THE ROLE OF SONOELASTOGRAPHY IN EVALUATING BREAST MASSES DETECTED ON MAMMOGRAPHY WITH HISTOPATHOLOGICAL CORRELATION AT KENYATTA NATIONAL HOSPITAL

DR. SIJABULE NDLOVU SWODZIWA
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STUDENT'S DECLARATION

I, **Dr. Sijabule Ndlovu Swodziwa,** do hereby declare that this dissertation is my original work and has not been submitted for the award of a degree at any other university.

Dr. Sijabule Ndlovu Swodziwa

Signed: Date: 10/11/2021

SUPERVISORS' APPROVAL

This dissertation has been submitted with our approval as university supervisors.

Dr. Ian Mathenge Muriithi
Consultant Radiologist and Lecturer
Department of Diagnostic Imaging and Radiation Medicine
University of Nairobi, Kenya.

Signed ..... Date 11/11/2021

Dr. Beatrice Mugi
Consultant Radiologist
Department of Radiology
Kenyatta National Hospital, Kenya.

Signed ..... Date 14/11/2021

Dr. Angeline Anyona Aywak
Consultant Radiologist and Senior Lecturer
Department of Diagnostic Imaging and Radiation Medicine
University of Nairobi, Kenya.

Signed ..... Date 10 NOVEMBER 2021

DEDICATION

To my husband Stanley Swodziwa and our children Jaden Abongiwe and Gabrielle Anashe Swodziwa who have been my source of strength and motivation through it all.

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ABBREVIATIONS

2D	Two Dimensions
3D	Three Dimensions
ACR	American College of Radiology
ACS	American Cancer Society
BIRADS	Breast Imaging-Reporting Data System
BRCA	Breast Cancer gene
CAD	Computer Aided Detection
CBE	Clinical Breast Examination
CC	Craniocaudal
DDIRM	Department of Diagnostic Imaging and Radiation Medicine
ERC	Ethical Review Committee
FNAC	Fine Needle Aspirate and Cytology
IAEA	International Atomic Energy Agency
KNH	Kenyatta National Hospital
MLO	Medio-lateral Oblique
MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
PPV	Positive Predictive Value
SBE	Self Breast Examination
SBI	Society of Breast Imaging
SR	Strain Ratio
UE	Ultrasound Elastography (Sonoelastography)
UON	University of Nairobi
US	Ultrasonography
VAB	Vacuum-Assisted Biopsy

DEFINITION OF TERMS

Mammography: This is a breast imaging technique which uses ionizing radiation. It is currently the principal screening and diagnostic test for women above 40 years.

Ultrasound: A non-ionizing imaging technique that uses sound waves. It is the primary diagnostic breast imaging test for women under 35 years and an adjunct to mammography above 35 years.

Sonoelastography: A relatively new sonographic imaging technique which looks at tissue stiffness to determine lesion benignity or malignancy.

ALARA principle: A radiation protection principle used in all radiological examinations as prescribed by the International Atomic Energy Agency (IAEA) to protect the general population from unnecessary/unwarranted radiation exposure.

ABSTRACT

Study background

Breast cancer is a high burden disease in Kenya and worldwide, therefore any efforts to reduce its morbidity and mortality are not misplaced. A relatively new and increasingly popular breast imaging modality, sonoelastography exploits differences in tissue stiffness to differentiate benign and malignant lesions, increasing the confidence of diagnosing breast lesions non-invasively.

Broad Objective: To determine the role of breast sonoelastography in assessing mammographically detected breast masses before histopathological diagnosis at Kenyatta National Hospital (KNH).

Study Design and Site: A descriptive cross sectional study was conducted at Kenyatta National Hospital Radiology Department and Department of Diagnostic Imaging and Radiation Medicine, over a period of six months (January to June 2021).

Methodology: Sixty seven (67) solid breast masses from fifty two (52) patients identified on diagnostic and screening mammography were assessed using the ACR BIRADS classification. The identified masses were further analyzed by sonoelastography and correlated with histopathology. Patients' bio-data was collected to determine the demographic characteristics associated with breast cancer in a Kenyan population. Data analysis was done using SPSS software version 20. The sensitivity, specificity and diagnostic accuracy of both imaging techniques and in combination were determined. Statistically significant data was defined as a p value <0.05.

Results: A total of 67 breast lesions from 52 patients were analyzed. All the participants were females, age range 35-81years, with a mean age of 53.8years. 8 (15%) patients had a positive family history of breast cancer. 47 (70%) lesions were malignant on histology with 20 (30%) benign lesions. Invasive ductal carcinoma was the single most common lesion, while fibroadenoma was the most common benign lesion. 38(56.7%) lesions were classified as BIRADS 4 which was the most prevalent BIRADS classification on mammography, with all BIRADS 2 and 5 lesions showing no discordancy on histological correlation. UE score of 4 was the most prevalent with 29(43.3%) lesions. Scores of 1 and 5 showed no discordancy on histological correlation.

UE sensitivity, specificity and accuracy were 89.3%, 90% and 89.5% respectively versus mammography 87.3%, 70%, 82% respectively and in combination 95.75, 90% and 92.5%

respectively. UE shows superior diagnostic accuracy compared to mammography though the best diagnostic accuracy is seen when the two modalities are used in combination.

Conclusion: Sonoelastography is a noninvasive technique that can be used to complement mammography. It has a high diagnostic accuracy in the evaluation of breast lesions. Combined, the two modalities show the best diagnostic accuracy and cancer detection rate. The study findings therefore, favor the routine and complementary use of UE with mammography in the work-up of breast lesions, with the potential of reducing benign biopsies and/or unwarranted follow-ups while increasing the cancer detection rate.

CHAPTER ONE: INTRODUCTION

Globally, breast cancer prevalence is second to lung cancer with an incidence rate of 11.6%. In females, breast cancer has been shown not only to have the highest incidence but is also the chief cause of cancer deaths[1]. With such a high burden of disease, diligence and early diagnosis are pivotal in the fight against breast cancer. Mammography and sonography are the two modalities that have demonstrated the best sensitivity in detecting breast cancer, hence their use as first line radiological diagnostic tools. However, both methods are not without limitation[2].

Despite the high disease burden of breast cancer, the majority of clinically significant breast lesions have been shown to be benign, with a cancer detection rate of 10-30%[2,3] in breast biopsies. Similar studies done at Kenyatta National Hospital concur to the above detection rate. In a study by E.S Otieno et al, malignant breast lesions were detected in 22% of all breast biopsies, with 78% of the lesions being benign[4]. Another study done by A. Aywak et al, cancer detection rate was found to be 25%, with 75% benign lesions[5]. This implies that the majority of breast biopsies are done in benign cases and therefore potentially avoidable.

The introduction of sonoelastography as a complementary tool to the two conventional breast imaging modalities is a move towards optimum usage of non-invasive diagnostic means before resorting to invasive methods. In triple assessment of the breast, clinical palpation is the initial step. Clinical palpation is founded on the concept of tissue elasticity, the assumption that pathological tissue will be stiffer than normal breast tissue hence recognized by the clinician. Sonoelastography employs the same principle of tissue elasticity, but with the added value of differentiating the extent of tissue compressibility hence improving non-invasive differentiation of malignant and benign breast lesions.

This study therefore sought to assess whether the combined use of mammography and sonoelastography would improve the characterization and differentiation of malignant and benign breast lesions, thereby reducing the number of benign breast biopsies done at Kenyatta National Hospital.

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology

Breast lesions though common are usually benign with the greater number being fibroadenomas[4–6]. Regardless of the benign predominance, breast cancer remains the commonest cancer among females worldwide, affecting 2.1million women yearly and causing 15% of all cancer related deaths in women[7]. Kenya is no exception, with studies showing that breast cancer accounts for 22-23% of all female cancer cases, hence the leading cancer in women and leading cause of cancer related deaths in females[8]. Moreover, being female is a significant predisposing factor for developing breast cancer with 99% of breast cancers diagnosed in females[9] . Male breast cancer accounts for less than 1% of all breast cancer cases and less than 1% of all male cancers. However, it shows a higher mortality compared to females due to poor awareness and delayed presentation[10,11].

The incidence rate of breast cancer is higher in developed countries (84.8-94.2 cases per 100 000 women compared to 40.3 cases per 100 000 women in Kenya)[1], though the low income countries show higher mortality[12]. The latter is attributed to the improved diagnostic and therapeutic methods employed in developed countries [13]. Furthermore, about 85% of breast cancers are diagnosed in individuals with no known family history of breast cancer, while only 15% have a known family history of breast cancer[9]. Therefore, this calls for improved and more aggressive breast cancer screening, early diagnosis and subsequent management especially in low and middle income countries.

2.2 Breast Cancer Screening

Breast cancer screening involves examining women to identify cancer before any symptoms appear with the aim of lowering cancer related mortality and morbidity in a given population. Clinical breast examination(CBE) and mammography are the principal breast cancer screening tools [7]. African women show an incidence peak for breast cancer in the 35-45 years age range, which is at least a decade earlier than the western population[14–18]. Age is a crucial prognostic factor with early age of breast cancer diagnosis associated with more aggressive disease and therefore a poorer outcome[19–22]. Furthermore, women in low income countries typically present with late disease and with the added disadvantage of limited treatment options this further worsens the prognosis, Kenya being no exception to this[16,22,23].

The American College of Radiologists (ACR) and Society of Breast Imaging (SBI) recommend mammographic breast cancer screening from the age of 40years for all average risk women. US and/or MRI may be added as adjuncts to mammography in intermediate risk patients according to indication. In high risk women, mammographic screening is recommended below 40years guided by indication but not less than 25years of age. Women with a genetic predisposition, annual mammographic screening is advised from an age 10years earlier to the time the youngest relative was diagnosed of breast cancer but not less than 30years. Annual screening breast MRI is recommended from as early as 25years in BRCA positive patients and as a complementary study to mammography in the rest of the high risk women[24,25]. The average risk population incorporates women without the risk factors seen in the high risk population, though at least 80% of breast cancers occur in this population[18,26]. Breast cancer diagnosis in a first degree relative, previous breast cancer diagnosis and previous history of radiation to the chest wall are among the factors that define one as high risk[18].

The 2018 Kenya National Cancer Screening Guidelines have similar recommendations; mammography and CBE being the mainstay for screening average risk women from 40yrs of age, done annually in the 40-55years group and 2yearly from 56-74yrs. Above 75years, screening is not mandatory but is individualized according to clinical indication or woman's preference. Below 40years of age CBE and US are the mainstay, repeated every 1-3years as per individual indication. The guidelines do not commend self-breast examination (SBE) as a screening tool. MRI is not recommended as a routine screening instrument in the average risk women, while US though not recommended as a stand-alone screening device, it should complement mammography in women with dense breast parenchyma. In the high risk population, a more aggressive approach is recommended tailor made according to the individual risk factors[18].

The principal imaging modalities in suspected breast pathology comprise of mammography, sonography (US), Magnetic Resonance Imaging (MRI) and sonoelastography (UE), with histopathology as the reference standard.

2.3 Mammography

The origin of breast mammography dates back to 1913, emanating from simple radiography of mastectomy specimens done by Albert Salomon, a surgeon in Berlin[27,28]. It has seen its

evolution through non-screen film, screen-film imaging and currently digital mammography and computer aided detection (CAD). Its main uses include evaluation of breast signs and symptoms, follow-up of known breast cancer patients current and previous, breast cancer screening and localization of lesions for biopsy guidance. Mammography is pivotal in breast cancer screening above 35years of age, reducing breast cancer mortality in the 40-74 years age group by 40%, in women who do routine screening[26]. As a diagnostic tool, mammography is renowned for its high sensitivity in picking breast microcalcifications, aiding in the preclinical diagnosis of cancer.

However, mammography does not come without limitation. It has an overall sensitivity of approximately 80%. Therefore, an important limitation in screening mammograms is false negatives, seen in 15-20% of cases. This is particularly so in women with dense breasts[26]. Mammographic sensitivity is inversely proportional to breast density, the higher the breast density the lower the sensitivity. Patricia A. Carney et al, showed an overall 87% mammographic sensitivity in composition A breast, decreasing to 62.9% in extremely dense breast[29]. The ACR BIRADS is used to report breast density, with 4 categories; composition A being the least dense (almost entirely fatty) and composition D the most dense (extremely dense breast[30]. This limitation can be counteracted by the use of digital tomosynthesis, breast ultrasound and/or MRI. Digital tomosynthesis converts the conventional 2D mammographic projections into a 3D real time image therefore eliminating tissue superimposition associated with conventional mammography. Tissue superimposition is a cause for both false negatives (overlapping tissues obscuring tumor) and false positives (overlapping tissues misinterpreted as a lesion). False positives are seen in 10% of screening mammograms, and can be resolved by additional imaging or biopsy. Another limitation seen in mammography is over-detection, defined as detection of a clinically insignificant cancer. This is seen in 10% or fewer cases[26].

Scintimammography, an adjunct to mammography is an imaging tool that makes use of radioisotope to identify breast lesions especially in dense breasts[31]. The combined use of mammography and 99mTc-MIBI scintimammography was shown to lower the number of biopsies by 34% in one study[32]. However, both modalities come with risk of radiation induced breast cancer more so in younger patients. Therefore, a more ideal adjunct to mammography in a bid to reduce unwarranted biopsies should not come with further risk of radiation, and one such modality is sonoelastography.

2.4 Breast Ultrasound

Ultrasound is a radiological tool that utilizes sound waves to produce images and therefore does not pose radiation related risks to the concerned subject or organ. The breast is very sensitive to radiation induced carcinogenesis, especially if exposed at a young age[33] . B-mode ultrasound is therefore an everyday use tool in breast imaging, being the mainstay in screening young women below 35years. It is the best modality in differentiating solid and cystic breast lesions[34]. In a 1995 study done by Stavros et al,[35] they demonstrated sonographic classification of solid breast lesions as benign or malignant, with a negative predictive value of 99.5% and sensitivity of 98.4%, thus optimizing imaging follow-up over biopsy. In the study a number of parameters were used to classify lesions as malignant or benign and these features are the cornerstone for sonographic assessment of breast lesions as described by the ACR BIRADS[30,36].

Sonography has also found its place as an adjunct to other modalities, namely mammography and MRI, where it is used to evaluate and further characterize lesions detected in either modality. In breast screening it is used to complement mammography in dense breasts and/or negative mammographic findings[36]. It has been shown in a number of studies to have an improved diagnostic yield for breast cancer in dense breasts and on negative mammograms especially in dense breasts, more so if the US BIRADS lexicon is used. In one study a 3.6 per 1000 detection rate was seen with mammography alone increasing to 7.2 per 1000 on adding sonography in dense breasts. However, it comes with a concern for over-diagnosis, increase in false positives and increasing biopsy rate especially in asymptomatic women, due to the low specificity of ultrasound[37–41]. Ultrasound is the primary method in guiding interventional breast procedures[36].

Despite all these advances in its uses, ultrasound is notably disadvantaged by operator dependency limiting its optimum and accurate usage. It also shows a lower sensitivity compared to mammography in picking microcalcifications.

Technological advances in breast ultrasound include contrast enhanced ultrasound, Doppler imaging, high frequency probes, 3D reformats, Automated breast ultrasound(ABUS) and sonoelastography[31,36]. A new and emerging adjunct to breast sonography, optoacoustic (photoacoustic) imaging which combines structural and functional information has a promising future more-so in combination with sonoelastography[42].

2.5 Breast Sonoelastography

Breast sonoelastography (UE) is a relatively new imaging modality, an advancement of conventional B-mode ultrasound which exploits tissue elasticity and displays it as a color coded map. It supplies information on lesion stiffness similar to clinical palpation of lesions where pathological tissue feels harder than normal tissue, due to altered tissue elasticity in disease. More so, malignant lesions show greater stiffness compared to benign lesions, making sonoelastography an ideal modality to differentiate benign from malignant tissue[2,43]. Two approaches are available in breast imaging: strain elastography and shear wave elastography. Strain elastography measures the amount of displacement produced in any tissue when light compression is applied using an ultrasound probe. This displacement (strain) is higher on soft tissue than harder tissue. The measuring of tissue strain allows for a non-invasive and qualitative estimation of tissue stiffness[44]. Normal tissues (softest component/highest strain) are coded red while the hardest tissues (least strain) are coded blue, with the intermediate tissues coded green. A color coded map called an elastogram is thus produced, and it is superimposed on the grayscale image [43,44]. A displayed example of a benign and malignant lesion respectively is shown below.

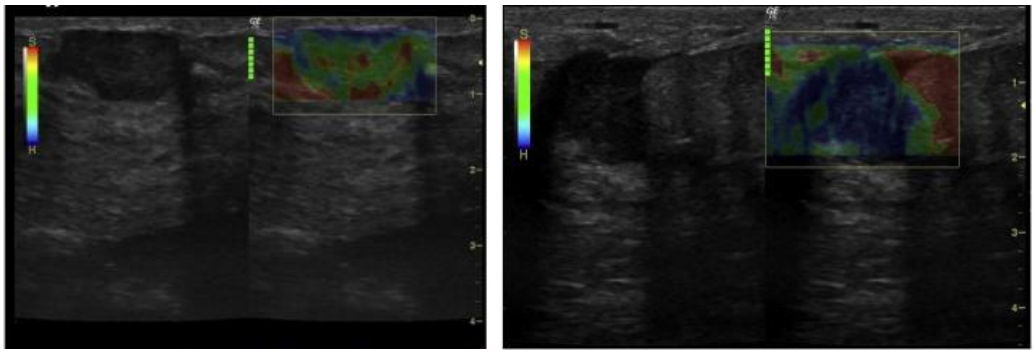


Figure 1:UE benign and malignant lesions respectively[43]

A five point elasticity score system is used to classify lesions as benign or malignant, with score one(1) showing the highest and most homogenous lesion strain decreasing inversely with score assigned. This is demonstrated below. A score of 4 and above is indicative of malignancy, while 2 and below are consistent with benign findings and a score of 3 is equivocal[2,44].

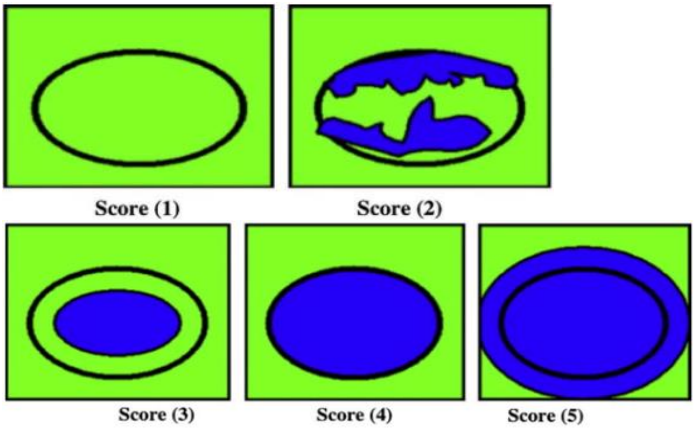


Figure 2:Diagrammatic elasticity score [43,44]

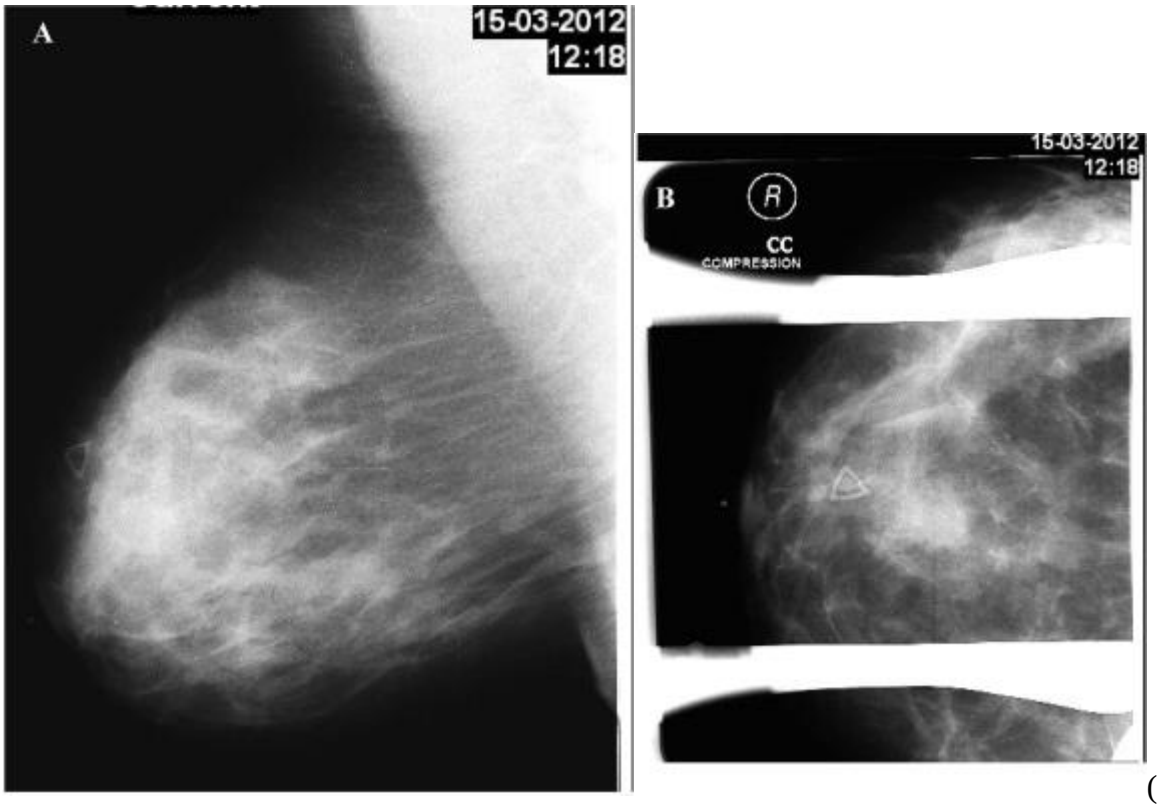
Lesion size is better evaluted on sonoelastography than B-mode mode US, with the former measurements correlating better with histopathology. A diameter ratio of the elastogram: B-mode image of more than 1 is suggestive of malignancy due to associated perilesional desmoplastic reaction seen in malignant lesions[(2,45).] Strain ratio/strain index is another parameter that is used to predict malignant potential of lesion. It is relative lesion stiffness against background fatty breast tissue[(2)].

Shear -wave Elastography is complementary to strain elastography, making up for some of the pitfalls seen in the latter. It provides quantitative information on tissue displacement. The velocity of the generated shear wave pulses on tissue compression is automatically captured by the machine and recorded in kPa. This is an absolute value of tissue stiffness, hence eliminating user dependence seen in strain elastography[(2)]. Various tissues show different pressure velocities; uncomplicated cystic lesions (0kPa), fatty tissue (3kPa), dense fibroglandular tissue (45kPa), benign lesions (<80kPa) and malignant lesions (>100kPa)[(46).]

In clinical studies that have been done to assess the diagnostic accuracy of sonoelastography(UE) compared to conventional US and mammography or in combination, UE has shown better accuracy and specificity, with even better accuracy in combination. Mohey N. et al, in a study done in Egypt with 114 lesions showed a diagnostic accuracy of 81.7% for UE, 71.9% for US, 82.5% for mammography and 93.8% for combined UE and US[(43)]. Zhi Hui et al produced similar results in a Chinese study (296 lesions), with a diagnostic accuracy of 88.2%(UE), 72.7%(US) and 93.9% for the combination of the 2

modalities[47]. Zhang H. et al in a study of 67 lesions showed a diagnostic accuracy of 89.6% for UE, 63.1% for mammography and a combined diagnostic value of 91%[48].

The 3 studies concluded than UE is superior to conventional methods in differentiating benign from malignant breast lesions. The complementary usage of UE with US or mammography further improves the diagnostic value of either modalities with the potential of reducing unwarranted biospies and/or follow-up time. This reduction is done by downgrading of BIRADS 3 and 4a lesions to benign without increasing the false negative rate.



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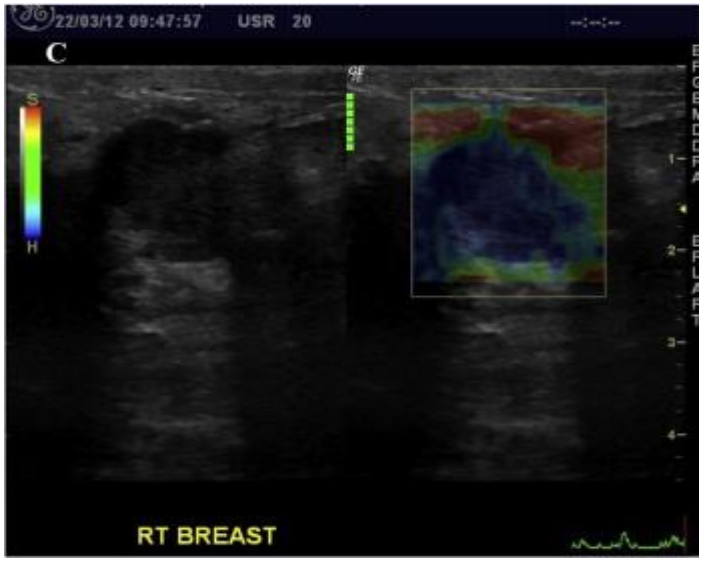


Figure 3: A) and (B) Diagnostic mammogram (C) US and UE

Figure 3: [A] and [B] Medio-Lateral Oblique (MLO) and compression diagnostic mammogram views in a 49 year old female patient show a heterogeneous fibroglandular breast density with a dense, irregularly shaped mass with spiculation. A skin marker was placed over the palpable mass. [C] US and UE respectively show a hypoechoic, irregularly shaped lesion, with a UE score of 5. Final histological diagnosis was right breast invasive ductal carcinoma.[43]

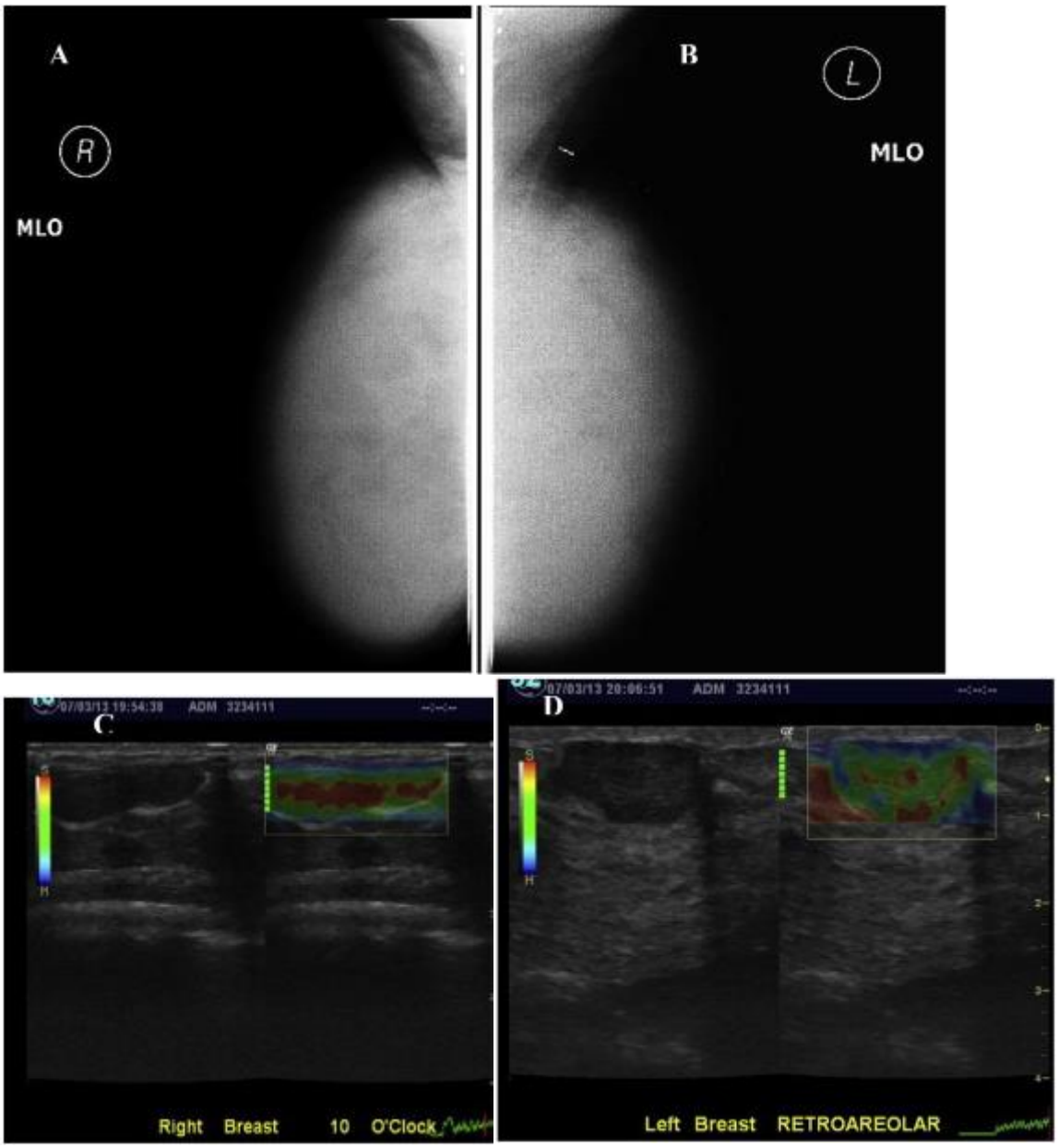


Figure 4: (A) and (B) Screening mammography (C) UE (D) UE

Figure 4: [A] and [B] Bilateral Medio-lateral Oblique(MLO) screening mammography in a 40 year old female patient show bilateral extremely dense breast parenchyma that reduce mammographic sensitivity. [C] US and UE show a right breast hypoechoic, well circumscribed mass with a UE score of 1. [D] US and UE show a well defined, hypoechoic left breast mass with a UE score of 2. Final histopathological diagnosis was bilateral fibroadenomas. [43]

2.6 Breast MRI

Breast mammography and ultrasound remain the primary and first line imaging modalities in breast imaging. However, breast MRI is gaining popularity too, due to its high soft tissue contrast, multiplanar imaging, 3D reconstructions and high sensitivity (>90%) in detecting breast carcinoma[49,50]. It is of value in both screening and diagnostic breast imaging. Its main uses currently are: screening in high risk females, staging of breast cancer in pre-treatment planning, post breast reconstruction surgery or breast implants , occult disease, recurring disease, breast conserving surgery follow-up, further characterization of inconclusive conventional imaging findings, assessing response post neo-adjuvant chemotherapy, multicentric or multifocal disease especially in dense breasts and male breast imaging[49–51].

As a screening tool, breast MRI has demonstrated a significantly superior sensitivity in detecting cancer over mammography in high risk individuals[52,53]. The American Cancer Society (ACS) guidelines, advise MRI screening in women with a 20-25% lifetime risk of breast cancer or greater. This encompasses females with a known family history of either breast or ovarian cancer and BRCA gene mutations. It is inadvisable in individuals with a lower than 15% lifetime risk of developing breast cancer.[54]

The main reluctance with breast MRI despite its superior sensitivity in detecting breast cancer is; its relatively lower specificity compared to the conventional breast imaging techniques. It has been known for overdiagnosis and false positive results; leading to unnecessary anxiety in patients, further investigations and increasing the biopsy rate. It also shows a lower sensitivity in picking microcalcifications which can be the only sign of breast cancer[50]. Other limitations to its usage especially in low income countries are its availability and cost in comparison to the traditional imaging techniques.

In recent developments an abbreviated breast MRI protocol which comprises of a pre and post contrast T1 weighted study and a T2 weighted sequence has been shown to reduce time and cost of a typical breast MRI study (multi-parametric imaging), with the intention of expanding MRI breast uses as a screening instrument[55,56]. Multi-parametric breast MRI protocol further incorporates diffusion weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI)[56].

2.7 Interventional Breast Radiology

Interventional Radiology (IR) has a diagnostic and therapeutic role in breast imaging. Diagnostic image guided biopsy involves selecting the most suitable imaging technique in guiding the biopsy and the most appropriate biopsy instrument[57]. The available methods for tissue diagnosis include FNAC, core biopsy, vacuum-assisted biopsy (VAB) and open surgery. VAB and core biopsy are the preferred methods, due to fewer false positives and false negatives[57]. FNAC is the least popular due to associated operator dependency, higher rates of false negatives and false positives, high incidence of tissue insufficiency and its inability to differentiate invasive and non-invasive carcinoma[58,59]. However, it is an indispensable tool in nodal sampling for preoperative breast cancer staging.

X-ray Stereotaxis, US and MRI are the most commonly utilized biopsy guiding techniques, with US being the most frequently used due to its numerous advantages. Stereotactic biopsy is principally indicated in lesions identified only on mammography or cannot be accurately localized sonographically. These include microcalcifications, areas of architectural distortion or asymmetry and some masses[30,57]. Likewise, MR guided biopsy is reserved for lesions only identified on MR imaging[60].

2.8 Clinical Application at KNH

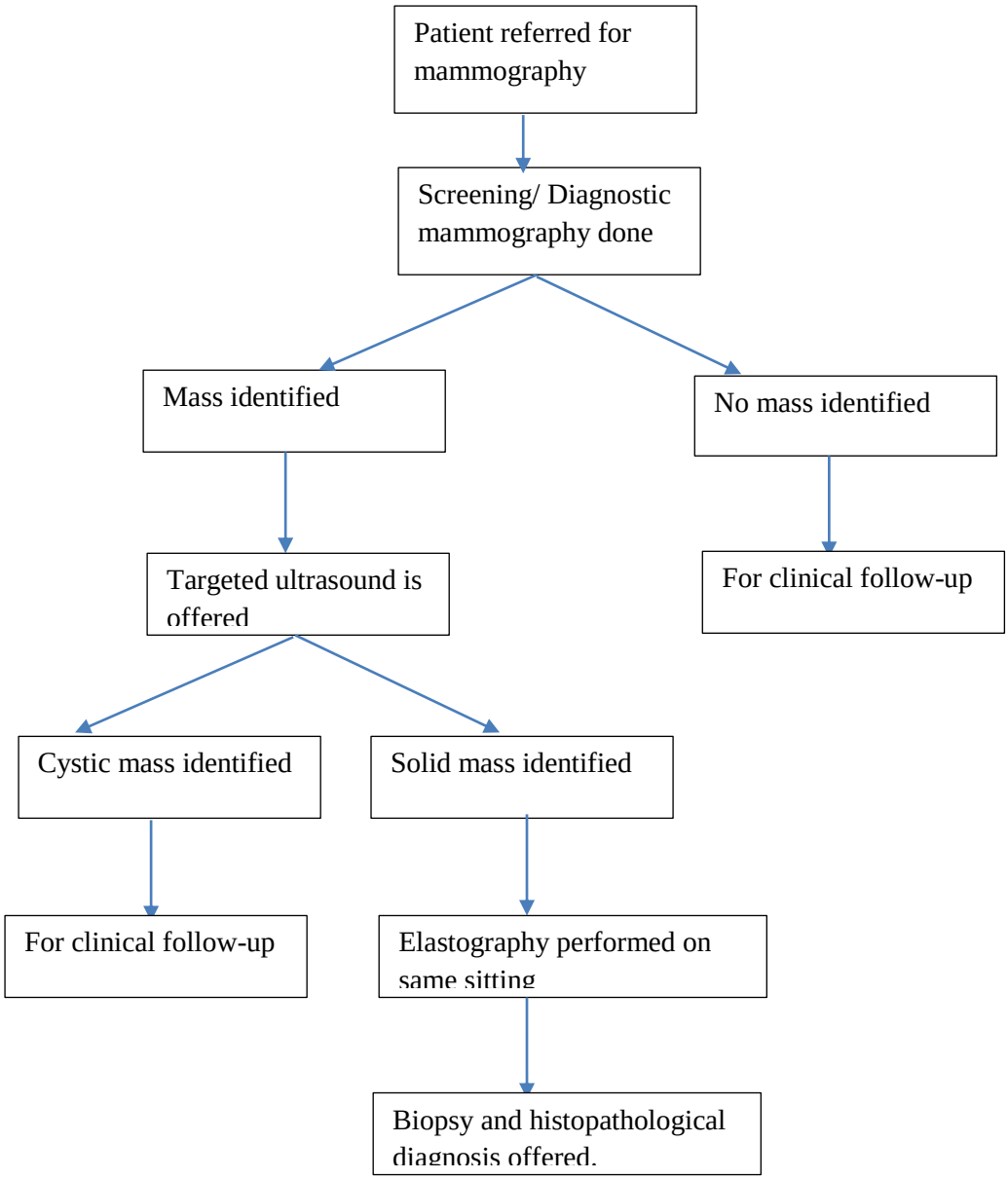
The clinical breast signs and symptoms typically referred for diagnostic mammography include but are not limited to: breast lump, breast pain, spontaneous nipple discharge or changes and skin changes. This is so in patients 40years of age and above with younger patients offered US as the primary imaging technique. In contrast, screening mammography is offered to women with no breast signs and symptoms, for the preclinical detection of breast cancer. Complementary sonography may be offered after either a screening or diagnostic mammogram as indicated. It is indicated to further characterize lesions/masses seen on mammography, to separate cystic from solid masses, in suspected ductal ectasia, to guide

biopsies, image dense breasts and negative mammographic findings with persistent clinical symptoms.

Sonoelastography is indicated in patients with solid breast masses on B mode ultrasound to further characterize and differentiate aggressive from benign lesions. Its use is limited in cystic masses which show variable firmness not related to mass aggressiveness or benignity.

In the management of breast cancer at Kenyatta National Hospital, multidisciplinary team (MDT) approach is pivotal. This is a team consisting of different specialties (Radiologists, Surgeons, Oncologists and Histopathologists) that bring in their different clinical expertise and collaboratively decide on a patient's management plan. A weekly MDT meeting is done at KNH with at least 10 patients discussed per week. This includes discussing the patient's clinical history, critical analysis of availed images, histological reports and mapping patient's best way forward.

2.8.1 Conceptual Framework



All study patients were referred for biopsy regardless of imaging findings. Histopathological diagnosis was used as the reference standard. All biopsies were done under image guidance.

Figure 5: Conceptual framework

2.9 Study Rationale and Justification

The breast is an organ of high cosmetic value in any female person and therefore a diseased breast does not only affect one's physical well-being but their psychological and social well-being is inadvertently compromised too. Having established the following: the high prevalence and high mortality of breast cancer worldwide and in Kenya [1,7,8,61] the earlier peak incidence in African women[14–18] and the poorer prognosis in low income countries[12]; these call for diligent diagnosis and subsequent treatment of breast masses. Moreover, 80-85% of breast cancer cases occur in individuals without the known high risk factors[9,18,26], hence the need for aggression in detecting breast lesions.

Mammography and ultrasound are the primary imaging techniques for any patient presenting with breast symptoms though the adjunctive use of elastography has been shown to improve the diagnostic value of both modalities [43,47,48]. A typical patient in Kenyatta National Hospital after mammographic evaluation with suspicious or unequivocal findings is booked for ultrasound, post which they are sent for a histological diagnosis. This setup has a fortnight plus of delay in patient diagnosis and a percentage of patients may be lost to follow-up during that period. The adjunctive use of sonoelastography to mammography will allow a diagnosis for most breast lesions to be made in one sitting therefore optimizing the quality of services provided to individual patients.

The high specificity rendered by adjunctive sonoelastography reduces the need for invasive methods and/or follow-up in the diagnosis of benign breast lesions, instead promoting non-invasive and faster diagnosis which is more favorable for any individual patient. Furthermore, tissue stiffness may be employed in guiding biopsies[61], improving the quality of specimens sent for histological diagnosis, and consequently lowering the rate of false negative findings associated with suboptimal lesion sampling procedures.

Lastly, in Kenya there is no recorded study on the role of sonoelastography as an adjunct to mammography. A related study by P. Ndaiga et al[61] compared the diagnostic accuracy of elastography in differentiating benign and malignant solid breast masses detected on conventional ultrasound, with histological correlation. This study, therefore sought to address some of the salient points not addressed in the above study, emphasize and promote the widespread and maximal use of non-invasive methods in the classification of breast masses as benign or malignant, more so in public health institutions. Recommendations aimed at improving individual patient management are made.

2.10 Research Question

Can the routine use of sonoelastography as an adjunct to mammography improve the accuracy and specificity of breast mass diagnosis non-invasively?

2.11 Objectives

2.11.1 Broad Objective

To determine the role of breast sonoelastography in assessing mammographically detected breast masses before histopathological diagnosis with the aim of reducing unwarranted breast biopsies at Kenyatta National Hospital.

2.11.2 Specific Objectives

a) To determine the sociodemographic characteristics of patients presenting for mammography at KNH.
b) To determine the value of UE in characterizing masses detected on mammography.
c) To determine the histopathological diagnosis of breast lesions detected on mammography and UE.
d) To compare the diagnostic accuracy of the combined use of mammography and UE against mammography alone in assessing breast masses with histopathological diagnosis.

CHAPTER THREE: METHODOLOGY

3.1 Study Area

The study was conducted at the Kenyatta National Hospital Radiology department and the University of Nairobi, Department of Diagnostic Imaging and Radiation Medicine. Kenyatta National Hospital was established in 1901, making it not only the oldest but also the biggest referral and teaching hospital in the country. The University of Nairobi School of Medicine campus is found within its premises. More than 600 patients are seen annually at the KNH Radiology department mammography suite. In 2018 and 2019, 608 and 698 patients were seen respectively, making the average number of patients seen annually to be 654. Of these, 97(2018) and 106(2019) had complementary US done at KNH which averages to 102(15.6%) patients annually.

3.2 Study Design

A descriptive cross sectional study was done.

3.3 Study Population

The study population included all patients referred to Kenyatta National Hospital Radiology Department for mammography.

3.4 Inclusion Criteria

All patients with a baseline mammogram showing a breast mass.
Patients who consented to targeted sonographic evaluation post mammography.
Patients who gave consent for biopsy.

3.5 Exclusion Criteria

Patients with no breast mass identified on mammogram.
Patients who declined complementary sonographic evaluation post mammography.
Patients who declined biopsy.

3.6 Sample Size

Sample size was calculated as below:

$$n = \frac{Z_{1-\alpha/2}^2 \rho (1-\rho)}{d^2}$$

Where n= sample size

Z1-α/2 = two-sided significance level = 1.96

p = diagnostic accuracy of combined mammography and UE.

d = Precision error (5%)

From literature review, the diagnostic accuracy range of combined mammography and UE in detecting breast cancer is 75% to 95%. In the absence of previous data in Kenya, an assumptive diagnostic accuracy of 85% was made. Substituting into the formula

n = (1.96 x 1.96) x (0.85 x (1-0.85)) /0.05x0.05

=3.8416 x (0.85x 0.15) / 0.0025 =196

To achieve an adequate and representative sample size within the study period, an adjustment was made based on the number of patients who access combined mammography and US services (there being no data on patients who had UE) at Kenyatta National Hospital in a year as below:

$$N = \frac{n}{1+\frac{(n-1)}{T}}$$

Where N = adjusted and final sample size.

n= first sample size = 196

T = Total number of patients who access combined mammography and US at KNH in a year = 102.

N = 196/ (1+1.91) = 67.

The total sample size was 67.

3.7 Sampling Procedure

Purposive (consecutive) sampling was used to select participants for the study, where all patients who satisfied the study inclusion criteria were enrolled. Patients who presented to the KNH Breast Clinic were seen by the attending clinician and referred for mammography where indicated. Patients in whom a breast mass was identified on mammography were eligible to be study participants. If no mass was identified on imaging, patient was referred back for clinical follow-up and would not be part of the study.

Targeted ultrasound was used to separate solid and cystic masses, with the latter excluded from the study. Only solid masses were further assessed by elastography. An impression was made based on the findings from both modalities (mammography and UE). Patients were then referred for biopsy; core biopsy was done under image guidance by an Interventional Radiologist. All biopsies were done under image guidance due to its superiority over non-guided biopsies. The combined mammography and elastography findings were correlated with histopathological results.

3.8 Study Personnel

Principal Investigator
Radiographers stationed at the KNH mammography unit
Biostatistician for data analysis

3.9 Study Collecting Tool

A specially designed and structured questionnaire was used for data collection. This is found in Appendix 5.

3.10 Study Variables

Breast Density
Lesion density on mammography
Lesion shape and margins
Color of the lesion on elastogram
Patient Age
Age at menarche

3.11 Study Procedure

Following approval from KNH/UON ERC, introductory letters were sent to concerned work stations at KNH and DDIRM. Data collection was done by the Principal Investigator by administering the questionnaire to participants. Selected patients were given information on the study and informed consent obtained before data collection. Staff and patient safety was observed on conducting the study in line with the current guidelines on COVID-19 prevention. These included but not limited to wearing of surgical facemasks by both staff members and patients, hand washing before and after attending to each patient, one patient allowed in the examination room and at most two staff members per time, and sanitization of all radiological equipment after each patient guided by the manufacturer's instructions.

3.11.1 Mammography

Mammography was performed using a GE Essential Senographe Digital mammography unit at the KNH Radiology Department. Mammography was the primary imaging modality to identify lesions/masses with both diagnostic and screening mammography offered. Standard mediolateral oblique (MLO) and craniocaudal (CC) views were performed for all participants and additional views such as magnification, spot compression and axillary views done where indicated. Images were reviewed by the Principal Investigator on workstations approved for mammography reading, supervised by the supervisors who have vast experience in mammography interpretation and general breast imaging. The ACR BIRADS was used for image description, interpretation and final categorization. The mammographic features assessed include breast density; mass shape, margins and density; microcalcifications shape and distribution; architectural distortion and associated features like skin/nipple retraction, skin thickening and axillary adenopathy.

Table 1: Final BIRADS categories

BIRADS Final Assessment Categories			
Category		**Management**	**Likelihood of cancer**
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	n/a
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably Benign	Short interval follow-up (6months)	>0% but <2%
4	Suspicious	Tissue diagnosis	4a.low suspicion for malignancy (>2% to <10%) 4b. moderate suspicion for malignancy (>10% to <50%) 4c.high suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Known biopsy-proven	Surgical excision when clinical appropriate	n/a

3.11.2 Sonoelastography

Ultrasound Elastography was performed using a GE Logiq S7 US machine situated at the DDIRM Ultrasound suite. The sonoelastography examinations were done by the Principal Investigator supervised by any of the three supervisors according to availability. A 7.5MHz ultrasound linear array high frequency probe was used and radial ultrasonic breast examinations done. A gray scale image was generated by default for the patient's clinical benefit with sonographic BIRADS classification of the concerned lesion(s). B-mode US was also used to exclude cystic lesions.

Using the same machine and probe, sonoelastography was performed on the same sitting by applying gentle pressure on the lesion in question. Different lesions within the same patient/breast were examined separately. This was done at no added cost or significant increase in examination time for the patient as the elastography examination is essentially part of an ultrasound examination. An elastogram was generated for each lesion displayed

against the gray-scale image representing a post and pre- compression image respectively. The elastogram is a color coded map ranging from red (most elastic), green (intermediate) and blue (stiffest). A five point elasticity score was assigned to each elastogram and used to decide on lesion benignity or malignancy.

Table 2: Elasticity Score

Elasticity score	
1	Even strain for entire lesion. Displayed as green.
2	Strain in most of the lesion with some areas of no strain. Inhomogeneous elasticity displayed with green and blue.
3	Strain in the periphery of the lesion with sparing of the center. Displayed as green periphery with blue center.
4	No strain in entire lesion. Entire lesion displayed as blue.
5	No strain in entire lesion and surrounding area. Entire lesion and surrounding area displayed as blue.

Strain Ratio (SR) was also calculated for all lesions by selecting the region of interest (ROI), contrasted with background fatty breast tissue compressibility. The SR value was auto-generated by the US machine and used to further classify lesions as benign or malignant.

3.11.3 Histopathology

The core needle biopsy method was used for breast tissue specimen collection due to availability and associated low false positives and low false negatives rate. This was done under US guidance at the KNH Interventional and Angiography suite, situated within the KNH Radiology Department. The individual procedures were done by an Interventional Radiologist.

The procedure was done under sterile conditions, with local anesthesia administered. Using an 18gauge core needle 3-6 samples were collected per lesion. Histological assessment of the specimen was done and the generated results either confirmed/disputed the imaging findings.

3.12 Data Management

All study images and histopathological reports were saved in soft copy format in flash disks kept by the Principal Investigator under lock and key when not in use. The collected data was each assigned a serial number for anonymity. The data was then entered into Microsoft Excel sheet and double checked against hard copies for consistency. Completed questionnaires were kept under lock and key for both security and patient confidentiality.

3.13 Data Analysis

Questionnaire samples were double checked by supervisors for validation. Data was analyzed using SPSS software version 20. Descriptive terms like mean, mode, frequency distribution and proportions were used to analyze demographic characteristics. Using the software; specificity, accuracy and sensitivity for mammography, elastography and in combination were determined.

3.14 Results Dissemination

The results of this study will be bound into a thesis book and shared with the DDRIM and KNH Radiology Department. It will be disseminated to bigger audiences through publications in review journals and presentations in local, regional or international forums.

3.15 Ethical Considerations

The study was done post approval by the University of Nairobi and the Kenyatta National Hospital Scientific and Ethical Review Committee. The study objectives and purposes were clearly explained to eligible participants and informed consent obtained. Clinical results were released to patients for subsequent management by referring practitioner.

Mammography being an ionizing radiographic examination comes with potential but very low to almost negligible radiation risk and its benefits therefore outweigh the risks by far. This is according to the ACS and ACR guidelines[25,54]. Regardless, the ALARA (As Low As Reasonably Achievable) principle was observed for all participants, to ensure that all examinations are necessary, appropriate and beneficial to the patient.

Elastography has no known clinically significant risks and is therefore a safe adjunct to mammography. Clear cut benign lesions were referred for further management with histological confirmation done post lumpectomy/excision where indicated.

CHAPTER FOUR: RESULTS

4.1 Patient Clinico-demographic Characteristics

Using consecutive sampling a total of 52 patients with 67 breast lesions who satisfied the study inclusion criteria were enrolled. All the patients were female, with no male participants meeting the inclusion criteria during the study period. The 50-59 year age group was the modal age group at 40.4% (n=21) of the participants, followed by the 40-49 year age group at 26.9% (n= 14). The least participants were seen in the elderly (≥70years) and those below 40 years.

Table 3: Demographic characteristics

	Total Number of Patients = 52
Characteristic	**Frequency n (%)**
Age (years)	
< 40	5 (9.6)
40-49	14 (26.9)
50-59	21 (40.4)
60-69	7 (13.5)
≥ 70	5 (9.6)
Gender	
Female	52 (100)

4.1.1 Clinical Characteristics

The predominant presenting complaint was a breast mass, reported in 42 (80.4%) participants, with pain being the chief complaint in 8 (15.4%) patients, and nipple discharge only reported in 2 (3.8%) patients as the chief complaint. 29 participants (55.8%) had menarche between the ages of 12-14years with 13years being the modal age. Pertaining to parity 31 participants (59.6%) had 1-3 children, with 3 children being the modal number at 30.8% (16 participants). 6 participants (11.5%) reported a parity of zero, and only 5 participants (9.6%) had parity of ≥7. 8 participants (15.4%) reported a positive family history of breast cancer in first degree relatives, with the bulk 84.6% (n=44) reporting a negative family history. History of hormonal contraceptive usage was reported in 31 participants (59.6%), with negative usage in 21 (40.4%) participants.

Table 4: Clinical characteristics

	Total Number of Patients = 52
Characteristic	**Frequency n (%)**
Chief Presenting Complaint	
Mass	42 (80.8)
Pain	8 (15.4)
Nipple discharge	2 (3.8)
Menarche	
≤ 11	19 (36.5)
12-14	29 (55.8)
≥ 15	4 (7.7)
Parity	
0	6 (11.5)
1-3	31(59.6)
4-6	10 (19.2)
≥7	5(9.6)
Breast Cancer Family History	
Positive	8 (15.4)
Negative	44 (84.6)
Hormonal Contraception	
Positive	31 (59.6)
Negative	21 (40.4)

4.2 Final Histopathological Diagnosis

Histopathological diagnosis was done for all the 67 breast lesions. 70.1% of the lesions were shown to be malignant and only 29.9% were benign. These corresponded to 47 and 20 lesions respectively. The actual diagnoses are as illustrated in Table 5. Invasive ductal carcinoma was the most prevalent lesion accounting for 56.7% (n=38) of all lesions and 80.9% of all malignancies. Fibroadenoma was the most common benign lesion contributing 22.4% (n=15) of all lesions.

Table 5: Final Histopathological diagnosis

Diagnosis	Frequency	Percentage (%)
Malignant	**47**	**70.1**
Invasive Ductal Carcinoma (IDC)	38	56.7
Invasive Lobular Carcinoma (ILC)	3	4.5
Ductal Carcinoma in situ (DCIS)	3	4.5
Mucinous (Colloid) Carcinoma	1	1.5
Malignant Breast Sarcoma	1	1.5
Metastatic disease	1	1.5
Benign	**20**	**29.9**
Fibroadenoma	15	22.4
Intraductal papilloma	2	3.0
Benign Breast Lesion	2	3.0
Phyllodes	1	1.5
Total	**67**	**100**

4.2.1 Age versus Histological Outcome

A correlation of the patient age and histological outcome showed that patients below 40 years and those above 70years had 100% malignant outcome, with 86% malignant outcome in the 60-69 years (6 out of 7 participants). Benign lesions were more prevalent in the 40-49 and 50-59 age groups. A p-value of 0.148 was obtained in keeping with statistically insignificant data.

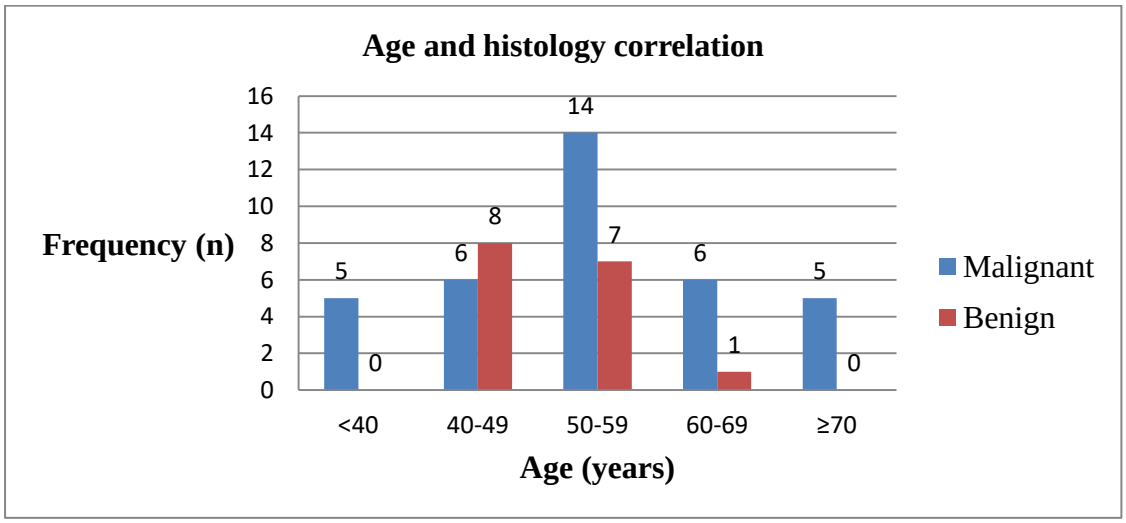


Figure 6: Age and histology correlation

4.3 Digital Mammography Characteristics

4.3.1 Breast Density (ACR)

The predominant breast density amongst participants was heterogeneously dense breasts (ACR-C), accounting for 53.8% (n=28) of the cases, with the least prevalent density being predominantly fatty breasts (ACR-A) at 5.8% (n=3) of the participants.

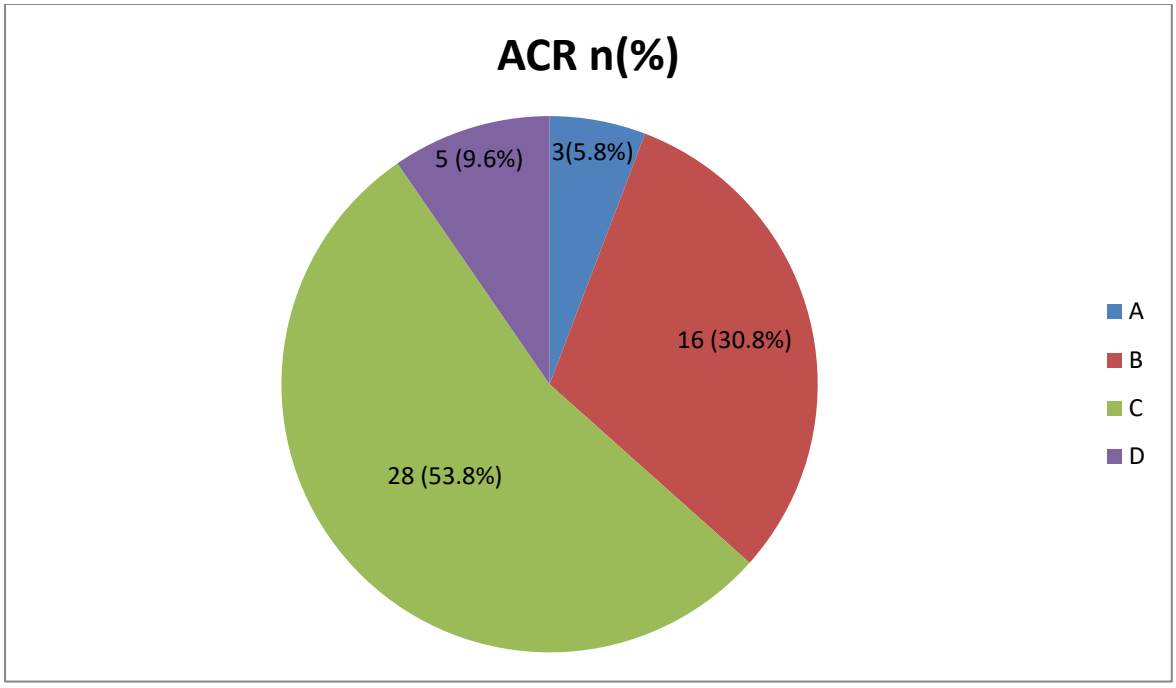


Figure 7: Breast Density (ACR)

4.3.2 Mammography Mass Characterization

A total of 67 breast lesions in 52 patients were evaluated on mammography, with 13 (25%) participants having multiple lesions. Most of the lesions were located in the intrammamary space accounting for 68.6% (n=46) of the lesions, with retromammary location seen in 23.9% (n=16) of the lesions. Only 7.5% (5 lesions) were localized in the premammary space. The prevalence of intralesional and parenchymal calcifications was 25.4% (n=17). These included both suspicious micro-calcifications and the likely benign macro-calcifications. The remainder of the lesions (74.6%) did not demonstrate calcifications (n=50).

A correlation of mass descriptors and histological outcome was done. High mass density, irregular shape and spiculated margins showed a significant correlation with malignant outcome, $p < 0.05$. High breast density and retromammary mass location both showed a higher positive predictive value (PPV) versus low breast density and intrammamary location

respectively, though p values showed statistical insignificant correlation with a malignant outcome.

Table 6: Mammography descriptors and histological correlation

Descriptor		*Total*	*Benign*	*Malignant*	*PPV*	*NPV*	*p-value*
Mass Density	High Density	28	4	24	0.86	0.14	
	Equal Density	39	16	23	0.59	0.41	**0.029**
Breast Density	Low	24	8	16	0.67	0.33	
	High	43	12	31	0.72	0.28	0.782
Mass Location	Retro-mammary	16	2	14	0.88	0.12	0.119
	Intra-mammary	51	18	33	0.65	0.35	
Mass Shape							
	Irregular	19	1	18	0.95	0.05	**0.029**
	Other	48	19	29	0.60	0.40	
Margins	Spiculated	11	0	11	100	0	**0.007**
	Other	56	20	36	0.64	0.36	

*p>0.05 insignificant, p<0.05 significant, p<0.01 highly significant

4.3.3 Mammography Final BIRADS Categories

38 lesions (56.7%) were classified as BIRADS 4, which was the most prevalent BIRADS classification. These included BIRADS 4A (14 lesions), 4B (10 lesions) and 4C (14 lesions). There were no lesions classified as BIRADS 0 as correlation with elastography was offered before final reporting and any negative findings were excluded from the study hence no BIRADS 1 category either. All lesions classified as BIRADS 4B and above were shown to be

malignant. All BIRADS 2 lesions were also proven to be benign on histology. There were discordant findings seen in the BIRADS 3 and BIRADS 4A categories.

Table 7: Final BIRADS Score on Mammography

BIRADS Score								
Category	**0**	**1**	**2**	**3**	**4A**	**4B**	**4C**	**5**
Malignant	0	0	0	6	8	10	14	9
Benign	0	0	8	6	6	0	0	0
Total	**0**	**0**	**8**	**12**	**14**	**10**	**14**	**9**
Percentage (%)	**0**	**0**	**12.0**	**17.9**	**20.9**	**14.9**	**20.9**	**13.4**

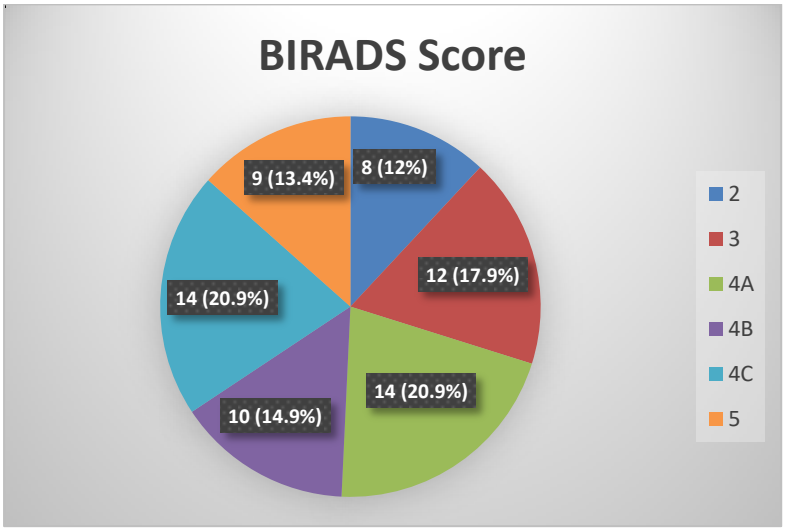


Figure 8: Final BIRADS categories on mammography

4.4 Mass Characterization on Elastography

All the 67 lesions seen on mammography were further evaluated using UE. UE color map score and Strain Ratio (SR) were both used to further characterize each mass individually. 29 lesions (43.3%) were scored as UE score 4 which contributed the majority of the lesions. The least scoring was UE score 3 with 2 lesions (3%). All lesions scored as score 1 and score 5 corresponded to benign and malignant lesions respectively without any discordant lesions. A score of 2 had a 73% Negative Predictive Value (NPV) while a score of 4 had 93% PPV. These corresponded to 3 and 2 discordant lesions respectively. A p value of 0.0001 was obtained in keeping with statistically significant data.

SR showed a NPV of 90% against 78% shown by UE color score, which corresponded to 3 lesions better resolved on SR. They both demonstrated a PPV of 96%.

Table 8: Mass characterization on UE

		Malignant	*Benign*	*Total*	*Percentage (%)*	*PPV*	*NPV*	*P value*
	UE Score							
	1	0	10	10	14.9	0.0	1.0	
	2	3	8	11	16.4	0.27	0.73	
	3	2	0	2	3.0	1.0	0.0	
	4	27	2	29	43.3	0.93	0.07	
	5	15	0	15	22.4	1.0	0.0	
	Total	**47**	**20**	**67**	**100**	**0.96**	**0.78**	**0.0001**
	SR							
	≤2.9	2	18	20	29.9	0.1	0.9	
	>2.9	45	2	47	70.1	0.96	0.04	
	Total	**47**	**20**	**67**	**100**	**0.96**	**0.9**	**0.0001**

*p>0.05 insignificant, p<0.05 significant, p<0.01 highly significant

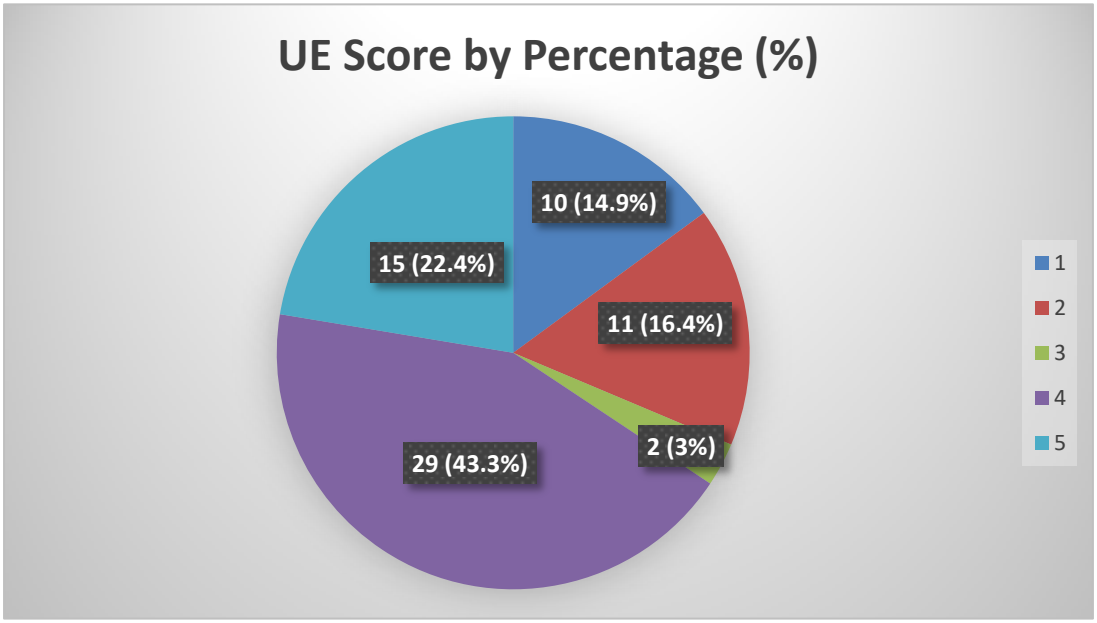


Figure 9: UE final color map scores

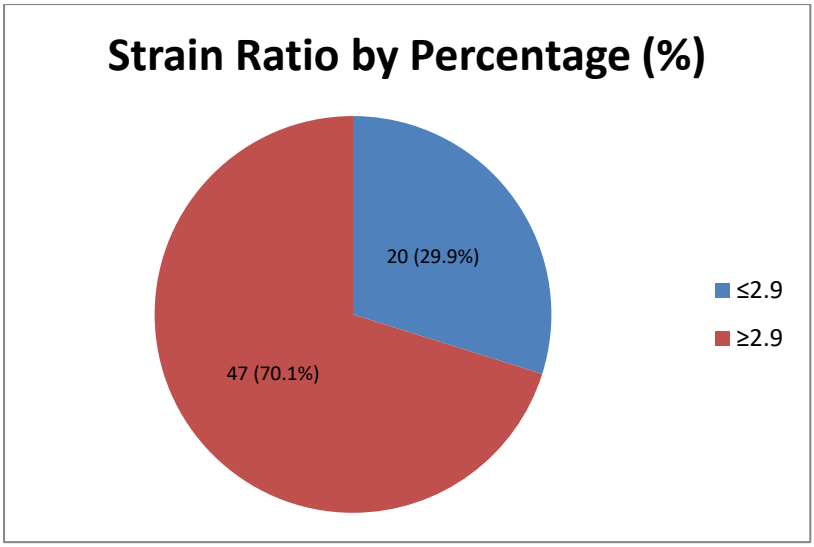


Figure 10: UE Strain Ratio

4.5 A Comparison of Mammography and UE

Table 9: Mammography versus UE Final score

UE Final Score	Mammography Final BIRADS							
	2	**3**	**4A**	**4B**	**4C**	**5**	**Total**	**p-value**
1	4	2	4	0	0	0	**10**	
2	2	5	3	1	0	0	**11**	
3	0	0	2	0	0	0	**02**	
4	2	5	5	7	9	1	**29**	
5	0	0	0	2	5	8	**15**	
Total	**8**	**12**	**14**	**10**	**14**	**9**	**67**	**<0.05**

*p>0.05 insignificant, p<0.05 significant, p<0.01 highly significant

A direct relationship between final BIRADS category and UE score was shown on correlating mammography and UE. All BIRADS 4C and 5 lesions were subsequently scored as either score 4 or 5, with 8 out of 9 BIRADS 5 lesions giving a score of 5. BIRADS 2 lesions also corresponded to lower UE scores with 6 out of 8 lesions scored as UE score of ≤ 2. An overall p-value of < 0.05 was obtained in keeping with statistically significant data.

Table 10: A comparison of the 2 modalities

Modality	Malignant	Benign	Total
Mammography			
Positive	41	6	47
Negative	6	14	20
Total	**47**	**20**	**67**
UE			
Positive	42	2	44
Negative	5	18	23
Total	**47**	**20**	**67**
Mammography +UE			
Positive	45	2	47
Negative	2	18	20
Total	**47**	**20**	**67**

Of the 47 malignant lesions, 41 were concluded as positive on mammography and 42 on UE alone increasing to 45 on combining the 2 modalities. Concerning benign lesions; 14 out of 20 were concluded as benign on mammography, increasing to 18 out of 20 in UE and in combination.

4.5.1 Diagnostic Accuracy

The sensitivity of mammography was comparable to Sonoelastography at 87.3% and 89.3% respectively, increasing to 95.7% in combination. UE showed a much higher specificity of 90% versus mammography 70%, and 90% in combination. The diagnostic accuracy was 82% for mammography, 89.5% for UE and 92.5% in combination. Mammography showed PPVs and NPVs of 87.23% and 70% respectively, UE 95.5% and 78.35 respectively and in combination 95.7% and 90% respectively. The p-value was 0.0001 in keeping with statistically significant data.

Table 11: Mammography, UE Diagnostic Accuracy

Modality	*Sensitivity*	*Specificity*	*Accuracy*	*PPV*	*NPV*	*p-value*
Mammography (%)	**87.3**	**70**	**82**	**87.3**	**70**	
(n)	41/47	14/20	55/67	41/47	14/20	
UE (%)	**89.3**	**90**	**89.5**	**95.5**	**78.3**	
(n)	42/47	18/20	60/67	42/44	18/23	
Combined (%)	**95.7**	**90**	**92.5**	**95.7**	**90**	
(n)	45/47	18/20	62/67	45/47	18/20	0.0001

*p>0.05 insignificant, p<0.05 significant, p<0.01 highly significant

4.6 Reference Cases

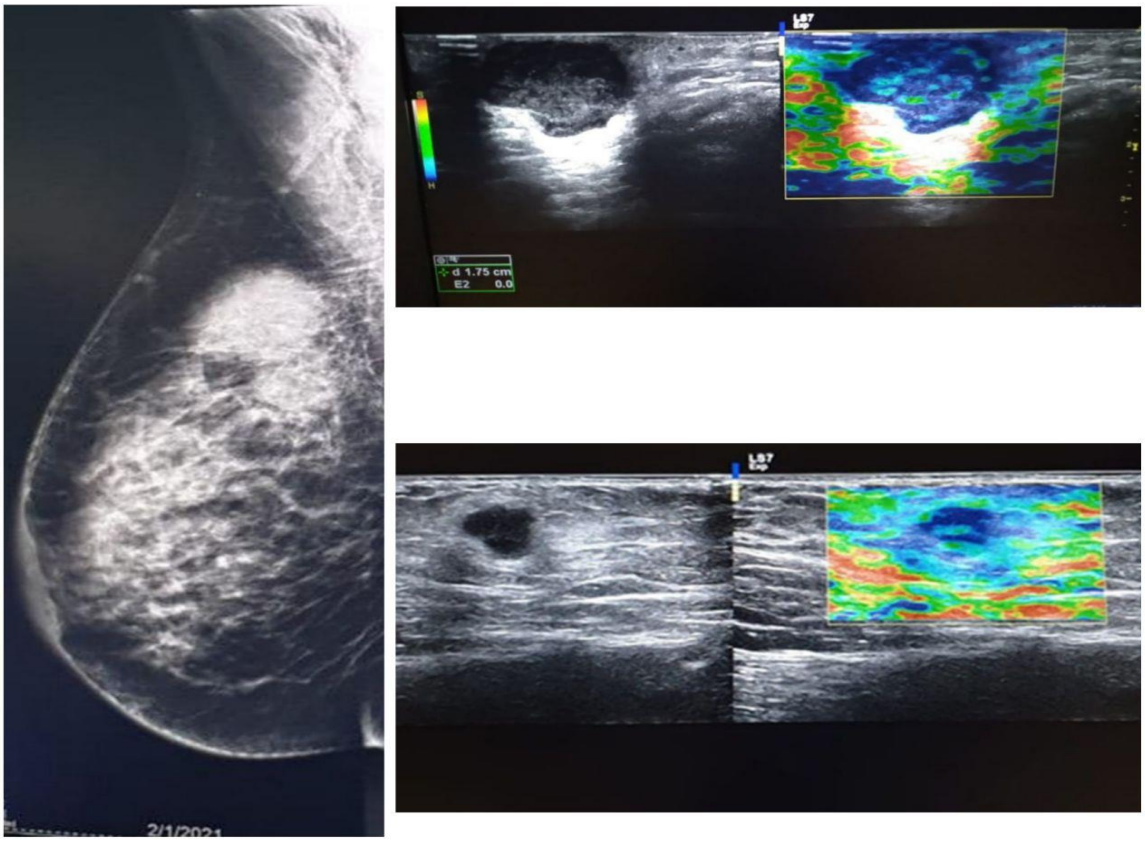


Figure 11: Case 1

A diagnostic mammogram Medio-Lateral Oblique (MLO) view in a 72 year old female shows heterogeneously dense right breast (ACR-C). Two masses are seen in the upper quadrant, a dense, oval mass with indistinct borders and a smaller equal density, irregular mass with partially obscured margins. No parenchymal or intralesional calcification is seen. BIRADS 4B findings. A) B-mode and UE show a heterogeneous lesion, angulated margins, acoustic enhancement and UE score 5, SR 5.2. B) B-mode and UE show a hypoechoic, lobulated mass, taller than wide and UE score 4, SR 4.0. Final histological diagnosis was multifocal right breast invasive ductal carcinoma.

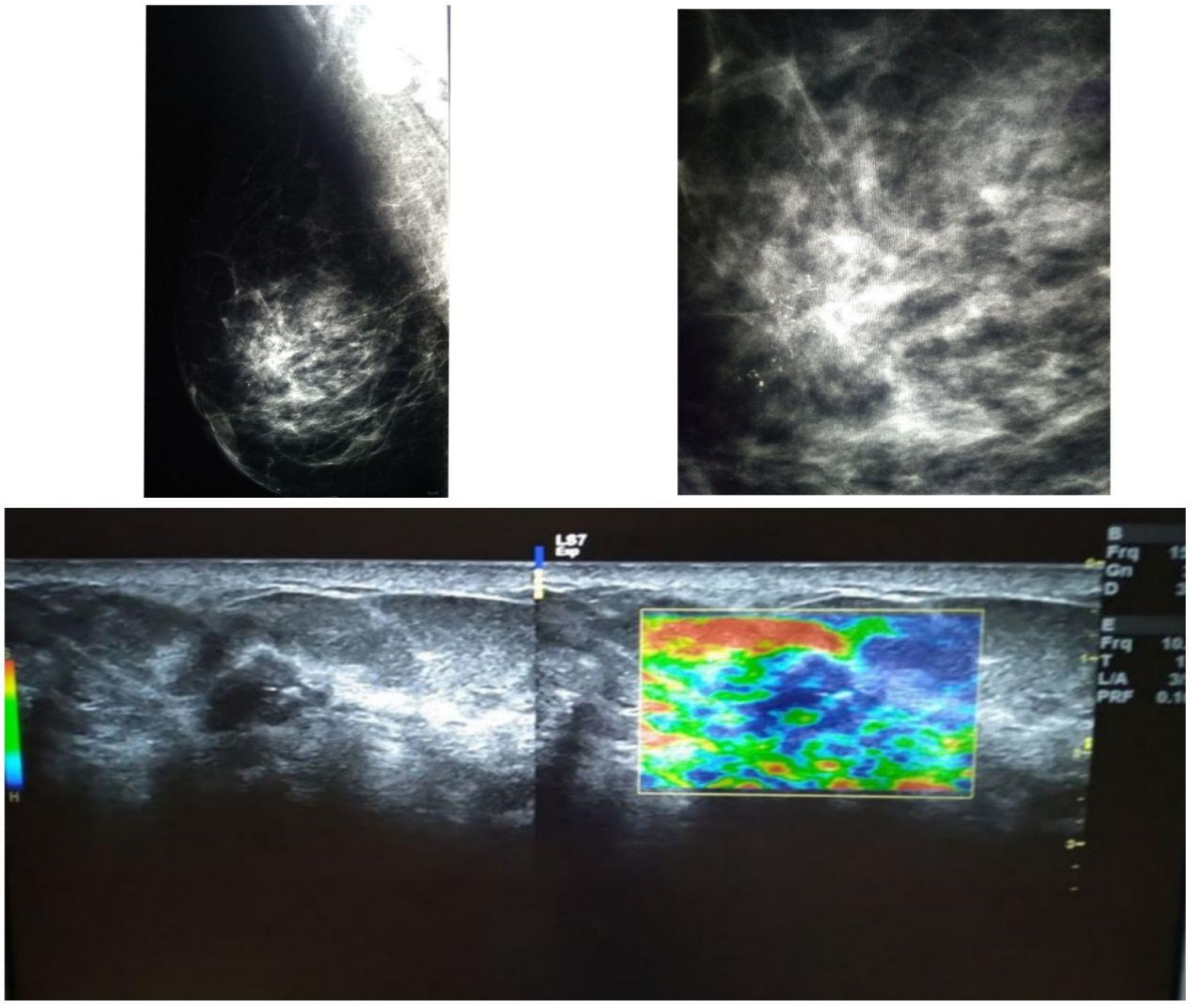


Figure 12: Case 2

Medio-Lateral Oblique (MLO) and zoomed MLO diagnostic mammogram views in a 37 year old female patient show heterogeneous fibroglandular breast density (ACR C). A dense, irregularly shaped mass with spiculation was seen in the right upper quadrant. Fine pleomorphic grouped parenchymal and intralesional microcalcifications were visualized. There are multiple enlarged ipsilateral axillary lymph nodes with loss of fatty hilum. Concluded as a BIRADS 5 finding. B mode and UE show a hypoechoic, irregularly shaped lesion with an echogenic halo and a UE score of 5, SR 5.1. Final histological diagnosis was right breast invasive ductal carcinoma.

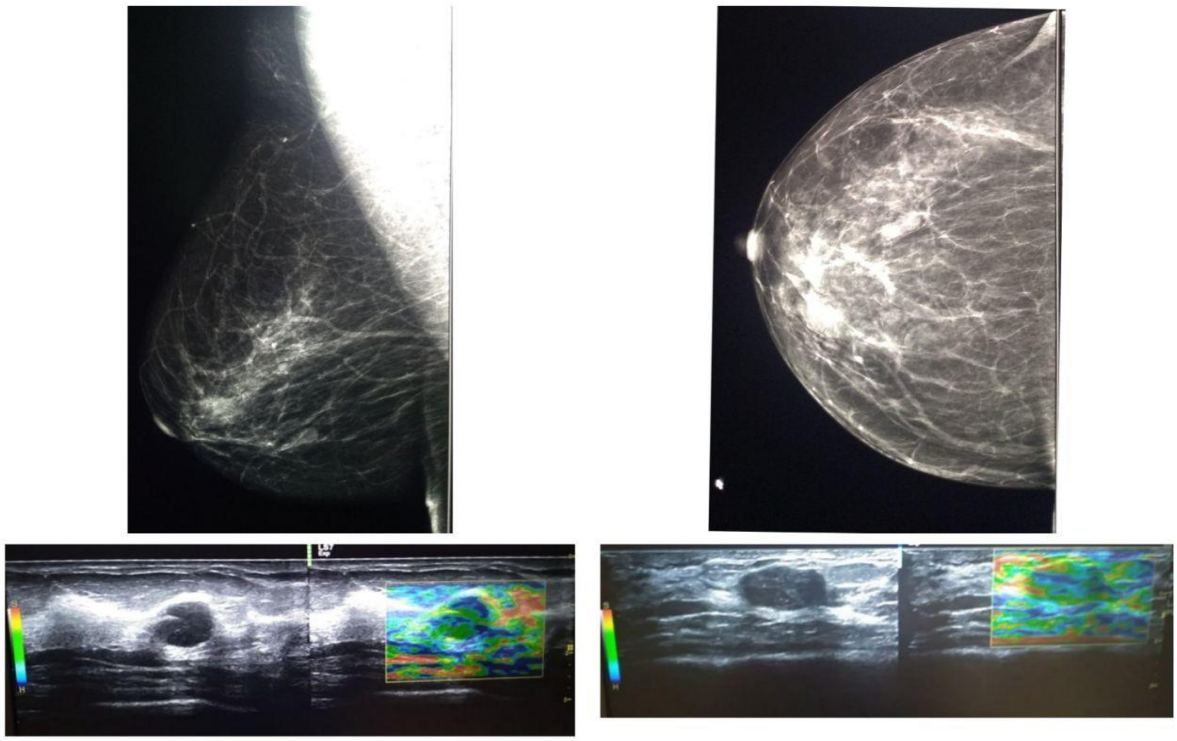


Figure 13: Case 3

Right Medio-lateral Oblique(MLO) and Cranio-caudal (CC) diagnostic mammogram in a 43year old female show heterogeneous fibroglandular breast density (ACR C). There are 2 equal density masses best seen on CC view. 1 mass shows obscured margins and the second one is lobulated. BIRADS 4A was assigned. B-mode showed multiple right breast hypoechoic, well circumscribed masses. UE assessment of the largest masses is diplayed with both showing a UE score of 2. Respective SR scores of 1.7 and 1.1 were recorded. Final histopathological diagnosis showed multiple fibroadenomas.

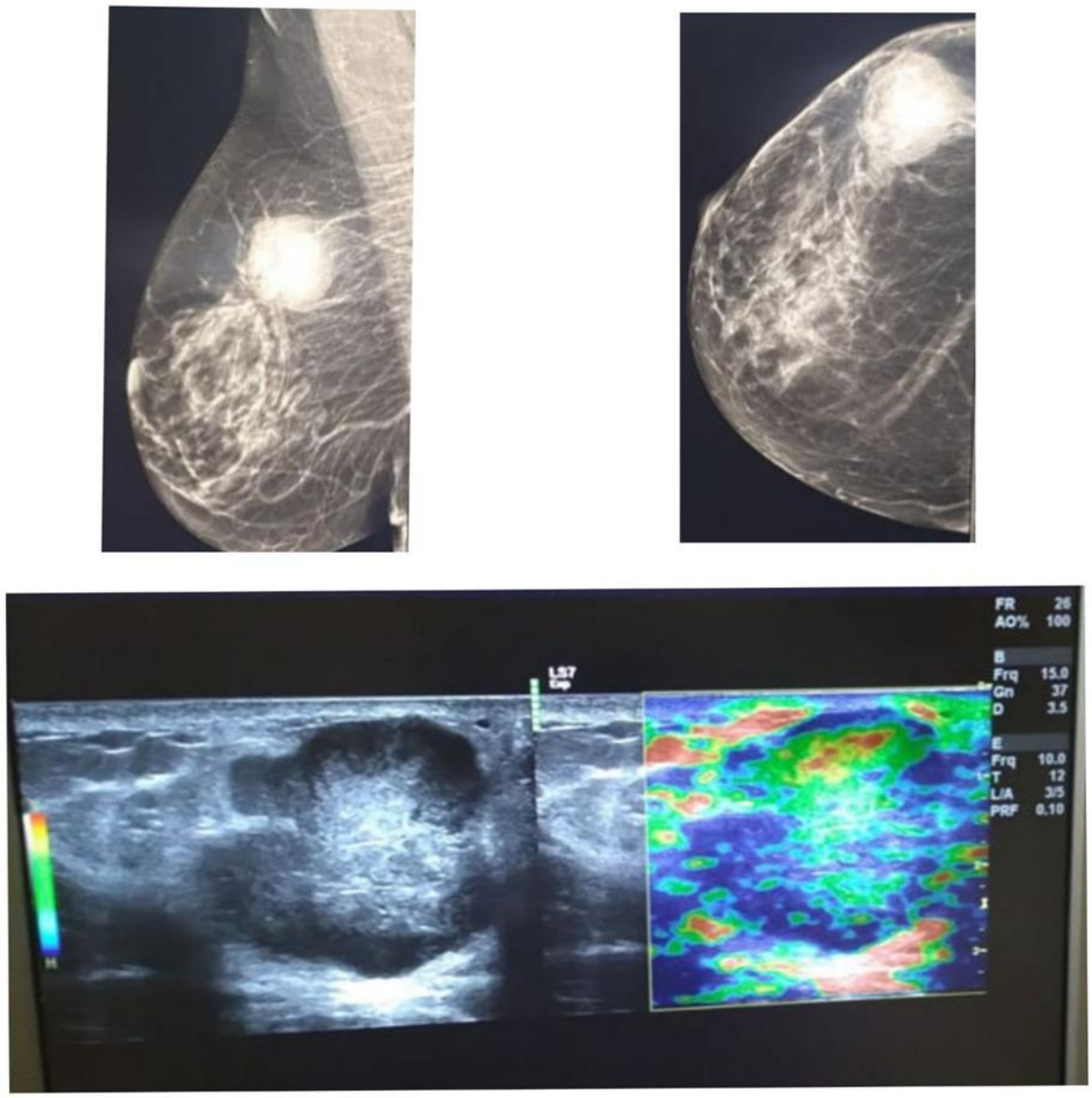


Figure 14: Case 4

Right breast diagnostic mammogram Medio-Lateral Oblique (MLO) and Cranio-caudal (CC) view in a 68 year old female shows scattered fibroglandular density (ACR-B). A round, dense mass is seen in the upper outer quadrant with partially indistinct margins. No parenchymal or intralesional calcification is seen. Concluded as a BIRADS 4B finding. B-mode and UE show a heterogeneous lesion, lobulated margins, acoustic enhancement and UE score of 2, SR 3.0. Final histological diagnosis was right breast invasive ductal carcinoma.

CHAPTER FIVE: DISCUSSION

5.1 Introduction

Breast cancer remains the most prevalent cancer in women globally. The hope to reduce its mortality or morbidity lies in early disease detection and subsequent management. Mammography is the backbone and the first line technique in early disease detection, both for screening and diagnostic indications. The main goal of this study was to assess the role of sonoelastography in evaluating masses detected on mammography with histopathological correlation at Kenyatta National Hospital. A descriptive cross sectional study with consecutive sampling of 52 patients with 67 lesions was done.

5.2 Clinico-demographic Characteristics

All the participants were female. The predominant female gender is in keeping with the ACS Breast cancer statistics which show that 99% of breast cancers are diagnosed in females[(9)]. The age range of patients seen was 35-81years, with a mean age of 53.8 years and modal age of 56years. The 50-59 years age group contributed 40.4% (n=21) of the participants, with participants < 60years contributing 76.9% (n=40) of the participants. The predominant young population can be explained by the life expectancy in Kenya which is estimated at 66.7years by WHO 2018 database. 42 patients (80.8%) presented with a breast mass, as the chief presenting complaint. This is in keeping with the study inclusion criteria which included all patients presenting to KNH Radiology department with a baseline mammogram showing a breast mass. The other chief presenting complaints were breast pain and nipple discharge.

Early menarche, defined as menarche at ≤ 11years is one of the known but non preventable risk factors for breast cancer. In this study population 29 (55.8 %) participants had menarche within 12-14years with a modal age of 13years and mean age of 12.2years. Only 4 (7.7%) participants had menarche at ≥15years, which may be protective.(62) 19 (36.6%) participants had menarche at ≤ 11years. In comparison with data found in women without breast cancer, 65% of the women had menarche within 12-14years age group, 19% at ≥15years and only 16% in the ≤ 11years age group.[(62)] Parity was reported in 46 participants (88.5%) with only 6 nulliparous participants (11.5%). Among the parous participants, all reported breastfeeding for at least 12months. Previous studies have shown an inverse relationship between parity and breast cancer, which is further strengthened by breastfeeding.[(63)] A positive family history of breast cancer was elicited in only 8 (15.4%) participants which compares well with previous studies which show a 15-20% family history of breast cancer in patients who are eventually

diagnosed of breast cancer.[9,18,26] Hormonal contraception usage was reported in 31 (59.6%) participants. This was a history of one ever using hormonal contraception in their reproductive years.

5.3 Final Histopathological Diagnosis

The single most common histological diagnosis was invasive ductal carcinoma, with malignant lesions accounting for 70.1% (n=47) of all lesions. Benign lesions accounted for 29.9% (n=20) of all lesions with fibroadenoma being the most prevalent. The high prevalence of malignant lesions could be explained by the inclusion criteria which required a baseline mammogram to be done, resulting in >90% of the participants being above 40years hence influencing the likelihood of malignancy over a benign outcome(64,65). Only 9.6% (n=5) of the participants were below 40years and all had a malignant outcome. This is explained by mammography indication guidelines below 40years, with its usage mainly indicated when the clinician has a high index of suspicion for malignancy or in high risk individuals [24,25]. This cohort of patients were also noted to present with advanced disease, which according to the study findings could be alluded to reduced awareness in the young population or low index of suspicion in clinicians in patients < 40years. In addition previous studies have shown more aggressive disease and worse prognosis with early age onset of breast cancer [19–22]. A number of studies have also shown the peak incidence of breast carcinoma in African women to be earlier than the western population, in the 35-45 year age range.[14–18] This could imply the 9.6% representation was actually an underestimation of breast cancer in this cohort, limited by the study inclusion criteria. A further correlation of the histopathological diagnosis and patient age showed that all the patients ≥70years also had a malignant outcome. This is consistent with previous studies which have shown age as a significant predictor of malignancy[64,65].

5.4 Mammography Characteristics

The predominant breast density amongst participants was heterogeneously dense breasts (ACR-C), accounting for 53.8% (n=28) of the cases. Mass density, shape and margins were used to further characterize the masses and conclude on the BIRADS classification. High mass density, irregular shape and spiculated margins showed a significant correlation with histological malignant outcome, $p < 0.05$. These findings correspond to other studies which have shown a significant association between high mass density, irregular mass and spiculated margins with probability of a malignant outcome[65,66]. The prevalence of

intralesional and parenchymal calcifications was 25.4% (17 lesions). These included both suspicious micro-calcifications and the likely benign macro-calcifications.

On Final BIRADS categories; 56.7% (n=38) of the lesions were classified as BIRADS 4, which was the most prevalent BIRADS classification. All lesions classified as BIRADS 4B and above were shown to be malignant. All BIRADS 2 lesions were also proven to be benign on histology. These findings are consistent with the ACR BIRADS classification which predicts 0% PPV in BIRADS 2 lesions, ≥ 95% PPV for BIRADS 5 lesions. PPVs of 10-50% and 50-95% for BIRADS 4B and 4C are expected respectively(30).

5.5 Mass Characterization on Sonoelastography

All the 67 lesions seen on mammography were further evaluated using UE. UE color map score and Strain Ratio (SR) were both used to further characterize each mass individually. All lesions scored as score 1 showed a benign finding. This concurs with prior studies which have also shown a 100% NPV in score 1 lesions, in keeping with even strain and stiffness similar to background tissue, thereby eliminating the need for invasive diagnostic techniques in such lesions [(43,44)]. All score 5 lesions also showed a malignant finding. This is in agreement with a study done by Mohey et al who also showed a 100% PPV in score 5 lesions.[(43)]

UE scores of 2, 3 and 4, all showed some discordant findings. Of the 11 score 2 lesions, 8 were benign and 3 were malignant resulting in a 73% NPV. 2 of the 3 discordant lesions were noted to be large masses, which could have limited elastography evaluation due to central necrotic degeneration that may be associated with tumors that have outgrown their blood supply hence reducing the central stiffness. One such lesion is demonstrated in Figure 14: Case 4. There were 2 score 3 lesions and both showed a malignant outcome. A total of 29 lesions were scored as score 4 with 27 malignant and 2 benign final outcomes resulting in a 93% PPV. The 2 benign lesions were fibroadenomas with extensive popcorn calcification likely increasing their stiffness. The discordant findings in scores 2,3 and 4 are consistent with what other previous studies have shown.[(43)]

In strain ratio assessment; a SR cutoff of ≤ 2.9 was used to indicate a benign finding with a SR>2.9 indicative of a malignant outcome.[(67)] With above cutoff, SR demonstrated a PPV of 96% and NPV of 90%. Of the 3 discordant Score 2 lesion, 2 showed an SR >2.9 and both

score 3 lesions as well in keeping with the final histology of malignant findings. Ndaiga et al also documented similar findings[61].

Correlating mammography and UE, a direct relationship was demonstrated. BIRADS 5 category was highly associated with a UE score of 5 and subsequent malignant outcome on histopathological correlation. BIRADS 2 lesions also predominantly showed low UE scores. 4 BIRADS 4A lesions and 3 BIRADS 3 lesions were correctly downgraded to BIRADS 2 on combined mammography and UE assessment. These were confirmed to be benign on histology. 4 BIRADS 3 lesions were upgraded to BIRADS 4 after elastography correlation, and showed a positive outcome after histopathology. Elastography has been shown to reduce benign biopsies by downgrading BIRADS 4A lesions to BIRADS 2. BIRADS 3 lesions may be either downgraded or upgraded reducing the need for follow up, which is unwarranted in benign lesions or delays a definitive diagnosis in malignant lesions.[43–45]

5.6 Mammography and Sonoelastography Diagnostic Accuracy

To classify lesions as benign or malignant on mammography the ACR BIRADS was used with lesions found to be ≤ BIRADS 3 classified as likely benign and lesions ≥ BIRADS 4 classified as likely malignant.(30) In elastography, lesions with a score of ≤3 were classified as likely benign while lesions with a score of ≥4 were classified as likely malignant[43,44]. The different statistical variables were thus calculated with histopathological diagnosis as the reference point.

The study showed mammography sensitivity of 87.3% which was comparable to sonoelastography at 89.3% increasing to 95.7% in combination. UE showed a much higher specificity of 90% versus mammography 70%, which remained at 90% in combination. The diagnostic accuracy was 82% for mammography, 89.5% for UE and 92.5% in combination. Mammography showed PPVs and NPVs of 87.23% and 70% respectively, UE 95.5% and 78.35 respectively and in combination 95.7% and 90% respectively. These findings are in agreement with what other similar studies have shown. This is illustrated in Table 12 below.

Table 12: Diagnostic Accuracy in comparison studies

Authors	Year	Sample size	Modality	Sensitivity	Specificity	Accuracy	P-value
Mohey et al	2014	114	Mammography	72.7	86.4	82.5	0.0001
			UE	69.7	95.1	81.7	
Zhi Hui et al	2007	296	UE	89.7	95.7	93.9	<0.05
Zhang H. et al	2014	67	Mammography	-	57.8	63.1	-
			UE	-	93.3	89.6	
			Combined	-	93.3	91	
Itoh et al	2006	111	UE	86.5	89.8	88.3	0.001

5.7 Conclusion

Sonoelastography is a noninvasive technique that can be used to complement mammography. In this study it showed a higher sensitivity, specificity and diagnostic accuracy versus mammography in differentiating malignant from benign lesions. Furthermore, the combination of the two modalities showed the best diagnostic accuracy and cancer detection rate. Therefore, this combination has potential to reduce benign biopsies while increasing the cancer detection rate, and reducing unwarranted follow-ups which could either delay treatment or cause unnecessary anxiety in benign lesions. Lesion stiffness may also be used to guide biopsies and reduce false negative biopsies due to poor specimen collection methods. The value of sonoelastography as an adjunct to mammography cannot be overemphasized; it should be maximally exploited for the benefit of the patient.

5.8 Recommendations

From the study findings we therefore recommend that clinicians should be made aware of the new and developing breast imaging techniques by offering complementary sonoelastography in every patient who has a mass seen on mammography. Correlational sonoelastography should be done on the same sitting with mammography, to improve the diagnostic accuracy of imaging in detecting breast cancer.

A dedicated one stop breast center with the requisite equipment and personnel, incorporating sonoelastography as an adjunct to mammography is recommended to minimize delays in patient care. The routine use of sonoelastography in guiding biopsies is also recommended.

A study looking at the prevalence and incidence of breast cancer in women below 40years is highly recommended. This will improve awareness in both the general public and clinicians. The bi-annual national breast screening program may also be extended to women below 40years to improve early cancer detection in this age group.

5.9 Study Limitations

Evaluating multiple closely related lesions on UE may distort the stiffness score as the lesion stiffness is measured against supposedly normal background breast tissue. This was overcome by changing the probe angulation to maximize background normal tissue for comparison.

A similar limitation was also seen in deeply located masses, which may show limited displacement versus superficial masses.

Sonoelastography is user dependent and therefore there may be intra and inter observer variability. The mammography images were reviewed by the Principal Investigator who also performed the sonoelastography examinations eliminating the benefit of blinding in the study.

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APPENDICES

Appendix I: Study Timeline

ACTIVITY	July 2020	Aug 2020	Sept 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021	March 2021	April 2021	May 2021	June 2021
Identify Research area												
Background Reading												
Formulate Research Questions												
Research Methodology planning												
Write Research proposal												
Proposal Submission and approval												
Data collection												
Data Analysis												
Write 1st draft												
Write 2nd draft												
Write final draft												
Dissertation Submission												

Appendix II: Study Budget

ITEM	QUANTITY	UNIT PRICE(Ksh)	TOTAL (Ksh)
Stationery			
Writing pens	1 box	200	200
Notebooks	5 Pieces	100	500
Files	8 Pieces	200	1600
Printing Paper	5 Rims	500	2500
Cartridge	1PC	7000	7000
Internet Surfing	200 HRS	75	15000
Flash Disks	2 PCS	1000	2000
Printing Drafts and final proposal	10 Copies	500	5000
Questionnaire Photocopies	100 Copies	10	1000
Photocopies of Final Proposal	6 Copies	150	900
Binding Copies of Proposal	6Copies	150	900
Ethical Review fee	1	2000	2000
Subtotal			**38600**
Personnel			
Research Assistant	1	30000	30000
Biostatistician	1	30000	30000
Subtotal		**60000**	**60000**
Thesis Development			
Printing of Thesis drafts	10 Copies	1000	10000
Printing final Thesis	6 Copies	1000	6000
Subtotal			**16000**
Examinations			
Breast ultrasound	67	2500	167500
Subtotal			**167500**
Grand Total			**282100**

Appendix III: Study Explanation and Consent Form

Title of Study: The role of sonoelastography in evaluating breast masses detected on mammography with histopathological correlation at Kenyatta National Hospital.

Principal Investigator\and institutional affiliation: Dr. Sijabule Ndlovu University of Nairobi/ Kenyatta National Hospital.

What Is This Study About?

I am interviewing individuals who had a breast mass identified on mammography. The purpose of the interview is to find out the role of breast elastography as an addition to mammography in investigating breast lesions.

What Is Breast Elastography?

This is a new ultrasound technique used to assess how hard or soft a tissue is hence helping in deciding if a breast mass is cancerous or not.

What Will Happen If You Decide To Be In This Research Study?

You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions. The interview will last approximately 15minutes. This will involve taking history from you and filling a questionnaire. A physical breast examination will be done to locate and characterize the breast mass. Thereafter, a mammography examination will be done and a breast elastography examination will be used to confirm the mammographic findings. Both examinations are painless, only mild discomfort may be experienced during mammography. You will be then referred for a biopsy.

The biopsy will be done under local anesthesia, rendering it painless too. There might be mild bruising due to the biopsy procedure, but no associated adverse effects.

Are There Any Risks, Harms Discomforts Associated With This Study?

Mammography comes with a low, almost negligible radiation risk and its benefits outweigh any potential risks. There are no documented risks to having elastography.

Are There Any Benefits Being In This Study?

You may benefit by receiving free counseling and health information .We will refer you to a breast specialist clinic for care and support where necessary. Also, the information you provide will help us better understand breast cancer management and diagnosis. This information is a contribution to science and research.

Will Being In This Study Cost You Anything?

There will be no further costs incurred by the participants except for the investigations requested by the referring physician. Your interview will start with a mammography, followed by an ultrasound/elastography then referral for biopsy.

What Are Your Other Choices?

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

If you have further questions or concerns about participating in this study, please call or send a text message at the numbers provided below.

Thank you for your cooperation.

1. Dr. Sijabule Ndlovu: 0776219954 (8am to 5pm).
   Email: drsijabule@students.uonbi.ac.ke
2. KNH-UoN ERC Secretary Contact telephone numbers 2726300 ext. 44102, email uonknh_erc@uonbi.ac.ke

Consent Form

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study. I understand that all efforts will be made to keep information regarding my personal identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study: Yes No

I agree to provide contact information for follow-up: Yes No

Participant printed name:_____

Contacts:_____

Participant signature / Thumb stamp _____ Date _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name: _____ Date: _____

Signature

_____

Role in the study: _____ [i.e. study staff who explained informed consent form.]

Witness Printed Name (If witness is necessary, A witness is a person mutually acceptable to both the researcher and participant)

Name _____ Contact information _____

Signature /Thumb stamp: _____ Date_____

Appendix IV: Fomu Ya Mafunzo Na Fomu Ya Ridhara

Kichwa cha Utafiti: Thamani iliyoongezwa ya sonoelastography katika kutathmini raia wa matiti wanaogunduliwa katika mammografia.

Mchunguzi Mkuu \ na ushirika wa kitaasisi: Daktari Sijabule Ndlovu University of Nairobi / Kenyatta National Hospital.

UTAFITI HUU UNAHUSU NINI?

Ninawahoji watu ambao walikuwa na misa ya matiti iliyotambuliwa kwenye mammografia. Kusudi la mahojiano ni kujua jukumu la elastografia ya matiti kama nyongeza ya mammografia katika kuchunguza vidonda vya matiti.

ELASTOGRAPHY YA MATITI NI NINI?

Hii ni mbinu mpya ya ultrasound inayotumika kutathmini jinsi ngumu au laini ya tishu inavyosaidia kuamua ikiwa umati wa matiti ni saratani au la.

NINI KITATOKEA UKIAMUA KUWA KWENYE UTAFITI HUU WA UTAFITI?

Utahojiwa na mhojiwa aliyefunzwa katika eneo la kibinafsi ambapo unahisi raha kujibu maswali. Mahojiano hayo yatachukua takriban dakika 15. Hii itajumuisha kuchukua historia kutoka kwako na kujaza dodoso. Uchunguzi wa matiti ya mwili utafanywa ili kupata na kuonyesha umati wa matiti. Baada ya hapo, uchunguzi wa mammografia utafanyika na uchunguzi wa elastografia ya matiti utatumika kudhibitisha matokeo ya mammografia. Mitihani yote miwili haina uchungu, usumbufu mdogo tu unaweza kuwa wakati wa mammografia. Kisha utaelekezwa kwa biopsy.

Biopsy itafanywa chini ya anesthesia ya ndani, ikitoa maumivu pia. Kunaweza kuwa na michubuko nyepesi kwa sababu ya utaratibu wa biopsy, lakini hakuna athari mbaya zinazohusiana.

Kuna Athari Zozote, Zinazidharau Hasara Zinazohusika Na Utafiti Huu?

Mammografia huja na hatari ya mionzi ya chini, na faida zake huzidi madhara Hakuna hatari zilizoandikwa za kuwa na elastografia.

Utafiti Huu Una Manufaa Gani?

Unaweza kufaidika kwa kupokea ushauri nasaha wa bure na habari za kiafya. Tutakupeleka kwenye kliniki ya wataalam wa matiti kwa utunzaji na msaada pale inapohitajika. Pia, habari unayotoa itatusaidia kuelewa vizuri usimamizi na utambuzi wa saratani ya matiti. Habari hii ni mchango kwa sayansi na utafiti.

Je, Kuwa Kwenye Utafiti Huu Kutanigharimu Chochote?

Hakutakuwa na gharama zaidi zilizopatikana na washiriki isipokuwa kwa uchunguzi ulioombwa na daktari anayetaja. Mahojiano yako yataanza na mammografia, ikifuatiwa na ultrasound / elastography kisha rufaa kwa biopsy.

Chaguo Zangu Zingine Ni Nini?

Uamuzi wako wa kushiriki katika utafiti ni wa hiari. Uko huru kukataa kushiriki katika utafiti na unaweza kujiondoa kutoka kwa utafiti wakati wowote bila udhalimu au kupoteza faida yoyote.

Ikiwa una maswali zaidi au wasiwasi juu ya kushiriki katika utafiti huu, tafadhali piga simu au tuma ujumbe wa maandishi kwa nambari iliyotolewa hapa chini.

Asante kwa ushirikiano wako.

1. Dr. Sijabule Ndlovu: 0776219954 (saa 8 asubuhi hadi saa 5 jioni).
   Barua pepe: drsijabule@students.uonbi.ac.ke
2. KNH-UoN ERC 2726300 ext. 44102, email **uonknh_erc@uonbi.ac.ke**

Fomu Ya Ridhara

Taarifa ya mshiriki

Nimesoma fomu hii ya idhini au habari hiyo imesomwa kwangu. Nimekuwa na nafasi ya kujadili utafiti huu wa utafiti na mshauri wa utafiti. Nimejibiwa maswali yangu kwa lugha ambayo ninaelewa. Hatari na faida zimeelezewa kwangu. Ninaelewa kuwa ushiriki wangu katika utafiti huu ni wa hiari na kwamba ninaweza kuchagua kujiondoa wakati wowote. Ninakubali kwa hiari kushiriki katika utafiti huu wa utafiti. Ninaelewa kuwa juhudi zote zitafanywa kutunza habari kuhusu kitambulisho changu binafsi kuwa siri.

Kwa kusaini fomu hii ya idhini, sijatoa haki yoyote ya kisheria ambayo ninayo kama mshiriki katika utafiti wa utafiti.

Ninakubali kushiriki katika utafiti huu: Ndio Hapana

Ninakubali kutoa habari ya mawasiliano kwa ufuatiliaji: Ndio Hapana

Jina la mshiriki aliyechapishwa: _____

Mawasiliano: _____

Saini ya mshiriki / Stempu ya kidole gumba _____

Tarehe _____

Kauli ya mtafiti

Mimi, aliyesainiwa chini, nimeelezea kabisa maelezo yanayofaa ya utafiti huu kwa mshiriki aliyetajwa hapo juu na ninaamini kwamba mshiriki ameelewa na kwa hiari na kwa hiari ametoa idhini yake.

Jina la Mtafiti: _____ Tarehe _____

Sahihi _____

Jukumu katika utafiti: _____ [i.e. wafanyikazi wa utafiti ambao walielezea fomu ya idhini ya habari.]

Jina Lililochapishwa la Shahidi (Ikiwa shahidi ni lazima, Shahidi ni mtu anayekubalika kwa mtafiti na mshiriki wote)

Jina _____

Maelezo ya mawasiliano _____

Saini / Stempu ya kidole gumba: _____ Tarehe _____

Appendix V: Questionnaire

Form No.	Date	
Patient X-ray No.	Age	Gender
Residence	Marital Status	
Level of education	Occupation	
Presenting Complaints (tick where applicable)		
Palpable mass ☐YES ☐NO	If Yes Duration_____weeks	
Breast Pain ☐YES ☐NO	If Yes Duration_____weeks	
Skin/Nipple retraction ☐YES ☐NO	If Yes Duration_____weeks	
Nipple discharge ☐YES ☐NO	If Yes Duration_____weeks	
Others	(Specify)	
History		
Age at menarche	Parity	
Contraception		
Family History of breast cancer	☐YES ☐NO	
Physical exam (tick applicable)		
Breast Mass ☐YES ☐NO	Skin retraction ☐YES ☐NO	
Asymmetry ☐YES ☐NO	Nipple discharge ☐YES ☐NO	
Tenderness ☐YES ☐NO	Lymphadenopathy ☐YES ☐NO	
Mammography findings (tick applicable) **Please attach a copy of the most representative image(s)**		
Breast composition	☐ entirely fatty ☐scattered fibroglandular ☐ heterogeneously dense ☐ extremely dense	
Mass	☐ Present ☐Absent	
Shape	☐ Round ☐ Oval ☐ Irregular	
Margins	☐ Circumscribed ☐ Obscured ☐Microlobulated ☐Indistinct ☐Spiculated	
Density	☐high ☐equal ☐low ☐fat-containing	
Calcifications	(specify type)	
Associated features	(specify)	
BIRADS classification	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6	
Elastography Findings		
Elasticity score_____	Elasticity Ratio_____	
Classification	☐benign ☐malignant	
Histopathological Findings		
Biopsy ☐ done ☐not done	Histology result ☐benign ☐malignant	
Histological diagnosis		