x-ray abdominal ultrasound and bone scanning.
Because breast cancer cases are detected early in Europe, many of the women can have breast conserving surgery (BCS). BCS is mostly used in the developed countries with well-equipped hospitals, with screening tools like mammography and ultrasound for detection of early cancer.

Most women in Africa have mastectomy followed by adjuvant therapy; hormonal therapy or chemotherapy and others receive palliative care because the tumor is advanced and inoperable at presentation. At Muhimbili National Hospital Mastectomy and axillary clearance is often used instead of Breast conserving surgery.

Breast cancer incidence is increasing especially in low and middle-income countries (1) and survival rate is longer in high income countries(6). In Tanzania many breast cancer studies have been done but none on survival (8,9,10).

The survival of patients with cancer of the breast is related to several prognostic factors, including number of positive lymph nodes, tumor size, hormone receptor status, histological type grade, and patient's age(1). However, there are limited studies on survival of breast cancer patients post mastectomy where studying breast cancer survival and prognostic factors gives us insight into the natural history of the disease.

1.1 Literature review

Survival of breast cancer patients

Breast cancer is more common in Western Countries compared to African populations. However in African population, it appears that the disease is more aggressive and occurring at a relatively younger age. The 5-year overall breast cancer survival rate tends to be lower in developing countries compared to developed countries(11).

Survival information is not always available in studies performed by cancer registries worldwide. It is known that mortality and survival rates can vary between countries. The role of population based cancer registries has evolved, not only to report the incidence and trends of cancer but to include survival information, which has become increasingly important for better evaluation and planning of cancer control measures. Several studies on survival of breast cancer patients have been done in high income countries. A study done in USA found a five year breast cancer survival of 84%. Other studies from northern, western and southern Europe report a five year breast cancer survival ranging from 81-84%(12). A study done in South Asia reveals that the 5 years adjusted survival was 82%(13).Similarly, a study done in Vietnam found the overall five year breast cancer survival rate to be 74%(2).

Few studies on breast cancer survival have been done in sub-Saharan African countries(11).

A study from Uganda shows that the overall five year survival was 56%whilea Sudanese study shows overal five years survival of 38% (14).

Breast cancer survival post mastectomy

A study done at a Brazilian public hospital showed the five-year breast cancer survival for the entire cohort of operable patients was 78.5% (6). Breast cancer survival rates vary greatly worldwide, ranging from 80% or over in North America, Sweden and Japan to about 60% in middle-income countries and below 40% in low-income countries(4). The low survival rates in less developed countries can be explained mainly by the lack of early detection programs, resulting in a high proportion of women presenting with late-stage disease, as well as by the lack of adequate diagnosis and treatment facilities(3).

A study from Uganda showed that 5- year breast cancer survival rate was 74% for early disease stage and 39% for advanced disease stage the overall 5-year survival rate, was 56% (15).

It is worth noting that there was limited data on survival among breast cancer patients post-surgery in both high and low income countries including Tanzania.

Types of treatment for breast cancer patients post mastectomy

Patients receive post-operative radiotherapy, hormonal therapy and chemotherapy or combination according to stage at operation. The status of axillary lymph nodes (ALNs) determines the need for radiation therapy and adjuvant systemic therapy.

ALN dissection at the time of surgery was standard care until the 1990s, but often resulted in pain, numbness, swelling, and decreased mobility in the affected arm. In patients with clinically negative nodes, a negative intraoperative sentinel lymph node (SLN) biopsy precludes the need for ALN dissection. SLN biopsy reduces arm symptoms compared with ALN dissection(15,16)**.**

Typically, whole-breast radiation is performed following breast-conserving surgery to treat subclinical disease. A review of 10 randomized controlled trials (RCTs) comparing breast-conserving surgery with and without radiation showed that radiation in addition to surgery significantly reduced the five-year local recurrence rate, regardless of the use of adjuvant systemic therapy (7 versus 26 percent), and appeared to decrease the 15-year breast cancer mortality risk (30.5 versus 35.9 percent(17).

A study done in Istanbul, Turkey showed those patients who underwent mastectomy and did not receive radiation, chemotherapy or hormonal therapy developed recurrent local regional or distant metastasis. The study showed that the chance of developing local regional recurrence was4% in patients who received radiation therapy. But 12.2%didnot develop local regional recurrence. Findings from the study also showed that the chances of developing distant metastasis increases by 25.7% in patients who received radiation and by 28.5% for those who

did not (18). Furthermore, a study from Vietnam showed that there were 74.6% of cases receiving hormone therapy during 5 years post mastectomy (19).

Determinants of breast cancer survival

a) Demographic characteristics

Age at diagnosis is an important independent prognostic indicator for breast cancer survival post-surgery. In an analysis that examined breast cancer outcomes by age group those in the younger age category had the poorest 5-year cancer specific survival of about 70%(20). Patients aged 70years and older had shorter survival than young age (6). Those with 5-years breast cancer specific survival (84%) were between the ages of 71-80 at diagnosis. The oldest age group had the worst result (40%). In stage adjusted 12 analyses, again the youngest age category had the poorest survival compared to all the other age groups, except for women diagnosed at stage I where survival was similar(20). A more recent study that also investigated breast cancer survival in women younger and older than age 40 and adjusted for stage at diagnosis found different results. While all stage survival was poorer for the younger age category, stage adjusted analyses revealed that the survival difference occurred for those diagnosed at stages I and II, but not the higher stages (21).

b) Co-morbidities

Breast cancer survival rate is impacted by other parameters besides the tumor. Studies have shown that patients with co-morbid conditions such as cardiopulmonary disease, metabolic disease hypertension and heart disease were unable to tolerate the post-surgery consequences. This contributes in reducing the survival rate post mastectomy. Having concurrent or multiple medical conditions has been shown to elevate the risk of death among women diagnosed with breast cancer, based on the results of a longitudinal analysis (n=559) of mainly white women in the United States (16). The percentage of women who died during a 10-year follow up period with no co morbidity was 8%. With one co morbidity the proportion of women who died rose to 25%, with two it increased to 48% and 59% of those with 3 or more co morbidities (22).

c) Stage

The stage at diagnosis is a very important determinant of breast cancer survival. Survival declines with advance in disease stage. Studies have shown that survival rate was high for stage I and II compared to stage III and IV for patients who underwent mastectomy with or without adjuvant therapy(23). Generally, stage 0 (ductal carcinoma in situ) diagnoses were 100% curable with appropriate treatment and declining survival with increasing stage. Data from one cancer centre in Canada revealed that the relative 5-year survival of breast cancer for stage I was 96.0%, 85.6% for stage II, 59.2% for stage III and 25.5% for stage IV(23).

d) Family history

Having a family history of breast cancer increases the likelihood of developing breast cancer but it may not influence survival. In review that assessed the effect of family history on breast cancer survival, four studies showed statistically significant better survival in patients with a family history, while two studies demonstrated a significantly worse prognosis(24). The authors suggest that some of the discrepancies may be explained by differences in methodologies across studies. Furthermore, knowing about a hereditary risk may change screening behavior and increase the likelihood of detecting smaller cancers with better prognosis.

e) Tumor size

Studies have shown that tumor size is an important prognostic factor. Patients with tumors larger than 5 cm (T3) had an hazard ratio of dying due to breast cancer of 2.31 (95% CI 1.41-3.80) compared to patients with tumors measuring up to 2 cm (T1). In addition, patients with tumors infiltrating the skin or chest wall had hazard ratio of 4.34 (95% CI 2.77-6.79) in relation to T1 patients.

f) Lymph node status

The factor with the highest impact on survival is lymph node involvement. High number of involved lymph nodes was associated with lower survival. Patients with 9 or more positive

axillary lymph nodes had an HR of 3.59 (95% CI 2.35-5.48) in relation to patients with negative nodes(6)**.**

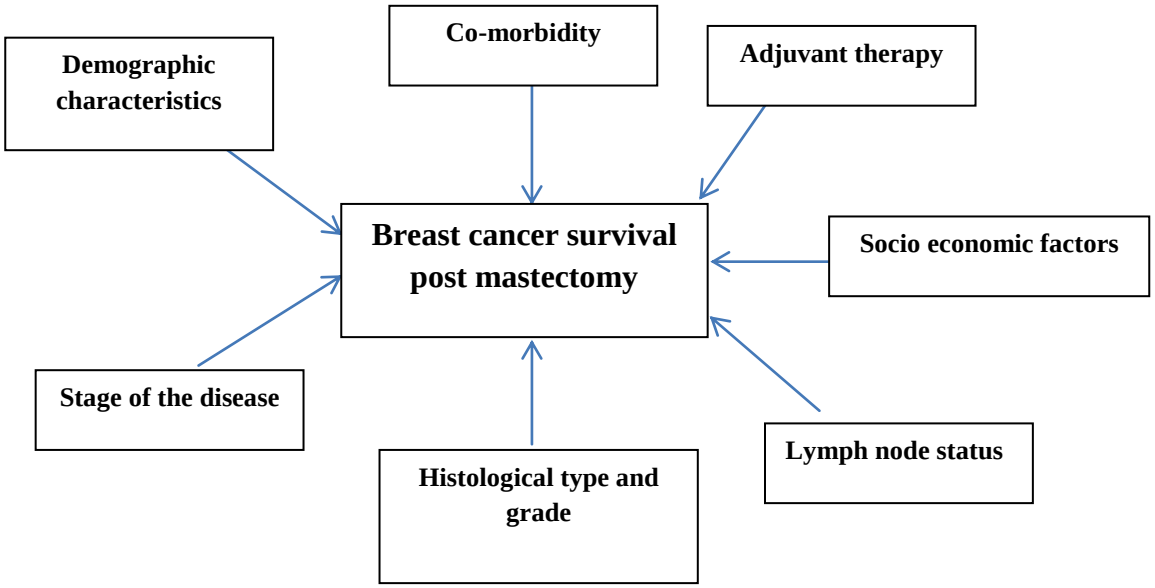
g) Histological grade

A study done in Brazil found that patients with high-grade tumors had an HR of 2.54 (CI 1.62-3.96) associated with low survival(6). Another study from Uganda showed high pathological grade with poor survival for advanced disease 51.5%(14).

h) Socio-economic status

Socioeconomic status is known to be an intervening factor, mostly because of low frequencies of patients undergoing interval screening, treatment delay and lack of widely available modalities of treatment such as chemotherapy, hormone, and radiotherapy, among the less affluent populations(25).

1.2 Conceptual framework



Explanation of Conceptual Framework

Age at the diagnosis is an important independent prognostic indicator for breast cancer survival post-surgery. Studies have shown that the younger patient with breast cancer disease have the second poorest five years survival than the older patient due to aggressiveness of the disease in young. Breast cancer survival rate is impacted by other parameters besides the tumor. Studies have shown that co-morbid conditions like cardiopulmonary disease, metabolic disease hypertension and heart disease has chances unable to tolerate the post-surgery. This contributes in reducing the survival rate post mastectomy.

The stage at the diagnosis is a very important determinant of breast cancer survival. Survival declines with increase in stage. Studies have shown that stage I and II survival rate is high compared to stage III and IV for patients who undergo mastectomy with or without adjuvant therapy. Five-year overall survival rate tends to be lower in lower income countries but higher in high income countries. This is due to lack of screening programs for breast cancer, treatment delay and lower availability to modalities of treatments. Patient's survival also relates to other several prognostic factors like histological type and grade, and lymph node status.

1.3 Problem Statement

Breast carcinoma is not a rare disease among patients being attended in different tertiary hospitals in Tanzania including Muhimbili National Hospital, and other public and private hospitals in Dar es Salaam, Tanzania. A study done in 1997 in Dar es salaam showed that among 50 patients with breast cancer, most of them presented with advanced stage with no single patient in stage I, and the majority were in stage IIIB (8,10). In Tanzania MRM is mostly performed among women with breast cancer in stage I,II and III.

One of the reasons for poor survival amongst women with breast cancer in the developing countries is late presentation for medical treatment since they have advanced disease stage at that time (8, 10,12). There are various factors that influence survival in breast cancer patients such as patients' age, adjuvant chemotherapy and radiotherapy, socioeconomic factors, histological type and grade and stage. These factors have been confirmed by several studies done in developed and few developing countries (17,26).

In Tanzania, studies on survival rates of breast carcinoma are not available in the indexed publications. There are good numbers of publications in developed countries that have reported good survival rates for patients with breast cancer (6, 12, 13). Few studies have been done in Asia and some parts of Africa (11,13). It is clear that survival rate for breast carcinoma is an important surgical parameter to measure outcomes following treatment of these patients. Therefore, there is a need to study the survival rates among breast carcinoma patients post mastectomy in Tanzania.

1.4 Rationale of the study

There are no studies available for breast cancer survival from Muhimbili National hospital which is also a public university, teaching hospital and Ocean Road cancer Institute.

This study is important for the management outcome and audit of this disease in surgical department and all the oncological team where these patients are being attended. The result of this study will provide evidence which can inform surgical practice.

The results of this study will help to establish and fill the existing knowledge gap on survival rates among patients with breast cancer disease in Tanzania. The results of this study could help health policy makers engaged in planning for breast cancer interventions and can be used in models of cost effectiveness analysis of interventions for breast cancer in the country. This study will also add to the body of knowledge on determinants of five years survival rate among post mastectomy breast cancer patients and will open way for other studies on determining the surgical practice and treatment modalities for breast cancer in Tanzania and other settings with similar context.

1.5 Research Questions

The following were the research questions for the proposed study:

1. What is the overall five-year survival of breast carcinoma in patients who had mastectomy at MNH in Dar es Salaam, Tanzania?
2. What are types of additional treatment options offered to breast cancer patients post mastectomy at MNH?
3. What are the factors that influence survival of breast cancer patients who had mastectomy at MNH?

1.6. Objectives

1.6.1. Broad Objective

To determine five year breast cancer survival and its determinants among patients who had mastectomy at Muhimbili National Hospital, Dar es Salaam.

1.6.2 Specific Objectives

1. To determine the 5-year breast cancer survival among patients who had mastectomy at Muhimbili National Hospital between January 2007 and June 2010.
2. To document types of additional treatments modalities offered to breast cancer patients post mastectomy at between January 2007 and June 2010.
3. To identify factors that influence survival of breast cancer patients who had mastectomy at between January 2007 and June 2010.

CHAPTER TWO

2.0 METHODS

2.1 Study setting and design

A hospital based retrospective cohort study of 367 patients' postmastectomy conducted at Muhimbili National Hospital. Data was extracted from theatre operation register books, patients' case files, medical records and follow up detail at Ocean Road Cancer Institute for patients treated between January 2007 to June 2010 was performed.

Telephone communication was used to obtain patients' information, whether she is alive or not from phone numbers of patients or relatives recorded in the patients register book.

Muhimbili National Hospital is a Public University Teaching Hospital and National referral centre for Tanzania with a bed capacity of 1,500 out of which 120 beds are dedicated to adult general surgery services. It is positioned to serve patients from different parts of the country and is, in effect, the pinnacle of the clinical health services in Tanzania.

Ocean Road Cancer Institute (ORCI) located in Dar Es Salaam, is the only public designated facility for cancer treatment in Tanzania with a capacity of 300 beds and offer mainly Radiotherapy and Chemotherapy services after surgery has been done at MNH.

2.2 Study population

Study population included patients who underwent mastectomy for breast cancer in the general surgery department of MNH.

2.2.1 Inclusion criteria

Female patients confirmed carcinoma of the breast that underwent mastectomy in MNH during the period of January 2007 to June 2010.

2.2.2 Exclusion criteria

Male patients operated for breast cancer

Patients after mastectomy who died from other diseases

Patients whose clinical records could not be traceable

2.3 Sample size estimation

Sample size estimation was based on the Log rank test for survival studies(27).Assuming 40% of the patients with advanced disease survive after 5 years(14), 90% power, a ratio of 1:2 and 10% withdrawal, the minimum required number of breast cancer patients who had mastectomy for the study was estimated at 330.

2.4 Sampling methods

A total of 367 files for patients who had undergone mastectomy during the period January 2007 and June 2010 were retrieved from MNH and ORCI. Of these, we excluded 30 patients with 23 from MNH and 7 from ORCI who had no single follow up post mastectomy or phone number. Three hundred and thirty seven cases were included in the study.

2.5 Data collection tool and technique

Data collection was done using a pre-tested data collection tool with the help of two trained research assistants. The date of last visit in the follow up clinic was obtained from the patients files.

Follow up of patients to determine their survival status 5 years after surgery was done by using telephone communication and outpatients follow up clinics at MNH and ORCI. All patients' records, irrespective of their co-morbidities, performance status, and treatment modalities were included. The following details were recorded from the patients' data medical records:

i. Age of the patients at presentation
ii. Stage of the disease diagnosis
iii. Histological types
iv. Histological grades
v. Date of surgery and type of mastectomy done
vi. Treatment modality given to the patient after surgery, for example, radiotherapy, chemotherapy and hormonal therapy. Those who would not have received any of these were also noted

vii. Time in months when they died or got lost to follow up or if they were still on follow-up.

2.6 Reliability and validity of data collection tool

In order to ensure reliability, the data collection tool for this study was pretested (n=50 patients) for comprehensibility, appropriateness of questions, extent of missing data. The tool was then refined and research assistants instructed appropriately on data collection. This ensured that the tool could consistently be used to collect the required information.

Validity of an instrument refers to as the extent to which an instrument measures what it aims to measure. The data collection tool was developed based on the literature reviewed. In addition, the tool was reviewed by a subject matter expert to assess whether the content was appropriate for measuring the intended concepts.

2.7 Data analysis

Data was entered and analyzed using SPSS version 20. Study findings are presented using proportions for categorical data and mean or median for continuous variables. Chi-square test was used to compare proportions. The 5-year breast survival was estimated using the Kaplan–Meier curve (6). The 5-year breast cancer survival rate was taken as the proportion of breast cancer patients who were still alive, not necessarily disease-free, 5 years after mastectomy. Stage IV patients were excluded in calculating survival because for them doing mastectomy is to improve quality of life\ rather than improving/prolonging survival. The survival rate was estimated using the date of surgery and date of death or date of last visit. The log-rank test was used to compare survival between groups of interest. Cox proportional hazards model was used to examine the association between the characteristics measured at time of surgery with time to death after surgery. Hazard ratios (HRs) and 95% confidence intervals are presented. A two-sided p-value of < 0.05 was considered as statistically significant.

2.8 Ethical considerations

This study was carried out in accordance with existing ethical guidelines. Ethical clearance for the study was obtained from MUHAS ethical committee. Permission to carry out the study was obtained from authorities of ORCI and MNH. For those who were contacted by phone, description of the study was explained to the patient or patients relative to ensure that they understand and consent verbally to participate in the study. The author had to bear in mind that she was going to talk with a patient with breast cancer or relative of the patient whom might be a husband, his or her child or and the patients might have died or seriously sick. The use of a structured way of calling was important. When calling and the phone was picked, the author introduced herself then asked for the name of the respondent and compared it to the one in the list. If it was the same, then the author asked for verbal consent first and requested to ask some few questions concerning her treatment. Confidentiality was ensured.

CHAPTER THREE

3.0 RESULTS

3.1 Demographic characteristics of the study population

A hospital based retrospective study involved 337 women who underwent mastectomy for breast cancer between January 2007 and June 2010. Among these139 (41.2%) of the participants were aged between 46 to 60 years. The mean age at the time of surgery was 51years (standard deviation=14 years). One hundred ninety three of the study subjects (57.3%) had only primary education and half of the patients (49.6%) were not formerly employed as shown in Table 1.

Table 1: Demographic characteristics of respondents (n=337)

Characteristics	Frequency (%)
Age group (years)	
15-30	17 (5.0)
31-45	106 (31.5)
46-60	139 (41.2)
Above 60	75 (22.3)
Education	
None	84 (24.9)
Primary	193 (57.3)
Secondary	60 (17.8)
Occupation	
Employed (formal)	50 (14.8)
Not employed	167 (49.6)
Self employed	120 (35.6)

3.2 Clinical and pathological characteristics

3.2.1 Histological type

Ninety five percent (95.2) of patients had invasive ductal carcinoma, very few presented with either lobular (1.8%) or other types (medullary and papillary 3.0%) as indicated in Figure 1.

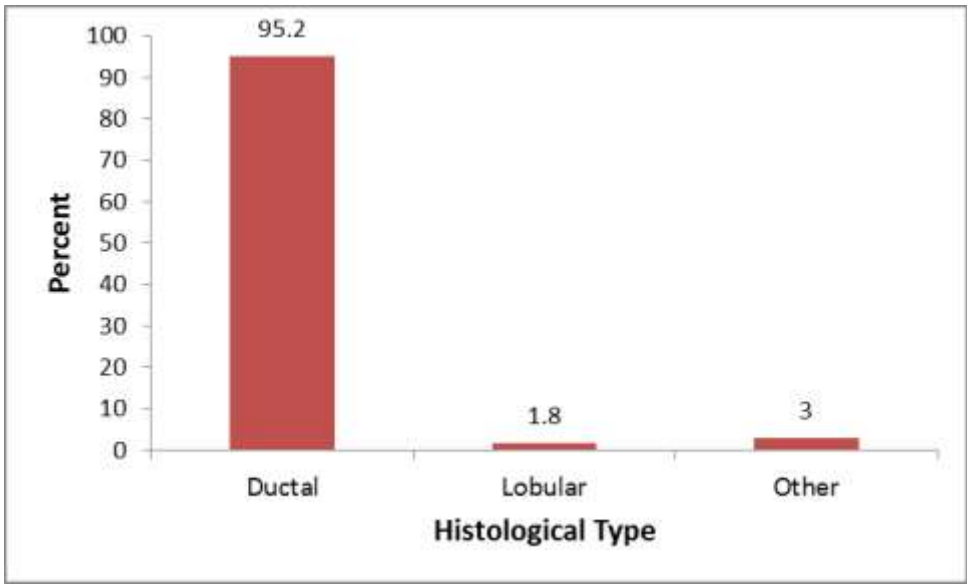


Figure 1: Distribution of patients according to Histological Type

3.2.2. Pathological grade

Moderately differentiated pathological grade was the most common grade in 156 (46.3%) of cases followed by well differentiated in 151 (45.1%) of the patients. Twenty nine (8.6%) patients had poorly differentiated pathological grade (Figure 2).

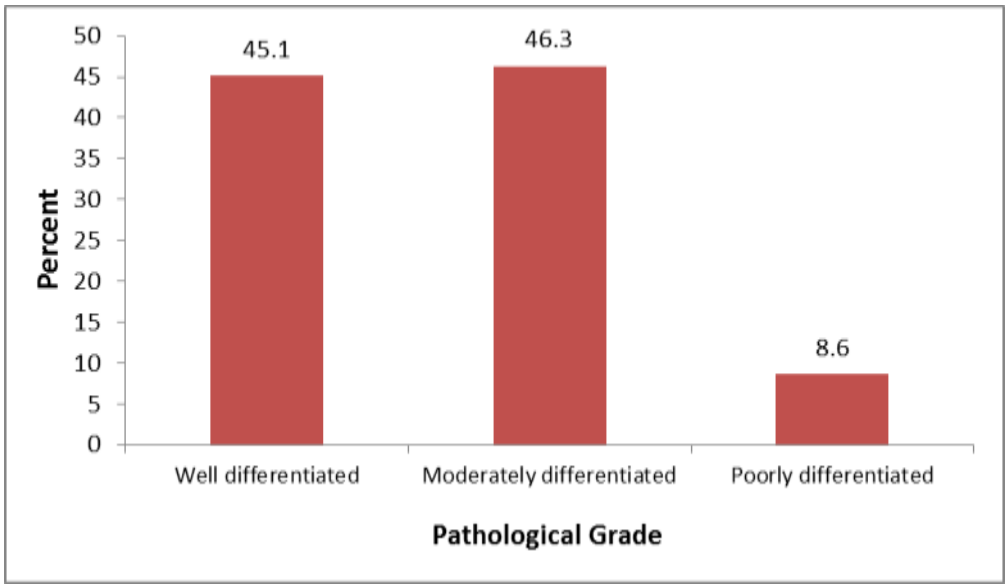


Figure 2: Distribution of patients according to Pathological grade

3.2.3 Number of patients according to stage of disease at diagnosis

Among 337 patients, forty nine percent were stage III of the disease, 39.5% stage IV and11.3% stage II There were no patients in stage one.

Table 2: Stages of Breast Cancer (N=337)

Stage	Frequency	Percentage
2	38	11.3
3	166	49.3
4	133	39.5

3.2.4 Type of surgery

Modified radical mastectomy was done on 62.9% of the breast cancer patients. The rest of the patient had toilet mastectomy.

Table 3: Type of surgery

Type of surgery	Frequency	Percent
MRM	212	62.9
Toilet mastectomy	125	37.1
Total	337	100.0

3.3 Five-year survival proportion among patients who had mastectomy

Five-year breast cancer overall survival for the entire cohort of 204 stage 11 and 111 patients was 66% (95% CI=54% to 75%). The five year breast cancer survival for stage 11 patients was 84%and 65% for stage 3. Among the 204 patients, 39 (19%) died.

3.4 Factors influencing survival of breast cancer patients post mastectomy

Table 4 shows the univariate results for factors influencing survival. Young age (15-30 years) is associated with higher risk of dying than older age (40-60 years). However, this association was not statistically significant (HR=2.58; 95% CI=0.83 - 7.98). Women with stage three of the disease had a significantly higher risk of dying (lower chance of survival) than stage two disease patients (HR=2.74; 95% CI=1.06- 7.07). Figure 3 shows the comparison of survival between stage two and three (Log rank test p=0.03). Furthermore, patients with poorly differentiated tumor were more likely to die than those with moderately differentiated grade tumors (HR=2.54; 95% CI=1.06 – 6.08). This finding is also illustrated in Figure 4. It can be seen that patients with poorly differentiated grade had poor survival compared to those with moderately or well differentiated grade (Log rank test p=0.02).

Table 4: Univariate analysis of factors influencing survival of breast cancer patients post mastectomy (n=204)

Variable	Total	Number of deaths (%)	P value*	HR (95% CI)**
Age group (years)			0.38	
15-30	14	4 (29)		2.58 (0.83 - 7.98)
31-45	67	13 (19)		1.33 (0.62 - 2.88)
46-60	78	13 (17)		Reference
>60	45	9 (20)		1.56 (0.66 - 3.66)
Occupation			0.16	
Employed	27	2 (7)		0.30 (0.07 – 1.27)
Not employed	107	22 (21)		Reference
Self employed	70	15 (21)		1.16 (0.60 – 2.23)
Education			0.99	
None	50	9 (18)		1.01 (0.47 - 2.18)
Primary	120	23 (19)		Reference
Secondary	34	7 (21)		1.08 (0.46 - 2.51)
Co morbidities			0.86	
No	168	31 (18)		Reference
Yes	36	8 (22)		1.07 (0.49 – 2.34)
Pathological Grade			0.02	
Well differentiated	90	14 (16)		0.72 (0.36 – 1.45)
Moderately differentiated	99	18 (18)		Reference
Poorly differentiated	15	7 (47)		**2.54 (1.06 – 6.08)**
Type of surgery			0.77	
MRM	132	27 (20)		Reference
Toilet mastectomy	72	12 (17)		1.11 (0.56 – 2.20)
Histological Type			0.64	
Ductal	194	36 (19)		Reference
Lobular	4	2 (50)		1.76 (0.42 – 7.35)
Medullary & papillary	6	1 (17)		0.61 (0.08 – 4.44)
Stage of disease				
2	38	5 (13)	0.03	Reference
3	166	34 (20)		**2.74 (1.06 – 7.07**)

*Log-rank test; **95% confidence interval; HR=hazard ratio

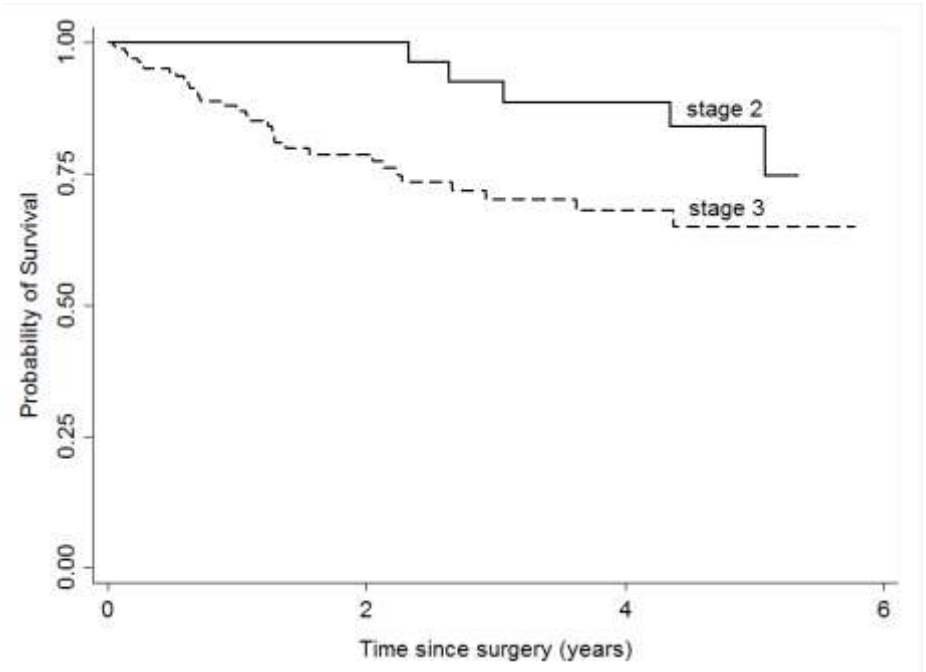


Figure 3: Survival probability by stage of disease

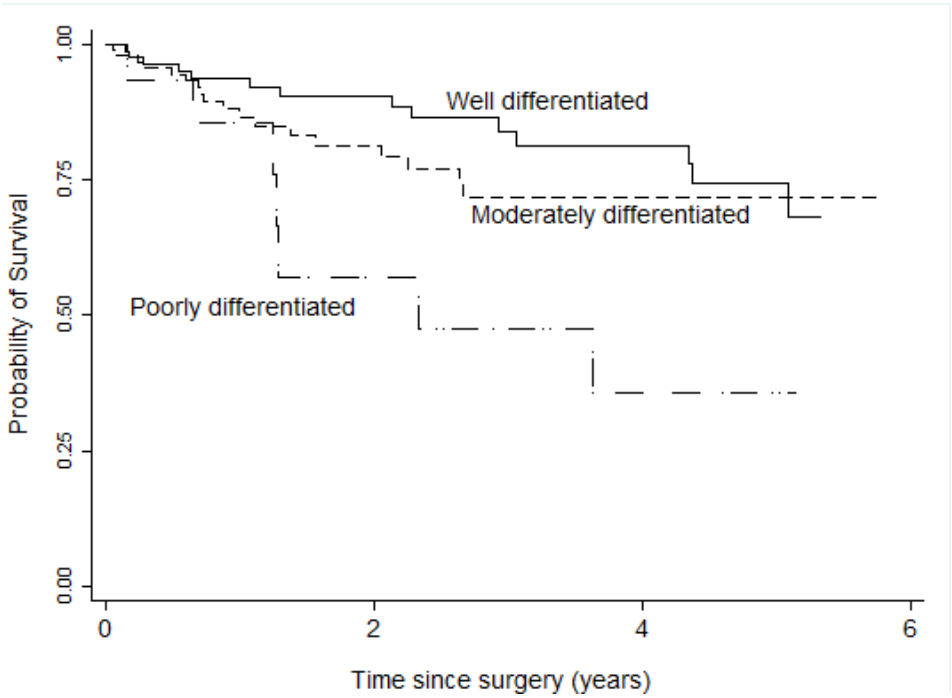


Figure 4: Survival probability by pathological grade

Table 5 shows multivariate results for factors influencing breast cancer survival post mastectomy. Results show that patients aged 15-30 years had a significantly higher risk of dying than patients aged 46 to 60 years (AHR=3.41; 95% CI=1.08 - 10.77). In pathological grade, clients with poorly differentiated tumors were more likely to die than those with moderately differentiated cancer (AHR=2.72; 95% CI=1.12 - 6.59). Likewise, women with stage three disease at diagnosis had a significantly higher risk of dying (lower chance of survival) than stage two patients (HR=2.74; 95% CI=1.06 - 7.07; p=0.029).

Table 5: Multivariate analysis of factors influencing survival of Breast cancer patients post mastectomy

Variable	AHR	95% CI	P value
Age group (years)			
15-30	**3.41**	**1.08 – 10.77**	**0.036**
31-45	1.41	0.65 – 3.05	0.387
46-60	Reference		
>60	1.56	0.66 – 3.68	0.312
Pathological Grade			
Well differentiated	0.82	0.40 – 1.68	0.588
Moderate differentiated	Reference		
Poorly differentiated	**2.72**	**1.12 – 6.59**	**0.027**
Stage of disease			
II	Reference		
III	**2.91**	**1.11–7.62**	**0.029**

AHR= adjusted hazard ratio

CHAPTER FOUR

4.0 DISCUSSION

In this study, most of the patients with breast cancer enrolled were aged between 46 to 60 years (41.2%). Findings from our study differ from the study done in Uganda where the peak age in their series was 30–39 years, which is young age group(14). The mean age in our study was 51 years which is 11 years older than the Ugandan study but 4 years older compared to studies done in India and United States(11)(28)(29). In this study, 57.3% of the study subjects had primary education and this low level of education may impact the patients' understanding, knowledge on cardinal features of breast cancer symptoms and signs, therefore lead to late presentation to the hospital with advanced disease.

Surgery remains an important and essential component of management of breast cancer and operability of breast cancer depends on the stage of the disease. In this study 49% presented with stage III. This was also found in a study in Dar es Salaam by Amir where most of the patients were in stage III (10). Similarly, a study done in Brazil showed that 40% were stage III of breast cancer disease(6). Stage at diagnosis is the key determinant of breast cancer survival which decreases with increased stage. In this study about 90% of patients with breast cancer that underwent mastectomy had stage III and IV. Studies showed that there is higher survival rate in stage II compared with stage III(23).

As for the pattern of histology types seen in this study (95.2%) had invasive ductal carcinoma and very few (1.8%) presented with either lobular carcinoma or others (medullary and papillary). Findings from Nigeria and China demonstrated that 81.8% had invasive ductal carcinomas and 3.5% had invasive lobular cancers(30,31). In this study (46.3%) had moderatetely differentiated tumors which was the most common pathological grade and the least (grade III) 8.6% was poorly differentiated which is also associated with poor survival. However in Uganda 57% of these tumors were poorly differentiated which indicated that a large proportion of patients had more aggressive type of disease(14). The most common

pathological grade reported in Brazil was grade 2 (moderately differentiated) which accounted for (43%) followed by grade 3 (36%)(6).

In this study the five-year survival rate for stage II disease was 84% and 65% for stage III while the overall survival was 66%. This finding differs from Ugandan study which showed survival rate for stage I and II was 100% and the overall five years survival in their study was 51.8%(32).Another study from Uganda showed a bit lower survival rate of 74% for early stage disease and overall survival was 56% (14). A study in Brazil reported slightly lower (51%) overall five year survival rate than that reported in Uganda. Another study from Vietnam shows that the overall survival rate was 74% (2).

When comparing survival rates in this study and that of Nigeria it showed that black Africans have three features in common i.e. late stage at line of seeking treatment, lower age at peak incidence and severe tumor burden that takes a more aggressive course and consequently lower survival rates(33). Possible reasons for the poorer survival rates in countries with low income vary, which include delayed individual health seeking behavior, low social economic status, lack of capacity for early detection and inadequate diagnostic measures and supportive treatment(25). In high-resource to medium-resource settings, advances in breast cancer therapy in recent years have made a considerable contribution to improved survival and the subsequent reduction or stabilization of breast cancer death rates. The knowledge that breast conservation is possible may have a multiplier effect on early presentation, as it encourages patients to come even earlier. In our study there were no cases of breast conserving surgery, all subjects underwent mastectomy. Post mastectomy more than one adjuvant therapy was given to patients as a combination depending on the stage of the disease. The most frequently used adjuvant therapy was chemotherapy (43.4%) but this means many patients post mastectomy did not receive chemotherapy probably due to the cost of travelling long distances to a hospital, cost of chemotherapeutic agents in case they are not available in cost exemption policy or out of stock at ORCI, those may be the reason for patients having limited their therapeutic options. (NB: At the time that patients in this study were treated proven cancer patients were exempted from paying for chemotherapeutic agents**).** The problem been most of

our patient do not have health insurance to cover for the chemotherapy cost which is very expensive. Both of these explanations may have contributed to the low percentage of patients who received chemotherapy. But radiotherapy and immunotherapy were less used. A study from Tanzania showed that management of those patients included mastectomy with axillary lymph node clearance followed by adjuvant hormonal therapy or chemotherapy and they were used with radiation(8). Similarly in India a combination Adjuvant therapy was mentioned as being the appropriate additional treatment given post mastectomy. Hormonal therapy (74.6%) was also commonly used in Vietnam after Mastectomy (2).

In this study, age, stage of disease at diagnosis and pathological grade were significant predictors of survival after controlling for other factors. This compares well with study from Vietnam which showed that stage at diagnosis was an important predictor for survival of breast cancer. Patients with early stage diagnosis had better chance for survival than those who came at advanced stage of the disease (2), Findings from this study revealed that patients in the young age group, 15-30 years old had low survival compared to those in the 40-60 years age group. In contrast to this, a study from Brazil showed that patients older than 70 years old had low survival rate compared to patients 35 to 69 years old (6). For the young age group this could be due to their predisposition to aggressive type of tumors but also it could be because of gene mutation in the young age which seems to start early and is severe, gene mutation like BRCA2, ER, PR and HER2(34) while for the older age group (i.e.>70 years) it could be due to co-morbid conditions.

There were several limitations in this study. It was difficult to contact patients using telephone due to several reasons. Sometimes patients may have changed or lost her number. Moreover, the telephone number of a patient or relative may not be documented in the patients file. Due to poor telecommunication coverage, it was difficult to reach every patient especially those in remote areas. The study may have overestimated overall survival due to large number of censored patients (lost to follow-up), that was not known whether the patient's still alive or had died.

CHAPTER FIVE

5.0 CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

The overall five-year survival was sixty-six percent. Most patients had late stage disease at diagnosis. Good survival rate is achieved for patients with early stages (i.e. stage (II). The most common surgical treatment performed was modified radical mastectomy. Toilet mastectomy was done for late stage disease as palliative treatment. Factors which were important predictors of five year survival were stage at diagnosis, age and pathological grade.

5.2 Recommendations

These findings call for strengthening health education and promotion of early health seeking behavior and advocating on screening for early detection of breast cancer for good survivals

There should be a specific and reliable National data coding system for cancer, where data can be accessed.

There should be a good referral and feedback system to health care units which are in close proximity to patients' residential area.

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APPENDICES

Appendix I: Data extraction tool

S/No……..

1. Date of interview __ __/__ __/__ __
2. Hospital registration number----------
3. Patient age / Date of birth ----------
4. Sex 1. Male 2. Female
5. Marital status: 1. Married 2. Single 3. Widow 4. Separated/ Divorced
6. Patient level of education 1. None 2. Primary 3. Secondary and above
7. Patient occupation 1. Employed 2. Not employed 3. Self employed
   4. Others
8. Patient region of residence ----------
9. Tumor locations 1) Right 2) Left 3) Both
10. TNM status:
    1) Tumor size <2cm
    2) Tumor size ≥2cm and <5cm
    3) Tumor size ≥ 5cm
    4) Ulcerative
    5) Peau d' orange
11. lymph node status
    1) NO
    2) N1
    3) N2
    4) N3
12. Distant metastasis:
    1) M0
    2) M1

13. Duration of the lump 1. Months---------- 2.Years ----------

14. Histological type
    1) Ductal
    2) Lobular
    3) Others

15. Grade of the tumor
    1) Carcinoma insitu
    2) Well differentiated
    3) Moderate differentiated
    4) Poorly differentiated

16. Type of surgery
    1) MRM
    2) BCS
    3) Debulking (toilet mastectomy)
    4) Others

17. Was chemotherapy given 1) Yes 2) No If Yes?
    What type of chemotherapy
    1) CMF-cyclophosphamide ,methotrexate, 5fu
    2) ECF-Epirubin,Cisplatin,5fu
    3) CA/EC-Cisplatin,Adriamycin
    4)5FU-Five fluorouracil
    5) How many cycle ……

18. Was hormonal Given 1) Yes 2) No If Yes which one
    1) Tamoxifen
    2) Progestin:
    3) GnHR agonist

4) Aromatase inhibitors

5) Ophorectomy

19 Was immunotherapy given: 1) Yes 2) No If Yes which one

1) Trastuzumab (Herceptin**)** 2) Monoclonal antibody binds to HER-2

Combination ……..

20 Was radiotherapy given 1) Yes 2) No if yes

1) External beam radiation 2) Brachytherapy 3) both

21. Date of surgery __ __/__ __/__ __

22. Survival status: was through Phone communication: by self introduction, purpose of the call, enquires about the clients:

1) Alive
2) Dead Date of death __ __/__ __/__ __
3) Not known

23. Co-morbidities:

1. Yes
2. No
3. If yes, mention ……

24. 1. Date of last follow up at MNH----------

2. Date of last follow up at ORCI----------

25. Phone numbers

1) Patient _____
2) Relative of patient _____