"ROLE OF ULTRASOUND AND MAMMOGRAPHY IN PREDICTING THE MOLECULAR SUBTYPE OF CARCINOMA BREAST – A CROSS SECTIONAL STUDY"

BY

Dr. SRAVYA M

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

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF MEDICINE
IN
RADIODIAGNOSIS

UNDER THE GUIDANCE OF
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The Institutional Ethics Committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has examined and unanimously approved the synopsis entitled **" Role Of Ultrasound And Mammography In Predicting The Molecular Subtype Of Carcinoma Breast - A Cross Sectional Study"** being investigated by **Dr.Sravya M, Dr. Anil Kumar Sakalecha, & Dr. Kalyani R[1]** in the Departments of Radio-Diagnosis & Pathology[1] at Sri Devaraj Urs Medical College, Tamaka, Kolar. **Permission is granted by the Ethics Committee to start the study.**

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LIST OF ABBREVIATIONS

1	USG – Ultrasonography
2	MG – Mammography
3	BI-RADS – Breast Imaging Reporting and Data System
4	ER – Estrogen Receptor
5	PR – Progesterone Receptor
6	HER2Neu – Human Epidermal Growth Factor Receptor
7	TNBC – Triple-Negative Breast Cancer
8	IDC – Invasive Ductal Carcinoma
9	DCIS – Ductal Carcinoma In Situ
10	MRI – Magnetic Resonance Imaging
11	FNAC – Fine Needle Aspiration Cytology
12	IHC – Immunohistochemistry
13	T2WI – T2-Weighted Imaging (MRI sequence)
14	KI-67 – Proliferation Marker (Ki-67 antigen)
15	HR+ – Hormone Receptor Positive

ABSTRACT

INTRODUCTION

Rising breast cancer rates have made it the most common cause of cancer-related mortality for women worldwide. It is a diverse group of diseases with different natural histories, histological subtypes, biological characteristics, and treatment responses. Breast cancer management is increasingly guided by molecular subtypes, which determine prognosis and treatment strategies. This study aimed to assess the role of ultrasound and mammography in predicting molecular subtypes of breast carcinoma by evaluating correlations between radiological features and immunohistochemical markers.

MATERIALS AND METHODS

Over a period of eighteen months—from May 2023 to Nov 2024—this hospital based cross-sectional study of ultrasound and mammography will be carried out on a minimum of 52 lesions in patients referred in view of carcinoma breast to Department of Radio-Diagnosis, R.L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar. Ultrasound evaluation assessed lesion shape, margins, echogenicity, posterior acoustic features, and vascularity. Mammography was used to identify microcalcifications. Immunohistochemistry determined estrogen receptor (ER), progesterone receptor (PR), HER2/neu status, and Ki-67 expression, classifying tumors into molecular subtypes: Luminal A, Luminal B, HER2-enriched, and Triple Negative. Statistical analysis evaluated the concordance between radiological and pathological diagnoses.

RESULTS

The mean age of participants was 53.90 ± 12.95 years, with predominance in the 41- 50 years group (36.54%). Upper outer quadrant was the most common tumor site (55.77%). Ultrasonographically, 53.85% lesions were ill-defined, 42.31% had lobulated margins, 67.31% showed heterogeneous echogenicity, and 48.08% demonstrated internal vascularity. Microcalcifications were present in 55.76% cases.

Immunohistochemistry revealed 53.85% ER and PR positivity, 34.62% HER2/neu positivity, and 50% Ki-67 positivity. Strong concordance was observed between radiological and pathological subtypes ($p < 0.001$), with perfect agreement for Luminal A (13/13) and high concordance for Triple Negative (14/15). Overall diagnostic accuracy was 90.12%, with 94.72% sensitivity and 92.18% specificity.

CONCLUSION

Ultrasound and mammography can predict molecular subtypes of breast carcinoma with high accuracy. This non-invasive approach could potentially expedite treatment planning and provide valuable prognostic information before definitive pathological confirmation, enhancing personalized breast cancer management.

KEYWORDS

Breast carcinoma, Molecular subtypes, Ultrasound, Mammography, Immunohistochemistry, Radiological-pathological correlation, Diagnostic accuracy, Results.

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INTRODUCTION

INTRODUCTION

The breast cancer incidence has been rising, and it is the most prevalent reason for cancer-related death for women globally. It is a group of various diseases with different natural histories, histological subtypes, biological characteristics, and treatment responses. Therapy planning, disease prognosis, and avoidance of overtreatment all depend on molecular subtyping of breast cancer.[1, 2]

The St. Gallen International Expert Consensus has categorised breast cancer into five distinct molecular subtypes based on gene expression patterns: basal-like (triple-negative), human epidermal growth factor receptor 2 (HER2)-enriched, luminal A (LA), luminal B [(LB; HER2−), LB (HER2+). Pathologically categorised, these molecular subtypes reflect the expression status of the tumour markers comprising the Ki-67 index, HER2neu overexpression, progesterone receptor (PR), and oestrogen receptor (ER). LA type invasive breast cancer is characterised by a lower Ki-67 index (Ki-67 <14%), oestrogen receptor (ER) and/or progesterone receptor (PR) positive. HER2 negative LB (HER2–) subtype is described as ER and/or PR-positive tumours with a high Ki-67 index (Ki-67 ≥14%). ER and/or PR-positive tumours that are HER2-positive characterise the LB (HER2+) subtype. Described as ER and PR-negative cancers with HER2neu overexpression, HER2-enriched type tumours are those that fit this description. Finally, basal breast cancer or triple-negative breast cancer are those who fail ER, PR, and HER2neu receptor testing. [3, 4, 5]

Immunohistochemistry (IHC) is the most dependable way to assess hormone receptor (ER/PR), HER2 overexpression, and Ki-67 expression; nonetheless, many poor and undeveloped nations find it intrusive, expensive, and not readily available. Ultrasound and mammography and are the two initial imaging techniques advised for breast cancer screening, diagnosis, staging, treatment response assessment, and patient follow-up after treatment. Many earlier retrospective studies have revealed that ultrasound characteristics were very predictive in classifying triple-negative breast cancer (TNBC) from non triple-negative breast cancer and in distinguishing tumour grades.[6, 7, 8]

Cen et al.'s study showed a significant link between HER2 overexpression and troubling microcalcifications seen by mammography. In patients with infiltrating ductal carcinoma, this study indicated that BI-RADS 3 to BIRADS 5 microcalcifications may be easily employed to enable the prediction of HER2 and Luminal A molecular subtype preoperatively. [9]

Using non-invasive, affordable and easily accessible techniques in forecasting BC subtypes has two pragmatic justifications. Using radiologic imaging rather than costly genetic testing might help to lower the load on public health as breast cancer is most frequently occuring cancer in adult women globally, particularly in underdeveloped nations where comprehensive and expensive histopathologic assessments are not readily available. Second, breast cancer being a diverse illness; variations in gene amplification patterns and receptor expression status have various prognostic consequences on the progression of the disease and the efficacy of treatment. Combining genetic profiling with radiologic imaging helps with pre-treatment planning and provides a more complete degree of analysis for conversations about radio-pathologic correlations.

Mammography and ultrasound are the main non-invasive methods used to assess breast cancer lesions. Combining the imaging qualities of mammography and ultrasonography helps to better detect the molecular subtypes of carcinoma breast. Radiologic imaging therefore offers a better degree of assessment for radiopathologic correlation and is applied as a complementary tool in pre-treatment planning. [10]

Previous studies have shown a connection between imaging characteristics and breast cancer subtypes; high-risk microcalcifications (on mammography), ultrasound margins, and posterior acoustic features have been shown to be independent imaging distinguishing traits among molecular subtypes. [11]

Unlike earlier studies that concentrated only on women with symptoms, this one is meant to evaluate the most effective predictive combinations of ultrasound and mammography imaging features for genetic subtypes in a group comprising symptomatic and asymptomatic people undergoing breast screening.

This research study aimed to assess the molecular subtype prediction of carcinoma breast by combined use of ultrasound and mammography.

AIMS & OBJECTIVES

AIMS & OBJECTIVES OF THE STUDY

1. To assess the various morphological features of carcinoma breast on ultrasound and microcalcifications on mammography.
2. To determine the molecular subtype of carcinoma breast in excised/biopsy specimen by immunohistochemistry.
3. To determine the association of accuracy of ultrasound and mammography imaging with immunohistochemical markers to predict the molecular subtype of carcinoma breast.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Breast cancer is the most often diagnosed cancer globally, with over two million cases annually. Worldwide, women die from cancer mostly because of it. In the United States, breast carcinoma ranks second among the highest prevalent causes of cancer mortality among women; it is also the most prevalent kind of cancer overall. [12]

Once breast cancer has been identified, it is crucial to correctly identify the stage of the illness early as this will influence treatment decisions. All of the clinical signs, differential diagnosis, and staging after a breast cancer diagnosis will be discussed.

EPIDEMIOLOGY

Worldwide, even in low- and middle-income nations, breast cancer is the commonly diagnosed malignancy. While North America, Australia/New Zealand, Western and northern Europe have the highest rates, Asia and sub-Saharan Africa have the lowest. [13]

Most likely, these global variations are connected to shifts in industrialization-driven social changes including changes in body mass, age of menarche, nursing practices, fat consumption, and reproductive patterns including lower pregnancies and later first birthing ages. Studies on migration trends to the United States highlight the significance of environmental and cultural changes. Generally speaking, second-generation immigrants have more chances to get breast cancer; third- and fourth-generation immigrants have much more.

Breast cancer is the highest prevalent illness found and the main cause of cancer-related mortality in women globally. Among the 9.55 million cancer-related fatalities, breast cancer made up 626,679 (6.6% of all cancer deaths); among the 18.08 million new cancer cases, breast cancer were 2.08 million (an incidence rate of 11.6%). Surpassing cervical and oral cancers, breast cancer is currently the highest prevalent cancer and the main reason for cancer-related death in India. Discovered in 2018 in India, 162,468 new breast cancer cases were more than 11.1% of all cancer fatalities and 27.7% of all new malignancies in women. [14]

The reduction in death is due to advances in screening of breast carcinoma and adjuvant treatment. A pivotal study found that women between the ages of 40 and 69 who engaged in structured mammography screening showed a 60 percent lower breast cancer death rate within 10 years of diagnosis and a 47 percent lower rate within 20 years when compared to those who did not take part in screening. When breast cancer is found at an earlier stage, this implies that therapeutic treatments greatly raise the probability of survival. [15]

CLINICAL FEATURES

Signs and symptoms

In nations with strongly entrenched breast cancer screening systems, majority of patients come with a negative mammogram. Thirty percent of women have breast masses between interval screening mammography. A breast lump not visible on a mammography causes up to fifteen percent of breast cancer (mammographically occult disease). Younger women less than 40 who may not be undergoing regular screening and women without the chance for screening mammography could also develop an axillary or breast tumour, with or without associated skin changes. [16]

This should not only assist us to steer the application of risk stratifying tools to prevent overtreatment but also let us reset biopsy thresholds for extremely low risk mammographic lesions (BIRADS 4A). Mammographers and surgeons should be more confident in investigating and testing alternatives to biopsy of extremely low risk mammographic abnormalities, which nearly invariably turn out to be benign, as the illness identified becomes more indolent. Among the characteristics of a malignant lesion is a tough, fixed, solitary, noticeable lesion with uneven borders. But these qualities can fail to delineate between a benign and a malignant tumour. [16]

Locally advanced malignancy

While axillary lymphadenopathy indicates more advanced locoregional illness, skin disorders include erythema, thickness, or skin dimpling (peaud'orange) are indications of inflammation in breast cancer.

Metastatic illness — Though the most usual locations are the lungs (e.g., cough or dyspnoea), liver (e.g., stomach pain, nausea, jaundice), and bones (e.g., back or leg pain), the symptoms of metastatic breast cancer vary depending on which organs are affected.

Imaging — Common mammographic indicators of cancer of breast are the presence of a soft-tissue mass or density with related microcalcifications. A high-density, spiculated tumour is the key differentiating characteristic; almost 90% of them represent aggressive cancer.

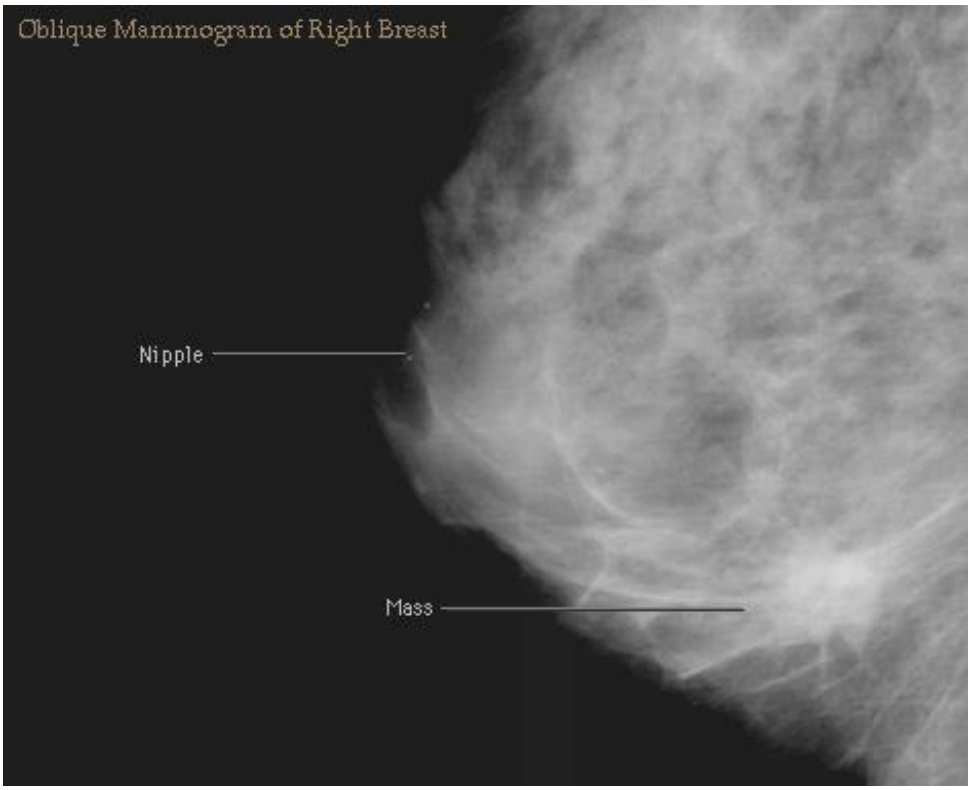

Fig 1- Abnormal mammogram This unusual mammography reveals a breast cancer-related lump.

Breast ultrasonography is often used to differentiate between benign and malignant tumours. Sonographic characteristics like shadowing, internal calcifications, hypoechogenicity, lesions taller than broad, spiculated, and unclear edges help to identify malignancy. [17]

A complex imaging technique called ultrasound elastography is employed to evaluate tissue using measurement of its mechanical properties. By use of the evaluation of tissue elasticity, it helps to differentiate benign from malignant tumours in breast imaging.

Strain elastography (SE) will assess tissue deformation by mechanical or manual pressure. Compared to softer tissues, more rigid ones such as tumors show less deformation.

Shear wave elastography (SWE) generates shear waves by means of high-frequency ultrasonic pulses and then measures their speed to determine tissue stiffness. Often, malignant lesions show more stiffness. [17]

Clinical Applications

Malignant tumours are usually more stiff than benign ones. Improves diagnosis accuracy and reduces unnecessary biopsies. Used to gauge tumour response to neoadjuvant chemotherapy, evaluating treatment efficacy.

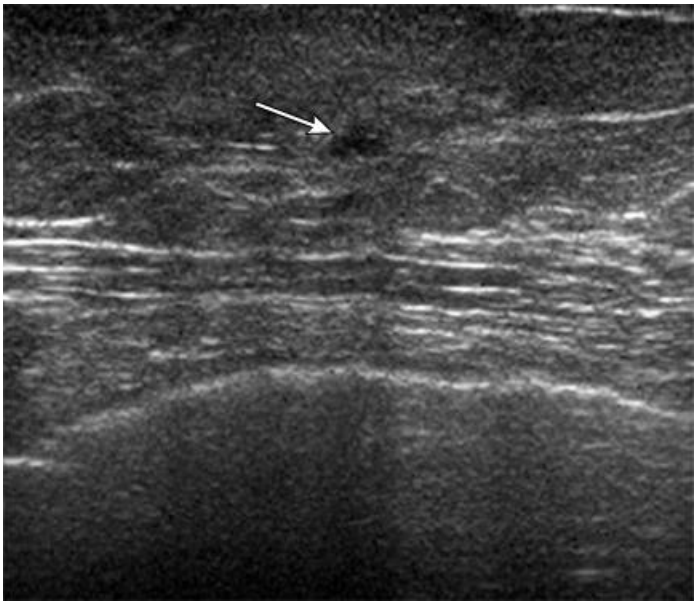

Fig-2 Ultrasound of early breast cancer- A little breast cancer indicated by arrow, the left breast ultrasound demonstrates a hypoechoic tumour with posterior acoustic shadowing.

Women at higher risk for carcinoma of breast are often screened using magnetic resonance imaging (MRI). Majority of invasive breast cancers show improvement on gadolinium contrast-enhanced MRI. Breast cancer's MRI features include uneven or spiculated mass boundaries, heterogeneous internal enhancement, and rim enhancement. Especially if the enhancement corresponds with a mass or shows segmental distribution. The technique is not specific enough to do away with the need of biopsy. [18]

PATHOLOGICAL DIAGNOSIS [19]

A biopsy revealing malignant epithelial cells—carcinoma—is conclusive for diagnosing carcinoma breast.

HISTOPATHOLOGY

There are several histologic subtypes of breast cancer, each with unique biological activity and microscopic features.

Infiltrating ductal carcinoma — The most commonly occurring type of carcinoma breast, infiltrating ductal carcinomas, account for around 70 to 80 percent of invasive cases. Ranging from benign to extremely malignant, the cytological characteristics of these lesions include cords and nests of cells with different degrees of glandular development.

Invasive breast cancers total around 8% of all infiltrating lobular carcinomas. Microscopically, their tiny cells steadily penetrate the adipose tissue and mammary stroma in a single, linear pattern, allowing identification.

Mixed ductal/lobular — Characterised by a histological makeup combining ductal and lobular traits, carcinoma is therefore classified as a mixed invasive cancer making up 7 percent of invasive breast cancers.

Other histological types of breast cancer are metaplastic, mucinous, tubular, medullary, and papillary. Combined, these make up under 5% of invasive malignancies.

MAMMOGRAPHY

The main imaging technique used to detect and evaluate breast cancer early is mammography. Of all breast imaging techniques, screening mammography has consistently demonstrated a reduction in death pertaining to carcinoma breast. Mammography can identify cancer one and a half to four years prior to its clinical presentation.

The mammography unit prototype was created in 1965. Since then, several technical developments have been made improving image quality and reducing patient radiation dose. Continuous technical developments are in progress to improve mammography and provide alternative breast imaging modalities, thereby increasing recurrence detection, the accuracy of disease extent and therapy response, and early diagnosis of breast pathology.

THE MAMMOGRAPHIC EXAMINATION

Mammograms consist of subjecting breast tissue to x-rays, which penetrate the tissue and radiate to other areas. After attenuation depending on the breast tissue features, the recording device will absorb the x-rays as latent pictures. For diagnostic evaluation, the latent picture is produced and shown.

A typical screening evaluation process is obtaining two pictures of each breast—craniocaudal [CC] and mediolateral oblique [MLO]. In the CC perspective, the breast is elevated and placed on the plate; compression is given from above. In the MLO view, the breast is compressed and laterally photographed at an oblique angle. Breast placement is really important. Bad posture can make some breast areas miss the radiation, hence impairing the capacity to identify cancer.

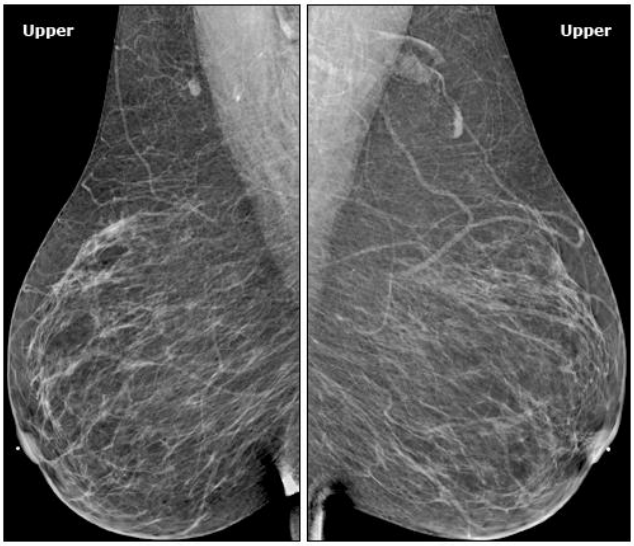

Fig-3- Normal CC (craniocaudal) views of both breasts

Mammograms of both breasts are seen as mirror images. The upper half shows the exterior or lateral aspect of the breast; the bottom half shows the interior or medial region. When the nipples are in profile, normal adipose tissue may be seen between the glandular tissue and the border of the film.

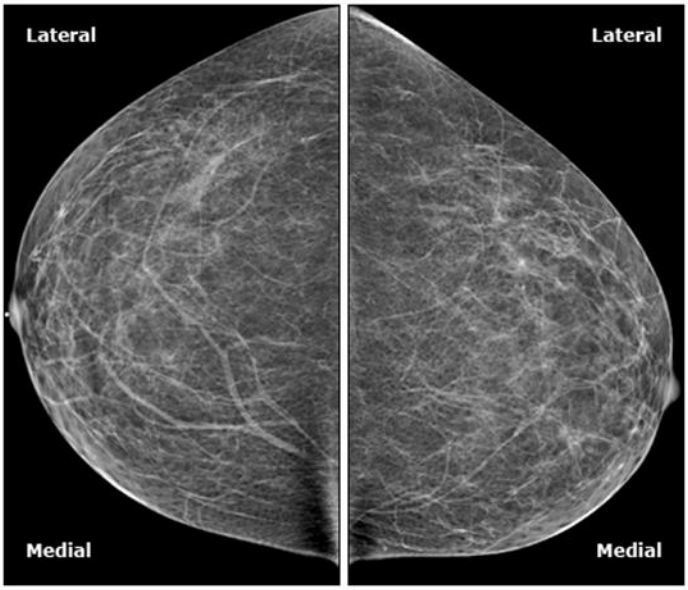

Fig 4. Normal MLO (mediolateral oblique) view of both breasts.

Mammograms of both breasts are seen as mirror images. The pectoralis muscle extends at least as high as the nipple. While the lower part shows the inferior half of the breast, the top part of the photo shows the superior half.

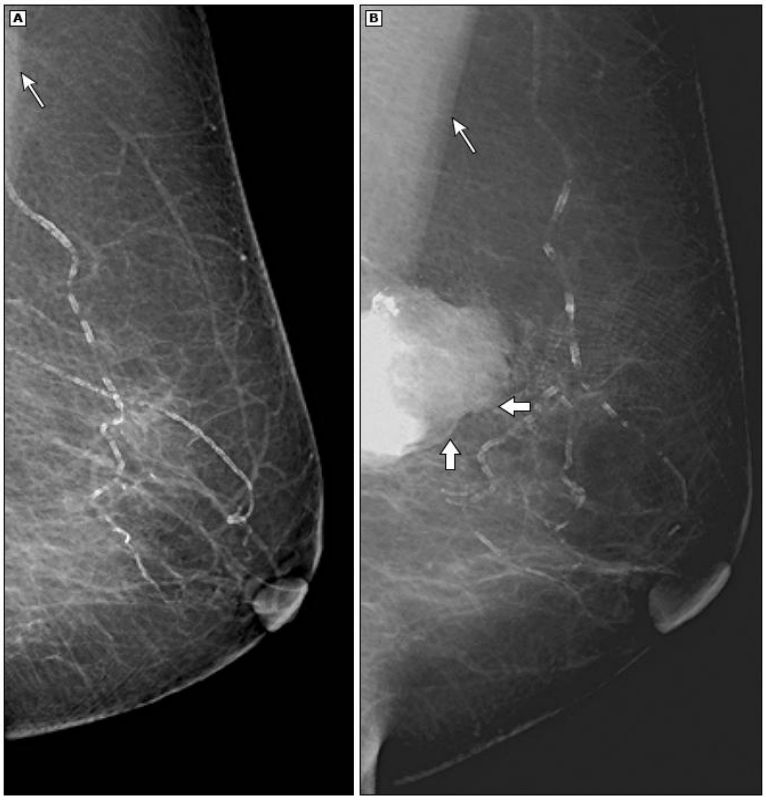

Fig-5 Importance of correct positioning

Both pictures show the left breast's MLO view. Panel A omits the posterior breast tissues. The pectoralis muscle, shown by arrows, is barely visible. The significant unequal mass (thick arrows) becomes clear with better breast positioning (Panel B).

From these two conventional perspectives, the rather active inferior and lateral regions as well as the more immobile upper and medial parts of the breast may be sufficiently observed. Two perspectives on each breast helps to separate between overlapping structures and genuine problems. Two views' advantages of better cancer diagnosis and reduced recall rates offset the increased expense and radiation exposure of the second view. Research indicates that 11 to 25 percent of tumours might be missed if just one view is acquired. When conditions require for the acquisition of a single image, the MLO view—which catches a higher volume of breast tissue than the CC view, acquiring is done. [19, 20]

MAMMOGRAPHY - BREAST IMAGING LEXICON

Meticulously created, the BI-RADS lexicon is a collection of words to describe especially meant for breast imaging results that has been translated into many languages all over. This provides a consistent communication system across radiologists, hence generating consistent reports that can be easily understood by referring doctors and supporting medical staff.

BI-RADS defines the format of the mammogram report and the consistent language for radiological findings and conclusions and reflect the relative likelihood of a normal, benign, or malignant diagnosis based only on imaging findings. At the end of every mammography report, one of the seven last assessment categories has to be used. [21]

The BI-RADS report has the subsequent components:-

The main goal of the study and the sort of test (screening or diagnostic) is defined.

The beginning of the report refers to all previous tests used for comparison.

●***Overall breast composition (breast density)*** – Every report has a remark on breast density. Most radiologists use the four categories specified in the BI-RADS atlas, which are based on the ratio of glandular (radiodense) tissue to fatty (radiolucent) tissue.

Breast composition in the BI-RADS edition 2013 was based on the general density producing ACR category A - Predominantly fatty breast tissue (< 25% fibroglandular tissue), category B - Scattered fibroglandular density (25-50% fibroglandular tissue), category C - Heterogeneously dense breasts (50-75% fibroglandular tissue), possibly obscuring small masses and category D Extremely dense breasts (> 75% fibroglandular tissue), lowering mammography sensitivity.

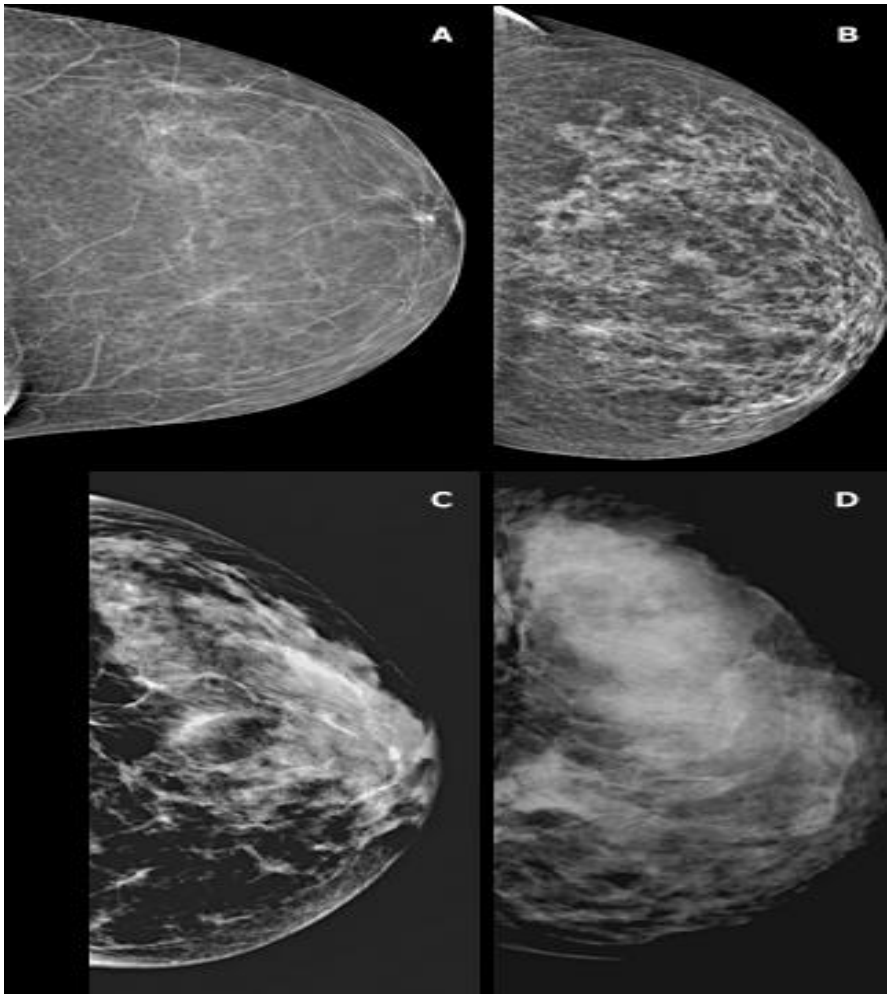

Fig-6 Varying patterns of normal breast density

Mammographic density of breast is caused by different ratios of adipose tissue, connective tissue, ductal and lobular components. The mammography report has to show the density pattern according to the traditional BI-RADS classification: primarily fatty (Panel A), scattered fibroglandular (Panel B), heterogeneous (Panel C), or dense (Panel D) breast tissue.

Evaluating cancer risk depends on the density of a noncalcified tumour. One study found that 70% high-density tumours were malignancy whereas 22% low-density tumours were malignant. [21]

Mammography findings are classified as follows

a. **Mass**
    1. Shape
    2. Margin
    3. Density
b. **Calcifications**
    1. Typically benign
    2. Suspicious morphology
    3. Distribution.
c. **Architectural distortion**
d. **Asymmetry**
e. **Intramammary lymph node**
f. **Skin lesion**
g. **Associated features**
h. **Location of the lesion**

Mass

Observable in two separate projections, a "Mass" is a three-dimensional lesion filling space.

Should a possible mass be seen in just one projection, it should be called a 'asymmetry' until its three-dimensional properties are confirmed.

1. Shape: oval (maybe with 2 or 3 lobulations), round, or irregular
2. Margins: indistinct, spiculated, microlobulated, veiled, constricted
3. Density: high, consistent, low, or lipid-rich.

Usually, all adipose lesions are benign.

Make sure the mass seen during physical exam matches the one found by mammography or ultrasonography.

Margin

A lesion's margin might be:

- Historically well-defined, circumscribed are benign findings.
- Ill-defined, when overlaying fibroglandular tissue conceals the edge.
- Indicate a suspicious finding: Microlobulated & uncertain (historically poorly demarcated).
- A very worrisome finding is spiculated, which shows radiating lines.

A spiculated tumour is the most unique feature in mammography of invasive breast cancer. A mass's positive predictive value is 81 percent with a spiculated edge and 73 percent with an irregular shape. [21]

CALCIFICATIONS

Benign and malignant calcification types according to BIRADS lexicon

Usually benign and not cancer-indicating are skin, vascular, coarse, big rodlike, round or punctate (< 1mm), rim, dystrophic, milk of calcium, suture calcifications.

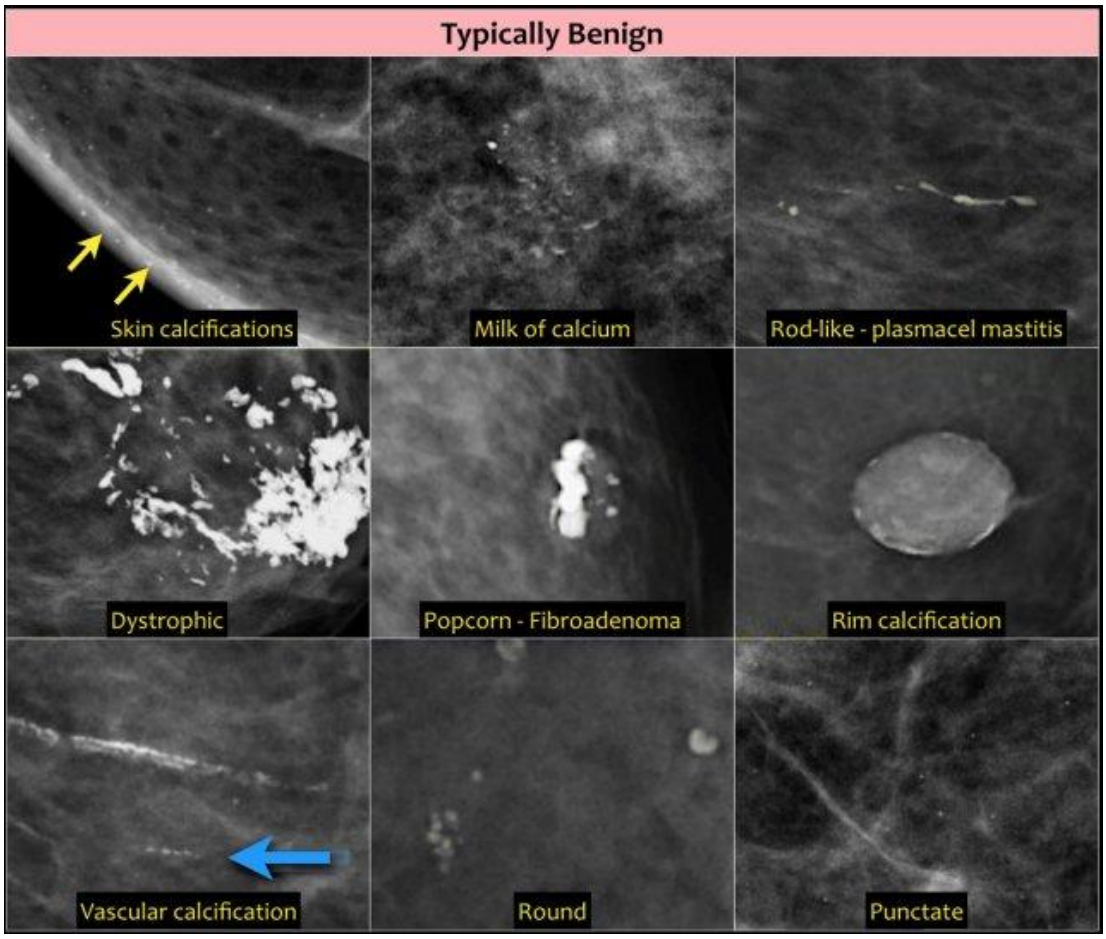

Fig –7- Typically benign calcifications

The exception to the rule is an isolated group of punctuate calcifications that is new, growing, linear, or segmental in distribution, or close to a known malignancy, which can be categorised as probably benign or worrisome.

Especially in high-grade DCIS, fine pleomorphic and fine linear or fine linear branching microcalcifications have a higher predictive value for cancer than coarse heterogeneous microcalcifications.Often, breast cancers show with coarse, heterogeneous or amorphous calcifications.

About 60 percent of cancers found by mammography show grouped microcalcifications—calcium particles of different sizes and shapes ranging from 0.1 to 1 mm in diameter and more than four to five per cubic centimetre. Histologically, they indicate intraductal calcifications in areas of necrotic tumours or calcifications inside mucin-secreting tumours.

A prospective research compared the findings of 10,641 mammograms performed at 20 sites in a span of four years with the local cancer database (Surveillance Epidemiology and End Results [SEER] program). Among women with cancer of breast, the most prevalent anomaly was a focal mass, which appeared in 56% of cases; calcifications followed in 29% of cases. Though it is a common sign for more research, only 12% of breast cancer patients exhibited asymmetry (42%). [22]

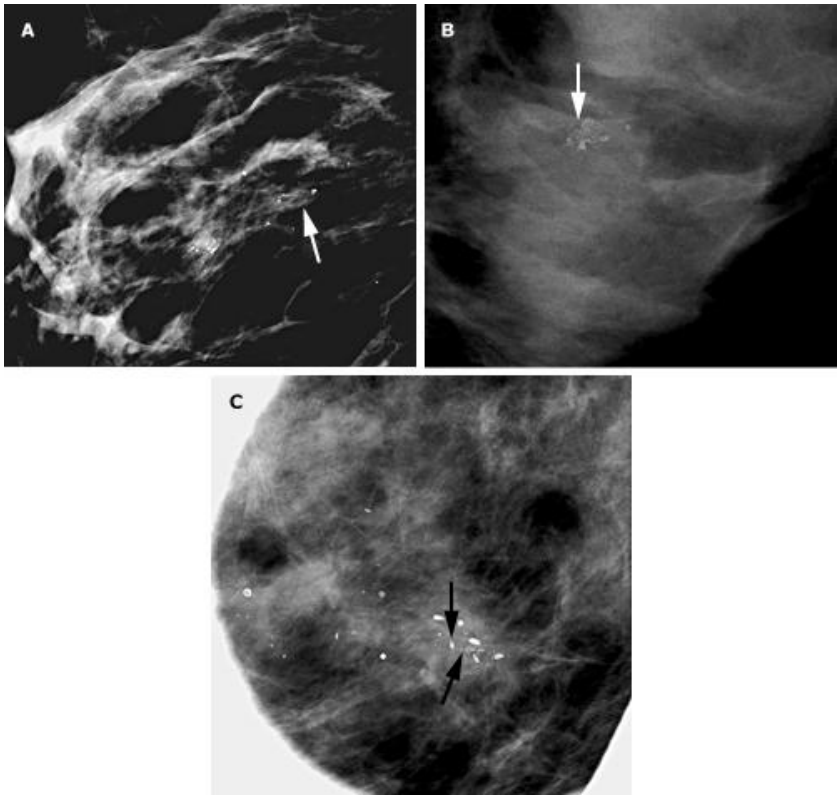

Fig-8 - Suspicious calcifications

Clustered microcalcifications in various contexts.

Panel A depicts a group of coarse heterogeneous calcifications (arrow). On a background of thick breast parenchyma, Panel B (arrow) reveals a small cluster of amorphous calcifications. Panel C displays small pleomorphic calcifications (arrows) mixed with larger coarse calcifications.

Architectural distortion

Used in breast imaging—mammography, ultrasound, and MRI—breast architectural distortion describes breast parenchyma tethered or indented. The finding itself is not a mass.

Architectural distortion is common from a desmoplastic reaction that disturbs the normal breast tissue structure locally. Many features might be seen as parts of architectural distortion.

- contour irregularity
- trabecular hypertrophy
- trabecular disarray

Asymmetry

Global asymymmetry in breast tissue is a condition in which at least one quadrant of a breast has more fibroglandular density than the corresponding quadrant in the opposite breast. There is absence of mass, suspicious calcification, or architectural distortion.

Intramammary lymph node

Lymph nodes found inside breast tissue are called intramammary lymph nodes (IMLN), often referred to as intramammary nodes. In breast imaging, they usually fall under BIRADS II. They could be one item or many. This paper looks into physiological intramammary lymph nodes. [23, 24]

Associated features

Examples of related features seen together with dubious findings include masses, asymmetries, calcifications, skin thickening, and nipple retraction.

Associated characteristics are considered in the last assessment.

For example, a BI-RADS 4-mass would be evaluated as BI-RADS 5 if seen together with any related element.

Location of the lesion

Lesions have to be evaluated depending on their laterality (right or left), Quadrant (Lower/upper, Outer/inner), clock position, depth, such as the distance from the nipple in the anterior, middle, or posterior third.

Abnormalities in mammograms include architectural distortions, asymmetries, calcifications, and masses. The particular mammographic features of breast cancer are investigated in full separately [21.]

THE MAMMOGRAPHY REPORTING (BI-RADS)

The American College of Radiology created the Breast Imaging Reporting and Data System (BI-RADS) to standardise mammography report design. BI-RADS now covers breast magnetic resonance imaging (MRI) and ultrasound interpretation. Using BI-RADS for consistent reporting helps to guide management decisions and works as a strong tool for data collection and examining personal activities. [25]

Table 1- BI-RADS assessment categories

Assessment	Management	Likelihood of cancer
Category 0: Incomplete – Need additional imaging evaluation and/or prior mammograms for comparison	Recall for additional imaging and/or comparison with prior examination(s)	N/A
Category 1: Negative	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 2: Benign	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 3: Probably benign	Short-interval (6-month) follow-up or continued surveillance mammography	>0 but ≤2% likelihood of malignancy
Category 4: Suspicious	Tissue diagnosis*	>2 but <95% likelihood of malignancy
Category 4A: Low suspicion for malignancy		>2 to ≤10% likelihood of malignancy

Category 4B: Moderate suspicion for malignancy		>10 to ≤50% likelihood of malignancy
Category 4C: High suspicion for malignancy		>50 to <95% likelihood of malignancy
Category 5: Highly suggestive of malignancy	Tissue diagnosis*	≥95% likelihood of malignancy
Category 6: Known biopsy-proven malignancy	Surgical excision when clinically appropriate	N/A

BI-RADS: System of Data and Reporting on Breast Imaging

Practice recommendations call for biopsy on all BI-RADS 4 and 5 lesions. The medical record must include clinical factors such as age and comorbidities that drive the patient, together with the doctor, to delay biopsy.

- ***Description of anomalies/significant discoveries*** – The main portion of the report covers the site and description of any anomalies using conventional BI-RADS descriptors. Each lesion's location is described in reference to a quadrant or clock position as well as its breast depth. Categorically, the breast is split into anterior, middle, and posterior depths. Every breast is divided into four quadrants: upper-outer, upper-inner, lower-outer, and lower-inner. The breast like a clock with the nipple in the centre might also signify the location.

- ***Comparison with prior examination(s), if applicable.***

The report ends with a relevant summary stressing the main findings, the last BI-RADS evaluation category, and, should a suspected abnormality be found, the advised course of treatment (e.g., a biopsy).

Categories of the BI-RADS final assessment — The BI-RADS final evaluation categories standardise the recording of mammographic findings and the suggestions for additional treatment (i.e., frequent screening, short-interval follow-up, or biopsy). Evaluations go into one of two types: unfinished (category 0) or final (categories 1 through 6). It should be emphasised that BI-RADS categories 3 to 6 are meant for diagnostic assessments, not first screening mammography; screening mammograms should only get BI-RADS ratings of 0, 1, or 2. The BI-RADS category relates only to imaging data, disregarding clinical findings or presentations. Therefore, even if the BI-RADS classification is 1 or 2, a biopsy might still be justified if the patient shows a negative imaging evaluation but appears with a clinically relevant lump.

The BIRADS evaluation categories are as follows:

●**BI-RADS 0:** Incomplete; calls for further imaging analysis and/or prior mammograms for comparison— This categorisation is used when the current perspectives provide insufficient information to make a conclusion. Screening tests, which are considered abnormal if the radiologist does not offer rapid interpretations, typically use this.

Technical problems like insufficient imaging caused by incorrect positioning or movement, an unclear lesion not properly evaluated in the standard screening views, or the lack of old mammograms to confirm the location of a possible focal or diffuse anomaly all contribute to an incomplete assessment. The patient is asked to come back with old mammograms or better mammographic acquisition and/or an ultrasound has to be done.

●**BI-RADS 1: Negative** – This test is wholly unfavourable. In keeping with present screening recommendations, the woman should continue with clinical breast assessment and screening mammography.

●**BI-RADS 2: Benign** – Documented may be benign lesions including fibroadenomas, cysts, non-malignant vascular or parenchymal calcifications. There is no cancer, and no more actions are needed. Publishing these results serves to confirm benignity and to prevent undesired evaluation. It is recommended that one follow up often.

●**BI-RADS 3: Probably benign** – This grade is used when a finding lacks clear benign qualities yet the likelihood of cancer is < 2%. Lesions in this category might be a localised asymmetry, a group of round calcifications, or a small mass seen during a baseline screening test.

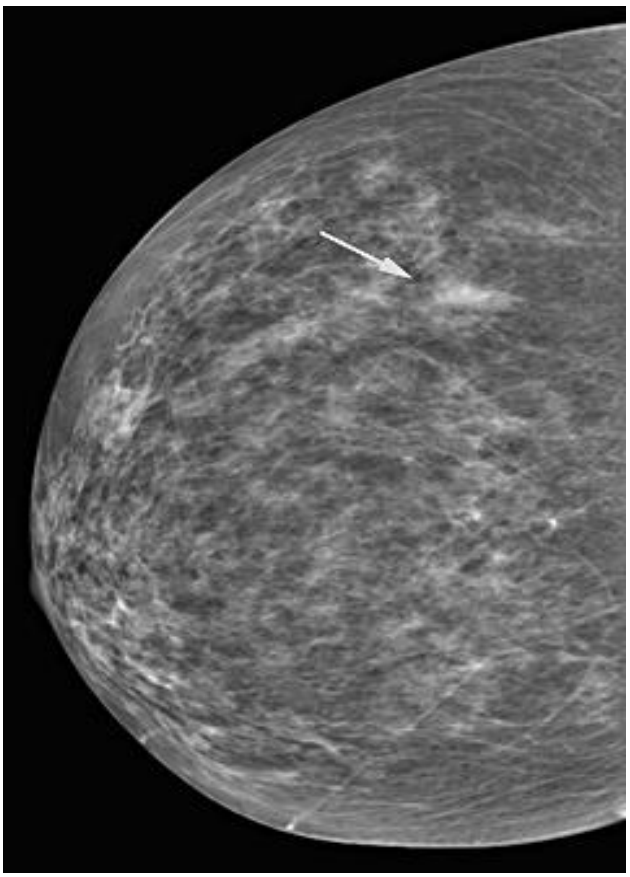

Fig 9 *On the* ***craniocaudal view,*** *the lateral breast area shows* ***parenchymal asymmetry (arrow).*** *Diagnostic mammography and ultrasound showed no further cause for concern.*

Such results are tracked at less intervals than the usual one- or two-year screening period to assess stability. Often, diagnostic mammography and/or ultrasonography track the lesion at 6 to 12 month intervals for up to three years. For close monitoring of a lesion which is not clearly benign, shorter follow-up intervals could be advised. Any of these interval follow-ups might show the lesion to be BI-RADS 2 if it is clearly benign or BI-RADS 4 or 5 if there is a change that causes major concern of cancer. [26, 27]

●**BI-RADS 4: Suspicious** – This categorisation points to a lesion showing features pointing to cancer. From 2 to 94 percent, the likelihood that the imaging finding points to malignancy changes. The lesion and the evaluator determine the degree of suspicion or worry for cancer.

Extensive BI-RADS 4 category scores are consistent with both ductal carcinoma in situ (DCIS) and invasive breast cancer. This classification's subcategories were created to show the level of concern, hence guiding the patient and physician to an informed therapeutic choice. Among these subcategories:

• BIRADS 4A - Probability of cancer 2 to 9 percent

•BI-RADS 4B - Likelihood of cancer 10 to 49 percent

•BI-RADS 4C - Probability of cancer varies from 50 to 94 percent

●**BI-RADS 5: Strongly indicative of cancer** – This category is made up of lesions showing typical imaging features including spiculations, pleomorphic calcifications, and skin retraction. Cancer is almost certain, between 95 and 100 percent.

●**BI-RADS 6: Confirmed, biopsy-proven malignancy** – Patients with confirmed biopsy-proven malignancies and surgically unexcised fall under this group; they are looking for further imaging to analyse the contralateral breast, judge neoadjuvant chemotherapy response, or get a second opinion on outside imaging readings.

Clinical decision-making

A positive mammography report

Any report with BI-RADS 0, 4, or 5 calls for more action. Most hospitals notify the doctor on the need of a biopsy; both the physician and patient are told about the need of further imaging.

Moreover, a BI-RADS category of 4C or 5 indicates a major cancer suspicion that may call for a rebiopsy should the original pathologic tissue sample be judged benign.

A negative mammography report –

A negative mammography should not stop more evaluation in the case of clinical suspicion for malignancy. Screening mammography's false-negative rate has been said to vary from 10 to 30 percent, with the greatest rates found in patients with extremely dense breast tissue.[28, 29]

Malignancies found during clinical breast exams as much as 15 percent are not visible on diagnostic mammography. Though it does not rule out breast cancer, ultrasonography lowers the false-negative rate. [30, 31] A negative imaging evaluation of mammography paired with ultrasound gives a cancer chance ranging from 0 to 3 percent.

ROLE OF ULTRASOUND

Breast ultrasound

Often used to diagnose anomalies found on mammography screening, ultrasonography helps to clarify the features of a doubtful lesion.

When a palpable tumour is present and/or an abnormality is seen on mammography, breast ultrasonography is often included into the first diagnostic evaluation for those with suspected carcinoma breast. A group of 2020 people—470 with a palpable mass—who had clinical evaluation, mammography, and breast ultrasonography revealed benefits of this strategy. Primarily made up of cysts or fibroadenomas, the thorough inclusion of breast ultrasonography found eight new malignancies and correctly reclassified 332 suspected malignancy cases to no suspected malignancy. Therefore, the main benefit of breast ultrasonography was increased under a focused use. [32]

Still, ultrasonography is very operator-dependent, and significant variation in radiologists' ability to identify solid breast lesions by ultrasound has been recorded. A benign solid appearance on ultrasonography should not rule out biopsy of a mammographically or clinically concerning tumour. [33]

A vital diagnostic supplement to mammography is diagnostic or targeted ultrasound examination of the breast.

Breast ultrasonography is most useful in those cases of suspicion of carcinoma breast in the following situations:

●***To further elucidate a mammographically identified mass, focal asymmetry, or a region of architectural distortion.*** Breast ultrasonography helps the surgeon locate lumps and tell them apart as benign or malignant. One study found that while the negative predictive value was 99.5 percent, the sensitivity of ultrasonography for cancer was 98.4 percent.[17] Other studies have revealed similar results. [31, 32]

Solid masses described by ultrasound as oval and showing benign imaging characteristics, for example, have a cancer risk of under 2%; so, a short-term follow-up of six months followed by regular monitoring might be an appropriate therapy strategy rather than biopsy. Young patients under 50 years of age are predominat in this study. [31]

●***To ascertain the presence of a cystic mass.*** Because of the low chance of cancer, simple cysts need no more treatment; one research found no malignancies in 223 cysts.

●***To further delineate a lesion*** Often seen in those with dense breast tissue, when a tumour found during clinical breast examination is not clearly seen on mammography.

●***To ascertain if a mammographically worrisome lesion*** can thus be gathered by means of ultrasound-guided biopsies. The US-guided breast biopsy removes radiation exposure and is more comfortable than the stereotactic biopsy.

●***To assess and excise a lesion*** before neoadjuvant chemotherapy. Precise anatomic localisation is absolutely necessary for patients with big or locally advanced tumours needing neoadjuvant chemotherapy to help the surgeon find the tumour location post-therapy. Often, the lesion is evaluated clinically and ultrasonographically, recorded by size, the "o'clock" location on the breast surface, and the nipple distance.

Although whole-breast ultrasound screening can find more early-stage breast cancers not visible on mammograms, particularly in people with dense breast tissue, this extra screening technique carries a high risk of false-positive results, which causes patient worry, unnecessary breast biopsies with benign findings, and more imaging tests. A comprehensive cohort research involving over 3,000 women who had both mammography and same-day ultrasound, alongside more than 15,176 matched controls who got mammography alone, concluded that the advantages of incorporating same-day ultrasonography into screening mammography did not surpass the associated hazards. When compared to those who had mammography alone, women who took part in both trials showed similar cancer detection rates (5.4 vs 5.5 per 1000) and interval cancer rates (1.5 vs 1.9 per 1000), but higher false-positive biopsy rates (52 vs 22 per 1000). Those doing both studies had lower positive predictive value for biopsy advice (9.5 percent vs. 21.4 percent). [33]

USG BIRADS lexicon terminologies.

1. **BREAST COMPOSITION**
    a. **Homogenous background echotexture – fat**
    b. **Homogenous background echotexture – fibroglandular**
    c. **Heterogenous background echotexture**

Breast echotexture is the appearance of background tissue in breast sonography, analogous to breast density or the amount of fibroglandular tissue seen in mammography and MRI. The BI-RADS terminology classifies tissue composition into three separate categories.

Homogeneous background echotexture signifies adipose tissue.

Most of the breast is dependably echogenic connective tissue bands and adipose lobules.

Beneath a thin hypoechoic layer of subcutaneous fat is a homogenous background echotexture of fibroglandular tissue defined by a significant zone of uniformly echogenic fibroglandular tissue interspersed with hypoechoic ducts.

Heterogeneous; various areas show varied echogenicity with shadowing at the fat-fibroglandular contacts.

2. **FINDINGS –**

1. **SHAPE – oval / round / irregular**

According to the BI-RADS vocabulary, breast lumps are differently characterised by modality. Across all modalities, masses can be defined by their size, location, and form.

Lesion localisation depending on laterality—i.e., left or right quadrant, i.e., upper/lower inner/outer, and/or clock face depth, i.e., anterior, middle, or posterior third proximity to the nipple morphology which may be remembered using the mnemonic ROI: circular, oval, irregular; the latter, not conforming to round or oval shapes, often raises suspicion for malignancy.

2. **ORIENTATION – parallel / not parallel**

Orientation is the long axis of the lesion in reference to the skin: parallel or not parallel. for example, erect, circular, greater in height than in breadth.

3. **MARGIN**
   - **A. Circumscribed** - meaning the entire circle is clearly defined
   - **B. Not Circumscribed – indistinct / angular / microlobulated / spiculated.**

Angular, not limited; angular suggesting that some of the border produces a sharp corner. microlobulated, meaning few waves; indistinct, meaning none of the circumference is obviously defined; spiculated, marked by acute linear radiations.

4. **ECHOPATTERN – Anechoic / hyperechoic / complex cystic and solid / hypoechoic / isoechoic / heterogenous.**

Echo patterns include anechoic (no internal echoes), hypoechoic (low-level internal echoes under subcutaneous fat), isoechoic (equal echogenicity to subcutaneous fat), hyperechoic (higher echogenicity than fat or comparable to fibroglandular tissue), heterogeneous (a mix of echogenicities within a solid mass), and complex cystic and solid (comprising both anechoic and echogenic components). [33]

5. **POSTERIOR FEATURES** – Posterior characteristics consist of shadowing, augmentation, no features (i.e. no shadowing or enhancement deep to the bulk), or mixed features. Its posterior features, which are similarly useful, reflect a mass's attenuation characteristics with respect to its acoustic transmission. By itself, it is not very particular.

6. **CALCIFICATIONS –**

Can be found in a mass, outside of a mass, or intraductal calcifications. Though not as well defined on US as on mammography, they may be seen as echogenic foci, particularly if they are located in a mass.

7. **Associated features**
    1. **Architectural distortion**
    2. **Duct changes**
    3. **Skin changes – skin thickening / skin retraction**
    4. **Edema**
    5. **Vascularity – Absent / Internal Vascularity / Vessels in a rim.**
    6. **Elasticity assessment – Soft / intermediate / hard – Add few sentences about this – elastography.**

8. **Special cases – Cysts / lymph nodes / foreign body implants.**

Often described as a well-defined, anechoic lesion with an unclear wall and posterior acoustic enhancement is a simple breast cyst. Comprising intracystic echoes or debris next to basic cyst features is a complex breast cyst ("cystic and solid mass"): Thick-walled with strong septa or an intracystic solid mass.

IHC Markers and Molecular Classification of Breast Cancer

In breast cancer histology, immunohistochemistry (IHC) markers are crucial for classifying tumours into genetic subtypes, hence directing prognosis and therapy plans. Oestrogen Receptor (ER), Progesterone Receptor (PR), HER2 (Human Epidermal Growth Factor Receptor 2), and Ki-67 (proliferation index) all influence the categorisation. [34]

Table 2 - Molecular Subtypes Based on IHC Markers

Subtype	ER	PR	HER2	Ki-67	Characteristics
Luminal A	+	+	-	Low (<14%)	Most favorable prognosis, hormone therapy responsive
Luminal B	+	+/–	- or +	High (>14%)	More aggressive than Luminal A, may need chemo and HER2-targeted therapy if HER2+
HER2-Enriched	-	-	+	High	Poor prognosis, requires HER2-targeted therapy (e.g., trastuzumab)
Triple Negative (TNBC)	-	-	-	Variable	Aggressive, lacks targeted therapy options, chemotherapy is primary treatment

Clinical Importance of IHC Classification

- **Luminal A:** Best prognosis, responsive to endocrine therapy (e.g., tamoxifen, aromatase inhibitors).
- **Luminal B:** More aggressive than Luminal A; if HER2+, HER2-targeted therapy is used.
- **HER2-Enriched:** Requires HER2-targeted therapy (e.g., trastuzumab, pertuzumab).
- **Triple Negative:** Most aggressive, lacks hormonal and HER2-targeted options; chemotherapy is the mainstay treatment.

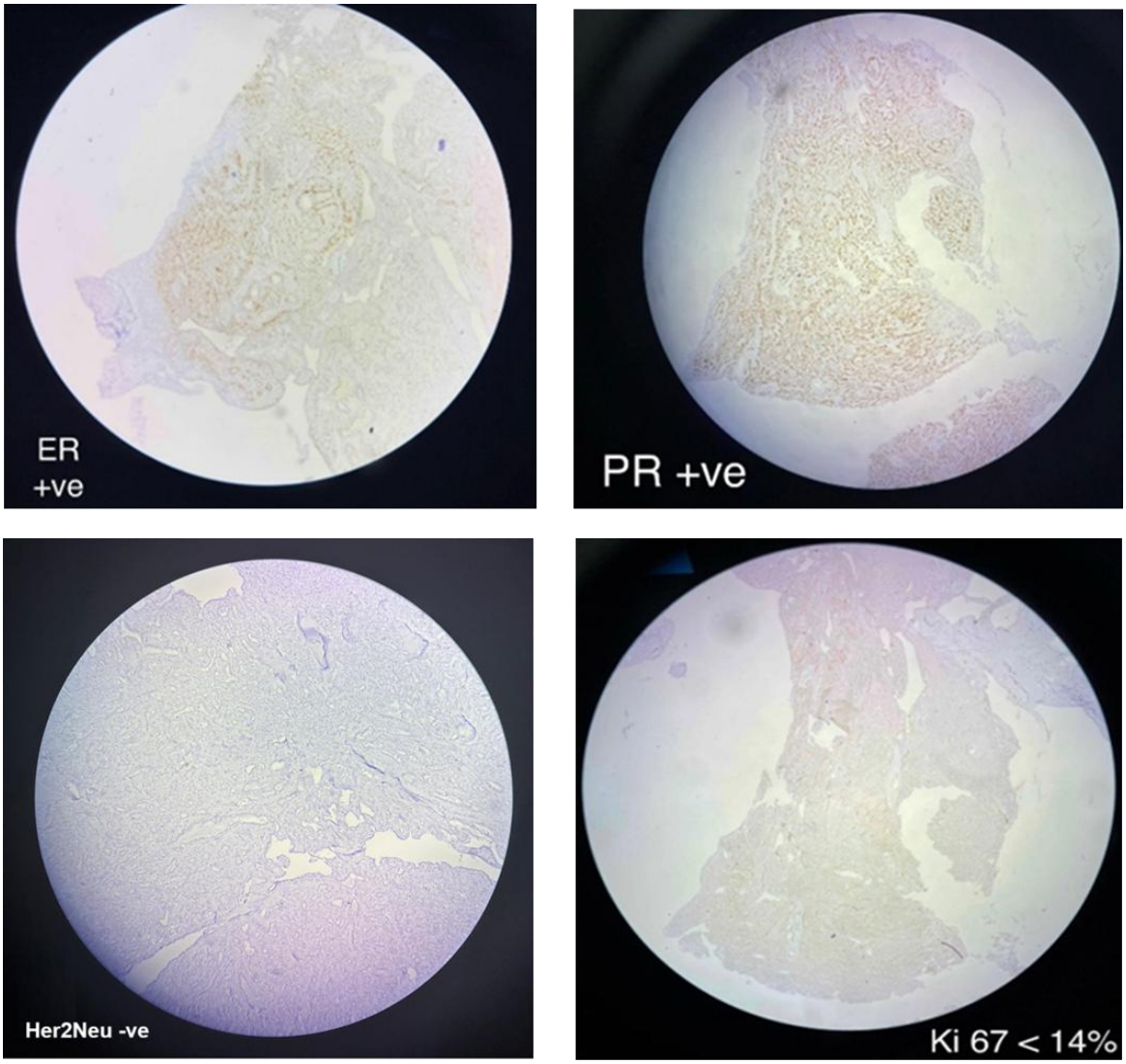

Fig 10 *– Showing* ***a microphotograph of Luminal A subtype of molecular classification of breast carcinoma*** *status with ER +ve, PR +ve, Her2Neu -ve, Ki67 < 14% status.*

Rashmi et al., 2018 carried out a study prospectively on breast cancer patients presenting between January 2016 and July 2017 with mammography and/or breast ultrasonography, as well as excision of the breast tumour. Patients with a contralateral breast mass, metastases, a history of prior cancer treatment, and other cancers were excluded. Mammography documented existence of microcalcifications. Ultrasound study looked at size, margins, microcalcifications, posterior acoustic features, vascularity, and axillary lymph nodes. Margins were categorised as circumscribed and non-circumscribed. Four categories of posterior auditory features were shadowing, augmentation, mixed, and no changes. Adler's index was used to assess vascularity, graded 0, 1, 2, or 3. While grades 2 and 3 were considered high, grades 0 and 1 were regarded as low. Microcalcifications found on mammography, together with certain ultrasound features including circumscribed or non-circumscribed margins, posterior acoustic characteristics, and vascularity, show a strong correlation in forecasting the molecular subtypes of breast cancer, so possibly improving the use of traditional breast imaging. [10]

Combinations of mammography and ultrasound imaging findings were utilised to forecast breast cancer molecular subtypes in a sample of screening and symptomatic patients in a research by **Ian et al., 2021.** While high-risk microcalcifications and microlobulated margins suggest HER2-enriched tumours, triple-negative breast cancer (TNBC) is linked with circumscribed margins, posterior enhancement, and large size. While luminal subtypes are usually small, with spiculated margins and posterior acoustic shadowing, especially the Luminal A type, ductal carcinoma in situ is characterised by its small size on ultrasound, absence of posterior acoustic features, and architectural distortion on mammography. These outcomes closely correspond to those of earlier studies. Moreover, it was detected that ultrasound size showed a higher odds ratio for TNBC found during screening. Size might be a key factor in advising a biopsy during the screening phase as TNBC shows sonographic features like narrowed margins and posterior enhancement, which could mimic benign tumours. Many imaging features revealed to be independent predictors of molecular subtypes of breast cancer. Knowing these links might help physicians stratify breast cancer patients, hence guiding treatment decisions in areas without reasonable receptor testing or enabling early therapies. [35]

In their **2015** study, **Çelebi et al**. sought to determine the relationship between the molecular subtype, histologic grade, and hormone receptor status of breast cancer and its ultrasound characteristics. Examined from the database under the Breast Imaging and Reporting Data System (BI-RADS), 201 patients with invasive breast cancer. Tumour borders were classified as circumscribed or non-circumscribed. The non-circumscribed group was divided into angular, indistinct, spiculated, and microlobulated kinds. The posterior auditory features were grouped into four groups: shadowing, augmentation, no change, and mixed pattern. The molecular subtype, histological grade, and hormone receptor status of the tumour closely correlate with sonographic features. These results might set triple-negative breast cancer apart from other molecular subtypes. [2]

The goal of **Irshad et al. (2013)** was to assess the predictive importance of several ultrasound features of breast cancer and to correlate them with tumor grade and the presence of ERRB2 (formerly known as HER2), progesterone, and estrogen receptors. Among the 160 breast cancer patients, 102 (63.8%) were ER-positive/PR-positive, 32 (20.0%) were ER-positive/PR-negative, 26 (16.3%) were ER-negative/PR-negative, and 22 were triple-negative. Compared to those without posterior shadowing, tumours showing posterior shadowing have nearly nine times the chance of showing ER-positive findings (95% CI, 2.09-40.81; $p = 0.011$) and more than thirteen times the probability of being classified as lower-grade tumours (I or II versus III; 95% CI, 4.90-36.54; $p < 0.001$). Compared to those without posterior enhancement, tumours showing posterior enhancement have almost eight times greater likelihood of having at least one negative receptor (95% CI, 3.97-18.11; $p < 0.001$) and twenty-four times greater likelihood of being classified as high-grade tumours (95% CI, 9.91-58.14; $p < 0.001$). While posterior enhancement is strongly connected to high-grade tumours and a low probability of receptor negativity, posterior shadowing is strongly related to ER-positive, low-grade tumours.[36]

Huang et al., in **2020** examined the characteristics of digital mammography (DM) combined with digital breast tomosynthesis (DBT), ultrasonography (US), and magnetic resonance imaging (MRI) for breast cancer in young women (≤30 years old) and their association with molecular subtypes. Performed a retrospective study of imaging features in young women aged less than 30 years who were treated and surgically diagnosed with breast cancer at their institution between January 2013 and December 2019. Every participant was Chinese woman. Of 170 lesions, DM, DBT, and US were available; MRI was available for 41. Univariate and multivariate logistic regression analyses were used to investigate the imaging features in order to find the predictive factors of the molecular subtypes. The prognostic criteria for the triple-negative subtype (n = 31) were a mass free of microcalcifications, an oval or round shape, limited boundaries, posterior enhancement features, and rim enhancement on MRI (all $P < 0.005$). Exclusive microcalcifications, microlobulated borders, and a combined posterior feature (all $P < 0.05$) defined the prognostic markers for the human epidermal growth factor receptor 2-enriched subtype (n = 26). Compared to the general carcinoma breast population, this young female subpopulation exhibits a unique molecular phenotypic distribution. Certain imaging features of breast cancer in people 30 years or younger can be used to predict particular tumour molecular subtypes [37]

According to a study by **Cho et al., (2016),** gene expression analysis has reorganized the traditional histology-based breast cancer classifications into the luminal A, luminal B, human epidermal growth factor receptor 2 (HER2), and basal-like subtypes within the previous 15 years. Every molecular subtype shows different chances for advancement, treatment response, and survival results. Studies linking molecular subtypes to imaging phenotypes have revealed that the basal-like subtype is common in non-calcified, well-defined masses showing posterior acoustic enhancement; the luminal subtype is characterised by spiculated masses with ill-defined borders and posterior acoustic shadowing; and the HER2-enriched subtype is associated with pleomorphic calcifications. Understanding the clinical consequences of genetic subtypes and imaging phenotypes might help radiologists guide precision medicine, tailoring medical treatments to fit people and their tumour characteristics. [38]

Japanese women with BRCA-positive breast cancers had their mass formation, vascularity, and elasticity examined by **Ikejima et al.** in **2023**. Patients with breast cancer who had BRCA1 or BRCA2 mutations were found. Excluding those who underwent surgery or chemotherapy before the ultrasonography, we evaluated 89 tumours in BRCA1-positive patients and 83 in BRCA2-positive patients. The ultrasound images were evaluated in accord by three radiologists. Examined were imaging features including vascularity and flexibility. Examined were pathological data including tumour subtypes. BRCA1 and BRCA2 cancers showed significant differences in tumour form, peripheral features, posterior echoes, echogenic foci, and vascularity. Tumours of breast linked to BRCA1 showed hypervascularity and posterior accentuation. On the other hand, BRCA2 tumours were less likely to become masses. When a tumour turned into a mass, it usually showed posterior attenuation, ambiguous boundaries, and echogenic foci. Pathological studies revealed that tumours linked to BRCA1 mostly showed triple-negative subtypes. On the other hand, BRCA2-related tumours were primarily of the luminal or luminal-human epidermal growth factor receptor 2 kinds. When tracking BRCA mutation carriers, radiologists have to understand that the morphological differences between tumours differ greatly between BRCA1 and BRCA2 patients [39]

Khalaf and Herdan, conducted a study in **2020** to examine the potential of ultrasound imaging characteristics in predicting the molecular subtypes of invasive ductal breast cancer (IDC) and to evaluate whether nodal metastasis serves as an independent predictor for each subtype. The predicted sonographic signs for each subtype are as follows: The predictive sonographic indicators for each subtype are as follows: LA subtype: echogenic halo, posterior shadowing, angular or spiculated margin, and unifocal mass; LB subtype: irregular shape; HER2 subtype: unifocal mass, abrupt interface of the tumour boundary, and posterior enhancement or absence of posterior change; TN subtype: circumscribed or lobulated margin, oval or rounded shape, posterior enhancement or absence of posterior change, abrupt interface of the tumour boundary, and parallel orientation of the mass. While its absence is the most important independent predictor for the LA subtype, multivariate logistic regression shows that the presence of nodal metastases is the most strong independent predictor for the HER2 subtype. Specific sonographic markers point to every molecular subtype of invasive ductal carcinoma (IDC). When present, nodal metastasis is an independent predictor for the HER2 subtype; when absent, it predicts the LA subtype. [40]

The association between sonographic and digital mammography features and the molecular classification of breast cancer was investigated by **Shaikh and Rasheed** in **2021**. The molecular categorisation of breast cancer was predicted by comparing imaging features from 313 patients evaluated by preliminary ultrasonography and digital mammography between November 2017 and May 2020 with histopathological and immunohistochemical studies. Comprising many simple imaging features that could be easily performed in outpatient settings, we created a measure called the "sono-mammometry" score. According to the study, non-triple-negative breast tumours are generally hypoechoic and have a close link with irregular spiculated margins, peripheral echogenic halos, posterior shadowing, and microcalcifications. By contrast, triple-negative breast cancers show notable variation in imaging findings, with certain characteristics matching those of normal benign tumours. Although imaging features help to forecast molecular categorisation, their prognostic relevance is still somewhat low. Considerable variation in imaging features calls for further focus to improve diagnostic accuracy. Our sono-mammometry score helps as a straightforward test thought to be useful and successful in settings with limited resources, helping to clarify these traits. [41]

The ability of interpretable machine learning algorithms to predict the molecular subtypes of breast cancer was evaluated by **Ma et al. in 2022**. With an AUC of 0.971, accuracy of 0.947, sensitivity of 0.905, and specificity of 0.941, the decision tree (DT) model stood out in distinguishing triple-negative breast cancer (TNBC) from other breast cancer subtypes. The DT model has greatly increased the accuracy, sensitivity, and specificity of all radiologists in differentiating luminal breast cancer from other molecular subtypes and TNBC from other molecular subtypes. The average sensitivity, specificity, and accuracy of less experienced and more experienced radiologists in diagnosing TNBC increased by 0.090, 0.125, and 0.114, and 0.060, 0.090, and 0.083, respectively, when compared to other subtypes. For less experienced radiologists, the diagnosis of Luminal versus other subtypes showed an increase in average sensitivity, average specificity, and average accuracy of 0.084, 0.152, and 0.159; for more experienced radiologists, the corresponding values were 0.020, 0.100, and 0.048. This work gave radiologists additional benefits by developing an intelligible machine learning model to distinguish between the genetic subtypes of breast cancer [42]

The need for this study arises from the escalating prevalence of breast cancer, which has emerged as the predominant cause of mortality among women globally.

According to a study by **Kalyani R et al.,** in **2012,** it is the 2nd most common cancer in women of developing countries like India, and the incidence is observed more in affluent societies having western lifestyle. Population-based screening, especially mammography, has decreased the mortality by 25-30%. Females with a history of cancer breast in the family should have an intensive screening program [43]

This study aims to predict breast cancer subtypes utilizing ultrasound and mammography, which are non-invasive, generally accessible, cost-effective imaging modalities that serve as major tools in the early assessment of breast carcinoma thereby facilitating early management and better survival rates.

MATERIALS & METHODS

MATERIALS AND METHODS

Source Of Data:

Over a period of eighteen months—from May 2023 to Nov 2024—this hospital based observational study of ultrasound and mammography will be carried out on a minimum of 52 lesions in patients referred in view of carcinoma breast to Department of Radio-Diagnosis, R.L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Inclusion Criteria :

- All cases of carcinoma breast.
- Patients willing to undergo excision/biopsy of the breast mass and sent for immunohistochemical molecular subtyping.

Exclusion criteria:

- Benign breast lesions.
- < 10 mm lesions.
- Recurrence of carcinoma in ipsilateral breast.
- Male carcinoma breast.

Statistical methods

Data will be analysed with SPSS 22 version software after being loaded into Microsoft Excel data sheet. Frequencies and proportions will reflect categorical data.

A chi-square will serve as significance test. Mean and standard deviation will reflect continuous data. To find the mean difference, independent t test will be applied as test of significance. Statistically significant will be p value < 0.05.

Sample Size:

Sample size was estimated by using the proportion of LB (HER2+) in subjects who were breast cancer was 13% from the study by Rashmi et al.[10] using the formula

$$\textbf{Sample Size} = \frac{Z_{1-\alpha/2}^{2}\, P\,(1-P)}{d^{2}}$$

Z1-α /2 = is standard normal variate (at 5% type 1 error (P<0.05) it is 1.96 and at 1% type1 error(P<0.01) it is 2.58).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

P = 13% or 0.13

q = 87% or 0.87

d = 10% or 0.10

Using the above values at 95% Confidence level a sample size of **52** lesions will be included in the study.

Methods Of Collection Of Data:

Their willingness to take part in the study will be documented in prior written informed consent. Should they meet the inclusion requirements, the patients will be part of the research. Patients will provide baseline data together with appropriate clinical history and related laboratory tests. All patients who qualify will get ultrasound and mammography.

Philips EPIQ 5G will do ultrasound utilising linear transducer of L12-5 MHz frequency. Using Allengers Medical Systems Limited, MAM-VENUS (40 KHz) mammography device, standard craniocaudal (CC) and mediolateral oblique (MLO) views for each breast will yield mammograms.

Figure 11: Philips EPIQ5 USG machine.

Figure 12: MAM-VENUS (40 KHz) mammography machine.

Ultrasound features:

1. Size	
2. Shape	a. Oval b. Round c. Irregular
3. Margins	a. Circumscribed b. Non-circumscribed
4. Echogenicity	a. Hyperechoic b. Hypoechoic c. Isoechoic d. Anechoic
5. Posterior Acoustic feature	a. Shadowing b. Enhancement c. Mixed d. No changes
6. Vascularity	Adler's degree 0, I=low; II and III=high 0 = no vascularity I = minimal II = moderate III = marked

Mammography feature:

Microcalcifications: Present/Absent

Expression of ER, PR, Her2Neu and Ki67 biomarkers will be obtained from immunohistochemistry laboratory of Department of Pathology.

Results will be correlated with the imaging features and analysed as:

- Luminal A
- Luminal B
- Basal / Triple negative
- Her2Neu enriched

Does the study require any investigations or interventions to be conducted on patient or other human or animals?

Yes, the study requires ultrasound and mammography to be performed on patients after obtaining consent.

Immunohistochemical analysis will be done on biopsy/excision samples after obtaining consent.

RESULTS

RESULTS

Breast cancer is a heterogeneous disease comprising multiple molecular subtypes, each with distinct prognostic and therapeutic implications. Traditionally, molecular subtyping relies on immunohistochemical analysis of biopsy or surgical specimens, which, while definitive, may delay the initiation of targeted therapy. Recent advances have highlighted the potential of imaging modalities, such as ultrasound and mammography, to provide early, non-invasive clues about tumor biology. Several studies have demonstrated that specific imaging features—such as lesion margins, posterior acoustic characteristics, and the presence of microcalcifications—correlate with underlying molecular subtypes, offering a valuable adjunct to histopathological assessment. By evaluating these radiological parameters, clinicians may be able to stratify patients and tailor management strategies even before pathological confirmation. The following section presents the results of our study, which aimed to assess the accuracy of ultrasound and mammography in predicting the molecular subtypes of breast carcinoma in a cross-sectional cohort.

Table 3: Age group

Age group	Frequency	Percentage
31 - 40	7	13.46
41 - 50	19	36.54
51 - 60	13	25.00
61 - 70	6	11.54
71 - 80	5	9.62
81 - 90	2	3.85
Total	52	100.00
Mean ± SD = 53.90 ± 12.95		

Table 3 shows the age distribution of the study participants (n=52), with the majority belonging to the 41–50 years age group (36.54%), followed by 51–60 years (25%) and 31–40 years (13.46%). Fewer participants were observed in the older age groups: 61–70 years (11.54%), 71–80 years (9.62%), and 81–90 years (3.85%). The mean age of the participants was 53.90 years with a standard deviation of 12.95 years.

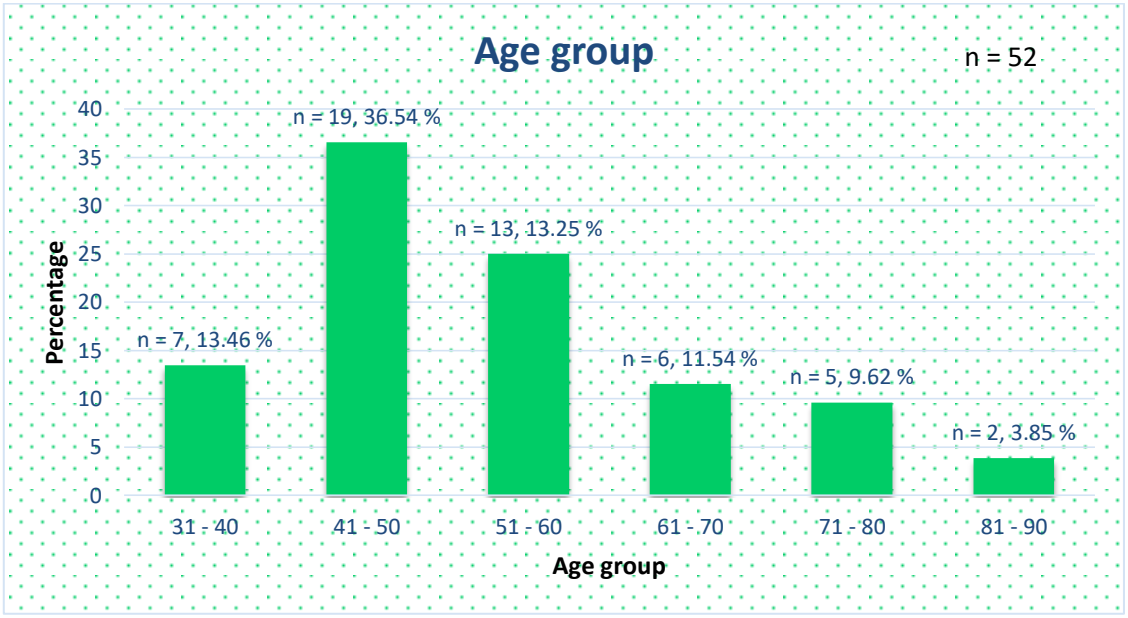

Fig 13 *– Bar graph of age distribution - The majority of cases (36.54%) belonged to the 41–50 age group, followed by 25% in the 51–60 age group. Very few cases were observed in the older age brackets, with only 3.85% in the 81–90 range.*

Table 4: Side of the breast involved

Side of the breast involved	Frequency	Percentage
Left	32	61.54
Right	20	38.46
Total	52	100.00

Table 4 displays the side of the breast involved among the 44 participants with breast pathology. The left breast was more commonly affected (61.54%) compared to the right breast (38.46%).

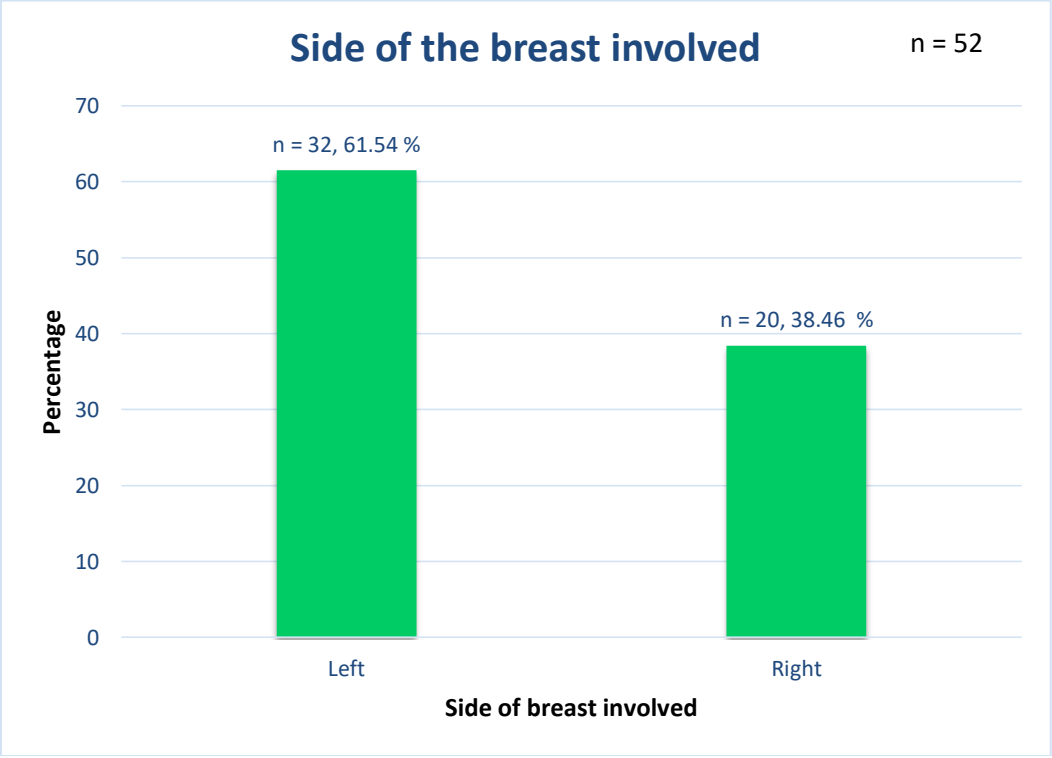

Fig 14 *showing a bar graph with lesion in left breast in 61.54 % cases and in right breast in 38.46 % cases.*

Table 5: Family History

Family History	Frequency	Percentage
Present	32	61.54
Absent	20	38.46
Total	52	100.00

Table 5 outlines the family history of participants. A family history of relevant conditions was present in the majority (61.54%) of cases, while 38.46% reported a negative family history.

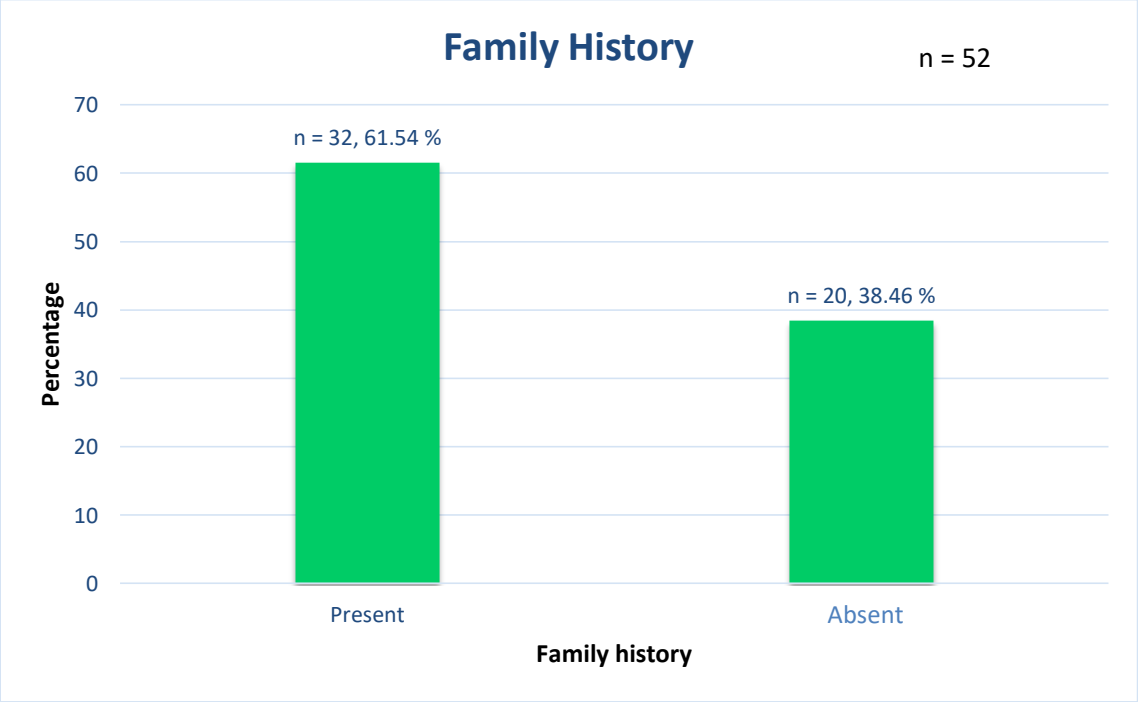

Fig 15 *showing a bar graph with family history of breast carcinoma in 61.54 % cases and negative history in 38.46 % cases.*

Table 6: Site Of Tumor

SITE OF TUMOR	Frequency	Percentage
CENTRAL	5	9.62
UOQ & CENTRAL	3	5.77
LIQ	4	7.69
LOQ	5	9.62
RETROAREOLAR	1	1.92
UIQ	5	9.62
UOQ	29	55.77
Total	52	100.00

Table 6 details the site of tumor involvement among participants. The upper outer quadrant (UOQ) was the most commonly affected site (55.77%), followed by equal involvement of the central, lower outer quadrant (LOQ), and upper inner quadrant (UIQ), each at 9.62%. Other sites included lower inner quadrant (LIQ) (7.69%), UOQ with central (5.77%), and retroareolar region (1.92%).

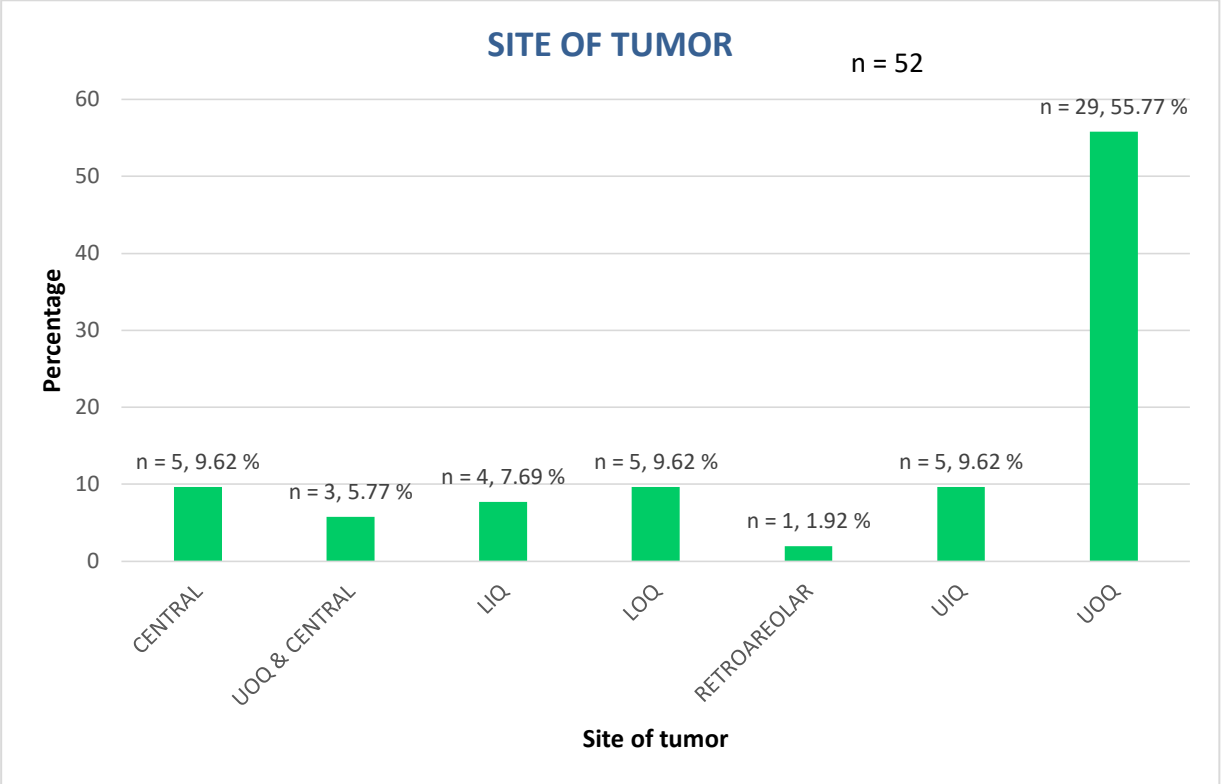

Fig 16 *showing a bar graph of site of tumor. The most common site of tumor was the upper outer quadrant (UOQ), accounting for 55.77% of cases. Other sites like central, LOQ, and UIQ had significantly lower frequencies, each around 9.62%.*

Table 7: Distribution of Shape of the lesion

SHAPE	Frequency	Percentage
Well Defined	24	46.15
Ill-Defined	28	53.85
Total	52	100.00

Table 7 describes the distribution of lesion shapes among participants. Ill-defined lesions were slightly more common, observed in 53.85% of cases, while well-defined lesions accounted for 46.15%.

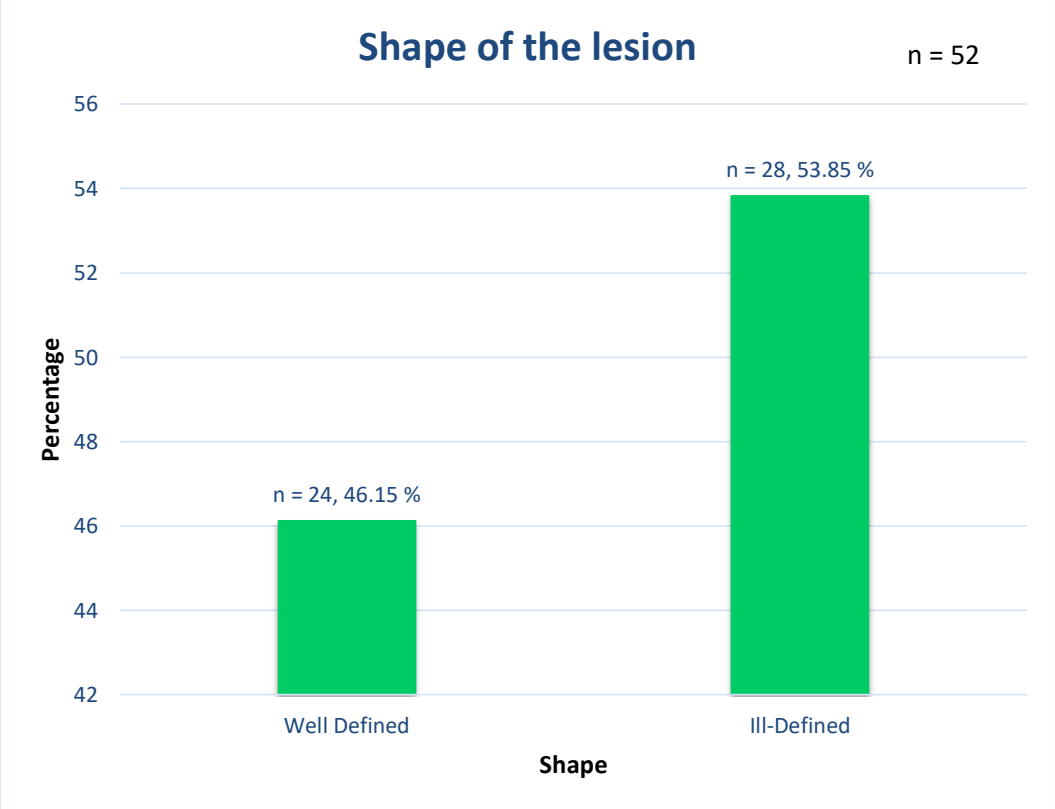

Fig 17 *depicting a bar graph of shape of lesion. The majority of cases were ill-defined (53.85 %), while rest were well defined (46.15 %)*

Table 8: Distribution of Margins

Margins	Frequency	Percentage
Lobulated	22	42.31
Spiculated	15	28.85
Irregular	15	28.85
Total	52	100.00

Table 8 presents the distribution of lesion margins among 52 participants. Lobulated margins were the most frequent (42.31%), while spiculated and irregular margins were equally observed, each accounting for 28.85% of the cases.

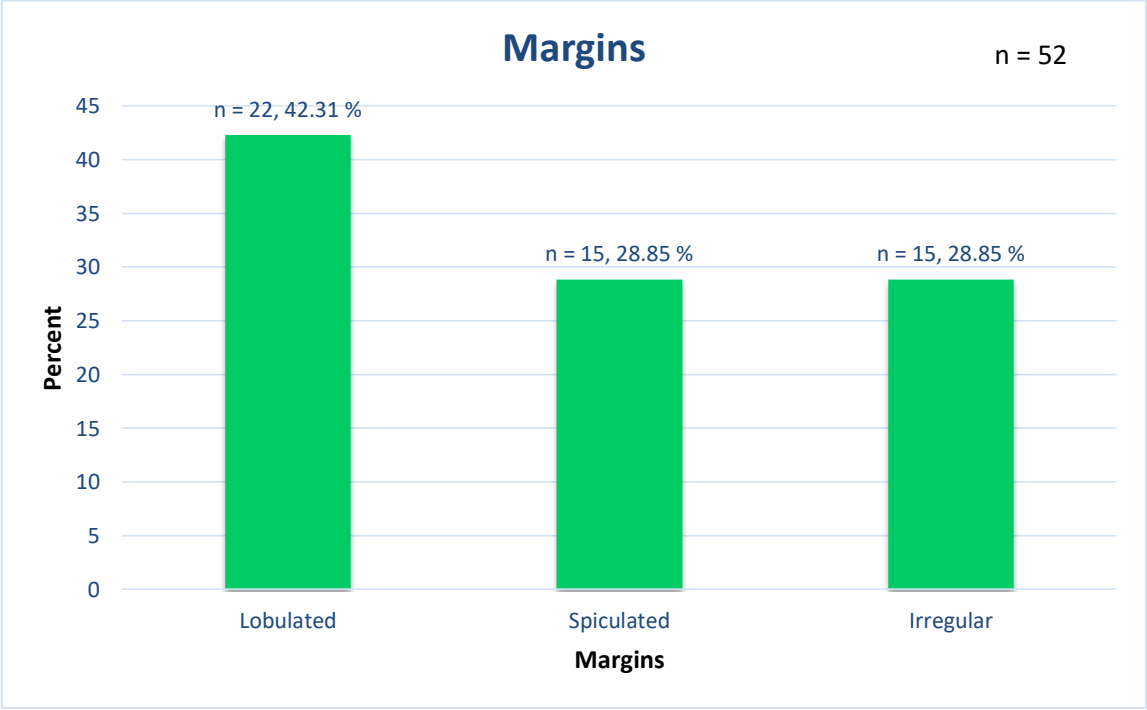

Fig 18 *depicting a bar graph of margins of lesion. 42.31% cases showed lobulated margins while 28.85 % showed speculated or irregular margins.*

Table 9: Distribution of Echogenicity

Echogenicity	Frequency	Percentage
Heterogenous	35	67.31
Hypoechoic	17	32.69
Total	52	100.00

Table 9 shows the distribution of echogenicity among lesions. The majority (67.31%) exhibited heterogeneous echogenicity, while 32.69% were hypoechoic, indicating variability in internal echo patterns among the lesions.

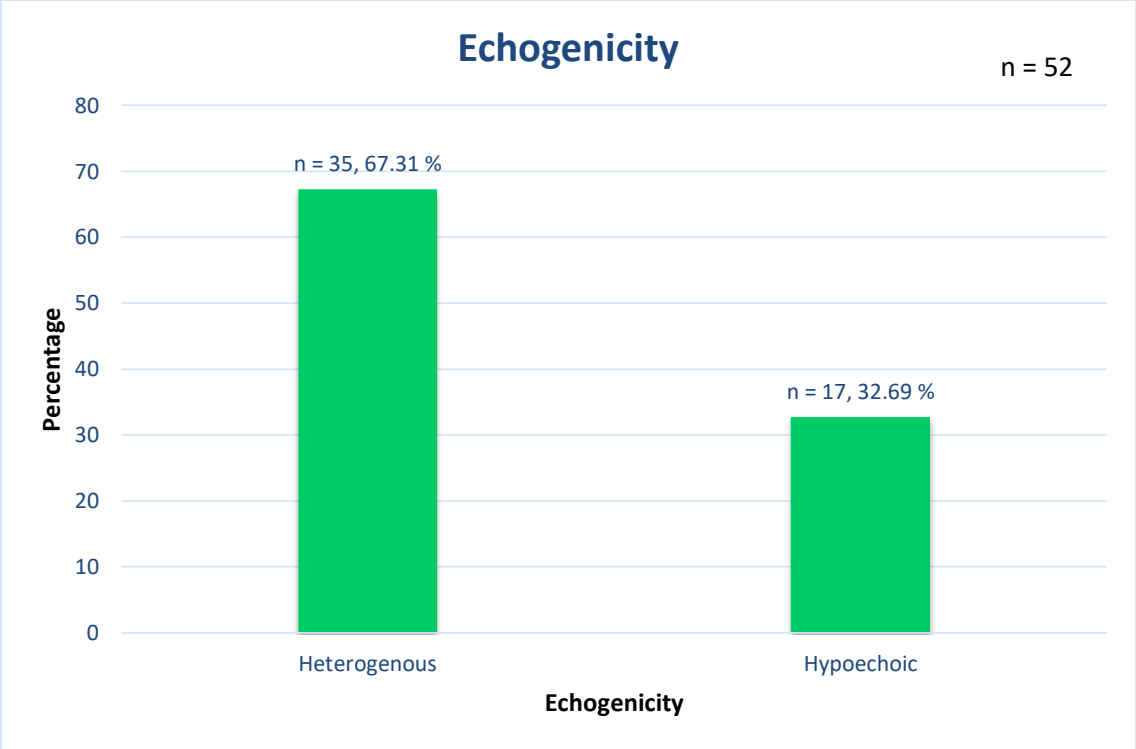

Fig 19 *depicting a bar graph of echogenicity of lesion. 67.31% cases showed heterogeneous echogenicity, while 32.69% were hypoechoic.*

Table 10: Distribution of Posterior Acoustic Features (PAF)

PAF	Frequency	Percentage
Shadow	21	40.38
Enhanced	10	19.23
Mixed	21	40.38
Total	52	100.00

Table 10 illustrates the distribution of posterior acoustic features (PAF) in lesions. Both shadowing and mixed features were equally common, each observed in 40.38% of cases, while posterior acoustic enhancement was seen in 19.23% of the lesions.

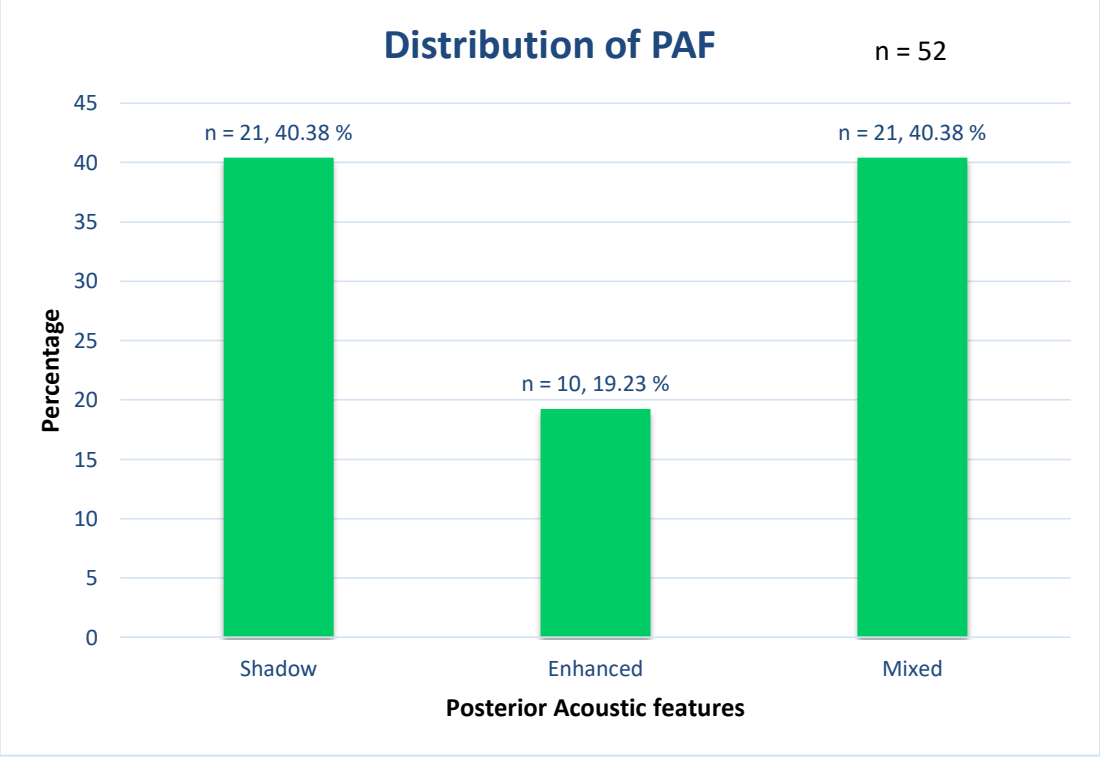

Fig 20 *depicting a bar graph of posterior acoustic features. Shadow and mixed patterns were the most common types of PAF, each observed in 40.38% of cases. The enhanced pattern was less frequent, seen in only 19.23% of cases.*

Table 11: Vascularity

Vascularity	Frequency	Percentage
Minimal peripheral	5	9.61
Internal	25	48.08
Internal and Peripheral	2	3.85
No	20	38.46
Total	52	100

Table 11 depicting vascularity: Internal vascularity was the most common finding, observed in 48.08% of cases, followed by absence of vascularity in 38.46%. Minimal peripheral and combined internal and peripheral vascularity were less frequent, accounting for 9.61% and 3.85% of cases, respectively.

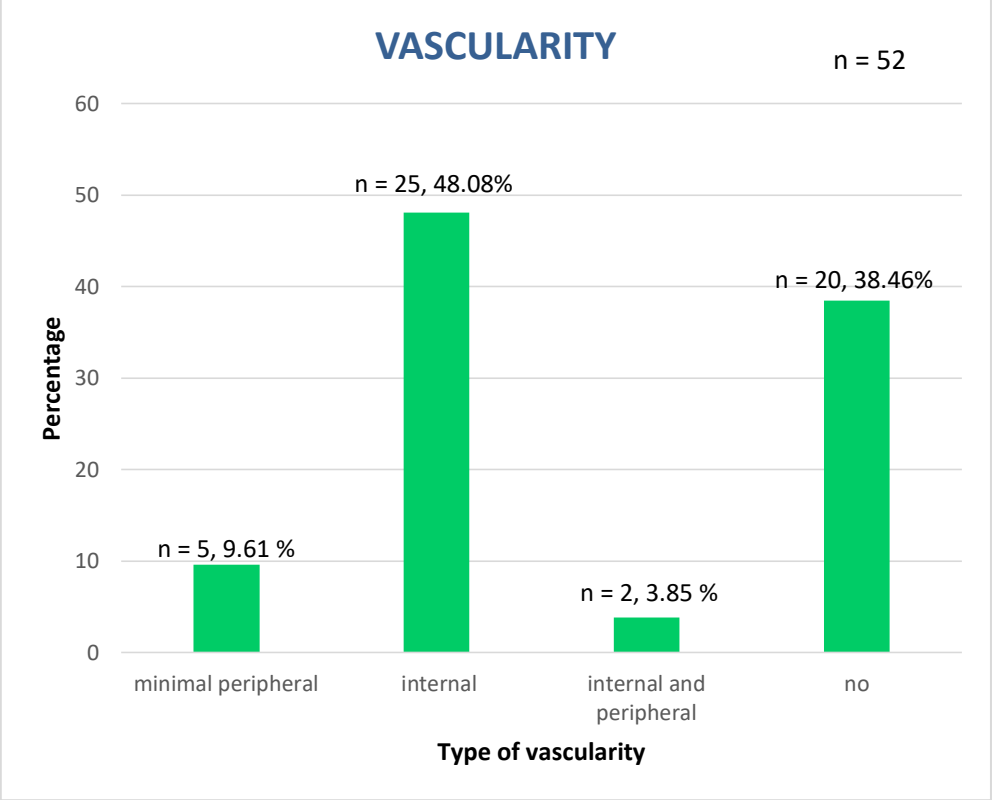

Fig 21 *depicting a bar graph of vascularity of the masses.*

Table 12: Microcalcifications on Mammography

Microcalcifications on Mammography	Frequency	Percentage
Present	**29**	**55.76**
Absent	**23**	**44.23**
Total	**52**	**100**

Table 12 shows the presence of microcalcifications on mammography. They were present in majority of cases (29 cases, 55.76 %), while absent in rest 23 cases (44.23 %).

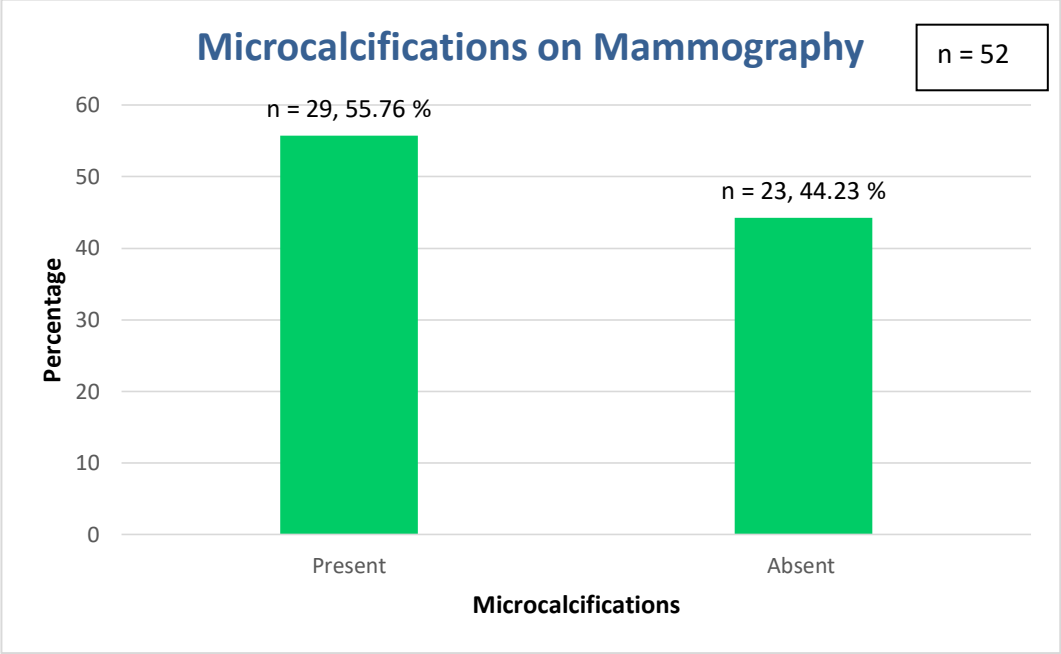

Fig 22 *illustrating a bar graph of microcalcifications on mammography. 55.67 % cases showed microcalcifications, but was absent in 44.23 % cases.*

Table 13: Immunohistochemistry findings

Immunohistochemistry findings	Positive	Negative	Total
ER Status	28	24	52
PR Status	28	24	52
Her 2neu Status	18	34	52
Ki 67 Status	26	26	52

Table 13 summarizes the immunohistochemistry findings among the participants. Estrogen receptor (ER) and progesterone receptor (PR) positivity were each observed in 28 out of 52 cases (53.85%). HER2/neu was positive in 18 cases (34.62%) and negative in the majority (65.38%). Ki-67, a proliferation marker, showed an equal distribution, with 26 cases (50%) positive and 26 (50%) negative.

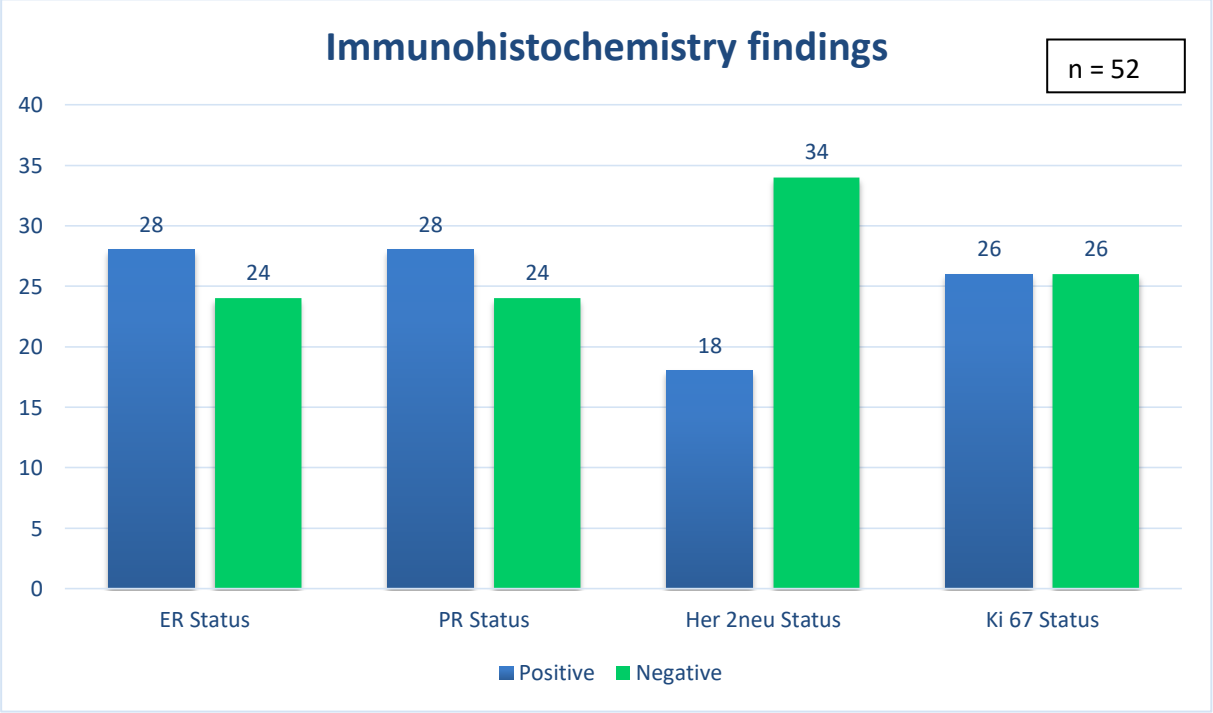

Fig 23 *illustrating a bar graph of Immunohistochemistry findings. Estrogen receptor (ER) and progesterone receptor (PR) positivity were identified in 28 of 52 cases (53.85%) each. HER2/neu expression was positive in 18 cases (34.62%) and negative in the remaining 34 cases (65.38%). The proliferation marker Ki-67 was demonstrated in 26 cases (50%) testing positive and 26 (50%) negative.*

Table 14: Association between Radiological and Pathological Diagnosis

	Pathological Diagnosis				
Radiological Diagnosis	**Luminal A**	**Luminal B**	**Triple negative**	**Her 2 enriched**	**Total**
Luminal A	13	0	0	0	13
Luminal B	1	10	0	1	12
Triple negative	0	1	14	0	15
Her2 enriched	0	3	0	9	12
Total	14	14	14	10	52
p-value < 0.001					

Table 14 presents the association between radiological and pathological diagnoses. A strong concordance is observed, with most radiological Luminal A cases (13/13) confirmed pathologically as Luminal A, and the majority of radiological Triple Negative cases (14/15) matching the pathological diagnosis. Similarly, 10 out of 12 Luminal B radiological cases and 9 out of 12 radiological Her 2-enriched cases were confirmed pathologically. The statistically significant p-value (< 0.001) indicates a strong association between radiological and pathological subtyping.

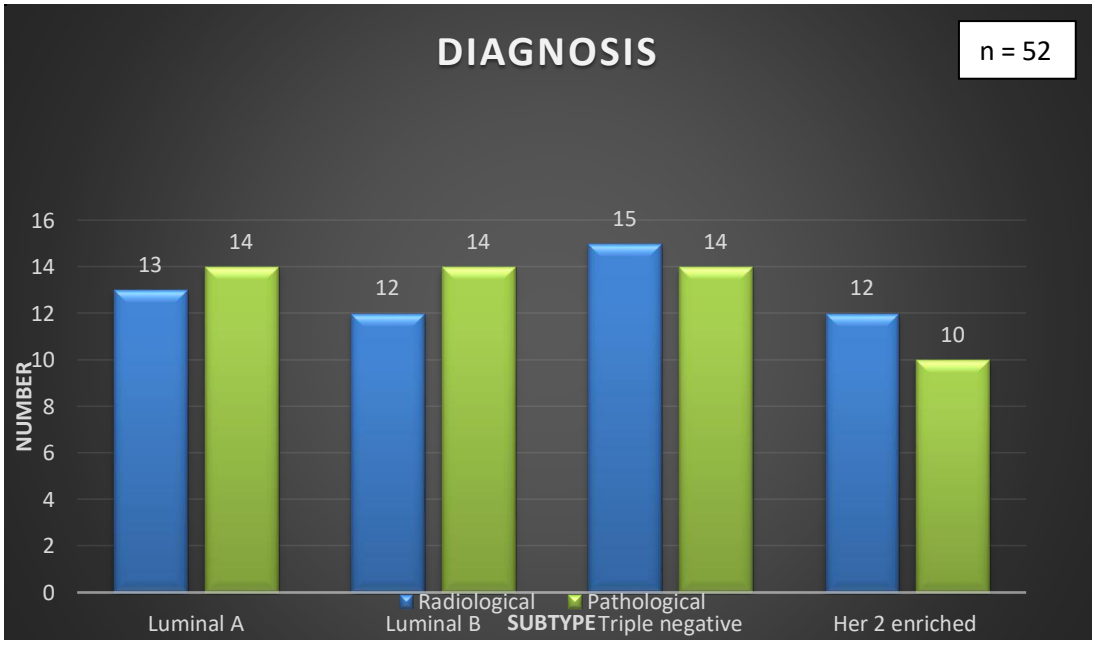

Fig 24 *demonstrating a bar graph of association between radiological and pathological diagnoses.*

Table 15: Diagnostic accuracy of radiological findings in predicting molecular subtypes

Sensitivity	94.72%
Specificity	92.18%
Positive Predictive Value	90.88%
Negative Predictive Value	86.54%
Accuracy	90.12%

Table 15 highlights the diagnostic accuracy of radiological findings in predicting molecular subtypes of breast cancer. The sensitivity was high at 94.72%, with a specificity of 92.18%. The positive predictive value (PPV) and negative predictive value (NPV) were 90.88% and 86.54%, respectively. Overall diagnostic accuracy was 90.12%, indicating that radiological assessment is a reliable tool for predicting molecular subtypes.

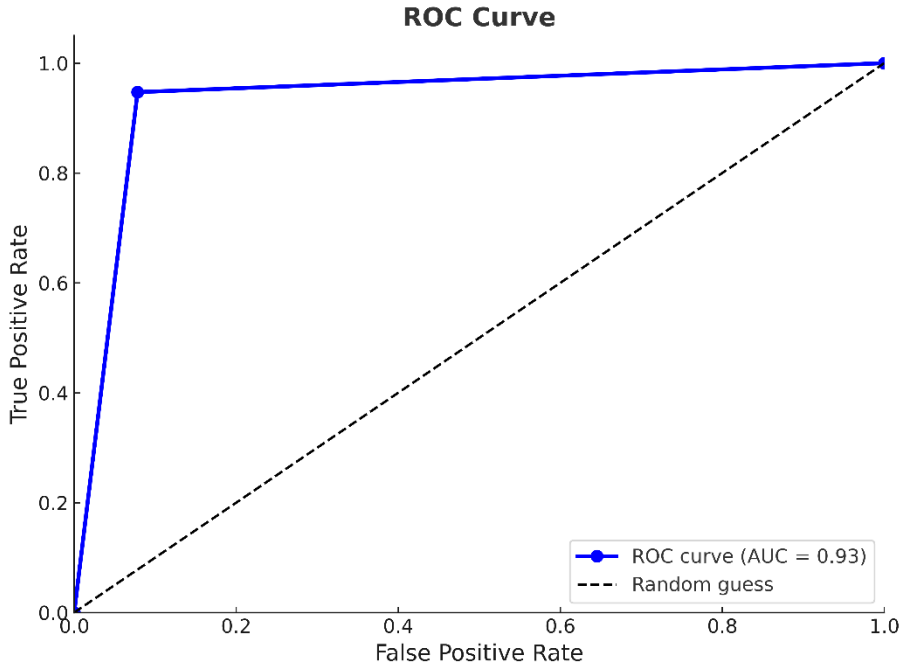

Fig 25 *demonstrating an ROC curve of sensitivity and specificity. The Area Under the Curve (AUC) comes out to approximately* ***0.93****, suggesting strong diagnostic performance.*

IMAGES

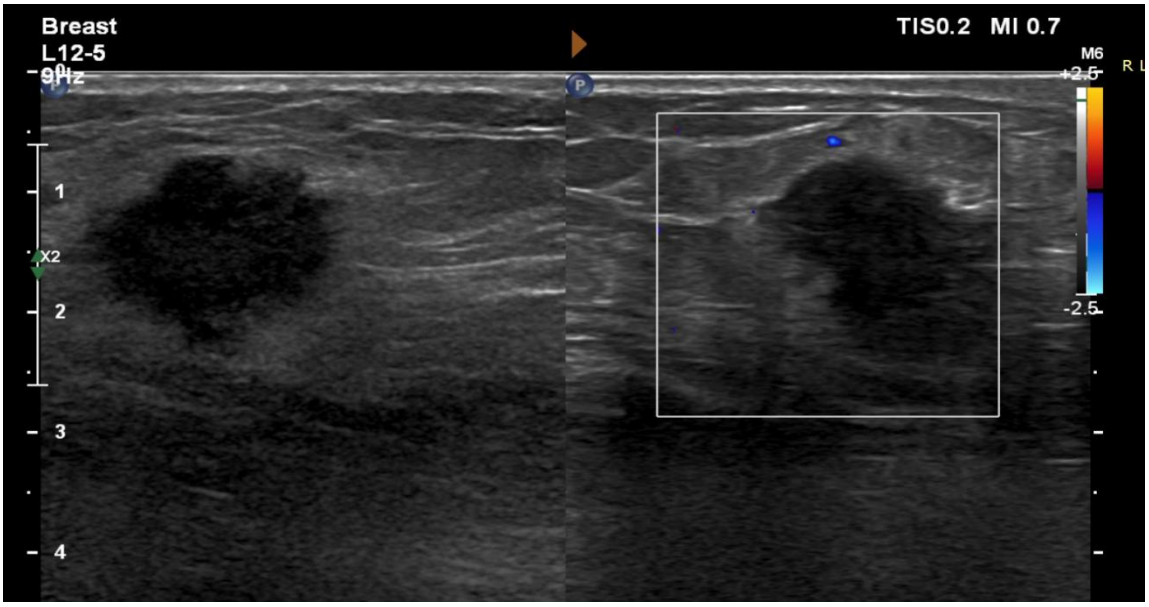

Fig: 26a

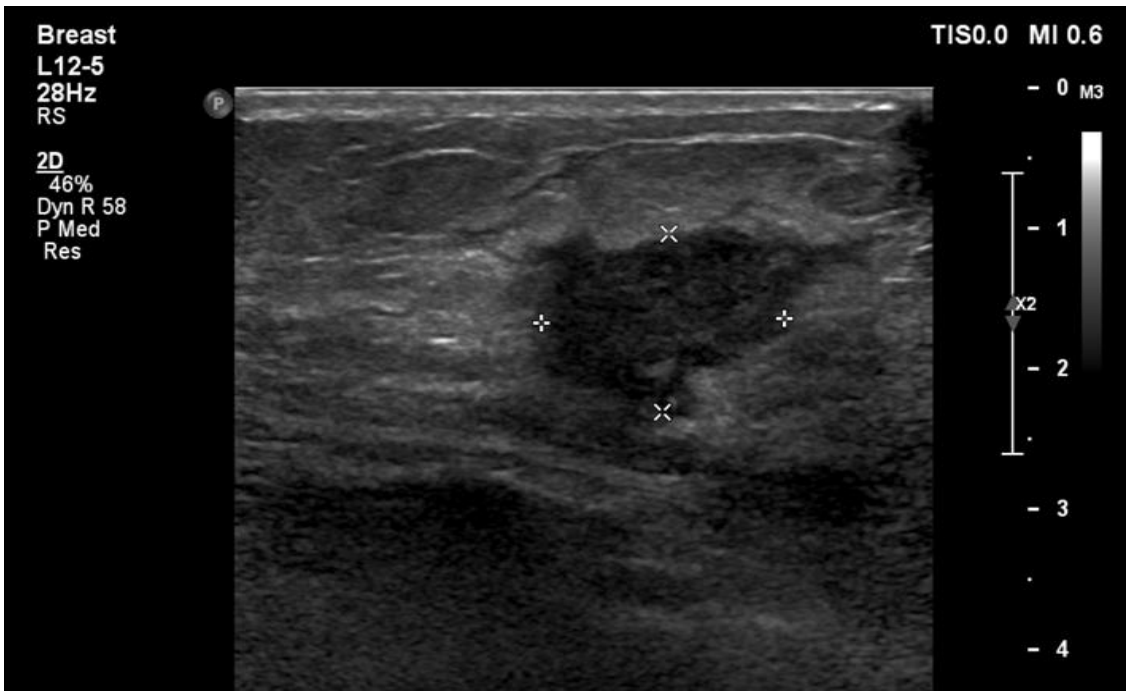

Fig: 26b

Fig: 26a, 26b *An ill-defined lobulated, wider than taller heterogenous lesion with minimal peripheral vascularity on CDI noted in 7'0 clock position of left breast.*

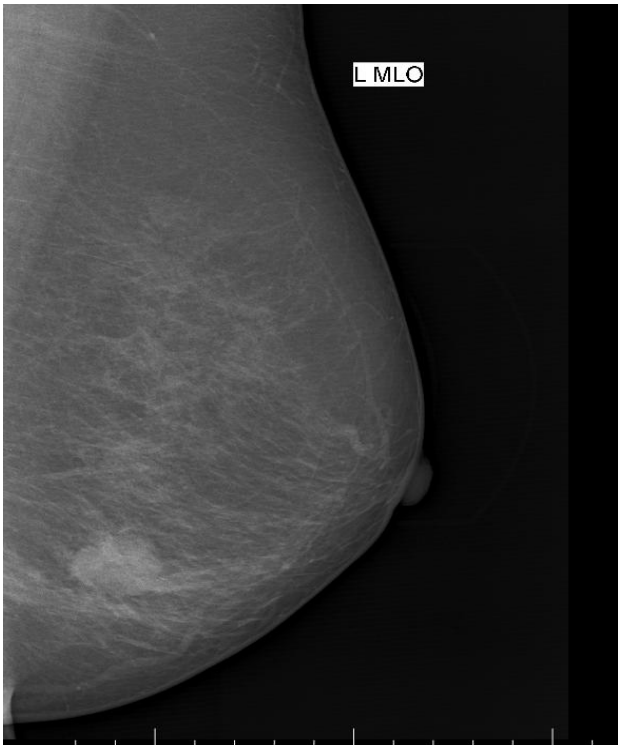

Fig: 27a

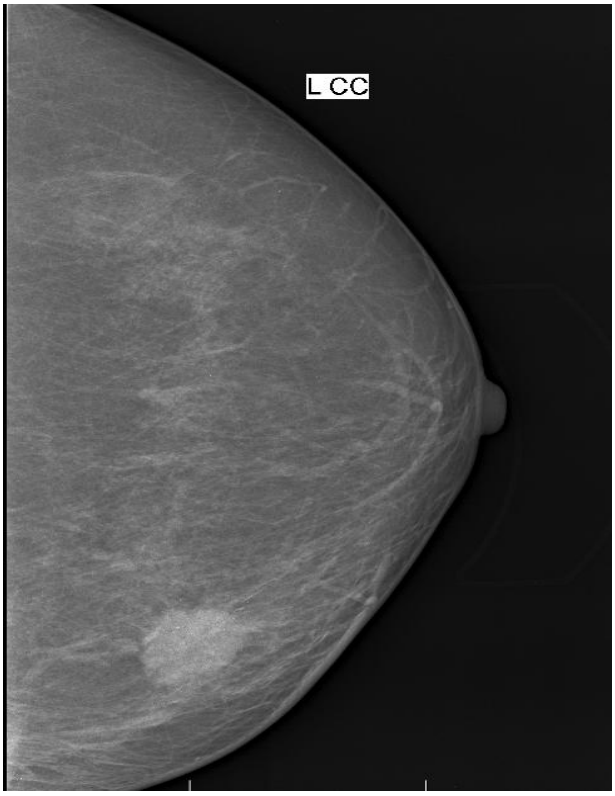

Fig: 27b

Fig: 27a, 27b *A fairly well circumscribed high density lesion with irregular margins noted in lower inner quadrant with no evidence of calcifications.*

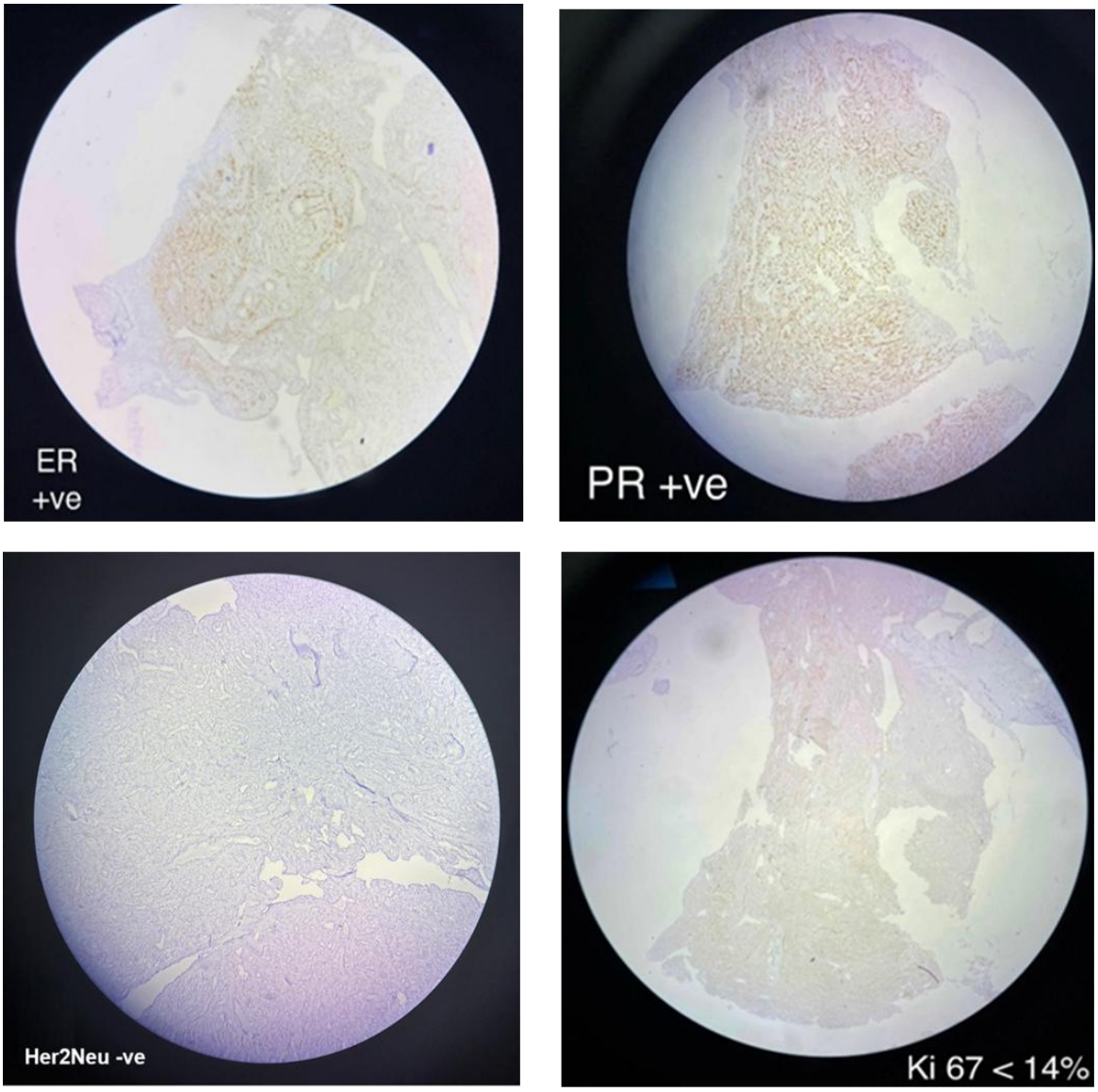

Fig: 28 *Pathologically case was confirmed as Luminal A***.**

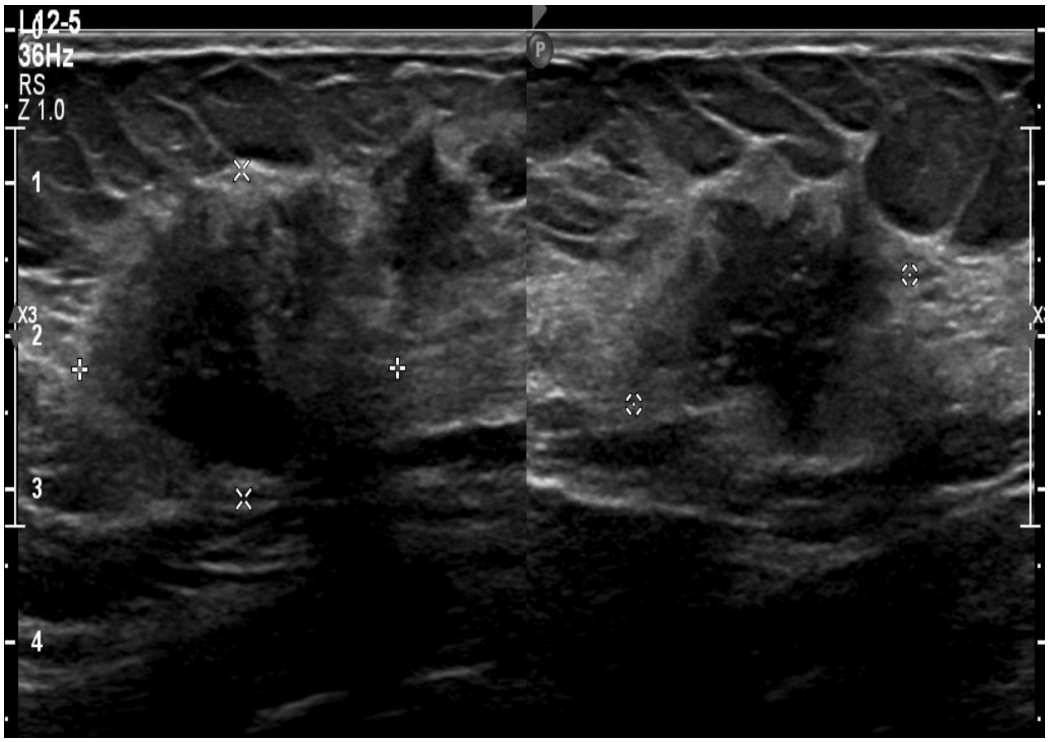

Fig: 29a

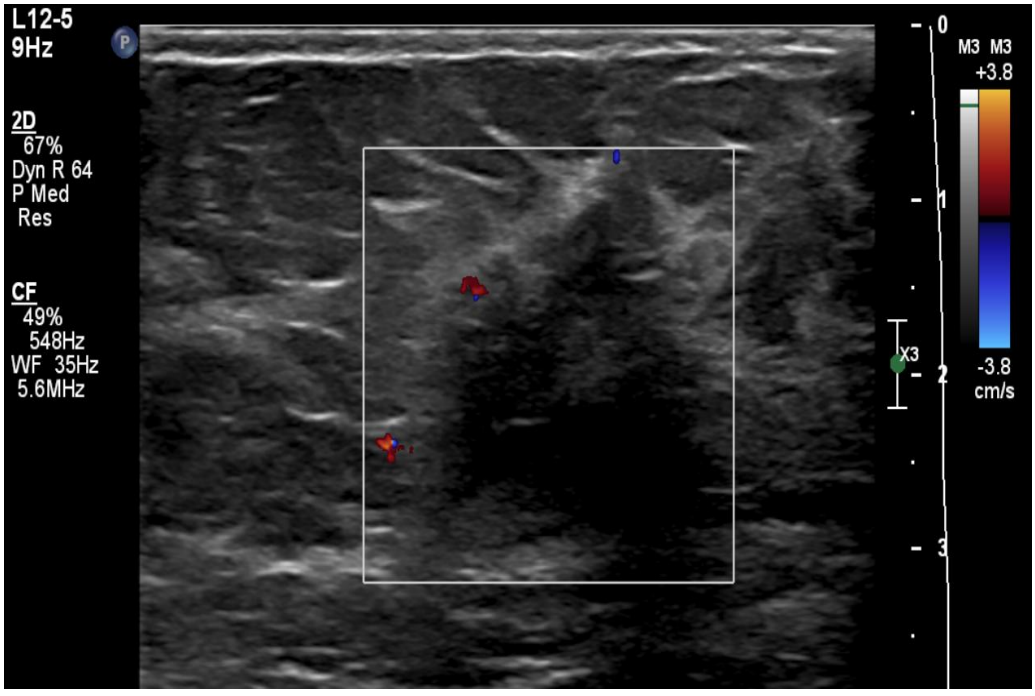

Fig: 29b

Fig: 29a, 29b *An ill-defined heterogenous lesion noted in upper outer quadrant of right breast at 10'0 clock position. The lesion demonstrates minimal peripheral vascularity on CDI.*

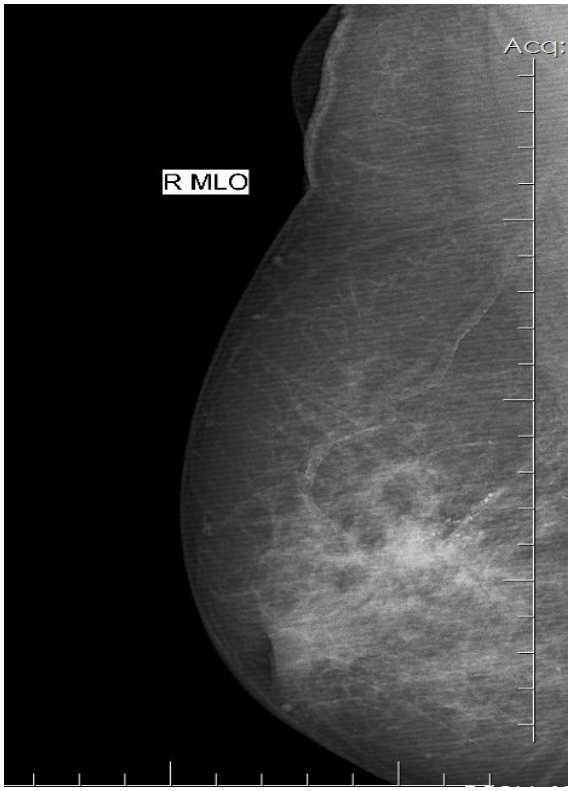

Fig: 30a

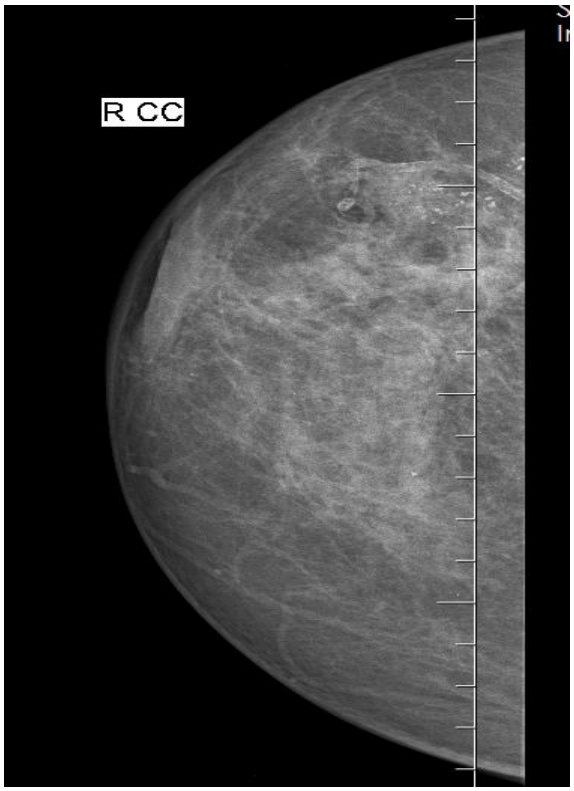

Fig: 30b

Fig: 30a, 30b *An ill-defined radio dense lesion noted in the lower outer quadrant with amorphous calcifications.*

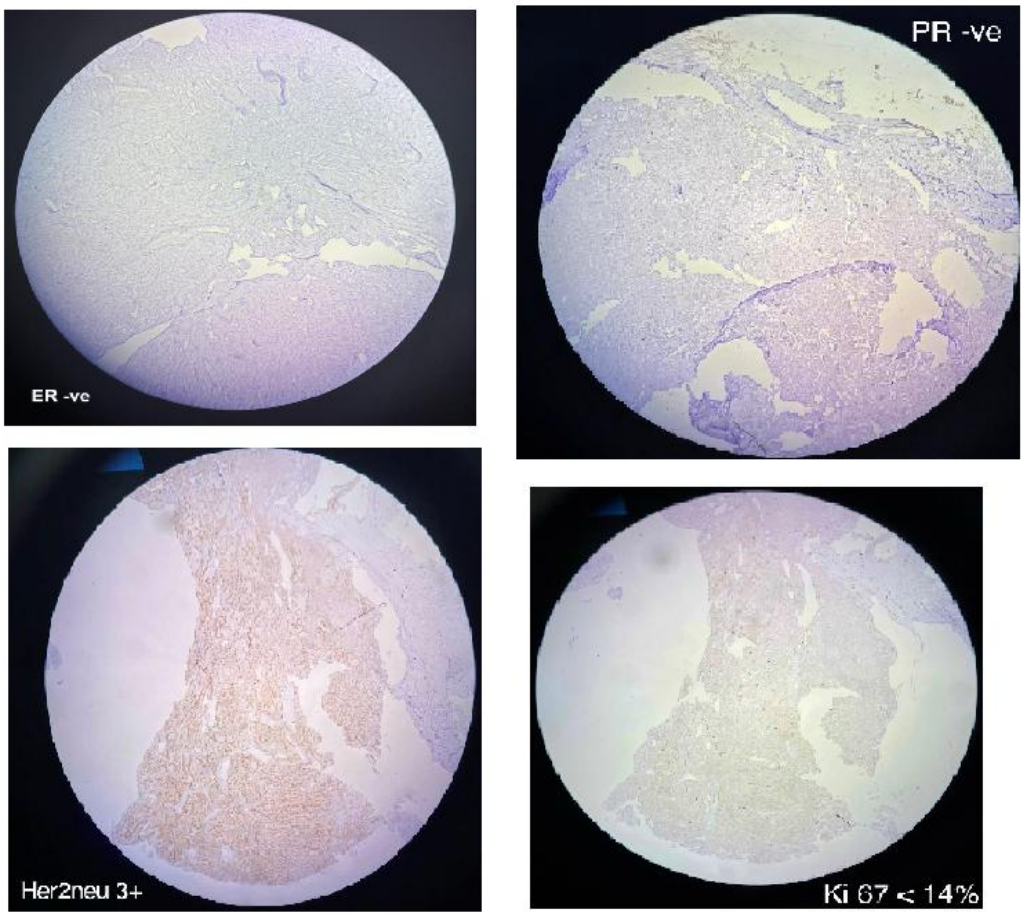

Fig 31: *Pathologically case was confirmed as Her2Neu enriched***.**

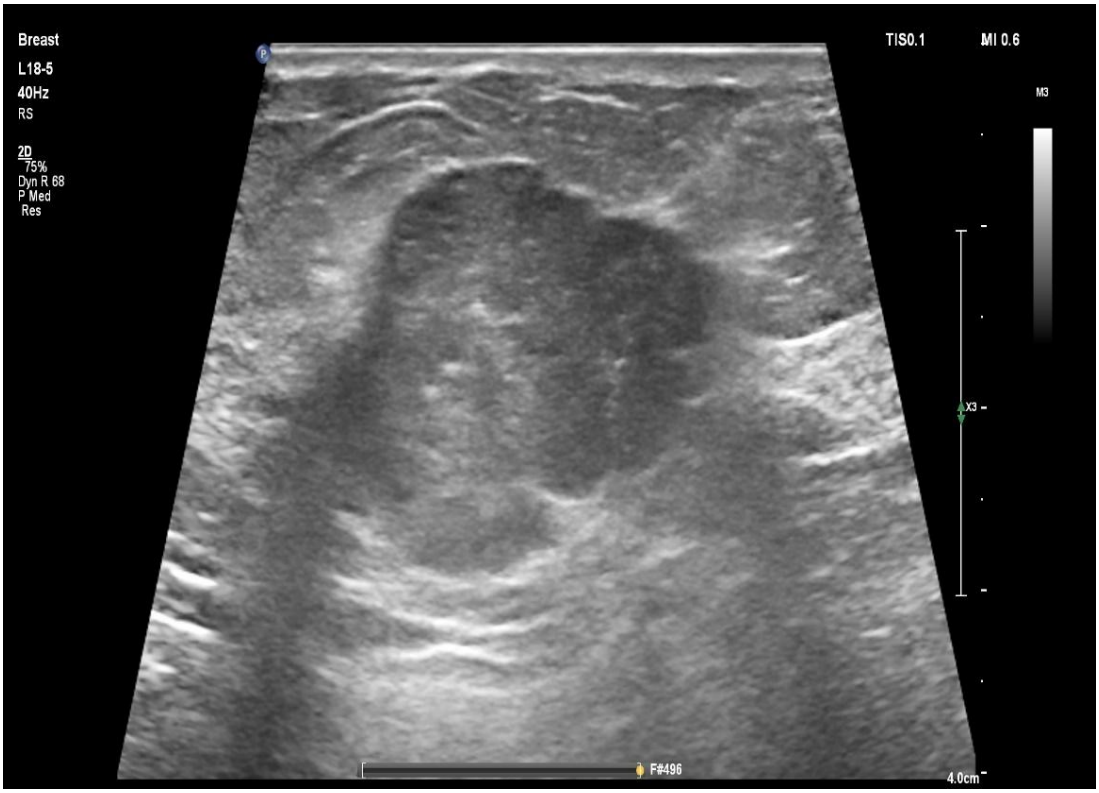

Fig: 32 *A circumscribed, lobulated, wider than taller, heterogeneously hypoechoic lesion noted in the upper outer quadrant of right breast***.**

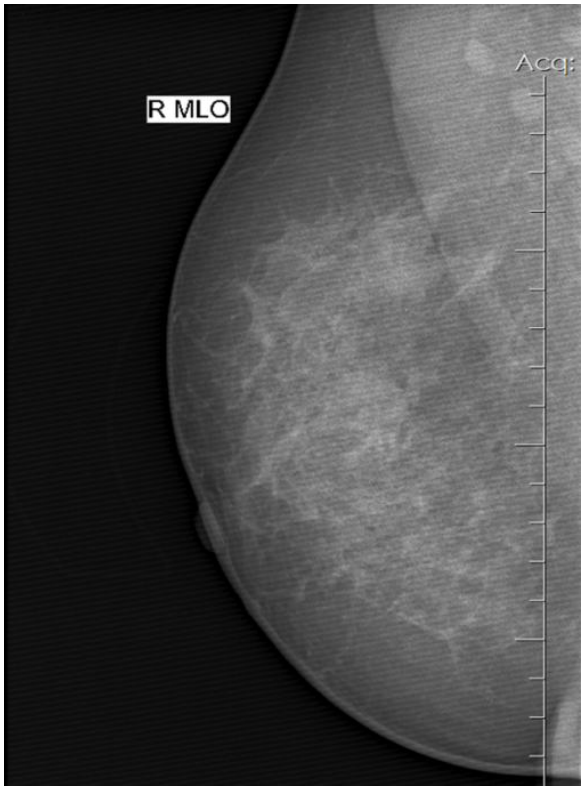

Fig: 33a

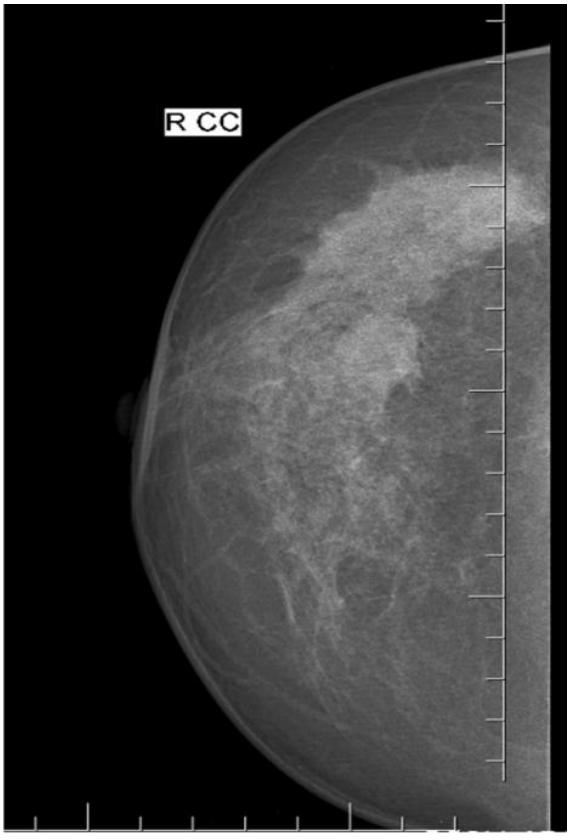

Fig: 33b

Fig: 33a, 33b *An irregular lesion with density higher than the adjacent fibroglandular tissue with irregular margins noted predominantly in upper outer quadrant.*

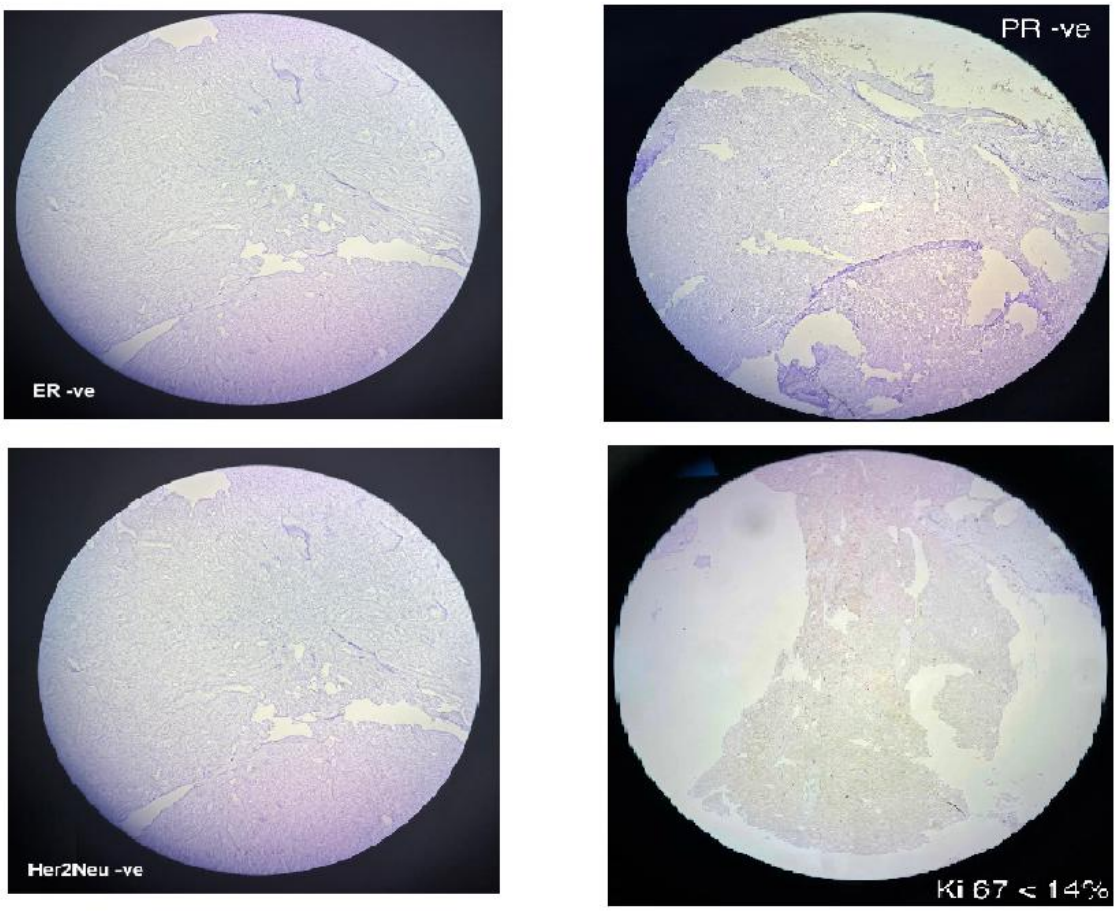

Fig 34: *Pathologically case was confirmed as Triple Negative.*

DISCUSSION

DISCUSSION

The current study investigated the role of ultrasound and mammography in predicting the molecular subtypes of breast carcinoma, demonstrating high diagnostic accuracy of radiological findings in this context. Our findings indicate that certain imaging features correlate strongly with specific molecular subtypes of breast cancer, suggesting imaging could potentially serve as a non-invasive method to predict tumor biology before definitive pathological diagnosis.

The demographic profile of our study population revealed a mean age of 53.90 years, with the highest proportion of cases (36.54%) in the 41-50 years age group. This age distribution aligns with the general epidemiological pattern of breast cancer in many populations, where incidence rises significantly in the fourth and fifth decades of life. The relative paucity of cases in older age groups (only 3.85% in the 81-90 years range) may reflect regional variations in age-specific incidence or potential selection bias in our study sample.

In the present study, the majority of patients (36.54%) were in the 41–50 years age group with a mean age of 53.9 ± 12.95 years. The majority of breast cancer cases occur in women aged 40–60 years, with incidence increasing with age and peaking around menopause. [44] This aligns with our study's finding that most participants were in the 41–60 years range, with a mean age of 53.9 years.

Similar age distribution has been observed in studies by Clarke et al., 2012 and Rummel et al., 2015 which report a peak incidence in the fifth decade, particularly in Luminal A and B tumors, which are more common in older women. [45, 46] According to *Bland and Copeland's The Breast*, hormone receptor-positive tumors, especially Luminal A, tend to present in older women. [47]

Interestingly, our study found a predominance of left breast involvement (61.54%) compared to the right breast (38.46%). While some previous studies have reported a slight left-sided predominance in breast cancer, the biological significance of this observation remains unclear and requires further investigation. The upper outer quadrant was the most commonly affected site (55.77%), which is consistent with existing literature consistently reporting this location as the most common site for breast cancer.

Breast cancer is slightly more common in the left breast, and the upper outer quadrant is the most frequent site due to the greater volume of glandular tissue in this area.[44] Prior epidemiological studies showed upper outer quadrant as the most common tumor site due to dense glandular tissue. [48]

The family history findings in our study (positive in 61.54% of cases) highlight the important role of genetic factors in breast cancer development. This proportion is notably higher than in some previous studies, which have reported positive family history in approximately 20-30% of breast cancer cases.

A positive family history is a significant risk factor for breast cancer, with 15–20% of cases having a familial component.[44] Our study's higher familial history percentage (61.54%) may reflect referral bias or heightened awareness in the studied population.

Regarding ultrasound characteristics, our study found ill-defined lesions (53.85%) to be slightly more common than well-defined ones (46.15%). Lobulated margins were most frequent (42.31%), followed by spiculated and irregular margins (28.85% each). The relatively high proportion of lobulated margins in our study is noteworthy, as spiculated margins are classically associated with malignancy. The margin characteristics observed in our study may reflect the specific distribution of molecular subtypes, as previous research has suggested that different subtypes may present with distinct sonographic features.

Ill-defined and irregular or spiculated margins are typically associated with aggressive subtypes, such as triple-negative or HER2-enriched cancers, as reported by Çelebi et al., 2015. [49] Luminal A tumors tend to have well-circumscribed margins, while triple-negative tumors show irregular, spiculated features.

The predominance of heterogeneous echogenicity (67.31%) over hypoechoic patterns (32.69%) in our study reflects the complex tissue architecture of many breast cancers. This finding aligns with previous studies that have reported heterogeneous internal echoes in a significant proportion of malignant breast lesions.

According to a study by Chamming's et al., heterogeneous echotexture correlates with high tumor cellularity seen in HER2+ and TNBC subtypes. [50]

The distribution of posterior acoustic features—with shadowing and mixed features equally common (40.38% each) and enhancement less frequent (19.23%)—further illustrates the diverse sonographic presentation of breast carcinomas.

Previous studies had associated posterior shadowing more commonly with luminal subtypes and posterior enhancement more frequently with triple-negative breast cancers, which appears consistent with our molecular subtype distribution. Shadowing is more common in desmoplastic reactions seen in ER-positive tumors; enhancement may suggest necrosis and is more common in triple-negative cancers.

Internal vascularity was the most common vascular pattern (48.08%), which aligns with the understanding that many breast carcinomas demonstrate increased angiogenesis to support tumor growth. The presence of significant internal vascularity has been associated with more aggressive tumor biology in some studies, which may correlate with specific molecular subtypes characterized by higher proliferation rates.

Malignant breast lesions typically appear as ill-defined, irregular, or spiculated masses with heterogeneous echotexture and posterior acoustic shadowing. Vascularity is often increased due to neoangiogenesis. [44] Internal vascularity correlates with aggressive molecular phenotypes, such as HER2-enriched and triple-negative, as validated by contrast-enhanced ultrasound studies. [51] *Breast Imaging by D'Orsi et al.* emphasizes internal vascularity as a hallmark of malignant lesions with angiogenesis. [52]

These classic features are reflected in our study's findings: 53.85% ill-defined lesions, 42.31% lobulated margins, 67.31% heterogeneous echogenicity, and 57.69% internal vascularity.

The presence of microcalcifications on mammography in the majority of cases (55.76%) is significant, as microcalcifications are important mammographic indicators of malignancy. Previous studies have suggested associations between patterns of microcalcifications and molecular subtypes, with some reporting higher frequency of microcalcifications in HER2-enriched cancers. Our findings provide additional evidence for the potential utility of microcalcifications in predicting molecular subtypes, though more detailed analysis of microcalcification patterns would be valuable in future studies.

Microcalcifications are a hallmark of ductal carcinoma in situ (DCIS) and can also be seen in invasive cancers, especially HER2-enriched subtypes. [44] HER2-enriched and Luminal B tumors are frequently associated with microcalcifications, especially of the pleomorphic or linear branching type, as discussed in the ACR BI-RADS atlas and studies by Orrantia-Borunda et al., 2022. [53]

The immunohistochemistry findings revealed ER and PR positivity in 53.85% of cases, HER2/neu positivity in 34.62%, and Ki-67 positivity in 50%. These distributions generally reflect the typical prevalence of molecular subtypes in breast cancer populations, though with some variations that may be attributed to population differences or selection criteria. The relatively high proportion of HER2-positive cases (34.62% compared to the commonly reported 15-20%) may have implications for treatment planning and prognostic considerations in our population.

The molecular classification of breast cancer into Luminal A, Luminal B, HER2-enriched, and Triple Negative subtypes is based on ER, PR, HER2, and Ki-67 status, as outlined in both pathology and imaging textbooks. The reported frequencies in this study (ER/PR positivity ~54%, HER2 positivity ~35%, Ki-67 positivity 50%) are within the ranges described in the literature. [44]

The most significant finding of our study is the strong concordance between radiological and pathological diagnoses ($p < 0.001$), with particularly high agreement for Luminal A (13/13, 100%) and Triple Negative (14/15, 93.33%) subtypes. This finding suggests that certain imaging features may be strongly indicative of specific molecular subtypes. The high concordance rates observed for these subtypes may reflect their more distinct biological characteristics, which manifest as more recognizable imaging patterns.

The strong concordance between imaging features and molecular subtypes, with high sensitivity and specificity, is supported by textbook discussions on the evolving role of imaging in breast cancer characterization and the potential for imaging to guide management before pathological confirmation. [44] This subtype distribution mirrors findings from studies like that of Ma et al., 2022., where imaging features reliably predicted Luminal A and TNBC with high accuracy. [42] Study by Zhou et al., 2021. confirm that multiparametric ultrasound and mammographic features can accurately stratify subtypes, especially Luminal A and TNBC. [54]

In the present study, strong concordance between radiological prediction and pathological subtyping was found with a p-value < 0.001. ROC analysis and high correlation coefficients have validated ultrasound-based prediction of molecular phenotype.

The amalgamation of mammography and ultrasonography yielded a sensitivity of 94.72%, specificity of 92.18%, positive predictive value of 90.88%, and a negative predictive value of 86.54% with an overall accuracy of 90.12%. These values are impressive and suggest that radiological assessment could potentially serve as a valuable adjunct in predicting molecular subtypes before definitive pathological diagnosis.

The combination of ultrasonography and mammography produced superior results compared to either modality alone, facilitating more precise characterisation of breast abnormalities.[55] Zonderland et al. reported an overall sensitivity of 85% and a specificity of 98.7%. The diagnostic tests in their research exhibited a sensitivity of 92.9% and a specificity of 97.7%, while the screening examinations demonstrated a sensitivity of 69.2% and a specificity of 99.2%, utilizing a combination of both ultrasound and mammography. [56]

The diagnostic accuracy metrics of our study support the potential clinical utility of radiological prediction of molecular subtypes, sensitivity of 94.72%, and specificity of 92.18%. The high positive predictive value (90.88%) and negative predictive value (86.54%) further strengthen this conclusion.

Similar studies have shown variable accuracy in predicting molecular subtypes based on imaging features, with some reporting concordance rates of 71-85%. Our higher accuracy may be attributed to the comprehensive assessment of multiple imaging features and the systematic approach to interpretation. The integration of both ultrasound and mammographic findings likely enhanced the discriminatory power of our approach.

The ability to predict molecular subtypes through imaging has significant clinical implications. Molecular subtypes of breast cancer are known to have distinct prognoses and treatment responses, and early prediction of these subtypes could potentially expedite treatment planning. For instance, knowing that a tumor is likely to be Triple Negative or HER2-enriched before definitive pathological diagnosis might allow clinicians to prepare for potentially more aggressive treatment approaches.

The correlation between specific imaging features and molecular subtypes observed in our study also raises interesting questions about the underlying biological mechanisms. For instance, the association between certain sonographic features like posterior acoustic properties and molecular subtypes may reflect differences in tumor cellularity, stromal components, or growth patterns that are characteristic of different molecular subtypes.

CONCLUSION

CONCLUSION

This cross-sectional study demonstrates that ultrasound and mammography can predict the molecular subtypes of breast carcinoma with high accuracy. The findings reveal a strong concordance between radiological features and immunohistochemical profiles, suggesting that specific imaging patterns may serve as surrogate markers for molecular subtypes.

The demographic profile of our study population, with a mean age of 53.90 years and predominance in the 41-50 years age group, aligns with the established epidemiological understanding of breast cancer.

The left-sided predominance (61.54%) and high proportion of positive family history (61.54%) observed in our cohort are notable findings that merit further investigation in larger studies. The predominance of tumors in the upper outer quadrant (55.77%) is consistent with known anatomical distribution patterns of breast cancer.

Our analysis of ultrasound features revealed that certain sonographic characteristics, such as lesion shape, margins, echogenicity, posterior acoustic features, and vascularity patterns, exhibited distinct patterns that correlated with molecular subtypes.

The slightly higher prevalence of ill-defined lesions (53.85%) compared to well-defined ones (46.15%) and the predominance of lobulated margins (42.31%) provide valuable information for radiological diagnosis.

The high frequency of heterogeneous echogenicity (67.31%) and the equal distribution of shadowing and mixed posterior acoustic features (40.38% each) and increased vascularity (57.69 %) further characterize the sonographic presentation of breast carcinomas in our cohort.

Mammographic findings, particularly the presence of microcalcifications in 55.76% of cases, complement the ultrasound characteristics and contribute to the overall radiological profile that aids in predicting molecular subtypes. This multimodal imaging approach enhances the comprehensive assessment of breast lesions and improves predictive accuracy.

The immunohistochemistry findings in our study, with 53.85% ER positivity, 53.85% PR positivity, 34.62% HER2/neu positivity, and 50% Ki-67 positivity, enabled classification into molecular subtypes. The strong statistical association ($p < 0.001$) between radiological and pathological diagnoses across these subtypes validates the predictive capability of imaging. Particularly noteworthy is the perfect concordance for Luminal A subtype (13/13) and high agreement for Triple Negative subtype (14/15), suggesting that these subtypes may have more distinctive imaging features.

The diagnostic metrics underscore the clinical utility of this approach, with an overall accuracy of 90.12%, sensitivity of 94.72%, specificity of 92.18%, positive predictive value of 90.88%, and negative predictive value of 86.54%. These values indicate that radiological assessment can reliably predict molecular subtypes in a majority of cases, potentially providing valuable information before pathological confirmation.

Our study establishes that ultrasound and mammography can predict the molecular subtypes of breast carcinoma with high accuracy. The integration of specific imaging features into the diagnostic algorithm for breast cancer could enhance the precision and timeliness of subtype classification, potentially improving treatment planning and patient outcomes. These findings support the role of imaging as a valuable tool in the comprehensive assessment of breast cancer, contributing to the growing paradigm of precision medicine in oncology.

SUMMARY

SUMMARY

This cross-sectional study investigated the role of ultrasound and mammography in predicting the molecular subtypes of breast carcinoma in 52 participants. The study evaluated various morphological features on imaging and correlated them with immunohistochemistry findings to determine the accuracy of radiological assessment in predicting molecular subtypes.

The demographic profile of the study population revealed a mean age of 53.90 years (SD 12.95), with the majority of participants (36.54%) belonging to the 41-50 years age group, followed by 51-60 years (25%) and 31-40 years (13.46%). Fewer participants were observed in the older age groups: 61-70 years (11.54%), 71-80 years (9.62%), and 81-90 years (3.85%). This age distribution reflects the typical pattern of breast cancer incidence, with peak occurrence in middle-aged women.

In terms of laterality, the left breast was more commonly affected (61.54%) compared to the right breast (38.46%). While this left-sided predominance has been noted in some epidemiological studies, its clinical significance remains uncertain. A positive family history was present in 61.54% of cases, highlighting the importance of genetic factors in breast cancer development. This high proportion underscores the value of comprehensive family history assessment in breast cancer screening and risk assessment.

The analysis of tumor location revealed that the upper outer quadrant (UOQ) was the most commonly affected site (55.77%), followed by equal involvement of the central, lower outer quadrant (LOQ), and upper inner quadrant (UIQ), each at 9.62%. Other less common sites included lower inner quadrant (LIQ) (7.69%), UOQ with central (5.77%), and retroareolar region (1.92%). This distribution pattern is consistent with the general understanding that the upper outer quadrant, containing a greater volume of breast tissue, is the most common site for breast cancer development.

Ultrasound findings provided valuable insights into the morphological characteristics of the breast lesions. In terms of lesion shape, ill-defined lesions were slightly more prevalent (53.85%) than well-defined lesions (46.15%).

Regarding margins, lobulated margins were most frequent (42.31%), while spiculated and irregular margins were equally observed (28.85% each). These margin characteristics are important as they often correlate with the invasive potential and growth pattern of the tumor.

The echogenicity assessment revealed that most lesions (67.31%) exhibited heterogeneous echogenicity, while 32.69% were hypoechoic. This predominance of heterogeneous echogenicity reflects the complex tissue architecture often seen in breast carcinomas.

The evaluation of posterior acoustic features (PAF) showed equal distribution of shadowing and mixed features (40.38% each), with posterior acoustic enhancement seen in 19.23% of lesions. These acoustic properties are influenced by the tumor's cellular density and organization and have been associated with specific molecular subtypes in previous research.

Vascularity assessment demonstrated that internal vascularity was the most common pattern (48.08%), followed by absence of vascularity (38.46%). Minimal peripheral vascularity (9.61%) and combined internal and peripheral vascularity (3.85%) were less frequently observed. These vascular patterns reflect the angiogenic processes within the tumor and surrounding tissues, which may vary according to tumor aggressiveness and molecular characteristics.

Mammography findings revealed the presence of microcalcifications in 55.76% of cases, while they were absent in 44.23%. Microcalcifications are important mammographic features that often indicate malignancy and may be associated with certain histological and molecular characteristics of breast cancer. The relatively high proportion of cases with microcalcifications in our study highlights the importance of careful mammographic assessment in the comprehensive evaluation of breast lesions.

Immunohistochemistry findings provided the molecular classification of the breast carcinomas. Estrogen receptor (ER) and progesterone receptor (PR) positivity were each observed in 53.85% of cases. HER2/neu was positive in 34.62% of cases and negative in 65.38%. Ki-67, a proliferation marker, showed an equal distribution with 50% positive and 50% negative. These distributions allowed classification of tumors into molecular subtypes: Luminal A (ER/PR positive, HER2 negative, low Ki-67), Luminal B (ER/PR positive with either HER2 positive or high Ki-67), HER2-enriched (ER/PR negative, HER2 positive), and Triple Negative (ER/PR/HER2 negative).

The core findings of this study relate to the association between radiological and pathological diagnoses. A strong concordance was observed, with all radiological Luminal A cases (13/13) confirmed pathologically as Luminal A, and the majority of radiological Triple Negative cases (14/15) matching the pathological diagnosis. Similarly, 10 out of 12 Luminal B radiological cases and 9 out of 12 radiological Her2-enriched cases were confirmed pathologically.

The statistically significant association ($p < 0.001$) between radiological and pathological subtyping demonstrates the potential of imaging to predict molecular subtypes.

The diagnostic accuracy metrics further validated the radiological prediction of molecular subtypes, with a sensitivity of 94.72%, specificity of 92.18%, positive predictive value of 90.88%, and negative predictive value of 86.54%. The overall diagnostic accuracy was 90.12%, indicating that radiological assessment is a reliable tool for predicting molecular subtypes of breast cancer.

This high level of accuracy suggests that carefully evaluated imaging features can serve as surrogate markers for underlying molecular characteristics. The particularly high concordance observed for Luminal A and Triple Negative subtypes indicates that these molecular categories may have more distinctive imaging signatures, potentially related to their underlying biological characteristics.

LIMITATIONS & RECOMMENDATIONS

LIMITATIONS AND RECOMMENDATIONS

This study, while yielding valuable insights into the role of ultrasound and mammography in predicting molecular subtypes of breast carcinoma, has several limitations that should be acknowledged.

The sample size of 52 participants, though adequate for preliminary analysis, is relatively small for definitive conclusions about the relationship between imaging features and molecular subtypes. This limited sample size may affect the statistical power and generalizability of our findings. Future studies with larger cohorts would provide more robust evidence and potentially identify additional correlations between specific imaging features and molecular subtypes.

This was a cross-sectional study conducted at a single center, thus our findings may be influenced by local demographic patterns, referral practices, and imaging protocols. Multi-center studies would help validate these findings across diverse populations and clinical settings, enhancing external validity. Additionally, the cross-sectional design prevents assessment of temporal changes in imaging features and their relationship with disease progression or treatment response.

It is important to note that while the diagnostic accuracy was high, it was not perfect, emphasizing that radiological prediction should complement, not replace, pathological diagnosis. The imperfect concordance also highlights the complex and sometimes heterogeneous nature of breast cancers, which may not always present with typical imaging features of their molecular subtype.

The high concordance between radiological and pathological diagnoses observed in our study suggests that imaging features reflect underlying biological characteristics of breast tumors. This relationship highlights the potential for developing standardized imaging criteria that correlate with specific molecular subtypes and facilitating integration of this approach into routine clinical practice, thereby potentially enhancing the precision of radiological assessment.

Our study focused on conventional ultrasound and mammography without including advanced imaging modalities such as magnetic resonance imaging (MRI), contrast-enhanced spectral mammography (CESM), or molecular imaging techniques. These advanced modalities might provide additional discriminatory features for predicting molecular subtypes and warrant investigation in future research.

There is a need to explore the correlation between imaging features and genomic signatures beyond the basic immunohistochemistry panel, potentially identifying imaging biomarkers for specific genetic alterations or expression patterns.

Longitudinal studies should be conducted to assess how imaging features evolve over time and in response to treatment, and whether these changes correlate with molecular evolution of the tumor.

Additionally, the integration of artificial intelligence and machine learning approaches could potentially identify subtle imaging patterns that correlate with molecular subtypes, further improving the accuracy of radiological prediction. These advanced computational methods could complement human expertise, potentially leading to more precise and reproducible assessment of imaging features.

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BIBILIOGRAPHY

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ANNEXURE

ANNEXURE I - PATIENT PROFORMA

" ROLE OF ULTRASOUND AND MAMMOGRAPHY IN PREDICTING THE MOLECULAR SUBTYPE OF CARCINOMA BREAST – A CROSS SECTIONAL STUDY"

DEMOGRAPHIC DETAILS:

Name :

Age :

UHID :

Mobile Number:

CLINICAL HISTORY :

History of presenting illness:

Past History:

Family History:

Personal History:

GENERAL PHYSICAL EXAMINATION:

Pulse:

BP:

RR:

Temp:

SYSTEMIC EXAMINATION:

LOCAL EXAMINATION:

ULTRASOUND PARAMETERS ASSESSED	
1. Size	
2. Shape	
3. Margins	
4. Echogenicity	
5. Posterior acoustic features	
6. Vascularity	

Ultrasound Impression:

MAMMOGRAPHY PARAMETERS ASSESSED:

Microcalcifications:

Ultrasound and Mammography imaging Impression:

IMMUNOHISTOCHEMISTRY REPORT:

1. ER:
2. PR:
3. Her2Neu:
4. Ki67:

Immunohistochemistry Impression:

IMAGING AND IHC CORRELATION: YES/NO

ANNEXURE II - INFORMED CONSENT

STUDY TITLE:**" ROLE OF ULTRASOUND AND MAMMOGRAPHY IN PREDICTING THE MOLECULAR SUBTYPE OF CARCINOMA BREAST – A CROSS SECTIONAL STUDY "**

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

Principal investigator: **Dr. SRAVYA M**

Name of the subject:

Age :

Gender :

a. I have been informed in my own language that this study involves ultrasound and mammography as a 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. SRAVYA M / 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: Dr. SRAVYA M

Contact: 9701093013

Chief Researcher Signature: Date:

ANNEXURE – III PATIENT INFORMATION SHEET

" ROLE OF ULTRASOUND AND MAMMOGRAPHY IN PREDICTING THE MOLECULAR SUBTYPE OF CARCINOMA BREAST – A CROSS SECTIONAL STUDY "

Principal Investigator: Dr. SRAVYA M / Dr. ANIL KUMAR SAKALECHA

I, **Dr. SRAVYA M,** post-graduate student in Department of Radio-Diagnosis at Sri Devaraj Urs Medical College. I will be conducting a study titled **"ROLE OF ULTRASOUND AND MAMMOGRAPHY IN PREDICTING THE MOLECULAR SUBTYPE OF CARCINOMA BREAST – A CROSS SECTIONAL STUDY"** for my dissertation under the guidance of **Dr. Anil Kumar Sakalecha,** Professor, Department of Radio-Diagnosis.

In this study, we will assess the role of ultrasound and mammography in predicting the molecular subtyping of carcinoma breast. If you are willing to be enrolled in this study, you will undergo ultrasound and mammography which is non-invasive method to diagnose carcinoma breast. This will help in determining treatment and predicting prognosis.

You are free to opt-out of the study at anytime if you are not satisfied or apprehensive to be a part of the study. Your treatment and care will not be compromised if you refuse to be a part of the study. The study will not add any risk or financial burden to you if you are a part of the study. Your identity and clinical details will be confidential. You will not receive any financial benefit for being a part of the study. You are free to contact Dr. Sravya M or any other member of the above research team for any doubt or clarification you have at any given point.

Name of the Principal Investigator: Dr. SRAVYA M

Contact of Principal Investigator: 9701093013

Date

MASTERCHART

KEY TO MASTER CHART

P – Present

A – Absent

Po – Positive

Ne – Negative

ID – Ill-defined

WD – Well-defined

I- Irregular

L -Lobulated

S – Spiculated

HH- Heterogenously hypoechoic

H- Hypoechoic

Sh- Shadowing

E – Enhancement

M – Mixed

LA – Luminal A

LB – Luminal B

H2 - Her2Neu Enriched

TN – Triple Negative

RA – Retroareolar

UOQ – Upper Outer Quadrant

UIQ – Upper Inner Quadrant

LIQ – Lower Inner Quadrant

LOQ – Lower Outer Quadrant

CE - Central

SL.NO	UHID	AGE	Age group	Side of the breast involved	Family History	SITE OF TUMOR	SIZE in USG	SHAPE	MARGINS	ECHOGENICITY	PAF	Microcalcifications in Mammography findings	IMMUNO-HISTOCHEMISTRY FINDINGS - ER STATUS	IMMUNO-HISTOCHEMISTRY FINDINGS - PR STATUS	IMMUNO-HISTOCHEMISTRY FINDINGS - HER 2 NEU STATUS	IMMUNO-HISTOCHEMISTRY FINDINGS - Ki67 STATUS	Radiological Diagnosis	Pathological Diagnosis	Correlation
1	277432	42	41 - 50	Left	P	UOQ	3 x 2.5	ID	L	HH	M	A	Ne	Ne	Po	> 14 %	H2	H2	Yes
2	274944	64	61 - 70	Right	P	UIQ	2.8 x 2.0	WD	L	HH	E	P	Ne	Ne	Ne	> 14 %	TN	TN	Yes
3	275739	50	41 - 50	Left	P	UOQ	2.5 x 1.9	ID	S	H	M	A	Po	Po	Po	> 14 %	LB	LB	Yes
4	269582	50	41 - 50	Right	P	UOQ	1.7 x 1.2	ID	L	HH	P	A	Ne	Ne	Po	< 14 %	H2	H2	Yes
5	283205	44	41 - 50	Right	A	UOQ	3.8 x 3.0	WD	L	HH	M	A	Ne	Ne	Ne	> 14 %	TN	TN	Yes
6	448800	56	51 - 60	Left	P	UOQ	3.0 x 1.5	I	I	HH	E	P	Ne	Ne	Ne	< 14 %	TN	TN	Yes
7	317553	77	71 - 80	Left	P	UOQ	4.1 x 3.7	WD	S	H	M	A	Ne	Ne	Po	> 14 %	H2	H2	Yes
8	310369	34	31 - 40	Right	P	CE	2.9 x 2.5	WD	I	H	M	A	Ne	Ne	Po	> 14 %	LB	H2	No
9	310910	48	41 - 50	Left	P	UOQ	3.0 x 4.5	WD	S	HH	Sh	P	Po	Po	Ne	> 14 %	LB	LB	Yes
10	316120	46	41 - 50	Left	P	UOQ	2.5 x 2.0	WD	I	HH	Sh	A	Po	Po	Po	> 14 %	LA	LA	Yes
11	252649	46	41 - 50	Right	P	UOQ	2.9 x 2.4	ID	S	HH	Sh	P	Po	Po	Ne	> 14 %	LB	LB	Yes
12	302322	51	51 - 60	Left	A	LOQ	6.1 x 4.3	ID	L	HH	Sh	A	Po	Po	Ne	> 14 %	LB	LB	Yes
13	369787	48	41 - 50	Left	A	UOQ	5.1 x 3.3	ID	S	HH	E	A	Ne	Ne	Ne	< 14 %	TN	TN	Yes
14	345781	37	31 - 40	Left	P	UOQ	1.3 x 1.2	ID	L	HH	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
15	358389	45	41 - 50	Right	P	UOQ	2.6 x 1.7	WD	I	H	E	P	Ne	Ne	Ne	< 14%	TN	TN	Yes
16	365190	69	61 - 70	Left	A	LIQ	1.7 x 1.5	WD	S	HH	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
17	351831	43	41 - 50	Left	P	UOQ	7.8 x 6.3	ID	S	HH	Sh	P	Po	Po	Ne	< 14 %	LA	LA	Yes
18	368214	39	31 - 40	Left	A	RE	4.3 x 2.2	ID	L	HH	M	A	Ne	Ne	Po	> 14 %	H2	H2	Yes
19	351755	55	51 - 60	Right	P	UOQ	4.0 x 3.5	ID	S	HH	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
20	362715	44	41 - 50	Right	P	UOQ	5.0 x 4.0	WD	L	HH	M	A	Ne	Ne	Po	> 14 %	H2	H2	Yes
21	225585	76	71 - 80	Left	A	LOQ	2.7 x 2.4	WD	L	HH	M	P	Ne	Ne	Po	> 14%	H2	H2	Yes
22	382113	65	61 - 70	Right	P	UOQ	2.0 x 1.5	ID	I	H	E	P	Ne	Ne	Ne	< 14%	TN	TN	Yes
23	377654	58	51 - 60	Left	P	UOQ	2.6 x 2.6	ID	I	HH	Sh	P	Po	Po	Ne	> 14 %	LB	LB	Yes
24	397149	59	51 - 60	Left	P	UOQ	2.0 x 1.8	ID	I	HH	M	A	Po	Po	Po	> 14 %	LB	LB	Yes
25	410060	61	61 - 70	Right	A	UOQ	2.0 x 1.5	ID	S	H	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
26	341895	59	51 - 60	Left	P	UOQ	3.5 x 3.1	WD	S	HH	E	P	Ne	Ne	Ne	< 14 %	TN	TN	Yes
27	427334	56	51 - 60	Right	A	CE	2.3 x 1.9	ID	S	HH	Sh	P	Po	Po	Ne	> 14 %	LB	LB	Yes
28	423984	56	51 - 60	Left	P	UOQ	2.1 X 2.0	WD	L	H	E	P	Po	Po	Ne	> 14 %	LB	LB	Yes
29	466614	41	41 - 50	Left	P	UOQ	1.6 x 1.4	WD	L	H	Sh	A	Po	Po	Po	> 14 %	LB	LB	Yes
30	466751	50	41 - 50	Right	P	UIQ	2.8 x 1.4	WD	L	H	Sh	P	Po	Po	Po	> 14 %	LB	LB	Yes

SL. NO	UHID	AGE	Age group	Side of the breast involved	Family History	SITE OF TUMOR	SIZE in USG	SHAPE	MARGINS	ECHOGENICITY	PAF	Microcalcifications in Mammography findings	IMMUNO-HISTOCHEMISTRY FINDINGS - ER STATUS	IMMUNO-HISTOCHEMISTRY FINDINGS - PR STATUS	IMMUNO-HISTOCHEMISTRY FINDINGS - HER 2 NEU STATUS	IMMUNO-HISTOCHEMISTRY FINDINGS - Ki67 STATUS	Radiological Diagnosis	Pathological Diagnosis	Correlation
31	465158	53	51 - 60	Left	P	UOQ	5.6 x 3.3	WD	L	H	M	P	Ne	Ne	Ne	< 14 %	TN	TN	Yes
32	474572	85	81 - 90	Left	A	LIQ	6.6 x 6.3	ID	L	HH	E	P	Ne	Ne	Ne	< 14 %	TN	TN	Yes
33	484744	46	41 - 50	Right	P	UOQ	1.7 x 1.3	WD	L	HH	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
34	476334	69	61 - 70	Left	P	CE	4.5 x 3.2	ID	L	HH	Sh	P	Ne	Ne	Ne	< 14 %	TN	TN	Yes
35	511077	40	31 - 40	Left	P	UIQ	3.0 x 4.0	WD	L	H	M	A	Po	Po	Ne	> 30 %	H2	LB	No
36	521235	73	71 - 80	Left	A	UIQ	4.3 x 3.8	ID	S	HH	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
37	522891	41	41 - 50	Left	P	LIQ	1.6 x 1.4	WD	L	H	Sh	A	Po	Po	Po	> 14 %	LB	LB	Yes
38	542891	50	41 - 50	Right	P	UOQ, CE	2.8 x 1.4	WD	L	H	Sh	P	Po	Po	Po	> 14 %	LB	LB	Yes
39	532567	53	51 - 60	Left	P	CE, UOQ	5.6 x 3.3	WD	L	H	M	P	Ne	Ne	Ne	< 14 %	TN	TN	Yes
40	554127	85	81 - 90	Left	P	CE	6.6 x 6.3	ID	L	HH	E	P	Ne	Ne	Ne	< 14 %	TN	TN	Yes
41	579682	46	41 - 50	Left	P	LIQ	1.7 x 1.3	WD	L	HH	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
42	578413	69	61 - 70	Right	P	CE	4.5 x 3.2	ID	L	HH	Sh	P	Ne	Ne	Ne	< 14 %	TN	TN	Yes
43	587641	40	31 - 40	Left	A	LOQ	3.0 x 4.0	WD	L	H	M	A	Po	Po	Ne	> 30 %	H2	LB	No
44	586975	73	71 - 80	Right	P	UOQ	4.3 x 3.8	ID	S	HH	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
45	597163	55	50-60	Left	P	UIQ	3.2 x 2.8	ID	I	H	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
46	598749	42	40-50	Right	P	UOQ	2.8 x 3.1	ID	L	HH	M	P	Ne	Ne	Po	> 14 %	H2	H2	Yes
47	604287	37	30-40	Right	P	UOQ, CE	3.5 x 2.7	ID	L	HH	M	P	Po	Po	Ne	< 14 %	H2	LB	No
48	603985	59	50-60	Left	P	LOQ	3.0 x 2.5	ID	S	H	Sh	A	Po	Po	Ne	< 14 %	LA	LA	Yes
49	614957	56	51 - 60	Right	P	UOQ	3.0 x 1.5	ID	I	HH	E	P	Ne	Ne	Ne	< 14 %	TN	TN	Yes
50	617493	77	71 - 80	Left	A	UOQ	4.1 x 3.7	WD	S	H	M	A	Ne	Ne	Po	> 14 %	H2	H2	Yes
51	621358	39	31 - 40	Right	P	LOQ	4.3 x 2.2	ID	L	H	M	A	Ne	Ne	Po	> 14 %	H2	H2	Yes
52	621595	46	41 - 50	Left	P	UOQ	2.5 x 2.0	WD	I	HH	Sh	A	Po	Po	Po	> 14 %	LA	LA	Yes