"ROLE OF ULTRASONOGRAPHY AND ELASTOGRAPHY IN DIFFERENTIATING BENIGN FROM MALIGNANT BREAST MASSES WITH PATHOLOGICAL CORRELATION"

By

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DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR, KARNATAKA

In partial fulfilment of the requirements for the degree of

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IN

RADIODIAGNOSIS

Under the Guidance of

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Dr. PARAMESHWAR KEERTHI B.H.

LIST OF ABBREVIATIONS

ARFI – Acoustic Radiation Force Impulse

B – Benign

BA- Breast Abscess

B-C – Benign Cyst

BGR – Blue-Green-Red

BIRADS – Breast Imaging Reporting and Data System

CA – Carcinoma

CECT – Contrast Enhanced Computed Tomography

CT – Computed Tomography

DBT – Digital Breast Tomosynthesis

DCE – Dynamic Contrast Enhancement

EI – Elastographic Index

Elasto – Elastography

FA - Fibroadenoma

FCD – Fibrocystic Disease

FDG – Fluorodeoxyglucose

FNAC – Fine Needle Aspiration Cytology

HPE – Histopathological examination

ICP – Intracystic papilloma

IDC – Infiltrating Ductal Carcinoma

L – Left

MHz – Mega Hertz

MRI – Magnetic Resonance Image

MRM – Magnetic Resonance Mammogram

NPV – Negative Predictive Value

PEM – Positron Emission Mammography

PET – Positron Emission Tomography

PT – Phyllodes Tumor

PPV – Positive Predictive Value

R – Right

SCC – Squamous cell carcinoma

SR – Strain Ratio

SWE – Shear Wave Elastography

TB – Tuberculosis

TDLU – Terminal Duct Lobular Units

USG – Ultrasonography

ABSTRACT

Background: Elastography has the potential to improve specificity of breast ultrasound in differentiating benign from malignant mass, thereby reducing the number of benign biopsies.

Purpose: The objectives of the study were to evaluate morphology of the breast masses with routine ultrasonography and elastography, to assess the role of elastography and conventional B-mode ultrasonography in differentiating benign from malignant breast masses and to correlate elastography and B-mode ultrasonography results with pathological findings.

Material and Methods: This prospective observational study was conducted over a period of eighteen months from January 2018 to June 2019 on 86 patients with 101 clinically palpable breast lump who underwent sonomammography and elastography of breast. Baseline data, ultrasound features (BIRADS classification), modified colour score and mean strain ratio was recorded and compared with final diagnosis.

Results: There were total of 101 breast lesions in 86 patients. There was increasing trend in malignant cases with increasing age. Ultrasound showed sensitivity of 89.8%, specificity of 96.15%, positive and negative predictive values of 95.65% and 90.91% respectively and overall diagnostic accuracy of 93.07%. Modified colour score showed sensitivity of 65.2%, specificity of 75.8%, positive and negative predictive values of 87% and 46.8% and overall diagnostic accuracy of 68.32%. A new modified colour score showed sensitivity of 97.8%, specificity of 87.0%, PPV of 86.79% and NPV of

87.08% with a diagnostic accuracy of 92.08%. The risk of missing a malignant case with the new colour score was 2.1%. Mean strain ratio showed sensitivity of 100%, specificity of 98.11%, positive and negative predictive values of 97.96% and 100% respectively and diagnostic accuracy of 99.01%.

Conclusion: Elastography can play a major role in differentiating benign from malignant breast masses and should be performed whenever available. We recommend a new modified colour scoring system to categorize the lesions as benign and malignant. A mean strain ratio cut off of 3.25 effectively helps to differentiate benign from malignant lesions with high diagnostic accuracy.

Keywords: elastography, ultrasonography, modified colour score, BIRADS, mean strain ratio, strain elastography, breast lesion, carcinoma breast, fibroadenoma, phyllodes tumour, infiltrating ductal carcinoma, breast abscess, mastitis, fibrocystic disease of breast, breast mass, breast cancer.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

India constitutes one third of global breast cancer along with China and USA. India is facing an increase in incidence of breast cancer as well as and mortality rate due to breast cancer. Recent epidemiological surveys show an alarming increase in rate of breast cancer incidence in Indian women, making it the most common cancer among all. From 2012, a 13.8% increase in mortality rate because of breast cancer is observed. Survival rate of patients with breast cancer is among the lowest in India when compared with developed and as well as some developing countries[1].

Lack of awareness, education and lack of screening programs are the leading causes for delay in diagnosis of breast cancer. Most of the patients present with advanced stages of breast cancer, thus making treatment difficult. Locally aggressive lesions or distant metastases are the causes for death in breast cancer[1].

Relatively slow progression of breast cancers has made it possible to explore newer diagnostic techniques. Currently, pathological examination is the standard investigation to differentiate benign from malignant breast mass. It is however, an invasive procedure and yields a benign diagnosis in more than 75% of patients, making it challenging to deploy effective cancer screening programs[1].

Breast cancers are generally harder than normal breast tissue. Many non-palpable lesions are detected by routine ultrasound technique but findings are equivocal in many cases making it difficult to differentiate benign from malignant lesions. Elastography can provide additional information about tissue stiffness or hardness. This data is helpful as it can help differentiating malignant lesions which are usually hard from benign lesions, which are relatively softer[2].

The basic principle in elastography is similar to clinical palpation. In this technique, the relative stiffness or strain on the tissue in response to manual force applied is calculated. Strain elastography is now being used to assess various structures like breast, prostate, liver, blood vessels, thyroid, and musculoskeletal structures. Breast is currently most widely and successfully imaged with elastography[2].

Elastography has the potential to improve specificity of breast ultrasound in differentiating benign from malignant mass, thus reducing the number of benign biopsies. We performed this study to evaluate if elastography can help differentiate benign from malignant lesions of the breast.

AIMS AND OBJECTIVES

The aims and objectives of the study were:

1. To evaluate morphology of the breast masses with routine ultrasonography and elastography.

2. To assess the role of elastography and conventional B-mode ultrasonography in differentiating benign from malignant breast masses.

3. To correlate elastography and B-mode ultrasonography results with pathological findings.

REVIEW OF LITERATURE

DEVELOPMENT OF BREAST

Breast is a derivative of ectoderm and mesoderm (Figure 1). Lactiferous ducts are ectodermal derivative whereas connective tissues, fat cells, vessels and muscles are mesodermal in origin[3].

Development of mammary gland involves two stages, which are formation of primary breast bud followed by development of rudimentary mammary glands. During the first trimester at fourth to sixth week of gestation, mammary-specific progenitor cells appear. By 35th week of gestation, these progenitor cells proliferate in the epidermis to form mammary crest. Proliferation of progenitor cells extends in a line from fetal axilla to inguinal region thus forming milk line of Schultz[3].

First Trimester

Mammary buds are developed by the end of first trimester. Epithelial cells followed by the mesenchymal cells start to develop (Figure 1). The mesenchymal cells give rise to blood vessels, fibroblast, myocytes and fat cells[4].

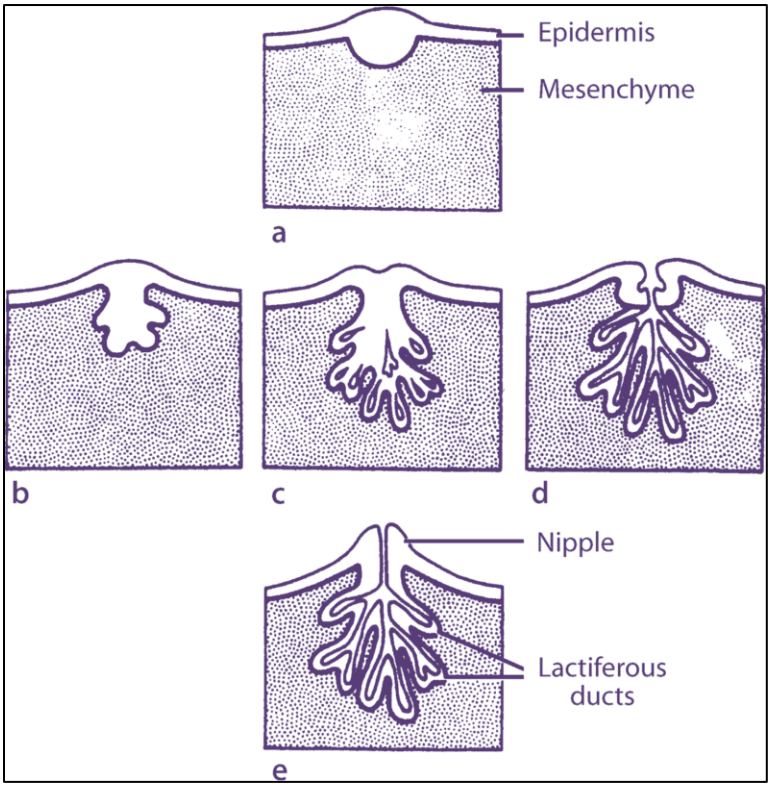

Figure 1. Development of the breast. a–e stages in development of duct and formation of glandular tissue from the epidermis. Connective tissue septa develops from mesenchyme. Nipple shows eversion near birth.

Second Trimester

In second trimester, there is development of secondary breast bud. It is an epithelial derivative that arises from primary breast bud. During the development, mesenchymal tissue is seen surrounding the primary breast bud. The secondary breast bud develops during the second trimester which invades into mesenchymal tissue and further divides & channelizes to forms multiple canal like structures called as lactiferous ducts. Two layers of epithelial cells are present in ducts. One layer is lines the lactiferous ducts and is secretory in nature. Another

layer forms the basement layer that gives rise to myoepithelial cells. At 24 to 28 weeks of intrauterine life, well-defined breast architecture is developed[4].

Third Trimester

Development of nipple areola complex starts in the third trimester. Portion of the epidermis that gives rise to nipple will initially form a depression called mammary pit. Lactiferous ducts developed in the second trimester will drain into ampulla in the retroareolar region[2]. These retroareolar ampullae converge onto the mammary pit forming nipple. Further, proliferation of smooth muscle fibres from mesoderm will clearly delineate the nipple. Areola is the derivative of ectoderm that is developed during second trimester[4].

Glandular tissue developed in term infants contain 16 – 20 lobes. Each of the lobes have lactiferous ducts. The lactiferous ducts open into the skin pit through the mammary pit. Breast is fixed to the underlying pectoralis muscle by Cooper's ligament and skin provides support to the breast glandular tissues. Nipple is inverted during birth and elevated from the skin surface at childhood[3].

Infant Breast

Important period for development of mammary glands is after birth is upto 2 years of age. After that, till puberty, no significant increase in the size of gland

noted. No gender-based difference in the size of the breast at birth. Fall in the levels of maternal oestrogens in the neonate will stimulate the pituitary gland and produce prolactin, which leads to unilateral or bilateral breast enlargement with transient secretion of milk in about 70% term neonates. It has been speculated that the infant breast undergoes stimulation at approximately 3 to 4 months postnatally through a surge of the infant's hormone[4].

Pubertal Breast

Dimorphic breast differentiation starts during puberty. Human breasts become sexually distinct at this period of time. Estrogen is the sex hormone which has main role in its development. According to Tanner staging, growth of breast tissue is the major indicator of development[4].

Elevation of papilla is the anatomic changes noted in the stage I of Tanner (Figure 2). Stromal and parenchymal development does not occur at this stage. Breast development is secondary sexual character, first to occur. It is usually, succeeded by pubic hair development. Growth hormone is important for estrogen surge which leads to pubertal breast development. Other important function of the growth hormone is stimulation of IGF -1 (Insulin like-growth factor -1) in the mammary gland. These hormonal changes occur between 8 and 13 years of age. No clinically significant breast development beyond 14 years needs to be evaluated with further investigation[4].

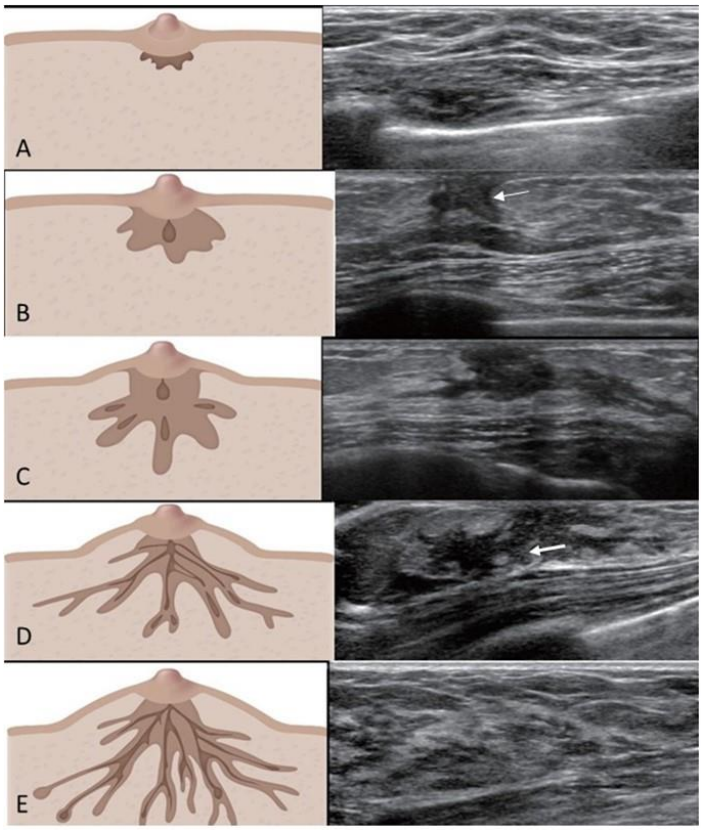

Figure 2. Tanner stages A) Stage 1. Clinically papilla visualized. On ultrasound a small echogenic subareolar area is seen. B) Stage 2. Clinically both the papilla and breast are seen with small enlarged areolar diameter. On ultrasound the subareolar breast bud (thin white arrow) is seen as hypoechoic structure and breast parenchyma, composed of adipose tissues and loose connective tissues are seen as hyperechoic structure. C) Stage 3. Palpable subareolar nodule with enlargement of breast and areola. USG - hyperechoic central spider-like fibroglandular tissue extension with hypoechoic retroareolar ducts systems. D) Stage 4. Secondary mound above the breast is formed. USG shows more widely elongated hypoechoic breast bud and loss of rounded appearance (thick white arrow). Subcutaneous fat is present. E) Stage 5. USG - mature breast showing heterogeneous breast parenchyma with echogenic glandular and stromal tissue. Also noted abundant subcutaneous fat.

ANATOMY OF BREAST / MAMMARY GLAND

Anatomy of mammary gland

Mammary gland (Breast) is secondary sexual structure that helps in feeding neonates. Mammary gland is a modified sweat gland. It extends superoinferiorly from second to sixth rib. Mediolaterally the breast extends from sternum to mid axillary line. Upper and outer quadrant of the breast extends further laterally along the inferior and lateral edge of the pectoralis major muscle and forms axillary tail of Spence[5].

Deep pectoral fascia forms the bed over which the breast lies. Deep to the deep pectoral fascia are pectoralis major, serratus anterior and external oblique muscle and its aponeurosis. Pectoralis major and serratus anterior are located superiorly and external oblique muscle is located inferiorly[5].

Anatomy of nipple and areola

Nipples are anterior projections from the center of the breast. Position of nipples vary in the women depending upon the puberty and parity; however most

commonly in young adult females and males, it lies along the mid clavicular line over the 4th intercostal space, almost 20 to 23 cm inferior from the suprasternal notch (Figure 3). Colour of the nipples vary from pink colour in nulliparous to dark brown in child bearing mothers due to deposition of melanin[5].

Sweat glands and sebaceous glands are situated in the nipple and areola and secrete sebum that serves as a lubricant during lactation and prevents cracking and soreness of the nipple. Montgomery's tubercles are the sebaceous glands that are visible in lactating mothers which are located around the nipple and areola complex[5].

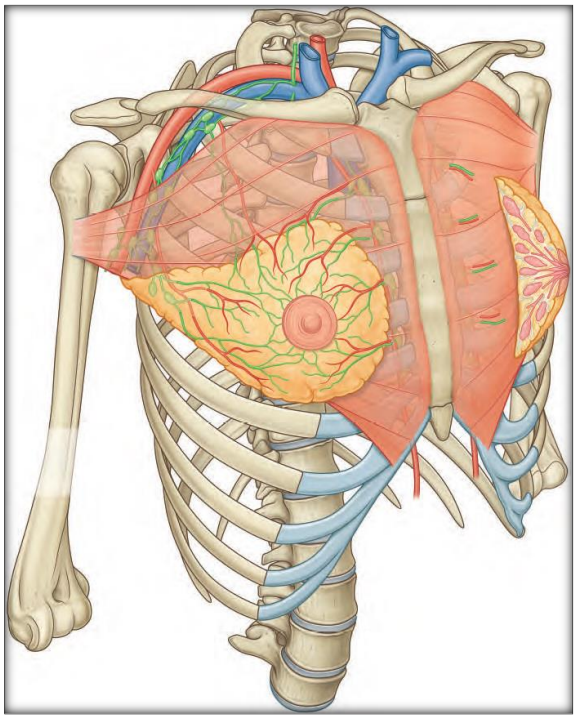

Figure 3. Location of mammary gland.

Composition of Mammary gland

Human breast is composed of stroma and parenchyma. The breasts architecture is composed of glandular tissues and connective tissue called stroma. Parenchyma of breast is composition of glandular tissues consisting of branching ducts and terminal secretory lobules. Terminal duct forms the functional unit which secretes milk during lactation. The connective tissues are seen surrounding as well as within the glandular structures[4].

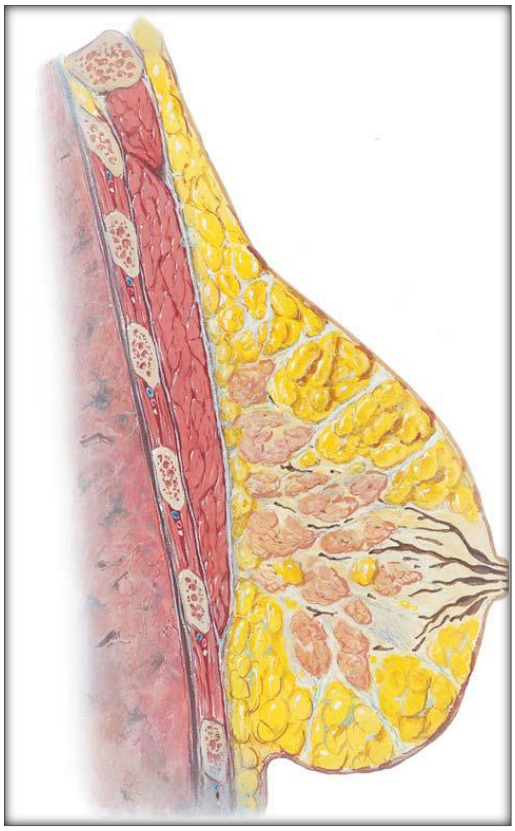

Figure 4. Mammary Gland – Normal Anatomy.

These connective tissues are called as stroma. Stroma surrounding the glandular structures is dense and fibrocollagenous, whereas intralobular connective tissue has a loose texture that allows the rapid expansion of secretory tissue during pregnancy. Interlobular stroma is composed of fat. Increase in the size and number of adipose tissue responsible for increase in the breast size during puberty[5].

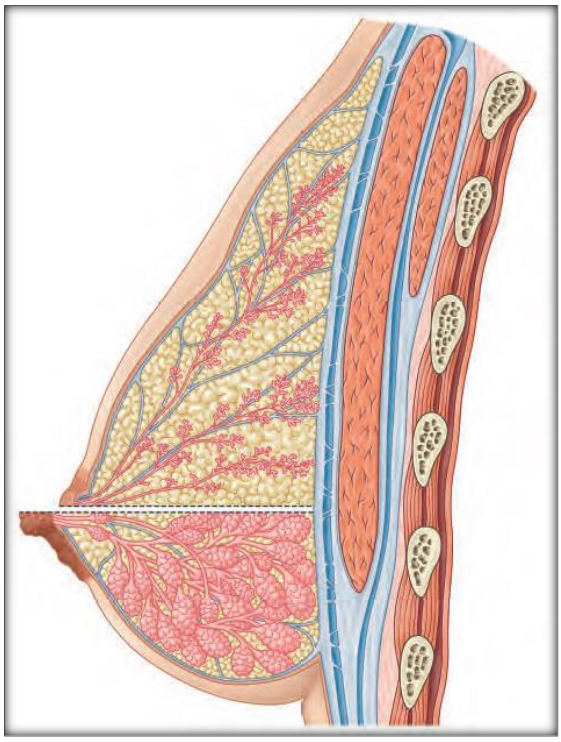

Figure 5. Changes in breast during lactation

Suspensory Ligament

Astely Cooper ligament is the suspensory ligament of the breast that is derived from the fibrous strand that contains collagen extending between the deep

fascia and muscles. It is well developed in the superior quadrants of the breast and forms a covering over muscle and dermis. It has an important aesthetic function i.e., it prevents sagging of the breast. In lower quadrants, fibrous tissues extend further into the skin and nipple and give a mechanical support to the gland. The interlobar stroma contains variable amounts of adipose tissues, which are responsible for increase in breast size at puberty[5].

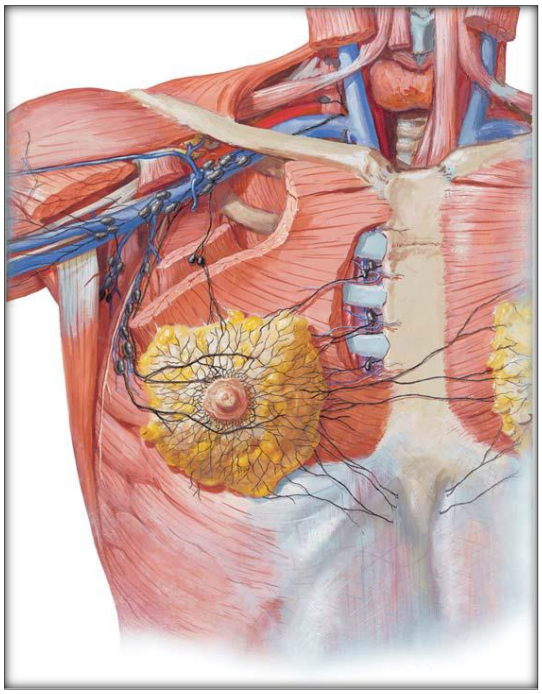

Figure 6. Lymphatic system and lymph nodes in the breast and axilla.

Vascular Anatomy of Breast

Mammary glands are supplied by branches from the axillary, internal thoracic and intercostal arteries. Major arterial supply to the mammary gland is the

axillary artery. Branches of axillary artery are superior thoracic artery, lateral thoracic artery, pectoral branches of thoracoacromial artery, and subscapular artery. Medial quadrants of the breast receive blood supply from the perforating branches of internal thoracic artery also. Perforating branches from second to fourth anterior intercostal arteries supply lateral quadrants of the breast, nipple and areola (Figure 7)[5,6].

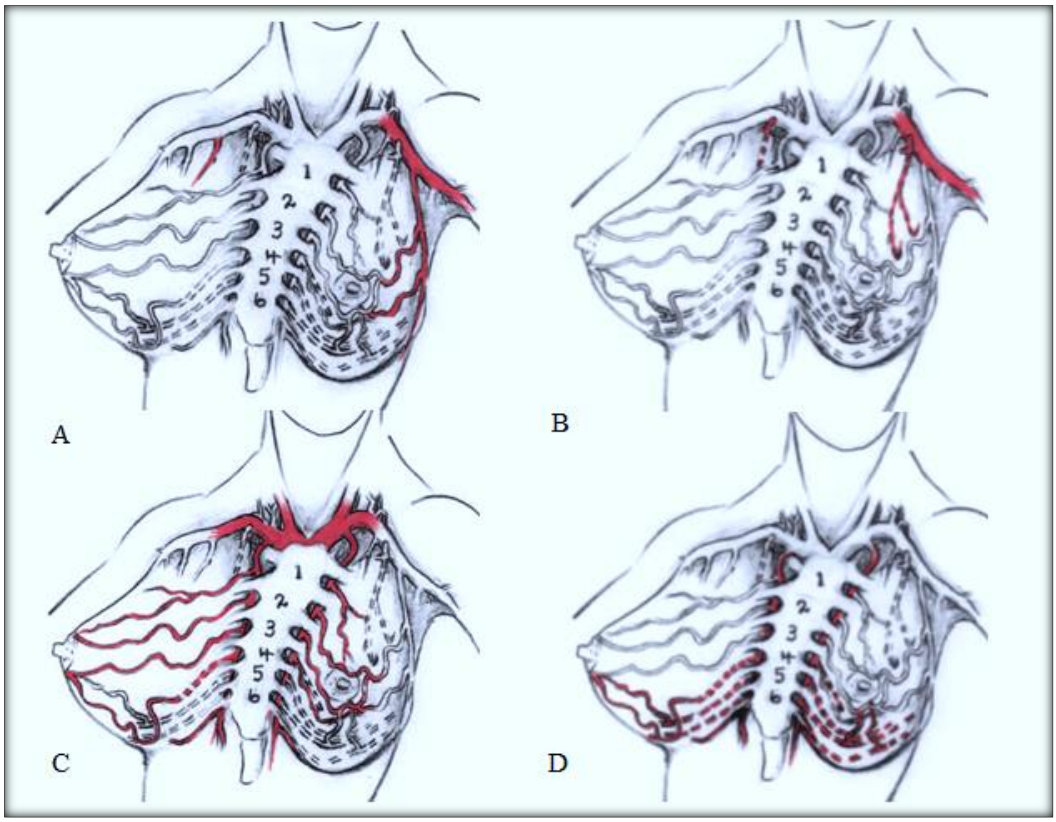

Figure 7. Vascular anatomy of the breast. A, lateral thoracic artery. B, acromiothoracic (thoracoacromial) artery. C, perforating branches of the internal thoracic artery. D, fourth to the sixth anterior intercostal arteries.

Nerve Supply of Breast

Nerve supply of the breast is by anterior and lateral cutaneous branches of the fourth to sixth intercostal nerves[6]. However, sixth intercostal nerve supplies only small portion of the mammary gland. Sometimes there is no contribution from sixth intercostal nerve[7].

Fourth intercostal nerve is the major nerve that supplies mammary gland. Lateral cutaneous branch of fourth intercostal nerve gives extensive superficial nerve plexus that provides sensory supply to the nipples. Areola and nipple also receives nerve supply from anterior cutaneous branch of fourth intercostal nerve. The anterior division of the lateral cutaneous branch is further divided into superficial and deep branches (Figure 8)[7].

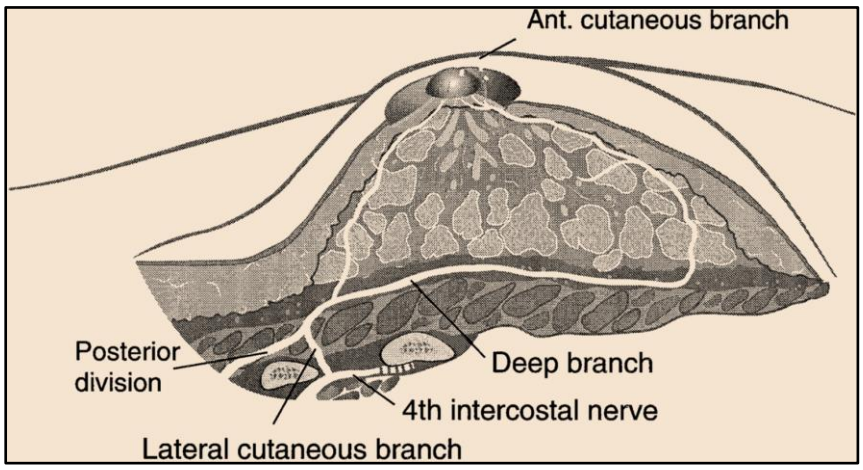

Figure 8. Nerve supple of mammary gland

DISORDERS OF BREAST

Developmental Disorders of Breast

Congenital anomalies of breast may be either unilateral or bilateral and may involve either the nipple or breast or sometimes both. Congenital lesions in mammary gland are confined to the axillopectoral region[8]. Various types congenital anomalies are

Polythelia

Condition where there are more than two nipples is called as polythelia. Each nipple is associated with an areola. Not every supernumerary areola has a nipple, but every supernumerary nipple has areola. Along milk line of Schultz (Figure 9), supernumerary nipples develop. Urinary tract anomalies like renal agenesis, renal cell carcinoma, supernumerary kidneys, cardiac disorders like conduction disturbances (especially left bundle branch block), hypertension & congenital cardiac anomalies are frequently associated with polythelia. Other congenital anomalies associated are pyloric stenosis, ear abnormalities and arthrogryposis multiplex congenita. Accessory nipple can be confused for a nevus[3,9].

An accessory nipple and breast are due to incomplete regression of the mammary ridge. Embryonic mammary ridge is located along the milk line of Schultz from the axilla to the groin. But most commonly accessory mammary gland or nipple occurs along the axilla or inframammary fold regions[10].

Athelia

Congenital condition characterized by unilateral or bilateral absence of nipples and areolae is athelia. It is a rare breast anomaly associated with developmental failure of lower cervical and upper thoracic somites. Amastia is the term to describe absent breast tissue and nipple-areolar complex and amazia where there is absence of only breast tissues. These are the conditions that should be differentiated from athelia[10].

Polymastia

Also known as ectopic or supernumerary breast. It is defined as the presence of two or more breasts which are located along the mammary ridge. Polymastia constitutes approximately 1-2% incidence among all live births. Pathology is not known. These ectopic breast tissues are also equally subjected to diseases like

mastitis, cancer, etc. Most commonly polymastia is associated with renal anomalies[10].

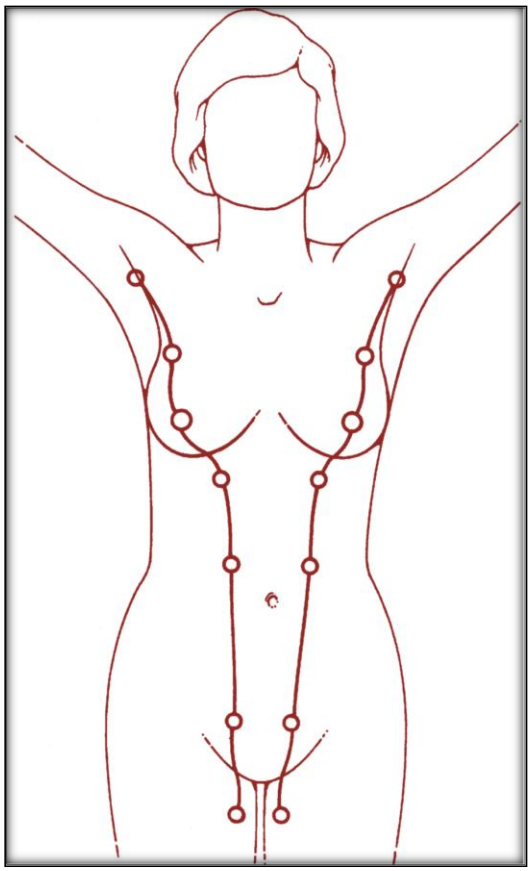

Figure 9. Milk line Schultz. Supernumerary mammary structures develop along this line.

Amastia, Amazia & Hypoplasia

Amastia is a condition which refers to absence of breast tissue, areola and nipple. It is associated with Poland syndrome. Amazia is term indicating absent breast tissue with preserved nipple-areolar complex. Iatrogenic causes like surgical resection or radiotherapy on breast bud are causes for amazia[10].

Benign Breast Lesions

Heterogeneous group of lesions originating from the mammary epithelium or secondary to inflammatory, vascular or traumatic pathologies. Benign breast lesions may or may not have a specific characteristic feature. Some of them are palpable, nodular lesions and others do not have any specific nature[10].

Classification of Benign Breast Lesions

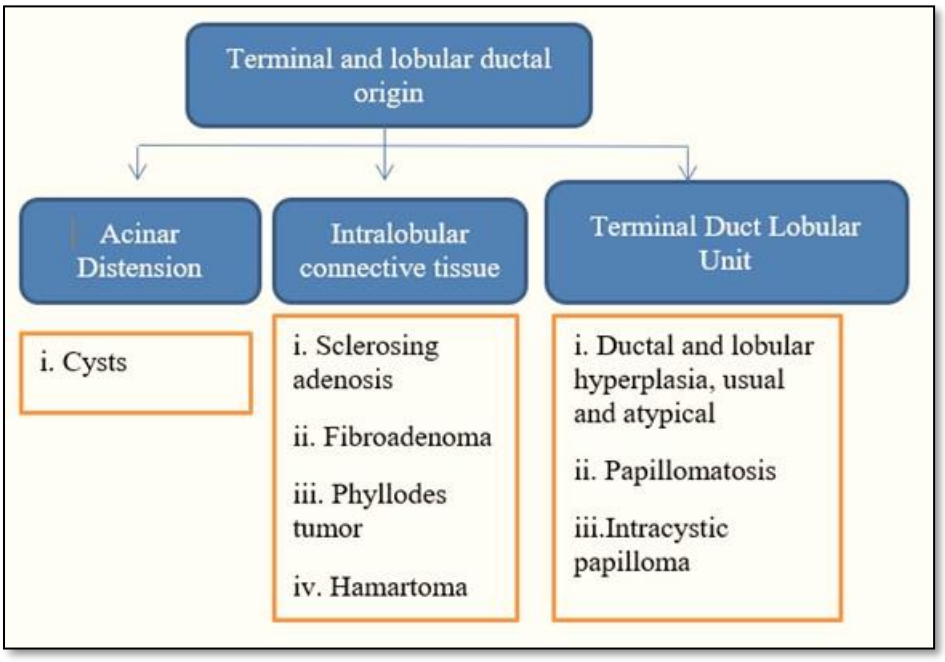

Figure 10. Classification of benign breast lesions.

Benign breast lesions are classified according to histology pattern (Figure 10). The tissue of origin can be terminal and lobular ducts, ductal system or other tissues like fatty tissue, fibrous tissue, and vascular origin. Others can be inflammatory and lymph nodal pathologies[10].

Acinar Distension – Cysts

Distension of the terminal duct lobular units (TDLU) with filling of fluid results in cysts formation in mammary gland. The cysts are tensile because of sclerosis of the surrounding loose connective tissue. Cysts are divided into i. simple cyst, ii. complicated and iii. complex cysts[10].

Simple cysts are common in age range between 30 and 50 years. Five characteristics of cysts in ultrasonography (USG) are well circumscribed, anechoic, thin echogenic capsule, posterior acoustic enhancement and acoustic shadowing at the edges. Treatment is not necessary unless the cysts become symptomatic[10,11].

Complex cysts are most commonly associated with malignancy. Chen et al., defined complex cysts as cysts with thick walls, thick septa, or mixed solid and cystic components[11].

Lesions Arising from Intralobular connective tissue

a. Fibroadenoma

Fibroadenoma have bimodal age distribution. First peak is common at 3rd decade and second peak at 5th decades. Fibroadenoma can also occur after menopause due to hormone replacement therapy (HRT). It is a benign tumor grows rapidly upto 2 – 4 cm in diameter. Giant and juvenile fibroadenoma can attain upto 6 - 10 cm. Fibroadenoma have excessive stromal cell proliferation, hence it should be pathologically differentiated from benign phyllodes tumor[10]. Adolescent girls and women of younger age group can have fibroadenoma commonly. On clinical examination, fibroadenoma are smooth and firm. They are mobile lesions. Sometimes in young women, fibroadenoma attain very large size, which is known juvenile giant fibroadenoma[12].

On imaging, fibroadenoma are well-defined, hypoechoic or isoechoic, elliptic mass with uniform echogenicity. Most of them are wider than taller and well demarcated lesions[12].

Pathological findings in fibroadenoma include proliferation of stromal as well as glandular elements. Two histologic types are: intracanalicular and pericanalicular. In intracanalicular type the ducts are compressed by the lesion. As a

result, the ducts appear slit like. In pericanalicular lesions, ducts are not compressed. Occasionally, small punctate, dystrophic, or pleomorphic calcifications may be seen[12].

Special types of fibroadenoma are lactating adenoma, juvenile fibroadenoma, and tubular adenoma. A lactating fibroadenoma occurs at the time of pregnancy. Tubular adenomas are type of pericanalicular fibroadenoma and juvenile fibroadenoma is shows prominent stromal cellularity with hyperplasia of epithelium[12].

b. Phyllodes Tumor

Phyllodes tumors account for 3% of all intralobular connective tissue lesions. It can occur in varied age groups from 12 to 87 years of age. It has bimodal age peaks. First peak incidence occurs at the range of 11 to 20 years of age decade of life and second peak incidence occurs at perimenopausal age group. In lesions with malignant changes, there is hematogenous transmission rather than lymphatic spread[10,13].

On palpation the lesion is firm to hard. Large tumors can be aggressive and cause cutaneous ulceration and chest wall invasion. On histology, the lesion shows rapid intralobular stromal proliferation in the duct giving a leaf-like origin[12].

Sunderland and Treves in 1951 classified phyllodes tumor into benign, borderline and malignant. In January 1931, Lee and Pack described the first case of phyllodes tumor in the name of intracanalicular fibroadenomyxoma of breast[14,15].

On mammograms, phyllodes tumor appears as a large, well-defined, isodense mass that contains plaque-like calcifications. On sonomammography, the tumor is characterized by smooth and solid lobular surface with few cystic components within. Kalambo et al., in their study showed that a phyllodes tumor with size > 7 cm has higher likelihood of malignancy[12,13]. Pathological diagnosis is indicated in phyllodes tumor. FNAC has low sensitivity of ~ 50% in diagnosing a phyllodes tumor compared to core needle biopsy which has sensitivity of ~ 80 % in identifying phyllodes tumor[16].

c. Hamartoma

Breast hamartomas is a pseudocapsulated oval shaped lesion. The composition of glandular tissue, fat and fibrous connective tissue varies. However, these structures are well differentiated histologically. Depending on the amount of fat, consistency of the lesion varies. On sonomammography, hamartomas are heterogeneous from isoechoic because of fat components to hyperechoic due to fibrous connective tissue. Hamartoma are more common in fourth decade and have low tendency for malignant transformation[10].

On colour Doppler study, the lesion shows less vascularity. Presazzi et al., on mammography described hamartomas as ‘target’ or ‘slice of salami’ appearance. Hamartomas containing high amounts of fibrous tissue show well defined, homogeneous opacity, making it difficult to differentiate from fibroadenoma[12].

d. Sclerosing Lobular Hyperplasia

It is also known as fibroadenomatoid mastopathy. Sclerosing lobular hyperplasia is a benign proliferative lesion. Clinically it is palpable and appears as well defined solid mass. The mean age of presentation is 32 years. On mammography, the lesion is similar to a fibroadenoma. Pathologically, enlarged lobules with increased number of intralobular ductules and intralobular septa are seen[12].

Epithelial changes in TDLUs (Terminal Duct Lobular Units)

Intracystic Papilloma

Intracystic papilloma (ICP) is a benign lesion with vascular pedicle, growing within the dilated mammary duct. It most commonly affects women of age groups 30 to 55 years. By imaging, it is difficult to differentiate intracystic papilloma from intracystic papillary carcinoma. Intracystic papilloma most often have a single echogenic solid nodule of < 3 cm, whereas intracystic papillary carcinoma will have

multiple echogenic solid nodules, each > 3 cm. In Dynamic Contrast enhanced (DCE) MRI, benign as well as malignant solid lesions will demonstrate early enhancement and early washout. Hence pathological diagnosis is required to differentiate benign and malignant intracystic papillary neoplasm[17].

Benign breast lesions of terminal and lobular ductal origin

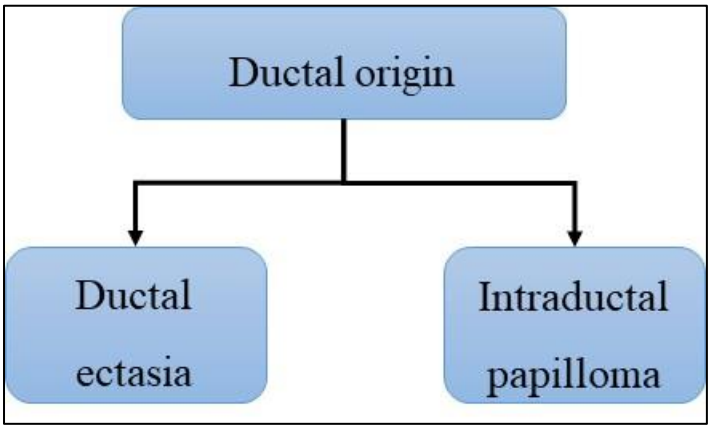

Figure 11. Classification of ductal lesions.

Lesions with Ductal Origin

a. Ductal ectasia

Duct ectasia by definition is nonspecific dilatation of one or more ducts, more than 2 mm in general and equal to or more than 4 mm near ampullary region. Duct ectasia predominantly in the retroareolar region. Most common clinical presentation is nipple discharge. Sometimes patients are presented with palpable

breast mass. Imaging findings in mammography, depends upon density of the parenchyma and degree dilatation of the ducts. By definition, the duct is typically larger than 2 mm in diameter and in the ampulla, it is greater than 3 mm in diameter[18].

Duct ectasia appears as tubular radiodensities converging on the nipple-areolar complex in mammography. Dilated ducts contain fluid and debris. Occasionally the ducts are calcified. On sonomammography, ducts appear dilated and show anechoic fluid collection with low level echoes within[18].

Duct ectasia can also be seen in the malignancies. On ultrasonography, duct ectasia occurs secondary to malignancy are frequently located in the periphery, whereas in benign conditions, the duct ectasia are central in location. In malignant breast disease other features like irregular duct margin, focal area of duct wall thickening and hypoechoic mass lesion near dilated ducts are seen in ultrasonography[18].

b. Intraductal Papilloma

Intraductal papillomas are either central or retroareolar in location. It can be solitary or multiple. Most common clinical symptom will be clear or blood discharge from the nipple. Traditionally, these lesions were most commonly observed in

symptomatic perimenopausal patients. However, with the more widespread use of breast ultrasound, solitary intraductal papillomas are being detected with increasing frequency in younger asymptomatic patients[19].

Other Breast lesions

I. Fat Origin

a. Lipoma

Lipomas are the common benign tumors of the breast. They are composed of mature adipocytes. Lipoma can be either solitary or multiple and unilateral or bilateral. On clinical examination, the lesions are soft on palpation. On ultrasound, the lesion is homogeneous. It can be hypoechoic, isoechoic, or hyperechoic with no significant internal or peripheral vascularity. Lipomas appear radiolucent on mammography. Lipomas enlarge due to hormonal stimulation. Enlarging lipomas need surgical excision[20].

b. Angiolipoma

Uncommon lesion composed of fatty tissue intermixed with vascular proliferation. There are two types of angiolipoma. They are infiltrative type and the non-infiltrative type. Both the types are benign lesions only. Imaging features of

angiolipoma are nonspecific. On USG, echogenic mass with internal vascularity is seen. Since imaging findings are indeterminate, biopsy is required for diagnosis[20].

c. Fat Necrosis

Fat necrosis is a non-suppurative inflammatory condition of fat tissue of mammary gland most commonly due to injury. It is also called as liponecrosis Etiologies for fat necrosis are direct trauma, cyst aspiration, infection, biopsy, implant removal, silicone or paraffin injections, reconstructive surgery, lumpectomy and radiation therapy. Imaging findings of echogenic lesion in a patient with history of trauma is more probably due to liponecrosis or fat necrosis[20].

II. Vascular Origin - Hemangioma

It is a benign breast tumor which is vascular origin affecting patients from 18 to 82 years. They are two types of hemangiomas: capillary and cavernous, with cavernous hemangioma being more common. Histologically, hemangiomas are composed of vein or capillaries encased with in normal fibrous stroma. The vessels which intermingle with ductal structures do not disrupt the ducts[21].

Hemangiomas are often diagnosed incidentally on a mammogram. They appear as a lobulated mass on mammograms. Unlike soft tissue Hemangiomas calcifications due to phleboliths are less common in breast hemangioma. If present, they are punctate or coarse. On ultrasonography, hemangiomas are oval, circumscribed, hyperechoic, hypoechoic or isoechoic lesions in superficial location[21].

III. Breast Hematoma

Hematoma is a localized collection of blood. Causes for breast hematomas include trauma, intervention or surgical procedures. Based on the age of hematoma, appearance in ultrasound varies. Hematomas are anechoic when hyperacute, hypoechoic when acute and mixed cystic and solid masses with indistinct margins and a thick hyperechoic wall when subacute. In the chronic phase, hematoma will become hyperechoic due to clot formations and forms an echogenic debris-fluid level. History of trauma, bleeding disorder and surgical intervention are important in arriving at the correct diagnosis[21].

IV. Infective Etiology

a. Abscess

Lactating women are frequently affected by breast abscess. Staphylococcus aureus is the commonest organism to cause breast abscess. Nipple fissures are penetrated by the bacteria that will lead to breast abscess. Granulomatous mastitis is associated with a sterile abscess. On clinical examination, patient presented with fever, chills, rigors, erythema and tenderness of affected breast on palpation[21].

On mammography, skin thickening is seen with non-calcified mass. On USG, mixed solid and complex cyst with echogenic debris and septations are seen with increased vascularity. On elastography, Blue-Green-Red (BGR) artifact is seen[21].

b. Tuberculosis

Cooper reported the first case of tuberculosis of the breast in 1829. He termed tuberculous mastitis as the ‘scrofulous swelling of bosom’. Conventionally, three distinct patterns of tuberculosis mastitis are present which includes, nodular, diffuse and sclerosing forms[22].

The nodular is a slow-growing non-caseating granuloma or an abscess with perilesional edema. Sometimes the lesion shows scarring which will mimic a malignancy. On ultrasonography, a non-caseating nodular lesion is well defined hypoechoic with posterior enhancement mimicking a fibroadenoma or an intramammary lymph nodes which are usually smaller in size (<1 cm)[22].

Diffuse forms are multifocal lesions which will evolve into abscess. This form is virulent and it is most often associated with immune deficiency status. These lesions will have irregular margin with perilesional edema. These lesions mostly mimic malignancy[22].

Fibrosis is more specific imaging findings than granuloma in tuberculous mastitis. Imaging features in fibrosis variants are asymmetry between the two breasts and reduction in breast volume followed by retraction of the breast due to involvement of Cooper's ligament due to fibrosis. The retraction of breast is more useful in differentiating malignancy from tuberculosis mastitis[22].

Malignant Breast Lesions

Malignancy on ultrasonography appears markedly hypoechogenic, spiculation, posterior acoustic shadowing, angular margins, microcalcifications,

branching pattern, 1–2-mm microlobulations and ductal extension. The lesions are taller-than-wide with a nonparallel orientation to the skin. Malignancy is associated with thickening of skin and Cooper ligaments. Spiculation is the most specific imaging feature, whereas the most common imaging feature in malignancy is angular margin[23].

Carcinoma in Situ

Carcinoma in situ is a pre-invasive state where the basement layer is not breached. No invasion to the adjacent structures here. Mostly carcinoma in-situ is occult in mammography. Occasionally, microcalcifications are seen in carcinoma in situ. On ultrasound hypoechoic mass is seen[23].

On USG, the mass is hypoechoic with irregular shape, few microlobulations, architectural distortion and duct abnormalities. Posterior acoustic shadowing or significant vascularity may not be seen in this condition. On USG, microcalcifications in clusters are seen, each approximately 10 mm in size. Ultrasonography is particularly useful in performing biopsies of the breast masses. But microcalcifications in carcinoma in situ are better seen with mammography than in sonomammography [23].

Imaging in Malignant Breast Lesions

Based on Lexicon fifth edition, several changes have been made in sonomammographic evaluation of breast masses. Several imaging features which are used in identifying malignant breast masses include, irregular, microlobulated (≥ 4 lobules) or spiculated margin, taller than wider lesion, heterogeneous (hyperechoic/ hypoechoic or mixed echogenic lesion), posterior acoustic shadowing, microcalcifications, architectural distortion, overlying skin retractions and intramammary and axillary lymphadenopathy. Doppler and elastography are the adjuvants recently included in Lexicon fifth edition to improve the accuracy of ultrasonography in diagnosing malignant breast lesions[24].

Elastography of Breast

Recent advance incorporated in ultrasound is elastography. Elastography is an upcoming ultrasound-based modality which helps to determine the elastic property of the lesion. Elastic property is assessed based on the stiffness of the lesion. Elastography relies on the stiffness rather than morphology of the lesion. Images obtained by the elastography will show relative stiffness between the tissues. Thus, elastography is nothing but an ultrasound based palpation of the lesion to assess the hardness rather than clinical palpation. There are two types of elastography techniques. They are strain and shear wave elastography techniques[2].

Clinically, malignant breast masses are harder than the surrounding tissues on palpation. However it is difficult to palpate smaller breast lesions. There is high degree interobserver variation among surgeons in diagnosing a smaller breast lesion. Also, with manual palpation, it is difficult to differentiate necrotized breast malignancies from cysts and abscesses. With the advent of elastography this has been overcome[25].

In elastography, the tissue strain created as a result of deformation due to manual compression with the probe is calculated. There are various techniques by which tissue strain can be detected. These techniques work on a simple concept that malignant lesions are harder and benign lesions are softer or similar in stiffness to the surrounding normal tissues[26].

Lesions already detected by the ultrasonography are characterized by elastography. Thus, elastography can characterize a lesion rather than diagnosing it. Gentle pressure should be applied with probe. Newer machines are more sensitive to the movement. Thus, even a pressure from breath movements are enough to create an elastogram image[27].

Strain elastography provides images either in grey scale pattern or rainbow colour pattern. This image is superimposed on the image acquired by the

conventional ultrasonography. Based on the various scoring systems mentioned in literature, results are interpreted. Scoring depends upon the size and stiffness of the lesion in comparison to the adjacent normal breast adipose tissue. Malignant lesions are harder and stiffer than adjacent breast tissue whereas benign masses like fibroadenoma and cyst are either equal or less in stiffness in comparison to the surrounding breast parenchyma. Former is equal or less in stiffness whereas later is lesser in stiffness compared to the surrounding breast parenchyma[28].

ROLE OF IMAGING IN EVALUATION OF BREAST

Mammography in breast mass evaluation

Mammography is a radiographic technique for breast with high spatial resolution and high contrast effect. To attain high contrast effect, low kilovolt is used in mammography. Thus, breast which is predominantly a soft tissue structure with little inherent contrast is more highlighted with low kilovolt mammography technique and thereby, helps in differentiating normal and abnormal breast structures. Low energy photons are produced by molybdenum or rhodium anodes[29].

With the technological advances conventional mammography is replaced by digital mammography where the digital detectors came into use. The principle based

on which digital mammography works is conversion of x-rays into electronic images. Digital mammography detectors are of two types which include indirect and direct detectors. In indirect detectors x-rays are converted into light followed by which it is converted into electronic images. The direct detectors are 'flat panel detectors' which convert X-rays directly into electronic images[29].

Important factor assessed with mammography is mammographic density which indicates the percentage of dense tissues in breast. Mammographic density was defined by Nazari et al as 'fibroglandular mammary tissue consisting of fibroblasts, epithelial cells and connective tissue'[30]. Radiologically, fat is radiolucent so it is less dense compared to connective tissues like glandular structure which are radiodense[29,30].

Mammographic density is classified by BIRADS into 4 categories based on mayo clinic foundation for medical education and research. Category 1 indicates predominantly fatty breast with glandular tissue composition of < 25%. Category 2 comprises of breast tissues with scattered area of glandular density comprising greater than 25% and less than 50% of glandular tissue. Category 3 is defined as heterogeneous breast with glandular tissue composition of ~ 50 – 74%. Category 4 includes breast with glandular composition of ≥ 75%[30].

Reporting of mammography is based on Lexicon fifth edition in which the breast lesions are categorized based on various imaging findings including mammographic density, mass characterization, calcification, architectural distortion and asymmetry[30].

Digital Breast Tomosynthesis Mammography

Digital breast tomosynthesis (DBT) is an advance technology in breast mammography in which more than one X-ray detectors used here helps in visualizing the breast mass. Disadvantage of conventional mammography is the diagnostic accuracy is severely affected in young female with glandular breast. To overcome the difficulties of mammography, newer technology of DBT developed, which uses multiple detectors to produce 0.5 mm thin slices images. The advantage of DBT over mammography is margins of the breast masses are well defined[31].

Role of Computed Tomography in Breast Lesions

Computed tomography (CT) is relatively having lesser diagnostic accuracy of breast lesions in comparison with other imaging modalities. But certain information like invasion of adjacent muscles, lymph nodes and distant metastasis to lung and liver are diagnosed with the help of contrast enhanced CT. Accuracy of

characterizing benign lesions with CT is poor. Irregular shape and margins with heterogeneous enhancement on contrast enhanced CT suggest the probability of malignant etiology[32].

Clinical history is important in cases with prior breast surgery because post-operative scar may be misdiagnosed as malignant breast lesion. Diagnostic accuracy is very poor with CT for benign breast lesions. So additional imaging like mammography or ultrasonography should be performed to come to the final diagnosis. Son et al., stated that CT is capable of detecting 24 to 70% of breast masses. Although only less information about breast lesions are provided by the CT, it is important to assess the mammary gland in CT thorax[32]

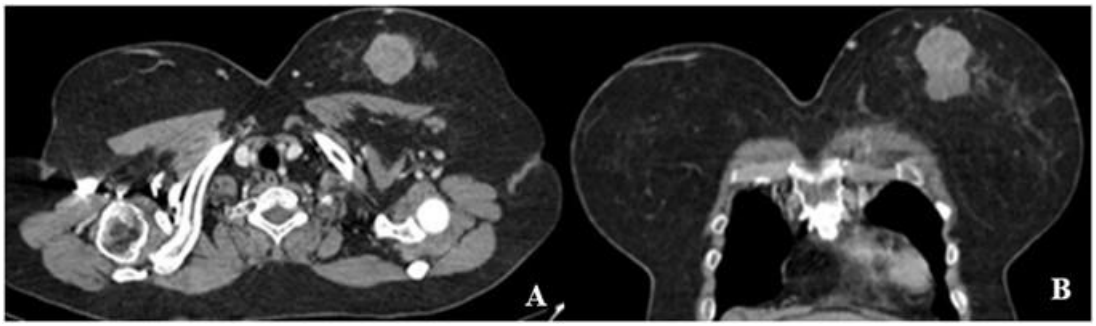

Figure 12. CECT image of breast showing enhancing lesion in left breast in axial (Image A) and coronal reformatted image (Image B).

Positron Emitted Tomography in Breast Lesions

^{18}FDG Positron Emission Tomography (PET) is not a primary imaging modality although it has high accuracy in detecting malignant breast lesions. However, PET- CT is not accurate in diagnosing subcentimetric breast lesions or lesions with low cell turnover[33].

Role of FDG PET in breast lesions is that, it is helpful in staging metastatic and recurrent breast masses. It is also helpful in assessing the response to chemotherapy. Recent advance with PET-CT is that it can help in diagnosing breast lesions as small as one cm. Radiation exposure, however is the main concern[33].

Use of PET-CT includes identifying and staging of the breast lesion, assessing the recurrent lesion and also to assess the response of the mass to chemotherapy. PET-CT is also helpful in identifying lymph nodal and distant organ metastasis as well as staging of the recurrent lesions. PET-CT is also useful in evaluating the response of locally advanced as well as metastatic breast masses to treatment[33].

Positron Emission Mammography

Positron emission mammography (PEM) is the dedicated PET scanning for diagnosing metastasis from primary breast carcinoma. PEM consist of two detectors placed opposite to each other. PEM is a dedicated system that helps to improve spatial resolution, image acquisition time and geometric sensitivity in comparison with routine whole-body PET systems[33].

Magnetic Resonance Mammography

With the recent advancements in field of radiology, MR mammography (MRM) is increasingly used along with conventional mammography and ultrasonography for evaluation of a breast mass. MR mammogram has important role in diagnosing mass lesions in the young female with family history of breast cancer, since they have dense glandular structure within. Other uses include assessment of silicone implants after breast augmentation surgery, recurrent breast masses and staging of local breast lesions[34].

Most of the researchers used dynamic contrast enhancement pattern along with morphological characteristics to differentiate benign from malignant lesions. However, the drawback with MRI is that some of the benign breast masses have

increased vascularity and demonstrate enhancement pattern similar to malignant lesions. So, the accuracy of MR mammogram in differentiating a benign and malignant breast mass is still questionable[34].

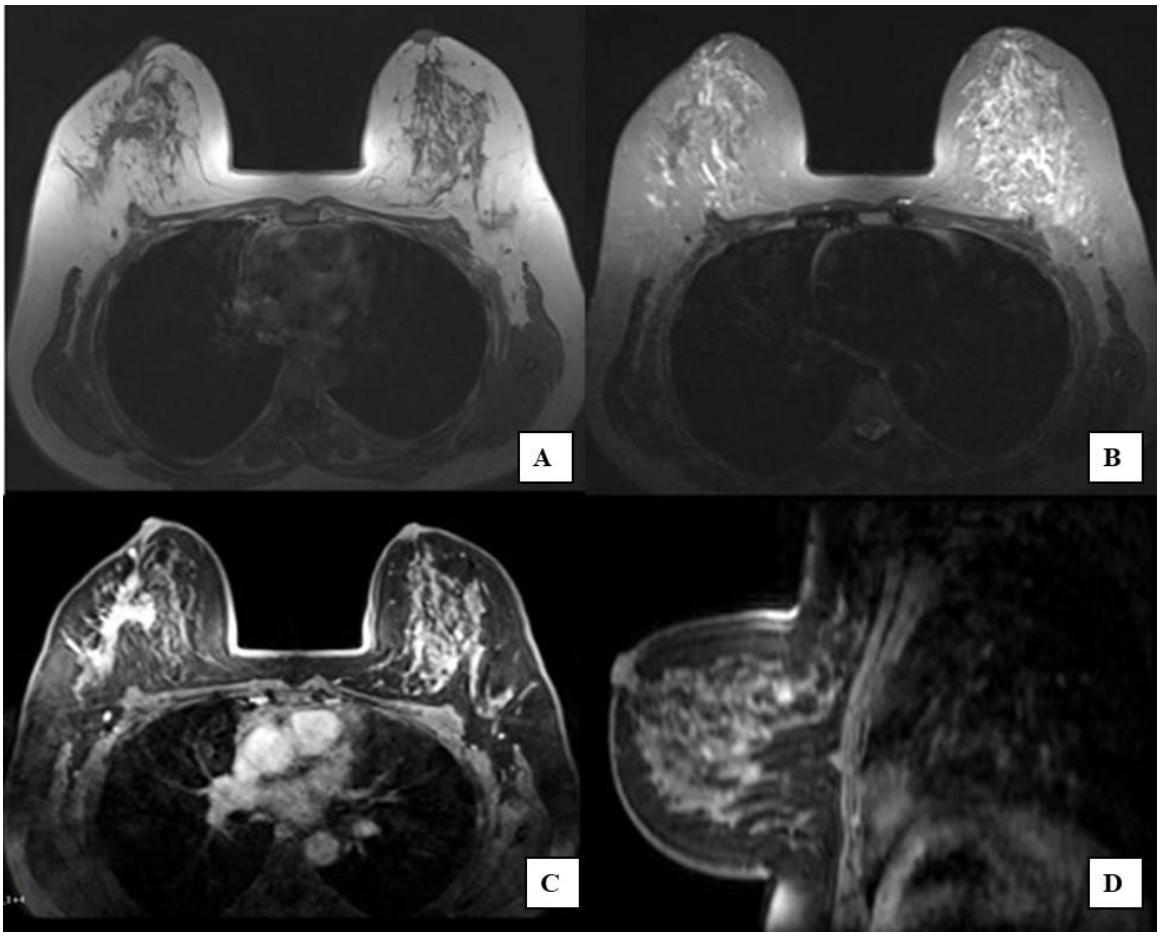

Figure 13 MR Mammogram image in 42-year lady with palpable right breast mass. T1 and T2 fat saturation image showed an ill-defined hypointense lesion in right breast (A & B). On T1 FS post contrast axial and sagittal images (C & D) the lesion demonstrated heterogeneous avid enhancement.

Ultrasonographic anatomy of Breast

Breast is divided into three zones based on ultrasound echotexture. They include subcutaneous, mammary and retromammary zones from superficial to deep[35].

Zonal Anatomy of Mammary gland on Ultrasound

Most superficial zone in the breast situated adjacent to skin is subcutaneous zone. It is also called as premammary zone. Subcutaneous fat, suspensory ligament of Astely Cooper, few superficial blood vessels and ectopic ducts & lobules together constitutes premammary zone. Most of the premammary zone structures arise from skin and subcutaneous fat but not from the breast tissue[35].

Between the premammary zone and the deeper retromammary zone lies the mammary zone which harbors most of the mammary ducts and terminal ductal lobular units. Mammary zone constitutes various types of breast pathologies, including invasive ductal carcinoma[35].

The retromammary zone constitutes the deep zone of breast. It is present in between the mammary zone and thoracic wall. This zone appears thinner in the

ultrasound as it is compressed between the mammary zone and chest wall when probe pressure is given in the supine position. This zone is composed of adipose tissue. Pathologies from retromammary zone are very rare. Most commonly diseases arising from the mammary zone are extending to the retromammary zone[35].

Imaging in Prepubertal Breast

Developing breast has only few ducts around the nipple. Most of the times breast development is asymmetric which gives an appearance like a subareolar mass and resembling a gynecomastia in male. This condition is known as asymmetric premature ripening. If surgical excision is performed in this condition, it will lead to hypoplasia of mammary gland. Hence, it is very important to recognize premature asymmetric ripening[36].

Echotexture of the layers

Based on the tissue echogenicity, breast is classified into 5 layers from superficial to deep. They are alternating hyper and hypoechoic in nature. Skin, fibroglandular structures and pectoralis major muscles are hyperechoic whereas subcutaneous fat and retromammary fat are isoechoic to hypoechoic in nature.

Suspensory ligament of Astely Cooper is a derivative of fibrous stroma and it is hyperechoic structure[36].

PRINCIPLES OF ELASTOGRAPHY

Historic background

Research in elastography started in 1987 when Krouskop T A along with Dougherty B S and Vinson F S, developed a pulsed Doppler system for measuring the mechanical properties of amputated residual limb so as to predict its interaction with prosthetic socket. In this study, they found that pulsed Doppler system is helpful in characterizing the mechanical properties of the soft tissue. They also demonstrated the strain rate and level on the elastography[37,55] (Figure 14).

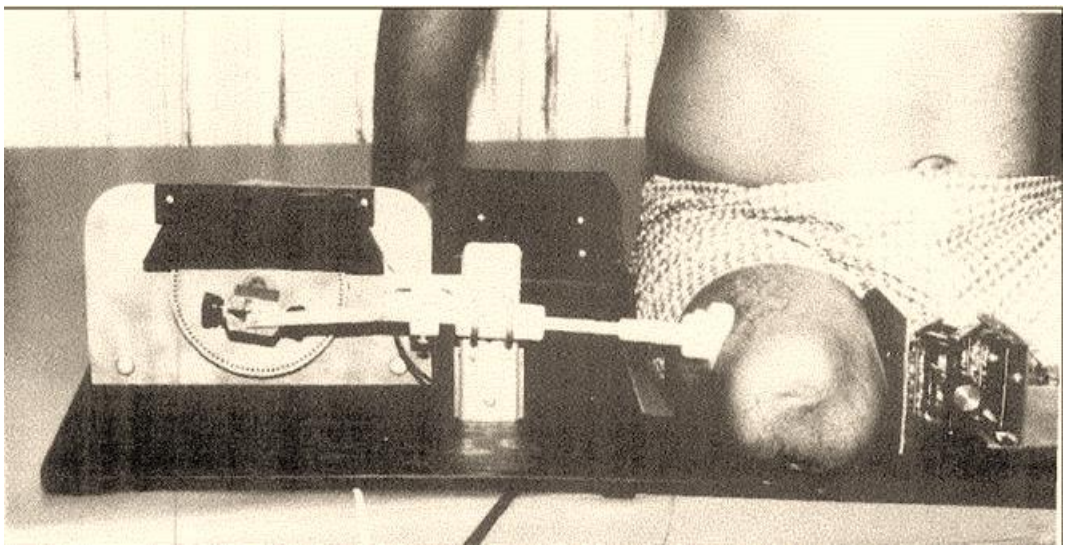

Figure 14. Historic pulsed Doppler system that was useful in characterizing the mechanical properties of soft tissue.

A study conducted at University of Rochester at 1988 in which they developed a colour Doppler to look out for tissue movement and stiffness. This method was named as sonoelasticity. This principle was first applied for a prostatic lesion. In this technique the lesion was relatively dark compared to a colour background of vibrating tissue. The images produced by this technique had poor resolution[37].

Cespedes and Ophir in 1991 demonstrated first elastography by gentle compression which was later known as strain elastography. Better resolution strain images were first developed for prostatic carcinoma. Later this technique was applied in breast masses to differentiate benign from malignant mass[38].

Garra et al in 1997 conducted a study on elastographic appearances of various breast lesions and published it. The study was conducted with single colour map elastography. The inferences from the study was that most of the malignant lesions showed uniform dark shades of grey whereas benign lesions had varied pattern of grey colour. Cysts were bright compared with solid benign lesions[39].

With the advent of rainbow colour maps in elastography, Itoh et al, in 2006 published a ground-breaking research article in which they formulated a score with elastography to categorize the breast masses based on its elasticity and named it as Tsukuba score. Values ranges from 1 to 5, where the lesions with score 1 are

absolute benign and score 5 are absolutely malignant. Researches are still going on to assess the accurate elastography score for breast masses and thereby unnecessary biopsies for benign breast masses can be avoided[40].

Tsukuba colour score failed to give accurate diagnoses of malignant lesions. Chang et al in April 2011 modified the colour scoring system. They devised a three-point rainbow colour system. The scores ranged from 0 to 2. Score 0 is normal where entire lesion is either green or red with no blue colour within. Score 1 is borderline where there is mixture of green and blue which indicates that the lesion is equivocal or indeterminate. Score 2 is abnormal where entire lesion is uniformly blue in colour, indicating malignancy[41].

There are two types of elastography techniques. They are **strain and shear wave elastography** [2].

In strain elastography, images are produced based on the amount of displacement force produced by the external transducer causing deformation of the lesion. The range of deformation of the lesion is calculated based on the elastography scorings available. Thus, strain elastography is the qualitative technique where the lesions are assessed with a ratio of stiffness calculated within the lesion and to the surrounding normal tissue[2].

Shear wave elastography (SWE) is the newer, technique which is still under research where images are developed based on acoustic radio frequencies that are generated from the transducers. SWE is a quantitative technique where stiffness is assessed either in kPa or m/sec^2.

Strain Elastography:

Strain elastography assess the degree of strain or elasticity of tissue. It depends on the amount of deformation produced in the lesion due to the strain applied from the external force. External force is applied with the transducer. Softer lesions will deform more with the external probe pressure[2].

Hard breast lesions are stiffer and resist deformation to the external pressure. Thus, there is lesser degree of strain in comparison to the surrounding normal tissue. Normal adipose tissue surrounding the mass is taken for calculation of strain ratio. A real time rainbow colour pattern elastogram is generated which is super imposed on conventional ultrasound image and values are interpreted. Strain differences are calculated by inbuilt elastogram software that generates values based on ratio of strain causing deformation of the lesion to strain causing deformation of the surrounding adipose tissue. Based on these values strain ratio is created[42].

Methods to perform strain elastography

The principle based on which the strain elastography works is the amount of changes occurring in the lesion to the external pressure. External pressure includes pressure by the radiologist with the transducer, movements from heart beat and breathing. However, in strain elastography accurate measurement of stiffness cannot be assessed. Thus, value produced by strain elastography is the qualitative index rather than a quantitative index[2].

Advancement in strain elastography is the introduction of transducer probe with low frequency pulses. These pulses are called as acoustic radiation force impulse (ARFI) or push pulse. These ARFI pulses generate deformation in the lesion , the values of strain are calculated and computer-generated strain values are given by the software. Manual probe compression for generating deformation is replaced by ARFI pulse[2].

Strain elastography can be performed by two excitation methods. It includes the following steps[43]:

i. Operator dependent manual compression by operator. This method is helpful in assessing the organs like breast and thyroid.

ii. Non-operator dependent methods in which the deformation is because of the internal physiologic motions such as respiratory movement or cardiac pulsations etc. Deeper organs like liver can be evaluated by this method.

Colour Coding Scale

Final strain values are given in a semitransparent grey scale or rainbow colour coded map which is known as elastogram. It is overlaid on the B-mode image[43].

In elastogram map, blue depicts low strain which shows the lesion is highly resistant to deformability due to external manual compression. This indicates the lesion is hard in nature and thus there is high probability for the lesion to be malignant. Red colour indicates the lesion has low resistance to the deformation due to external force. These lesions are soft indicating mostly benign in nature. Green indicates the deformation due to external pressure within the lesion is similar to the adjacent normal structure[43].

An exception to this is a malignant lesion with necrotic degeneration will show red or green colour on rainbow colour map. Caution should be taken to avoid necrotic areas being taken into the consideration[43].

Strain Ratio

A semi-quantitative measurement used in elastography is the strain ratio. It is similar to the palpation method by ultrasound. Strain ratio is the ratio of strain measured in adjacent normal adipose tissue with the reference region of interest (ROI) to strain in a target lesion. Low strain ratio indicates that the target lesion compresses more than the normal reference tissue, indicating less stiffness and more deformability. These are the benign lesions. Cysts are more compressible than benign solid lesions like fibroadenoma[43].

CLINICAL STUDIES

Garra et al in 1997 conducted initial research works about the role of elastography in assessing the breast masses. He found that soft lesions are bright and hard lesions are dark on elastogram. He also evaluated the size of various breast lesions and found that malignant masses were appearing larger on elastography in comparison to ultrasonography which was statistically significant (P <0.05). They also found that 56 percent of benign solid breast masses could be distinguished from malignant masses by brightness and lesion size[38].

Ginat et al., stated that elastography is a good adjunct tool to ultrasonography. Along with ultrasonography, elastography can improve the specificity, sensitivity and diagnostic accuracy of differentiating benign from malignant breast masses. Also, breast elastography can accurately diagnose benign breast mass, thereby reducing unwanted benign breast biopsies in young females. Elastography can also be used in appropriate guided fine needle aspiration cytology (FNAC) or biopsy of non-necrotic areas in breast masses[44].

A Japanese study conducted in 2005 showed that average strain index for malignant breast masses were 4.2 ± 0.9 (mean ± standard deviation (SD)) which ranged from 3.3 – 5.1 whereas for benign masses, the average strain ratio was 2.1 ± 1.0 (mean ± SD) with a range of 1.1 to 3.1). Masses with strain ratio between 4 and 5

proved that elastography has more sensitivity in differentiating the mass from conventional ultrasonography. However, this study failed to derive the average strain ratio values for benign cystic lesions of the breast[40].

A study conducted in Seoul university in South Korea assessed various factors that were affecting the quality of an elastography image and they found that, depth of the lesion, size of the lesion and breast thickness were the important factors that affect an elastographic image quality of the breast mass. They also modified the Tsukuba colour scoring system used previously. They also found that the modified colour scoring system, has better ability to identify the malignant breast masses. In modified colour scoring system, score 0 constituted score 1 & 2 of Tsukuba score. Score 1 indicated Tsukuba score 3 and modified colour score 2 indicated Tsukuba score 4 and 5. However, modified colour scoring systems for the benign lesions were inaccurate as some benign solid lesions had score 1 which was indeterminate and few had malignant scores (score 2)[41].

In a study conducted in Romania on 58 patients, a strain ratio of > 3 was found to be a malignant mass. Mean strain index for benign breast mass was 2.08, and for malignant breast mass, it was 6.28. Strain ratio of 3.67 was considered as cutoff to differentiate benign from malignant breast masses. This study also stated that with a strain ratio of 3, the sensitivity and specificity of elastography in differentiating benign from malignant breast masses were 86.7 and 92.9 % respectively[26].

A study published in the Egyptian journal of Radiology and Nuclear Medicine showed that there was a statistically significant difference (p = 0.02) in strain ratio between benign and malignant breast masses. This study showed that mean strain ratio for benign masses is 1.92 ± 2 (mean ± SD) and the mean strain ratio for malignant breast masses is 8.57 ± 4.2 (mean ± SD) for malignant masses. Elastographic index of 3.6 is considered as a good cutoff. With this cut off, they found that elastography has 94.3 % of sensitivity and 94.2% specificity and accuracy[45].

Menezes et al., in his study compared four parameters in ultrasonography and elastography to assess which among them is the best parameter for differentiating benign from malignant breast masses. The parameters he used are elasticity score, strain ratio, distance ratio and area ratio. The mean distance ratios for benign and malignant masses were 1.02 ± 0.25 (mean ± SD) and 1.13 ± 0.36 (mean ± SD) respectively. The mean area ratios for benign masses were 1.11 ± 0.66 and that of malignant masses were 1.71 ± 0.86 (mean ± SD). Among these four parameters, he assessed the sensitivity and specificity and found out that elasticity score had highest sensitivity and specificity of 100 % and 82.6 % respectively[46].

Yilmaz et al., in their study conducted on 79 Turkish patients concluded that elastography was having a significant role in differentiating benign from malignant breast masses. It should be used as adjunct in conjunction with ultrasonography. The mean strain ratio they derived were 2.79 ± 2.16 (mean ± SD) for benign breast lesion

and 6.59 ± 3.44 (mean ± SD) for malignant lesions with a threshold strain ratio of 4.25. At the threshold ratio of 4.25, Yilmaz et al achieved 86 % sensitivity and 76 % specificity[47].

Wojcinski et al., conducted a study on BIRADS 3 breast masses showed that the sensitivity and specificity of sonoelastography was 62.5% and 80.5 % respectively. The positive predictive value was 13.2 %, whereas the negative predictive value was 97.8%. Also, they found that BIRADS 3 cystic lesions are most probably benign and they showed BGR artifact, a trilaminar colour interface pattern with blue occupying the upper portion of the lesion, green occupying the center and red occupying the bottom. BGR artifact is more specific for cystic lesions[48].

An article published in Journal of Medicine and Biology in 2016 found that combination of elastographic parameters like elastographic score , strain ratio, ultrasound findings with BIRADS score and cytological findings in lesions with size ranging from 2 to 3 cm had significantly high sensitivity of 100%, specificity of 92.3% and diagnostic accuracy of 95.2%. In this study, mean strain ratio of 3.8 was taken as an optimal cut off for differentiating benign from malignant breast masses[49].

Balcik et al., in their study showed that breast lesions with size more than 5 cm and lesions with extensive necrosis are prone to give false results on elastography. In this study the threshold strain ratio was fixed at 4.52. Because of

this, six patients with biopsy proven invasive ductal carcinoma (strain ratio of around 3.5) were considered soft and reported as benign lesions[50].

A study published by Dong et al., in European journal of Radiology about the interobserver variation in assessing the elasticity of breast mass showed that interobserver value for elasticity score between two observers was 0.438, whereas with three observers interobserver value ranged between 0.365 and 0.655[51].

MATERIALS AND METHODS

Source of data

The study was conducted over a period of eighteen months from January 2018 to June 2019 on 86 patients with 101 clinically palpable breast lumps who underwent sonomammography and elastography of breast at the Department of Radiodiagnosis at R. L. Jalappa Hospital and Research Center attached to SDUMC, Kolar. Prior informed consent was taken from the patients for their willingness to participate in the study.

Study design: Prospective observational study

Sample size: A sample size of 86 patients with 101 masses were selected using n masters' software.

Sample size was estimated by using the proportion of subjects with benign and malignant lesions detected by ultrasonography, elastography and pathology from the study conducted by Menezes et al[46].

$$\text{Sample size} = \frac{Z_{1-\alpha/2}{}^2\, p(1-p)}{d^2}$$

$Z_{1-\alpha/2}$ = 1.96 at 5 % error alpha. As in majority of studies *p* values are considered significant below 0.05 hence 1.96 is used in formula.

p = Expected proportion in population based on previous studies or pilot studies.

d = Absolute error or precision – Has to be decided by researcher.

p = 86 or 0.86

q = 14 or 0.14

d = 10 % or 0.1

Considering 10% Nonresponse a sample size of 47 + 4.7 ≈ 52 subjects were planned to be included in the study. A total of 86 patients with 101 breast masses were included in the final analysis. The patients were included in the study if they fulfilled the inclusion/exclusion criteria listed below:

Inclusion criteria: All the patients with clinically palpable breast lump.

Exclusion criteria: Prior biopsy proven breast masses.

Method of collection of data:

Baseline data of the patients participating in the study were recorded. Individuals having clinically palpable breast masses underwent ultrasonography and elastography. B mode ultrasonography and elastography was performed in PHILIPS EPIQ 5G ultrasound machine using a 5–12 MHz linear array transducer. Ultrasonography was first performed with the patient lying in supine position followed by strain elastography. Morphological changes seen on ultrasonography

were interpreted based on BIRADS lexicon, which included the imaging characteristics.

During strain elastography, the probe was placed perpendicular to the lesion and gentle compression was applied. Two criteria were considered and used to determine the nature of lesion on elastography, modified colour score and strain ratio. The modified colour score uses colour pattern to determine the nature of lesion, with blue indicating malignancy (hard lesions), red indicating benign lesions (soft lesions) and green indicating strain similar to normal adjacent tissue. Blue colour was given score 2, uniformly green and Blue-Green-Red (BGR artifact) were given score 0 and mixture of blue and green as score 1. Strain ratio is ratio of hardness of the target tissue with adjacent normal breast fat. Lesions with higher score were considered as hard and suspected as malignant mass. Similarly, lesions with low strain ratio were considered as benign. Strain ratio was calculated by placing region of interest (ROI 1) on normal breast fat and similar size ROI 2 was placed in the lesion. The two ROIs should be near horizontally placed. The strain ratio was calculated as ratio of ROI 1 to ROI 2 and values were generated. The cut off strain ratio used to differentiate benign and malignant lesions was 3.25, beyond which the lesions were considered malignant. The cut off value of 3.25 was taken based on our initial experience, which showed a good correlation for differentiating benign from malignant lesions. Both ultrasonography and elastography findings were recorded and interpreted. The patients underwent pathological investigation, either ultrasound guided FNAC or trucut biopsy following ultrasound and

elastography studies. The pathological results were compared with ultrasonographic and elastographic findings.

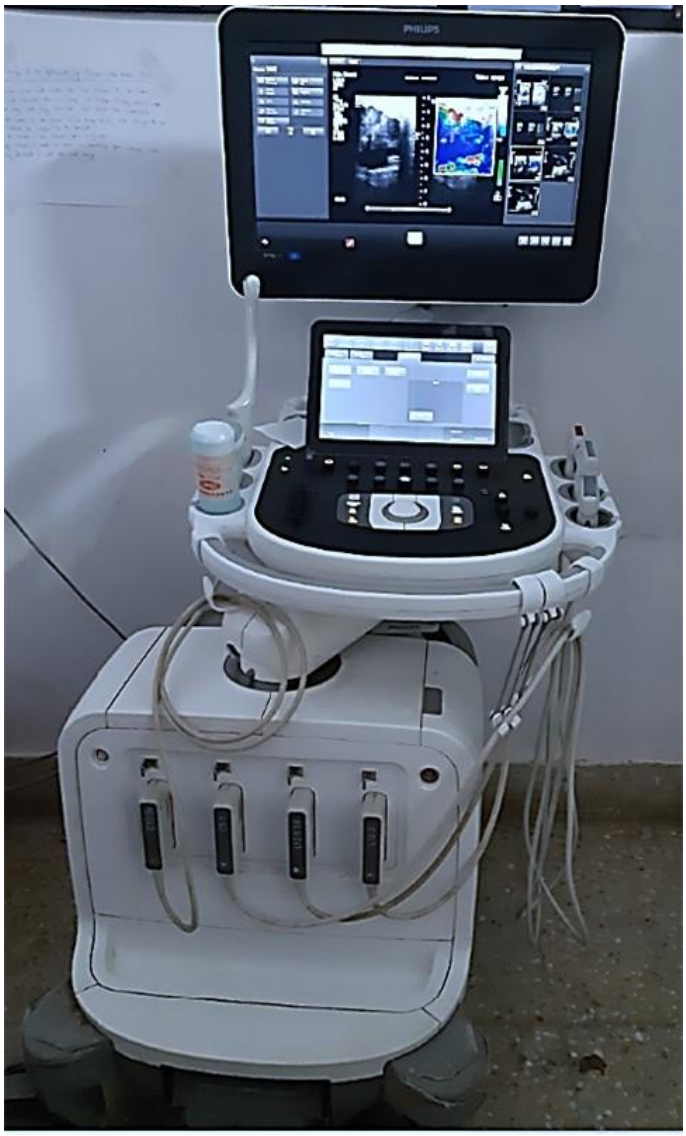

Figure 15. Philips EPIQ 5G premium ultrasound machine.

Data analysis

The data were entered in Microsoft excel sheet. The measurable variables were analyzed and interpreted between them by the student's t test and the ordinal and categorical variables between them were interpreted by Chi-square (χ^2) test. The predictive value of strain elastography for differentiating benign and malignant lesions was estimated. The statistical procedures were performed with the help of an SPSS statistical package (ver 21) and OpenEpi ver 3.01. *P* value less than 0.05 ($P<0.05$) was considered as statistically significant.

RESULTS

In the study 101 breast lesions from 86 patients were included in which 85 (98.9 %) were females and 1 (1.1 %) was male (Figure 16; Table 1). A total of 100 lesions were present in females (99%) and one lesion was seen in the male patient (1%).

Gender Distribution

Table 1. Gender Wise Distribution.

Gender	No. of patients	%	No of lesions	%
Females	85	98.8	100	99
Males	1	1.2	1	1
Total	86	100.0	101	100

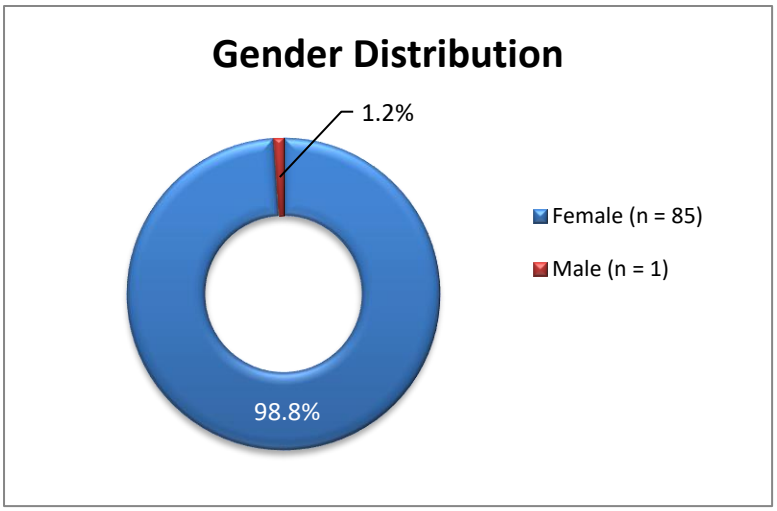

Figure 16. Gender-wise distribution.

Age group distribution

Commonest age group in our study was 41-60 years (n = 36; 41.86%), followed by 21-40 years (n = 32; 37.21%). Patients with age group of 61 years and above were 13.95% (n = 12) and patients with age group 20 years and below constituted 6.98% (n = 6) (Figure 17; Table 2). The mean age of the patients was 42.45 ± 16.2 years (mean ± SD) with range of 14 to 95 years.

Table 2. Age Group Distribution.

Age group	Number of patients	%
0-20 years	6	6.98
21-40 years	32	37.21
41-60 years	36	41.86
>60 years	12	13.95
Total	86	100

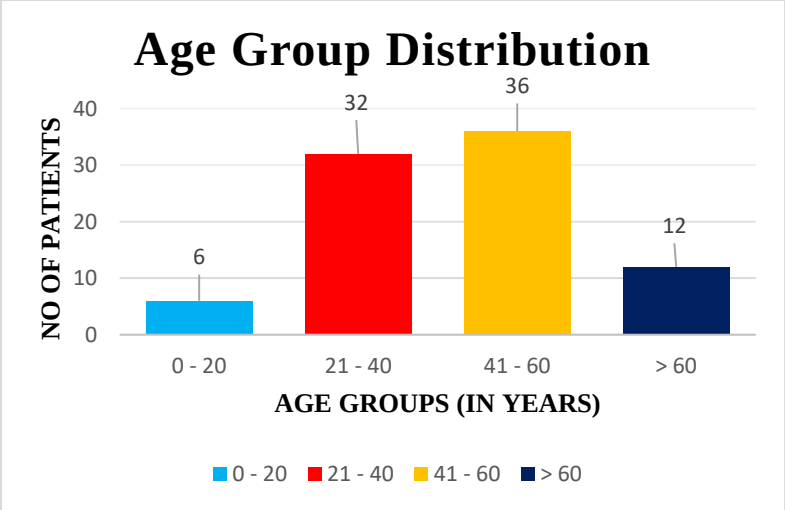

Figure 17. Age group distribution.

Baseline Demographics of Age Compared with other parameters

Table 3. Baseline demographics with average age

Category	**Average age (in years) (mean ± SD)**	***P* value**
Laterality of lesions		*P* = .17
Right (n = 51)	39.78 ± 13.93	
Left (n = 38)	46.21 ± 18.3	
Bilateral (n = 6 × 2= 12)	40.45 ± 19.52	
BIRADS Category		*P*<.001
BIRADS 2 (n = 21)	31.24 ± 13.69	
BIRADS 3 (n = 31)	34.06 ± 12.21	
BIRADS 4 (n = 34)	50 ± 11.16	
BIRADS 5 (n = 15)	58.4 ± 14.53	
Modified colour score		*P*<.001
0 (n = 22)	35.13 ± 10.498	
1 (n = 25)	31 ± 15.18	
2 (n = 54)	50.74 ± 13.73	
Mean strain ratio		*P*<.001
<3.25 (n = 52)	33.1 ± 13.55	
>3.25 (n = 49)	52.39 ± 12.45	
Pathological Diagnosis		*P*<.001
Benign lesions (n = 53)	32.96 ± 13.46	
Malignant lesions (n = 48)	52.94 ± 11.98	

Most of the lesions were situated in the right side (n = 51; 50.5%) followed by 38 lesions (37.62%) in the left breast. There were six patients with bilateral lesions (total of 12 lesions) (11.88%). Table 3 shows the baseline demographics of average age with laterality of lesions, BIRADS category, modified colour score,

mean strain ratio and pathological diagnoses of the lesions. It can be seen that there was no significant difference in mean age and laterality of lesion. When BIRADS category was considered, there was an increase in average age with increasing BIRADS score, which was statistically significant. A similar statistically significant association was also seen with modified colour score and mean strain ratio with increasing age. There was also a statistically significant difference with benign and malignant lesions and mean age i.e., benign lesions were seen in younger age group (32.96 ± 13.46 years) (mean ± SD) when compared with malignant lesions, which were common in elderly (52.94 ± 11.98 years; mean ± SD).

Age-group distribution of lesions based on BIRADS scoring, modified colour scoring, strain elastography and histopathological correlation

Table 4. Distribution of breast masses based on age group of patients and BIRADS Score, Modified Colour Scoring, Strain Elastography Ratio and Pathological Diagnosis

Classification of lesion	**Age group (in years) (No of lesions; %)**				
	<21	21-40	41-60	>60	Total
Ultrasonography					
BIRADS 2	5 (4.9%)	12 (11.8%)	3 (2.9%)	1 (1%)	**21 (20.8%)**
BIRADS 3	5 (4.9%)	17 (16.8%)	7 (6.9%)	2 (2%)	**31 (30.6%)**
BIRADS 4	0 (0%)	10 (9.9%)	19 (18.8%)	5 (4.9%)	**34 (33.6%)**
BIRADS 5	0 (0%)	1 (1%)	9 (8.9%)	5 (4.9%)	**15 (14.8%)**
Elastography					
Modified colour Scoring					
0	1 (1%)	15 (14.8%)	5 (4.9%)	1 (1%)	**22 (21.8%)**
1	8 (7.9%)	12 (11.9%)	3 (3%)	2 (2%)	**25 (24.8%)**
2	1 (1%)	13 (12.9%)	30 (29.7%)	10 (9.9%)	**54 (53.5%)**
Mean strain ratio					
<3.25	10 (9.9%)	30 (29.7%)	8 (7.9%)	4 (4%)	**52 (51.5%)**
>3.25	0 (0%)	10 (9.9%)	30 (29.7%)	9 (8.9%)	**49 (48.5%)**
Pathological Diagnosis					
Benign cystic	2 (2%)	11 (10.9%)	4 (4%)	1 (1%)	**18 (17.8%)**
Benign solid	8 (7.9%)	20 (19.8%)	4 (4%)	3 (3%)	**35 (34.7%)**
Malignant	0 (0%)	9 (8.9%)	30 (29.7%)	9 (8.9%)	**48 (47.5%)**
Total	**10 (9.9%)**	**40 (39.6%)**	**38 (37.6%)**	**13 (12.9%)**	**101 (100%)**

In our study, benign lesions constituted for 52.48% of cases (n = 53), while remaining cases were malignant (n = 48; 47.52%). Among 53 benign lesions, 35 were benign solid lesions, which included fibroadenoma, benign phyllodes tumour and benign papillary neoplasm and remaining 18 lesions were benign cystic lesions. There were 48 malignant lesions, which included infiltrating ductal carcinoma and squamous cell carcinoma.

Table 4 shows further classification of breast lesions on the basis of age group and the type of lesions based on BIRADS score, elastography features (modified colour score and strain ratio), and pathological diagnosis. It was observed that all lesions in patients with age <21 years were classified as BIRADS 2 and 3. On modified colour score, nine lesions were in score of 0 and 1 and one lesion was categorized in score 2. All these lesions showed mean strain ratio of <3.25, suggestive of benign nature. All these lesions turned out to be benign on pathological findings. In the age group between 21 and 40 years, nearly 3/4th of lesions were in BIRADS 2 and 3 (29 of 40 lesions), with 10 lesions under BIRADS 4 and one lesion in BIRADS 5. A similar trend was also observed in the modified colour scoring and mean strain ratio. Modified colour score of 0 and 1 were observed in 27 lesions and modified colour score of 2 was seen in 13 lesions. Mean strain ratio of <3.25 was seen in 3/4th of patients and mean strain ratio >3.25 was seen in remaining 1/4th of patients. Pathological diagnosis showed 31 benign lesions and 9 malignant lesions. One lesion was a case of granulomatous mastitis, which showed mean strain ratio of 7.8 and was incorrectly classified as malignant on ultrasound (BIRADS 4), modified colour score (2) and mean strain ratio (7.8). Similarly, there was a case of mastitis with abscess, which was categorized into BIRADS 4, but had a modified colour score of 0 and mean strain ratio 0.87, suggestive of benign etiology. In the age group

between 41 and 60 years, there was an increasing trend in malignancy as evidenced by greater number of lesions in BIRADS categories 4 and 5 (73.6% of lesions), modified colour score of 2 and strain ratio of >3.25 (78.9% of lesions in each group). Pathological diagnosis showed 30 lesions as malignant. There were two lesions, which were classified as BIRADS 3. Modified colour score was 2 for both the lesions and they showed mean strain ratio >3.25 and were classified as malignant on elastography. Pathology showed squamous cell carcinoma in one and infiltrating ductal carcinoma in other. Ultrasound (BIRADS 4) incorrectly classified one case of infiltrating ductal carcinoma as mastitis. Modified colour score and mean strain ratio classified the lesion as malignant. There was one case of benign phyllodes tumour, which was incorrectly classified as BIRADS 4 lesion on ultrasound and malignant on modified colour score (score 2). Mean strain ratio for the lesion was 1.46, indicating that the lesion is benign in nature. There was one patient with infiltrating ductal carcinoma, which was classified as malignant on ultrasound (BIRADS 4) and mean strain ratio (4.86), but incorrectly classified as equivocal on modified colour score (score 1). All the cases were classified correctly as benign or malignant by mean strain ratio. In patients with age group >60 years, there were 13 lesions of which 10 (76.9%) were classified as malignant on ultrasound (BIRADS 4 and 5) and modified colour score (score 2) and nine (69.2%) were classified as malignant on mean strain ratio. On pathological diagnosis, all the cases classified as malignant on mean strain ratio were malignant and four lesions (31.8%) were benign. There was a case of benign papillary neoplasm, which was classified as BIRADS 4 on ultrasound. Modified colour score of 1 was suggestive of equivocal lesion and mean strain ratio was 2.15, which suggested that the lesion was benign. Rest of the lesions

showed malignant features on ultrasound, modified colour score and mean strain ratio.

Size of lesion

Table 5. Comparison between lesion size, mean strain ratio and pathological diagnosis

Mean strain ratio	**Benign**		**Malignant**	
	<2 cm	>2 cm	<2 cm	>2 cm
<3.25	20	32	0	0
>3.25	1	0	15	33
Total	21	32	15	33
P = .19; not significant				

Table 5 shows comparison between the lesion size, mean strain ratio and pathological diagnosis. It can be seen that there was only one lesion, which was <2 cm with mean strain ratio of >3.25. The lesion was classified as malignant on strain ratio, however, the lesion turned out to be benign (granulomatous mastitis). Rest of the lesions were accurately diagnosed as benign or malignant irrespective of their size. The mean size of benign lesions was 2.56 ± 1.74 cm (mean ± SD) and the mean size of malignant lesions was 2.87 ± 1.52 cm (mean ± SD). There was no statistically significant difference between the mean size of lesions in benign or malignant (*P* = .35; not significant).

Benign Cystic Masses

Cystic masses showed less resistance to compression with external pressure. They revealed classic the BGR colour interface artefact on modified colour scoring scale in elastography. Cystic lesions included fibrocystic disease and infective breast lesions such as breast abscess. Among 18 benign cystic lesions, 10 lesions were diagnosed with fibrocystic disease and 8 lesions were diagnosed as breast abscess. Among the eight breast abscesses one patient had long standing breast discharge. Clinically tuberculous mastitis was suspected. It was diagnosed as breast abscess on ultrasonography (BIRADS 3) and elastography (BGR artifact and mean strain ratio of 3.0) AFB staining of breast aspirate was negative for tuberculous bacilli.

Table 6. Benign cystic breast masses.

Benign cystic breast lesions	Number	%
Fibrocystic disease	10	55.55
Breast abscess	8	44.45
Total	18	100

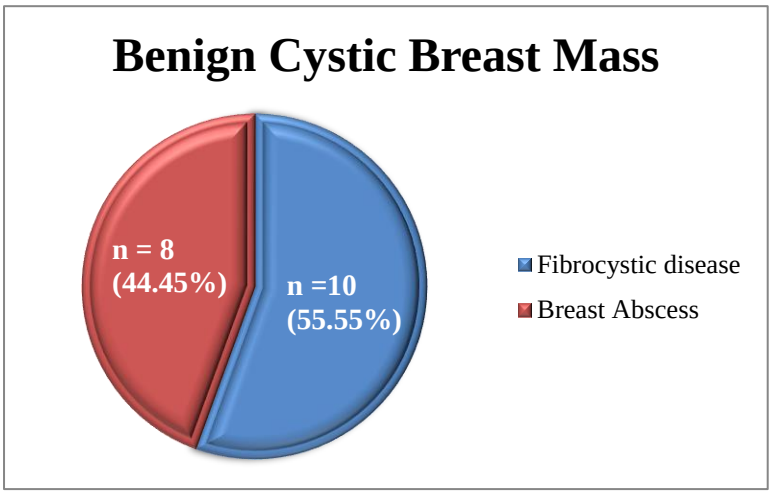

Figure 18. Benign cystic breast masses.

Pathological Results

Pathological investigation included either fine needle aspiration cytology or histopathological examination. In 101 breast masses in which either cytology or histopathology was performed, 48 were malignant and 53 were benign breast masses. Among 53 benign breast masses, 18 were benign cystic lesions in which aspiration cytology was performed and 35 were benign solid lesions. In 18 cystic lesions, 10 were fibrocystic diseases and 8 were breast abscesses and among 35 solid breast masses, 32 were fibroadenoma, two were benign phyllodes tumours and one was benign papillary neoplasm. Among 48 malignant breast masses, 47 were infiltrating ductal carcinoma and one was squamous cell carcinoma.

Table 7. Final Pathological Diagnoses.

Pathology Results	**Number**	**%**
Fibrocystic disease	10	9.9%
Breast abscess	8	7.92%
Fibroadenoma	32	31.68%
Benign phyllodes tumor	2	1.98%
Benign papillary neoplasm	1	0.99%
Infiltrating ductal carcinoma	47	46.54%
Squamous cell carcinoma	1	0.99%
Total	101	100%

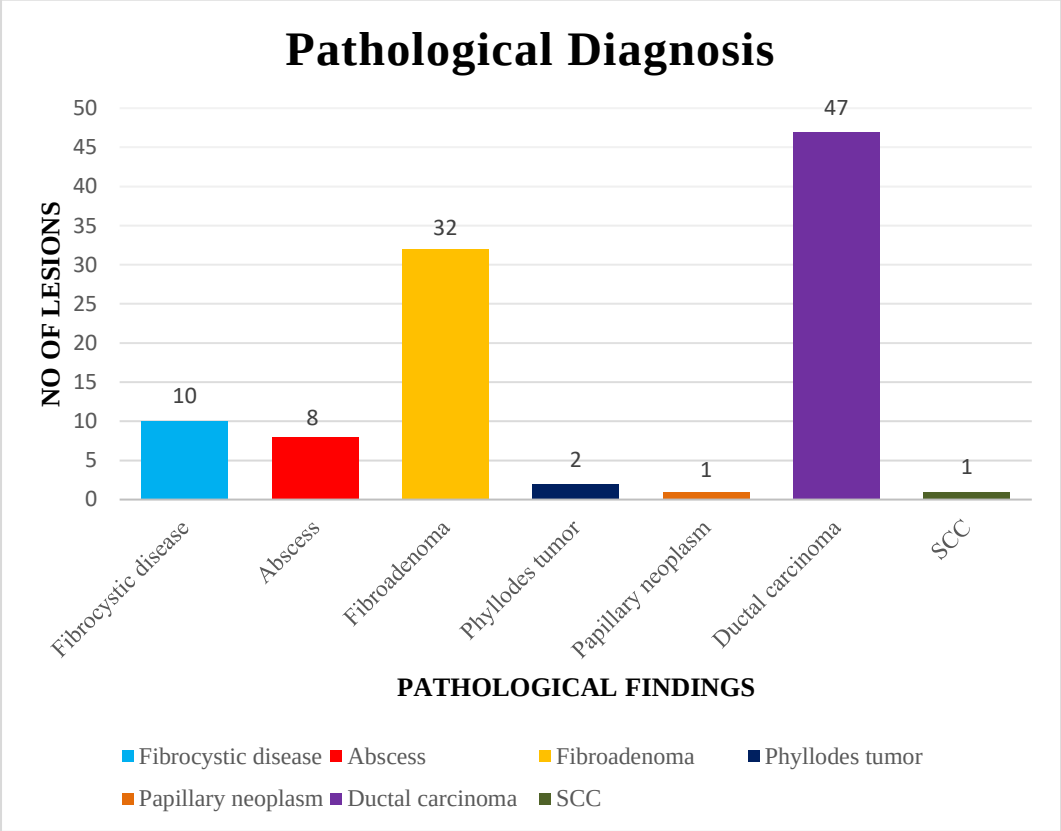

Figure 19. Final pathological diagnoses.

Categorization of breast masses based on modified colour scoring

In 101 breast masses, most of the lesions (n = 54) were categorized as score 2. Out of these 54 lesions, 47 were pathologically proven as malignant breast masses and seven were benign lesions. A total of 25 breast masses had score of 1 and 22 lesions were categorized with score 0. Of the 25 breast masses with 1, 24 lesions were benign and one lesion was malignant. All the 22 lesions with score of 0 were benign. Modified colour score showed sensitivity of 65.2%, specificity of 75.8%, positive (PPV) and negative predictive values (NPV) of 87% and 46.8% respectively for differentiating benign from malignant lesions with overall diagnostic accuracy ranging upto 68.32% (Table 8).

We further modified the modified colour score to include only 2 categories, benign and malignant. Table 9 shows the results obtained with the new colour scoring system. The new colour scoring system was named as Indian colour scoring system. Modified colour scores of 0 and 1 (Tsukuba scores of 1 to 3) can be considered as benign and modified colour score of 2 (Tsukuba scores of 4 and 5) be considered as malignant. This modification has sensitivity of 97.8%, specificity of 87.0%, PPV of 86.79% and NPV of 87.08% with a diagnostic accuracy ranging to 92.08%. This modification has overall improved diagnostic accuracy when compared with 3-category classification, which has low diagnostic accuracy of 68.32%. In this category, there was one case, which was considered as benign (score 0) and was revealed as malignant on pathological diagnosis. The lesion was

classified as BIRADS 4 on ultrasound and mean strain ratio of >3.25. With the new Indian colour scoring system, the chance of missing malignant lesion was 2.1%.

Table 8. Classification of Breast Lesions Based on Modified Colour Scoring System and Correlation with Pathological Diagnosis

Modified colour scoring system*	**Number**	**Benign**	**Malignant**
0	22	22	0
1	25	24	1
2	54	7	47
Total	101	53	48
*Modified colour score showed sensitivity of 65.2%, specificity of 75.8%, positive (PPV) and negative predictive values (NPV) of 87% and 46.8% respectively for differentiating benign and malignant lesions with overall diagnostic accuracy ranging to 68.32%.			

Table 9. New Indian Colour Scoring System Modified From Modified Colour Score

New Indian colour scoring system*	**Number**	**Benign**	**Malignant**
0 (Benign)	47	46	1
1 (Malignant)	54	7	47
Total	101	53	48
*New Indian colour scoring system has sensitivity of 97.8%, specificity of 87.0%, PPV of 86.79% and NPV of 87.08%. The diagnostic accuracy here was ranging upto 92.08%.			

Categorization of breast masses based on strain ratio

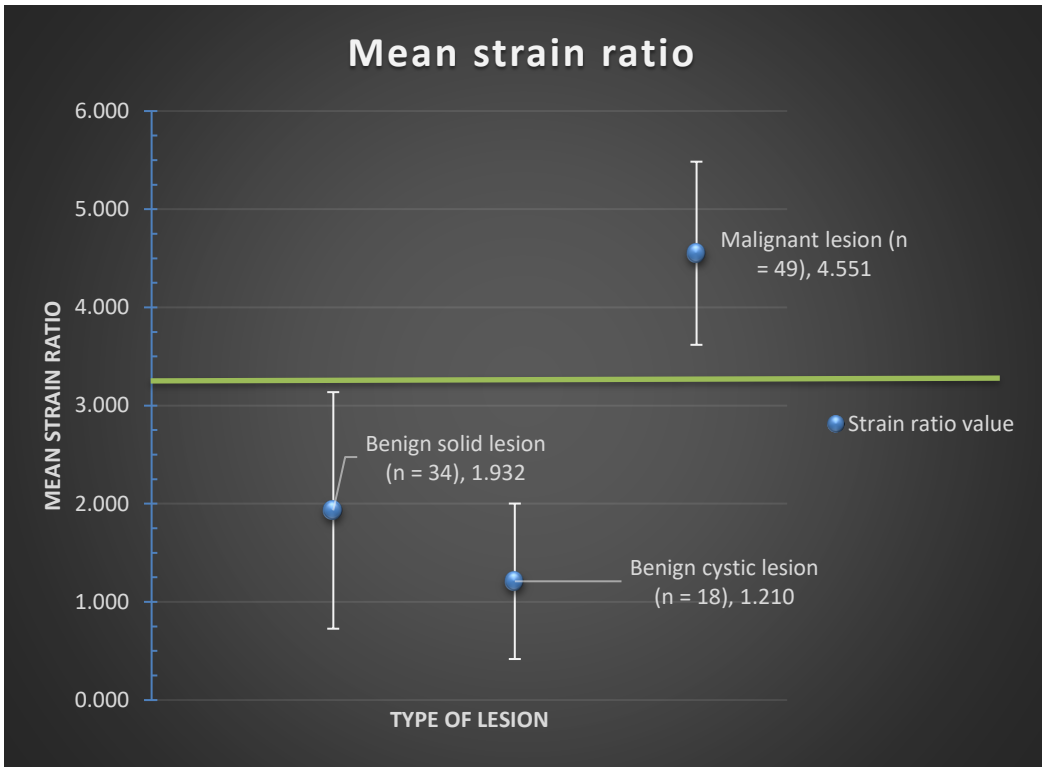

Figure 20. Mean strain ratio (± SD) in benign solid lesions, benign cystic lesions and malignant lesions. Note the green line represents strain ratio of 3.25, which was used as cut off to differentiate benign from malignant lesion in our study. None of the malignant lesions had strain ratio of <3.25.

A cut off strain ratio of 3.25 was used to differentiate benign from malignant breast masses. In 101 breast masses, 52 breast masses had strain ratio <3.25, suggesting a benign etiology and 49 breast masses had strain ratio >3.25, indicating the mass was malignant. Mean strain ratio for benign solid breast lesions was 1.932 ± 1.205 (mean ± SD), mean strain ratio for benign cystic lesion was 1.210 ± 0.792 (mean ± SD) and the mean strain ratio of malignant breast masses was 4.551 ± 0.933

(mean ± SD); (Figure 20). Statistically there was a significant difference between mean strain ratio between benign solid and benign cystic lesions ($P<.05$). The overall mean elastography index for benign lesions was 1.686 ± 1.135, which was statistically significant when compared with mean strain ratio of malignant lesions ($P<.001$) (Table 10). One lesion (a case of granulomatous mastitis) had a mean strain ratio of 7.8 and was given as malignancy; however, the lesion turned out to be benign. Strain ratio when used as an individual elastographic parameter in assessing the malignant breast masses showed sensitivity of 100%, specificity of 98.11%, positive (PPV) and negative predictive values (NPV) of 97.96% and 100% respectively. The diagnostic accuracy was 99.01% in diagnosis of malignant breast lesion. Similarly, strain ratio showed sensitivity of 98.11%, specificity of 100%, positive (PPV) and negative predictive values (NPV) of 100% and 97.96%.

Table 10. Average mean strain ratio (mean ± SD) for benign solid, benign cystic and malignant breast masses.

Nature of the Breast Lesion	**Mean Strain Ratio (mean ± SD)**
Benign Solid Lesion*	1.932 ± 1.205
Benign Cystic Lesion*	1.210 ± 0.792
Malignant Lesion**	4.551 ± 0.933
*$P<.001$ between benign and malignant lesions; **$P<.05$ between benign solid and benign cystic lesions.	

Comparison of Modified colour scoring, Strain ratio and Pathological Findings

Mean strain ratio identified all 48 malignant masses correctly. Modified colour score on the other hand overestimated malignant cases as shown in Table 11. One malignant case was reported as indeterminate on modified colour scoring. It was observed that modified colour score of 0 is definitely benign, while score of 1 and 2 require biopsy. Almost all cases of colour score 1 were benign. Meanwhile, the seven of 54 cases of colour score of 2 turned benign. This indicated low sensitivity. Mean strain ratio could identify all malignant lesions correctly and only one benign lesion was classified as malignant. All cases, which were benign on strain ratio were benign on histopathology.

Table 11. Comparison of modified colour score, strain ratio with pathology

Diagnosis based on modality		**Pathological Diagnosis**		**Total**
		Benign	Malignant	
Modified colour scoring	Benign	22	22	22
	Indeterminate	24	1	25
	Malignant	7	47	54
Mean strain ratio*	Benign	52	0	52
	Malignant	1	48	49
Total		53	48	101

*A mean strain value of <3.25 is considered as benign and ≥3.25 is considered as malignant.

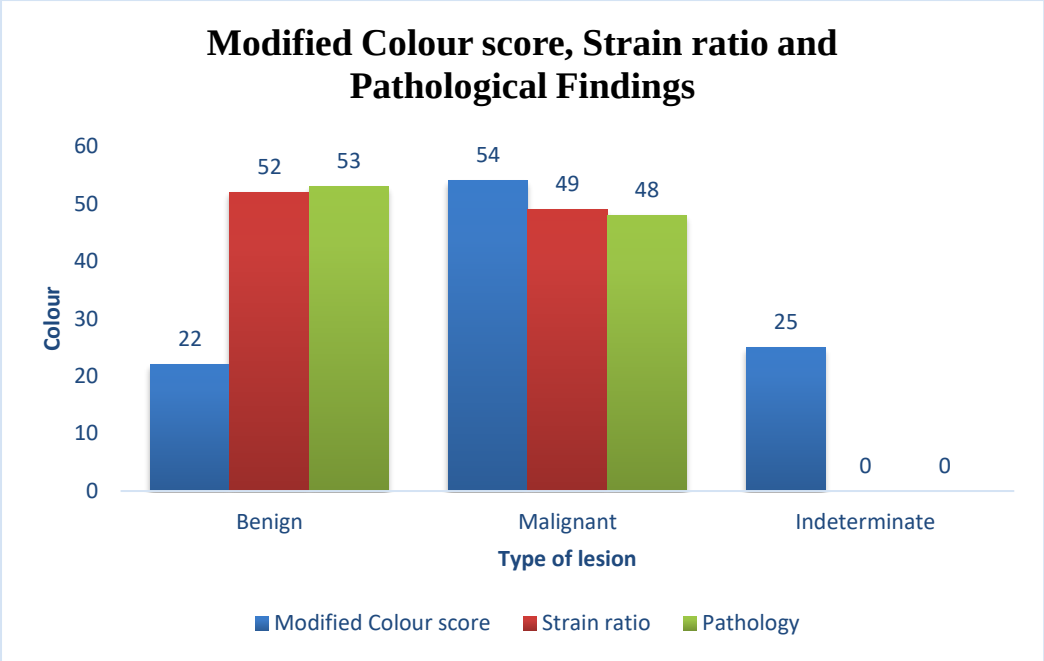

Figure 21. Comparison of modified colour score, strain ratio with pathology. Note: Using strain ratio, the lesions are divided into either benign or malignant. In modified colour score, a score of 1 indicates the lesion is indeterminate, i.e., it could be either benign or malignant.

Comparison of Ultrasonography, Elastography and Pathology Findings:

In 101 breast masses, 35 solid and 18 cystic lesions were proven benign by pathological examination. Ultrasonography was accurate in picking only 33 solid and 17 cystic benign lesions, whereas elastography diagnosed 34 solid and all 18 cystic masses correctly (Table 12). For final comparison with ultrasound, mean strain ratio was used as elastography parameter as it showed high sensitivity and specificity and is an objective measurement. Among the 48 pathologically proven malignant breast masses, elastography diagnosed all malignant masses accurately, whereas ultrasonography was able to diagnose only 44 malignant masses (Table 13). Overall, ultrasound showed sensitivity of 89.8%, specificity of 96.15%, PPV of 95.65%, NPV of 90.91% and overall diagnostic accuracy of 93.07%.

Table 12. Comparison of Benign Solid Lesion, Benign Cystic Lesion and Malignant Lesions with Ultrasound, Elastography and Pathology Findings.

Modality	**Ultrasonography**	**Elastography**	**Pathology**
Benign Solid Lesion	39	34	35
Benign Cystic Lesion	17	18	18
Malignant Lesion	45	49	48

Note: On ultrasound BIRADS score of ≤ 3 are considered as benign and >3 are considered as malignant.
Elastography findings are combination of both strain ratio and modified colour score. For differentiating solid and cystic lesion BGR artifact is considered and for differentiating benign from malignant lesion, strain ratio of 3.25 is considered.

Table 13. Correlation Between Ultrasound and Elastography Diagnosis with Pathological Diagnosis.

Diagnosis based on modality		**Pathological Diagnosis**		**Total**
		Benign	Malignant	
USG	Benign	50	2	52
	Malignant	5	44	49
Elastography	Benign	52	0	52
	Malignant	1	48	49
Total		53	48	101

Note: On ultrasound BIRADS score of ≤ 3 are considered as benign and >3 are considered as malignant.
On elastography, strain ratio is considered as an important parameter for differentiating benign from malignant lesion. A strain value of <3.25 is considered as benign and ≥3.25 is considered as malignant.

Two malignant breast masses were misdiagnosed by ultrasonography as benign, one was a case of infiltrating ductal carcinoma and another one case was squamous cell carcinoma. Ultrasound incorrectly diagnosed five benign lesions as malignant, which included one case of benign phyllodes tumour, two cases of mastitis with breast abscess, one benign papillary neoplasm and one case of granulomatous mastitis. Elastography and ultrasound diagnosed one benign case as malignant. It was a case of granulomatous mastitis.

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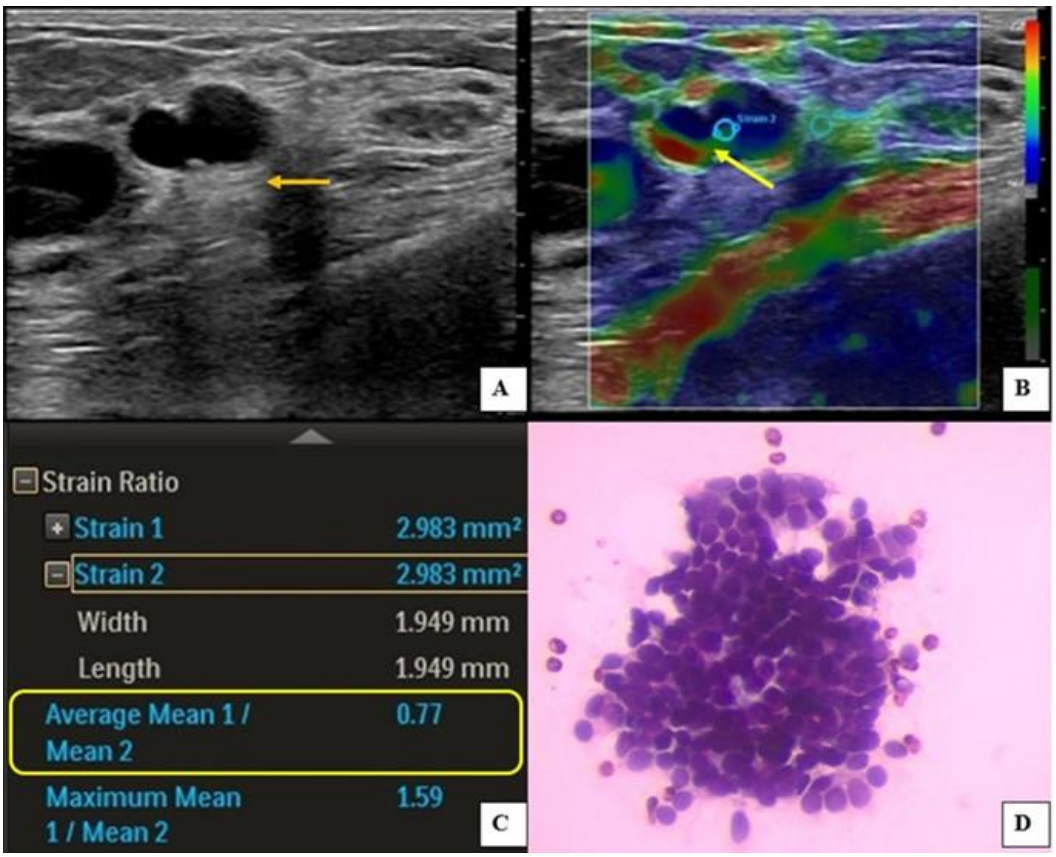

Figure 22: Ultrasonography in 40-year lady with left mastalgia showed (Fig A) well-defined, ovoid, anechoic cystic lesion with posterior acoustic enhancement (thick orange arrow), suggestive of BIRADS 2 lesion. On elastography (Fig B), the lesion demonstrated BGR trichromatic interface pattern (thick yellow arrow, score 0) in modified colour score. Mean strain ratio was 0.77 (Fig C; yellow box) suggestive of benign cystic lesion. FNAC showed benign ductal epithelial cells arranges in sheets and clusters (Fig D)

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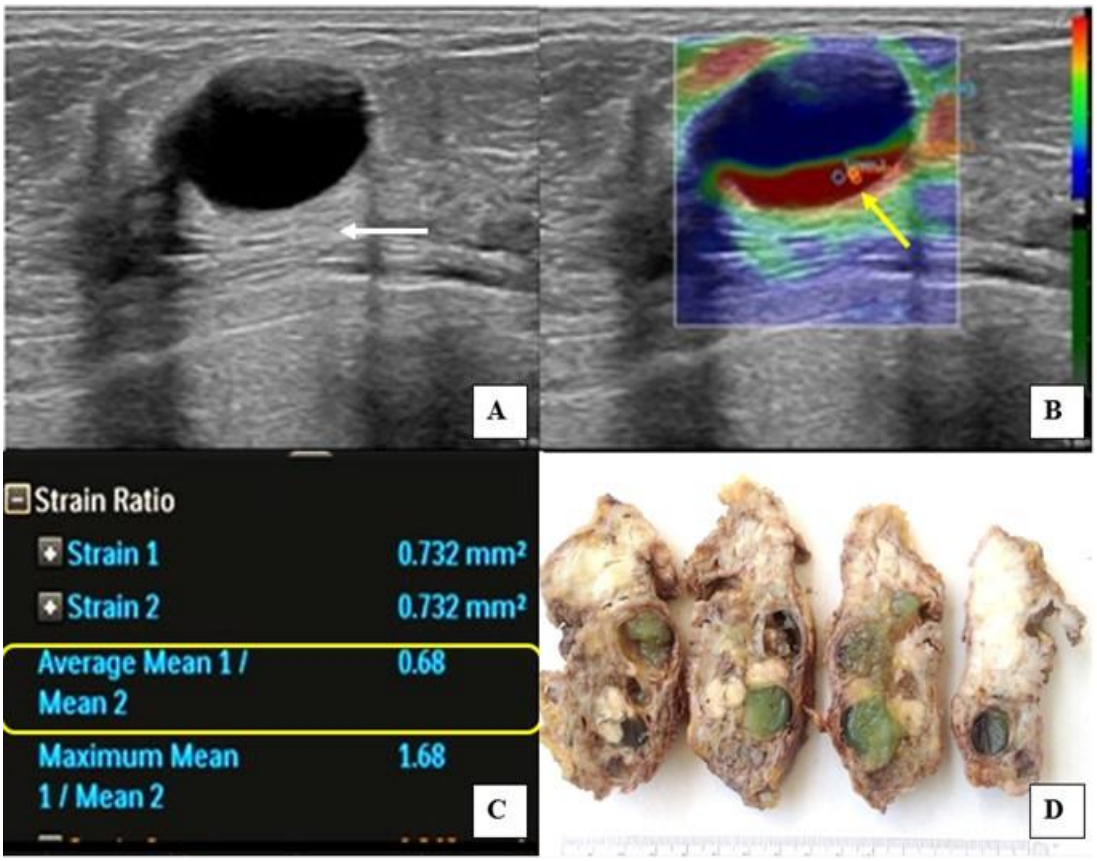

Figure 23: Ultrasonography in 36-year old lady with palpable right breast lump showed well-defined, ovoid, anechoic cystic lesion with posterior acoustic enhancement (thick white arrow), suggestive of BIRADS 2 lesion (Fig A). On elastography, the lesion demonstrated BGR (thick yellow arrow) trichromatic interface pattern (score 0) in modified colour score (Fig B). Mean strain ratio was 0.68 (yellow box, Fig C). On gross image, multiple cysts filled with greenish fluid and grey white areas representing fibrosis were seen (Fig D).

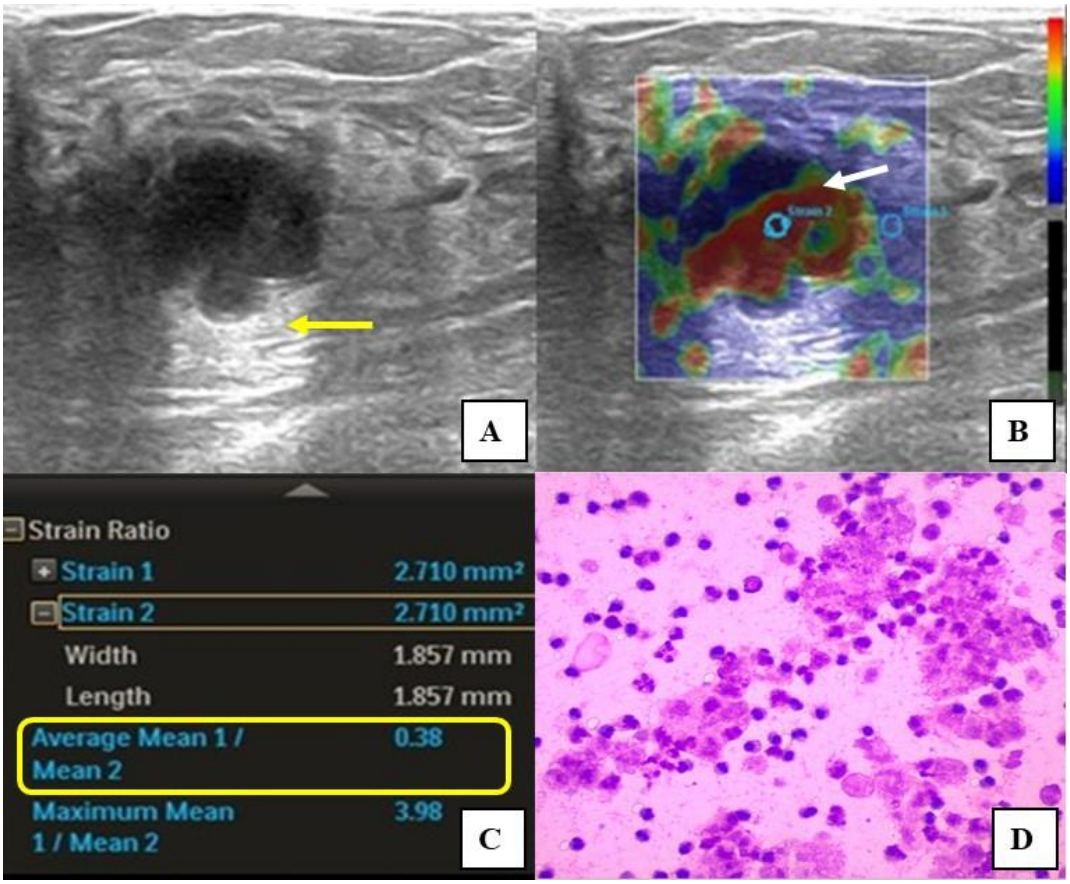

Figure 24: Ultrasonography in 38-year old lady with fever and left mastalgia showed a well-defined, ovoid, anechoic cystic lesion (thick yellow arrow) with echogenic debris and posterior acoustic enhancement, suggestive of BIRADS 3 lesion (Fig A). On elastography, the lesion demonstrated BGR trichromatic interface pattern (thick white arrow) in modified colour score (score 0, Fig B). Mean strain ratio was 0.38 (yellow box, Fig C). Correlating ultrasonography and elastography, a diagnosis of breast abscess was given. The same was confirmed with fine needle aspiration cytology (Fig D).

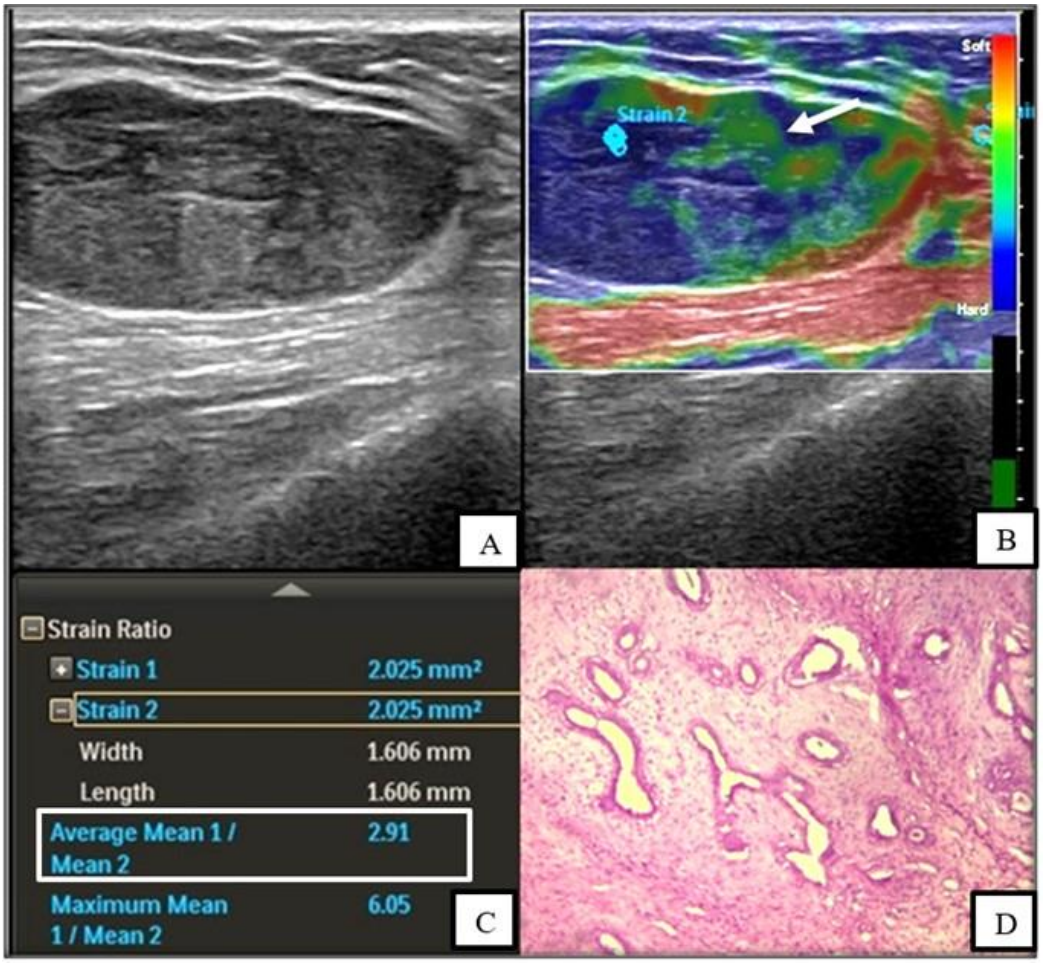

Figure 25: Ultrasonography in 29-year female patient with palpable right breast mass showed a well-defined, hypoechoic solid lesion with posterior acoustic enhancement, suggestive of BIRADS 3 lesion (Fig A). On elastography, the lesion demonstrated mosaic patterns of blue and green (score 1, thick white arrow) suggestive of equivocal lesion (Fig B). Mean strain ratio was 2.91 (white box) suggestive of benign solid lesion (Fig C). FNAC and histopathology confirmed it as fibroadenoma (Fig D).

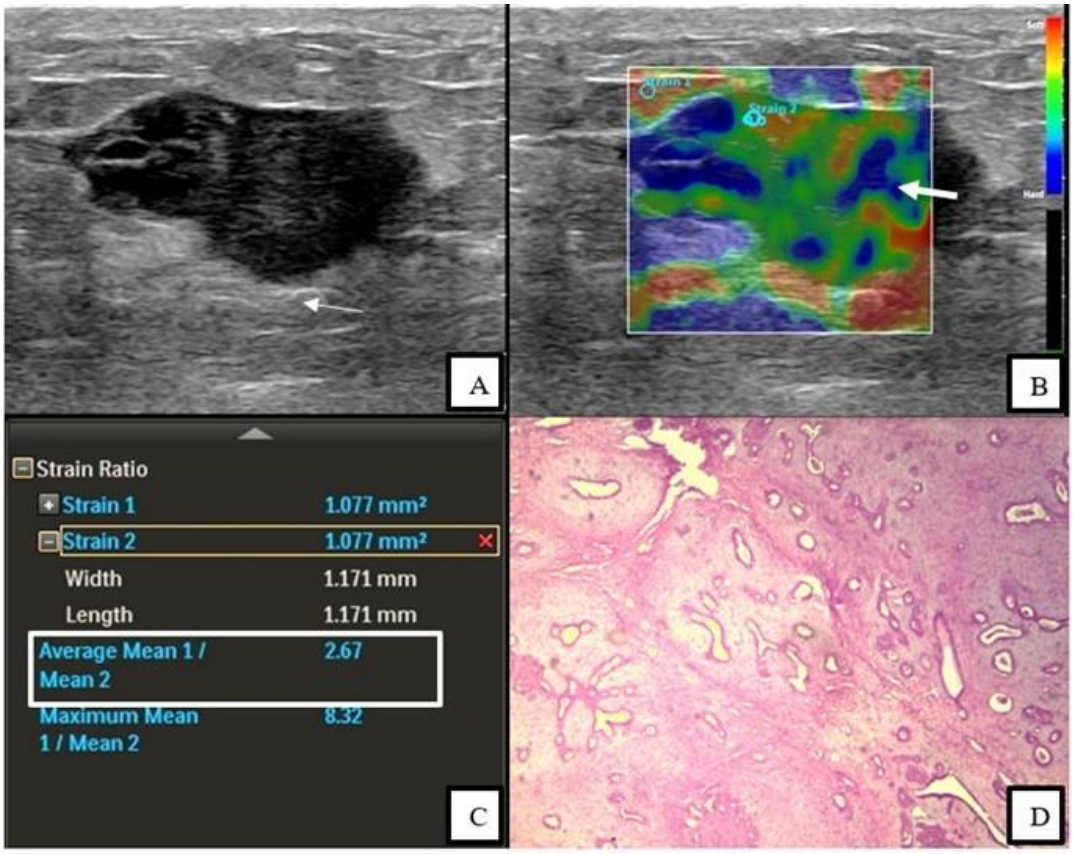

Figure 26: Ultrasonography in 26-year female patient with palpable left breast lump showed a well-defined, hypoechoic solid lesion with posterior acoustic enhancement, suggestive of BIRADS 3 lesion (Fig A). On elastography, the lesion demonstrated mosaic patterns of blue and green (score 1, thick white arrow) suggestive of equivocal lesions (Fig B). Mean strain ratio was 2.67 (white box) suggestive of benign solid lesion (Fig C). Histopathology showed mixture of epithelial and mesenchymal cells suggestive of fibroadenoma (Fig D).

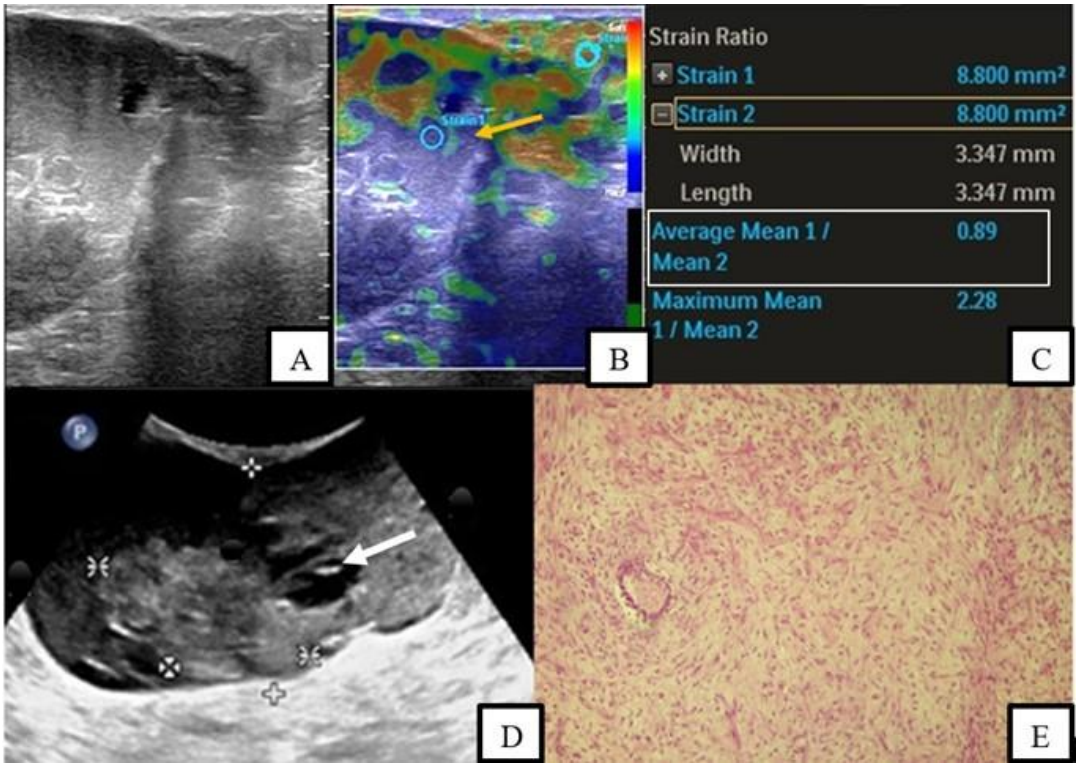

Figure 27: Ultrasonography in a 45-year lady with a right breast mass, clinically suspected as malignancy showed a large, ovoid, lobulated, hypoechoic predominantly solid lesion with few areas of cystic degeneration (thick white arrow) suggestive of BIRADS 4 lesion (Fig A & D). On elastography, the lesion demonstrated mosaic pattern (thick orange arrow) of blue and green (score 1) suggestive of equivocal lesion (Fig B). Mean strain ratio was 0.89 (white box) suggestive of benign solid lesion (Fig C). Patient underwent modified radical mastectomy and histopathology confirmed it as benign phyllodes tumour (Fig E).

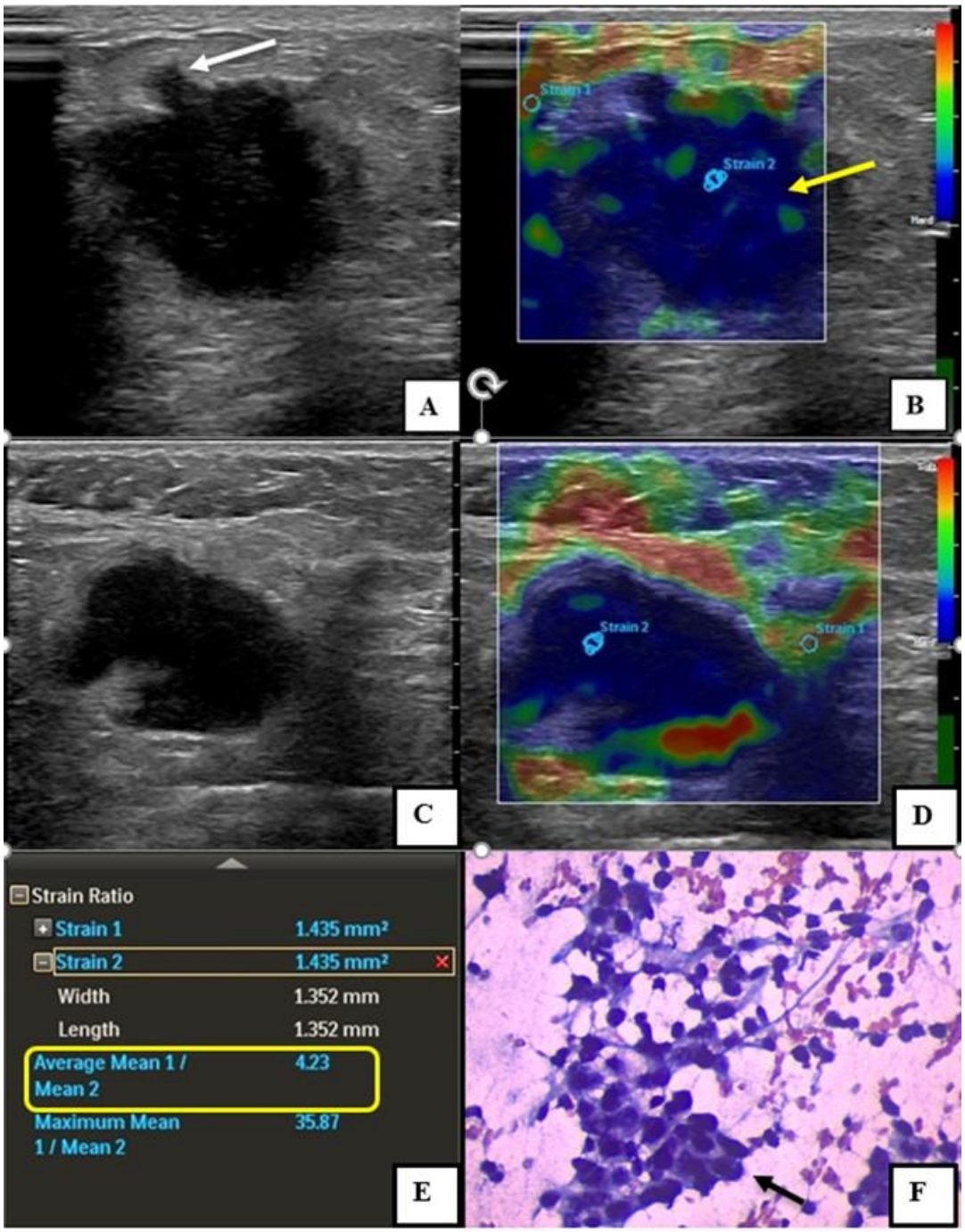

Figure 28: Ultrasonography in 40-year lady showed a spiculated (thick white arrow), hypoechoic solid lesion (Fig A) with multiple right axillary lymph nodes enlargement and loss of fatty hila (Fig C) suggestive of BIRADS 5. On elastography, (Fig B & E) the lesion (thick yellow arrow) and lymph nodes showed uniform blue colour pattern suggestive of malignancy (score 2). Mean strain ratio was 4.23 (Fig E; yellow box) and 4.03 for mass and axillary lymph node respectively. FNAC showed ductal epithelial cells with high nuclear cytoplasmic ratio suggestive of infiltrating ductal carcinoma (Fig F).

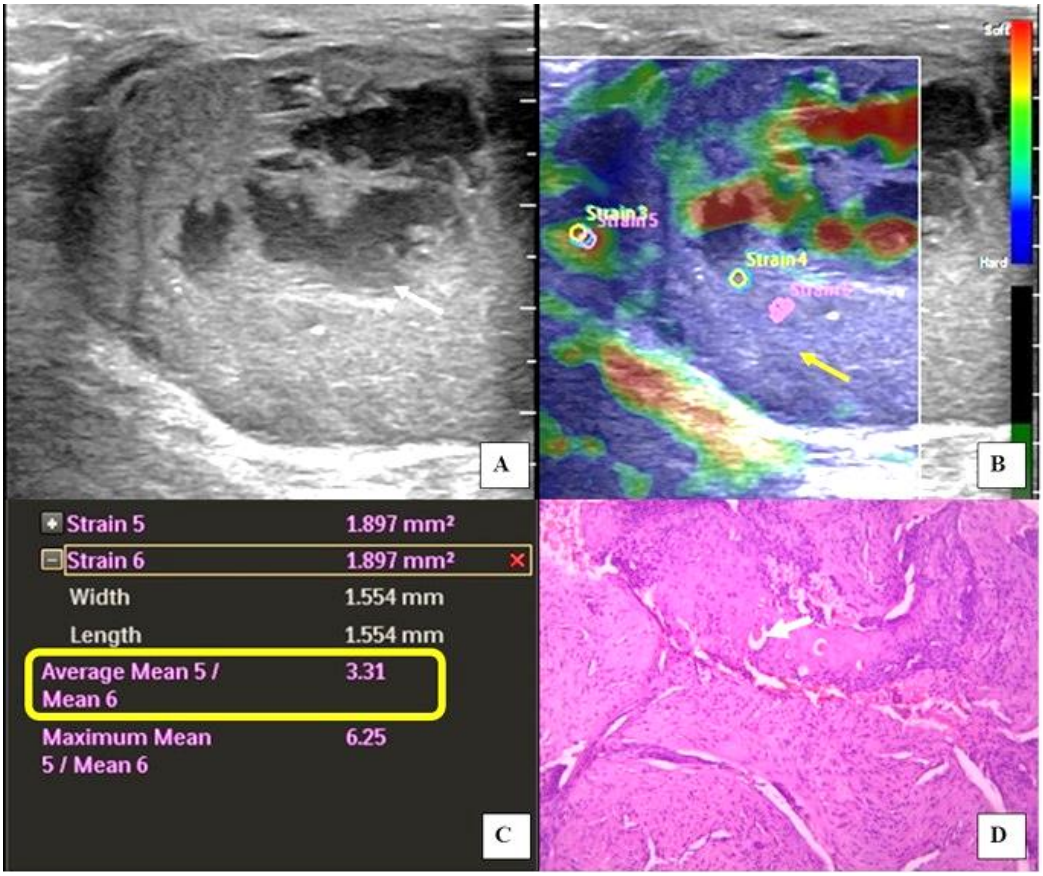

Figure 29: Ultrasonography in 35-year female patient showed a well-defined, lobulated, ovoid, hypoechoic solid lesion with central necrosis (thin white arrow) and posterior acoustic enhancement, possibly breast abscess (Fig A). Elastography (Fig B & C), showed features of malignancy with uniform pattern (score 2) of blue (thick yellow arrow) and mean strain ratio of 3.31 (white box). Ultrasound guided core needle biopsy (Fig D) revealed islands of squamous epithelium (thick short white arrow) with dyskeratosis, in a fibrous stroma suggestive of squamous cell carcinoma.

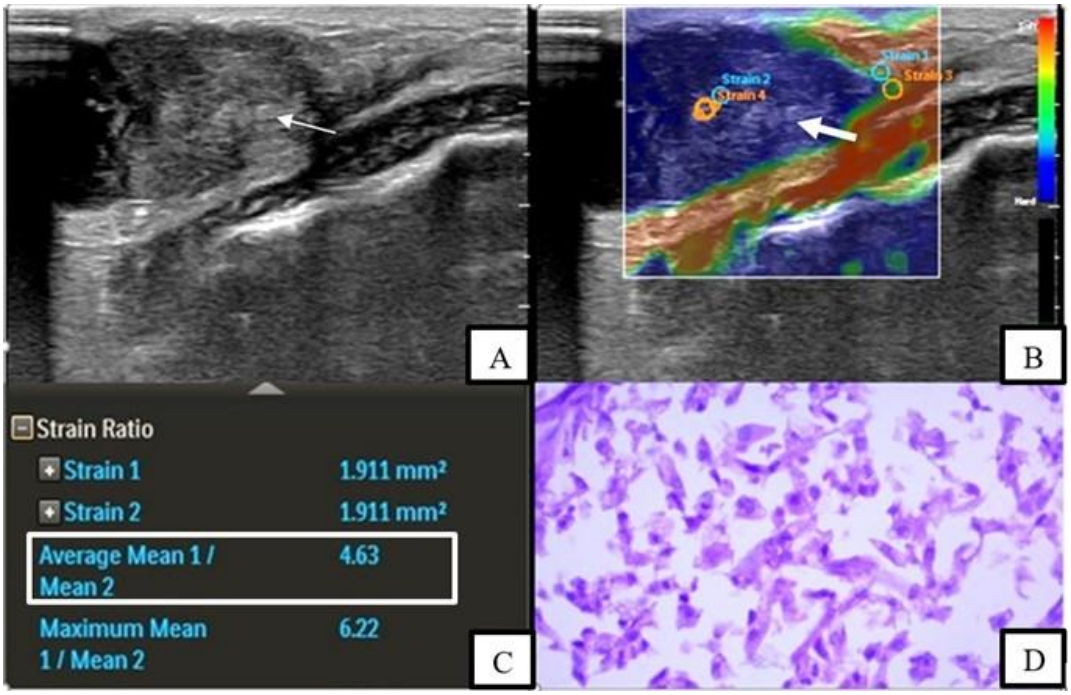

Figure 30: Ultrasonography in 80-year male patient with swelling in left mammary region. Ultrasonography showed (Fig A) multiple micro-lobulated, hypoechoic solid lesion (thin white arrow). The lesion was diagnosed as malignant by both ultrasonography (BIRADS 5) and elastography (modified colour score – 2 showed by thick white arrow and mean strain ratio – 4.63, showed by white box, Fig B & C). Histopathology confirmed the diagnosis as invasive ductal carcinoma (Fig D).

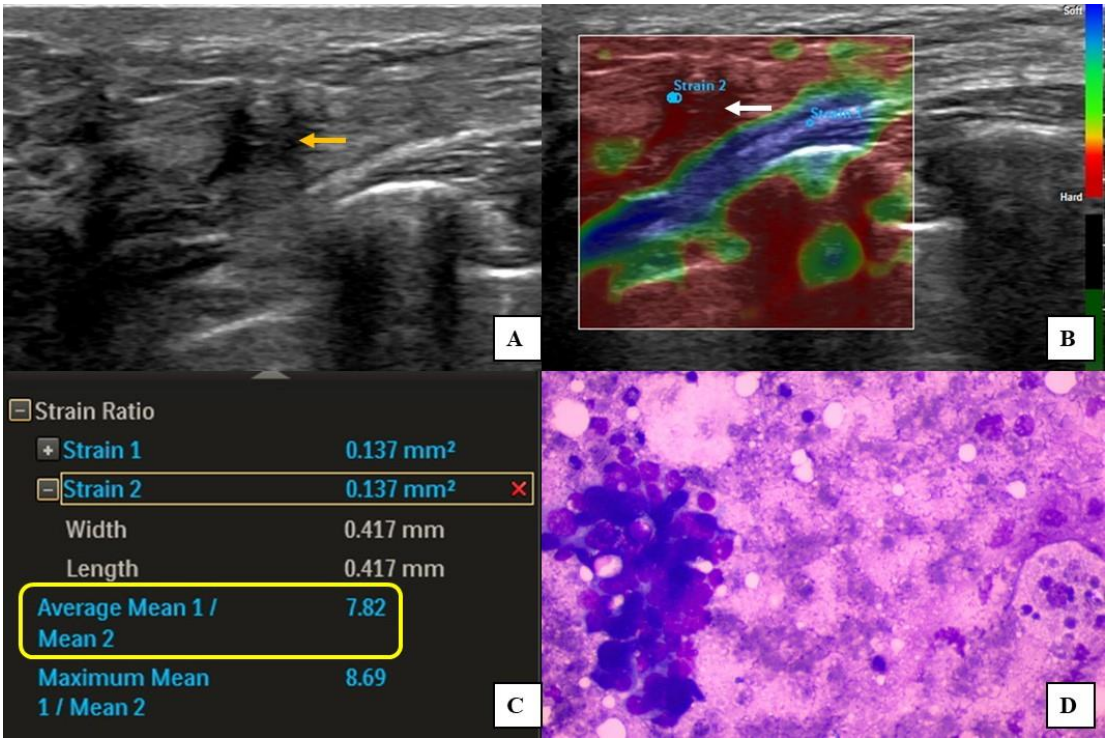

Figure 31 Ultrasonography in 32-year female patient with palpable left breast lump showed a spiculated solid lesion with posterior acoustic enhancement, suggestive of BIRADS 5 lesion (Fig A). On elastography, the lesion demonstrated uniform patterns of red colour (red colour was considered as hard) (score 2, thick white arrow) suggestive of malignant lesions (Fig B). Mean strain ratio is 7.82 suggestive of malignant solid lesion (Fig C). FNAC confirmed it as mastitis (Fig D).

DISCUSSION

Diagnosing a breast lesion as benign or malignant is clinically important because it can avoid unnecessary biopsies. Addition of elastography technique helps to differentiate benign from malignant breast masses. Especially it is important in the lesions with BIRADS score 3 and 4. Elastography is having a potential in reducing unwanted biopsies particularly in benign and/or cystic lesions.

In our study we compared ultrasonography and elastography findings in 101 breast masses from 86 patients. The most common age group in our study was 41-60 years (37.6%), followed by 21 to 40 years (34.6%) with a mean age of 42.45 ± 16.2 years (mean ± SD) with a range 14 to 95 years. Our results are similar to study by Menezes et al[46] who reported the commonest age of women with breast lesions to be 45-60 years of age. A similar observation was also made by Dong et al. They reported a mean age of 45.39 ± 12.97 years (range 21 to 77 years) in women presenting with breast lesions[51].

Incidence of breast carcinoma is more common in females. Males are very rarely present with breast carcinoma. Male to female ratio in our study was 1:85 (1.2% of males) which was in correlation with a global survey conducted by National cancer institute, Bethesda, USA, which showed ratio of male to female breast carcinoma among Asians at 1:112[52]. A study in North India has also shown

lower incidence of male breast carcinoma at 1.03%. This is consistent with our finding. There is variation in male breast cancers among Indians, with highest incidence being 4.1% in Jammu and Kashmir[53,54]. A study conducted in South India also showed that incidence of breast cancer in male was 1%[55].

In our study, more than half the lesions were present in the right breast (50.5%) and 37.62 % had left sided lesions. Six patients had bilateral breast masses (11.88% of lesions), making total of 56.4% of lesions on right side. The laterality ratio (L:R) in our study is 0.75. A similar observation was also made by Akthar et al also who reported that more than half of breast lesions were present in the right side (56.1%)[56]. A study conducted by Nwadike et al., was also comparable with our study with laterality ratio of 0.81[57]. Shugrue et al in his retrospective study on 1.2 million breast masses showed that the laterality ratio was influenced by number of factors like age, ethnicity and sex. In most of the countries left side breast masses were more common but, in some countries, right sided breast mass were more common. The reason for left predominance is not clearly understood[58].

In our study, most of the breast masses were categorized under BIRADS 4 (n=36) constituting 35.64% of cases followed by BIRADS 3 (n=30) which included 29.7% of the breast masses and BIRADS 5 constituted 14 masses (13.86 %). Yilmaz E et al., also showed that BIRADS 4 lesions constituted majority in his study constituting about 43.09% of total cases[47].

In our study, 53 masses (52.47%) were benign and 48 masses (47.53%) were malignant. Among the 53 benign lesions, 18 (17.8% of overall lesions) were cystic and 35 (34.6% of overall lesions) were solid masses. Özel et al, in their study reported high incidence of benign lesions (71%) of which benign solid lesions constituted 47.8% of overall lesions and benign cystic lesions formed 23.3% of overall cases. Malignant lesions constituted only 28.9% of overall lesions[59]. Our findings also differ from observations made by Xiao et al., who in their study observed that cystic lesions constituted about 39% of overall cases and solid benign lesions constituted about 25.3% of overall lesions. They also reported more benign lesions (64.2%)[60]. These differences could be attributed to the different geographic areas, where the studies were conducted i.e. in Poland[59] and China[60] respectively.

Among 18 benign cystic lesions in our study, 10 (55.55%) were fibrocystic disease and 8 (44.45%) were breast abscess. All cystic lesions in our study demonstrated chromatic tri-stratification artifact called BGR interface artifact. Cho et al., in their study of 13 cystic lesions showed that strain elastography showed BGR artifact. The authors proposed that the presence of trichromatic pattern (BGR artifact) helps in differentiating a cystic lesion from solid mass[61]. The formation of BGR artifact in cystic lesions can be explained by the fact that the gradient of the tissue displacement, which happens following compression of tissue is near to 0 in a cystic lesion. For smoothing the resultant images on output screen, a linear interpolation of data occurs in the machine, wherein the gradient of displacement gets reversed in the superficial layer of lesion (therefore coded blue). The displacement of bottom layer of cyst is overestimated and this is coded red, resulting

in this artifact. This artifact can effectively differentiate between a cyst and a solid lesion. Ultrasound may sometimes show internal echoes in complicated cysts, which contain necrotic cellular debris and/or amorphous proteinaceous material. These components when seen with improper setting may mimic a solid mass and may warrant unnecessary cytology/biopsy. Sometimes, it is also possible that the BGR artefact may not always indicate a benign cystic lesion as large malignant breast mass with extensive necrotic/cystic components may also show similar finding. We avoided this pitfall by considering the colour pattern in the whole lesion. Furthermore, we included strain ratio of the solid areas in the periphery to rule out possibility of malignancy.

Modified colour score is used as one of the parameters in our study. It is a modification of Tsukuba scoring. Chang et al in their study proposed modification of Tsukuba score into three categories as negative (score 0), borderline (score 1) and malignant (score 2)[41]. The Korean Breast Elastography Study Group released the practice guideline for breast elastography. They recommended a similar modification of Tsukuba scoring into three categories: score of Tsukuba 1 as negative, Tsukuba scores 2 and 3 as equivocal and scores of 4 and 5 as positive (malignant)[62]. We used the same scoring systems and classified lesions as benign (negative category; score 0), equivocal (borderline/equivocal category; score 1) and malignant (positive category; score 2). In our study, most of the benign lesions (24 of 53; 45.3%) were classified into equivocal category and seven benign lesions were classified as malignant lesions. Our findings shows that the modified colour scoring may be further modified to include negative (benign lesion) or positive (malignant lesion)

finding, which has been described in results. This modification has sensitivity of 97.8%, specificity of 87.0%, PPV of 86.79% and NPV of 87.08% with a diagnostic accuracy of 92.08% for benign lesions. This modification has overall improved diagnostic accuracy when compared with 3-category classification, which has diagnostic accuracy of 68.32%. With new Indian colour scoring system, the chance of missing malignant lesion was 2.1%. A similar finding was observed by Shamla et al., who reported a sensitivity of 85.3%, specificity of 87.8%, PPV of 92.7%, NPV of 76.5 % and overall diagnostic accuracy of 86.2%[55]. Further studies with larger sample sizes may be required to assess the efficacy of this modified colour scoring.

In our study, mean strain ratio of 3.25 was considered as cut off to differentiate benign from malignant breast mass. Among 101 breast masses, 52 (51.48%) had strain ratio values less than 3.25 and 49 (48.52%) were having strain ratio values more than 3.25. One benign case of granulomatous mastitis showed a higher mean strain ratio (7.8) and was classified under malignant category. None of the malignant lesions were classified as benign. This is important as it avoids unnecessary breast biopsy, particularly in patients with strain ratio of <3.25. Moreover, strain elastography ratio can itself be established as an indicator for differentiating benign from malignant lesion without the need to resort to ultrasound BIRADS category or use of modified colour scoring system.

Malignant breast lesions show large aggregates of elastin fibres, a process called elastosis. It is believed that the stromal (fibroblasts and myofibroblasts) and

malignant cells cause aggregation of elastotic material in breast tissue. Furthermore, other changes like changes in extracellular matrix and high cellularity all cause the malignant area to be stiff resulting in increased stiffness of malignant lesions[63].

Özel et al., obtained a strain elastography ratio of 3.1 as cut off for differentiating benign from malignant lesions, which is comparable to our study[59]. Bojanic et al., obtained a higher strain elastography ratio cut off of 3.8 for differentiating benign from malignant lesions with sensitivity and specificity of 90.5% and 93.2% respectively[49]. Various studies done by Gheonea et al[26], Mousa A E et al[45] and Blacik et al[50] showed that strain ratio more than 3.0 will be most probably malignant breast mass. Conversely, Thomas et al., reported strain elastography ratio of 5.1 ± 4.2 (mean ± SD) for malignant masses and strain elastography ratio of 1.6 ± 1.0 (mean ± SD) for benign lesions with $P<.001$ and a cut off value of 2.45 for differentiating benign from malignant lesion[64]. A high strain elastography ratio was also reported by Liu et al. They observed that a cut off of 4.15 was helpful in differentiating benign from malignant lesions with sensitivity of 92.2%, specificity of 72.5% and overall accuracy of 86.1%. It was reported that strain ratio was significantly better in identifying breast lesions when compared with ultrasonography[65]. The variation in cut off strain ratios can partly be explained by elastography procedure. During the procedure, compression is applied to evaluate the stiffness of tissue. When compression is applied on the fat, it will increase the stiffness of fat. Inadequate or overcompression may result in reduced or increased strain ratio. Additionally, elastography is operator dependent as it requires use of external compression[49]. In our machine, the machine itself provides the optimal

pressure to be applied and this reduces the bias of inadequate or overcompression, thus reducing these biases. Another reason for difference in strain ratios could be attributed to inconsistent ROI. Ideally, ROI should be placed in fatty tissue and measurements should be taken at the same depth. It is known that degree of compression varies with depth and this may affect the values[49]. In our study, we ensured that the ROI is placed horizontally at the same level and in fatty tissue to avoid these biases. This also increases the reproducibility of our study as combination of optimal compression, ROI placement in fatty tissue and placing ROI at same level as that of lesion offers objective evaluation and reduces operator bias. However, in larger lesions it may be difficult to place ROI at same level and this may have led to some bias.

In our study, the strain ratio was able to differentiate the benign from malignant lesion accurately irrespective of size of the lesion. This assumes significance as previous work by Bojanic et al., Itoh et al., and Liu et al., the authors reported that strain ratio showed better sensitivity and specificity in diagnosing lesions <3 cm[40,49,65]. Furthermore, Giuseppeti et al., reported that lesions <2 cm and >2 cm had sensitivity of 86% and 65% and specificity of 100% and 62% respectively. The authors argued that lesion size had an influence on degree of elasticity[66]. Since there was no significant difference between the mean size of benign and malignant lesions in our study, it is possible that we could not identify impact of size on mean strain ratio. It is also possible the modern machines have better software, which would result in consistent results irrespective of size of lesion.

Pathology was considered as gold standard investigation which comprised either cytology or histopathological examination. Among 101 breast masses in our study, 53 were benign and within which, 18 were cystic lesions. Among 18 benign masses 10 were fibrocystic diseases and eight were breast abscesses. Remaining 35 lesions were benign solid. Among them 32 were fibroadenoma, two were benign phyllodes tumor and one was benign papillary tumour. Among 48 malignant breast masses, 47 were infiltrating ductal carcinoma and one was squamous cell carcinoma.

In our study, we observed that elastography and ultrasonography incorrectly diagnosed granulomatous mastitis. Mutala et al., also reported higher mean strain ratio for granulomatous mastitis in their study. The authors hypothesized that presence of granulomatous tissue may result in increased stiffness and can explain the increased mean strain ratio[67]. Our finding is contrary to data reported by Yağcı et al., and Durur-Karakaya A et al., who reported lower strain ratio for granulomatous mastitis with strain ratios ranging from 1.5 ± 0.8 (range 0.2 to 4) and 1.10 ± 0.79 (range 0.29 to 4) respectively[63,68].

Our study shows that strain ratio cut off had excellent prediction rate in comparison with modified colour in diagnosing both benign and malignant breast masses. With strain ratio cutoff of 3.25, all 48 malignant breast masses were correctly diagnosed and 52 out of 53 benign breast masses (98.11%) were correctly correlated with pathological diagnosis.

Our study had certain limitations. Our sample size was relatively small to provide more meaningful data on rare conditions such as phyllodes tumour, granulomatous mastitis and squamous cell carcinoma. Elastography is operator dependent. This may be a potential limitation. However, our ultrasound machine provided the optimal compression required for a meaningful result. We did not categorize the BIRADS 4 lesions into 4A, 4B and 4C, which might have affected the results. A larger study with BIRADS 4 category lesions is recommended. In our study, FNAC was performed and this provided inconclusive results in many cases, who finally had to undergo core biopsy or surgical excision for pathological diagnosis. FNAC is the initial mode of investigation in many centers and therefore one may have to rethink the risks/benefits of FNAC versus core biopsy as initial investigation. We also did not evaluate the inter- or intra-observer variability in our study because it was not designed initially.

CONCLUSION

In our study we concluded that elastography acts as an adjuvant to conventional B mode ultrasonography and plays a major role in differentiating benign from malignant breast lesions. Sensitivity, specificity, positive, negative predictive values and diagnostic accuracy increased significantly with addition of elastography to ultrasonography. There is statistically significant increase (P<.001) in the BIRADS, modified colour score and mean strain ratio with increase in age of the patient. Our study showed that there is no statistically significant difference between mean size (P = .35; not significant) and laterality (P = .17; not significant) in benign and malignant lesions.

Our study also found that elastography has significant role in characterizing a lesion whenever diagnosis by ultrasonography was equivocal. By performing elastography, unwanted invasive procedures for simple cyst, breast abscess and benign solid breast lesions with BIRADS 3 can be avoided since it as 100% correlation with pathological diagnosis.

We recommend a new Indian modified colour scoring system to categorize the lesions as benign and malignant. A cut off mean strain ratio of 3.25 effectively helps to differentiate benign from malignant lesions with high diagnostic accuracy. Elastography should be performed in evaluation of breast lesions, whenever the facility is available.

SUMMARY

Breast cancer is becoming relatively more common worldwide. Early detection of malignancy will provide various treatment modalities and thereby help in reducing mortality rate. Elastography has potential to improve specificity of breast ultrasound in differentiating benign from malignant mass, thereby reducing the number of benign biopsies.

The aims and objectives of the study were to evaluate morphology of the breast masses with routine ultrasonography and elastography, to assess the role of elastography and conventional B-mode ultrasonography in differentiating benign from malignant breast masses and to correlate elastography and B-mode ultrasonography results with pathological findings.

This is a prospective observational study which was conducted over a period of eighteen months from January 2018 to June 2019 on 101 patients with clinically palpable breast lump who underwent sonomammography and elastography of breast at the Department of Radio-Diagnosis at R. L. Jalappa Hospital and Research Center attached to SDUMC, Kolar. Prior informed consent was taken from the patients for their willingness to participate in the study. The inclusion criterion was all the patients with clinically palpable breast mass and exclusion criterion was prior biopsy proven breast masses.

Baseline data of the patients participating in study were recorded. Individuals with clinically palpable lump in breast underwent ultrasonography and elastography. B mode ultrasonography and elastography were performed in PHILIPS EPIQ 5G ultrasound machine using a 5–12 MHz linear array transducer. First ultrasonography was performed in patient lying in supine position followed by strain elastography. Morphological changes seen on ultrasonography were interpreted on the basis of BIRADS lexicon, which included the imaging characteristics.

During strain elastography the probe was placed perpendicular to the lesion and gentle compression was applied. Two criteria were considered to determine the nature of lesion on elastography, modified colour score and strain ratio. Blue colour was given score 2, uniformly green and BGR artifact were given score 0 and mixture of blue and green as score 1. Strain ratio is ratio of hardness of the target tissue with adjacent normal breast fat. The cut off strain ratio used to differentiate benign from malignant breast masses was 3.25. Both ultrasonography and elastography findings were recorded and interpreted. The patient underwent pathological investigation, either ultrasound guided FNAC or trucut biopsy following ultrasound and elastography studies. The pathological results were compared with ultrasonographic and elastographic findings.

The data were entered in Microsoft excel sheet. The measurable variables were analyzed and interpreted between them by the student's t test and the ordinal and categorical variables between them were interpreted by Chi- square (χ^2) test.

The predictive value of elastography for differentiating benign and malignant lesions was estimated. The statistical procedures were performed with the help of an SPSS statistical package (ver 21) and OpenEpi ver 3.01. *P* value less than 0.05 ($P<0.05$) was considered as statistically significant.

The study included 86 patients with 101 lesions of which 85 (98.9 %) were females and 1 (1.1 %) was male patient. The mean age of the patients was 42.45 ± 16.2 years (mean ± SD) with range of 14 to 95 years. The benign lesions were seen in younger age group (32.96 ± 13.46 years) when compared with malignant lesions, which were common in elderly (52.94 ± 11.98). Benign lesions constituted for 52.48% of cases (n = 53), while remaining cases were malignant (n = 48; 47.52%).

Patients with age <21 years mostly had BIRADS 2 and 3 breast lesions. On modified colour score, nine lesions were in score of 0 and 1 and one lesion was categorized in score 2. All these lesions showed mean strain ratio of <3.25, suggestive of benign nature which turned out to be benign on pathological examination. In the patients with age group of 21 to 40 years, nearly $3/4^{th}$ of lesions were in BIRADS 2 and 3 (29 of 40 lesions), with 10 lesions classified under BIRADS 4 and one lesion in BIRADS 5. A similar trend was also observed in the modified colour scoring and mean strain ratio. Modified colour score of 0 and 1 were observed in 27 lesions and modified colour score of 2 was seen in 13 lesions. Mean strain ratio of <3.25 was seen in $3/4^{th}$ of patients and mean strain ratio >3.25 was seen in remaining $1/4^{th}$ of patients. Pathology showed 31 benign lesions and 9

malignant lesions. In patients with age group between 41 and 60 years, there was an increase in trend of malignant masses as evidenced by greater number of masses in BIRADS categories 4 & 5 (73.6% of lesions), modified colour score of 2 and strain ratio of >3.25 (78.9% of lesions in each group). Pathological diagnosis showed 30 lesions as malignant.

There were 2 lesions, which were classified as BIRADS 3. Modified colour score was 2 for both the lesions and they showed mean strain ratio >3.25 and were classified as malignant on elastography. Pathological diagnosis was squamous cell carcinoma and infiltrating ductal carcinoma in one case each. Ultrasound (BIRADS 4) incorrectly classified one of the cases of infiltrating ductal carcinoma as mastitis. Modified colour score and mean strain ratio classified the lesion as malignant. There was a case of phyllodes tumour, which was incorrectly classified as BIRADS 4 lesion on ultrasound and malignant on modified colour score (score 2). Mean strain ratio for the lesion was 1.46 thereby indicating the benign nature of the lesion. There was one case of infiltrating ductal carcinoma, which was classified as malignant on ultrasound (BIRADS 4) and mean strain ratio (4.86), but incorrectly classified as equivocal on modified colour score (score 1). All these cases were correctly classified as benign or malignant by mean strain ratio.

In patients with age group >60 years, there were 13 lesions of which 10 (76.9%) were classified as malignant on ultrasound (BIRADS 4 and 5) and modified colour score (score 2) and nine (69.2%) were classified as malignant on mean strain

ratio. On pathology, all the cases classified as malignant on mean strain ratio were malignant and four lesions (31.8%) were benign. There was a case of benign papillary neoplasm, which was classified as BIRADS 4 on ultrasound. Modified colour score of 1 was suggestive of equivocal lesion and mean strain ratio was 2.15, which suggested, it was benign mass. All other lesions showed malignant features on ultrasound, modified colour score and mean strain ratio.

Most of the lesions were located in the right side (n = 51; 50.5%) followed by 38 lesions (37.62%) in the left breast. There were six patients with bilateral lesions (total of 12 lesions). There was no significant difference in mean age in and laterality of lesion. When BIRADS category was considered, there was increase in average age with increasing BIRADS score, which was statistically significant. A similar statistically significant association was seen with modified colour score and increasing age, mean strain ratio (<3.25 and >3.25) with increasing age and also statistically significant difference in benign and malignant lesions with mean age.

There was one lesion, which was <2 cm with mean strain ratio of >3.25. The lesion was classified as malignant on strain ratio, however, the lesion turned out to be benign (granulomatous mastitis), whereas rest of other lesions, were diagnosed accurately as benign or malignant irrespective of the size. The mean size for benign lesions was 2.56 ± 1.74 cm (mean ± SD) and the mean size of malignant lesions was 2.87 ± 1.52 cm (mean ± SD). No statistically significant difference observed between mean size in benign or malignant lesions (P = .35; not significant).

There were 48 malignant and 53 benign breast masses on pathology. Among 53 benign breast masses, 10 were fibrocystic diseases, 8 were breast abscesses, 32 were fibroadenoma, 2 were benign phyllodes tumours and 1 was benign papillary neoplasm. Among 48 malignant breast masses, 47 were infiltrating ductal carcinoma and 1 was squamous cell carcinoma.

In 101 breast masses, most of them (n = 54) were categorized as score 2. Out of these 54 lesions, 47 were pathologically proven as malignant breast masses and 7 were benign. 25 breast masses had score of 1 and 22 lesions were categorized with score 0. Of the 25 breast masses with score 1, 24 lesions were benign and one lesion was malignant. All the 22 lesions with score of 0 were benign. Modified colour score showed sensitivity of 65.2%, specificity of 75.8%, positive (PPV) and negative predictive values (NPV) of 87% and 46.8% respectively for differentiating benign from malignant masses with overall diagnostic accuracy of 68.32%.

We further modified the modified colour score to include only 2 categories, benign and malignant. Modified colour scores of 0 and 1 (Tsukuba scores of 1 to 3) can be considered as benign and modified colour score of 2 (Tsukuba scores of 4 and 5) be considered as malignant. This modification has sensitivity of 97.8%, specificity of 87.0%, PPV of 86.79% and NPV of 87.08% with a diagnostic accuracy of 92.08%. This modification has overall improved diagnostic accuracy when compared with 3-category classification, which has an overall diagnostic accuracy of

68.32%. With new Indian colour scoring system, the chance of missing malignant lesion was 2.1%.

In 101 breast masses, 52 breast masses had strain ratio <3.25, suggesting a benign etiology and 49 breast masses had strain ratio >3.25, indicating the mass was malignant. Mean strain ratio for benign solid breast lesions was 1.932 ± 1.205 (mean ± SD), mean strain ratio for benign cystic lesion was 1.210 ± 0.792 (mean ± SD) and the mean strain ratio of malignant breast masses was 4.551 ± 0.933 (mean ± SD). There was statistically significant difference between mean strain ratio between benign solid and benign cystic lesions (P<.05). Strain ratio, when used as an individual elastographic parameter for diagnosing malignant breast masses, it showed sensitivity of 100%, specificity of 98.1%, positive (PPV) and negative (NPV) predictive values of 97.96% and 100% respectively and diagnostic accuracy of 99.01%. Similarly, strain ratio showed sensitivity of 98.11%, specificity of 100%, PPV and NPV of 100% and 97.96% with diagnostic accuracy of 99.01% in diagnosis of benign breast lesion.

We concluded that elastography as an adjuvant to conventional B mode ultrasonography, plays a major role in differentiating benign from malignant breast masses. We recommend a new Indian modified colour scoring system to categorize the lesions as benign and malignant. A cut off mean strain ratio of 3.25 effectively helps to differentiate benign from malignant lesions with high diagnostic accuracy. Elastography should be performed in evaluation of breast lesions, whenever the facility is available.

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ANNEXURE I

Proforma for dissertation

Demographic details:

Name:

UHID No:

Trial ID:

Age:

Sex:

Clinical History:

Local Examination:

Ultrasonography Diagnosis:

Size and shape of the lesion:

Lesion characteristics (BIRADS lexicon):

BIRADS: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Axillary Lymphadenopathy:

Elastography Diagnosis:

Modified Colour score: 0 ☐ 1 ☐ 2 ☐

Mean Strain Ratio:

Pathological Diagnosis:

Correlation between elastography and pathology:

ANNEXURE II

Patient consent form

Chief researcher/ PG guide's name: Dr. ANIL KUMAR SAKALECHA

Principal investigator: Dr. PARAMESHWAR KEERTHI B.H

Name of the subject:

Age :

Gender :

a. I have been informed in my own language that this study involves ultrasonography and elastography as part of procedure. I have been explained thoroughly and understand the procedure.

b. I understand that the medical information produced by this study will become part of institutional record and will be kept confidential by the said institute.

c. I understand that my participation is voluntary and may refuse to participate or may withdraw my consent and discontinue participation at any time without prejudice to my present or future care at this institution.

d. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

e. I confirm that Dr. Parameshwar Keerthi B. H. / Dr. Anil Kumar Sakalecha (chief researcher/ name of PG guide) has explained to me the purpose of research and the study procedure that I will undergo and the possible risks and discomforts that I may experience, in my own language. I hereby agree to give valid consent to participate as a subject in this research project.

Participant's signature/thumb impression

Signature of the witness: **Date:**

1)

2)

I have explained to _____ (subject) the purpose of the research, the possible risk and benefits to the best of my ability.

Chief Researcher/ Guide signature **Date:**

Patient information sheet

Principal Investigators: Dr. PARAMESHWAR KEERTHI B H / Dr. ANIL KUMAR SAKALECHA

I, Dr. Parameshwar Keerthi B H, post-graduate student in Department of Radio-Diagnosis at Sri Devaraj Urs Medical College. I will be conducting a study titled "Role of ultrasonography and elastography in differentiating benign from malignant breast masses with pathological correlation." for my dissertation under the guidance of Dr. Anil Kumar Sakalecha, Professor, Department of Radio-Diagnosis. In this study, we will assess the diagnostic value of Conventional ultrasonography and elastography in evaluation of breast mass. You would have undergone ultrasonography before entering the study. You will not be paid any financial compensation for participating in this research project. You will not be paid any financial compensation for participating in this research project.

All of your personal data will be kept confidential and will be used only for research purpose by this institution. You are free to participate in the study. You can also withdraw from the study at any point of time without giving any reasons whatsoever. Your refusal to participate will not prejudice you to any present or future care at this institution

Name and Signature of the Principal Investigator:

Date:

ANNEXURE III

Master Chart – Role of ultrasonography and elastography in differentiating benign from malignant breast masses with pathological correlation

Key to Masterchart

B – benign

BA – breast abscess

BPN – Benign papillary neoplasm

BPT – Benign phyllodes tumor

Ca – carcinoma

Fa – Fa

FCD – fibrocystic disease

GM – Granulomatous mastitis

IDC – infiltrating ductal carcinoma

L – left

M – malignant

R – Right

SCC – squamous cell carcinoma

TB – tuberculous;

USG - ultrasound

Master Chart – Role of ultrasonography and elastography in differentiating benign from malignant breast masses with pathological correlation

s.no	Trial ID	Age	Clinical Diagnosis	USG Diagnosis		BIRADS	Size (in cm)	Side	Modified Colour score	Mean Strain Ratio	Elastography (B/M)	Final Diagnosis
				Diagnosis	B/M							
1	378445	50	Ca	Ca	M	4	2.4	R	2	5.3	M	IDC
2	992396	20	Fa	Fa	B	2	3.66	R	1	1.5	B	Fa
3	107806	28	Fa	Fa	B	2	2.1	R	1	1.5	B	Fa
4	346827	28	Fa	Fa	B	2	1.3	L	2	1.8	B	Fa
5	193609	38	? Ca	Ca	M	4	3.51	L	2	6.14	M	IDC
6	343524	26	? Ca	Ca	M	4	0.8	L	2	7.8	M	GM
7	649536	14	Fa	Fa	B	2	3.01	L	1	0.8	B	Fa
8	474008	14	Fa	Fa	B	2	1.48	R	1	1.87	B	Fa
9	81395	14	Fa	Fa	B	2	2.76	R	1	1.96	B	Fa
10	174820	51	Ca	Ca	M	5	3.5	R	2	5.13	M	IDC
11	835127	27	Fa	Fa	B	2	1.48	R	1	1.25	B	Fa
12	636196	53	Ca	Ca	M	4	1.25	L	2	3.5	M	IDC
13	829225	60	? Fa	Fa	B	2	2.22	R	2	3.15	B	Fa
14	588294	35	Ca	? BA	B	4	2.21	L	2	3.31	M	IDC
15	416790	38	? Ca	Ca	M	4	3.05	R	2	6.49	M	IDC
16	103601	45	Fa	Cyst	B	3	2.25	L	0	0.38	B	Fa
17	473793	42	? Ca	Ca	M	4	3.4	R	2	3.78	M	IDC
18	232991	62	Ca	Ca	M	4	3.21	L	2	3.26	M	IDC
19	296914	55	Ca	Ca	M	4	2.8	R	2	4.12	M	IDC

B – benign (solid), BA – breast abscess, BPN – Benign papillary neoplasm, BPT – Benign Phyllodes tumour, Ca – carcinoma, Fa – Fibroadenoma, FCD – fibrocystic disease, IDC – infiltrating ductal carcinoma, GM – Granulomatous Mastitis, L – left, M – malignant, R – Right, SCC – squamous cell carcinoma, TB – tuberculous; USG - ultrasound

Master Chart – Role of ultrasonography and elastography in differentiating benign from malignant breast masses with pathological correlation

s.no	Trial ID	Age	Clinical Diagnosis	USG Diagnosis		BIRADS	Size (in cm)	Side	Modified Colour score	Mean Strain Ratio	Elastography (B/M)	Final Diagnosis
				Diagnosis	B/M							
20	396706	45	? Ca	Ca	M	4	10.9	R	1	1.46	B	BPT
21	27341	54	Ca	Ca	M	4	2.75	R	2	4.39	M	IDC
22	626153	40	? Ca	Cyst	B	2	2.1	R	0	0.34	B	FCD
23	846227	48	? Ca	Cyst	B	3	2.6	R	0	1.22	B	BA
24	422673	42	Ca	Ca	M	5	2.7	R	2	3.68	M	IDC
25	284369	57	Ca	Ca	M	6	1.83	R	2	3.38	M	IDC
26	341077	60	Ca	Ca	M	5	1.6	R	2	5.31	M	IDC
27	216426	48	Ca	Ca	M	4	3.65	R	2	5.01	M	IDC
28	204343	40	? Fa	Cyst	B	2	1.5	L	0	0.69	B	FCD
29	442231	24	BA	BA	B	2	7.48	R	0	1	B	BA
30	5926	34	Breast pain	FCD	B	2	2.32	L	0	0.89	B	FCD
31	950997	25	Galactocele	Fa	B	2	1.81	L	0	2.12	B	Fa
32	87139	60	Ca	Ca	M	4	1.53	R	2	4.3	M	IDC
33	641885	50	? Ca	DE	B	3	2.21	R	2	3.41	M	IDC
34	423312	55	Ca	Ca	M	5	3.7	R	2	6.67	M	IDC
35	288697	41	Ca	Ca	M	5	5.13	L	2	4.41	M	IDC
36	952151	40	? Ca	Ca	M	4	2.1	R	2	4.33	M	IDC
37	56692	70	? Ca	Ca	M	4	1.97	L	2	5.18	M	IDC
38	10578	26	BA	BA	B	3	3.32	R	0	0.76	B	BA

B – benign (solid), BA – breast abscess, BPN – Benign papillary neoplasm, BPT – Benign Phyllodes tumour, Ca – carcinoma, Fa – Fibroadenoma, FCD – fibrocystic disease, IDC – infiltrating ductal carcinoma, GM – Granulomatous Mastitis, L – left, M – malignant, R – Right, SCC – squamous cell carcinoma, TB – tuberculous; USG - ultrasound

Master Chart – Role of ultrasonography and elastography in differentiating benign from malignant breast masses with pathological correlation

s.no	Trial ID	Age	Clinical Diagnosis	USG Diagnosis		BIRADS	Size (in cm)	Side	Modified Colour score	Mean Strain Ratio	Elastography (B/M)	Final Diagnosis
				Diagnosis	B/M							
39	246427	26	Fa	Fa	B	3	1.43	L	1	2.91	B	Fa
40	212824	66	Ca	Ca	M	5	2.01	L	2	3.74	M	IDC
41	982208	32	Fa	Cyst	B	2	1.01	L	0	3.18	B	Breast cyst
42	98419	32	Fa	Fa	B	3	3.97	L	0	1.03	B	Fa
43	598076	28	Fa	Fa	B	3	1.47	R	1	1.50	B	Fa
44	197364	57	Ca	Ca	M	4	2.24	L	2	4.95	M	IDC
45	885710	29	Fa	FCD	B	2	3.80	R	0	0.76	B	FCD
46	871866	48	Ca	Ca	M	4	2.28	L	2	3.54	M	IDC
47	287938	42	Fa	Cyst	B	3	4.30	L	0	0.92	B	FCD
48	535313	47	? Fa	Fa	B	4	4.53	R	2	6.77	M	IDC
49	241154	63	Ca	Ca	M	4	1.90	L	2	4.40	M	IDC
50	930113	64	Ca	Ca	M	4	1.32	R	2	5.41	M	IDC
51	684164	59	Ca	Ca	M	4	2.57	R	1	4.86	M	IDC
52	415216	65	Ca	Ca	M	5	3.48	R	2	4.61	M	IDC
53	432841	54	Ca	Ca	M	4	1.89	R	2	4.87	M	IDC
54	284277	50	? Ca	Ca	M	4	2.68	R	2	4.95	M	IDC
55	199170	68	Ca	Ca	M	5	2.18	L	2	4.43	M	IDC
56	608024	27	Nodule in breast	Cyst	B	2	3.26	L	0	0.85	B	BA
57	496606	51	? Ca	Ca	M	4	1.98	L	2	3.82	M	IDC

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Master Chart – Role of ultrasonography and elastography in differentiating benign from malignant breast masses with pathological correlation

s.no	Trial ID	Age	Clinical Diagnosis	USG Diagnosis		BIRADS	Size (in cm)	Side	Modified Colour score	Mean Strain Ratio	Elastography (B/M)	Final Diagnosis
				Diagnosis	B/M							
58	919329	28	Fa	Fa	B	2	1.32	R	0	2.02	B	FCD
59	648858	19	Fa	Fa	B	3	3.32	R	1	1.41	B	Fa
60	814772	19	Fa	Fa	B	3	2.28	R	1	1.57	B	Fa
61	670208	28	Fa	Fa	B	3	2.45	R	0	1.18	B	Fa
62	335776	29	Fa	Fa	B	3	0.72	R	0	1.30	B	Fa
63	364107	19	Fa	Fa	B	3	4.43	L	1	1.53	B	Fa
64	272179	20	Fa	Fa	B	2	3.22	R	1	1.72	B	Fa
65	134292	45	Fa	BA	B	4	4.73	L	2	3.31	M	SCC
66	694355	25	Mastalgia	Fa	B	3	1.08	R	1	1.89	B	Fa
67	233625	69	? Fa	Fa	B	3	1.09	L	1	2.40	B	Fa
68	925630	69	? Fa	Cyst	B	2	0.68	L	0	0.58	B	FCD
69	833610	80	Ca	Ca	M	5	3.12	L	2	4.56	M	IDC
70	287282	41	Fa	Cyst	B	2	2.5	R	0	0.49	B	FCD
71	94500	41	? Fa	Fa	B	3	2.32	L	1	1.32	B	Fa
72	212483	30	Ca	Ca	M	4	1.7	L	2	6.39	M	IDC
73	534101	60	Ca	Ca	M	4	4.1	L	2	4.00	M	IDC
74	559148	54	? Fa	Ca	M	4	1.3	L	2	3.58	M	IDC
75	941895	63	Ca	Fa	B	3	3.43	L	2	2.14	B	BPT
76	774878	95	Ca	Ca	M	5	2.4	L	2	3.90	M	IDC

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				Diagnosis	B/M							
77	484184	20	? TB mastitis	BA	B	3	2.31	L	2	3.01	B	BA
78	294969	35	Lump	Fa	B	3	2.5	R	1	0.86	B	Fa
79	194387	29	Fa	Fa	B	3	2.8	R	1	1.58	B	Fa
80	814175	60	Ca	Ca	M	4	2.57	L	2	3.27	M	IDC
81	970136	19	Fa	BA	B	3	6.3	L	0	1.45	B	BA
82	826889	60	Ca	Ca	M	4	1.98	L	2	4.5	M	IDC
83	554770	40	Ca	Ca	M	4	1.94	R	2	4.48	M	IDC
84	312636	37	Fa	Fa	B	3	0.76	R	0	1.3	B	Fa
85	285530	37	? Fa	Fa	B	3	1.79	R	1	2.11	B	Fa
86	872260	36	Fa	Ca	M	4	1.72	R	0	0.87	B	Mastitis with BA
87	81184	54	Ca	Ca	M	5	8.32	L	2	4.87	M	IDC
88	950530	54	Ca	Ca	M	5	8.68	R	2	3.91	M	IDC
89	421238	50	Ca	Ca	M	5	1.48	R	2	5.85	M	IDC
90	955380	35	? Ca	Ca	M	4	2.43	R	2	3.91	M	IDC
91	789820	28	Fa	Fa	B	3	1.4	R	1	1.45	B	Fa
92	764213	40	? Ca	Ca	M	4	5.2	R	2	5.5	M	IDC
93	736536	42	Lump	Cyst	B	2	2.6	L	0	0.84	B	FCD
94	587943	29	Fa	Fa	B	3	1.7	R	1	3.2	B	Fa

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s.no	Trial ID	Age	Clinical Diagnosis	USG Diagnosis		BIRADS	Size (in cm)	Side	Modified Colour score	Mean Strain Ratio	Elastography (B/M)	Final Diagnosis
				Diagnosis	B/M							
95	130555	53	? Ca	Ca	M	4	2.48	R	2	4.35	M	IDC
96	32385	28	BA	BA	B	3	3.16	R	1	1.91	B	BA
97	640778	32	Fa	Fa	B	3	2.28	R	2	3.03	B	Fa
98	108915	32	Fa	Fa	B	3	1.51	R	1	1.54	B	Fa
99	58038	70	Ca	BPT	B	4	2.9	R	1	2.15	B	BPN
100	790827	29	Fa	Fa	B	3	1.12	R	2	2.91	B	Fa
101	84661	38	Fa	Ca	M	5	1.72	L	2	4.64	M	IDC

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