THE PATTERN OF PROGNOSTIC INDICATORS AMONG WOMEN WITH BREAST CANCER UNDERGOING MODIFIED RADICAL MASTECTOMY AT MUHIMBILI NATIONAL HOSPITAL (MNH) AND TUMAINI HOSPITAL, DAR ES SALAAM TANZANIA

By

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A dissertation submitted in (partial) fulfillment of the requirements for the award of the degree of Master of Medicine (General Surgery) of the Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The under signed certifies that he has read and hereby recommend for acceptance by Muhimbili University of Health and Allied sciences a dissertation entitled: **"The pattern of Prognostic indicators among women with breast cancer undergoing modified radical mastectomy at MNH and Tumaini Hospital, Dar es Salaam from April 2011 to January 2012"** 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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DECLARATION AND COPYRIGHT

I, **Rabiel Happiness**, declare that this **dissertation** is my own 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 dissertation is dedicated to my parents Mr. and Mrs. Rabiel Christopher, for their love and investing in my education, my dearest son Colin Godfrey who didn't live to see his first birthday, he was the best thing that ever happened to me, my dear husband Godfrey J. Shoo and all women who have survived breast cancer.

List of abbreviations and acronyms

AJCC	American Joint Committee on Cancer
ASR	Age Standardized Rate
DCIS	Ductal Carcinoma Insitu
ER	Estrogen receptor
ERB2	Epidermal Growth Factor Receptor gene family 2
FFPE	Formalin-fixed and Paraffin Embeded
FNAC	Fine Needle Aspiration Cytology
HER2	Human Epidermal Growth factor Receptor
MRM	Modified Radical Mastectomy
MUHAS	Muhimbili University of Health and Allied Sciences
MNH	Muhimbili National Hospital
ORCI	Ocean Road Cancer Institute
PR	Progesterone Receptor
SPSS	Statistical Programme for Social Sciences
TNM	Tumor, Node, Metastasis classification
UICC	International Union against Cancer
UK	United Kingdom
USA	United States of America
WLE	Wide local excision

Definition of terms

Modified radical mastectomy refers to a procedure combining excision of breast tissue, skin and nipple areolar complex (total mastectomy) with removal of axillary lymphnodes en-block with the mastectomy specimen. It has three modifications as by Patey, Scanlon and Auchincloss. All three modifications include excision of the breast tissue, skin and nipple- areolar complex, the difference is in handling the pectoral muscles where Patey preserves pectoralis major muscle and sacrifice pectoralis minor to allow removal level of I, II and III lymphnodes. Scanlon modified Patey's procedure by dividing the attachment of pectoralis minor on the coracoid process of the scapula in order to reach level III group of lymphnodes. Auchincloss spared both pectoralis muscles, axillary dissection and removed level II nodes between the two pectoral muscles by mere separation of the two muscles.

At MNH patients with operable breast cancer, stage I to III undergo modified radical mastectomy i.e. excision of breast tissues, skin, nipple areolar complex and axillary dissection of level I nodes.

Axillary lymph node groups. Level I includes lymph nodes located lateral to the pectoralis minor muscle (PM); level II includes lymph nodes located deep to the PM; and level III includes lymph nodes located medial to the PM.

Surgical margins: in this study, surgical margins are referred to as side margins and the base where the tumor lies.

ABSTRACT

Background: Breast cancer represents the most common cancer in women in the world. It is the second most common malignancy among females in sub-Saharan African countries including Tanzania, the leading cancer being that of uterine cervix. Worldwide, the incidence of breast cancer is 1, 000,000 cases per year and causes approximately 373,000 deaths yearly. Prognostic indicators in breast cancer have been found to influence use of adjuvant therapy following mastectomy by predicting patients with risks on survival and recurrence. In Tanzania, data on prognostic indicators is lacking. The main objective of the study was to determine the pattern of prognostic indicators among women with breast cancer undergoing modified radical mastectomy (MRM) at Muhimbili National Hospital and Tumaini Hospital, Dar es Salaam.

Methodology: A hospital-based prospective cross-sectional study was carried out that included female patients undergoing MRM from April 2011 to January 2012 with calculated minimum sample size of 84 patients. Patients with clinical stage I-III disease were enrolled in the study after being scheduled for mastectomy. Patients with evidence of distant metastasis after a chest x-ray and abdomino-pelvic ultrasound i.e. stage IV were excluded. The surgical specimen consisting of mastectomy tissue and axillary lymphnodes was submitted to the histopathology laboratory to determine grade, type, nodal status and margins status. Data collection was done using a structured questionnaire and analyzed using SPSS software.

Results: During 10 months of study, 348 patients were admitted with breast cancer. Eighty six (86) patients met the inclusion criteria to the study. Age at diagnosis was 28-79yrs with mean age of 52.08years. Ten percent (10.6%) were ≤35years, 55% were 36 - 55 years and 33.1% were above 55years. Eighty nine percent (89%) of study population attained menarche above the age of 11yrs, with mean age of 14.3years. About fifty six percent (56%) were postmenopausal with 22.9% attaining menopause at the age of 55yrs or more. Majority (78%) were multipara and only 7.1% nulliparous.

Most (87.3%) of them had their first live birth below the age of 30years. Family history of breast cancer was reported in 14.1% of patients and 37.6% reported use of hormonal contraceptives.

Among the study population, 5.9% were smokers and 27.1% were social alcohol drinkers. Most of our patients (61%) had T4b disease, 75.6% had positive axillary nodes where 42.7% had 4-9 (N2 disease).The commonest histological type was invasive ductal carcinoma (91.9%). Lobular carcinoma, medullary and mucinous carcinoma together accounted for only 8.1%. Eighty three percent (83.7%) of our patients presented with stage III, 16.3% with stage II disease, and none at stage I. The intermediate and high grade tumor accounted for 73.5%. Twenty five percent (25%) of our patients had positive surgical margins with 25% positive base following MRM.

Conclusion: Most breast cancer patients treated surgically at MNH present with a stage III disease and have been shown to have unfavorable prognostic indicators. The presentation is of primary tumor size with skin infiltration, positive axillary lymph nodes and a risky histological grade i.e. intermediate and high grade. Despite locally advanced disease the majority have negative surgical margins following modified radical mastectomy.

Recommendation: A sustainable screening program to diagnose patients at early stage of disease is mandatory. Public education on breast self examination is required to involve women in early diagnosis of disease. A follow up study is needed to determine how these patients fare after treatment to allow individualized type of management.

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INTRODUCTION

Breast cancer is a malignant tumor of the breast usually a carcinoma. It represents the most common cancer in women in the world, with incidence of 1,000,000cases per year and approximately 373,000 deaths yearly.[1] In 1998, the incidence in Europe was 210,000 with about 73,500 deaths, [2] while in New Zealand over 600 women each year die from the disease.[3] Breast cancer is the second most common malignancy among females in sub-Saharan African countries including Tanzania, the leading cancer been of uterine cervix.[4]

The origin of breast cancer is related to breast cells of either epithelial origin in tubular-ductal or mesenchymal cells which misbehave from normal growth and division for reasons which are not yet clearly known. So far there is no known single cause of breast cancer. However, extensive research suggests that genetic, hormonal and environmental factors may be among the possible factors related to its aetiology.[5]

Breast cancer is rarely found before the age of twenty five years except in familial cases, where family history has shown 5-10% increased risk due to inheritance of an autosomal dominant gene. The risk is even higher (90%) in families with four or more cases. Women in their teens and twenties (but not at older ages) undergoing mantle irradiation for Hodgkin lymphoma are said to have increased risk of 20-30% of developing breast cancer 10-30 years after the treatment.[6]

A retrospective study done in Cyprus found family history of breast cancer to be the strongest

predictor of breast cancer risk while late menarche after the age of 15years and breastfeeding were strong protective factors.[7] There is still difficulty in obtaining family history for those women at risk due to decreased awareness of breast cancer in sub-Saharan Africa and due to the desire for secrecy that is sometimes found within families following a diagnosis of cancer[8]. Among Tanzanian females with breast cancer who presented to hospital only 4.2% had a positive family history of breast cancer.[9]

Age by itself has been found to be associated with increased risk, In Maringa Brazil, the mean age of patients with breast cancer was 53 years, with menopause starting at the age of 47 years and their menarche at 13years.[10] In Tanzania, the mean age of patients with breast cancer was found to be 51years, mean age at menarche at 14.4years.[9]

Early detection of breast cancer has positive effect on treatment options, [11] and the mortality has been reduced by evolution of screening programs and adjuvant therapy. Attention to prognostic factors has been stimulated by the success of systemic adjuvant therapy for early-stage, operable cancer of the breast. Any feature of a tumor, or combination of features, that accurately segregate those patients destined for recurrence and those who are not, is of considerable importance[12].

LITERATURE REVIEW

The incidence of breast cancer is high in more-developed regions of the world, in urban populations, and among Caucasian women. The Globocan database for 2002, indicates the Age-standardized rate (ASR) of breast cancer to be 67.8 per 100,000 in more-developed regions (Europe, Australia, New Zealand, North America and Japan) compared to 23.8 per 100,000 in less- developed regions (Africa, Central America, South America, all regions of Asia except Japan, the Caribbean, Melanesia, Micronesia and Polynesia).[13]

Current Australian guidelines for the treatment of early breast cancer recommend that women be treated using a multidisciplinary approach involving appropriate surgery, radiotherapy, and systematic adjuvant therapy.[14]

The prognosis of patients with breast cancer is influenced by a number of factors including those which are tumor related; the size of the primary carcinoma, Lymph node involvement and the number of lymph nodes involved by metastases. Studies have shown the presence of Estrogen and progesterone receptors and currently HER2 to influence the prognosis of patients with breast cancer.[15]The presence of estrogen and progesterone receptors is important clinically as predictor for response to adjuvant hormonal therapy rather than prognostic factors.[16]

Primary tumor size and regional lymphnodes involvement

Patients who are clinically node-negative with very small tumors (1 cm) have been found to have good prognosis with a 10-year disease free survival rate of 88%, [17] and 75% of patients showing no evidence of disease at 30 years after surgery alone , hence it is difficult to justify the use of adjuvant therapy in these patients .[18]For node-negative patients with larger tumors, the 5-year relative survival rate decreases to about 85% (range 82.2%–92.3%) with surgery alone.[19]

The survival rate decreases with each involved lymph node and is less than 50% with 16 or more involved nodes. [5] Other studies propose percent of tumor positive ipsilateral axillary lymphnodes out of submitted axillary nodes to be more precise predictor of survival than the absolute number of positive nodes.[20]Patients with distant metastasis are rarely curable, although chemotherapy may prolong survival.

Recently, attention to combined effect of prognostic indicators to assess mortality in patients with breast cancer has been reported. In one study where the effect of tumor size and lymph node status were combined, it was shown that women who had 3 or more positive axillary lymph nodes had a greater risk of death by 25% compared with lymph node–negative women with tumors of the same size and women who had 5 or more positive lymph nodes had a greater risk of death by 30%.[21] So, the increased risk of death to patients with breast cancer was found to be associated not only by lymph node status, but rather the number of positive lymph nodes.

Studies have shown that patients with positive axillary lymph nodes are at high risk of relapse and deserve postoperative adjuvant treatment. The ten year recurrence rate in this group of patients has been found to approach 70%.[18] Patients without lymph node involvement, older than 35 years of age, with steroid receptor positivity, with a tumor size less or equal to 2 cm and with grade 1 tumor are considered at minimal risk of relapse.

For patients with at least one of these factors (i.e. age less than 35 years or negative receptor status or pathological tumor size more than 2 cm or grade 2/3 tumor), are considered at average risk and must be treated with adjuvant systemic therapy.[22] A study of breast carcinoma surgical specimen done in Tanzania following simple or modified radical mastectomy found that the mean tumor size was 8cm and none of the tumor was less than 2cm, and 68.8% of the tumors exceeded 5cm in the greatest diameter.[9]

The clinical stage of disease

The clinical stage of breast cancer is among the factors influencing the prognosis of these patients. Studies have shown only 5% to 12% of Stage I/II patients die in the first 10 years after diagnosis, compared with over 60% of Stage III patients and over 90% of Stage IV patients. Breast cancer staging also provides valuable information about appropriate treatment options for each cancer stage.[23]Post-mastectomy radiotherapy is always recommended for patients with stage IIB disease who have four or more positive axillary nodes, in stage IIIB patients with T3–T4 tumors independent of the nodal status, in young patients with T1 tumor and 1–3 positive axillary lymph nodes as well as those with T2 or greater tumors which show signs of biological aggressiveness (receptor-negative, grade 3, HER2-positive, high proliferation activity, e.g. Ki-67).[24]

Age as prognostic indicator

A study done in USA on effectiveness of adjuvant chemotherapy in old women showed improved survival in women with node positive operable breast cancer aged 65–69 living in the community, but not in women aged 70 years or more.[25]It has been found that younger patients in general have favorable prognosis as compared to older women.[26,27] However age under 30yrs has been postulated to have worse prognosis.[28,29] Recent studies done in Brazil among women diagnosed with breast cancer under and over 40years of age found that death caused by the disease was higher among patients under 40 years of age (46.9%) than among patients between 40 and 50 (26.9%) and over 50 (22.6%). The logistic analysis showed that 'age under 40' and the 'presence of more than one metastatic axillary node' were independent death risk factors.[30]

Histological type of the tumor

The histological type of the tumor is one of the important prognostic indicators in breast cancer as it influences the form of treatment. Ductal carcinoma in situ (DCIS) is a pre-invasive breast cancer that can almost always be cured by local-regional therapy.

Only one percent of these early cancers are associated with metastasis to axillary nodes, and almost all (98 %) are cured by local-regional therapy regardless of their size.[31] In patients with DCIS who undergo breast conserving therapy, local recurrence is associated with poor nuclear grade and comedo-type necrosis, but because dissemination is infrequent, systemic adjuvant therapy is unnecessary.[32,33]Studies have shown excellent prognosis in patients with invasive breast carcinoma variants of tubular and cribriform histological types, even when there is metastasis to regional lymphnodes. Other histological types with good prognosis with surgery alone include medullary and mucinous types.[34]

Histological grade of tumor

The most common grading system for breast cancer evaluates tubule formation, nuclear grade, and mitotic rate to divide carcinomas into well-differentiated carcinomas which have a significantly better prognosis as compared with poorly differentiated carcinomas. Moderately differentiated carcinomas initially have a better prognosis, but survival at 20 years approaches that of poorly differentiated carcinomas.[5] In Finland, a study on the influence of histological grade to patient selection for adjuvant therapy showed that women with well-differentiated node-negative cancer had a 97% 5-year distant disease-free survival rate as compared with 78% for women with poorly differentiated cancer.

When grade of the tumor was included as independent prognostic indicator in a Cox multivariate model based on tumor size and hormone receptor status in node-negative cancer, increased the proportion of patients with 5% or less risk for distant recurrence at 5 years from 15% to 54%. Patients with high risk of recurrence needs adjuvant therapy when compared with those of low risk, results of this study makes histological grade an important prognostic indicator on its own.[35]

Hormonal receptors status

The presence of hormone receptors (ER and PR) in the tumor tissue correlates well with the response to hormonal therapy and chemotherapy.[36] Studies have shown that women with ER-positive tumors response rate to additive or ablative hormone therapy is 55 - 60%, compared with women with ER–negative tumors whose response rate is 8%. ER and PR positive tumors have also been associated with better differentiation and have a relatively better prognosis.[37,38]In Tanzania, pathological study of surgical breast specimen showed low proportion of expression of ER and PR by 36.5% and 19.8% respectively.[9]

Presence of ErB-2 and HER2

Studies done in India on ErbB-2 expression when associated with other biological parameters of breast cancer among Indian women, found that ErbB-2 over expression among other factors such as lymph node status, distant metastasis and stage of the disease, was a marker of poor prognosis.[39]HER2 over expression in patients with breast cancer has been associated with poor prognosis and resistance to treatment.[40] In Taiwan, studies on chemotherapy response in relation to HER2 found response rate of 62% in HER2-positive patients, and 46% in HER2-negative patients, a difference that was not statistically significant.[41]

PROBLEM STATEMENT

The incidence and mortality of breast cancer internationally have been stable for the past decade.[42] Worldwide though, breast cancer remains the most common cancer in women and the leading cancer-related cause of death in Europe.[43, 44] In developing countries the rates have been found to rapidly increase, like in Uganda breast cancer incidence has doubled from 11 per 100,000 in 1961 to 22 per 100,000 in 1995. This increase has been attributed to the adoption of westernized lifestyles.[45] Breast cancer is the second most common malignancy among females in sub-Saharan African countries including Tanzania, the leading cancer being that of uterine cervix.[4]

Late presentation to hospital is still a challenging factor in Tanzania where only 5.2% presents at Stage II disease, 57% stage III and 37.5% stage IV. Stage I disease patients are rarely found.[9]Besides late presentation, other traditional prognostic indicators including histological grade of tumor, axillary lymph node status, surgical margins and base status, presence of bilateral disease, hormone receptor status and others, have not been well elucidated in Tanzania and the data is scanty. This discrepancy is an impediment to the formulation of therapeutic and preventive strategies and negatively impacts efforts to reduce disease burden and mortality.

RATIONALE

Breast cancer is one of the commonest cancers among women. More than 200,000 women are diagnosed with invasive breast cancer in the United States each year.[46]In Tanzania Ocean Roar cancer institute is the centre of care for cancer patients. Its 2004 registry reported admission of 10-20 patients with breast cancer per month.[4]

The natural history of breast cancer influences its management in which both local control of the disease and systemic control are of great importance. Depending on the stage of the disease, management of breast cancer can be individualized[47].

Patients destined for recurrence can be selected for systemic adjuvant therapy, while patients who will not have a recurrence can be spared the morbidity of a treatment that offers no benefit[12]. Knowledge on the prognostic status of patients with breast cancer before and after surgical intervention will assist in proper management of these patients including the determination as to who will benefit from specific adjuvant therapy.

The current practice of treatment of breast cancer patients in our setup depending on the stage of the disease includes neoadjuvant therapy followed by mastectomy or mastectomy with adjuvant therapy. Determination of prognostic status will help make breast cancer management more cost-effective.

In Tanzania, studies on prognostic indicators of patients with breast cancer are not yet well documented, thus the current study being proposed is expected to enlighten surgeons and oncologists who care for breast cancer patients on the real picture of the presentation of our patients and how better their management can be individualized. This is particularly important in a country like Tanzania where post-treatment follow-up of patients is greatly limited by logistical constraints on the part of both the patient and cancer care providers.

OBJECTIVES

BROAD OBJECTIVE

To determine the pattern of prognostic indicators among women with breast cancer undergoing modified radical mastectomy at MNH and Tumaini Hospital Dar es Salaam from April 2011 to January 2012.

SPECIFIC OBJECTIVES

1. To determine demographic characteristics of the study population
2. To identify the clinical stage of the disease at first presentation to hospital
3. To establish the frequency and pattern of prognostic indicators among patients undergoing MRM
4. To determine relationship of demographic characteristics and prognostic indicators in patients undergoing MRM

METHODOLOGY

STUDY DESIGN

Hospital based analytical prospective cross sectional study

STUDY AREA

The study was conducted in the female general surgical wards as well as in the histopathology unit at MNH and female surgical wards at Tumaini Hospital Dar es Salaam from April 2011 to January 2012.The two hospitals were chosen to ensure a standard type of mastectomy performed during the study since both hospitals use Auchincloss type and most surgeons operating at MNH are the same operating at Tumaini Hospital.

STUDY POPULATION

All women admitted in general surgical wards with clinical stage I to III breast cancer as classified by TNM staging system undergoing MRM April 2011to January 2012.

Inclusion and exclusion criteria

Inclusion criteria

All patients admitted in female general surgical wards with clinical stage I to III breast cancer who underwent MRM from April 2011 to January 2012 were included in the study.

Exclusion criteria

- Patients with recurrent breast cancer
- Patients with breast cancer who underwent neoadjuvant therapy
- Patients with Stage I-III disease who didn't have axillary dissection
- Patients with stage IV disease

The patients with recurrent breast cancer and those who underwent neoadjuvant therapy were excluded since the therapy alters the primary lesion, stage III patients may be down staged to stage II. Since clinical stage was one of prognostic indicator studied, down staged patients were excluded to avoid getting the wrong impression of clinical stage of studied patients at presentation to hospital. Patients who didn't have axillary node dissection (both stage I-III and IV) were excluded since node status was also one of the prognostic indicators studied.

Limitations of the study

This study did not cover hormonal receptors determination i.e. Estrogen and progesterone receptors due to lack of reagents at our histopathology laboratory, the funding for the dissertation research is not enough to cover the costs for these reagents which are very expensive.

Sampling

There was no sampling, patients were recruited into the study as they got admitted and planned for modified radical mastectomy. The patients were staged by the researcher using TNM staging and workup for presence of distant metastatis by chest X-ray and abdomino-pelvic ultrasound was done. Patients with clinical stage I to III were requested to participate in the study by signing consent.

Data sources:

Histopathology reports following FNAC or incision biopsy were used to confirm diagnosis of breast carcinoma and chest X-ray and abdominal pelvic ultrasounds reports to exclude stage IV patients. Physical examination was done by researcher to obtain clinical stage, assess for clinically bilateral disease i.e. palpable breast lumps bilaterally and signs of metastasis (pleural effusion or ascites). Histopathology reports as well as slides following mastectomy and axillary dissection were reviewed and relevant information collected.

Biopsies: The whole breast and nodes were submitted to the histopathology department, formalin-fixed and paraffin embedded (FFPE). Glass slides were stained with hematoxylin-eosin. The sections were reviewed to determine the histological type, grade, node positivity, status of surgical margins and base. Nuclear pleomorphism, tumor differentiation (well differentiated, moderate and poorly differentiated), mitotic figure counts per one high power field were used to grade the tumor, where mitotic figure counts of 1-2(low grade), 3-5(intermediate grade) and above 5 (high grade).

Data collection

Data were collected by the researcher and two research assistants; one in the ward and another in the laboratory who took mastectomy specimens to the pathologist and also collected slides to review to get histological grades which were rarely reported on routine histopathology results. Questionnaires were filled by the researcher and one assistant to obtain demographic data, gynecological history and details of clinical findings of the patient like tumor size, regional node involvement, bilaterality of the disease and histopathology information of submitted breast and lymphnodes after surgery i.e. the type, grade, number of lymphnodes submitted, number of lymphnodes positive for tumor out of submitted and surgical margins, base status.

Data handling and analysis

The questionnaires were given serial numbers in addition to hospital file numbers to assist in keeping record in a systematic manner. The copy of histopathology report of every patient was attached to the respective questionnaire. All histopathology reports with inadequate information were identified and slide number recorded for review. Patient details and results were entered into Statistical programme for social scientists (SPSS) version 17 data sheet where clearing of data and analysis was done. Fisher's exact and t-test was used in analysis and attaining statistical significance. P-value of <0.05 was considered significant.

Ethical consideration

Ethical clearance of this study was sought from the Ethical Committee of MUHAS and permission to conduct the study was sought from relevant authorities at MNH. The study did not change the form of treatment planned for the patients. Informed consent with detail on the purpose of the study, the rights of the participant and benefits on participation was obtained in writing from prospective patients i.e. by signing the prospective consent form.

Results

Between the month of April 2011 and January 2012, a total of 348 patients were admitted with breast cancer and only 86 patients with breast carcinoma stage I-III underwent modified radical mastectomy hence met the inclusion criteria. The age range was between 28-79 years; with mean age at diagnosis of 52.08. Peak age at diagnosis was between 36-55years and accounted for 54.6% of patients studied. The majority were Africans with only about 1.2% Caucasians. This was expected because the study was done in Tanzania- Africa, so we expect to have more Africans than Caucasians. Among the study population, 5.8% were smokers and 26.7% were social alcohol drinkers.

Table 1

Social demographic characteristics of patients

Characteristic	Number of patients (%)
Age at Diagnosis(years)	
≤35	9(10.5)
36-55	47(54.6%)
>55	30(34.8%)
Mean age 52.08	
Ethnicity	
Africans	84(98.8)
Caucasians	1(1.2)
Alcohol intake	
Yes	23(26.7)
No	63(73.3)
Cigarette smoking	
Yes	5(5.8)
No	81(94.2)

Table 2

Clinical features of study population

Feature	Number of patients (%)
Age at Menarche(Years)	
< 11yrs	2(2.3)
≥11yrs	77(89.5)
Cannot recall	7(8.1)
Mean Age 14.4years	
Menopausal status	
Premenopausal	37(43)
Post menopausal	49(57)
Age at Menopause	
<55yrs	37(75.5)
≥55yrs	12(24.5)
Parity	
Primipara	12(14)
Multiparous	68(79)
Nulliparous	6(7)
Age at 1st live birth	
<30yrs	70(87.5)
≥30yrs	6(7.5)
Cannot recall	4(5)
Family History of breast cancer	
Yes	12(14)
No	74(86)
Use of hormonal contraceptives	
Yes	32(37.2)
No	54(62.8)

Eighty nine percent of study population attained menarche after the age of 11yrs, with mean age at 14.4years. Fifty seven percent were postmenopausal with 24.5% attaining menopause at the age of 55yrs or more. About 79% were multipara, with only 7% nulliparous.

Most of them had their first live birth before the age of 30years (87.5%). Family history of breast cancer was reported in 14% of patients and 37.2% reported use of hormonal contraceptives

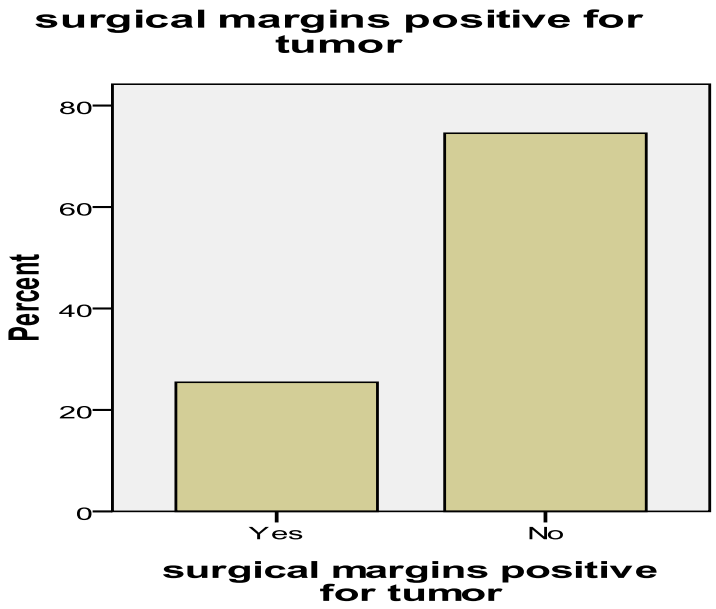
Table 3

Prognostic indicators of breast carcinoma in study population

Prognostic indicator	Number of patients (%)
Primary tumor	
Tx	2(2.3)
T1	0(0)
T2	18(20.9)
T3	14(16.3)
T4	52(60.5)
Positive axillary nodes	
0	20(24.4)
1-3	21(25.6)
4-9	35(42.7)
>10	6(7.3)
Histological Grade	
High	34(41)
Intermediate	27(32.5)
Low	22(26.5)
Histological type	
Invasive Ductal	79(91.9)
Invasive Lobular	2(2.3)
Medullary	1(1.2)
Others	4(4.7)
Clinical Stage	
Stage I	0(0)
Stage II	14(16.3)
Stage III	72(83.7)

Two patients (2.4%) presented after excision biopsy (Tx) at a peripheral hospital. No patient presented with T1 disease, 20.9% had T2 disease, 16.3% had a T3 disease and 61.2% had primary tumor infiltrating the skin (T4b). Among 86 patients studied, 82 had results for axillary lymphnodes dissected. Seventy five percent had tumor positive axillary nodes. Forty two percent had positive nodes ranging from 4-9, while 7.3% had ten or more tumor positive node. Most of patients were stage three disease(83.7%), with only 16.3% stage two disease while none had stage one disease. Infiltrating ductal carcinoma was the most common histological type of tumor seen, accounting for 91.9%, while infiltrating lobular carcinoma accounted for 2.3%. Medullary breast carcinoma was seen in 1.2%, other histological types were; both infiltrating ductal and lobular occurring in conjunction, metaplastic carcinoma, mucinous carcinoma and apocrine carcinoma constituting 4.7%. Forty one percent (41%) had high grade tumor, 32.5% intermediate grade and 26.5% low grade.

Figure 1



Following modified radical mastectomy, 25% of patients had tumor positive surgical margins (side) and 75% had margins free from tumor.

Table 4

Surgical margins (side) and primary tumor size

Margins Positive	**Tx-T2**	**T3-T4**	**Total**
Yes	3(15.8%)	17(27.9%)	20(25%)
No	16(84.2%)	44(72.1%)	60(75%)
Total	19(100%)	61(100%)	80(100%)

Patients with primary tumor size of T3-T4 were likely to have positive surgical margins (side) as compared to those with Tx-T2.

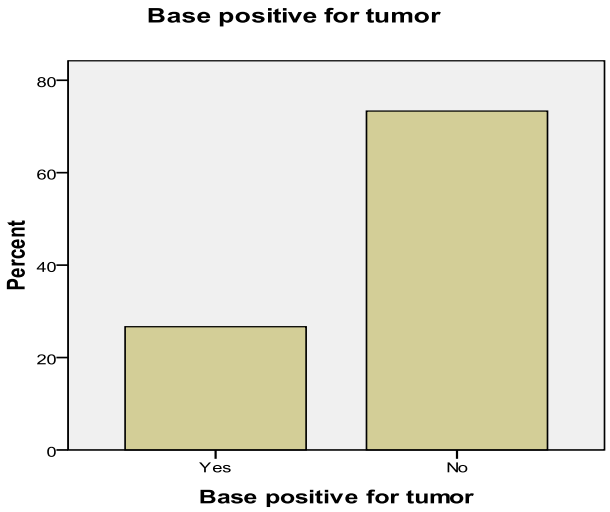
Table 5

Surgical margins (side) and lymph node status

Margins positive	**Lymph node status (%)**		
	Positive	**Negative**	**Total**
Yes	17(27.9%)	3(15.8%)	20(25%)
No	44(72.1%)	16(84.2%)	60(75%)
Total	61(100%)	19(100%)	80(100%)

Most of our patients with lymph node negative disease had negative surgical margins (side) (84.2%) with only 15.8% positive margins. (p-value 0.000, with 95% CI of 0.07 to 0.57)

Figure 2



Twenty five percent of patients had base positive for tumor following modified radical mastectomy.

Table 6

Side surgical margins and the base of the tumor

Side surgical margins positive for tumor	**Base positive for tumor**		
	Yes (%)	**No (%)**	**Total (%)**
Yes	14(70)	6(10)	20(25)
No	6(30)	54(90)	60(75)
Total	20(100)	60(100)	80(100)

Seventy percent (70%) of patients with positive tumor base had positive side surgical margins. (p-value 0.026, with 95% confidence interval of 1.13 to 4.83)

Table 7

Relationship of prognostic indicators and age of patients

Prognostic indicator	Mean Age	SD	t(df)	p-value
Primary tumor				
Tx-T2	48.15	7.59	-1.515(83)	.134
T3-T4	52.94	13.46	-2.01(57)	.049
Histological grade				
	52.99	12.38	0.187(70)	.852
Intermediate/high	51.44	13.77	0.177(26)	.861
Low grade				
Node status				
Node negative	55.89	12	1.575(70)	.120
Node positive	50.67	12.24	1.590(29)	.122

As seen from table 7, mean age of 52.94 was associated with larger primary tumor size of T3 and T4 (p-value 0.049). The association between the patient's age at diagnosis and histological grade of tumor was not statistically significant. Patients with node positive disease were diagnosed at an earlier age than node negative disease although statistically not significant.

Discussion

The clinical management of breast cancer patients at MNH involves surgical treatment of patients at MNH followed by adjuvant radiotherapy/chemotherapy at ORCI. Patients are further followed up at ORCI clinics and will only return to MNH in case of local recurrence requiring surgical treatment or when they have complications of distant metastasis such as pleural effusion requiring underwater seal drainage. This protocol hinder surgeons from following up these patients to understand how they fare after treatment hence it becomes difficult to establish the prognosis and survival of patients with breast cancer treated at MNH.

Clinical characteristics of study population

Although this study intended to cover pattern of prognostic indicators, clinical characteristics of the study population is worthy of mention. In breast cancer some factors have been mentioned to constitute risk to develop the disease; these include early age at menarche, late menopause, delay in first live birth, family history as well as use of hormonal contraceptives. In this study 89.4% of study population attained menarche after the age of 11yrs, with mean age of 14.3years which is the same as what was found in Tanzania 10yrs ago[9].

Fifty six percent of patients were postmenopausal with 22.9% attaining menopause at the age of 55yrs or more. Majority of women were multipara; with only 7.1% nulliparous which means multiparity is probably not protective for breast cancer as expected. Most of women had their first live birth before the age of 30years (87.3%), which should be protective from developing breast cancer. Family history of breast cancer was reported in 14.1% of patients compared with what was seen 10 year ago where only 4.2%[9] had positive family history, suggesting that breast cancer in our population is more likely a sporadic disease than familial. Hormonal contraceptive use was reported in 37.6%, common types used being injections (Depo-Provera) and oral contraceptives. Genetic susceptibility could be the most contributing risk factor to

developing breast cancer in these patients since most of the above factors seemed to be reported in less percent.

Primary tumor Size

The understanding of prognostic indicators among patients with carcinoma of breast is important in providing an individualized treatment. Primary tumor size is among the prognostic indicators investigated in this study where most patients presented with a tumor infiltrating the skin. The trend of presentation with large primary tumor has not changed for the past 10years where one study done on surgical specimens from breast cancer patients at MNH found the mean tumor size to be 8cm, none of the tumors was less than 2cm, and 68.8% of the tumors exceeded 5cm in the greatest diameter.[9] The reason could be due to behavior of breast cancer presentation which is painless initially, unorganized referral system, patients denial to mode of treatment after diagnosis and delayed biopsy results from histopathology unit. These findings are different when compared with the one done in Cuba whereas T1 disease was more prevalent (49.2%) followed by T2 disease (45.7%).[48]The difference could be due to the existing screening programs which are better established in Cuba, hence identifying patients at an earlier stage with smaller primary tumors. Tumor size has been found to be the strongest predictive factor for relapse even in node negative patients.[49]In the study in Japanese patients with node negative disease, clinical tumor size was a strong prognostic factor.[50]Generally, disease free survival decreases by tumor size[51], but some studies have shown a better outcome in extremely large primary tumors when compared with those with intermediate size, the reason being a possibility of lower potential for metastatic spread in the former.[52] Our study shows that most likely patients are at high risk of relapse of disease due to presentation with larger primary tumor size and hence poor prognosis.

Axillary lymph node status

In the current study majority of patients had tumor positive axillary nodes. Axillary lymph node status is the most important prognostic factor in breast carcinoma and prognosis worsens with increasing number of metastatic lymph nodes.[53] According to the American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) tumor (T)-node (N)-metastasis (M) classification, nodal disease is classified in three groups based on the number of axillary metastatic lymph nodes: N1, 1–3 metastatic lymph node(s), N2, 4–9 metastatic lymph nodes and N3, 10 or more metastatic lymph nodes.[54] In this study 42.7% had N2 disease which is an unfavorable prognostic indicator . These findings differs from the study done in Cuba whereas 46.6% of tumors examined were node-negative (N0); 25.7% exhibited N1 disease, and 27.4% exhibited N2 disease.[48] In Germany, one study had results comparable to ours; positive axillary nodes were seen in about 66% of patients, and 33% had node negative disease. The positive axillary nodes were 1-3 in 23.6% and ≥4 in 42.8% of patients and survival rates decreased with increasing positive nodes.[55]Studies have shown increased tumor recurrence among patients with metastatic axillary nodes of up to 70% within 10yrs after mastectomy.[56, 57] Most of patients treated at MNH and Tumaini hospital for breast cancer are likely to have poor prognosis due to high number of metastatic axillary nodes.

Histological type of the Tumor

In the present study most women had invasive ductal carcinoma. Similarly most studies have shown invasive ductal carcinoma to be the most common histological type in breast carcinoma. One study in Japan among patients with breast cancer found invasive ductal carcinoma in 90% of patients, 5% had invasive lobular carcinoma, 1.5% medullary carcinoma and 3% mucinous type.[50] In Nigeria, comparable findings were seen where 95% of patients had infiltrating ductal carcinoma and 5% were papillary, lobular and unspecified types of carcinoma.[58] Another similar results was seen in a large register-based study in Norway of 22,867patients of breast cancer where 81.4% of all cases were ductal carcinoma, 6.3% lobular and 5.5% other unspecified carcinomas.[59] Histological

type of tumor is a known factor influencing prognosis and survival of patients with breast cancer. Tubulo-lobular and mucinous type have usually an excellent prognosis[60, 61] with a 10years survival of >80%.[62] Tubular mixed, mixed ductal with special type, atypical medullary[63] and alveolar lobular carcinoma have a good prognosis with a 10-year survival of 60-80%.[64]Invasive papillary, classic lobular and medullary carcinoma have a worse prognosis.[64]

Patients with ductal, solid lobular, mixed ductal and lobular carcinoma have been found to have a 10year survival below 50%.[65]

The findings of the current study implies that most of our patients have a risk to poor prognosis due to the dominating histological type of tumor which is ductal carcinoma.

Histological Grade

Intermediate and high grade were the common grades seen in this study. These findings agree with what was reported in Cuban women who underwent surgery for breast cancer, whereby 54.87% were intermediate grade and 30.82% were high grade tumors.[48] Higher grades have been quite consistently associated with lower long-term survival[66] and has been associated with increasing tumor size where only 10% of <2cm tumor have high grade compared to >50% of >5cm tumor.[67] In Irish study involving 293 cases of invasive primary breast cancer, found 53% of cases had low and intermediate grades while 47% had high grade tumor.[68]The histological grade seen in this study might as well be due to the fact that most patients have large primary tumor size which is associated with higher histological grade. This implies that about 73% of patients undergoing MRM at our setup are likely to have relapse due to the histological grade of their tumor.

Clinical Stage

Clinical stage of the disease at time of diagnosis can significantly affect the prognosis and outcome of the patient. Most of patients in this study had stage three disease (83.5%), with only 16.5% stage two disease while none had stage one disease. Ten years

ago, a pathological study of surgical specimens of patients with breast cancer was done at Muhimbili National Hospital; 5.2% were stage II and 57% stage III, none were stage I disease.[9] The picture is more or less the same, though the percentage of patients with stage II disease has increased by three fold. In Ibadan Nigeria, a study involving 763 cases of breast cancer showed 2% had stage I disease, 13% stage II and 46% stage III.[57] In Canada most patients are seen at early stage of disease, in one study 37% had stage I disease, 38.5% stage II and 7.1% stage III disease.[69] Among Cuban women, breast cancer was as well diagnosed at early stage compared to Tanzanian, 23% stage I, 59.94% stage II and 15.3% stage III disease.[48] Clinical stage II and III disease are considered high risk stage for relapse as well as overall survival.

In Germany one study showed low risk of relapse in stage II compared to III, and 3year survival rate after adjuvant therapy to be 74% in stage II and 36% in stage III patients.[70] Early diagnosis and improved survival in western countries reported in several studies has been attributed to screening programs, where prognosis of breast cancer has been good and a 10 year relative overall survival of 70% has been archieved.[71, 72] The late presentation seen in our study population may be due to lack of well established screening programs, myths on breast cancer surgery and adjuvant therapy which are linked to death.

Age as an independent prognostic factor

In this study 10.6% were ≤35yrs. Young age at diagnosis has been associated with aggressive disease and poor prognosis. A retrospective study done in Tanzania among females with breast cancer recorded in Cancer Registry 1974-1987, suggested young-age onset of breast cancer in female Tanzanians and other Sub-Saharan African countries when compared with those from North America and Europe whereby in Tanzania 8% of patients with breast cancer were under 30yrs of age and prevalence peak age was 35-44years[73] while 6.4% of patients in Sudan were under 30yrs and 14.7% in Nigeria.[74] This study differs from those in Western countries where breast cancer diagnosis at age below 35yrs is rare and accounts for only 4% of cases.[75] Studies have shown poor

prognosis in younger women compared to the middle aged.[76] In Nigeria 28.96% of patients with breast cancer were diagnosed at ≤40yrs out of which 42% were under 35 years.[57] Comparable results are seen among females with breast cancer in Korea where in cancer registry of 2002, the proportion of young-age onset was found to be higher than in western countries and accounted for 9.5%.[77] A study done in Korea among young patients with breast cancer also found operable young breast cancer patients (<35 years old) have a worse prognosis than older patients in terms of both overall survival and recurrence.[78] In the present study the size of primary tumor was found to increase with increased age at diagnosis and patients with node positive disease diagnosed at an earlier age than node negatives likely due to aggressiveness of the disease. On the other hand, there was no association of mean age at diagnosis with histological grade of tumor.

Surgical Margins as a prognostic factor

Tumor positive surgical margin is definitely a risk for local recurrence in breast cancer. In this study 25% of patients had positive surgical margins of which 70% had both base and margins positive for tumor. Considering large number of patients presented with locally advanced disease, the expectation would be different in the sense that more patients would have positive surgical margins. There is no direct response to why this was not the case. Adjuvant local radiotherapy and systemic therapy may limit recurrence but not to levels observed in patients with negative margins.[79, 80] In UK in a study including 773patients with breast cancer treated by Wide Local Excision (WLE), 11.8% had positive margins.[81] This is low compared to what was found in our patients, most likely it is due to early disease seen in UK patients which allowed patients to be treated by WLE alone instead of MRM as in this study. Concern in positive margins has been more in patients with negative lymph nodes as compared to positive lymphnodes since the latter is by itself an indicator for poor prognosis. The same UK study, when margin status were associated with lymph node status, 461 patients with node negative disease had 9.9% positive margins and of 312 node positive patients 14.42% had positive

margins and also positive margins were associated with a significantly higher local recurrence rate and reduced overall survival.[81] In our study 18patients had node negative disease of which 16.7% had positive margins, while out of 55node positive patients 29.1% had positive margins. The difference could be due to other local factors like primary tumor size where most of our patients had T4 disease.

Conclusion

At the time of diagnosis most of our patients have unfavorable prognostic factors which predispose them decreased survival rates. Patients present with locally advanced tumors. Most patients have intermediate and high grade tumors which are associated with poor prognosis. Following mastectomy the percentage of positive margins is low hence less probability to local recurrence when margin status alone is considered, so the majority of our patients may not require local radiotherapy after mastectomy. Young age as a factor to poor prognosis may not affect a large number of our patient population since a large proportion of breast cancer patients were above the age of 35years.

Recommendations

i) Sustainable screening programs should be put forward to identify patients with early disease

ii) Continued public education is needed on breast self examination to involve patients in early diagnosis of the disease

iii) The histopathology unit to be supplied with reagents and facilities for Estrogen Progesterone and HER2 receptor studies.

iv) A possibility of a separate breast cancer clinic to allow for a more comprehensive and focused care is recommended.

v) A detailed study is needed on survival of breast cancer patients in our setup based on clinical presentation and type of treatment given

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APPENDIX I

QUESTIONNAIRE

Serial no. _____

Hospital reg number _____

Admission date _____/_____/_____

Biodata

1. Age(yrs) _____
   a. ≤ 25yrs_____
   b. 26-35yrs_____
   c. 36-45yrs_____
   d. 46-55yrs_____
   e. 56-65yrs_____
   f. >65 yrs_____

2. Residence _____

3. Ethnic group
   a. Asian
   b. Africans
   c. Whites

Gynaecological history

4. Age at menarche
   a. ≤11yrs _____
   b. >11yrs_____

5. Age at first delivery
    a. ≤ 30yrs_____
    b. >30yrs _____

6. Parity
    a. Primigravida_____
    b. Multipara_____
    c. Nulliparous_____

7. Menopausal status
    a. Premenopausal_____
    b. Postmenopausal_____
8. Age at Menopause
    a. ≤55yrs _____
    b. >55yrs _____

9. Use of oral contraceptive pills
    a. Yes_____, type_____
    b. No_____

10. Any female relative with or who died of breast cancer or intra-abdominal malignancy
    a. Yes _____
    b. No _____
11. Any male relative died of breast cancer
    a. Yes _____
    b. No _____

Social history:

12. History of smoking cigarettes
    a. Yes_____
    b. No _____

13. History of habitual alcohol drinking
    a. Yes_____
    b. No _____

14. Occupation_____

Physical findings

15. Size of the primary tumour ; 1) Tx_____
    2.) T1(<2cm) _____
    3) T2 (2cm-5cm)_____
    4) T3 (>5cm) _____
    d) T4 _____

16. Bilaterality of the disease;
    a. YES _____
    b. NO _____

17. Regional lymhnode involvement (axillary):
    a) ipsilateral not fixed_____
    b) ipsilateral fixed/matted_____
    c) ipsilateral supraclavicular nodes_____
    d) contralateral nodes_____

18. Chest X-ray findings
    a. Features of metastatis_____
    b. No features of metastasis_____

19. Abdominal pelvic ultrasound findings
    a. Features of metastasis_____
    b. No features of metastasis_____

20. Histopathological findings:

a). Histological type of the tumour
    1. Ductal carcinoma_____
    2. Lobular carcinoma_____
    3. Inflammatory breast cancer_____
    4. Medullary carcinoma_____
    Other specify_____

C). Histological grade of the tumor
    1. High grade
    2. Intermediate grade
    3. Low grade

d). Number of lymphnode positive for tumor
    1. 1-3_____
    2. 4-9_____
    3. ≥10_____
    4. 0_____

e). Surgical margins positive for invasive tumor
    1. YES _____
    2. NO _____

f). Base positive for tumor
    1. YES_____
    2. NO_____

APPENDIX II

Histopathology investigation form for patients undergoing Modified radical mastectomy MNH from April 2011 to January 2012

Hospital reg. number……

Surname……..
Other
Names……
…

Postal/residential address……

Date of birth……Sex……

Religion……..Ward…….

Firm……Head of firm……..

Clinical Notes:

Clinical stage (TNM)……..

Previous HP/HC number……

Number of lymphnodes submitted with mastectomy specimen…….

Surgeon's name……Signature……date…….

For pathologist:

Please report on: a) Histological type, Differentiation and Grade of the tumor

b) Base and surgical margins status

c) Number of lymphnodes submitted and positive nodes for tumor

APPENDIX IV

Informed consent form

ID no…….

Consent to participate in the study on prognostic indicators of breast cancer among women undergoing modified radical mastectomy in female general surgical wards at MNH between April 2011 to January 2012.

Greetings!

My name is Dr Rabiel Happiness; I am a postgraduate student at MUHAS, studying the prognostic indicators of breast cancer in women undergoing surgery of removal of breast in female general surgical wards at MNH.

The purpose of the study;

To determine the prognostic indicators of breast cancer among women undergoing modified radical mastectomy in female general surgical wards at MNH from April 2011 to January 2012.

What participation involves;

On agreeing to participate in this study, you will be required to answer some questions and you will be examined clinically and by imaging investigations including a Chest x-ray and abdominal ultrasound. You will be informed of the results and about next step in management of your disease .

Confidentiality;.

All information collected on questionnaires will be entered into computer with identification number. The questionnaires will be handled only by persons involved in the study secrecy to maintain confidentiality.

Risks:

There is no risk associated with this study

Right to withdraw and alternatives:

Taking part in this study is completely voluntary. If you choose not participate in the study, you will continue to receive all services that you would normally get from the hospital.

Benefits:

If you agree to take part in this study, you will benefit from knowing the details about your disease in a short period of time and treated accordingly.

Who to contact:

If you have any question about the study, you should contact D. Rabiel Happiness 0787-477096. If you have questions about your rights as a participant, you may contact Prof M. Aboud, Chairman of MUHAS Research and Publications Committee. P.O. BOX 65001 Dar es Salaam. Tel 0713-292617

Signature

Do you agree to participate?

Agrees……

Does NOT agree……

I ……... have read the content of this form. My questions have been answered. I agree to participate in this study.

Signature of participant ……..

Signature of witness……..

Date of signed consent……

FOMU YA RIDHAA (SWAHILI VERSION)

Utafiti juu ya viashiria vya makali ya saratani ya matiti kwa wanawake wanaofanyiwa upasuaji wa kuondoa ziwa lenye saratani kwenye wodi za upasuaji muhimbili.

Nambari ya usaili ……

Salaam! Mimi naitwa Dr Rabiel Happiness, mwanafunzi wa udhamili Chuo Kikuu cha Sayansi za Afya. Nafanya utafiti juu ya viashiria vya makali ya saratani ya matiti kwa wanawake wanaofanyiwa upasuaji wa kuondoa ziwa lenye saratani kwenye wodi za upasuaji za wanawake hospitali ya Taifa muhimbili.

Madhumuni ya utafiti

Kujua aina ya viashiria vya makali ya saratani kwa wanawake wenye saratani ya matiti wanaofanyiwa upasuaji wa kuondoa ziwa lenye saratani na jinsi vinavyoweza kusaidia matibabu ya ziada kwa kutumia dawa zenye uwezo wa kuua chembe hai zenye saratani.

Kama utakubali kushiriki, nita kuhoji maswali machache kuhusu ugonjwa wako na kukupima ukubwa wa kivimbe kwenye ziwa na tezi kwapani kwa kupapasa kwa viganja. Pia utafanyiwa kipimo cha X-ray ya kifua na tumbo kuona kama ugonjwa wako umeene sehemu nyingine za mwili.

Utunzaji wa siri

Taarifa zitatunzwa kwa siri kwa kutumia herufi au nambari bila majina ya mgonjwa

Madhara/Athari

Hakuna athari au madhara yoyote yanayotegemewa yatokanayo na utafiti huu.

Uhuru wa kushiriki

Kushiriki kwenye utafiti ni hiari yako. Unawaweza kujiota wakati wowote.
Kama utachagua kutoshiriki, utaendelea kupata huduma kama hapo awali.

Taarifa

Endapo unahitaji kupata maelezo kushusu haki zako au taarifa, wasiliana na Dr Rabiel Happiness 0787-477096, au Prof M. Aboud, Mwenyekiti wa Kamati ya Utafiti S.L.P 65001, Dar es Salaam. Simu 0713-292617

Je unakubali kushiriki kwenye utafiti? (weka alama) vema
ndiyo……
Hapana……..
Mimi ……., nimeelezwa/nimesoma maelezo
Nimekubali kushiriki kwenye utafiti huu
Sahihi ya mgonjwa ……
Sahihi ya ndugu/shahidi ……
Sahihi ya Mtafiti ……..
Tarehe …….

TNM CLINICAL CLASSIFICATION OF BREAST CANCER(FROM SCHWARTZ'S PRINCIPLES OF SURGERY 8TH EDITION(2007) CHAPTER 16	
Primary tumor (T) Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3); if other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1-cm increment	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis(DCIS)	Ductal carcinoma in situ
Tis(LCIS)	Lobular carcinoma in situ
Tis(Paget's)	Paget's disease of the nipple with no tumor (**Note:** Paget's disease associated with a tumor is classified according to the size of the tumor)
T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Edema (including peau d'orange), or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional lymph nodes—Clinical (N)	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent[a] ipsilateral internal mammary nodes in the absence of

	clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent[a] ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent [a] ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph nodes(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)
Regional lymph nodes—Pathologic (pN)	
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0[b]	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (**Note:** Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains; ITCs do not usually show evidence of malignant activity [e.g., proliferation or stromal reaction])
pN0(i–)	No regional lymph node metastasis histologically, negative IHC

pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph nodes dissection, not clinically apparent[c]
pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection, not clinically apparent[c]
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent [c] (if associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)
pN2	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent[a] internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastasis in clinically apparent[a] internal mammary lymph nodes in the absence of axillary lymph node metastasis

pN3	Metastasis in 10 axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[a] ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at lease one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent[a] ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection, not clinically apparent[c]
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

[a]*Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

[b]Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node" e.g., pN-(l+) (sn).

[c]*Not clinically apparent* is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

RT-PCR = reverse transcriptase polymerase chain reaction.

SOURCE: Modified with permission from American Joint Committee on Cancer: *AJCC Cancer Staging Manual,* 6th ed. New York: Springer, 2002, pp 227–228.

Table 16-12 TNM Stage Groupings			
Stage 0	Tis	N0	M0
Stage I	T1[a]	N0	M0
Stage IIA	T0	N1	M0
	T1[a]	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1[a]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

[a] T1 includes T1 mic.

SOURCE: Modified with permission from American Joint Committee on Cancer: *AJCC Cancer Staging Manual*, 6th ed. New York: Springer, 2002, p 228