<u>ULTRASOUND ELASTOGRAPHY IN THE EVALUATION OF SOLID THYROID NODULES.</u>

A DISSERTATION SUBMITTED AS PART FULFILMENT FOR THE DEGREE OF MASTER OF MEDICINE IN DIAGNOSTIC RADIOLOGY, UNIVERSITY OF NAIROBI.

BY

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DECLARATION

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DEDICATION

I dedicate this book to The Lord Almighty. Truly, “Nothing is impossible with God”.

To my loving mother,Alexina Moraa Nyakoe, to whom I owe everything I am today!

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My sincere gratitude goes to my supervisors and mentors, Prof Joseph Kitonyi and Dr. Gladys Mwango for their guidance, encouragement, patience and support during preparation of this book, and during my residency in Diagnostic Imaging.

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LIST OF ABBREVIATIONS

DDIRM - Department of Diagnostic Imaging and Radiation Medicine

ERC - Ethics and Research Committee

H/o - History of

KNH - Kenyatta National Hospital

UON - University of Nairobi

TC - Thyroid Clinic.

FNA - Fine Needle Aspiration.

FNAC - Fine Needle Aspiration Cytology.

US - Ultrasound

USE - Ultrasound Elastography.

ATD - Autoimmune thyroid disease.

NPV - Negative Predictive Value

PPV - Positive Predictive Value.

AUC - Area under curve.

ROC - Region of characteristics.

ABSTRACT

Introduction: Ultrasound elastography has recently emerged as a dynamic technique that uses high resolution ultrasonography to provide an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force.

Objective: The aim of this study was to evaluate the diagnostic accuracy of ultrasound elastography in the differentiation of malignant and benign thyroid nodules, using fine needle aspiration cytology as a standard reference.

Study Design: A prospective cross-sectional study.

Setting: Kenyatta National Hospital and University of Nairobi, Department of Diagnostic Imaging and Radiation Medicine (DDIRM),

Sample Size: A total of 84 patients were evaluated over a period of 6 months, from July 2014 to December 2014.

Materials and Methods:

*Study subjects:*Patients from KNH thyroid clinic who had a provisional diagnosis of nodular thyroid disease and fulfilled the inclusion criteria for the study.

Ethical considerations: Ethical approval and clearance was obtained from the KNH-UON Ethics Review Board.

Methodology: Conventional B-mode ultrasonography and ultrasound elastography was done on solid thyroid nodules. Ultrasound elastography included an elastography colour scale score system (1 to 5) and offline acquisition of stain ratios (cutoff of greater than or equal to 4 as malignant). Correlation with fine needle aspiration cytology/ histopathology was subsequently done. A data collection form was used to record all the relevant data.

Statistical analysis: Data analysis was performed using the STATA version 12. Statistical significance was set at $p < 0.05$.

Results: A total of 173 solid thyroid nodules in 84 patients were examined. Majority, 72/84 (85.7%) were females, while 12/84 (14.3%) were males. The median age range was 40 to 50 years. Most patients presented with multiple thyroid nodules, 53/84 (63%).

Elastography scores of 1 to 3 produced 124 true negative (benign) cases, while elastography scores 4 and 5 revealed 39 true positive (malignant) cases on FNA/Histopathology. Sensitivity of 0.91 and specificity of 0.97 was obtained using the elastography score system for thyroid cancer diagnosis. Positive predictive value of 90.9% and Negative predictive value of 96.9%. Diagnostic accuracy of the technique was 93.17%.

Strain ratio acquisitions for the same thyroid nodules revealed a sensitivity of 0.89 and specificity of 0.96, positive predictive value of 88.6% and Negative predictive value of 96.1% in the differential diagnosis of benign and malignant thyroid nodules. However, there were 5 false positive and 5 false negative findings which markedly reduced the reliability of elastography.

Conclusion:

This study has shown that ultrasound elastography has no added benefit in determining whether a thyroid nodule is likely malignant and the final diagnosis should solely depend on FNA cytology and histopathology findings.

1.0 INTRODUCTION

Thyroid nodules are a common entity found in about 4-8% of adults by palpation, 41% by ultrasound and 50% at autopsy according to studies done. A minority of these, less than 5% are malignant.[1,2]Thyroid nodules are commonly seen in areas of iodine deficiency, females ,increasing age and after radiation exposure.Several local studies on thyroid disease in kenya havegiven an overall malignancy rate beween 11.7% and 23.3%,[3] . There is therefore need to screen thyroid nodules to determine which are more likely to be malignant to enable early treatment of patients with thyroid cancer[2].

Ultrasound has over the decades played an important role in the diagnostic evaluation of thyroid disease mainly because of the glands superficial location, availability and cost effectiveness of the ultrasound examination. Normal thyroid anatomy and pathologic conditions are displayed with remarkable clarity using high resolution real time gray scale (B-mode) and color Doppler sonography.Several sonographic patterns of malignant thyroid nodules described include: hypoechogenicity, blurred or spiculated margins,spot microcalcifications,absent halo sign and intranodular vascularity (type 2 vascularity). These patterns have a low sensitivity and specificity hence rendering the examination inaccurate in differentiating benign and malignant thyroid nodules[4,5,6].

In view of this limitation in conventional ultrasound imaging, there has been in recent years development of a dynamic ultrasound technique called elastography which utilises variations in tissue stiffness in differentiating between benign and malignant lesions in different body tissues. Studies have shown very promising results in the usefulness of elastography in the differential diagnosis of thyroid nodules.[1]This study therefore sought to demonstrate the diagnostic accuracy and utility of elastography in differentiating between benign and malignant thyroid nodules in our local setting.

1.1 LITERATURE REVIEW

Elastography was first suggested by Ophir et al (1991). It refers to imaging of the mechanical properties of tissues (elastic/ Young's modulus) [7] which in simpler terms means assessment of tissue stiffness or elasticity. Ultrasound, MRI and tactile imaging have been used to assess tissue stiffness.

This technique is still relatively new and under research, it has been studied extensively in the Asian continent. It is however seldom mentioned in Europe and America.Based on expert opinion,the European Federation of Societies for Ultrasound in Medicine and Biology EFSUMB on the Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography recommend that thyroid elastography may be used to guide follow up of lesions negative for malignancy at FNA. [8]

1.2 Principles of elastography

Since 400 B.C physicians have used manual palpation to detect cancers as cancerous lesions are harder and firmer to touch than the surrounding tissues.

The principle behind which is known as tissue stiffness can be calculated using Young's modulus or Elasticity (E). E is obtained as the ratio between a uniform compression (i.e. stress) and the resultant deformation (i.e. strain). The tissue stiffness can then be converted and displayed as an image known as an elastogram, which is usually color coded [9]

Young's Modulus (E) =Stress(s) /Strain (e)

Elasticity is measured in Kilopascals (Kpa). Cancers tend to be hard on palpation and will produce lower strain values with a resultant higher Young's modulus.[9]

1.3 Types of elastography:

There are two types of elastography; namely:Strain and Shear wave Elastography.

1.3.1 Strain Elastography:

Synonyms include - Static or Compression elastography.

In strain elastography repeated gentle compressions to the tissue under examination is applied using an ultrasound probe. This will result in tissue deformation (strain) which is measured by assessing the longitudinal movement of the tissue caused by the compression using radiofrequency (RF). Owing to the variability of the initial stress, Elasticity of the tissue cannot be calculated, therefore providing qualitative information only. However, obtaining strain index of the region of interest can provide semi quantitative information on the nature of the tissue under examination which is deemed more accurate than quantitative information only. [9]

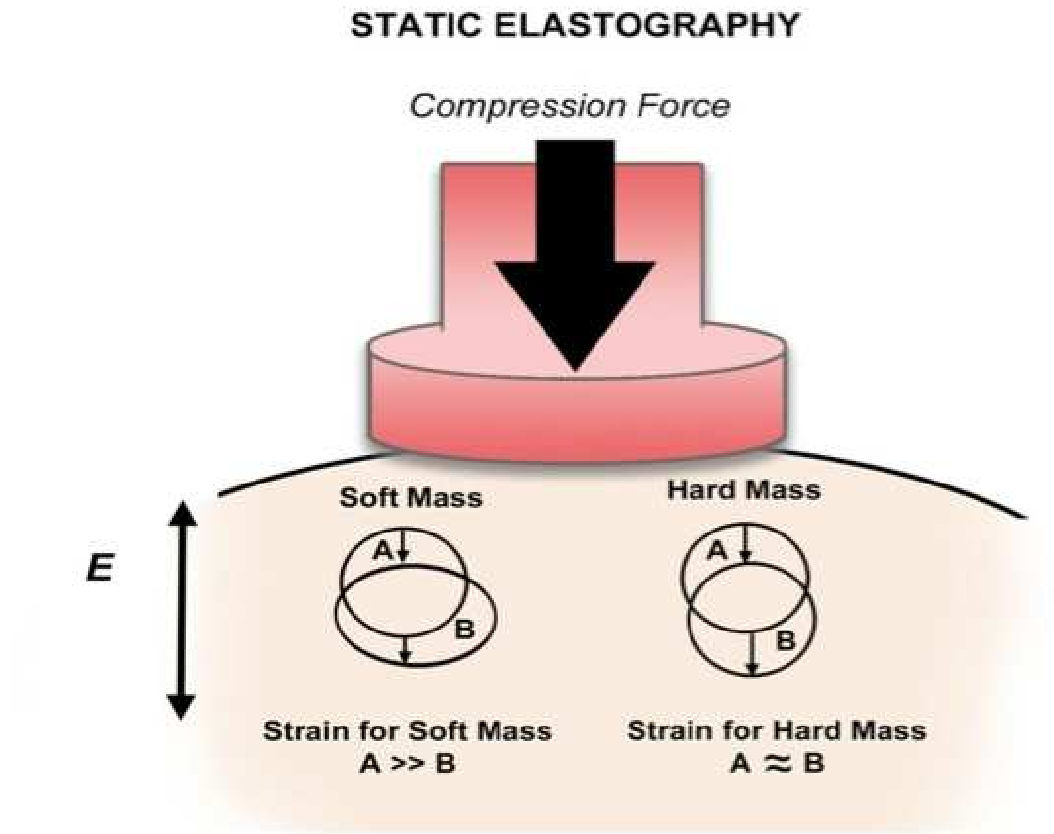


Figure 1:**Diagrammatic representation of strain wave elastography**

[diagram courtesy of institute of advanced medical education].[9]

1.3.2 Shear Wave Elastography:

Also as referred to as transient elastography.

As opposed to strain elastography which uses manual compressions, shear wave elastography is automated. Pulses from the ultrasound probe are introduced transversely into the tissue under examination.

In this technique a gentle initial compression force is applied and automatic pulses generated by the ultrasound probe will produce transversely oriented shear waves within tissue. The speed of the shear waves is directly proportional to stiffness (E).

$$E = 3PV^2$$

E=elasticity

P=density of tissue

V= velocity

Very fast acquisition sequences are used (about 5000 frames/sec) to obtain real time images. Due to its automated nature, the initial stress is readily quantified in Kpa (elasticity). Cancers will have a high elasticity on shear wave elastography because the waves travel faster in hard tissue. [9]

Shear Wave elastography has shown several advantages over strain/ Static elastography in terms of its operator independence and reproducibility. It is thought to have a higher sensitivity and specificity compared to Strain elastography (85% and 93% respectively versus 82-88% and 81.8 - 96% respectively). However, larger studies are still required to confirm shear elastography results and test its diagnostic accuracy further. In addition the ultrasound equipment required is not widely available because of the cost. [1, 10, 11]

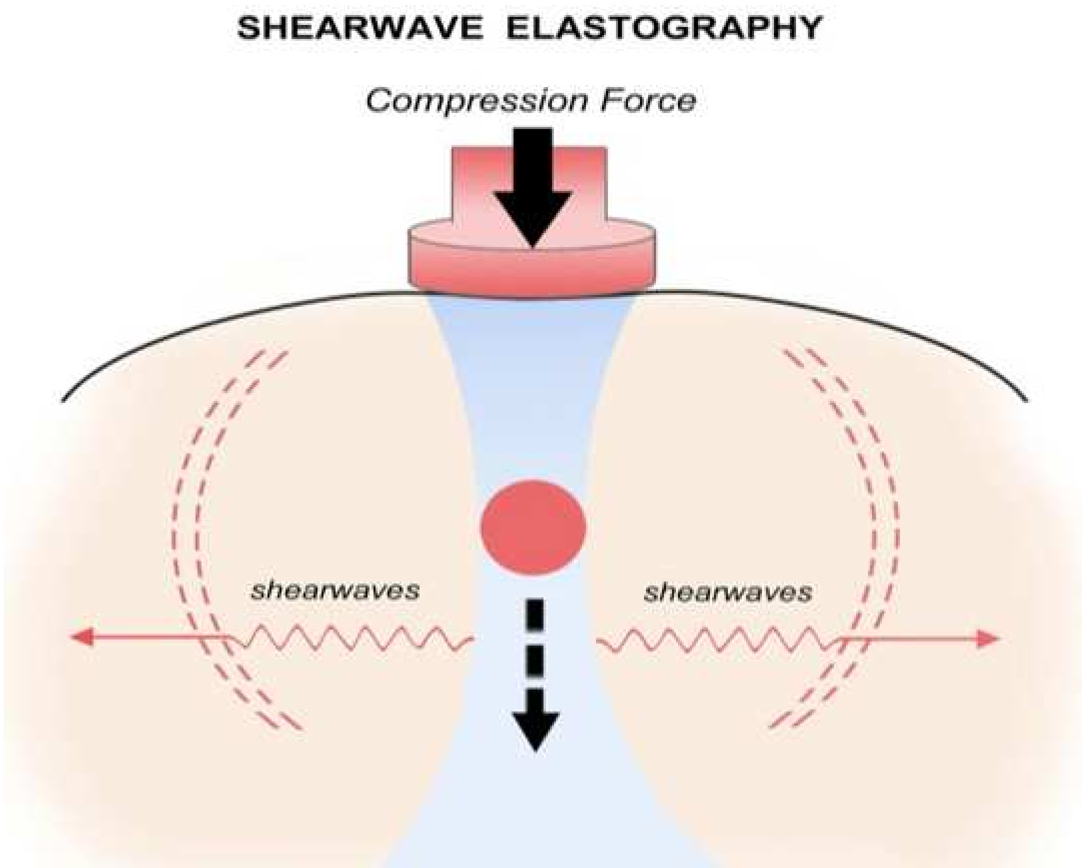


Figure 2: Diagrammatic representation of shear wave elastography

[diagram courtesy of institute of advanced medical education] [9]

Both strain or shear wave elastography convert the tissue stiffness information into a color coded image known as an elastogram. This is usually superimposed on a gray scale image of the region of interest. [9]

1.4 Elasticity scores:

The elasticity score is color based as follows:

SCORE 1 - The nodule evenly displays green.

SCORE 2 - The nodule displays all three colors (mosaic pattern) i.e. red green and blue.

SCORE 3 - the nodule displays green at the periphery with a blue center.

SCORE 4 -The nodule displays predominantly blue and surrounding tissue green and red.

SCORE 5 - The nodule and surrounding tissue is displayed completely in blue.

Several studies on ultrasound elastography have been done to validate its diagnostic accuracy in differentiating benign and malignant thyroid nodules. This has been because of the low specificity that conventional ultrasound confers in determining malignancy, as shown in a study by Frates MC et al (2005)that described several features that were associated with malignancy. These features are microcalcifications, hypoechogenicity, intranodal vascularity, irregular margins and an absent halo sign [2]. It has been shown that all these features alone are poorly predictive of malignancy, but in combination their specificity increases at the expense of decreased sensitivity [12]. A local dissertation on the diagnostic role of ultrasonography in patients with thyroid gland enlargement at KNH, Nairobi by Dr.Khainga K.A.(2007) further reiterated that no single sonographic criterion or group of criteria can reliably distinguish benign thyroid nodules from malignant ones[13].Fine needle aspiration has therefore over time played a central role in screening malignant from benign thyroid nodules with 65-75% specificity seen in expert centers. [12].

Hafez et al (2013) at Cairo University in a prospective study where the role of fine needle aspiration and ultrasound elastography in predicting malignancy in thyroid nodules was compared, showed that USE had a higher sensitivity (100% vs. 97.1%), specificity (93.4% vs. 75.4%), higher Positive predictive value (PPV), Negative predictive value (NPV) and higher diagnostic accuracy (95.8% vs. 83.8%) when correlated to FNAC. These authors recommended the introduction of USE into routine clinical practice in combination with FNAC for diagnostic utility. [14]An earlier study by Y Hong *et al*. in 2009 also demonstrated similar findings where ultrasound elastography yielded a sensitivity of 88%, specificity of 90%, PPV of 81% and NPV 93% in the differentiation of benign from malignant thyroid nodules [1].

Mireen Friedrich Rust and others in support of the diagnostic utility of USE evaluated the Thyroid Imaging Reporting and Data System (TIRADS) developed by Howath et alversus strain elastography for the assessment of thyroid nodules. They found that inclusion of strain elastography had a high negative predictive value for exclusion of thyroid malignancy in the diagnostic work up. [15]

Similar findings were also shown in a study by Carmela Asteria et al (2008) where 86 thyroid nodules were evaluated .USE revealed a sensitivity of 94.1%, specificity of 81%, NPV of 98.2% and a diagnostic accuracy of 87%, only showing limitation in sensitivity for follicular thyroid carcinoma. [16].Some of these nodules can be soft despite the fact that they are cancerous, therefore limiting the utility of elastography in accurately identifying them.[17]

Hui Wang et al prospectively compared strain ratio to elastography score system in 168 thyroid nodules and showed that the strain ratio distribution of malignant thyroid nodules differed significantly from those of benign nodules with a p value <0.001. Strain ratio was also seen to have a significantly higher specificity (p< 0.05) in detecting malignant nodules. No significant difference was seen in the sensitivity of the elastography score system (color mapping) and the strain ratio. [18]. In another study, Chun–Ping Ning et al (2012) found that strain ratio improved the diagnostic confidence due to the quantitative information provided on nodule characterization[19]. Both these studies used a cutoff of 4 to differentiate malignant or hard nodules (4 and above) from benign or soft thyroid nodules (below 4).

Lippolis PV et al (2011) underlined the importance of a quantitative USE method in the evaluation of nodular thyroid disease. These authors looked at the usefulness of elastography in the pre-surgical selection of thyroid nodules with indeterminate cytology using elastography color scale scoring system only**.** Malignancy was detected in 50% of the nodules with an elastography score of 1–2 and in 34% of those with score of 3–4. Both the PPV (34%) and the NPV (50%) were clinically negligible which effectively negated the reported usefulness of USE. The authors attributed these findings to the use of a qualitative elastography method and emphasized the need for quantitative methods to confirm tissue stiffness [20].

Cystic degeneration of thyroid nodules and co-existent autoimmune thyroid disease (ATD) have been listed as some of the factors thought to hamper the diagnostic accuracy of ultrasound elastography in some studies [21, 22]. However, a study by Magri F et al 2013 showed that elastography strain ratio still had a high sensitivity, specificity and negative predictive value for the diagnosis of thyroid malignancy both in the presence and absence of autoimmune thyroid disease. [21].

A study done to evaluate the effect of cystic change in thyroid nodules using color scaled elastography scores by Bhatia KSS and others, showed that the score was not significantly different between benign and malignant nodules ($p = 0.09$) unless partially cystic nodules were excluded ($p = 0.005$). However, solid nodules, with a high elastography score i.e.>2 optimally predicted malignancy, achieving 74% sensitivity, 77% specificity, and 76% accuracy [22]. These findings necessitated the exclusion of cystic nodules and further underscored the limitation in the effectiveness of elastography in clinical practice. It is on this basis that cystic nodules were excluded from the study.

Similarly, thyroid nodules with a calcified shell cannot be optimally evaluated as demonstrated by Rago.T and others (2007) who revealed that the ultrasound beam does not cross the 'egg shell' calcification and that the probe compression during elastography does not result in tissue strain deformation [23]. It is on this basis that the thyroid nodules with calcified shells were excluded from the study.

2.0 STUDY RATIONALE AND JUSTIFICATION

Local and international studies on the role of ultrasound in differentiating benign and malignant thyroid nodules have shown that it cannot firmly predict that a nodule is benign or malignant and have therefore recommended that such a diagnosis be established by FNA cytology or histopathology diagnosis after excision biopsy [13]

Over the last two decades, a newly developed dynamic technique called elastography that utilizes ultrasound to estimate tissue stiffness or elasticity has shown promising results in the differential diagnosis of diseases of the thyroid, breast, liver, prostate and pancreas. [18].

Currently elastography is not locally used to evaluate thyroid nodular disease.

The aim of this study was to evaluate whether the inclusion of ultrasound elastography to screen potentially malignant thyroid nodules would improve the diagnostic accuracy of ultrasound in our set up and thereby propose an imaging protocol for the use in thyroid nodular disease.

2.1 RESEARCH QUESTIONS

1. What is the spectrum of elastography findings (strain ratio and color mapping findings) in thyroid nodules?

2. How do these elastography findings relate with the ultrasound appearance of the nodule?

3. What is the correlation between elastography of the thyroid nodules with the fine needle aspiration cytology or the histopathology findings?

2.2 STUDY OBJECTIVES

2.2.1 Broad objective

1. To evaluate the diagnostic accuracy of elastography of thyroid nodules in differentiating benign and malignant nodules.

2.2.2 Specific objectives

1. To determine the elastography findings in thyroid nodules.
2. To relate these elastography findings to the ultrasound appearance of the thyroid nodules.
3. To correlate the ultrasound elastography with the FNA and/or histopathology findings.

3.0 STUDY DESIGN AND METHODOLOGY

The study was conducted at the Kenyatta National Hospital (KNH), Thyroid Clinic and DDIRM as a prospective cross sectional study.

3.1Study population

Patients newly enrolled or on follow-up at the thyroid clinic in KNH awaiting investigations after a provisional diagnosis of nodular thyroid disease.

3.2 Sample size determination

Sample size calculation was calculated using a formula for estimating sample size for a single proportion with finite population correction (Daniel 1999):

$$n = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

n = sample size with finite population correction

N = Population size (During the 6-month study period approximately 240 patients were expected to be referred to radiology department for investigation of thyroid nodules by ultrasonography. Based on review of monthly records at the radiology department we anticipated 75% (n =180) of these referrals were eligible for the study after accounting for exclusion criteria, i.e. underage, nodules, calcification , inconclusive or missing cytology/ histopathology reports and refusals to consent.

Z = statistic for 95% confidence = 1.96

P = expected proportion of investigated patients with malignant nodules on ultrasonography investigation (prevalence = 11.5%, P = 0.115)

d = precision (desired precision = 5%, d = 0.05)

$$n = \frac{180 \times 1.96^2 \times 0.115(1-0.115)}{0.05^2(180-1)+1.96^2 \times 0.115(1-0.115)}$$

n = 84

3.3 Sampling method

The sample population was a convenient sample and was defined as the outpatients from the thyroid clinic in KNH who were either new patients or on follow-up and were awaiting investigations concerning a palpable thyroid nodule(s). Consecutive sampling was done in the hospital at different clinic days and the patients booked for thyroid sonoelastography on different days of the week until the desired thyroid nodule sample size was achieved.

3.3.1 Inclusion criteria

1. Adult 18years of age and above.
2. Referral from thyroid clinic (TC), KNH with either nodular thyroid disease or solitary thyroid nodule.
3. Also sent for biopsy of thyroid nodule/s.
4. Approved consent from patient.

3.3.2 Exclusion criteria

1. Age below 18 years.
2. Declined consent.
3. Cystic nodules.
4. Patients with no final cytology or histopathology diagnosis.
5. Nodules that ultrasound reveals presence of calcified shell.

3.4 Materials and methods

The study was conducted using a LOGIC S7GE ultrasound machine at the DDIRM, UON (which is an extended arm of the radiology team) at the KNH. The ultrasound machine was used to perform thyroid elastography on the selected patients referred from the thyroid clinic (TC), KNH as per the stipulated inclusion criteria, and following approval from KNH/UON scientific and ethical review committee.

The ultrasound elastography (USE) method used was strain elastography. The ultrasound features of the nodule, the color mapping and strain index were recorded in a data collection tool.

The thyroid ultrasound elastography was carried out using a linear 7.5 – 12 MHz transducer and findings recorded in print or electronic media.

The principle investigator performed two separate ultra sound elastography examinations and recorded the findings in a data collection form. In cases where two measurements varied, an independent investigator repeated the examination and the correlating findings were recorded.

3.5 Methodology

3.5.1 Thyroid elastography

TECHNIQUE:

The patient was examined in the supine position, with the neck extended. A soft pillow was placed under the shoulders to provide better extension of the neck. The entire thyroid gland was examined in both transverse and longitudinal planes. The cervical lymph node chain was also evaluated for any nodal enlargement and the findings documented [23].

Ultrasound elastography was performed during the conventional ultrasound examination of the thyroid gland. The linear probe was placed on the neck with light pressure and a box was highlighted by the operator to include the nodule under examination in the center of the region of interest (ROI). A 50% allowance around the nodule was included in the ROI where attainable. Gentle repetitive compression was then applied. Adequate compression displayed a green color on all the compression bars at the top of the image. An elastogram was then displayed over the conventional ultrasound image in a color scale. These results were interpreted using a universal elasticity score system. Q analysis was then automatically done to obtain the most adequate compression done in the ROI over time. Strain index and strain ratio were then calculated by the GE machine using manufacturer's settings.

3.5.2 PROCEDURE FOR FNATHYROID NODULE BIOPSY COLLECTION.

This was carried out by a pathologist or a consultant radiologist in the case of ultrasound guided biopsy. Both were carried out at the KNH.

3.5.2.1 Ultrasound guided FNA biopsy:

This was carried out when requested by pathologist due to inadequate or difficult localization of the thyroid nodular lesions via palpation for traditional FNA biopsy.

The neck was cleansed with antiseptic. Local anesthesia was not routinely used. The linear probe of a GE (E series) ultrasound machine was cleaned with an antiseptic and dressed in a sterile glove. Ultrasonic gel was introduced both into the glove around the probe and on the patients neck. The gloved transducer was then placed on the patient's neck over the thyroid nodule. A spinal biopsy needle 21 gauge was then inserted through the skin under direct imaging guidance and advanced it to the site of the thyroid nodule and samples of tissue aspirated. New needles were used if additional samples were required. Several specimens were collected and smeared on slides for a complete analysis. These slides were then stored in a stand with 10% formalin solution. Once the biopsy was complete, pressure was applied to the area to decrease the risk of bleeding. A bandage was placed over the area if necessitated.

3.5.2.2 Traditional/conventional FNA biopsy:

The anterior neck was cleaned to sterilize the region of interest .The nodular thyroid lesion was then palpated for localization and stabilization of the lesion. A 21 gauge needle was then used to obtain cellular sample material from the lesions palpated. This was then smeared onto several slides and fixed in 10% formalin solution before evaluation under the microscope.

3.5.3 PROCEDURE FOR HISTOLOGY SPECIMEN ANALYSIS

This was carried out by a consultant Pathologist at the UON.

Thyroid biopsy samples were received in the laboratory reception having being fixed in 10% formalin. This was following surgery for removal of a thyroid nodular mass lesion either through a lobectomy or near total thyroidectomy. Laboratory number was allocated. Tissue biopsy were then trimmed to appropriate size (up to 10mm in thickness) and placed in tissue cassettes ready for laboratory processing. Tissue samples were treated overnight through various reagents (e.g. decalcifying reagent) in an automatic tissue processor then embedded in paraffin wax. Sectioning was done using a microtone, the sections were then treated in warm water to remove wrinkles. Sections were then fixed on glass slides and placed in a warm oven for 15minutes to adhere to the glass slide. Staining was carried out as follows; Depolarization of tissues, done by dipping them in xylene to alcohol to water. Standard Hematoxylin & Eosin was used for staining. Mounting and drying followed. The tissue was then examined under the microscope for characterization.

3.6 Study variables

Non – modifiable variables

1. Age
2. Sex

Modifiable variables.

1. Number of thyroid nodules in each patient.
2. Elastography score of thyroid nodule.
3. Conventional sonographic characteristics of the thyroid nodules,

3.7 Study limitations

1. Intra-observer findings in the sonoelastography examination were reduced by having two measurements (elastography scoring) for each nodule. Moreover, strain ratio a semi-quantitative analysis of nodule elasticity was obtained.
2. Some patients were lost to follow-up after ultrasound elastography therefore biopsy correlation was not possible. In view of this all FNA findings in the category Thy 3 (follicular neoplasms) were considered malignant in the study.
3. A few deep seated thyroid nodules were difficult to attain adequate compression during elastography and were consequently not assessed.
4. Not all thyroid biopsies were ultrasound guided.

3.8 Data management

3.8.1 Data collection

Patient bio data, conventional ultrasound and elastography findings were documented in a data collection sheet.

3.8.2 Data analysis

Analysis using STATA version 12 was done. The demographic characteristic of patients was summarized using descriptive statistics. Mean age was calculated with standard deviation using calculations for grouped data. Sex distribution was described using frequency distribution of percentage of male and female patients.

Analysis of characteristics of thyroid nodules involved calculating mean (SD) and median (range) for number of nodules and calculating percentage of patients with different sonographic findings (echogenicity, halo, vascularization, elasticity, FNAC and histopathology).

Elastographic scores for thyroid nodules was determined using references and the distribution of elasticity scores (possible range 1 to 5) was presented using frequency distributions. To determine the predictive value of elastographic scores for FNAC or histopathology, the area under the receiver operating characteristics curve (ROC) was calculated with 95% confidence intervals. The sensitivities and specificities of commonly used cut-off values of elastographic score and strain ratio against gold standard diagnosis based on cytology or histopathology of thyroid nodules was examined. Predictive values and likelihood ratios were also be calculated.

The relationship between the fine needle aspiration, histopathology, and elastography and strain ratio was established using Pearson Correlation analysis at 95% confidence level (α = 0.05).

3.8.3 Data representative

Continuous numerical data was presented using descriptive statistics (mean [SD] and median [range] in tables. Distribution of categories for patient characteristics and thyroid nodule sonographic findings was presented as frequency distributions including number with characteristic and corresponding percentage. These distributions were presented in form of graphs, pie charts and frequency tables.

3.9 ETHICAL CONSIDERATION

The study was undertaken after approval by the University of Nairobi and Kenyatta National Hospital Scientific and Ethical Review Committee. Authorization was sought from the management of the respective institutions before commencement of the study. The objectives and purposes of the study were clearly explained to eligible participants and only patients who gave informed consent were enrolled using predetermined inclusion criteria.

The ultrasound procedure had no radiation exposure and did not expose the patient to any harm whatsoever. In addition, it was a painless procedure and no additional cost was incurred other than the requested examination from the primary physician.

The names of the participants were kept private to the extent allowed by the law of the land. Access to needs assessment data was limited to staff working directly on this activity. This was determined by the chief investigators.

4.0RESULTS

4.1 Demographic Characteristics

The study was conducted on 84 patients with solid thyroid nodules. A total of 173 nodules (100%) in the 84 patients were examined: Those above the age of 40 years formed the bulk of the patients accounting for 65.5%. Most of these patients (46.4%), were between 40 and 50 years of age.

Table 1 Age distribution of patients with solid thyroid nodules at KNH

Characteristic	n (84)	Percent (%)
18-28	8	9.5
29-39	21	25.0
40-50	39	46.4
51-61	8	9.5
62-72	5	6.0
73-83	3	3.6
>84	0	-
Total	84	100.0

Majority of the patients were female accounting for 85.7% (72/84) of the respondents, 14.3% (12/84) were males.

Table 2 Gender of patients with thyroid nodules at KNH

Sex	n (84)	Percent (%)
Male	12	14.3
Female	72	85.7
Total	84	100.0

The clustered bar graph below presents the results on the patient distribution along their age and gender.

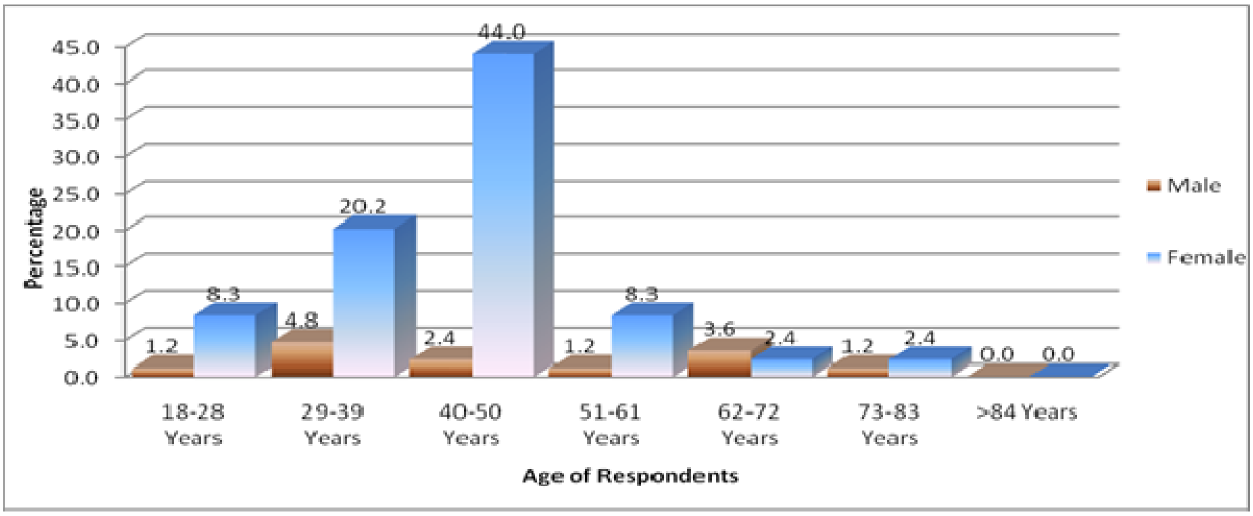


Figure 3 Distribution of patients' gender and age

4.2 Number of thyroid nodules

The study revealed that most of the patients (63.1%) had three or more nodules. Only 19% presented with a solitary thyroid nodule.

Table 3 Number of Thyroid Nodules per Patient

Number Of Thyroid Nodules	n (84)	Percent (%)
1	16	19.0
2	15	17.9
≥3	53	63.1
Total	84	100.0

4.3 Elastography and FNA/ histopathology results**:**

4.3.1 Elastography score findings**:**

Twenty three thyroid nodules representing 13.5% had scores of 1, seventy (40.9%) of the nodules had a score of 2, thirty-seven (21.6 %) of the nodules had a score of 3, thirty-six (21.1%) of the nodules had a score of 4 and five (2.9%) of the nodules had an elastography score of 5.

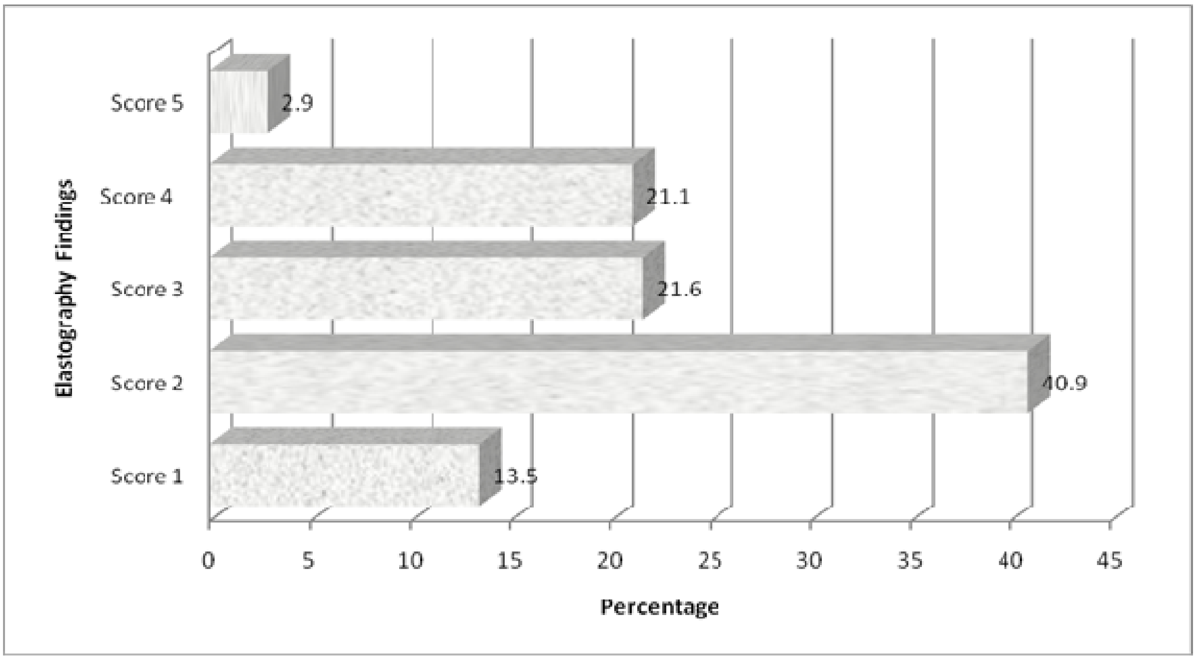


Figure 4 Elastography score Findings of the Thyroid Nodule

4.4 Strain ratio findings:

One hundred and twenty-five thyroid nodules (72.5%) had a strain ratio of less than 4 while 48 nodules (27.5%) had a strain ratio of greater than or equal to 4.

Table 4: Thyroid Nodules Strain Ratio

Strain Ratio	Frequency	Percentage
Less than 4	125	72.5
Greater than or equal to 4	48	27.5
Total	173	100.0

4.4.1 Fine needle aspiration/ Histopathology findings

Fine Needle Aspirate cytology/histopathology revealed that 129 (75%) of the nodules had benign disease while 44 (25%) of the nodules were malignant.

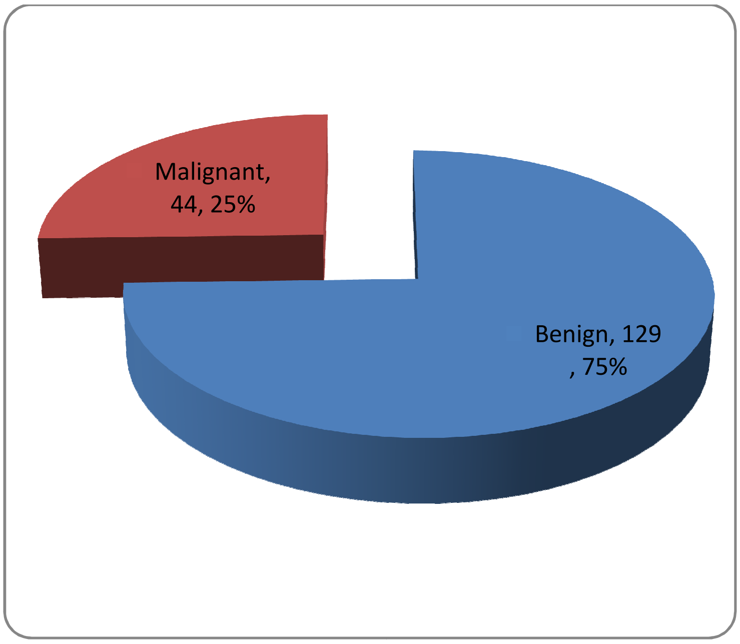


Figure 5: Fine Needle Aspirate (FNA) / Histopathology findings

A total of 173 nodules were studied. Fine needle aspirate (FNA) was performed in 159 nodules and the results reported using the Bethesda classification system (REF) while in 14 nodules histopathology analysis was done. Thy 1 result was not obtained from this study.

Table 5: FNA cytology results:

Thy 2 :	Number of nodules:	
Colloid nodules /goiter	52	
Multinodular goiter	72	
Focal thyroiditis	2	
Thy 3:		
Follicular neoplasm	10	
Thy 4 /5 suspicious for malignancy or malignant		
Papillary carcinoma	21	
Medullary carcinoma	0	
Anaplastic carcinoma	1	
Metastasis	1	
Lymphoma	0	
TOTAL	**159**	

For ease of analysis, the cytopathology results were thereafter considered as either benign or malignant. The benign thyroid nodules being Thy 2 and Thy 3, 4 and 5 representing the malignant thyroid nodules.

Table 6: Histopathology result

Benign	
Follicular adenoma	2
Multinodular goiter	1
Malignant	
Papillary carcinoma	7
Follicular carcinoma	3
Anaplastic carcinoma	1
TOTAL	**14**

Histopathology reported 3 benign nodules and 11 malignant nodules.

Overall using FNA and histology there were 129 benign nodules and 44 malignant nodules.

Table 7: Elastography versus thyroid nodule FNA/histology result.

Elastographic Score	FNA/Histopathology
	Benign
Score 1	23(17.8%)
Score 2	68(52.7%)
Score 3	33(24.8%)
False Positive	5(9.1%)(had score 4 or 5)
	Malignant
Score 4	35(79.5%)
Score 5	4(11.4%)
False Negative	5(3.1%) (had score 1-3)

The table above shows that thyroid nodules elastography scores of 1 to 3 brought about 124 (96.9%) cases of true negative (benign) cases on FNA/histopathology test. Elastography scores 4 or more revealed 39 (90.9%) cases of true positive (malignancy) nodules on FNA/histopathology. This gave rise to positive predictive value (PPV) of 90.9%.

The false positive cases were 5(11.4%) and the false negative cases were 5(3.9%) in FNA/histopathology. The negative predictive value (NPV) of 96.9%. The sensitivity and specificity of the elastography score system was 0.90909 and 0.9692, respectively with a diagnostic accuracy of 0.9317.

Correlation of strain ratio to FNA / Histopathology findings showed that strain ratio of less than 4 produced 125(96.2%) true negative (benign) on FNA/histopathology. Strain ratio of 4 or more produced 39(88.6%) true positive (malignant) cases on FNA/histopathology. The positive and negative predictive values were 88.6% and 96.1% respectively with sensitivity and specificity of 0.8863 and 0.9615 respectively.

Table 8 Strain ratio versus thyroid nodule FNA/histopathology results.

Strain Ratio	**FNA/Histopathology**
	Benign.
Less than 4	124(96.2%)
False Positive	5(11.4%)
	Malignant.
Greater than or equal to 4	39(88.6%)
False Negative	5(3.8%)

Using ROC analysis, the best cut-off strain ratio point is 3.5 for differentiating benign and malignant nodules with area under the curve (AUC) = 0.87 (0.8–0.95). The sensitivity of the strain ratio was 88%, while the specificity was 86.4%, PPV = 73.3%, NPV = 94.4% and accuracy = 86.9%. These tests were done at 95% confidence level.

4.4.2 Correlation between Elastography score system and Strain ratio

			Elastography	Strain Ratio
Fine Needle Aspirate	Elastography	Pearson Correlation	1	.615**
		Sig. (2-tailed)		0.037
	Strain Ratio	Pearson Correlation	.615**	1
		Sig. (2-tailed)	0.037	
Histopathology	Elastography	Pearson Correlation	1	.846**
		Sig. (2-tailed)		0.011
	Strain Ratio	Pearson Correlation	.846**	1
		Sig. (2-tailed)	0.011	

Table 9 Correlations between Elastography Findings and Strain Ratio

The study sought to establish the relationship between the FNA /histopathology, elastography and strain ratio. Pearson Correlation analysis was used to achieve this end at 95% confidence level ($\alpha = 0.05$). From Table 8, good linear relationship was established between elastography and strain ratio ($R = 0.842$, $p = .012$) for both histopathology/ FNA.

4.4.3 Elastography findings versus FNA/histology results:

	NUMBER OF NODULES	
FNA/HISTOLOGY RESULTS	**SCORES 1,2 AND 3**	**SCORE 4 AND 5**
Colloid nodules/goitre	51	1 **FP**
Multinodulargoitre	70	3 **FP**
Follicular adenoma	2	0
Focal thyroiditis	1	1 **FP**
Follicular neoplasm	4 **FN**	6
Follicular carcinoma	1 **FN**	2
Papillary carcinoma	0	28
Anaplastic carcinoma	0	1
Metastasis	0	1

Table 10: Elastography findings vs. cytology/histology findings.

The final FNA cytology/ histology results was correlated with the elastography scores and revealed the tabulated results above. A low (benign) elastography score below 3 was seen in 4 follicular neoplasms (FNAC) and in one follicular carcinoma. A high elastography score (score 4 and 5) was seen in 5 benign nodules on histology (false positives, FP), limiting the reliability of the elastography score in the absence of cytology or tissue correlation.

4.5 Conventional ultrasound findings

4.5.1 Echogenicity:

Out of the 173 solid thyroid nodules examined, 70 nodules (40.4%) were hypoechoic, 62 (35.7%) were isoechoic and 41 (23.9%) were hyperechoic.

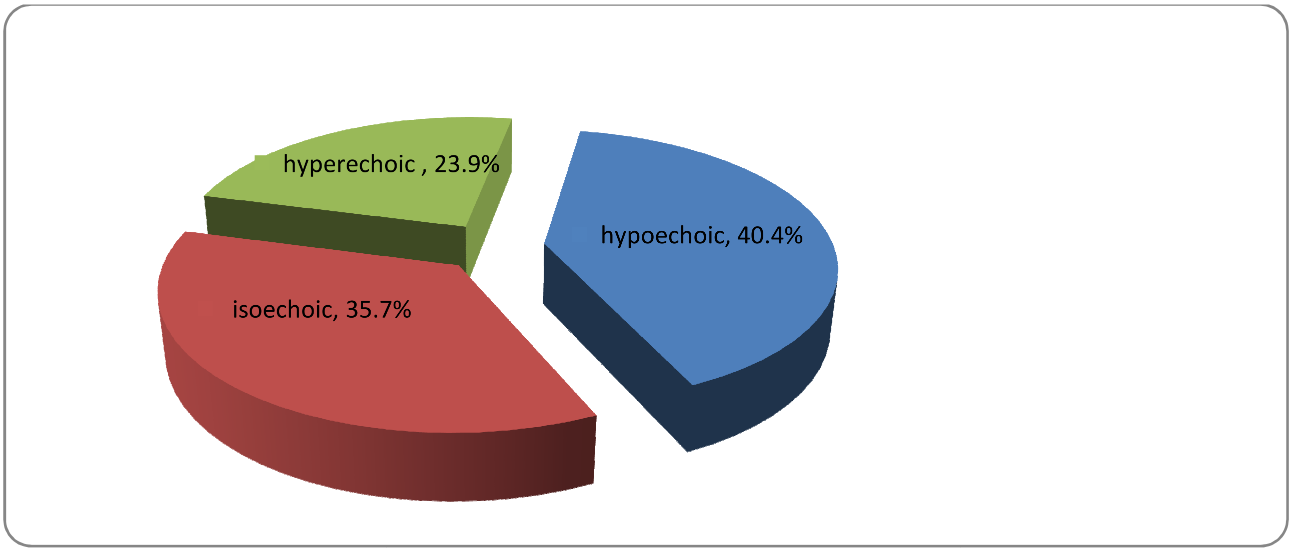


Figure 6: Echogenicity of the Thyroid Nodule

When the echogenicity was correlated with findings on FNA/histopathology; all the hyperechoeic nodules were benign. The malignant nodules were hypoechoeic (61.4%) or isoechoeic (38.6%). This was found to be statistically significant. (table 4 and 5)

Table 11 Echogenicity and Thyroid Nodule Diagnostic Result

Echogenicity	Benign (n=129)	Malignant (n=44)	p= value	Sensitivity %	Specificity %
Hypoechoic	33.6%	61.4%	.000	85.0	83.7
Isoechoic	33.6%	38.6%			
Hyperechoic	32.8%	0%			
Total	100.0%	100.0%			

4.5.2 Peripheral Halo:

The findings in Table 7 shows that peripheral halo was present in 109 (62.1%) of the thyroid nodules and absent in 64 (37.4%) of the nodules.

Table 12 Presence of Peripheral Halo around the Thyroid Nodule

Peripheral Halo	n (173)	Percent (%)
1. Present	109	62.1
2. Absent	64	37.9
Total	173	100.0

When correlated to FNA/histopathology, 66.4% of the benign thyroid nodules and52.3% of the malignant thyroid nodules had aperipheral halo present. These findings were statistically insignificant with a p value of 0.94 at 95% confidence level.

Table 13 Peripheral Halo and FNA/Histopathology Result

Peripheral Halo	Benign (n=129)	Malignant (n=44)	π p= value	Sensitivity %	Specificity %
Present	66.4%	52.3%	.094	92.0	72.9
Absent	33.6%	47.7%			
Total	100.0%	100.0%			

4.5.3 Microcalcifications:

Microcalcifications were present in 42 (24.3%) nodules and absent in 131(75.7%) of the nodules.

Table 14 : Microcalcifications in the thyroid nodule.

Microcalcifications	n (173)	Percent (%)
1.Present	42	24.3
2.Absent	131	75.7
Total	173	100.0

Fifteen perecnt (15.6%) of the benign thyroid nodules hadmicrocalcifications while 84.4% showed no micocalcifications Forty seven percent (47.7%) of the malignant nodules showed microcalcifications.

Table 15: Microcalcifications and FNA/Histopathology findings.

Microcalcifications	Benign (n=129)	Malignant (n=44)	π p-value	Sensitivity %	Specificity %
Present	15.6%(20)	47.7%(21)	.000	91.7	66.7
Absent	84.4%(109)	52.3%(23)			
Total	100.0%	100.0%			

A chi-square test value of 18.587 was established at $p < .001$ which shows statistical significance between the presence microcalcifications and malignancy at 95% confidence level.

4.5.4 Intranodal Vascularity:

Fifty six nodules representing 32.2% were hypovascular, 105 (60.8%) nodules were normovascular and 12 (7.0%) nodules were hypervascular.

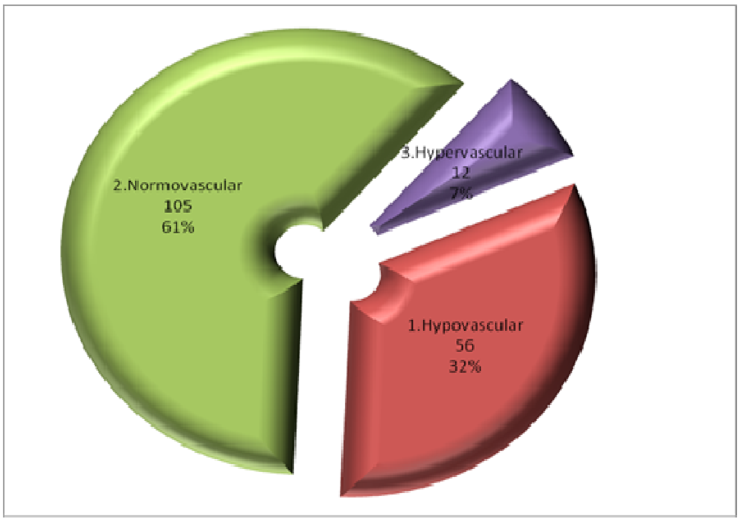


Figure 7: Vascularization of the Thyroid Nodule

43.0% of the benign cases were hypovascular, 54.7% were normovascular and 2.3% hypervascular. Two percent (2.3%) of the malignant cases were hypovascular, 77.3% were normovascular while 20.5% were hypervascular.

Table 16: Intranodal vascularity vs. FNA/Histopathology result.

Vascularization	**Benign (n=129)**	**Malignant (n=44)**	**п p= value**	**Sensitivity %**	**Specificity %**
Hypovascular	43.0%	2.3%	.000	92.0	72.9
Normovascular	54.7%	77.3%			
Hypervascular	2.3%	20.5%			
Total	100.0%	100.0%			

Chi-square test value of 34.813 was established at $p < .001$ which showed statistical significance between increased intranodal vascularity and malignancy at 95% confidence level.

4.6 Relationship between Sonographic appearance and elastography scores

The study looked at the sonographic appearance of the thyroid nodules and their relationship to theelastographic scores obtained.

4.6.1 Echo texture and Elastography scores

Thyroid nodules which had elastographic scores of less than 4, hence likely benign had varied echotexture with 29.8% being hypoechoiec, 39.7% isoechoic and 30.5% hyperechoic. Seventy three (73.8%) percent of thyroid nodules that had elastographic scores of 4 or 5 (likely malignant) were hypoechoic, 21.4 %(9) thyroid nodules were isoechoic while 4.8% (2) were hyperechoic. These findings had a p-value of 0.026.As all the hyperechoeic nodules were benign on histology this may partly explains the false positive findings on elastography.

Table 17: Echo-texture and Elastographic Scores

Echo-texture	Elastographic Scores		p
	<4	≥4	
Hypoechoic	39(29.8%)	31(73.8%)	0.026
Isoechoic	52(39.7%)	9(21.4%)	
Hyperechoic	40(30.5%)	2(4.8%)	
Total	100.0%	100.0%	

4.6.2 Peripheral Halo and Elastography scores.

Regarding presence of a peripheral halo, 73.3% of the thyroid nodules which had elastographic scores of less than 4 (likely benign) hadperipheral halo while 31.0% of thyroid nodules that had elastographic scores of 4 or 5 (likely malignant) had peripheral halo. No significant relationship was seen between the elastographic scores and presence of a peripheral halo at 95% confidence level.

Table 18: Peripheral Halo and Elastographic Scores

Peripheral Halo	Elastographic Scores		p
	<4	≥4	
Present	96(73.3%)	13(31.0%)	0.054
Absent	35 (26.7%)	29(69.0%)	
Total	100.0%	100.0%	

4.6.3 Microcalcifications and Elastography scores.

Majority of the thyroid nodules had no microcalcificationand produced a high elastographic score of 4 and 5 (likely malignant).) showing that the presence of microcalcifications may not impact on the elastography scores.

Table 19: Microcalcifications and Elastographic Scores

Microcalcifications	Elastographic Scores		p
	<4	≥4	
Present	30(22.9%)	12(28.6%)	0.001
Absent	101(77.1%)	30(71.4%)	
Total	100.0%	100.0%	

4.6.4 Intranodal Vascularity and Elastography scores.

Assessment of intranodal vascularity and elastography scores revealed that 39.7% of the thyroid nodules which had elastographic scores of less than 4 (likely benign) were hypovascular while all the hypervascular nodules had an elastography score of 4 and above. This was statistically significant indicating that thyroid nodules with increased vascularity will have higher elastographic scores and will most likely be malignancy. This was confirmed on histology (table 14).

Table 20: Vascularity and Elastographic Scores

Intranodal Vascularity	Elastographic Scores		p= value
	<4	≥4	
hypovascular	52(39.7%)	5(11.9%)	0.017
normovascular	79(60.3%)	25(59.5%)	
hypervascular	0(0.0%)	12(28.6%)	
Total	100.0	100.0	

4.6.5 Sonographic combinations and Elastography versus FNA/Histopathology

Nine solid thyroid nodules had a combination of hypoechogenicity, absent peripheral halo, presence of microcalcifications and hypervascularity (likely malignant) were malignant on FNA/histopathology. Strain ratios of the same showed that 8 out of the 9 nodules had a strain ratio of greater than or equal to 4. This shows that whereas elastography is a good diagnostic test of malignancy in thyroid nodule there is still need for FNA/histopathology correlation

Table 21: Combinations of Sonographic Features

	FNA/Histopathology		**Strain Ratio**	
	Benign	Malignant	<4	>4
Hypoechoic, Peripheral Halo Absent, Microcalcifications, Hypervascular (Likely Malignant)	0(0%)	9(100.0%)	1(11.1%)	8(88.9%)
Peripheral Halo, hypovascular, Microcalcifications Absent, Hyperechoic (Likely Benign)	24(88.9%)	3(11.1%)	25(92.6%)	2(7.4%)

4.7 EXAMPLES

4.7.1 Case one

A 38yr old female patient with history of anterior neck swelling for one year.

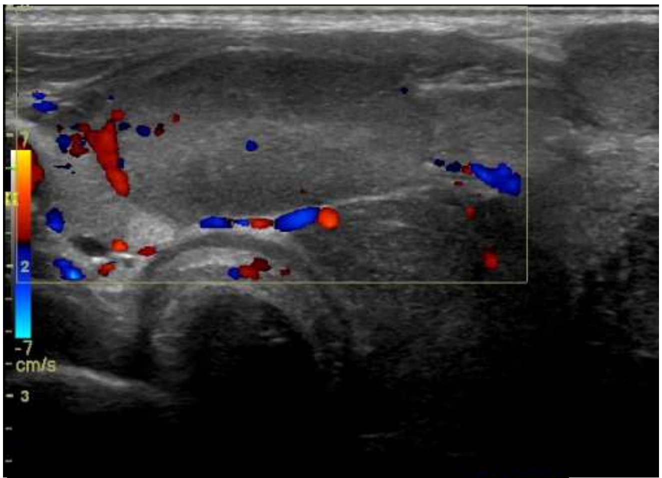
Findings:

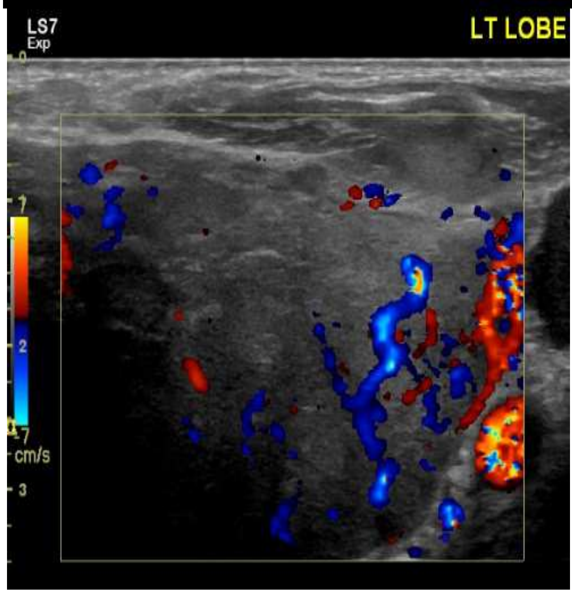
There was a solid hypoechoiec thyroid nodule at the isthmus with type 1 peripheral nodule vascularity. The left lobe was enlarged with coalescent nodular lesions and .increased vascularity was seen within the lobe. The right lobe was normal.

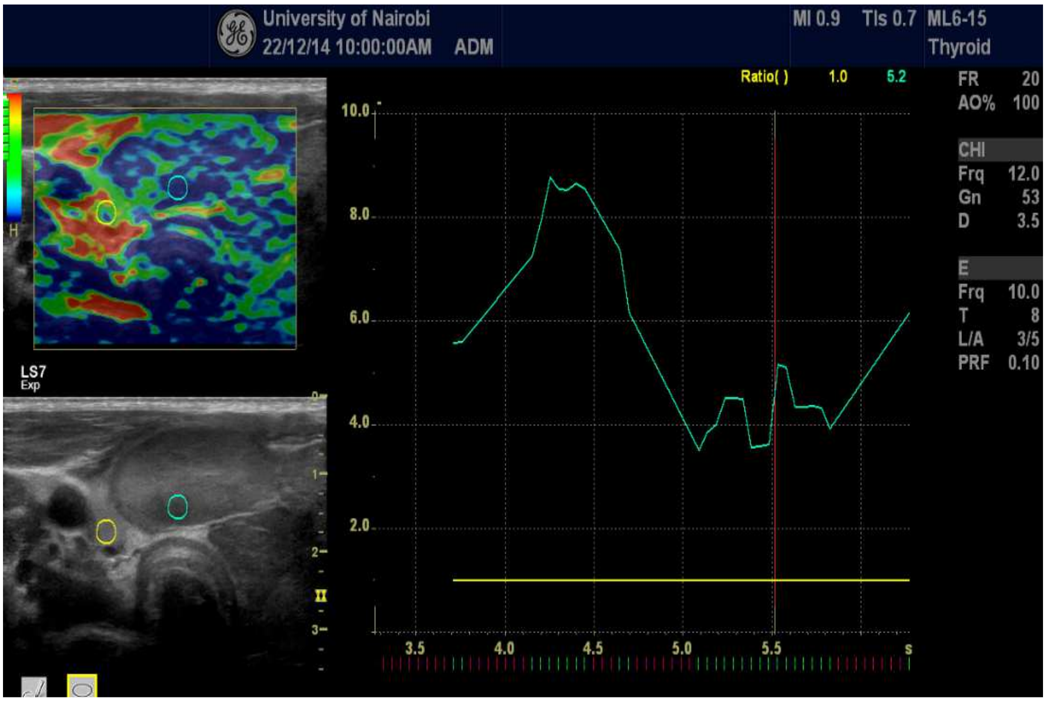
Ultrasound elastography of the nodule at the isthmus showed a predominantly blue colour (elastography score 4) and a high strain ratio of 5.2 was calculated from the Q- analysis.

These elastography findings were suggestive of malignancy.

Fine needle aspiration confirmed the findings.



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4.7.2 Case two

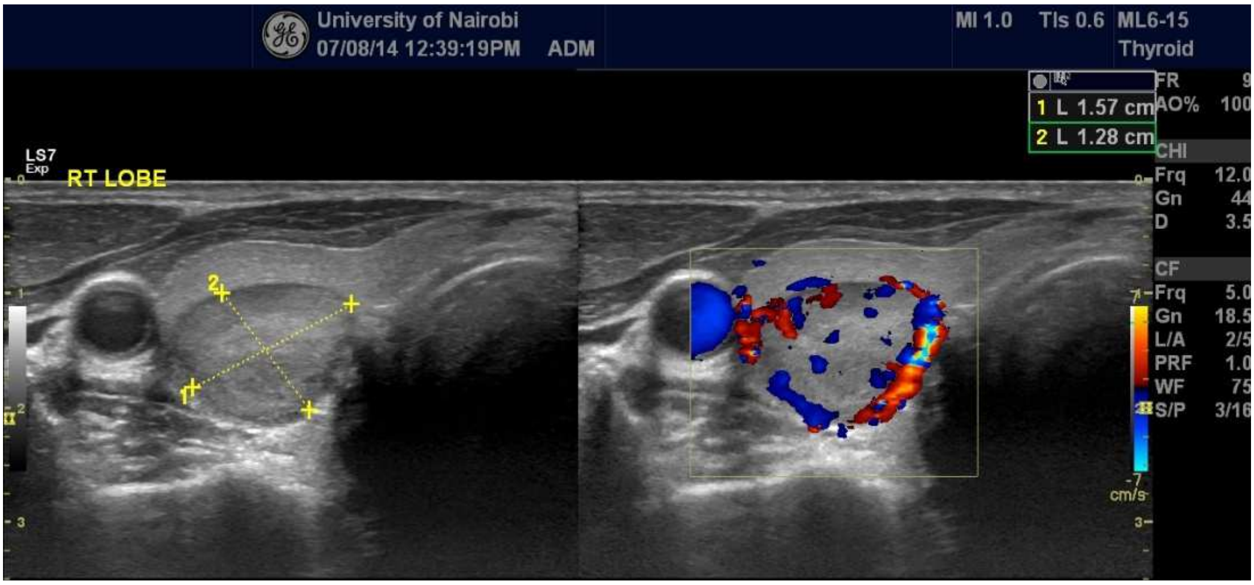
A 42 years old female patient with a 6 month history of anterior neck swelling prior to presentation.

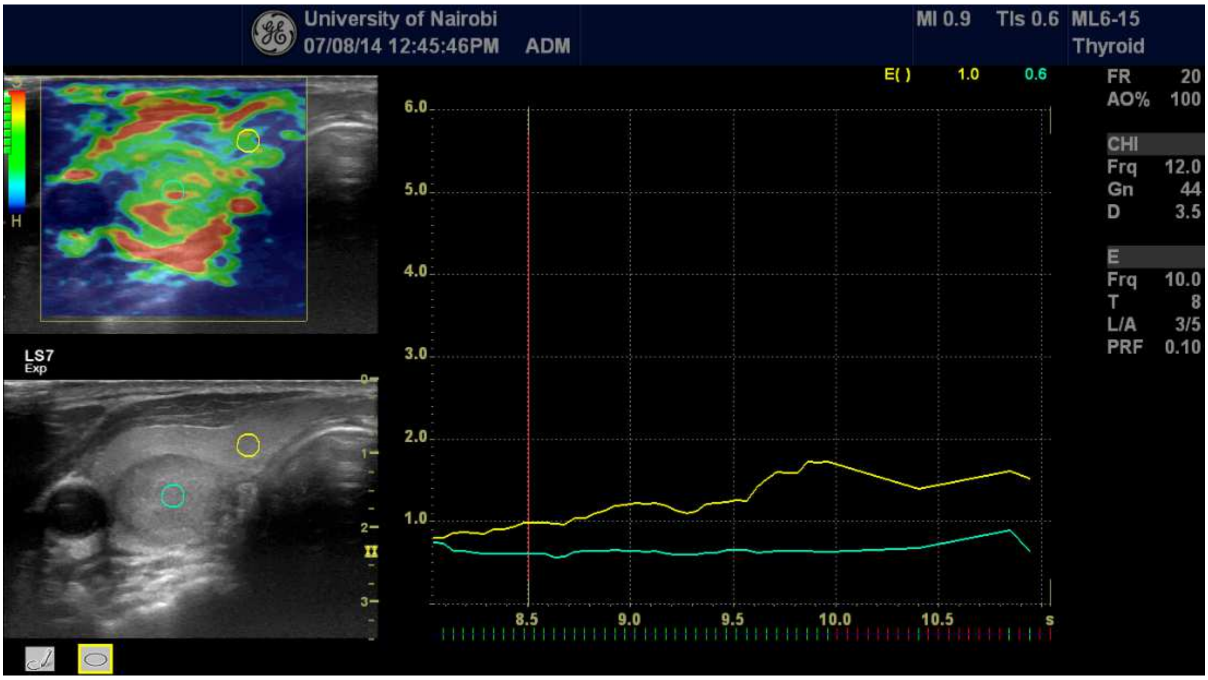
Findings:

There was an isoechoeic solitary thyroid nodule within the right lobe of the thyroid. A peripheral halo and increased intranodal vascularity was seen.

The nodule had a mosaic pattern and was assigned a score of 2. A low strain ratio of 0.6 was obtained after Q- analysis. These results were suggestive of benign disease

This was confirmed true at FNA cytology.





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5.0 DISCUSSION

Our study included 84 patients with 173 solid thyroid nodules. Majority of the patients were female, accounting for 85.7% (72). This correlated well with other studies which have shown female predominance in the occurrence of thyroid nodules [13].

Also noted was an increasing frequency of thyroid nodules with increasing age, peak age being between 40 and 50 years old accounting for 46.4% of the patients seen. A lower frequency was seen in the older age groups greater than 51 years, probably attributed to poor health seeking behaviors in the older population in our country that is dependent on the financial capability of their offspring. Other factors include: low socioeconomic status of the population, presentation at tertiary institutions in the rural areas without referral to the national hospital (KNH) for specialist care and co-morbidities occurring beyond this age causing mortality. These were also identified as factors contributing to a low frequency of patients presenting after the age of 70 years in a local dissertation on thyroid disease done KNH**.** [13]

A greater proportion of patients up to 63% enrolled in the study had multiple thyroid nodules as opposed to 19% of them who presented with a solitary thyroid nodule. This correlated well with studies that showed that additional thyroid nodules were demonstrated during ultrasound imaging in those initially thought to have a solitary thyroid nodule by palpation[2] This indicates the higher sensitivity of ultrasound when compared to palpation in the detection of thyroid nodules.

Various B-mode characteristics of the thyroid nodules were examined before elastography (table 9, 10, 11 and 12). This demonstrated that no single sonographic feature can confidently distinguish benign and malignant thyroid nodules. This is in agreement with previous studies doneby Frates MC et al in 2005,Papini et al (2002) and Jason D. Iannuccil et al (2004) where they evaluated the various sonographic characteristics in differentiating benign and malignant thyroid nodules.[2, 4, 25].

Various combinations of conventional ultrasound characteristics of thyroid nodules have been described by various authors that are highly suggestive of malignancy. These characteristics show increased specificity at the expense of its sensitivity[2, 4, 25].This finding was well demonstrated in the study in which only 9 out of 44 malignant thyroid nodules were identified using a sonographic combination of likely malignant characteristics comprising of hypoechogenicity, absent peripheral halo, presence of micro calcifications and intranodularhypervascularity(table19).

In view of this limitation in conventional ultrasonography, our study therefore sought to evaluate the diagnostic accuracy of elastography in the differential diagnosis of solid thyroid nodules and found a sensitivity of 90.9% and specificity of 96.9 %, PPV 70% and NPV 92.6% at 95% confidence using the elastography color score system. These findings correlated well with several reviewed studies with similar ranges of sensitivity specificity and diagnostic accuracy by Y. Hong et al (2009), Hafez et al (2013), Carmela Asteria et al (2008) and Hui Wang et al (2013)[1,14,16,18].Five false negative cases were identified on elastography color score system that on B-mode showed varied sonographic characteristics with only a normal vascularity being a common sonographic characteristic amongst them all on color Doppler. Four of the false positive results were follicular neoplasms (Thy3) and one was a follicular carcinoma. These nodules were soft on elastography therefore markedly reducing its utility. Similar findings have been shown in studies done. [17]

Offline strain ratio acquisition on the solid thyroid nodules showed a sensitivity of 88.6% and specificity of 96.1% in the differential diagnosis of solid thyroid nodules. Using the ROC curve, the best cut off strain ratio was obtained at 3.5.

The similar specificity and lower diagnostic accuracy of strain ratio compared to that of elastography score system could be attributed to the 0.5 higher strain ratio used in the study compared to the 3.5 obtained as the best cut off in the ROC curve. This could have attributed to some of the false negative results seen on offline strain ratio acquisition.

This study has revealed a good linear relationship between the elastography scores and the strain ratios obtained when correlated to FNA and histopathology findings (R=0.615, p=0.037, and R=0.846, p= 0.011 respectively) deducing that the elastography scores correlated with the strain ratio findings and FNA or histopathology findings. This supports the importance and utility of either qualitative and/or quantitative strain elastography and correlates with similar studies which found no added advantage of strain ratio acquisition over color mapping [10].

This study also went ahead and assessed the relationship between the elastography and the B-mode ultrasound findings. It was observed that a varied thyroid nodule echogenicity was seen for both high (likely malignant) and low (likely benign) elastography scores. Presence of microcalcifications was not seen to impact on the elastography score obtained, this was shown by the fact that majority of the nodules (71.4%) did not have microcalcifications and still produced a high elastography score. All thyroid nodules with increased vascularity on color Doppler showed high elastography scores of 4 and 5 with a p value of 0.017.

No significant conclusion could be drawn from presence of a peripheral halo and high or low elastography scores.

6.0 CONCLUSION

The study has shown that although ultrasound elastography of solid thyroid nodules can be utilized as an additional tool in screening of nodular thyroid disease with a diagnostic accuracy of 93.1%:- it still has a 5% chance of giving false positive and false negative findings. This effectively reduces the usefulness of strain elastography in the evaluation of thyroid nodular disease. In view of this fine needle aspiration (FNA) cytology or histopathology is required to conclusively determine the nature of a solid thyroid nodule.

In view of this finding US elastography has no additional value for inclusion in the imaging protocol for thyroid nodular disease

7.0 RECOMMENDATION

Elastography should not be used in isolation in the differential diagnosis of nodular thyroid disease and should therefore not be implemented as an isolated routine screening tool routine in our setting.

Multicentric studies are still recommended to further justify its role in thyroid nodular disease.

Further assessment of elastography findings for specific cytopathology and histology findings is recommended in view of the possible soft consistency of follicular neoplasms.

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APPENDICES

APPENDIX I

PATIENT INFORMATION DOCUMENT:

ULTRASOUND ELASTOGRAPHY IN THE EVALUATION OF SOLID THYROID NODULES

This study involves carrying out an ultrasound examination on the front area of the neck on an organ called the thyroid gland and thereafter documenting the results.

Aim of this study is to assess how accurate this examination is in identifying suspicious characteristics in a thyroid mass and thus necessitating early treatment of cancerous masses.

No risk is involved in this examination, as it does not use ionizing radiation and it is noninvasive.

The examination results will in turn increase the confidence level of the primary physician when making a diagnosis.

Prior to the examination one will be required to answer a few questions, mainly on their bio data.

The examination is short and relatively painless. It only requires one to extend the neck while the examiner uses an ultrasound device to examine. Gentle pressure may be applied in the course of the examination.

The thyroid ultrasound elastography results will be compared with those from a Fine Needle Aspiration Cytology or Histology results of the thyroid swelling under investigation .This is for better and comprehensive management of the disease. The fine needle aspirate cytology will be carried out by the pathologist after the ultrasound examination.

No additional cost will be incurred apart from what the primary physician has prescribed in the management plan.

Confidentiality will be observed within the extent allowed by the law.

APPENDIX II

VIDOKEZO MUHIMU KUHUSU UTAFITI WA THYROID ULTRASOUND.

ULTRASOUND ELASTOGRAPHY KWA KUCHUNGUZA UVIMBE WA KIUNGO CHA THYROID.

Utafiti huu wa ultrasound utafanywa kwenye shingo, ili kuangalia kiungo kinacho itwa '*thyroid gland*'.

Utafiti huu utasaidia wauguzi kutafautisha uvimbe aina aina za thyroid. Hii itasaidia kuanza matibabu mapema kwa uvimbe zenye cancer. Kabla ya utafiti huu maswali kadhaa yataulizwa kuhusu ukoo wako.

Picha hii ya *ultrasound* inachukua muda mfupi, na haina uchungu wowote ila uzito kidogo kutokana na kufinyilia kifaa cha *ultrasound* kwenye shingo. Ultrasound haina madhara yoyote kwa binadamu.

Matokeo ya picha hii italinganishwa na matokeo ya pathologia, ili kuwezesha matibabu yenye hali ya juu kuhusu uvimbe wa thyroid. Pathologia itafanywa punde tu picha ya *ultrasound* itakapo malizwa.

Hakuna malipo juu ya yale uliyoandikwa na daktari wa kwanza. Haki zako zitalindwa kamili. Habari utakayo toa ama ile itakayo patikana kukuhusu itawekwa siri wakati wote, na itatumika katika utafiti huu tu.

APPENDIX III:

Patient consent form

My name is Dr. Diana Nyakoe, a postgraduate student in the department of Diagnostic Imaging and Radiation Medicine at the University of Nairobi. I am carrying out a study on evaluation of thyroid nodules using ultrasound elastography.

All the information concerning this study is the patient information document provided.

I would like to recruit you in this study. Information obtained from you will be treated with confidentiality. Only your hospital number will be used. Please note that your participation is voluntary and you have a right to decline or withdraw from the study.

For any questions, clarifications, or comments concerning his study, please contact the chief investigator or the Ethics and Research Committee. Contacts are provided below.

Patient number: _______________ Signature: __________________

Date: _________________

I certify that the patient has understood and consented participation in the study.

Dr. Diana K. Nyakoe (Chief invesigator) 0722 957215

Signature ___________________ Date _______________________

ETHICS AND RESEARCH COMMITTEE.

KNH/UON-ERC

P.O. Box 20723, Nairobi

TELEPHONE NO : (254-020) 2726300 Ext 44355

APPENDIX IV

Kibali cha kushiriki katika utafiti

Jina langu ni Daktari Diana K. Nyakoe, mwanafunzi katika chuo cha udaktari, Chuo Kikuu cha Nairobi. Ninafanya utafiti kuhusu uvimbe zinazopatikana kwa kiungu cha thyroidi (thyroid gland kwa kiingereza) nikitumia *sonoelastography.*

Ni muhimu kuelewa ya kwamba ushiriki ni wakujitolea, sio lazima kushiriki katika utafiti huu, na pia waweza kubadili nia yako wakati wowote kuhusu kuendelea kushiriki, bila ya kuathiri huduma zako za kiafya.

Asante sana kwa ushirikiano wako. Nimekubali kwamba nimeelezewa kikamilifu kuhusu utafiti huu na nakubali kushiriki.

Kwa maswali yoyote kuhusu huu utafiti huu, tafadhali pigia mtafiti mkuu ama Ethics and Research committe.

Nambari ya mgonjwa: __________ Sahihi: ____________ Tarehe:____________

Nimekubali kwamba nimeeleza kikamilifu kuhusu utafiti huu na mgonjwa amekubali kushiriki.

Dr. Diana K. Nyakoe (Mtafiti Mkuu) 0722 957215

Sahihi: ____________________ Tarehe: ________________________

ETHICS AND RESEARCH COMMITTEE.

KNH/UON-ERC

P.O. Box 20723, Nairobi

TELEPHONE NO: (254-020) 2726300 Ext 44355

APPENDIX V

QUESTIONNAIRE: DATA COLLECTION FORM

Form N^{o}: __________

DATE:________________________

DEPARTMENT NUMBER: ________________________

Please tick where appropriate.

1. **AGE:**

   18 – 28 ☐

   29 – 39 ☐

   40 – 50 ☐

   51 – 61 ☐

   62 – 72 ☐

   73 – 83 ☐

   >84 ☐

2. **SEX:**

   Male ☐

   Female ☐

3. **NUMBER OF NODULES**

   1 ☐

   2 ☐

   3 ☐

   >3 ☐

4. **SONOGRAPHIC FINDINGS:**

Please tick where appropriate

NB: thyroid nodules seen will be tagged in a clockwise manner A1, A2 etc.

Nodule	A1	A2	A3
Echogenicity 1. Hypoechoic			
2. Isoechoic			
3. Hyperechoic			
Peripheral Halo 1. Present			
2. Absent			
Microcalcifications 1.Present			
2.Absent			
Vascularization 1.Type 0 (hypovascular)			
2.Type 1(peripheral)			
3.Type2 (intranodal)			
Elastography Findings 1.Score 1			
2.Score 2			
3.Score 3			
4.Score 4 5. Score 5 Strain Ratio			

Fine Needle Aspirate 1.Benign disease			
2.Malignant disease			
Histopathology Report 1.Benign			
2.Malignant			
3.Not applicable			

N.B

ELASTOGRAPHY FINDINGS

Using the indicated elastography scale, please tick the appropriate score.

Thank you for your participation.

The elasticity score is color based as follows:

SCORE 1 - The nodule evenly displays green. (Red, green and blue)

SCORE 2 - The nodule displays all three colors (mosaic pattern) i.e. red green and blue.

SCORE 3 - the nodule displays green at the periphery with a blue center.

SCORE 4 -The nodule displays predominantly blue and surrounding tissue green and red.

SCORE 5 - The nodule and surrounding tissue is displayed completely in blue.

APPENDIX VI

Characteristics of patients with thyroid nodules at KNH

Characteristic	Number (n)	Percent (%)
Age		
18-28	______________	(______________)
29-39	______________	(______________)
40-50	______________	(______________)
51-61	______________	(______________)
62-72	______________	(______________)
73-83	______________	(______________)
>84	______________	(______________)
Sex		
Male	______________	(______________)
Female	______________	(______________)
Thyroid nodules		
1	______________	(______________)
2	______________	(______________)
3	______________	(______________)
>3	______________	(______________)

Sonographic characteristics of thyroid nodules in patients at KNH

Nodule characteristic	Number (n)	Percent (%)
Echogenicity		
Hypoechoic	______________	(______________)
Isoechoic	______________	(______________)
Hyperechoic	______________	(______________)
Peripheral halo	______________	(______________)
Vascularisation	______________	(______________)
Site		
A1	______________	(______________)
A2	______________	(______________)
A3	______________	(______________)
Malignancy		
Histopathology	______________	(______________)
Fine needle aspiration	______________	(______________)
Elastography finding		
Score 1	______________	(______________)
Score 2	______________	(______________)
Score 3	______________	(______________)
Score 4	______________	(______________)
Score 5	______________	(______________)

Predictive value of elastographic scores for cytology/ histopathology

	Histopathology/ Cytology	
PART A	Malignant (n)	Benign (n)
Strain ratio		
<cut-off value	______________	______________
>= cut-off value	______________	______________
Part B		
Strain ratio performance (>=cut-off value)	**Percent (%)**	**95% CI**
Sensitivity	______________	(______ - ________)
Specificity	______________	(______ - ________)
Positive predictive value	______________	(______ - ________)
Negative predictive value	______________	(______ - ________)
PART C		
Area under ROC	**Area (%)**	**95% CI**
Cut-off value1	______________	(______ - ________)
Cut-off value2	______________	(______ - ________)
Cut-off value3	______________	(______ - ________)

APPENDIX VII:

Thyroid cytopathology was reported using Bethesda system, which is a universally accepted system of reporting thyroid FNA results. These include:

Thy 1- non diagnostic for cytological diagnosis / unsatisfactory

Thy2 **–** Non neoplastic / benign: including hyperplastic nodules, colloid nodules

Thy 3 **–** Neoplasm possible: majority of lesions in this category are follicular neoplasms. It is whereby the exact nature of the lesions cannot be determined solely by FNA cytology.

Thy 4 **–**Suspicious for malignancy, but they don't allow a confident diagnosis of malignancy. Upto 75% turn out malignant.

Thy 5 **–** Malignant

APPENDIX VIII

BUDGET

ITEM	QUANTITY	UNIT PRICE (Kshs)	TOTAL (Kshs)
WRITING PENS	1 BOX	200	200
NOTEBOOKS	5 PIECES	100	500
FILES	8 PIECES	100	800
PRINTING PAPER	5 RIMS	500	2500
CARTRIDGE	1 PC	6000	6000
INTERNET SURFING	4GB DATA	4000	4000
FLASH DISCS	2 PCS	1000	2000
PRINTING DRAFTS AND FINAL PROPOSAL	10 COPIES	500	5000
PHOTOCOPIES OF QUESTIONNAIRES	100 COPIES	10	1000
PHOTOCOPIES OF FINAL PROPOSAL	6 COPIES	100	600
BINDING COPIES OF PROPOSAL	6 COPIES	60	360
ETHICAL REVIEW FEE	1	2000	2000
SUBTOTAL			**24960**
PERSONNEL			
BIOSTATISTICIAN	1	20000	20000
SUBTOTAL			**20000**
DATA COLLECTION, DATA ANALYSIS AND THESIS DEVELOPMENT			
PRINTING OF THESIS DRAFTS	10 COPIES	1000	10000
PRINTING FINAL THESIS	6 COPIES	1000	6000
BINDING OF THESIS	6 COPIES	300	1800
DISSEMINATION COST			10000
SUBTOTAL			**27800**
CONTINGENCY (10% OF TOTAL BUDGET)			7276
GRAND TOTAL			**80036**

APPENDIX IX:

TIMETABLE.

Activity	Action by	Period																
		Oct 13	Nov 13	Dec 13	Jan 14	Feb 14	Mar 14	Apr 14	May 14	Jun 14	Jul 14	Aug 14	Sep 14	Oct 14	Nov 14	Dec 14	Jan 15	Feb 15
Writing Research Proposal	Student																	
Revising and Finalizing Proposal	Student & Supervisor																	
Ethical Approval	KNH-ERC																	
Data Collection	Student R. Assistant																	
Data Checks and Cleaning	Student																	
Data Analysis and Interpretation	Student Biostatistic-ian																	
Writing up	Student Supervisor																	
Dissertation submission	Student																	

APPENDIX X: KNH/UON-ERC APPROVAL LETTER

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke
Link:www.uonbi.ac.ke/activities/KNHUoN

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/RR/523

21st August 2014

Dr. Diana K. Nyakoe
Dept.of Diagnostic Imaging &Rad.Medicine
School of Medicine
University of Nairobi

Dear Dr. Nyakoe

Research proposal: Ultrasound Elastography in the Evaluation of Solid Thryoidnodules (P458/07/2014)

This is to acknowledge receipt of your research proposal and inform you that upon review the KNH/UoN-ERC made the following observations and suggestions:

1. Take note of the numerous typographical and grammatical errors throughout the text.
2. in abstract define study variables and statistical analysis to be used.
3. Sample size of 84 does not seem to take into consideration your exclusion criteria number 4 and 5.
4. Ethical issues
    a) Provide an itemized consent information document separately from the consent form. This must be concise and yet comprehensive, clearly highlighting the benefits and risks entailed in participation. Who shall pay for the multiple repeat investigations that may be indicated? A Kiswahili translation of this information is mandatory.
    b) Tone down language of consent to level of average Kenyan.
    c) State fate of all collected raw data at conclusion of study.
    d) Consent does not advise participants firstly a needle aspirate (or biopsy) will be taken and secondly that sonography and histological results will be compared.
    e) Include telephone number for ERC.
5. Data analysis
    - Cleary state statistical methods to be used in this study. There is more detail within text than in 6.8.2.
    - Include dummy tables of results.
6. References
    i. There are a significant number of incomplete references.
    ii. Two references in this section do not appear in the text.
    iii. Maintain consistency in the following use of 'et all', position of placement for year publication, use of first names as opposed to initials.
    iv. Remove 'MD' from references.

Protect to discover

Recommendation
Revise and resubmit three(3)copies of the proposal within a period of eight(8)weeks time with effect from the date of this letter for further processing.

Yours sincerely

PROF. M.L. CHINDIA
SECRETARY , KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chair, KNH/UoN-ERC
The Dean, School of Medicine, UoN
The Chairman, Dept. of Dignostic Imaging & Rad. Medicine UoN
Supervisors: Prof. Joseph M. Kitonyi, Dr.Gladys Mwango

Protect to discover