EVALUATIONOF DIAGNOSTIC ACCURACY OF ULTRASOUND ELASTOGRAPHY IN DIFFERENTIATING BENIGN AND MALIGNANT SOLID BREAST MASSES.

A STUDY DISSERTATION TO BE SUBMITTED AS PART OF FULFILMENT OF THE AWARD OF DEGREE OF MASTER OF MEDICINE IN DIAGNOSTIC IMAGING AND RADIATION MEDICINE.

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LIST OF ABBREVIATIONS

US – Ultrasonography

USE – Ultrasound Elastography

UON – University Of Nairobi

ACR - American College of Radiology

BI-RADS - Breast Imaging and Reporting Data System

DDIRM - Department of Diagnostic Imaging and Radiation Medicine

KNH - Kenyatta National Hospital

PI- Principal Investigator

CNB- Core Needle Biopsy

ROI- Region of Interest

SR- Strain Ratio

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ABSTRACT

Objective

The purpose of this study was to determine the diagnostic accuracy of breast ultrasound elastography in differentiating benign from malignant breast masses using histology diagnosis as the gold standard.

Material and Method

The study was carried out at Kenyatta National Hospital. 112 patients with solid breast lumps were reviewed. They fulfilled our inclusion criteria gave consent to standard breast ultrasound supplemented by strain elastography. The imaging was carried out using a logic E-9 GE Ultrasound machine with Elastography software packages. A specifically designed data collection form was used to record the demographic details of the patient, the clinical findings, gray scale and ultrasound elastography findings and the histological diagnosis. Histopathologic results and strain elastography results were correlated.

Results

Female patients accounted for 96.5% of the total number of patients reviewed. The age range was 15-79 years. The median age of presentation was 28 years (interquartile range 22 – 40). Using ultrasound elastography to differentiate benign and malignant breast lumps, with histology as the gold standard, the sensitivity for strain score and strain ratio was 92.9% and 96.4% respectively. Specificity was however the same for both (95.2%).Strain ratio yielded a higher sensitivity compared to elasticity score (96.4% versus 92.9%). However, strain ratio against elasticity score were positively correlated with a Spearman's coefficient of 0.7842 (P value <0.001) indicating that by performing both techniques, a more confident diagnosis can be made.

Conclusion

Strain elastography is a non invasive, fast, simple tool that can compliment conventional gray scale ultrasound of the breast. It has a high accuracy level and could be used as a good tool for the classification of breast masses prior to the decision to biopsy a lesion.

1. BACKGROUND

Breast masses are common and usually benign[1]. Although most breast masses are benign, breast cancer is the most common cancer worldwide[2][3].The most common screening test for breast masses is mammography and ultrasonography (US), both of which are highly sensitive in detecting breast cancer. However, both methods have some limitations. Mammography often yields false negative results in dense breasts[4].Ultrasound has a high sensitivity in detecting lesions but poor specificity. To improve specificity, the American College of Radiology (ARC) introduced the Breast Imaging and Reporting Data System (BI-RADS) which is used to categorize breast masses[5]. However BI-RADS generated a significant number of false positive results[6]resulting in an increase in biopsies performed with a cancer detection rate of 10-30%[7, 8]causing unnecessary discomfort, anxiety and increased cost to the patient[9]. Ultrasound is also unable to pick microcalcifications which is a strong and sometimes an early finding in cancer of the breast[10].

Ultrasound elastography (USE) was introduced to increase the accuracy of characterizing breast lesions. When a certain amount of force is applied in a tissue, elastic deformation occurs. Sonoelastography is a technique that applies compression to detect stiffness variation within the scanned tissues. Cancerous lesions are stiffer than non cancerous ones. Ultrasound elastography uses this principle to differentiate malignant breast lesions from benign lesion on compression. USE holds promise in improving the differentiation of benign from malignant breast lesions[11, 12].

2. LITERATURE REVIEW

2.1. BREAST CANCER

Breast cancer is the commonest cancer in women both in developed and developing world. Statistics in Kenya indicate that breast cancer contributes to 23.3% of cancer deaths and mostly affects young women aged 35 to 55 years[3]. The epidemiology varies greatly worldwide. The Incidence rates is low among women in Eastern Africa compared to Western Europe(19.3 per 100,000 women Vs. 89.7 per 100,000 women)[13]. A relatively younger age group is affected in Kenya compared to developed countries. While 51% of the cases in Kenya occur in women below 50years, less than five percent of all breast cancer cases in US are diagnosed in women less than 40 years. Male breast cancer is rare, and only accounts for below 1% of all breast cancers. it occurs at an older age (60-70years) in comparison to female breast cancer[14]and mortality is much lower among men than women[15].

2.2. MAMMOGRAPHY

Mammography has been the mainstay in breast cancer detection and is the only screening test proven to reduce mortality. In randomized clinical trials, screening mammography was shown to reduce breast cancer mortality among women, especially for those above 50 years[16].In another study done in Norway, M. Kalager et al demonstrated that screening mammography aloneprevented2.4 deaths per 100,000 persons-years[17]. It also provides adequate visualization of soft tissue abnormalities including microcalcifications.

Mammography has a number of limitations including false negative results in dense breast and there is risk of radiation induced breast cancer especially exposure in young patients. A multi-institutional study done in America with over 300,000 women aged 40 to 89 years found that mammography had a sensitivity of 62.9% in women with extremely dense breast and 87.0% in women with almost entirely fatty breast[18].

Women with extensive mammographic density have a five times increased risk of breast cancer compared to women with density less than 10% of the mammogram[19]. However, the increased risk was shown to be limited to the 12 months after a screening examination. Therefore annual mammograms in such women would have no impact on detection of cancers hence the need to evaluate alternative imaging techniques for such women.

Wang F.L et al studied the effect of age, breast density and volume on breast cancer diagnosis. They found that breast ultrasonography was more sensitive than mammography in premenopausal patients (81.4% vs. 61.1,, in women with high breast density (85.9% vs. 60.6%) and women with small breast volume (87.1% vs. 66.7%)[20].

2.3. BREAST MRI

Breast MRI is a relatively new but rapidly growing field in breast imaging. It is recommended for screening women with increased risk of breast cancer such as those with strong family history and/or mutation genes including BRCA1/BRCA2. Its main strength includes its fine delineation of soft tissue and ability to image the breast in multiple planes. MRI offers an alternative screening tool for young high risk patients who are at risk of radiation induced cancer if subjected to regular mammograms [20].

Kriege M et al found that MRI was better than mammography screening in detecting tumors in women who were at high risk for breast cancer[21].However, MRI was also associated with many unnecessary additional examinations and biopsies as compared to mammography [21].Other limiting factors in our setting include; it's limited availability and the prohibitive cost.

2.4. BREAST ULTRASOUND

Breast ultrasound was first introduced in the 1950s using radar techniques adapted from the US navy[22]. Its main role was in distinguishing solid and cystic masses. Its specificity in differentiating benign and malignant breast masses was however low and most breast masses required biopsy. Recent advances in US technology have allowed improved characterization of solid masses. In 1995, Stavros A.T, Thickman D, Rapp CL, et al demonstrated that benign and malignant solid breast masses could be differentiated using gray scale with a sensitivity of 98.4% and a negative predictive value of 99.5%[23, 24, 25]. Subsequent studies have validated these results and the features used to categorize breast masses as either benign or malignant remain essential in assessment of breast masses. These features formed a basis for Breast Imaging and Reporting Data System (BI-RADS) in characterizing solid masses[26] which is routinely used in assessment of breast lesions.

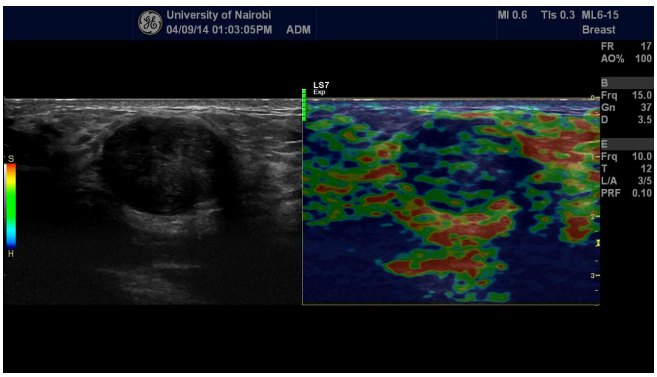
Ultrasound is used to evaluate breast lesions. It also acts as a complimentary tool to both mammography and MRI. Ultrasound may also be used as an adjuvant breast cancer screening modality in women with dense breast tissue and a negative mammogram. In addition, Ultrasound is currently the primary imaging modality recommended to guide interventional breast procedures.

The specificity of Ultrasound however remains low [6], resulting in many unnecessary biopsies and its ability to pick microcalcifications which is a strong and sometimes early finding in breast cancer is limited [10].

2.5. ULTRASOUND ELASTOGRAPHY

Normally, malignant tumors feel hard when compared with benign lesions on physical examination [11].US Elastography provides information on the strain or hardness of a lesion hence the capability to improve specificity in the diagnosis of breast masses [11,12]. Two techniques are currently available: strain and shear wave elastography.

In Strain Elastography, the elasticity or relative strain of a tissue is assessed by gently compressing the tissue repetitively with an ultrasound probe. These compressions result in tissue displacement or strain. A chromatic scale then assigns tissues that undergo strain (soft tissues) a different color (green in G.E machines) from those that are not deformed by the compressions (blue color in G.E machines). This color coded image is called an elastogram.The gray scale image and the elastogram are displayed side by side.An example of this display format is shown on the image below.



The following parameters are then evaluated on the images displayed.

- Elasticity score - A visual representation of how tissues deform under compression[27]. A five point score is used to categorize the mass. A strain score cut off of ≥ 4 indicates malignancy.

- Size ratio - The size change between the B-mode image and elastogram is evaluated[31]. Cut off point values for width ratio of more than 1.1 is considered significant.

- Strain ratio - Used to quantify the relative stiffness between the lesion and surrounding tissue[28, 29].A strain ratio of more than 4 shows a predictive value of malignancy.

Elasticity score provides qualitative information while strain ratio provides semi-quantitative information.

Shear-wave Elastography is based on the principle of acoustic radiation force. Using a light transducer pressure, transient automatic pulses can be generated by the Ultrasound probe, inducing transversely oriented shear waves in tissue. The Ultrasound system captures the velocity of these shear waves, which travel faster in hard tissue compared with soft tissue[30].

In a hospital based preliminary study done in China, Prajuly SS, Lan PY, Yan L, Gang YZ, et al found that ultrasound Elastography was superior in detecting breast cancer in terms of accuracy (95.8%), sensitivity (98.6%), specificity (96.0%), and positive predictive values (94.5%)[32]. G.M Giuseppetti et al evaluated the potential usefulness of real time elastography (RTE) in 91 breast lesions. The sensitivity and specificity of elastosonography was 79% and 89% respectively. They emphasized that the histotype and size of the lesion have an influence on the degree of elasticity[33].

Few studies have been done in Africa to assess accuracy of breast USE in differentiating benign from malignant breast masses. In Egypt, A. Maly et al carried out a prospective study to evaluate the accuracy of USE in distinguishing benign and malignant solid breast lesions[34].

They reported 87.2% sensitivity, 90.6% specificity and 90% accuracy and concluded that USE can facilitate improved classification of benign and malignant breast masses.

3. STUDY RATIONALE AND JUSTIFICATION

According to WHO statistics, more than a million women worldwide are diagnosed with breast cancer annually. In Kenya, breast cancer is the most prevalent cancer amongst women: 34per 100,000[3]. Locally, majority of those diagnosed with breast cancer are young between 20-50 years and hence will have more fibroglandular breast tissue unlike in the developed countries where the mean age at diagnosis is 63 years. In Kenya, increasing awareness to women about breast cancer has led to more women being screened routinely but this is in mainly in the urban centers. In the rural centers, majority of women still present with advanced disease.

Mammography is the only screening tool that has been shown to reduce mortality due to breast cancer[16]. In Africa, due to non availability of screening programs, majority of women have not had screening mammography. Good percentages however are women who have dense breast in whom cancer detection by mammography is difficult.

For the majority of women with dense breast tissue, mammography is not enough since the dense breast tissue and the tumor both have a similar appearance hence the sensitivity is reduced. These women need additional tests. They may benefit from ultrasound Elastography.

Breast ultrasound has been utilized in the diagnosis of breast lesions and is the preferred tool in women with dense breast. It however has low specificity which leads to unnecessary biopsies.

USE has the potential to improve specificity in differentiating benign from malignant breast lesions. This will in turn reduce the need for unnecessary biopsies of benign lesions and hence reduce cost and anxiety associated with these procedures and minimizes unnecessary invasive procedures in healthy women.

In Kenya, there are no recorded studies done to correlate breast USE with histological findings. This is despite Elastography holding a lot of promise in improving the diagnosis of breast cancer among our women and also increase the sensitivity of US guided biopsies since one can collect biopsies from the stiffest part of the mass.

4. RESEARCH QUESTION

What is the accuracy of breast ultrasound Elastography in differentiating benign from malignant breast masses at KNH?

5. AIMS AND OBJECTIVES

Broad objective

To determine the diagnostic accuracy of breast ultrasound Elastography in differentiating benign from malignant breast masses

Specific objectives

1. To determine correlation between elasticity values of solid breast masses and histological findings.
2. To determine if use of ultrasound elastography will lead to reduced number of interventional procedures for breast masses locally.

6. METHODS

6.1. STUDY DESIGN

This was a prospective study conducted at Kenyatta National Hospital.

6.2. STUDY POPULATION

Study population included patients with breast lesions referred to KNH who gave consent to be part of the study.

Inclusion Criteria

- All patients sent to KNH for evaluation of breast masses.
- Patients who consent.

Exclusion Criteria

- Declined consent
- Declined biopsy
- Known histology

6.3.SAMPLE SIZE

Sample size was calculated as follows:

$$n = \frac{z_{1-\alpha/2}^2 \, p \, (1-p)}{d^2}$$

Where n = Sample size, Z1-α/2 = Two-sided significance level (1-alpha)-95% = 1.96, p = p = Estimated proportion of patients with solid breast masses in Kenya and d = Precision error = ±10%

From literature review, the accuracy range of ultrasound Elastography in detecting breast cancer is 76.5% to 95.6%. In the absence of the previous data in Kenya, an assumption of accuracy of 80% was made. Substituting into the formula

N= (1.96 x1.96) x (0.8x (1-0.8)) / 0.075 x 0.075

=3.8416 x (0.8 x 0.2) / 0.005625 = 110

To have an adequate and representative sample size 5% was added for non responses. The total sample size was 115.

6.4.SAMPLING PROCEDURE

Patients who presented with breast lumps were screened from the outpatient department in KNH. Simple random sampling technique was used in selecting the patients who had breast lumps from clinical examination and had been send for breast ultrasound or mammography. 112 patients confirmed to have breast mass on conventional gray scale ultrasound were then assessed using Elastography. Majority of these patients then underwent fine needle aspiration or a core biopsy was obtained to get a histological diagnosis. The findings from the Elastography were then compared with histology results.

6.5.STUDY VARIABLES

- Size of the lesion
- Color of the lesion on elastogram
- Age
- Breast thickness and where the lesion is located
- Shallower lesion depth
- Current contraceptive use

6.6.MATERIAL AND METHOD

Following approval from KNH/UON scientific and ethical review committee, an introductory letter to the heads of the selected clinics in KNH and DDIRM was provided.

Data collection was done by the Principal Investigator who administered the questionnaire to the patients. The selected patients were informed about the study prior to the data collection.
A logic E-9 GE ultrasound machine at the DDIRM, UON with elastography module was used to evaluate selected patients referred from breast clinic.

6.6.1. BREAST ULTRASOUND ELASTOGRAPHY

The principal investigator did the ultrasound elastography examination supervised by Dr. Aywak who has vast experience in sonographic evaluation of breast masses.
The operator was not blinded at conventional ultrasound because the lesion was localized with conventional B-mode ultrasound and then strain elastography was performed. The patients were examined in supine position with the arm placed behind the neck. A7.5MHz US linear probe, lubricated with gel, was placed on the breast and a radial exploration of was made. A gray scale image of the mass was acquired.
Measured variables included:

- Size of the mass on B mode: Size was measured by taking the length and width of the mass.
- BI-RADS classification: This was classified based on the interpretation of the image characteristics on the conventional B-mode ultrasound image.

Using the same probe, elasticity of a tissue was assessed by gently compressing the mass repetitively with the ultrasound probe. Elastography strain image was then acquired and displayed side by side with the gray scale image.

Measured variables included:

- Elasticity score: a chromatic scale was used to assign soft tissues which can be compressed/strained green color and hard tissues which are not compressible blue color. The masses were categorized based on Ueno and colleagues strain score where score 1 to 3 are considered benign and score 4 and 5 malignant.

    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 centre. Displayed as green periphery with blue centre.
    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 was then calculated for all lesions by selecting a region of interest (ROI) on the mass and a corresponding ROI of the adjacent adipose tissue. Using specific software, the SR value was displayed on a static image. A cut-point of ≥4 for malignant lesions was used.

We used fine needle aspiration cytology (FNAC) or excision biopsy for histological analysis of benign lesions. The malignant lesions were diagnosed using a combination of FNAC and excision biopsy. Histology diagnosis i.e. benign or malignant was compared to strain score and strain ratio classification and accuracy of elastography calculated. Technique for biopsy is described below:

The type of biopsy procedure that was employed was the Core Needle Biopsy (CNB). A core biopsy of the breast mass was taken using a core needle. CNB was carried out in the outpatient setting in the minor theatre. The procedure was explained to the patient. After giving consent, the patient was positioned for the procedure. Under sterile conditions, local anesthesia was administered. The core needle was then put in 3 to 6 times to get the samples, or cores. Core biopsies were then taken for histology assessment. The pathologist or senior technologist was present to ascertain specimen collected was adequate and was correctly stored for transport to the histology lab.

7. DATA MANAGEMENT

All data was given a serial number and not the names of the participants. Data forms were kept in a secure lockable cabinet only accessible by the study investigator and the statistician. All questionnaires were scrutinized before being entered to the MsExel sheet. Upon completion of data entry, the principal investigator checked all the entered data against the hard copy forms for any inconsistencies.

7.1. DATA ANALYSIS

A sample of questionnaire was double checked for validation. Data was analyzed using STATA version 11. Simple descriptive statistics such as means, proportions and frequency distributions with 95% CI were used in the description of the study sample. Association between traditional risk factors and socio demographic characteristics were investigated using student t test and chi square. In addition, odds ratio was used to describe the magnitude of the difference between categories.

8. ETHICAL CONSIDERATION

The study was undertaken after approval by the University of Nairobi and the Kenyatta National Hospital Scientific and Ethical Review Committee. The objectives and purposes of the study were clearly explained to eligible participants and only patients who gave informed consent were enrolled. When cancer was diagnosed, the attending doctor was notified of the condition so as to initiate appropriate management.

9. RESULTS

The study was conducted between May and December 2014. A total of 118 patients were invited to participate in the survey, with 115 (97.4%) consenting. 112 breast lesions were confirmed by histopathology. 2 biopsy results could not be traced while one case was deemed as in-conclusive and a repeat biopsy requested.

Majority of the patients reviewed were female (96.5%). The median age of presentation was 28 years (interquartile range 22 – 40). There were 84 (75%) benign and 28 (25%) malignant lesions. The final pathologic diagnosis of all breast lesions is illustrated in table1.

Table 1: Final Histopathologic diagnosis of breast lesions

Diagnosis	Freq.	Percent
FIBROADENOMA	74	66.0
DUCTAL CARCINOMA	20	17.9
INVASIVE DUCTAL CARCINOMA	4	3.5
RECURRENT DUCTAL CARCINOMA	3	2.6
BENIGN BREAST LESION	2	1.7
DUCTAL PAPILLOMA	2	1.7
GYNACOMASTIA	2	1.7
LIPOMA	2	1.7
`DUCTAL ADENOCARCINOMA	1	0.9
GRANULOMATOUS MASTITIS	1	0.9
MASTITIS	1	0.9

Elasticity Score findings

The elasticity scores for benign and malignant lesions are listed in table 2. Fibroadenoma was the commonest lesion and demonstrated strain on compression (figure 1). Malignant lesions showed no strain on compression and appeared larger on the elastography due to better visualization of the surrounding desmoplastic reaction (figure 2).

Table 2: elasticity scores of benign and malignant breast masses

Final diagnosis/elasticity score	1	2	3	4	5
Benign lesion	2	67	12	1	2
Malignant lesion	0	0	4	10	14

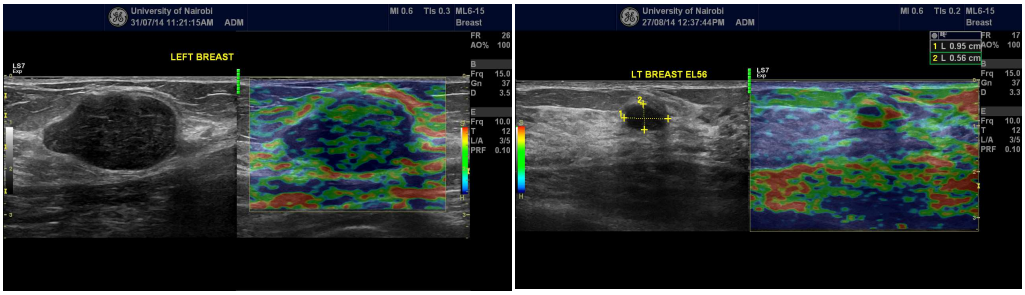


Figure 1: Benign Masses on USE

B-mode US image (A) and SE image (B) showing 2 hypoechoic circumscribed lesions that are predominantly elastic, assigned elasticity scores of 2 and 3 respectively. These were fibroadenomas with SR of 2.1 and 1.8.

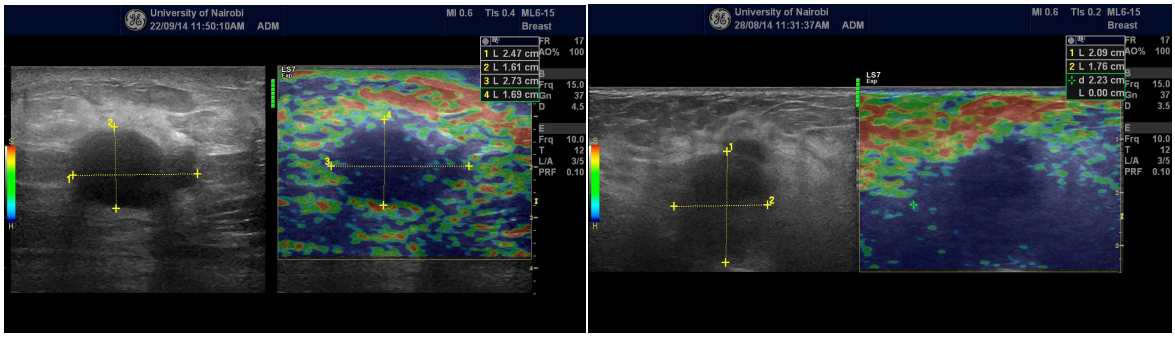


Figure 2: Malignant Masses on USE

B-mode US image (A) and SE image (B) showing 2 hypoechoic ill defined lesions that are predominantly blue assigned elasticity scores of 4 and 5 respectively. These were cases of invasive ductal carcinoma with SR of 5.8 and 9.8.

Following histology analysis, one lesion with elasticity score of 4 and two lesions with elasticity score of 5 were found to be benign.4 lesions with elasticity score of 3 were found to be malignant. Performance of elasticity score is summarised in table 3.

Table 3: performance elasticity scores

		Histology Classification		
		MALIGNANT	**BENIGN**	**Total**
Strain score	**MALIGNANT**	24	3	27
	BENIGN	4	81	85
	Total	28	84	112

Strain ratio findings

Malignant lesions showed significantly higher strain ratios (4.9-9.7) than benign lesions (1.2-3.4). Median strain ratios of benign and malignant lesions are listed in table 4.

The 4 lesions assigned elasticity score of 3 and confirmed on histology to be malignant had significantly high strain ratios (5.4-9.7) and were classified as malignant based on strain ratio. Figure 3 demonstrate B-mode US image (A), SE image (B) and strain ratio findings of a patient who was assigned a strain score of 3 but had a strain ratio of 9.7.

Figure 3:

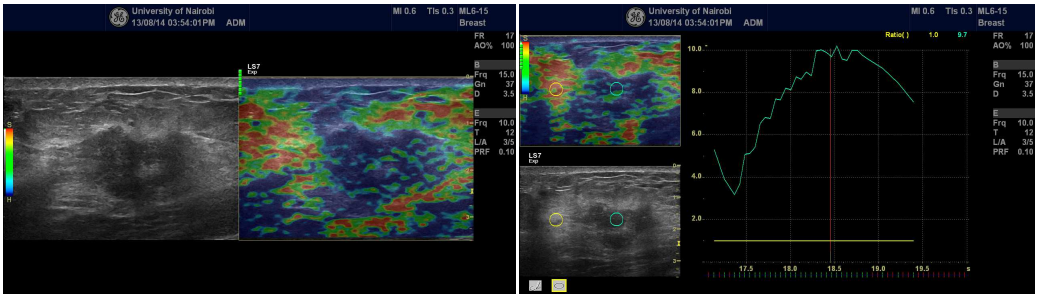


Figure 3: B-mode US image (A), SE image (B) of strain score of 3 but had a strain ratio of 9.7

3 benign lesions had high strain ratios (6.9-8.8) but were confirmed on histopathology to be benign. Strain ratio performance is summarized in table 5.

Table 4: summary of the median strain ratio for benign and malignant masses

		Benign	Malignant
Strain Ratio	Median	1.8	7.2
	IQR	1.2, 2.4	5.8, 8.5

Table 5: performance of strain ratio

		Histology Classification		
		MALIGNANT	**BENIGN**	**Total**
Strain ratio	**MALIGNANT**	28	3	31
	BENIGN	0	81	81
	Total	28	84	112

To assess accuracy of SE in differentiating benign and malignant solid breast lesions, analysis of these results was done. We got a sensitivity of 92.9%, specificity of 95.2%, PPV of 86.7% and NPV of 97.6% for elasticity score and sensitivity of 96.4%, specificity of 95.2%, PPV of 87.1% and NPV of 98.8% when a cut off point of 4 was used.

Strain ratio against strain score were positively correlated as shown on the graph below with

a Spearman's rho = 0.7842 (P value <0.001) indicating that strain score and strain ratio are dependent .

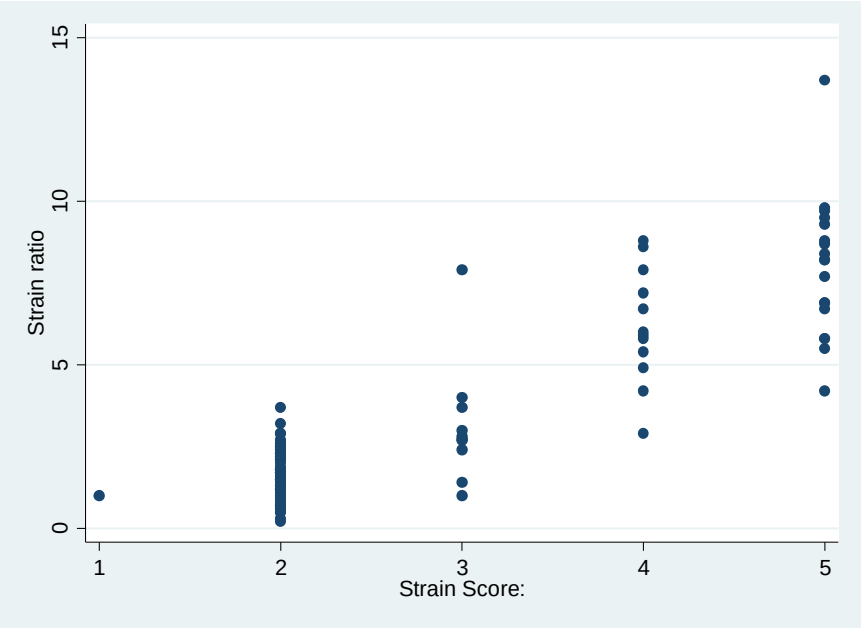


Figure 4: Graph of strain ratio against strain score

10. DISCUSSION

This prospective study assessed the accuracy of ultrasound elastography in differentiating benign from malignant solid breast masses. It was conducted in KNH and achieved 97% response rate underscoring the validity of our findings. Majority of the patients were female (96.5%) with a median age of 28 years which is reflective of benign breast lesions being more common (75%) and found in younger patients. These findings are similar to the study by Olu-Eddo A.N. et al[35]in Nigeria who found that benign breast lesions constituted 70% of breast lumps and occurred predominantly in young females (female to male ratio was 28.6: 1)with a peak incidence in the third decade.

Majority of the patients came from Nairobi (80%) and the surrounding counties since the study was done at KNH which is located in Nairobi. KNH is the national referral hospital and this explains why we also had a small number of patients from distant counties.

Breast mass was the presenting symptom in 99% of the participants. This correlates well with the inclusion criteria that included all patients send to KNH for evaluation of a breast mass. Breast pain was also a common finding seen in 27% of the patients. Other findings including skin changes (6.4%) and nipple retraction (3.4%) were not common since they are commonly associated with malignant breast lesions.

A small percentage (6.1%) of the patients had a family history of breast cancer. The small percentage is explained by the fact that inherited predisposition only increases the risk of getting breast cancer and not in benign disease.

Significant chronic disease was seen in two male patients who were on treatment for TB/HIV. Both patients were found to have lipomas. Feleke et al in Jimma, South West Ethiopia found the prevalence of lipodystrophy in patients taking HAART for more than one year to be 12.1%[36]. Lipohypertrophy occurs in many sites including the breast of both males and females. Other chronic illnesses included diabetes and hypertension. These had no effect in the type of breast lump that the patient presented with.

The single most common histologically proven solid breast mass was a fibroadenoma (64%) which compares with the study done by Olu-Eddo et al in Nigeria(2011) where 43.1% were fibroadenoma[35]. The lower percentage in Nigeria is because they included both solid and cystic breast masses in their study but fibroadenomas was still the most common lesion.

A total of 112 breast masses were classified according to the BI-RADS criteria and then assessed using strain elastography. In this study, a cut-off point of ≤3 was used. Elasticity score was higher in malignant lesions than in benign lesions. Itoh A, Ueno E et al found that malignant lesions had higher elasticity scores than benign lesions[37].

There were 4 lesions with elasticity score of 3 which were found to be malignant on both strain ratio and histology. The reason why some parts of these lesions were deformed under compression is because stiffness of benign and malignant lesions may overlap thus giving us false negative results. In a prospective study carried out in Romania, Ioana A.G et al found that one lesion(3.57%) with elasticity score of 4 and one lesion(3.57%) with elasticity score of 5 to be benign after FNAC and excision biopsy[38]. In the same study, one lesion (3.33%) with elasticity score of 1 and three lesions (10.72%) with elasticity score of 3 turned out to be malignant.

Malignant tumors showed a larger diameter at elastography as compared to gray scale US. Ioana A.G et al also found that benign lesions usually appear smaller or of the same size on sonograms as on the strain images while malignant lesions were depicted as larger masses on strain images than on sonograms[38]. This discrepancy in size between benign lesions and malignant lesions is due to strain images depicting regions around the tumor that have undergone desmoplastic reaction. These surrounding stiffer regions reflect underlying changes that are not captured on the sonograms.

The median strain ratio of benign lesions was significantly lower (1.8) than for malignant lesions (7.0). In previous studies, the average strain ratio related to malignant lesions was found to be significantly higher than the strain ratio related to benign lesions. However, the reported data are not comparable due to the use of different cut-off levels.

A total of 3patients with benign lesions were found to have a suspicious elastogram and a mean strain ratio of 5.4. The high strain ratio in these patients was probably due to presence of scar tissue and calcification thus making the lesion stiffer than it actually is. Ioana A.G et al found fibroadenomas with calcifications to have higher strain ratios comparable to malignant lesions[38].

10.1. ACCURACY OF STRAIN ELASTOGRAPHY

We found that ultrasound elastography can differentiate between benign and malignant lesions based on their firmness. Other published studies have similar findings. Barr et al concluded that elasticity imaging has high sensitivity (96.7-100%) in characterizing malignant lesions of the breast[39]. Wojcinski et al demonstrated that the complimentary use of Sonoelastography improved the performance in breast diagnostics[40]. Burnside et al found that the use of strain imaging can lead to improved discrimination of benign and malignant solid breast masses [41].

Strain ratio was found to have higher sensitivity compared to elasticity score (96.4% versus 92.9%). Specificity was however the same for both (95.2%).Strain ratio against strain score were positively correlated with a Spearman's coefficient of 0.7842 (P value <0.001) indicating that strain score and strain ratio are dependent. This compares with studies done elsewhere. Ioana A.G, et al found that there was a good correlation between qualitative and semi-quantitative elastography methods (elasticity score and strain ratio) and suggested that by performing both techniques a more confident diagnosis can be made [38].

Some studies have not found elastography to have an effect on performance when compared to B-sonography. Sohn et al did not find a statistically significant difference between B-mode and elasticity imaging with respect to sensitivity, specificity, positive and negative predictive values, or the area under the receiver operating characteristic curve [42]. Cho et al determined that performances of radiologists with regard to differentiation of solid breast masses were not significantly different for B-mode sonography and elastography [43].

Use of elastography as a discriminating tool is still under investigation. In the western countries, the number of users continues to increase but the numbers remain low as the role for the technology remains unclear [44]. Elastography is a technique that may be useful as an additional tool for characterization of lesions; however, continued research is needed for the technology to become included in clinical practice.

10.2. LIMITATIONS OF BREAST ULTRASOUND ELASTOGRAPHY

1. Degree of initial compression.
    - Gentle pre compression transducer pressure perpendicular to the lesion is optimal for analysis.
2. Variability to transducer pressure.
    - Inter and intra observer variability may be present because initial stress applied to tissue may not be constant.
3. Stiffness of benign and malignant lesions may overlap.
4. Posterior masses in the breast may be difficult to evaluate with elastography because the compression force may not displace deep tissue as much as superficial tissue.
5. Very large lesions(>3cm) may be difficult to evaluate because all of the tissue in the field of view is stiff and normal tissue may not be included for analysis

10.3. CONCLUSION

Ultrasound elastography was found to have high sensitivity and specificity in differentiating benign and malignant breast masses. Elastography holds a lot of potential. It is a fast, simple, noninvasive method that can compliment breast ultrasound examination and;

- Substantially reduce the need for biopsy in benign breast lesions and recommend follow-up.
- Increase diagnostic confidence of malignant lesions.
- Guide during ultrasound guided biopsy to demonstrate the stiffest part of the lesion and biopsies can be collected from that point.

Elastography has a significant role in imaging of patients with dense breast who have an increased risk of breast cancer and in whom the lesion if present will be obscured by the density of the normal breast if mammography is used for assessment.

When performing USE, elasticity score and strain ratio are dependent and for a more confident diagnosis, both techniques should be used.

10.4. RECOMMENDATIONS

It is my recommendation that ultrasound elastography should be routinely combined with conventional gray scale ultrasound in evaluation of breast masses. Breast ultrasound elastography should also be used routinely when taking ultrasound guided biopsies. All sonographers/sonologist should learn how to use real time strain elastography and include it during evaluation of breast masses.

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12. APPENDICES

12.1. APPENDIX 1: STUDY EXPLANATION

I am Dr. Purity Ndaiga, a postgraduate student in the department of Diagnostic Imaging and Radiation Medicine at the University of Nairobi. We are conducting a study in the university entitled:

"Evaluation of diagnostic accuracy of ultrasound elastography in differentiating benign and malignant breast masses"

What is ultrasound elastography? Ultrasound elastography is a new technique that assesses how hard or soft a tissue is. It is well known that malignant disease process makes tissues much stiffer than benign or normal tissues.

What is the study about? The study is about getting to know if ultrasound elastography can accurately discriminate between a benign mass and a malignant mass.

What does the study involve? The study will involve taking history from you and filling a questionnaire. We will then do physical breast examinations to locate and characterize the breast mass. An ultrasound machine with in-built elastography software will then be used to do a normal breast ultrasound scan. In the same sitting, ultrasound elastography will be performed. It is quite fast and will therefore not increase the time that will be spend scanning significantly.

A biopsy specimen will then be taken and analyzed. This will take approximately 15minutes in an outpatient clinic. You will be given anesthesia and will therefore not feel pain. Taking the biopsy can cause some bruising, but usually does not leave scars inside or outside the breast.

The findings on USE will then be compared with the histology results of the mass. This will then be used to assess accuracy of Ultrasound Elastography in differentiating benign and malignant lesions.

Ultrasound Elastography is used to diagnose and characterize the breast lumps. It is not a form of treatment.

Are there any dangers involved? There are no documented risks to having USE done.

Will I benefit from the study? Yes. This information will eventually help reduce the number of unnecessary biopsies on women if we prove that ultrasound elastography can accurately differentiate benign from malignant breast lesions.

Can I withdraw from the study? You are free to withdraw from the study and you will not be discriminated in any way.

Any queries can be addressed to me directly through phone number 0722484772 or email address wndaiga@yahoo.com.

Thank you for your cooperation.

Dr. Ndaiga Purity (principal Investigator) Tel 0722484772

12.2. APPENDIX 2: CONSET FORM

Study number…… Sex……

Name…… Age……

I, the above named, has been requested to take part in a study assessing the accuracy of ultrasound elastography in differentiating benign and malignant breast masses.

This study will help us ascertain if this tool can accurately discriminate between benign and malignant breast masses.

Any participant found to have malignant breast mass will urgently be referred to the surgical team for further management.

This study will involve taking history, breast examination, undergoing a breast ultrasound examination using B-mode ultrasound and elastography. This study will also involve getting tissue from the mass for histological diagnosis.

The cytological/histological results and any other information provided will be confidential.

This will put me at no risk.

I understand that I am free to either agree or refuse to participate in the study.

Having agreed on the above, I voluntarily agree to participate in the study.

Signed……... Date……

Witnessed by…….. Date……

12.3. APPENDIX 3: QUESTIONNARE

Form N^{o}	Date:

Patient Xray N^{o}	Age:	Gender:
Residence	Occupation	

Presenting complaints: (tick where applicable)	
Palpable Mass☐ YES ☐ NO	If Yes Duration _____months
Breast pain☐ YES ☐ NO	If Yes Duration _____months
Skin/Nipple retraction	If Yes Duration _____months
Nipple discharge	If Yes Duration _____months
Others	(specify)_____
History	
Family History of breast cancer	☐ YES ☐ NO
Physical Exam (tick appropriately)	
Breast mass ☐ YES ☐ NO	Skin retraction☐ YES ☐ NO
Asymmetry ☐ YES ☐ NO	Nipple discharge☐ YES ☐ NO
Tenderness ☐ YES ☐ NO	Lymphadenopathy ☐ YES ☐ NO
Ultrasound Findings (tick appropriately) ***Please attach a copy the most representative image(s)***	
Mass	☐present ☐absent
Shape	☐round ☐oval ☐irregular
Margins	☐circumscribed ☐indistinct ☐microlobulated ☐spiculated
Echogenicity	☐homogenous ☐ heterogeneous ☐hyperechoic☐hypoechoic☐ anechoic
Sound attenuation	☐posterior shadowing ☐ through transmission
Long axis	☐perpendicular to skin ☐parallel to skin ☐No long axis
BI-RADS classification - 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐	
Elastography Findings.	
Elasticity score……..	Elasticity ratio…….
Classification following Elastography	☐benign ☐malignant
Biopsy ☐Done ☐Not done	**Histological diagnosis**☐ benign ☐ malignant

12.4. APPENDIX 4: BUDGET

ITEM	QUANTITY	UNIT PRICE (Ksh)	TOTAL (Ksh)
WRITING PENS	1 BOX	200	200
NOTEBOOKS	5 PIECES	60	300
FILES	8 PIECES	50	400
PRINTING PAPER	5 RIMS	400	2000
CARTRIDGE	1 PC	6000	6000
INTERNET SURFING	200 HRS	60	12000
FLASH DISCS	2 PCS	2000	4000
PRINTING DRAFTS AND FINAL PROPOSAL	10 COPIES	500	5000
PHOTOCOPIES OF QUESTIONNAIRES	300 COPIES	10	3000
PHOTOCOPIES OF FINAL PROPOSAL	6 COPIES	100	600
BINDING COPIES OF PROPOSAL	6 COPIES	60	360
ETHICAL REVIEW FEE	1	1000	1000
SUBTOTAL			**34860**
PERSONNEL			
RESEARCH ASSISTANT	1	15000	15000
BIOSTATISTICIAN	1	15000	15000
SUBTOTAL			**30000**
DATA COLLECTION, DATA ANALYSIS AND THESIS DEVELOPMENT			
PRINTING OF THESIS DRAFTS	10 COPIES	1000	10000
PRINTING FINAL THESIS	6 COPIES	1000	6000