THE ROLE OF IMAGING IN THE DETECTION OF OVERT ABDOMINAL AND CHEST METASTASIS DUE TO BREAST CANCER, AND ASSOCIATED RISK FACTORS AT OCEAN ROAD CANCER INSTITUTE.

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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 (Radiology) of Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences

April, 2011

CERTIFICATION

The undersigned certify that he has read and hereby recommend for examination of dissertation entitled ***the role of imaging in the detection of overt abdominal and chest metastasis due to breast cancer, and associated risk factors at Ocean Road Cancer Institute,*** in fulfillment of the requirements for the degree of Master of Radiology of Muhimbili University of Health and Allied Sciences.

_____

Dr. R. R. Kazema

(Supervisor)

Date: _____

DECLARATION

AND

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I, Lulu Lunogelo Sakafu, 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.

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DEDICATION

This dissertation is dedicated to

My beloved husband Steven Mujarifu

And our children

Wilhelmeena and William

ABSTRACT

Background; Breast cancer is a disease which affects people worldwide, contributing to a substantial public health. It is estimated more than 1.1 million cases of breast cancer are diagnosed each year. This disease accounts for 10% of all cancers and 23% of all cancers in women worldwide. Breast cancer is the leading cause of mortality and morbidity in Asia and Latin America. In Tanzania it is estimated that approximately 1307 women with breast cancer register in different hospitals each year. Cancer of the breast is among the commonest cancers affecting women in Tanzania. The majority of women who are diagnosed with breast cancer seek hospital treatment when the disease has reached an advanced stage, at which point the metastasis of the disease to the lung or the liver are most likely.

***Broad objectives*;** To determine the role of imaging in detection of overt abdominal and chest breast cancer metastasis, and associated risk factors among patients at ORCI from June to December 2010.

Methods; This was a descriptive cross sectional study in which 103 patients with breast cancer attending ORCI new patient clinic were recruited consecutively. Standardized questionnaires were used to obtain socio-demographic characteristics, risk factors and physical examination details, all participants were then investigated for liver and lung metastases using abdominal ultrasound and chest x-ray respectively.

Results; The majority of breast cancer patients studied were above 45years (61.5%) with the mean age of 48(SD) ± (11.22) year, and only 27.2 % had post primary education. The prevalence of metastasis from breast cancer to the liver and lungs was 18.4% and 20.4% respectively. Majority of liver metastasis occurred at the age category of 45years and above, with the prevalence of 68.4%.The prevalence of lung metastasis was highest in the age category of 35-44 years and above. Majority of patients with breast cancer had locally advanced breast cancer disease that is either TNM stage three (59.2%) or four (32%) disease upon arrival to ORCI, only 8.8% had stage two and none had stage one.

Conclusion; This study showed that, the prevalence of lung and liver metastasis was very high accounting for 20.4% and 18.4% respectively. This is supported by the fact that most of newly

diagnosed breast cancer had locally advanced breast cancer at presentation. The results of this study strengthen the recommendation of doing baseline staging tests, especially LUS and CXR, to all new breast cancer patients in Tanzania. This study also showed that, premenopausal women and those who use alcohol have increased prevalence of lung and liver metastasis though the results were not significant.

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LIST OF ABBREVIATION

CT scan – Computed Tomography Scan

MRI – Magnetic Resonance Imaging

BRCA I &II – Breast cancer susceptibility genes

MNH – Muhimbili National Hospital

AJCC – American Joint Committee on Cancer

LFT – Liver Function Tests

CXR – Chest X-ray

LUS – Liver Ultrasound

PA – Postero anterior

CCOPGI - Cancer Care Ontario Practice Guidelines Initiative.

ORCI – Ocean Road Cancer Institute

DNA – deoxyribonucleic acid

MUHAS – Muhimbili University of Health and Allied Sciences

MEWATA – Medical Women Association of Tanzania

BSE - Breast Self-Examination

LABC-Locally Advanced Breast Cancer

Tis –Tumor in situ

+VE – Positive

-VE – Negative

1.0 INTRODUCTION AND LITERATURE REVIEW

Breast cancer is a disease which affects people worldwide, contributing to a substantial public health burden. Although breast cancer was once known to affect highly affluent communities, it has been realized that disadvantaged communities now are facing the heaviest disease burden. It is estimated that more than 1.1 million cases of breast cancer are diagnosed each year. This disease accounts for 10.9% of all cancers and 22.8% of all cancers in women worldwide[1]. In USA one out of eight women will be diagnosed of breast cancer in her lifetime. In Brazil breast cancer is the leading cause of death in women of all ages. Breast cancer is the leading cause of mortality and morbidity in Asia and Latin America[2]. In Tanzania it is estimated that approximately 1307 women with breast cancer register in different hospitals each year[3]. Cancer of the breast is among the commonest cancer affecting women in Tanzania. The majority of women who are diagnosed with breast cancer seek hospital treatment when the disease has reached an advanced stage, at which point metastasis from the disease are most likely.

Cancer is a situation whereby cells of the body grow and multiply out of control leading to formation of a mass or lump called tumor. Cancer is identified by the tissue or organ of the body where it originates. Thus cancer of the breast originates from breast tissue. Breast comprises of glands called lobules and ducts which carry milk to the nipple. Cancer arising from the glands is called lobular carcinoma and from the ducts, ductal carcinoma.

The precise cause of the breast cancer is not known. Certain risk factors which are not causal in nature have been linked. These are as follows;

i) **Gender**, although men do get breast cancer, it is about 100 times more common in women as such, less than 1% of patients with breast cancer are males.

ii) **Age**, in all countries of the world, breast cancer occurrence increases with age. It is extremely rare below the age of 20 years, but thereafter the incidence steadily rises so that by the age of 90 years about 20% of women are affected.

iii) **Race and geographical areas**, the incidence of breast cancer is significantly lower in Eastern Europe, Africa and most Asian countries, including Japan and China, than it is in North America, South America and Western Europe. It occurs commonly in the

Western world where it accounts for 3-5 per cent of deaths, yet is a rare tumor in Japan. In developing countries it accounts for 1 - 3 per cent of deaths.

iv) **Previous history of breast cancer,** a woman who has had cancer in one breast is at a greater risk of developing cancer in the other breast

v) **Family history,** it occurs more commonly to the women with family history of breast cancer than in general population. Women with a family history of breast cancer, especially a first degree relative (mother, sister, daughter), have an increased risk of developing breast cancer. The risk increases as the number of first degree relatives with breast cancer increases

vi) **Menstrual periods:** studies suggest that reproduction hormones influence breast cancer risk by affecting cell proliferation and DNA damage. Early menarche (younger than 12 years) and late menopause (older than 55 years) increase a woman's risk of breast cancer

vii) **Birth control pills,** studies have shown that women who have used or are currently on birth control have a slightly greater risk of breast cancer than women who have never taken birth control pills

viii) **Excess alcohol,** alcohol intake is linked to a slightly increased risk of breast cancer. Women who have two to five drinks daily have about one and a half times the risk of women who drink no alcohol.

ix) **Obesity,** obesity is linked to a higher risk of breast cancer, especially if the weight gain took place during adulthood. The risk seems to be higher if the extra fat is in the waist area

x) **Pregnancy,** women who have not had children, or had their first child after age 30, have a slightly higher risk of breast cancer. Being pregnant more than once and at an early age reduces breast cancer risk.

xi) **Ionizing radiation**, exposure of the breast/s to ionizing radiation, such as radiation therapy for Hodgkin's disease, is the best-established environmental factor associated with an increased risk of breast cancer.

xii) **Genetics**, recent research has shown that defects in one of two inherited genes, called BRCA-1 and BRCA-2, are linked to an increased risk of breast cancer. Defects in these genes carry a lifetime risk as high as 85 percent, but are rare in the global population[1,4].

Breast cancer is staged before treatment starts. Staging is one of the important factors in selecting management options and in determining prognosis. Breast cancer staging involve clinical examination, biopsy, certain imaging investigation such as chest radiograph (CXR), liver ultrasound (LUS), bone scan (BS), Computed tomography scan (CT scan) and Magnetic Resonance Imaging (MRI).

Breast cancer staging uses TNM classification, whereby T represents tumor size, N represents palpable lymph nodes and M represents metastasis.

In T the diameters are; Tis – tumor in situ, TX – size cannot be assessed, T0 – no evidence of tumor, T1- is 2cm or less, T2 – between 2 and 5 cm, T3 – is more than 5cm, T4 – any size but attached to the chest wall. Palpable nodes N, Nx – lymph node cannot be assessed, N0 – no spread to lymph nodes, N1 – spread to movable ipsilateral axillary lymph nodes, N2 – spread to matted axillary lymph nodes, N3 – spread to ipsilateral mammary or supraclavicular lymph nodes. Metastasis M, Mx – metastasis cannot be assessed, M0 – no metastasis detected and M1 – there is metastasis to other organs.

Table 1: TNM staging for breast cancer can be summarized as follows.[5]

Stage	Tumor size	Node	Metastasis
Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	MO
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	MO
	T1	N2	M0
	T2	N2	M0
	T3	N2,N1	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

In searching for distant metastasis, the following are usually done, Bone scanning to look for skeletal metastasis, Liver ultrasound to look for liver metastasis and chest radiograph to look for pulmonary metastases.

Ultrasound is used for investigating or looking for metastasis for almost all cancer patients attending medical or surgical clinics. The role of ultrasound is very important in patients with breast cancer disease because it can be used for early detection of overt abdominal metastasis when patients first come for chemotherapy or for evaluation of abdominal metastasis status in follow up patients. However, it is important to note that ultrasound may be normal when there are microscopic metastasizes hence complementary examinations like Positron emission tomography with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG–PET) should be done where resources are available[6]. Ultrasound is reliable, fast, cheap and easy modality in detecting liver metastasis and for predicting prognosis. Today, ultrasound is one of the most commonly used diagnostic modality the reasons being, it is non-invasive, cheap and widely available.

Chest radiograph (CXR) is the most widely used radiological examination in almost all departments. It is fast, cheap, easy to perform and very reliable in detecting lung metastasis in breast cancer patients. It is very beneficial because it can upgrade patient who had stage I or II to stage IV, and hence change the treatment plan[7]. Although chest x-ray is widely done, the interpretations maybe inconclusive, hence in some cases advanced radiological investigations like CT scan may be needed.

Bone scanning (BS) is considered a sensitive investigation modality for detection of metastatic breast cancer to the bones, but not all findings in BS are diagnostic of skeletal metastasis[8]. BS has high sensitivity but relatively low specificity. A positive BS can be due to degenerative or non degenerative disease. Recent studies have shown relatively low rates in detection of metastasis, only half of positive BS where proved to be real metastasis[9], and in other studies a low yield was noted of up to 3%[10]. In order to confirm that BS is positive; Radiographs, CT scan and or MRI are needed. These are very costly to the patient. CT scan exposes patients to more X-rays radiation. BS itself costs more than 240 Euros[8]. As such there is no need of doing BS to an asymptomatic breast cancer patient.

It has been debatable among Oncologist whether to use LUS, CXR and BS in early stages of breast cancer. Recent studies done in Europe, America and Asia, show that these investigations are not required in early stages (stage I and II) because they are expensive and they pick metastasis at a very low rate in these early stages[7, 9-13]. However this could be true in developed

countries because they are capable of identifying patients during their early stages. This is due to wide availability of mammography, screening facilities and earlier diagnosis is achieved through patients increased awareness of early breast cancer symptoms[14].

This study showed that in developing countries like Tanzania, LUS and CXR are still beneficial in staging, treatment planning, follow up and prognosis determination of breast cancer patients; because they are relatively cheap, fast, easily available and reliable. In Tanzania patient delay to reach Ocean Road Cancer Institute (ORCI) the only Tumor Centre in the country, for the management of cancer patients. They reach here after being diagnosed as cancer patients in periphery and zonal referral hospitals. When they finally reach ORCI most have locally advanced disease, and chances of metastasis are high.

Management for early breast cancer is aggressive, it consists of surgery, chemotherapy, local radiotherapy and hormonal therapy; whereby treatment for metastatic carcinoma is mainly palliative consisting of chemotherapy, hormonal therapy and rarely local irradiation. For example irradiation to the bones may be required and or toilet mastectomy[15]. Early detection of overt breast cancer metastasis is important to the oncologist for proper decision making.

Prognosis of breast cancer depends on its invasive nature and metastatic potential.

For Breast cancer if treatment is delayed, spread occurs by either direct invasion to adjacent organs, or spread via lymphatic or hematogenous route[4]. Cancer of the breast usually sends metastasizes to the Lymph glands**,** Bones**,** Lungs**,** Liver**,** Brain and Pleural cavity**.**

Liver metastasis is a primary clinically significant contributor to the mortality associated with breast cancer[16]. Oncologists often consider metastases to organs of the abdomen, especially the liver, the most serious of the prognostic signs. After bones and lungs, the liver is the third most common metastatic site, presenting as the first recurrence in about twenty five percent of cases and eventually present in about two-thirds of women with metastatic disease[17].

Most common malignant lesion to the liver is a metastatic lesion and one of the most common primaries, being breast cancer. Symptoms of liver metastases are subtle at first but become increasingly intense over time. Weight loss, loss of appetite, fever, and gastrointestinal disorders

may indicate liver metastases[5]. Hepatomegaly and raised LFT's may also be seen. Lesions are typically multiple and both lobes are usually involved. In 30% to 40% a solitary lesion is seen[18].

Ultrasound is extremely user dependent and image quality is often limited in patients with a lot of gas in the upper abdomen at the time of examination[19]. In some areas it has been shown to have high false positive results[20]. Liver metastases from breast cancer usually are irregular hypoechoic lesions; they can be solitary or multiple and can involve both lobes. Hepatomegaly may be associated.

Lung metastasis are common for many types of cancer[21]. Sixty to seventy percent of patients who die of breast cancer eventually have metastasis in their lungs. The lungs are the only site of metastasis in about twenty one percent of cases[17].

Common symptoms of lung metastasis are non productive cough, hemoptysis, chest pain and shortness of breath[21]. Dry cough can also be the presenting symptom. Some women do not have any symptoms, they are diagnosed on routine CXR or CT scan[22].

Before starting breast cancer therapy, most patients undergo staging investigations, including a chest radiograph, searching for metastatic disease in the lungs. The intention is to pick up women with lung metastasis as early as possible before they develop overt lung metastasis (asymptomatic)[23].

The gain in life expectancy in breast cancer patients with pulmonary metastases is based on chemotherapy and antihormone treatment[24].

The basic sign of haematogenous pulmonary metastasis is one or more discrete pulmonary nodules, usually in the outer portions of the lungs. These are more evident on CT. Nodules, can be spherical or can have irregular edges. Irregular edges usually come from adenocarcinoma. Cavitations are occasionally seen. Calcifications are not seen though the primary breast cancer could be having calcifications[25].

The simplest technique for diagnosing pulmonary metastases is the plain postero-anterior (PA) and lateral chest x-ray. High-kV techniques is often used routinely, since substantial portions of the lungs are obscured on low-kV radiographs by overlying structures such as the diaphragm,

heart, mediastinum, hila and ribs. Such radiographs will detect most lung metastases above 1 cm in diameter. Increasing sensitivity can be obtained by using CT scan which however should be limited to specific patients[25].

Lymphangitic carcinomatosis is the name given to permeation of pulmonary lymphatics and or their adjacent interstitial tissue by neoplastic cells. One of the tumors spreading in this way is breast cancer. This kind of spread is more localized. The radiological findings are fine reticulonodular shadowing and or thickened septal lines. These signs occur because of a combination of dilated lymphatics and interstitial edema, together with shadows due to the tumor cells. Another useful sign of lymphangitis carcinomatosis is subpleural edema resulting from lymphatic obstruction by tumor cells, a feature that is seen as thickening of the fissures. Pleural effusion is common, and is seen in about 30% [25].

Initial staging at the onset of disease is of primary strategic importance for an adequate diagnostic and therapeutic program. Nowadays biopathological data is being used for correct evaluation of breast cancer; however American Joint Committee on Cancer (AJCC) staging system has not evaluated this method. For these reasons LUS and CXR remain to be the standard procedures for the detection of possible metastatic disease at the time of diagnosis.

A study done in Italy in 2002 about Staging of breast cancer; came out with new recommended standard procedure. They concluded that CXR and LUS are expensive and, in a period of economic constraints, it is important to follow practices characterized by high/cost benefit and cost/effectiveness ratios. Complete instrumental staging in all the patients with breast cancer is expensive and probably unnecessary [26]. However this could be true in Italy where this study was done. In developing countries like Tanzania, due to limited facilities like mammography, lack of knowledge or awareness of symptoms of breast cancer and late coming of patients to ORCI the only tumor centre in Tanzania, these staging procedures, are very important.

AJCC suggests that stage I and II breast cancer should not be routinely staged by LUS and CXR at baseline. In fact, the prevalence of liver and lung metastases detected by LUS and CXR is equal to zero in early stage disease and dramatically increases in patients with stage III tumors. A study done in Italy in 2005 concurred with AJCC and they said that their study strengthens the

recommendation to limit baseline staging tests, especially LUS and CXR, to patients at higher risk (stage III) of distant metastases.

An indiscriminate use of diagnostic procedures in all patients with newly diagnosed breast cancer has a high chance of generating unjustified anxiety in patients and of increasing costs. Finally, the unproven effectiveness of these tests in routine follow-up casts doubt upon their usefulness as a baseline reference [9]. In Italy where this study was also done it might be feasible. In Tanzania most of our patients are diagnosed with stage III when they first come to hospital [27], here baseline radiological staging is essential.

CCOPGI (Cancer Care Ontario Practice Guidelines Initiative) reviewed the evidence for the use of routine chest X-rays, and liver ultrasounds in patients with Stage I, II and III breast cancer. The CCOPGI introduced a guideline for baseline radiological staging in 2000 (updated 2002). These recommendations apply to women with newly diagnosed breast cancer, who have undergone surgical resection, and have no symptoms, physical signs, or biochemical evidence of metastases. Specifically, these guidelines suggest that patients with pathological Stage I disease should not have baseline radiological staging, patients with Stage II disease a chest radiograph and ultrasound should be considered if a patient has four or more lymph nodes with metastases. For women with pathological Stage III tumors, chest radiograph and abdominal ultrasound are recommended. These guidelines reflect the increasing risk of a true positive radiological investigation with a more advanced cancer stage. They used two stage educational strategies for the staging guidelines, and then re-assessed the extent of radiological staging at their institution. They concluded that, there has been a significant reduction in unnecessary radiological staging in patients with Stage I breast cancer [28] This study also gives more evidence that radiological baseline staging is needed in more advanced stages of breast cancer. In Tanzania where there are a lot of delaying factors, majority of the patients come with advanced stages hence baseline radiological staging are very important.

The role of baseline radiological investigations for overt metastases in patients with early breast cancer is contentious, with many patients undergoing inappropriate radiological examination. And that study has shown that the prevalence of detectable metastatic disease in asymptomatic patients is low. However, rates of distant spread do increase from stage I to stage III disease,

underscoring the problems of current radiological techniques in asymptomatic patients. In 2008, the study of Prevalence of Overt Metastases in Locally Advanced Breast Cancer was done. They isolated 10.4% patient with metastatic breast cancer. Those who remained they used advanced confirmatory imaging and isolated metastasis in 2.8%. This raises the question of whether negative baseline investigations are sufficient to accurately stage patients with unexplained symptoms [29]. Data from this study seem to imply that in asymptomatic patients, negative baseline investigations can give false assurance.

A study was done to assess the use and yield of baseline diagnostic imaging in early-stage breast cancer patients and the cost involved. The conclusion of this study was that routine use of imaging modalities to detect metastases in asymptomatic early-stage breast cancer patients are not justified [30]. This is yet another evidence that baseline radiological staging in our country is still beneficial since our patients delay to reach the hospital. Most of new patients at MNH had stage III breast cancer when they arrived [27].

The study intends to see how imaging modalities can help in management of breast cancer patients, and also if there is any relationship between metastasis development and presence of risk factors. Risk factors like *family history, old age and menopause status* have been strongly associated with development of breast cancer[31-33], so are they also associated with early development of distant metastases? To my knowledge and through literature search, there is no study that looked into this, so this study intends to look at it.

The ability to accurately stage patients has many benefits. First, clinicians will be able to advise the patients on their prognosis. Second, appropriate palliative measures could be introduced at an earlier opportunity. Finally, clinicians will be able to individualize treatment to suit their patients. For instance, patients who have truly locally advanced cancer can be offered more aggressive chemotherapy with curative intent as the potential long term benefits far outweigh any short-term toxicities or quality-of-life disruption in these cases. Conversely, in those who present with metastatic disease, a more balanced, quality-of-life-oriented approach can be utilized. It is, however, considered beneficial for the accurate staging of disease to be known when decisions regarding adjuvant systemic therapy are made [23].

2.0. PROBLEM STATEMENT

In Tanzania it is estimated that approximately 1307 women with breast cancer register in different hospitals each year[3]. As a part of management of patients staging has to be done; this involves clinical examination, biopsy, imaging with chest radiograph and abdominal ultrasound.

In Tanzanian women, due to lack of facilities like mammography and due to lack of knowledge about breast cancer; most women are not aware of signs, symptoms and risk factors they have. As a result they delay to seek medical care. Even after they notice a breast lump, few will go direct to hospitals; most will go to tradition healers, chemists or dispensaries. Finally by the time they realize they are not getting better, few of them whom their financial status allows, will make their way to the Referral hospital or to ORCI[3].

A study done in 1996 at MNH found that more than 90% of breast cancer patients at diagnosis they had more than stage III disease, and thus a high probability of a distant metastasis [27].

Liver metastasis is a primary clinically significant contributor to mortality associated with breast cancer, and present in about two-thirds of women with metastatic disease[17].

Sixty to seventy percent of patients who die of breast cancer eventually have metastasis in their lungs[17].

Baseline radiological staging of breast cancer by LUS and CXR to determine metastasis in breast cancer patients in Tanzania are crucial and beneficial in treatment planning and outcome determination, taking in consideration our patients delay to reach the hospital.

3.0 RATIONALE

In our country, where resources are still limited, widely available modalities like ultrasound and chest radiograph can be used to establish early overt metastasis in breast cancer patients.

An accurate determination of the breast cancer stage is very important in the process of decision making by both, patients and Oncologists. The knowledge of the extent of the disease is directly related to the prognosis and it influences the choice of the therapy to be used on that particular patient.

Early detection of overt metastasis in breast cancer patients will guide the Oncologist to appropriate choice of management options, namely locoregional therapy or systemic treatment.

Currently there are new treatment options for advanced breast cancer which can increase 5 years survival rate [15, 34]. The role of imaging is to help Oncologist by detection of early overt metastasis. This will improve the outcome and the prognosis of the patients.

It is important to carry out this study in order to show that LUS and CXR are baseline staging tools for breast cancer patients received at ORCI for chemotherapy and radiotherapy. The outcome of LUS and CXR findings influences patient's management, which includes modality of treatment, outcome and prognosis. Findings of this study will be a challenge to Oncologists, Radiologists and medical community at large who may find it necessary to study more on breast cancer metastasis as it is predicted by the abdominal ultrasound and chest radiograph.

4.0 OBJECTIVE.S

4.1 Broad objectives

To determine the role of imaging in detection of overt abdominal and chest breast cancer metastasis, and associated risk factors among patients at ORCI from June to December 2010.

4.2 Specific objectives

1. To determine the distribution of breast cancer TNM stage by age upon arrival at ORCI from June to December 2010.
2. To determine prevalence of lung and liver metastasis in breast cancer patient attending ORCI from June to December 2010
3. To asses relationship between risk factors for breast cancer and prevalence of metastasis among breast cancer patient attending ORCI from June to December 2010.

5.0 HYPOTHESES

In this study, it is hypothesized that:

1) *Null*; Imaging by abdominal ultrasound and chest radiograph has no role in detection of overt metastasis in newly diagnosed breast cancer patients.
2) *Alternative*; Imaging by abdominal ultrasound and chest radiograph has a role in detection of overt metastasis in newly diagnosed breast cancer patients.

6.0 METHODOLOGY

6.1 Study design*;*

This was a hospital based descriptive cross sectional study.

6.2 Period of the study;

The study was conducted for six months from June –Dec 2010

6.3 Study setting*;*

The study was conducted at Ocean Road Cancer Institute (ORCI) in Dar es Salam Tanzania. ORCI is the only specialized center for cancer treatment in Tanzania. The hospital handles both referral and self referral cancer patients from all over the country. About 4000 new cancer cases are seen every year, two thirds of whom are women. Breast cancer cases comprise 10%- 14% of new cancer cases. Every day about one to two new cases of cancer of breast are admitted. ORCI was chosen because it is the only center in Tanzania which provides specialized treatment for cancer including chemotherapy, radio therapy, and palliative care, and has cancer specialists.

6.4 Study population*;*

The study population consists of all new breast cancer patients presented during the study period which comprises a group of women who had positive histological results.

6.5 Inclusion criteria:

The following patients were included in the study:-

- Newly diagnosed breast cancer patients with positive histological results
- Participants who gave written informed consent

6.6 Exclusion criteria

The following patients were excluded from the study:-

- Breast cancer patients with no histological results
- Male patients.
- Very sick patients who needed resuscitation.

6.7 Sampling technique*;*

All eligible participants were recruited consecutively until the sample size was reached. Information regarding this study was provided to participants and informed consent was sought for prior to recruitment.

6.8 Sample size estimation;

Considering the study power of 95%, a random likely error was estimated to be 0.05. The sample size of 75 patients to be studied was estimated based on the prevalence of abdominal and chest metastases in primary diagnosis of breast cancer, in a study done in Germany[35]. The standard sample size estimation (**Kish & Leslie**) formula is:

$$\mathbf{N = z^2 p\ (1\text{-}p) \div E^2}$$

Where by: **Z**- is the point of normal distribution corresponding to the significance level 1.96;

P-prevalence from the study in Germany is 0.05;

E - Maximum likely error 0.05.

From this formula the sample size is calculated as follows:

$$\mathbf{N = (1.96)^2 X\ 0.05(1 - 0.05) \div (0.05)^2 \approx 75.}$$

The sample size for the study was increased to 100 patients in order to take into consideration drop outs and exclude patients due to incomplete information.

6.9 Data Collection*;*

Questionnaires

Structured questionnaire was used to collect information from participants. The collected information consists of risk factors for breast cancer occurrence, socio-demographic details (age, marital status, occupation) and clinical findings whereby TNM staging was performed for those who mastectomy was not done. Patient case notes were used to provide information about breast

cancer TNM stage for those who had already undergone mastectomy prior to coming to ORCI. Histological results were obtained from case notes and documented.

Abdominal ultrasound

Abdominal ultrasound was done by a researcher using a PHILIPS HD 4000 system with broadband curve-linear transducers of 2MHz to 5MHz range (Best, Eindhovern, The Netherlands) which is in a routine use at the Radiology department. To reduce gas in the upper abdomen during the procedure, participants were given dulcolax tabs two (2) twelve hourly together with restriction of proteinous foods two days prior to the procedure. Liver ultrasound to search for metastasis was done and liver size documented. Apart from the liver other abdominal organs like kidneys, pancreas, spleen and lymph nodes were scanned and their sizes or any abnormality detected was documented. Metastasis was defined as any lesion in the liver which its echotexture was heterogeneous, hypoechoic, or isoechoic be it solitary or multiple with irregular margins and had a size of more than 1cm. If pleural effusion was encountered during LUS signified lung metastasis and CXR correlation in case of pleural effusion was done. All the images were acquired and stored in the machine memory, followed by hard copies for review by the radiologist afterwards.

Chest x-ray

A high KV technique chest radiograph postero-anterior (PA) view was obtained by an experienced radiographer using PHILIPS HD 30 system (Best, Eindhoven, The Netherlands). A lateral view was only done on Radiologist's request if PA view was not conclusive. All chest x-rays were read by the radiologist in the presence of a researcher. This minimized observer bias. Lung metastasis was defined as presence of solitary or multiple lung nodules with irregular margins, reticulo-nodulations, or presence of pleural effusion.

6.10 Data analysis

All questionnaires were daily checked for completeness and accuracy by the investigator. Filled questionnaires were coded before entering data into the computer using Statistical Packages for Social Science (SPSS) version 15. Data cleaning was done by consistence checks. Statistical analysis was performed using SPSS version 15. Categorical data is summarized as frequency

(percentage) and continuous data as mean (standard deviation). Chi-square and Fisher's exact tests were used to determine the association between independent and dependent categorical variables. P value of < 0.05 was considered statistically significant**.**

6.11Ethical issues

- Ethical clearance was sought from ethical clearance board (IRB) of the Muhimbili University of Health and Allied Sciences (MUHAS).
- Permission to conduct the study was sought from Ocean Road Cancer Institute to use the subjects for the Study.
- An informed consent (verbal and written) was sought from the patients prior to conduction of interview and performing of abdominal ultrasound and chest radiograph.
- Confidentiality was observed during talking to patient and performing abdominal ultrasound and chest radiograph.

6.12 Patient's disposal

The investigator worked in close collaboration with the attending health care team in the clinic and in the wards to which study participants were admitted, by providing results and facilitating continuum of care including the follow up of the participants.

7.0 RESULTS

Between the months of June to December 2010, a total of 110 patients were eligible for the diagnosis of breast cancer at ORCI. Seven patients were excluded of which five were males and two died before imaging studies were performed. Complete data was available for 103 patients and these form the basis for further analysis.

7.1 Baseline characteristics of study population

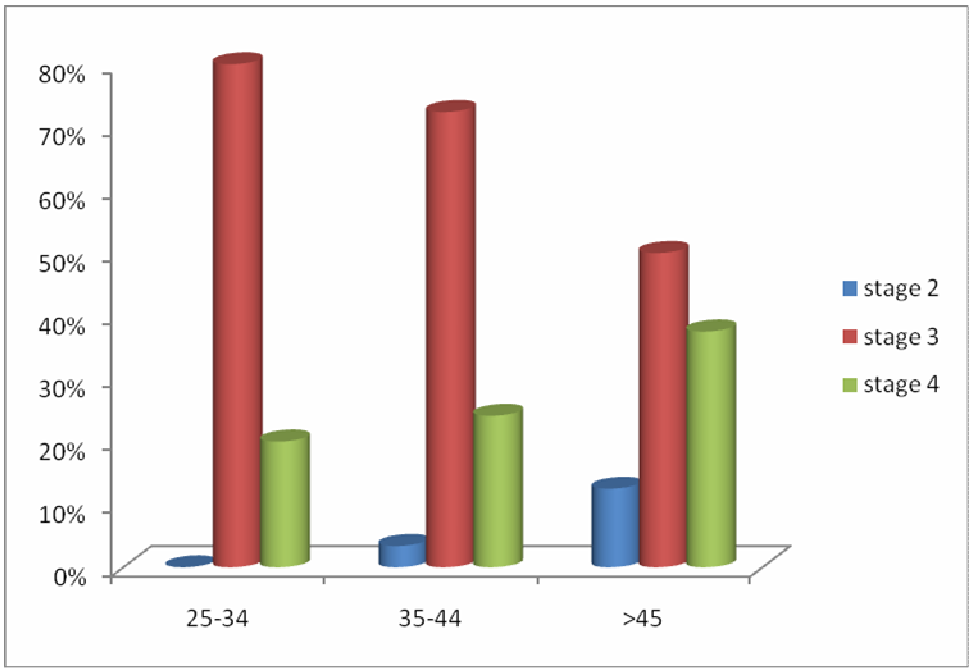
Baseline characteristics of the study population are shown in table 2. Participants' ages ranged from 26 to 77 years with majority of participants in the age category of 45 and above years (61.5%), with the mean age of 48±11.22. More than half of all participants sixty six (64.0%) were married. Majority of the participants had either primary education fifty five (48.5%), and 25(24.3%) had no formal education, while 27.2 % had post primary education. Most of the participants 56(54.5%) had no any kind of occupation.

Table 2: Demographic and baseline characteristics of study population N=103

Characteristics	**N (%)**
Age	
25-34yrs	10 (9.6%)
35-44yrs	29 (27.9%)
45 and above	64 (61.5%)
Mean age(SD), years	48±(11.22)
Marital status	
Single	10 (9.7%)
Married	66 (64.0%)
Divorced	27 (26.2%)
Education level	
No formal education	25 (24.3%)
Primary education	50 (48.5%)
Post primary education	28 (27.2%)
Occupation	
Formal and informal occupation	47 (46.2%)
No occupation	56 (53.8%)

7.2 TNM stage of newly diagnosed breast cancer patients

Figure 1: Distribution of study sample by age and TNM stage of newly diagnosed breast cancer patients at ORCI



Of those aged 25-34 years, 80% were in stage 3, while of those aged 35-44 yrs, 70% were in stage 3. There is a trend of decreasing in stage 3 with increasing age, while there is an increasing trend of stage 4 with increasing age. (Figure 1) (P value was 0.14).

Overall, the majority of newly diagnosed patients had locally advanced breast cancer with either TNM stage three 61(59.2%) or four 33(32.0%) disease, very few had stage II and none had stage I.

7.3 Prevalence of liver and lung metastasis according to age

Nineteen of 103 (18.4%) breast cancer patients had confirmed liver metastasis by abdominal ultrasound. Age category of 45 and above years had higher liver metastasis prevalence of 68.4% (13), as compared to age category of 25-34 years, which had the lowest prevalence 10.5%(2), however this difference was not statistically significant, (p =0.53).

Overall prevalence of lung metastasis was 20.4% (21/103). The age category of 45 and above years had lung metastasis prevalence of 21.9% (14), followed by age category of 35-44 years 20.7 % (6). The difference observed in the age categories with regard to lung metastases was not statistically significant (p=0.98), (Table 3).

These results were also demonstrated in Figure 2 and 3, by examples of liver metastasis scanograms of two asymptomatic breast cancer patients.

Two patients were asymptomatic with no chest symptoms, but there chest x-rays showed lung metastasis. Figure 4 & 5.

Table 3: prevalence of liver and lung metastasis according to age N=103

Age in years	**Presence of metastasis**	
	Liver	*Lung*
25-34	2 (10.5%)	1 (10.0%)
35-44	4 (21.1%)	6 (20.7%)
>45	13 (68.4%)	14 (21.9%)
Total	19 (18.4%)	21 (20.4%)
P value	0.53	0.98

χ^2 presence of metastasis versus absence metastasis

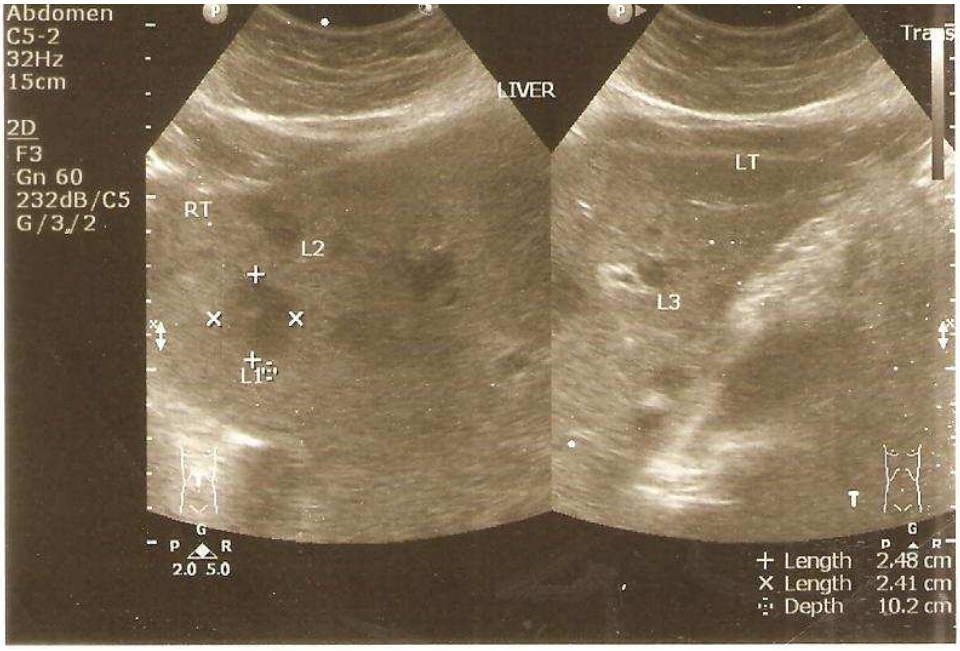


Figure 2: This is a liver scanogram of a 51 years old female with breast cancer. It shows multiple hypoechoic liver metastases.



Figure 3: Multiple hypoechoic liver lesions in a 65years old female with breast cancer. These were considered to be metastatic

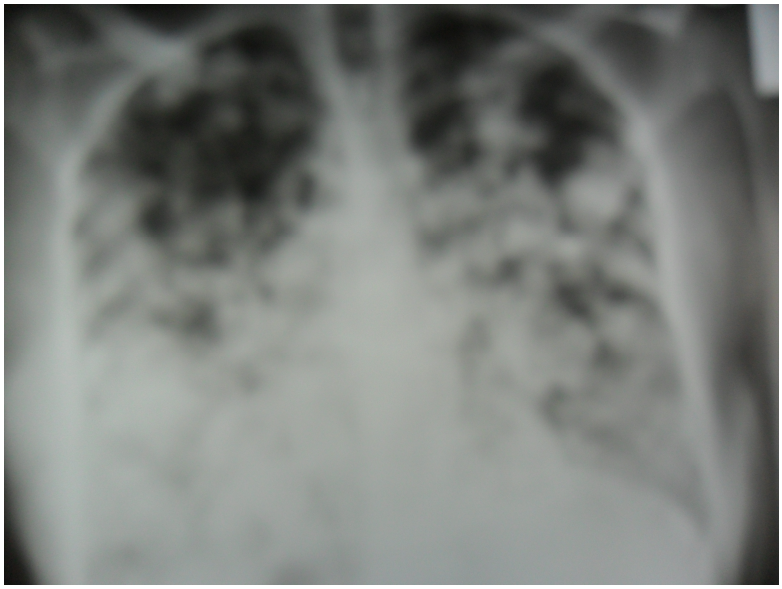


Figure 4: A CXR image showing multiple nodules seen more on lung bases bilaterally on this 55 years old lady who had breast cancer. This is a typical image of lung metastasis.



Figure 5: This is a CXR image of a 62 years old lady with lung metastasis, multiple nodules are seen scattered in both lungs, more in the bases.

7.4. Relationship between risk factors for breast cancer and prevalence of liver or lung metastasis

Premenopausal women were shown to have liver metastasis more than postmenopausal women by 63.2%, alcohol users had liver metastasis prevalence of (42.1%), these difference were not statistically significant (p=0.99) and (p=0.24) respectively. Those with positive family history had low prevalence of 10.5% (P=0.26).

Lung metastasis prevalence had high prevalence in premenopausal women (47.6%) and followed by alcohol users (38.1%); however the difference were not statistically significant (p=0.09) and (p=0.23) respectively. Positive family history had prevalence of 4.8% (p=0.90). (Table 4)

Table 4: relationship between risk factors associated with breast cancer and prevalence of liver or lung metastasis. N=103

Risk factors	Liver metastasis N (%)	P value	Lung metastasis N (%)	P value
Family history				
+VE	2 (10.5%)		1 (4.8%)	
-VE	17 (89.47%)	0.26	20 (95.23%)	0.90
Alcohol use				
Yes	8 (42.1%)		8 (38.1%)	
No	11 (57.9%)	0.24	13 (61.9%)	0.23
Age at menarche				
Below 12	1 (5.3%)		0 (0.0%)	
Above 12	18 (94.7%)	0.45	21 (100%)	0.06
Menopausal				
Postmenopausal	7 (36.8%)		11 (52.4%)	
premenopausal	12 (63.2%)	0.99	10 (47.6%)	0.09

χ^2 presence of risk factors versus absence of risk factors with liver or lung metastasis

8.0 DISCUSION

Lung and liver metastasis contributes to morbidity and mortality in women with breast cancer disease. Clinical and radiological staging in breast cancer is an important component of patient management. The purpose of staging is to rule out overt metastasis, with resultant treatment and prognostic implications. The aims of this study were to determine TNM stage of newly diagnosed breast cancer patients, the prevalence of lung and liver metastasis and if risk factors for breast cancer occurrence are related with prevalence of lung or liver metastasis among women with breast cancer at ORCI.

8.1 TNM stage of newly diagnosed breast cancer patients

In this study the findings of breast cancer TNM stages do not differ with studies done in other parts of Africa whereby more than 90% had locally advanced breast cancer which was either stage III or IV disease at the time of diagnosis and none of the women with newly diagnosed breast cancer came with a TNM stage I. The findings of this study are in agreement with a previous study done in Tanzania in 1997 [27] which showed that more than 90% of newly diagnosed breast cancer patients had locally advanced breast cancer either stage III or IV disease at the time of diagnosis.

This is attributed to, by lack of knowledge, awareness and poverty, which ultimately lead to delay in seeking medical attention hence high chances of having advanced disease at the time of presentation. Lack of information about signs and symptoms of breast cancer disease and lack of information about risk factors one has, may account for the late coming to the health care facility. All women worldwide are encouraged to do Breast Self-Examinations (BSE) monthly, which are quick and effective way of detecting palpable breast lumps[1]. This will facilitate early going to a healthy facility early diagnosis and management and hence good prognosis. Absence of mammograms in peripheral hospitals and lack of knowledge of its importance in early diagnosis of breast cancer contributes to poor prognosis and that early diagnosis has good prognosis. Presence of only one cancer centre in a country of more than 43 million people may lead to delay to reach ORCI.

More than half of the studied women had no any kind of work that generated income. Those who were married most likely they depended sorely to their partners for financial assistance. About half 45.6% had an income generating activity prior to seeking medical attention. In a research done in Spain pointed out that poverty conditions lead to limited access to information and treatment resources[36], lack of formal education also leads to lack of information and a distorted perception of the disease which leads to the avoidance of the breast self-exam, and restrict the request for mammograms and clinical breast examination among women living in poverty.

This was also seen in the report given by Medical Women Association of Tanzania (MEWATA). After doing several breast cancer campaigns all over Tanzania to raise mass awareness about breast cancer, their conclusion was that lack of mammography screening systems in many hospitals in Tanzania especially in the regional hospitals leads to advanced stages of breast cancer at diagnosis hence high chances of distant metastasis. Poverty, the bureaucracy of referral system, myths and misconceptions were other factors[37] accounting for late coming to heath facility, which resulted in an advanced disease in newly diagnosed breast cancer patients.

In South Africa a similar study was done about TNM stage of newly diagnosed breast cancer patients and they compared blacks and white breast cancer patients. Findings were similar to what was seen in this study whereby stages III and IV of breast cancer were the most prevalent in black women (77.7%) compared to white women (30.7%) [38]. They gave reasons that for blacks having locally advanced breast cancer at the time of diagnosis was; traditionally, black patients seek a cause for illness within the framework of indigenous beliefs. Cancer was interpreted as a reflection of conflicts, particularly in social relationships. Many patients with cancer believed that a special witchcraft caused their cancer, and, therefore, their first priority was to reverse the sorcery before presenting to hospital to be treated by modern medicine methods. The patient sought help first from a traditional healer as a way of dealing with the cause of the disease, and, in their views, this did not imply delaying medical treatment. The concept that a painless breast lump was a cancer and therefore a potentially fatal disease is difficult for many black rural women to accept [38].

Moreover locally advanced breast cancer is the most common form of presentation for breast cancer patients in countries of limited resources, and, along with stage IV disease, it represents

from 60% to 80% of new patients cases at presentation in Arabic and African communities [39]. What is seen in Africa is different from what is seen in developed countries or more fluent societies.

In USA[2] in a study about TNM staging of newly diagnosed breast cancer pointed out that due to increasing use of screening mammography, the average size of breast tumors when first detected has decreased significantly and was associated with a decreased probability of axillary lymph node metastases. This resulted in Stage 0 or Stage I detection increased from 42.5% in 1985 to 56.2% in 1995, whereas the percentage of patients presenting as Stage III or Stage IV decreased from 18.3% to 11.6%.

This means due to advanced cancer stage at the time of diagnosis, most likely our women have poor prognosis in comparison to breast cancer patients in developed world who are usually picked up with an early breast cancer disease stage I/II. This is a challenge to our health system to improve health care system so that breast cancer patients are picked up early when they are either in stage I or II which has a good prognosis. Furthermore death occurring due to breast cancer shows significant differences among stages: 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 [41].

The ability to accurately stage patients has many benefits. Firstly, clinicians will be better able to advise patients on their prognosis. Secondly, appropriate palliative measures can be introduced at an earlier opportunity. Finally, clinicians will be able to better individualize treatment to their patients. For instance, patients who have locally advanced tumor can be offered more aggressive chemotherapy with curative intent as the potential long- term benefits far outweigh any short-term toxicities or quality-of-life disruption. Conversely, in those who present with metastatic disease, a more balanced, quality-of-life oriented approach can be utilized. It is, however, considered beneficial for the accurate staging of disease to be known when decisions regarding adjuvant systemic therapy are made [23].

8.2. Prevalence of lung and liver metastasis

In this study the prevalence of lung and liver metastasis in newly diagnosed breast cancer was 20.4% and 18.4% respectively. This is very high compared to what was seen by other researchers elsewhere this is contributed by advanced stage of breast cancer at the time of presentation and diagnosing in our setup.

In Toronto Canada they found out that the prevalence of metastatic disease in locally advanced breast cancer (LABC) was 13.2%, with metastases to liver (3.5%) and lung (2.7%). This supports the continued need for full routine staging tests for patients with LABC as compared with those women with earlier stage disease. They took those patients who had negative results in LUS and CXR and did a confirmatory imaging investigations by computed tomography, magnetic resonance imaging (MRI) and/or positron emission tomography (PET), they found metastasis in 2.8%. So their conclusion was negative baseline investigations can be falsely reassuring[29].

In developed countries or more affluent societies studies have shown that the role of baseline radiological investigations for overt metastases in patients with early breast cancer is contentious, with many patients undergoing inappropriate radiological examination. The rate of them peaking metastasis in newly diagnosed breast cancer patients is very low as many of their patients have either TNM stage I or II at the time of diagnosis [2].

In a study done in USA[7] found out that the asymptomatic pulmonary metastasis detection rate is 0.099%. Hence their opinion was; based on the available data that staging chest x-ray may be ordered only for those with pulmonary symptoms or those with clinical stage III or IV disease where the disease burden portends a higher diagnostic yield for the screening exam.

In Netherlands in 2002, they found a low detection rate for liver ultrasound in all age groups of patients (six out of 399, 1.5% detection rate) and only 1% of lung metastasis by chest radiograph. They concluded that liver and lung metastases at the time of diagnosis of operable breast cancer was a rare event that could not justify a routine use of liver ultrasound or chest radiograph[12]. In contrast to what was found in this study, probably we have to make LUS be a routine to all newly diagnosed breast cancer patients.

A study done in Italy[9], had the detection rate of 5.6% and 7.2%, respectively for LUS and CXR. Hence indiscriminate use of diagnostic procedures in all patients with newly diagnosed breast cancer has a high chance of generating unjustified anxiety in patients and of increasing costs. They recommended using LUS and CXR only to patients with a prior high risk of metastases.

This lead to American Joint Committee on Cancer (AJCC) in its six version to give recommendation on proper staging of newly diagnosed breast cancer patients, whereby they recommended that newly diagnosed breast cancer patients do not need baseline radiological imaging (since most have TNM stage I or II) because it is a rare event. Imaging is only required to only newly diagnosed with locally advanced breast cancer [40]. In less privileged society like ours this probably has to change and be that all newly diagnosed breast cancer patients' need baseline radiological imaging since most of them have an advanced disease at presentation.

The Breast Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) reviewed the evidence for the use of routine chest radiography (CXR), and liver ultrasound in newly diagnosed breast cancer patients. They recommended that all breast cancer patients who have locally advanced disease which is TNM stage III or IV should have a liver ultrasound and a chest radiography as baseline radiological staging since chances of picking metastasis are high [23]. As we have seen above more than 90% of participants in this current study had locally advanced breast cancer at the time of diagnosis hence they needed these baseline radiological staging.

In summing up all these studies, it is evident that abdominal ultrasound and chest radiograph have a big role to play here in Tanzania because patients have advanced cancer stage at the time of diagnosis and hence they have high chances of having metastasis. This will lead to proper management of breast cancer patients and thus good prognosis.

8.3. Relationship between risk factors for breast cancer development and prevalence of lung or liver metastasis

The mean age for breast cancer occurrence in this study was found to be 48±11.22. The youngest age of occurrence of breast cancer in this study was 26years. Worldwide the breast cancer occurrence is extremely rare in those below 20 years[4]. The occurrence usually increases steadily

with age, in this study 61.5% women were above 45years. This is in keeping with what was seen by other researchers whereby the incidence rises steadily by age, so that by 90years, 20% of women will be affected, furthermore out of ten breast cancer patients eight will be aged more than 50 years[1]. In a study done in England [41] showed the incidence do increase with age, with a plateau in women aged 50-55 years and added that age is the most significant risk factor. The mean age of 51years was found in another study[29].

Lung metastasis prevalence increased with age, and the prevalence started to peak at the 35-44 age categories. While liver metastasis occurrence did increase with age and the prevalence was high in age category of 45 and above years. Studies have shown that tumors occurring in very young patients are reported to have a particularly aggressive biological behavior leading to a somewhat unfavorable prognosis, which was described extensively in the pre-adjuvant systemic therapy era [42].

Positive family history and early menarche (younger than 12 years) have been shown to have high association with development of breast cancer. Women with a positive family history of breast cancer, especially a first degree relative (mother, sister, daughter), have an increased risk of developing breast cancer[1, 4]. This study wanted to see if this factor contributed to lung or liver metastasis occurrence. Surprisingly findings in this study show that these factors contribute very little to occurrence of lung or liver metastasis.

On the other hand alcohol intake is linked to a slightly increased risk of breast cancer[1]. In terms of mechanism for causing cancer, it has been postulated that alcohol may alter estrogen levels, themselves known to be associated with breast cancer risk, or interfere with DNA repair[43]. In this study alcohol intake despite the quantity consumed, it contributed to lung and liver metastasis by 38.1% and 42.1% respectively.

Early metastatic growth dynamics shows a structured pattern that is correlated to menopausal status. Indeed, during the first 4 years, node-positive pre-menopausal patients display a split of the hazard function surge into two peaks, while post-menopausal patients always display a single peak[44]. This current study showed the distribution of lung metastasis between postmenopausal and premenopausal women to be almost equal, while 63.2% of liver metastasis occurred in

premenopausal women. These may mean that premenopausal women with breast cancer have high risk of developing metastasis hence they requires more close follow up, and it justifies the role of LUS and CXR in all premenopausal patients with breast cancer.

8.4. Study limitations

Various constrains was encountered during study performance;

Some of the patients were very sick especially those admitted into the wards, and thus mobilization into the Ultrasound or CXR units was difficult.

Findings reported in this study is in regards to the breast cancer patients who attended ORCI (sample for convenience), thus extrapolation to the general population may be limited however it can be used in secondary and tertiary hospitals.

Lastly but not the least, the study did not involve confirmatory tests as a result definitive diagnosis that lesions seen in the lung or liver were metastasis and not another primary lesion could not be reached.

9.0 CONCLUSION

This study showed that, the prevalence of lung and liver metastasis was very high accounting for 20.4% and 18.4% respectively. This is supported by the fact that most of newly diagnosed breast cancer had locally advanced breast cancer at presentation. The results of this study strengthen the recommendation of doing baseline staging tests, especially LUS and CXR, to all new breast cancer patients in Tanzania. Most of the patients have locally advanced breast cancer disease on arrival at ORCI and hence high chances of distant metastases. This study showed also that, premenopausal women and those who use alcohol have increased prevalence of lung and liver metastasis though the results were not significant.

10.0 RECOMMENDATIONS

- More study involving large sample size should be conducted to determine association between risk factors and occurrence of metastasis.
- LUS and CXR should be done to all newly diagnosed breast cancer patients.
- There is a need for more breast cancer studies using biopsy of the lesions picked up by LUS or CXR to be conducted in Tanzania.
- Mass breast care campaigns like those done by MEWATA should be supported to increase public awareness on breast cancer.
- Proper utilization of CXR and ultrasound at health facilities concerned with breast cancer should be improved to ensure correct staging and follow up of the patients.
- Ministry of Health and Social Welfare should ensure that facilities for doing CXR, ultrasound, and mammography; and training of human resources are universally available.

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11. APPENDICES'

Appendix I; Questionnaire

THE ROLE OF IMAGING IN THE DETECTION OF OVERT ABDOMINAL AND CHEST METASTASIS DUE TO BREAST CANCER, AND ASSOCIATED RISK FACTORS AT ORCI.

PART I: demographic data

1. Registration no: _____
2. Date of interview: ____/____/_____ **(dd /mm/yyyy)**
3. Date of birth _____/____/_____ **(dd /mm/yyyy)**___
4. District _____
5. Region _____
6. Religion
7. Marital status:
    1. Single
    2. Cohabiting
    3. Married
    4. Divorced
    5. Widowed
8. Level of education attained
    1. None
    2. Primary school
    3. Secondary school
    4. Post Secondary
9. What is your occupation?

1. Informal employment
2. Formal employment
3. None

10. How much alcohol do you usually take
    1. Two to five bottles daily
    2. One bottle daily
    3. One bottle per week
    4. One bottle in a while
    5. None
11. At what age did you attain your menarche
    1. Below 12 years
    2. above 12 years
12. when did you attain postmenopausal
    1. below 55 years
    3. above 55 years
13. at what age you had your first pregnancy
    a. below 30 years
    b. above 30 years
14. how many pregnancy did you had
    a. one
    b. more than one
    c. none
15. which family planning method have you been/ is using

a. Natural

a. pills
b. depo provera
c. implanon
d. condoms

16. Do you have any relative who had had similar illness?

Yes

No

17. if YES how were you related

a. mother
b. sister
c. grandmother
d. aunt

Part II: **Imaging Data**

1) Ultrasonography

Fill in immediately after each sonography and attach images

Liver size should be measured and documented. Liver is…….cm

If any lesion is encountered, document

	Right lobe	Left lobe
Number of lesions	……..	……
Size of the biggest	……..	……
Its shape	……..	……
Its outline	……..	……
Echotexture	…….	…….

2.CXR

Nodules

Right lung

Upper zone

Mid zone

Lower zone

Left lung

Upper zone

Mid zone

Lower zone

Reticulonodular shadowing

Right lung

Upper zone

Mid zone

Lower zone

Left lung

Upper zone

Mid zone

Lower zone

Cavitation

Right lung

Upper zone

Mid zone

Lower zone

Left lung

Upper zone

Mid zone

Lower zone

Pleural effusion

Right lung

Left lung

Patient's stage will be collected from case notes……

Appendix II; Informed consent

I am Dr Lulu Sakafu postgraduate student at Muhimbili University of Health and Allied Sciences (MUHAS). I am doing investigations on breast cancer patients. The aim of this study is to study the role of chest radiograph combined with liver ultrasound in early detection of overt metastasis to the lungs and liver and associated risk factors.

If you agree to participate in this study, you will be asked questions then abdominal ultrasound and chest radiograph will be done immediately on the same day before you start chemotherapy.

No information from this study will be available to unauthorized individuals. All information collected plus results of abdominal ultrasound and chest x-ray will be entered in a computer system and only registration numbers will be used for identification. We don't expect any harm from this study to happen to you.

Taking part in this study is completely voluntary. You can withdraw any time without giving reasons, even if you have already given consent. There will be no penalty on your further medical treatment, you will be treated and followed up as any other patient according to ORCI treatment protocol for cancer patients.

If you agree to participate you will benefit by having thorough check for any early sign of metastasis on your lungs, and screening not only of the liver but also abdominal organs by ultrasound which will help the oncologist to properly plan your management. Knowledge gained from this study will benefit management protocol of other breast cancer patients.

If you have any other questions regarding this study, feel free to contact me, the investigator, Dr. Lulu Sakafu through telephone number 0754299772 or 0715299772 or email address willymeena2007@yahoo.com. If you have any questions or concerns about your rights as a participant in this study you could discuss them with the current chairman of the Research Ethical Committee Prof E Lyamuya, MUHAS P.O.Box 65001, Phone 2152489 or 0754 495933.

Do you agree to participate? (*Tick the response*) .....YES …….NO.

I, ……..have read the consent form and my questions have been answered and I agree to participate in this study.

Signature of Participant……..

Signature of Investigator……

Date of signed consent…….

Appendix III; Consent: Swahili version

FOMU YA RIDHAA YA KUSHIRIKI UTAFITI

Mimi ninaitwa Dr Lulu Sakafu ni mwanafunzi wa uzamili chuo kikuu cha tiba Muhimbili. Nina fanya uchunguzi kwa wagonjwa wenye saratani ya matiti. Dhumuni la utafiti huu ni kuona uwezo wa picha ya kifua (chest x-ray) na picha ya tumbo(abdominal ultrasound) katika kuonyesha mapema na kwa usahihi maambukizi ya saratani kwenye ini na mapafu na kama kuna kisababishi chochote.

Ukikubali kushiriki katika utafiti huu utaulizwa maswali halafu utapigwa picha ya kifua ikifuatiwa na picha ya tumbo kabla hujaanza matibabu ya dawa za mionzi kwa njia ya mshipa(chemotherapy).

Taarifa zote kuhusiana na utafiti huu ni siri na mtu yeyote asiyehusika hataruhusiwi kuziona. Taarifa pamoja na majibu yote yataingizwa kwenye computer kwa kutumia namba yako ya utambulisho. Hatutegemei madhara yoyote yakupate kutokana na utafiti huu.

Ni hiari yako kukubali kushiriki kwenye utafiti huu. Unaweza kujitoa wakati wowote bila kutakiwa kutoa maelezo hata kama ulishathibitisha kushiriki. Hautaadhibiwa au kunyimwa haki yako ya matibabu. Utatibiwa kama wagonjwa wengine wa saratani ya matiti kufuatana na protokali ya ORCI.

Kama ukikubali kushiriki katika utafiti huu utafaidika kwa kuchunguzwa kwa kina kama una dalili za awali za usambaaji wa saratani si tu katika mapafu na ini lakini pia viungo vingine vya ndani ya tumbo vitachunguzwa pia. Matokeo ya uchunguzi huu yatasaidia katika kuboresha matibabu kwa wagonjwa wengine watakao gundulika kuwa na saratani ya matiti.

Kama una maswali kuhusu utafiti huu wasiliana nami Dr Lulu Sakafu Box 65007 Dar es Salaam, nambari ya simu 0715299772 au 0754299772 au kwa brua pepe willymeena2007@yahoo.com.

Kama una maswali yoyote juu ya haki zako katika kushiriki utafiti huu, unaweza kuzungumza na mwenyekiti, Kamati ya utafiti kuruhusu udhamini wa utafiti- Chairman of Ethical Committee MUHAS Prof. E. Lyamuya, S.L.P 65001, Simu: +255 22 2152489, +255 754 495933.

Je, umekubali kushiriki? .....NDIYO..... HAPANA.....

Mimi……..nimesoma maelezo na maswali yangu yamejibiwa na nimekubali kushiriki kwenye utafiti huu.

Sahihi ya Mshiriki……

Sahihi ya Mtafiti……

Tarehe……