MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN EVALUATION OF BENIGN AND MALIGNANT BREAST MASSES WITH PATHOLOGICAL CORRELATION

By

Dr. VARSHITHA G. R.

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

In partial fulfilment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

RADIODIAGNOSIS

Under the Guidance of

Dr. ANIL KUMAR SAKALECHA, MBBS, MD

PROFESSOR & HOD

DEPARTMENT OF RADIODIAGNOSIS

DEPARTMENT OF RADIODIAGNOSIS,

SRI DEVARAJ URS MEDICAL COLLEGE,

TAMAKA, KOLAR-563103

2022

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN EVALUATION OF BENIGN AND MALIGNANT BREAST MASSES WITH PATHOLOGICAL CORRELATION"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. ANIL KUMAR SAKALECHA**, Professor & Head, Department of Radiodiagnosis, Sri Devaraj Urs Medical College, Kolar, in partial fulfilment of University regulation for the award "**M.D. DEGREE IN RADIODIAGNOSIS**", the examination to be held in 2022 by SDUAHER. This has not been submitted by me previously for the award of any degree or diploma from the university or any other university.

Dr. VARSHITHA G. R.
Postgraduate in Radiodiagnosis
Sri Devaraj Urs Medical College
Tamaka, Kolar

Date:
Place: Kolar

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN EVALUATION OF BENIGN AND MALIGNANT BREAST MASSES WITH PATHOLOGICAL CORRELATION"** is a bonafide research work done by **Dr. VARSHITHA G. R.,** under my direct guidance and supervision at Sri Devaraj Urs Medical College, Kolar**,** in partial fulfilment of the requirement for the degree of "**M.D. IN RADIODIAGNOSIS"**.

Dr. ANIL KUMAR SAKALECHA, MBBS, MD
Professor & HOD
Department Of Radiodiagnosis
Sri Devaraj Urs Medical College
Tamaka, Kolar

Date:
Place: Kolar

CERTIFICATE BY THE HEAD OF DEPARTMENT

This is to certify that the dissertation entitled **"MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN EVALUATION OF BENIGN AND MALIGNANT BREAST MASSES WITH PATHOLOGICAL CORRELATION"** is a bonafide research work done by **Dr. VARSHITHA G. R.,** under direct guidance and supervision of **Dr. ANIL KUMAR SAKALECHA**, Professor & HOD, Department of Radiodiagnosis at Sri Devaraj Urs Medical College, Kolar**,** in partial fulfilment of the requirement for the degree of "**M.D. IN RADIODIAGNOSIS"**.

Dr. ANIL KUMAR SAKALECHA, MBBS, MD

Professor & HOD,

Department of Radiodiagnosis,

Sri Devaraj Urs Medical College,

Tamaka, Kolar.

Date:

Place: Kolar.

AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

ENDORSEMENT BY THE HEAD OF THE DEPARTMENT

AND PRINCIPAL

This is to certify that the dissertation entitled **"MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN EVALUATION OF BENIGN AND MALIGNANT BREAST MASSES WITH PATHOLOGICAL CORRELATION"** is a bonafide research work done by **Dr. VARSHITHA G. R.** under the direct guidance and supervision of **Dr. ANIL KUMAR SAKALECHA,** Professor & Head, Department of Radiodiagnosis, Sri Devaraj Urs Medical College, Kolar, in partial fulfilment of University regulation for the award "**M.D. DEGREE IN RADIODIAGNOSIS**"**.**

Dr. ANIL KUMAR SAKALECHA
Professor & HOD
Department Of Radiodiagnosis,
Sri Devaraj Urs Medical College,
Tamaka, Kolar

Date:
Place: Kolar

Dr. P. N. SREERAMULU
Principal,
Sri Devaraj Urs Medical College,
Tamaka, Kolar

Date:
Place: Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION

ETHICAL COMMITTEE CERTIFICATE

This is to certify that the Ethical committee of Sri Devaraj Urs Medical College, Tamaka, and Kolar has unanimously approved

Dr. VARSHITHA G. R.

Post-Graduate student in the subject of

RADIODIAGNOSIS at Sri Devaraj Urs Medical College, Kolar

to take up the Dissertation work entitled

"MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN EVALUATION OF BENIGN AND MALIGNANT BREAST MASSES WITH PATHOLOGICAL CORRELATION"

to be submitted to the

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA,

Member Secretary

Sri Devaraj Urs Medical College,

Kolar–563103

COPY RIGHT

I hereby declare that Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka shall have the rights to preserve, use and disseminate this dissertation/thesis in print or electronic format for academic/research purpose.

Dr. VARSHITHA G. R.
Post-graduate
Department of Radiodiagnosis

Date:

Place: Kolar

Drillbit Softtech India Pvt. Ltd

Certificate of Plagiarism Check for Dissertation

Author Name	Dr. VARSHITHA G. R.
Course of Study	M D RADIODIAGNOSIS
Name of Guide	Dr. ANIL KUMAR SAKALECHA
Department	RADIODIAGNOSIS
Acceptable Maximum Limit	10%
Submitted By	librarian@sduu.ac.in
Paper Title	MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IN EVALUATION OF BENIGN AND MALIGNANT BREAST MASSES WITH PATHOLOGICAL CORRELATION
Similarity	6%
Paper ID	421853
Submission Date	2021-12-02 10:31:45

Varshitha G.R.
Signature of Student

Signature of Major Advisor
Prof. & HOD,
Dept. of Radio Diagnosis,
K.L.J. Hospital & Research Centre
Tamaka, KOLAR-563 101.

Head of the Department
Prof. & HOD,
Dept. of Radio Diagnosis,
K.L.J. Hospital & Research Centre
Tamaka, KOLAR-563 101.

University Librarian
2/12/21
University Library Learning Resource Centre
Sri Devaraj Urs Academy of Higher Education & Research
Tamaka, KOLAR-563103

Coordinator, UG & PG Program
Sri Devarj Urs Academy
of Higher Education & Research,
Tamaka, Kolar- 563103

* This report has been generated by DrillBit Anti-Plagiarism Software

ACKNOWLEDGEMENT

I owe debt and gratitude to my parents ***Sri. G. R. RATHNAMAIAH SETTY*** *and* ***Smt. SUBHASHINI K.****, along with my brother* ***Dr. BHARATH G. R.*** *for their moral support and constant encouragement during the study.*

With humble gratitude and great respect, I would like to thank my teacher, mentor and guide, ***Dr. ANIL KUMAR SAKALECHA,*** *Professor and Head, Department of Radiodiagnosis, Sri Devaraj Urs Medical College, Kolar, for his able guidance, constant encouragement, immense help and valuable advices which went a long way in moulding and enabling me to complete this work successfully. Without his initiative and constant encouragement this study would not have been possible. His vast experience, knowledge, able supervision and valuable advices have served as a constant source of inspiration during the entire course of my study. I would like to express my sincere thanks to* ***Dr. RACHEGOWDA N.,*** *Professor, Department of Radiodiagnosis, and* ***Dr. AZADULLA BAIG,*** *Assistant professor, Department of Surgery, Sri Devaraj Urs Medical College for his valuable support, guidance and encouragement throughout the study.*

I would like to thank ***Dr. DEEPTI NAIK****, Professor, Sri Devaraj Urs Medical College for, valuable support, guidance, encouragement throughout the study****, Dr. RAJESWARI****, Asst. prof., Department of Radiodiagnosis, and* ***Dr. BUKKE RAVINDRA NAIK****, Asst. Prof., Department of Radiodiagnosis, Sri Devaraj Urs Medical College for their wholehearted support and guidance.*

I would like to thank ***Dr. VARUN S., Dr. GOWTHAMI., Dr. MADHUKAR., Dr. GAURAV YADAV, Dr. DARSHAN A. V., Dr. GNANA SWAROOP RAO POLADI*** *and* ***Dr. RAHUL DEEP G.,*** *and all my teachers for their constant guidance and encouragement during the study period.*

I would also like to express my sincere thanks to my seniors ***Dr. ESSAKI RAJULU, Dr. PARAMESHWAR KEERTHI, Dr. ATHIRA P. M., Dr. HITHISHINI, Dr. ANSHUL SINGH, Dr. T. SAI SOUMYA, Dr. AMRUTHA RANGANATH, Dr. E. VINEELA, Dr. SUSHMITHA S. PRASAD, Dr. DIVYA TEJA PATIL*** *and* ***Dr. SAHANA N. GOWDA*** *for their constant guidance and encouragement during the study period.*

I am extremely grateful to the patients who volunteered to this study, without them this study would just be a dream.

I am thankful to my fellow ***postgraduates, especially Dr. AASHISH, Dr. CHAITHANYA A., Dr. YASHAS ULLAS L., Dr. MONISHA V.*** *and* ***Dr. SURAJ H. S.*** *and all other postgraduates for having rendered all their co-operation and help to me during my study.*

I am also thankful to ***Mr. RAVI, Mr. SUBRAMANI,*** *and* ***Mr. ALEEM*** *with other* ***technicians*** *of Department of Radiodiagnosis, R.L Jalappa Hospital & Research Centre, Tamaka, Kolar for their help. My sincere thanks to* ***Mrs. HAMSA***, ***Mrs. NASEEBA***, ***Mr. Sunil*** *and* ***Mrs. SHOBHA***, *along with rest of the computer operators.*

Dr. VARSHITHA G. R.
Post-graduate
Department of Radiodiagnosis

LIST OF ABBREVIATIONS

GLOSSARY	ABBREVIATIONS
AAR	Age-adjusted incidence rate
ACR	Albumin to creatinine ratio
ADC	Apparent diffusion co-efficient
ALND	Axillary lymph node dissection
AUC	Area under the curve
BC	Breast carcinoma
BI-RADS	Breast imaging-reporting and data system
BPE	Benign prostate enlargement
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
BTTS	Breast tissue selection
CE	Contrast-enhanced
CECT	Contrast-enhanced computed tomography
CEM	Contrast enhanced mammography
Cho	Choline
CI	Confidence interval
CNB	Core needle biopsy
CT	Computed tomography
DCE	Dynamic contrast-enhanced
DCE-MRI	Dynamic contrast-enhanced MRI
DCIS	Ductal carcinoma in situ
DCIS	Ductal carcinoma in situ
DM	Digital mammography
DWI	Diffusion-weighted imaging
EOD	Extent of disease
EPI	Echo-planar imaging

FGT	Fibro glandular tissue
FNAC	Fine-needle aspiration cytology
FS	Fat suppression
GRE	Gradient-echo
HER2	Human epidermal growth factor receptor 2
HICs	High income countries
HU	Hounsfield unit
IHC	Immunohistochemistry
IMLN	Intramammary lymph node
LMIC	Low-to-middle-income country
LVI	Lymph vascular invasion
MIP	Maximum intensity projection
MIR	Mortality/incidence ratio
ML	Machine learning
mpMRI	Multiparametric MRI
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
MRM	MR mammography
nADC	Normalized apparent diffusion coefficient
NME	Non-mass enhancement
pCR	Pathologic complete response
PD1/PDL1	Programmed cell death protein 1/ programmed death-ligand 1
PET	Positron emission tomography
PPV	Positive predictive value
RADS	Reactive airways dysfunction syndrome
RF	Radio frequency
ROIF	Release of information
ROI	Region of interest

SNR	Signal-to-noise ratio in general
SPECT	Single-photon emission computed tomography
SRMs	Sparrow regional medical supply
T1W	T1 weighted images
T2W	T2-weighted
TNBC	Triple negative breast cancer
US	Ultrasonogram
WHO	World health organization

ABSTRACT

Background:

The MRI Breast Imaging-Reporting and Data System (BI-RADS) lexicon recommends that a breast MRI protocol contain T2-weighted and dynamic contrast-enhanced (DCE) MRI sequences. The addition of diffusion-weighted imaging (DWI) and apparent diffusion coefficient values significantly improves diagnostic accuracy. This study aims to study the descriptors from DCE-MRI, restricted diffusion on DWI, ADC values and choline peak on spectroscopy in breast cancer diagnosis.

Objectives:

1. To assess morphology of breast mass using multiparametric MR mammography.
2. To correlate findings on MR mammography with pathological findings.

Material and methods:

This study was a prospective observational study which involved subjects with breast lump with inconclusive mammography or sonomammography findings. Baseline data was collected from the patients along with pertinent clinical history and relevant lab investigations. MR Mammography was performed on 1.5 Tesla, 18 channel, MR Scanner (Siemens® Magnetom Avanto®) using dedicated double breast coil. The following sequences were performed: T1 and T2 axial images, T1 sagittal, T2 coronal, DWI at 50, 400 and 800 s/mm2 b values with corresponding ADC sequences, Dynamic contrast enhancement study, kinetic curves and Spectroscopy. Chi-square was used as test of significance for qualitative data and independent t test was used as test of significance for quantitative data. p value < 0.05 was considered as statistically significant.

Results:

41 subjects were included with a total of 54 breast masses in them. The mean age of the study population was 47.1 ± 14.7 years. From the MRI final diagnosis, majority (53.70%) were diagnosed as malignant lesions and 46.30% as benign. Out of 20 lesions diagnosed as benign on histopathology, only 5% had ADC value <1.3 and majority 95% had ADC value >1.3. All 20 lesions were circumscribed, ovoid or round in shape showing no restricted diffusion on DWI, with corresponding ADC value of >1.3×10−3mm2/s, homogenous post-contrast enhancement or with dark internal septations, type I kinetic enhancement curve and they showed no choline peak on spectroscopy. Out of 34 malignant lesions diagnosed on histopathology, majority (85.29%) displayed restricted diffusion on DWI and had an ADC value of <1.3×10−3mm2/s, most of them had spiculated margins, type 2/ 3 kinetic curve with choline peak on spectroscopy. Rest 14.71% had ADC value >1.3×10−3mm2/s, showing no restricted diffusion and were circumscribed, they were diagnosed to be mucinous carcinoma on histopathology. The difference in the proportion of ADC value between histopathological status was statistically significant (P value <0.001).

Conclusion:

Multiparametric MR mammography which included DCE-MRM, DWI, ADC values and spectroscopy correlated well with the histopathological diagnosis of benign and malignant breast masses.

Keywords: Breast cancer, MR mammography, DWI, ADC, spectroscopy

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Breast cancer is the most frequent cancer diagnosed in women and is the leading cause of death in them.[1] It is a multifactorial ailment and several factors contribute to its incidence. Even though the disease occurs globally, its frequency, death rate and survival rate differ noticeably among various parts of the world. This may be due to type of population, genetic factors and demography.[2] Variations in risk factors have led to an upsurge in the frequency of breast cancer, which is growing every day. Even though screening women can decrease the burden of breast cancer, over-diagnosis, side effects and expensive costs are the drawbacks of this method. Classification of women based on risk factors for breast cancer can be effective in improving risk-free methods and designing targeted breast cancer screening programs.[3]

According to the World Health Organization (WHO) the prevalence of breast cancer in women, globally is 2.3 million in 2020 and mortality was found in 6,85,000. The death rate in breast cancer is mainly due to extensive metastasis. From the last 5-year data up to 2020, there has been nearly 7.8 million new cases diagnosed with breast cancer**.** Therefore, making breast cancer as the most dominant cancer globally. Breast cancer can occur at any age post puberty however, the incidence is greater at older age. However, the mortality rate has decreased over the years due the early diagnosis by mammography, sonomammography, MRI and early intervention.[4]

MR Mammography (MRM) is relatively a new imaging technique, initially in the 1970s it was anticipated to help in early detection of breast cancer, it was then reinforced by identifying that abnormal tissue within breast revealed difference in T1 and T2 relaxation times in relation to normal tissue. It was later clarified that most cancers in breast demonstrated high signal on T1 weighted images (T1W) after administration of gadolinium contrast, later MRM became widely used tool for characterization of breast carcinoma. Common indications for contrast-enhanced (CE) MRM currently includes supplemental screening for high-risk female patients, pre-operative assessment of extent of breast cancer, evaluation of equivocal findings on other preliminary imaging and/or clinical examination, and evaluation of cancer response to neoadjuvant chemotherapy.[5]

The reason behind increasing adoption of MRM at many hospitals is its intense sensitivity for detection of breast cancer. Several studies showed that conventional CE-MRM has high sensitivity of all other imaging modalities in asymptomatically high-risk women;[6,7] clinically and mammographically occult disease in contralateral[8] or ipsilateral breast[9] in patients having breast cancer which was recently diagnosed. A foremost barrier in widespread implementation of the technique for an average/ intermediate risk patient is uncertain specificity of MRM due to intersection in imaging features of the malignant and benign lesions, with a wide discrepancies in positive predictive value (PPV) of MRM reported in literature (24 to 89%).[10]

Additionally, MRI is useful tool in determining which new breast carcinomas are probable to respond in pre-surgical or neoadjuvant chemotherapy. Numerous studies earlier investigated the use of MRM in assessing early response to neoadjuvant

chemotherapy. They found that change in size/volume along with improved kinetic curves on MRI were related with favourable response to the therapy, including pathologic complete response (pCR).[11] All these findings recommend that MRM can be used to improve medical therapy procedures for every patient. General superiority of MRM over common imaging techniques and clinical examination for predicting pCR was urged in many single centre studies,[12,13] and confirmed in a large multi-centre trials.[14] Although CE-MRI is most accurate modality for predicting outcomes in important neoadjuvant therapy, its clinical impact has been limited by its overall performance and cost.

"Dynamic contrast-enhanced MRI" (DCE-MRI) is the mainstay of MRI protocol. It is the subtlest method used in the diagnosis of breast cancer. [15,16] Its high resolution with good morphological data and information of Neo -angiogenesis makes it one of the best method for tumour detection. As its specificity is low, numerous functional MRI parameters were examined and use of these collective parameters is defined as multiparametric MRI (mpMRI) of the breast. The hallmarks of cancer development can be illustrated as: even in the absence of external growth factors there is proliferation, resist to growth inhibitory factors, dodging of apoptosis; unbounded duplication potential through recrudescence of telomerase; atypical angiogenesis; dodging of obliteration by the immune system; incursion; and metastasis.[17] There are few evidences that by employing various functional characteristics, mpMRI can be used to provide extensive information about hallmarks of cancer's hallmarks,[18] as well as increase specificity.[19,20]

The main goal of mpMRI of breast is to measure and envision physiological, biological and pathological courses at the molecular and cellular levels. This in addition describes the growth and expansion of carcinoma breast and treatment response. MpMRI in assessing breast pathology can be achieved at different field strengths (1.5–7 T) and comprises numerous functional MRI parameters, as well as hybrid imaging techniques such as positron emission tomography (PET)/MRI.

NEED FOR STUDY

MRI is an emerging modality in detecting and characterizing breast lesions. It is accurate in detecting lesions within dense breast, subcentimetric lesions and those not conclusive on X-ray mammography and sonomammography. MRM has a sensitivity of 90-100% and specificity of 85-90% in detecting breast carcinoma.[21] Nearly 27-37% of the breast lesions are missed out on sonomammography. As sonomammography misses the lesions in dense breast, whereas MRI is independent of breast density in detecting lesions.[22]

MRI protocols include diffusion weighted imaging (DWI) as it provides information about composition of tissue and cellularity. It can also assess regional lymph nodes which has metastasized.[22] ADC values of malignant lesion approximately ranges from 0.85 - 1.2 × 10^{-3} mm^2/s and for benign lesion it ranges from 1.3 – 1.5 × 10^{-3} mm^2/s. [22, 23]

Until now, the diagnostic value of multiparametric MRI from DCE and DWI are limited.[24,25,26] They have not definitely focused on the challenging cases where image-guided biopsy has been recommended based on standard 'Breast Imaging Reporting and Database System (BI-RADS)' assessment. BI-RADS 4 category comprises a wide range of probability for malignancy, from >2% to <95%, and this category accounts for many of the false-positive cases encountered on breast MRI. Therefore, additional approaches to improve the specificity of DCE-MRI in this patient cohort are essential. Therefore, the intention of this particular study was to evaluate the use of mpMRI in differentiating malignant and benign tumors.

AIMS AND OBJECTIVES

The aims and objectives of the study were:

1. To assess morphology of breast mass using multiparametric MR mammography.
2. To correlate findings on MR mammography with pathological findings.

REVIEW OF LITERATURE

I. Breast embryology

Breast is considered an epidermal gland because it develops as diverticula of the epidermis into the dermis. Also considered a modified and highly specialized apocrine gland. Mammary gland development begins at week 4 when ectoderm and underlying mesoderm proliferate and differentiate into the skin.[27]

The human breast of stromal and parenchymal elements. The parenchyma forms a system of branching ducts, finally leading to secretory acini development, and the stroma consists mainly of adipose tissue, providing the environment for the development of the parenchyma.[28] The course of advancement of the acini and ductal system is called as "branching morphogenesis", and even though it begins in the fetus, it pauses in early childhood till puberty when hormonal stimulus activates further differentiation.[29]

Prenatal Development:

The breast development at prenatal period can be rived into 2 important process; establishment of primary bud and later a rudimentary mammary gland. The initial stages of embryo development are greatly dependent on hormones and later in the second trimester regulatory factors and hormones play important role in development.[29,30] There is no difference in the development of breast in either genders during the prenatal period. The diagram below explains the sequential and discrete stages of the development of breast during the intrauterine life with a vague correlation with gestational age.[31] In the initial weeks (2-4wks) of gestation there is evidence of mammary-specific progenitor cells.[1] At 35th day of gestation there is proliferation of

paired areas of cells (epithelial) in the epidermis of the thoracic areas. These distinct areas of proliferation cover in a line between the fetal axilla and inguinal region and form 2 ridges called the "mammary crests or milk lines". (Figure. 1).[28]

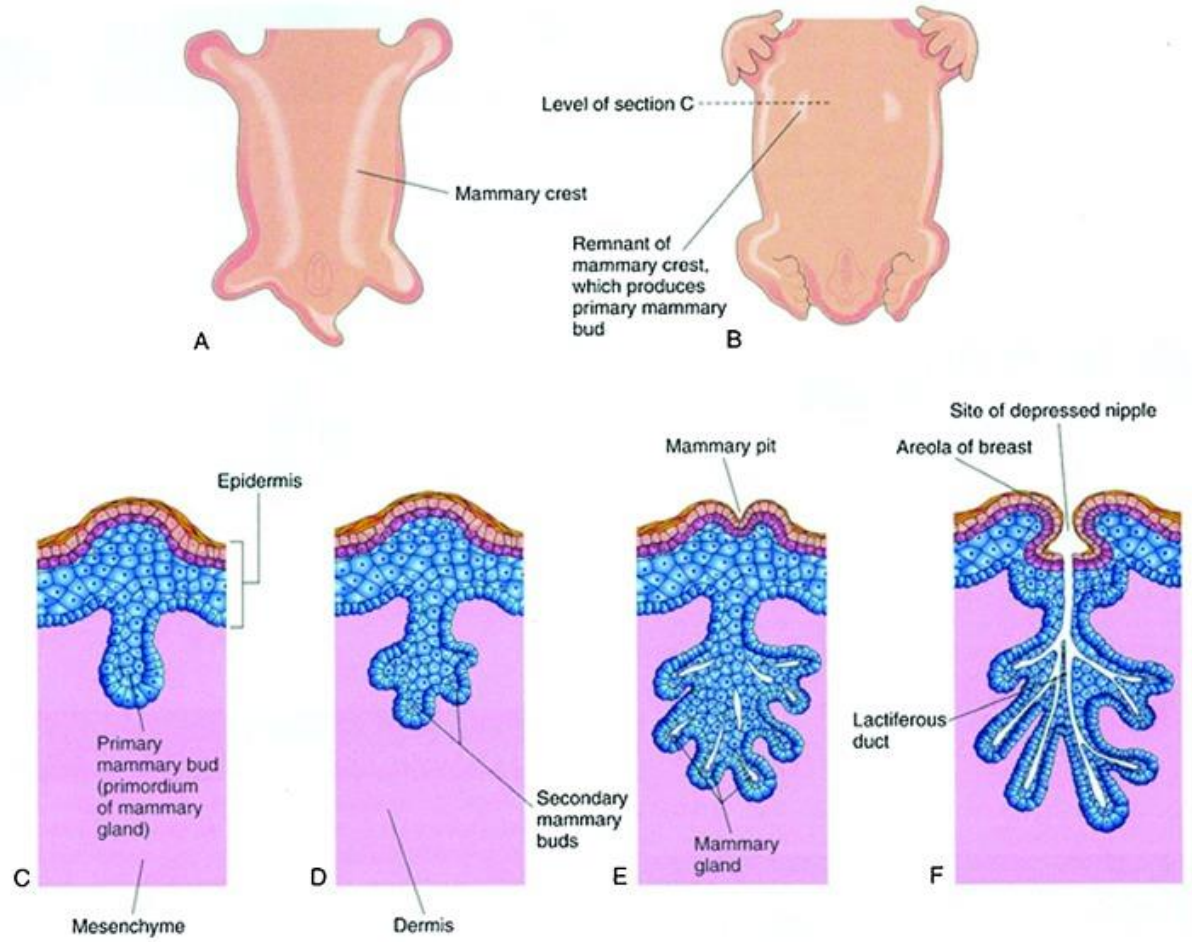


Figure 1: embryology of the mammary gland.

(A) "Ventral view of an embryo at 28-days gestation showing mammary crests". (B) "Similar view at 6-week gestation showing the remains of the mammary crests". (C) "Transverse section of a mammary crest at the site of the developing mammary gland". (D–F) "Similar sections are showing successive stages of breast development between the 12th week of gestation and birth".

II. Anatomy of the breast

Milk secreting glands for nourishing offspring are present only in mammals and are a defining feature of the class Mammalia. In humans, mammary glands are present in both females and males, but typically are functional only in the postpartum female. In rare circumstances, men have been reported to lactate. In humans, the breasts are rounded eminences that contain the mammary glands as well as an abundance of adipose tissue (the main determinant of size) and dense connective tissue. The glands are located in the subcutaneous layer of the anterior and a portion of the lateral thoracic wall. Each breast contains 15–20 lobes that each consist of many lobules. At the apex of the breast is a pigmented area, the areola; surrounding a central elevation, the nipple. The course of the nerves and vessels to the nipple runs along a suspensory apparatus consisting of a horizontal fibrous septum that originates a the pectoral fascia along the fifth rib, and two vertical septa, one along the sternum and the other at the lateral border of the pectoralis minor muscle.[33]

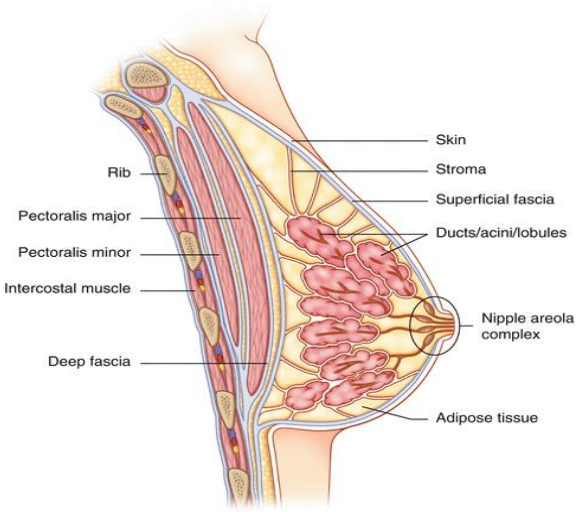


Figure 2: Sagittal section through the lactating breast.

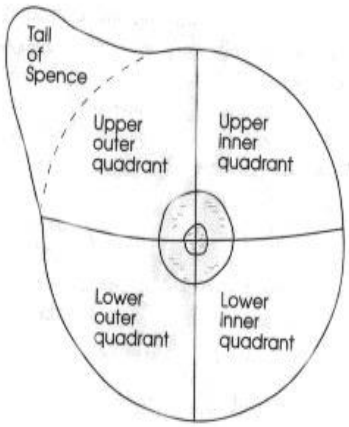


Figure 3: Breast quadrants: UO- upper outer, UI- upper inner, LO- lower outer and LI- lower inner.

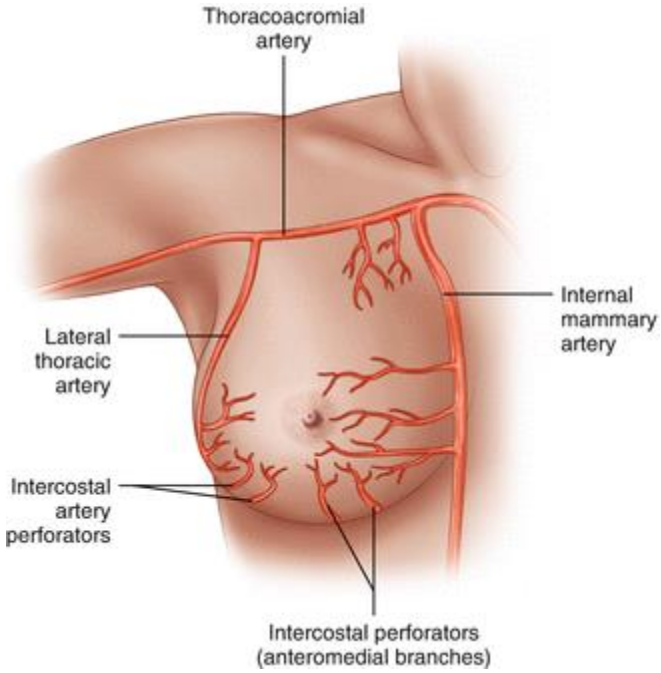


Figure 4: Vascular supply of the breast

Vascular supply of the breast:

Arterial blood is supplied by branches of the axillary artery (lateral thoracic and pectoral branch of the thoracoacromial trunk). Additional blood supply is from medial mammary branches of the internal thoracic (internal mammary) artery and from lateral

branches of the posterior intercostal arteries. Venous drainage is via veins that parallel the arteries with the addition of a superficial plexus.[34]

Nerve Supply:

Innervation of the breast is classically described as being derived from anterior and lateral cutaneous branches of intercostal nerves four through six, with the fourth nerve being the primary supply to the nipple. The lateral and anterior cutaneous branches of the second, third and sixth intercostal nerves, as well as the supraclavicular nerves (from C3 and C4), can also contribute to breast innervation. Most of the cutaneous nerves extend into a plexus deep up to the areola.[34]

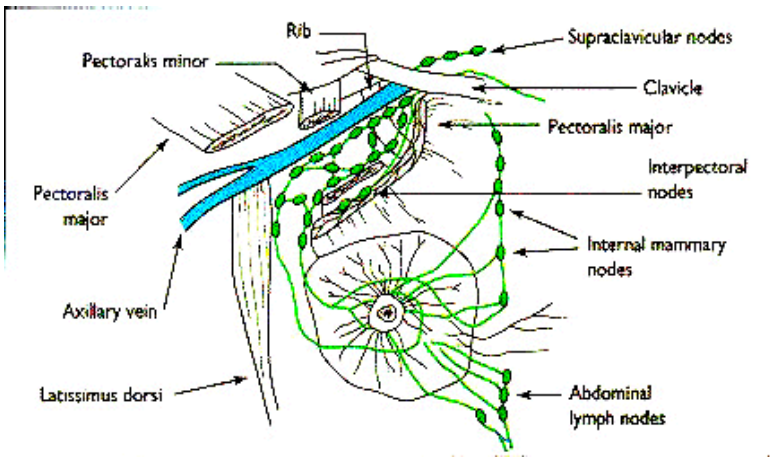


Figure 5: Lymphatic drainage of the breast.

Lymphatic drainage of the breast. Most drainage is into the axillary nodes indicated as level I, level II and level III based on their relationship to the pectoralis minor muscle. Level I nodes are lateral to the muscle, level II are behind it and level III are medial to it. Also, note the internal mammary nodes located just lateral to the edge of the sternum and deep to the thoracic wall musculature.[34]

Normal histology of breast tissue:

Each breast is composed of 15-25 secretory lobes which are embedded in the adipose tissue. Mammary gland is a modified sweat gland, and these secretory lobes are compound tubular acinar glands. Acini empty into its ducts, which are lined by low columnar or cuboidal epithelial cells which are surrounded by myoepithelial cells. These ducts from every lobule empty into lactiferous ducts that empties on the surface of nipple. These ducts are in turn are surrounded by smooth musculature in the area of nipple, contraction of this muscles makes the nipple to become erect.[35]

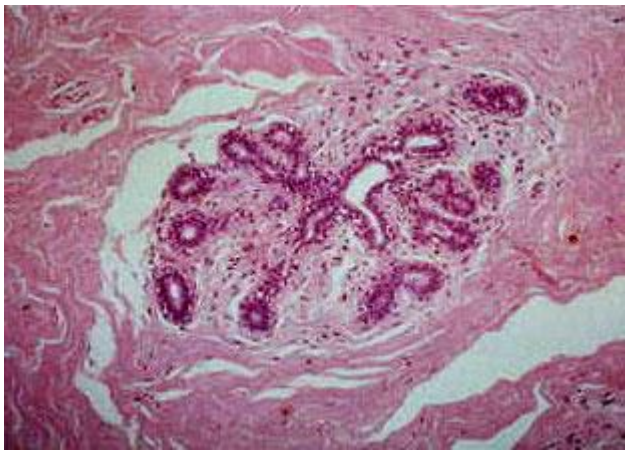


Figure 6: Histopathological image of the secretory lobe breast tissue at low power.

Breast cancer

Breast cancer is a disease in which cells in the breast grow out of control and they can be of different types. The kind of breast cancer depends on which cells in the breast turn into cancer. Cancer can begin in different parts of breast. Parenchyma of breast is moulded by three main parts: lobules, ducts and connective tissue. Lobules are the glands that produce milk, ducts are tubes that carry milk to the nipple and connective

tissue (which consists of fibrous and fatty tissue) surrounds and holds everything together. Most breast cancers begin in the ducts or lobules. Breast cancer can spread outside the breast through blood vessels and lymphatics. When these cancers spread to other parts of the body, it is said to have metastasized.[36]

Clinical features:

Predominant symptoms and signs of carcinoma breast are nipple discharge, "lumpiness," or a palpable mass and inflammatory changes. However, few symptoms are so severe as to require treatment, and the key reason for investigating their cause is to assess the possibility of malignancy. Most symptomatic breast lesions (>90%) are benign. Of females with cancer, about 45% have symptoms, however the remainder comes to attention through screening tests.[36]

- Palpable masses can arise from the proliferation of stromal cells or epithelial cells and are generally detected when they are 2 to 3 cm in size. Most (~95%) are benign; these tend to be round to oval and to have circumscribed borders. In contrast, malignant tumors usually invade across tissue planes and have irregular borders.
- "Lumpiness or diffuse nodularity" throughout the breast is usually a result of normal glandular tissue. When pronounced, imaging studies may help in determining whether a discrete mass is present.
- Nipple discharge - Discharges that are spontaneous, unilateral and bloody are of greatest concern for malignancy.
- Inflammation - An important mimic of inflammation is "inflammatory" breast carcinoma.

Epidemiology

a. Global burden of breast cancer

According to Global Burden of Disease Cancer Collaboration,[37] the incidence of carcinoma breast has increased with variability in the burden of disease across countries of different income order.[38] In low-income countries, nearly 69% of total disability-adjusted life years were lost due to breast cancer.[39] Even though the total incidence rate of breast cancer is lower in (Low-to-Middle-Income Country) LMIC compared to High income countries (HICs), there is an increase in the incidence rate in the LMICs.[38,40] The mortality rates of breast cancer since 1990 in few HICs have shown to be decreasing, but in other HICs and LMICs have been witnessing increasing mortality rates.[38]

b. Indian burden of breast cancer

According to Globocan 2012, India, along with the United States and China collectively accounts for almost one third of the global breast cancer burden. India is facing challenging situation due to 11.54% increase in incidence and 13.82% increase in mortality due to breast cancer during 2008–2012.[41,42] The main reasons for this observed hike in mortality is due to lack of inadequate breast cancer screening, diagnosis of disease at advanced stage and unavailability of appropriate medical facilities. Breast cancer attains top rank even in individual registries (Mumbai, Bangalore, Chennai, New Delhi and Dibrugarh) in females during the period of 2012–2014. The relative proportion of breast cancer in different registries varied from 30.7% in Chennai to 19% in Dibrugarh. A total district wise minimum age-adjusted incidence rate (AAR) per 100,000 for India. AAR > 20 per 100,000 has been recorded for districts like Chandigarh (39.5), Panchkula (34.6), Aizwal

(36.2) and Goa (36.8).[43] Mortality/incidence ratio (MIR) is another novel measure to evaluate cancer mortality in relation to incidence.

Etiopathogenesis of breast cancer

a. Etiology and risk factors of breast cancer

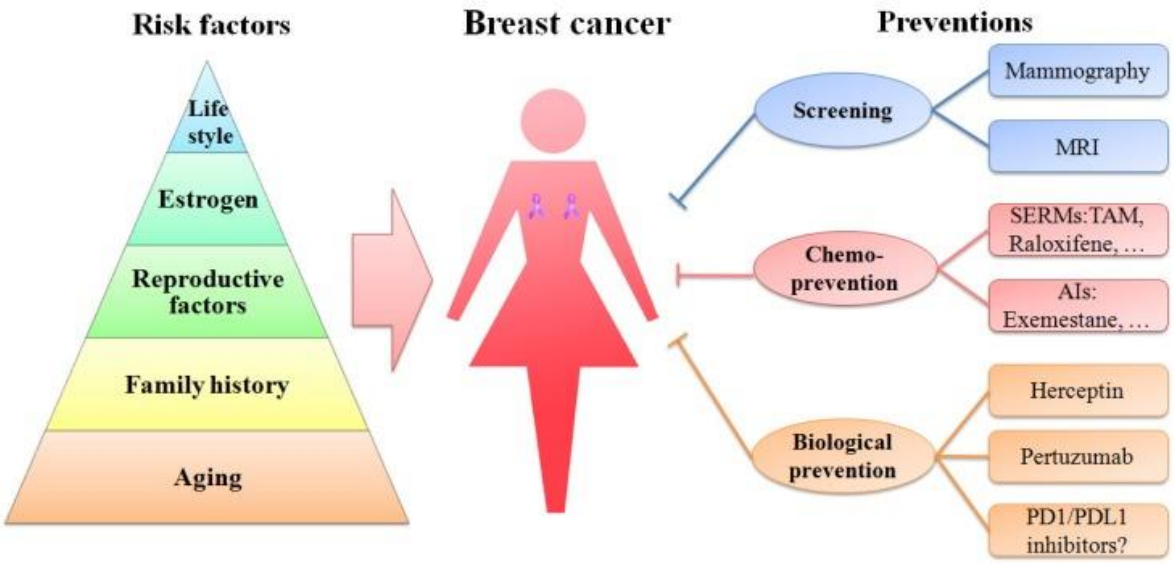


Figure 7: Schematic diagram of risk factors and preventions of breast cancer.

Age, family history, reproductive factors, estrogen and life style are five important risk factors of breast cancer, represented in the pyramid chart. Screening (mammography and MRI), chemoprevention (with SERMs and AIs) and biological prevention (using Herceptin and pertuzumab) are currently being used to prevent breast cancer. PD1/PDL1 inhibitors are immunotherapy drugs and might be promising strategies in treating triple negative breast cancer (TNBC).[44]

Pathogenesis of breast cancer:

Three main pathways have been identified (Figure 8). The most common pathway *(yellow arrow)* leads to luminal (ER-positive) carcinomas. Recognizable non-obligate precursor lesions include flat epithelial atypia and atypical hyperplasia. A less common pathway *(blue arrow)* leads to triple-negative breast cancer (ER-negative/HER2-negative). A possible precursor lesion consisting of morphologically normal cells that overexpress p53 has been identified (analogous to the "p53 signature lesions" for ovarian carcinoma). The third pathway *(green arrow)* consists of HER2-positive cancers. Amplification of HER2 can occur in either ER-positive or ER-negative lesions. A definite HER2-positive precursor lesion has not been identified.[36]

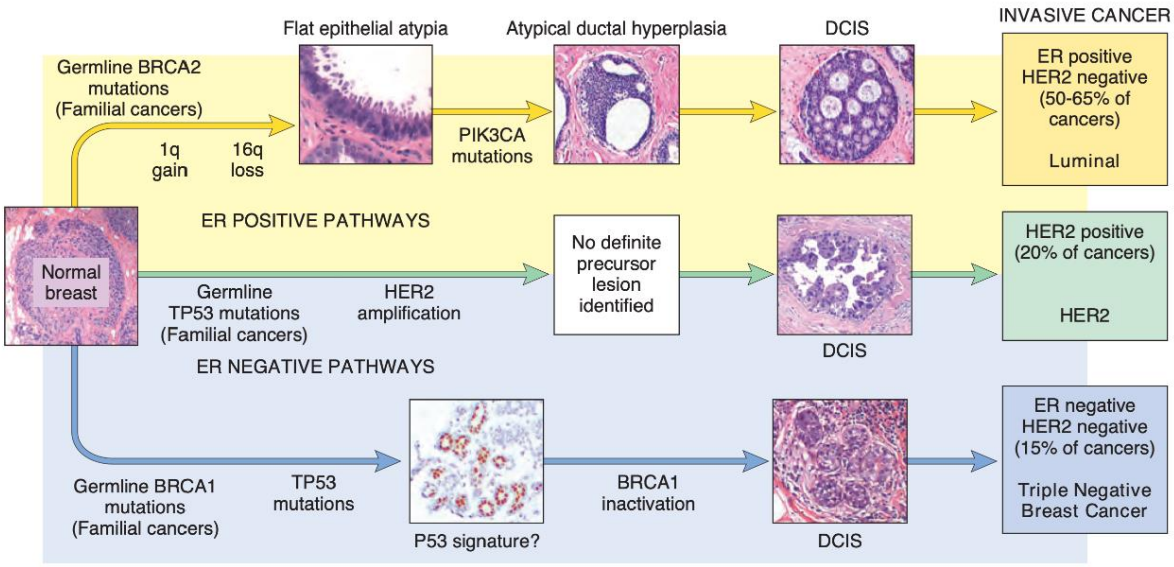


Figure 8: Major pathways of breast cancer development.

Lesions of breast

Benign breast lesions

Benign lesions constitute a heterogeneous group of diseases involving the epithelium of other tissues of breast & they may be related with inflammatory, vascular or traumatic pathologies. Most of the lesions are palpable. There may have specific or non-specific lesion characteristics with no specific clinical signs. Hence, imaging plays a very vital role in its diagnosis.[45]

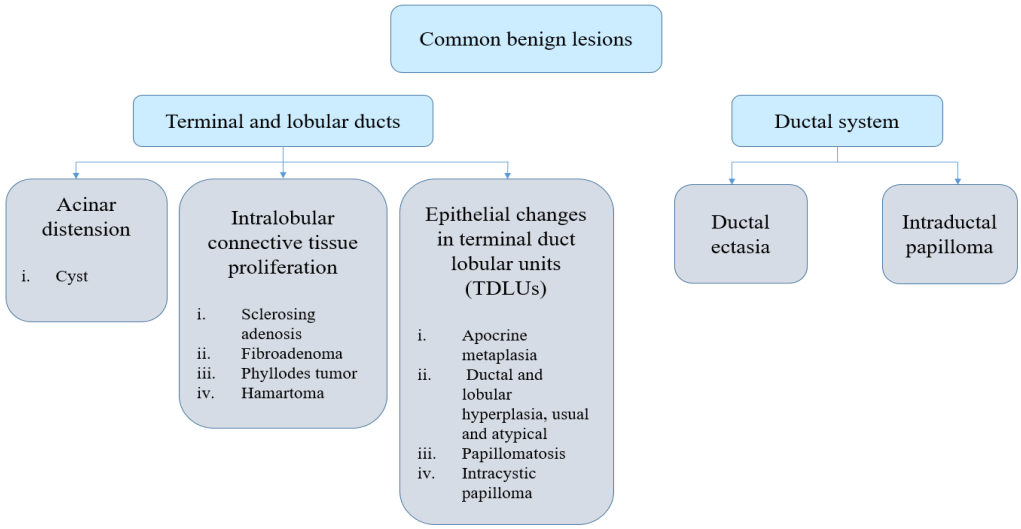


Figure 9: Classification of the benign breast lesions

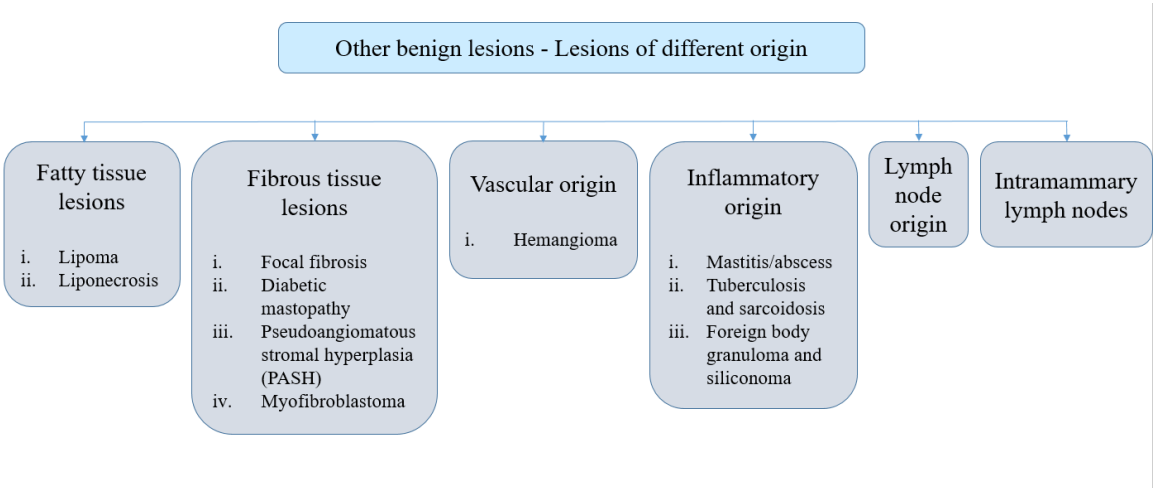


Figure 10: Classification of benign lesion with different origin

Malignant breast lesions

Malignant lesions are predominantly primary or they can be metastatic lesions. These lesions grow in and around the breast parenchyma and are seen mainly to involve fibroglandular tissue. They form a lump which is usually palpable due to abnormal increased cell growth. It can also lead to microscopic extension of the lesion into the parenchyma adjacent to the lesion. They usually metastasise to axillary or intramammary lymph nodes. Invasive ductal carcinoma is one of the most common malignant breast lesion noted.

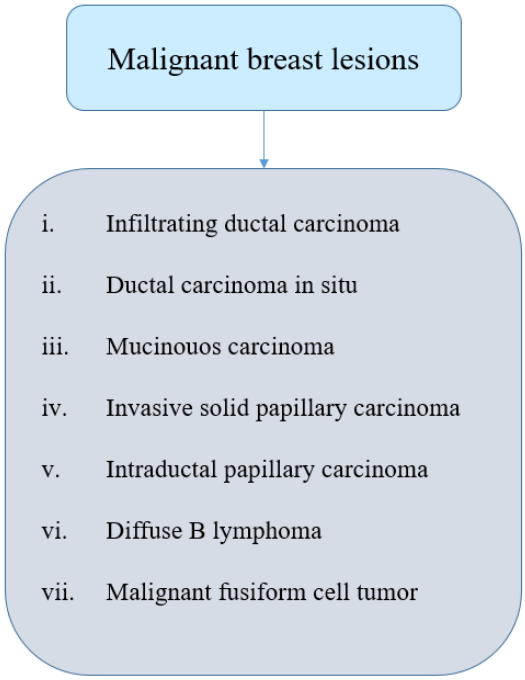


Figure 11: Classification of the malignant breast lesions

Diagnostic modalities of Breast Masses

A. ***Imaging techniques:***

Various imaging methods such as mammography, sonomammography, magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), Computed tomography (CT) and positron emission tomography (PET)

and may perhaps can aid in diagnosis and monitor breast cancer subjects at various stages.[46]

Imaging techniques:

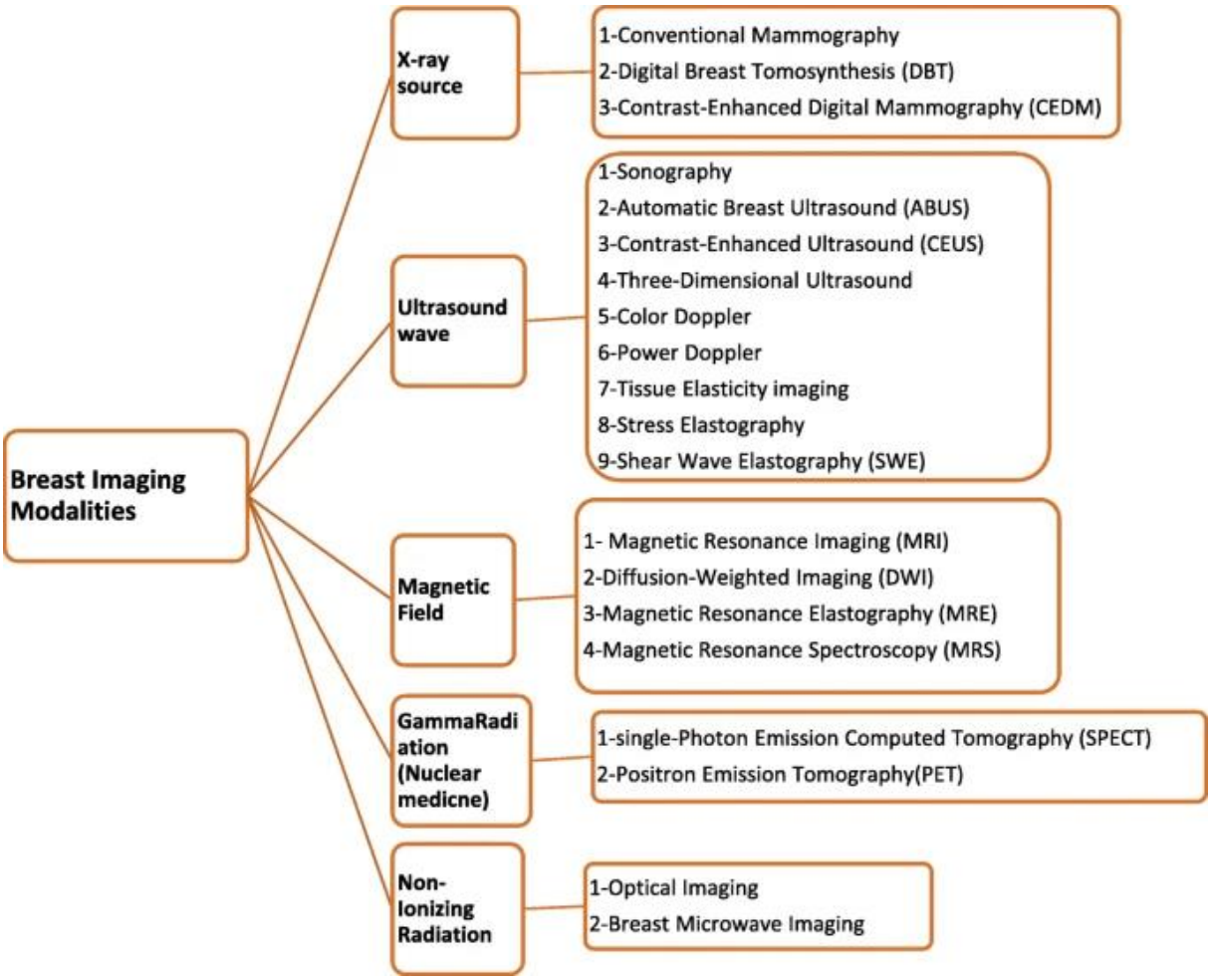


Figure 12: Schematic representation of different imaging methods in investigation of breast cancer

Mammography:

A mammogram is an X-ray of the breast. It is the most basic investigation in diagnosing breast lesions (Figure 13) of all the various methods available.[47] Digital mammography (DM) has replaced conventional (film screen) mammography in some breast screening services. Potential advantages of DM include its use of computer-aided detection, algorithm-based computer programs that alert the radiologist to possible abnormalities

on the mammogram and allowing centralized film reading. Moreover, false-positive calls lead to additional imaging or histopathological assessment, mainly percutaneous breast biopsy.[48]

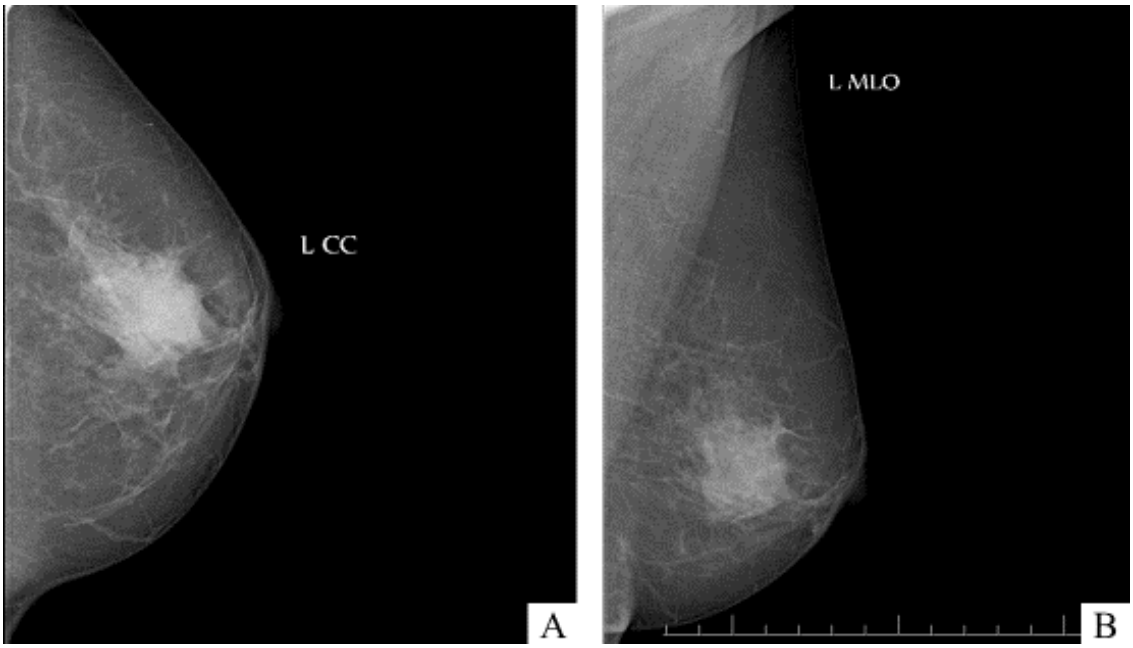


Figure 13: X-ray mammography images, craniocaudal (Fig A) and Mediolateral (Fig B) images demonstrating an irregular high density lesion with spiculated margins in lower outer quadrant of left breast.

Sonomammography:

Breast ultrasonography, also called as sonomammography, apart from assessing palpable breast mass, can extricate cysts from solid mass and trace anomalies in the peripheral view which is not spotted by mammography. It is a non-invasive method, free of radiations hence very beneficial in lactating and pregnant women. It is an appropriate method of assessment in post-surgical, irradiated breast and painful conditions where use of mammography is discouraged. Sonomammography has advantages but higher rate of false positive diagnosis in sonomammography is reported.[49]

Elastography:

Elastography is used to characterize a lesion that has already been detected in B mode. It is a characterization tool, not a detection tool.[49,50] It is a fast and easy technique to use. There are 2 types of elastography, shear wave and strain wave type. Shear wave elastography (SWE) technique is classically less operator-dependent as compared to strain wave elastography. Some degree of variability may occur if too much pressure is applied on the probe while performing elastography.[51]

Characterisation of benign/malignant solid lesions

The main interest of breast elastography is to improve the characterisation of malignant and benign breast lesions.[52] Literature have shown that use of elastography parameters in adjunct to ultrasound parameters can improve BI-RADS score.[53] These results have been obtained either with free-hand or shear wave modes. While elastography may be useful to characterize a cystic content without fine needle aspiration, it is mandatory to avoid a false interpretation when a malignant lesion presents as highly deformable. On the other hand, it appears to be useful for malignant lesions presenting as benign lesions on B mode, which appear poorly deformable on elastography. The best application seems to be applied to solid BI-RADS 3 or 4a lesions. Elastography can also increase the ultrasonographer's confidence in his/her diagnosis before a biopsy.[51]

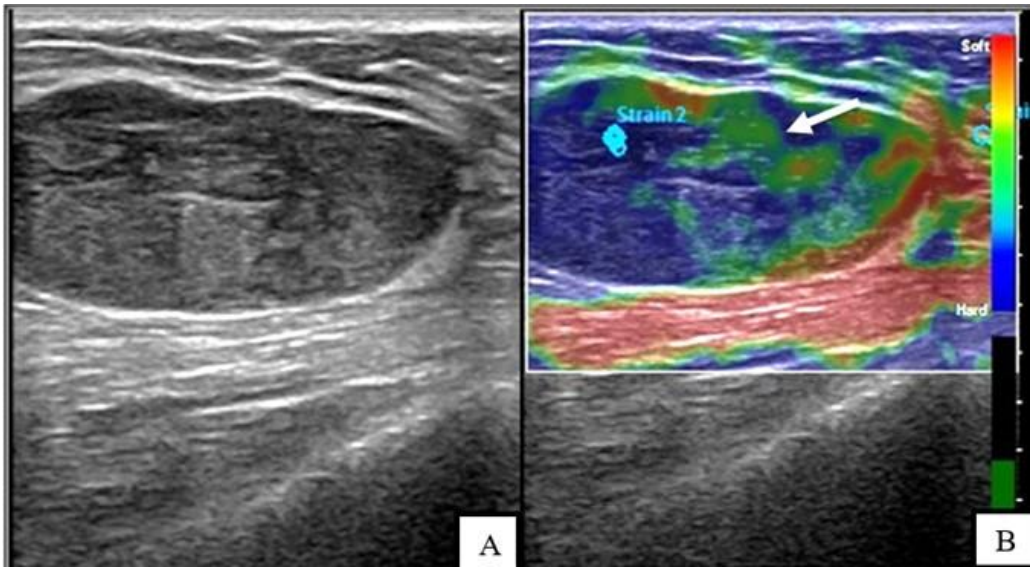


Figure 14: (A) Ultrasonography of a palpable breast lesion showing a well-defined, hypoechoic solid lesion with posterior acoustic enhancement, suggestive of BIRADS 3 lesion. (B) On elastography, the lesion demonstrated mosaic patterns of blue and green (thick white arrow) suggestive of equivocal lesion.

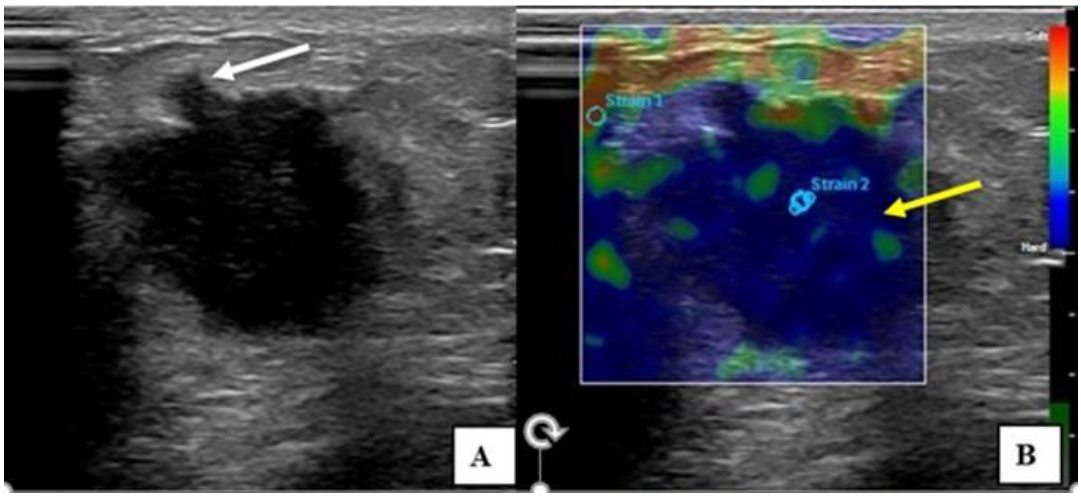


Figure 15: (A) Ultrasound grey scale image of a well-defined hypoechoic solid lesion with spiculated margins (thick white arrow) suggestive of BIRADS 5. (B) On elastography, the lesion (thick yellow arrow) showed uniform blue colour pattern suggestive of malignancy.

ROLE OF CT IN BREAST CARCINOMA

Computed tomography (CT) has been found in having high diagnostic efficacy in assessment of breast tumours. In CT scans of known breast tumours, the lesion morphology and enhancement pattern can be used for differentiating benign from malignant lesions (Fig both CT images).[55] Malignant lesions have significantly greater conspicuity than do benign lesions at CE breast CT, possibly improving the specificity of CECT of breast. In addition, the conspicuity of DCIS at CECT breast is significantly greater than that at unenhanced breast CT. CECT breast offers a promising quantitative technique with which we can predict malignancy in breast lesions.[56]

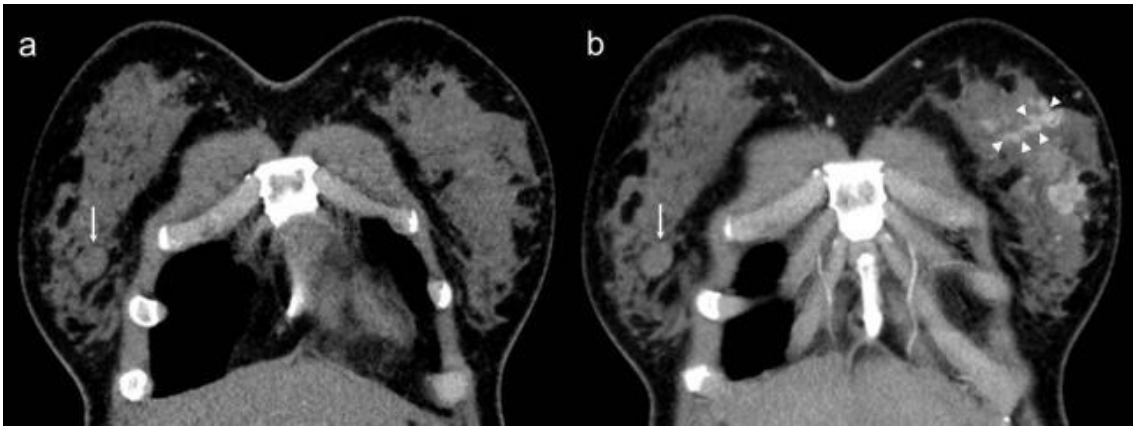


Figure 16(A): Coronal unenhanced (a) and contrast-enhanced (b) CT scans showed an ovoid, well-defined fibroadenoma (arrow, 41 HU in unenhanced CT and 47 HU in contrast-enhanced CT, ΔHU = 3) in right breast and multifocal non mass enhancement (arrowheads, 39 HU in unenhanced CT and 119 HU in contrast-enhanced CT, ΔHU = 77) in left breast. Histopathology revealed diagnosis of invasive ductal carcinoma.

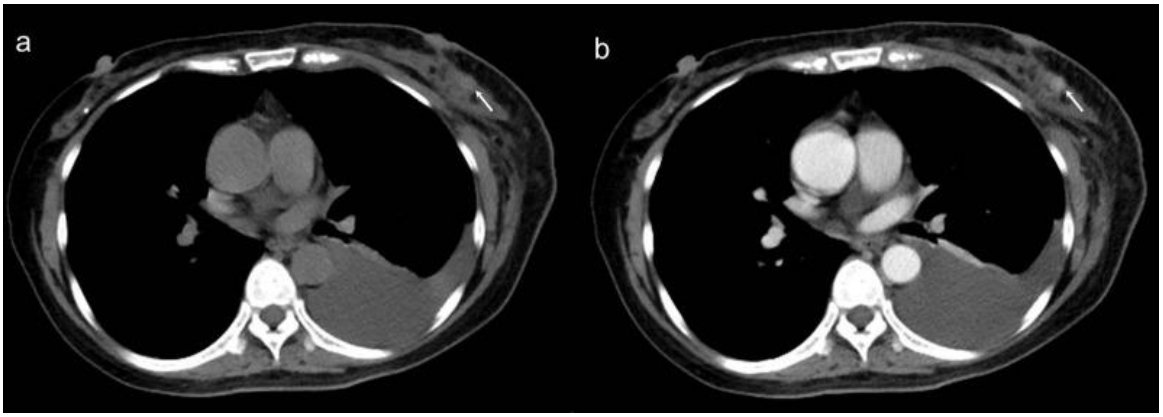


Figure 16(B): Axial unenhanced (a) and contrast-enhanced (b) CT scans showed an irregular enhancing lesion with indistinct margins in breast on left side.

MAGNETIC RESONANCE IMAGING (MRI):

MRI is a non-invasive method of mapping the internal structure and certain aspects of function within the body. It uses nonionizing electromagnetic radiation without exposure-related hazard. It employs radio frequency (RF) radiation in the presence of carefully controlled magnetic fields in order to produce high quality cross-sectional figures of the body in any plane. The MR Image is constructed by placing the patient inside a large magnet, which induces a relatively strong External magnetic field. This causes the nuclei of many atoms in the body, including Hydrogen, to align them with the magnetic field and later application of RF signal, Energy is released from the body, detected and used to construct the MR image by Computer.[57]

Requirements for Breast MRI

- Because mammographic and ultrasound investigations are frequently complementary, MRM results must be interpreted by competent radiologists in breast imaging, including X-ray mammographic and ultrasound studies.[58]
- When acquiring images with a high spatial resolution, it's idyllic to use a minimum field strength of atleast 1.5T.[59]

- Obtaining diagnostic-quality pictures necessitates the use of specialised breast coil.[74,76]
- Because breast MRI attempts to reveal lesions that aren't visible with other imaging modalities, it's critical that imaging centres have the tools to biopsy & localise these lesions so that surgery can be performed.[60,61]
- Additionally, because the injection of a needle, it can modify the form of parenchyma of breast as well as position of lesion to be assessed; a device that immobilises the breast during the biopsy is required.[60]

SURFACE COILS

- Evaluation is achieved with patient in prone position and a dedicated double breast phased array coil is used which allows examination of both the breasts at the same time with high temporal and spatial resolution. During the study, breasts on both sides should be well centred and hanging free in the coil within its recesses. It can be cushioned and patient has to be placed in a comfortable position. This design is made to allow the breast parenchyma to spread, making it easier to detect anomalies and eliminating its motion artefacts caused by breathing.[62]
- Every breast coil should have atleast 4 channels, but latest designs have about 16 channels or even more. Occasionally they also have dedicated channels for axillary regions.[63] Coils which have more channels have higher signal-to-noise ratio in general (SNR). Having more channels will also allow for higher parallel imaging factors and which will improve picture acquisition time.[60]

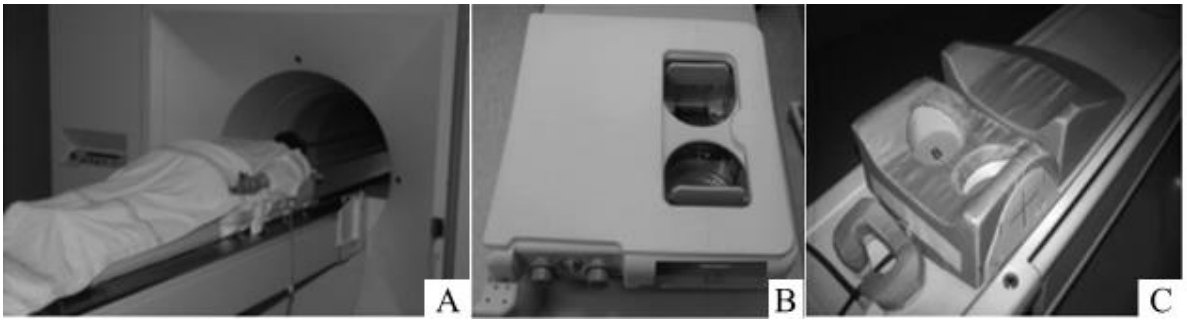


Figure 17: Patient in prone position on the breast surface coil before positioning in the magnet bore (Fig A). Bilateral breast coil with lateral slide plates for compression (Fig B & C).

Indications for MR Mammography:

- Subjects with lump in the breast- to assess morphology and the extent of disease (EOD)
- To characterise an indeterminate/ inconclusive breast lesion (BIRADS 0) following full assessment with mammography, ultrasonography and physical examination.
- Screening in high risk patients – Family history of carcinoma breast, BRCA1 / BRCA2 gene positivity.
- Screening of contralateral breast in case of suspicious extension.
- Positive margins – in assessing the extent of lesion beyond the lump.
- To assess residual disease following or response to neo-adjuvant chemotherapy.
- Metastatic axillary lymphadenopathy of unknown primary.
- To assess chest wall invasion in posteriorly located lesion.
- Recurrent carcinoma breast/ scar changes.
- To assess for synchronous, multicentric or multifocal disease.
- Evaluation of invasive lobular carcinoma.[61]

Contraindications:

- Claustrophobia.
- Patient unable to lie in prone position – Marked kyphoscoliosis or kyphosis, marked obesity.
- Extremely obese patients/ patients with large breasts.
- History of allergy/ contraindication to gadolinium-based contrast media
- Other general contraindications to MRI – metallic/ MR incompatible implants.

Advantages:

- Sensitivity of MRM for the detection of cancer is greatest of the all imaging techniques,
- MRM can be used as problem-solving modality.
- In general, a negative breast MRI excludes malignancy.[64]

Disadvantages:

- Only in case of mammographic microcalcifications, MRI is unable to exclude cancer adequately, and the decision to perform biopsy must be based on mammographic findings in this specific situation.[65]
- The major limitation of MRM is to have low to moderate specificity, however has high sensitivity which can lead to false positive diagnosis.[66]

MRI anatomy of breast

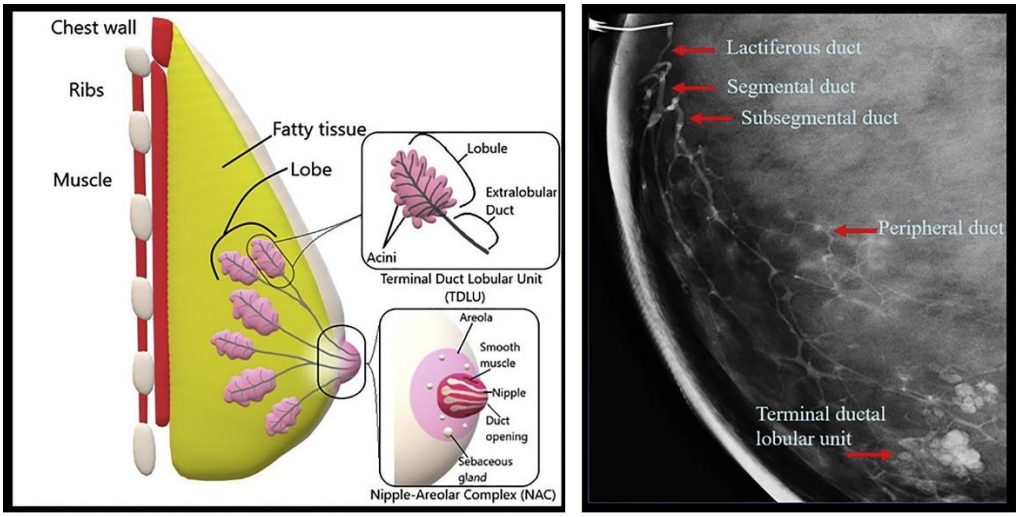


Figure 18: a) sagittal section of breast in a pictorial presentation b) MRI image of a normal breast

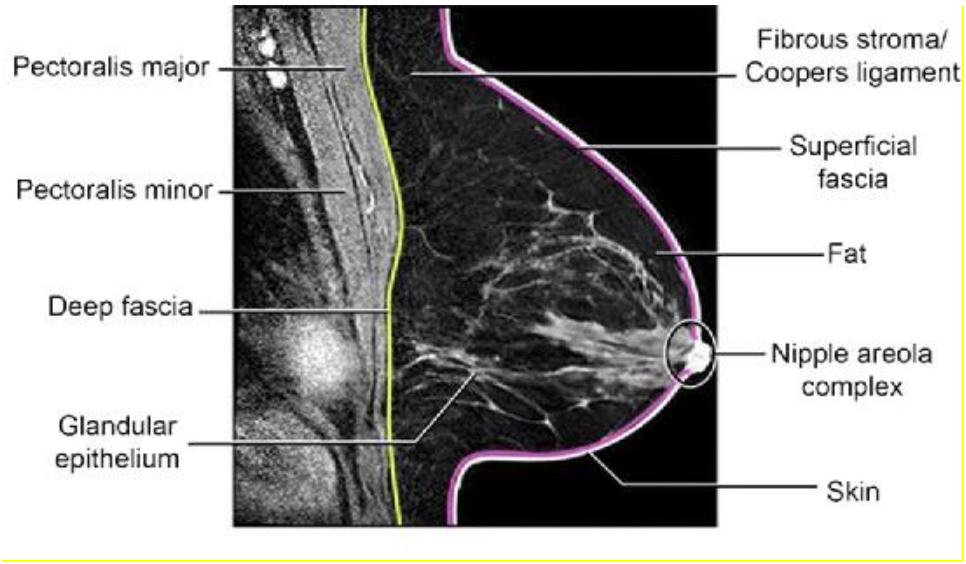


Figure. 19: Sagittal delayed post contrast image demonstrating major anatomic components of breast.

Components of the Multiparametric Breast MRI Protocol

MRM has advanced from primarily contrast-enhanced method to a multiparametric method, in which T1-weighted (T1W), T2-weighted (T2W) and diffusion-weighted

imaging (DWI) are commonly performed. Dynamic T1W contrast-enhanced sequence is still a foundation of any MRI programme.[60]

The Multiparametric Protocol

Figure 20[60] depicts the several components of basic multiparametric technique. For improvement of classification of lesions, other sequence types and post-processing methodologies are being appraised. These usually comprise quantifiable assessment of DCE-MRI, advanced DWI techniques and spectroscopic imaging.

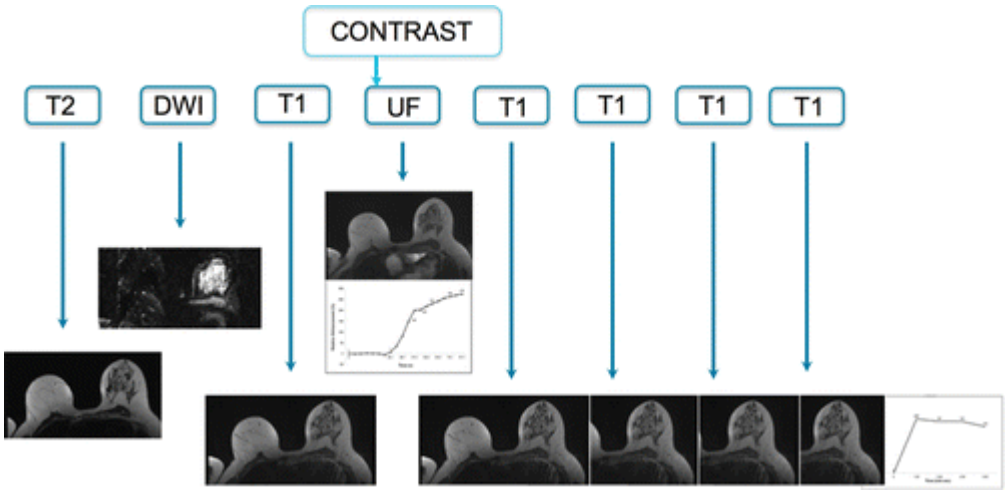


Figure 20: "Components of the basic multiparametric MRI breast protocol. In general, the protocol is begun with the non–contrast-enhanced acquisitions (T2W and DWI). This is followed by a native T1W acquisition and subsequently the CE series. For screening purposes, this protocol may be abbreviated to contain only the T1-weighted acquisitions before and directly after contrast material administration, with or without the acquisition of ultrafast images. For lesion discrimination, T2W imaging and DWI are beneficial". "After neoadjuvant chemotherapy the delayed phase is essential to document the presence of residual ductal carcinoma in situ".

T1-weighted Imaging

With or without any fat suppression, T1W imaging can be done (FS). The axial plane is used to acquire images since it is faster than the sagittal plane and it provides a better picture of both breasts. Prior to the delivery of contrast material, a native T1W sequence should be obtained. Contrast should be given at a max dose of 0.1 mmol/kg body weight. Larger doses have not been shown to improve performance.[69] A power injector with its flow rate of 2 ml/s should be used if possible. The bolus (nearly 20 mL) of contrast should be flushed with normal saline before use.[60]

The T1W acquisition is repeated after contrast injection to show enhanced anomalies. Most breast tumours will show a peak enhancement 60–90 seconds following contrast material injection, therefore getting an image at that time is critical. These post-contrast pictures are mostly used for lesion detection. Subtracted images from pre- and post-contrast acquisitions are necessary for the images obtained without any fat suppression.[69] Subtraction pictures are particularly useful for fat suppression acquisitions because they assist distinguish actually enhancing tissues of tumours showing high signal intensity on T1. Rapid lesion detection is aided by generating maximum intensity projection (MIP) from the subtracted pictures. On MIP pictures, however, chemical shift artefacts, motion artefacts, and poor suppression of fat may mask small lesions.[60]

By administering contract, MRM must usually depict all the enhancing cancers 5mm or even larger in size. Consequently, the cross-section thickness of T1-weighted attainments should not be > 2.5mm. The in-plane pixel size must be 11 mm or less because morphologic assessment requires much finer resolution. Greater resolutions (1

mm isotropic and lower) can be achieved with contemporary MRI units along with breast coils without increasing the acquisition time/ volume beyond 90 seconds. This will enable reconstruction in any plane, making it easier to assess any lesion, particularly that of distribution of non-mass lesions.

For any lesion recognition, the attainment of 2 T1W acquisitions at the detailed time points (one before & one approximately 90 sec after administration of contrast) is sufficient, as it can be incidental from the success of abridged protocols for MRM. All other sequences strive to improve breast lesion distinction and avoid false-positive and false-negative classification.[60]

T2-weighted Imaging

T2W imaging is included in standard MRI protocol. T2W images with FS will enable easy visualization of cysts. T2W images without FS allows better depiction of the lesion morphology. Many masses with high signal intensity on T2WI are benign (eg, apocrine metaplasia, myxoid fibroadenoma, fat necrosis, cyst, and lymph nodes).[70] Because of their low water content and high cellularity, most of the tumours will not show high signal intensity as compared to that of parenchyma on T2WI. On T2W pictures, mucinous carcinoma, metaplastic carcinoma and necrotic cancer might all show a lot of signal. T2W can also show prepectoral or perifocal edema in breast, which helps with lesion categorization and is a bad prognostic marker in patients with breast carcinoma. T2W has been shown in several studies to improve the specificity for distinguishing between malignant and benign tumours.[71,72] However, rest of the investigators have interrogated the added value of T2W in monotonous MRM, especially in inversion-recovery pulse sequences.[59]

Diffusion weighted imaging sequence

The random water molecular movement within tissue is influenced by microstructure of tissue and its cellular density, is quantified by DWI. Motion-sensitizing gradients (b factors) are used to a T2W echo-planar imaging (EPI) sequence to achieve this. Because of the increased cell density in cancers, water diffusion is reduced, resulting in a higher signal intensity during DWI. DWI takes only a few minutes to complete and does not require the use of a contrast agent. Selection of proper b values, adequate FS, avoidance of artefacts, and sufficient SNR are all critical for obtaining adequate DWI acquisitions.[73]

Apparent diffusion co-efficient (ADC) sequence & its corresponding values.

ADC is a quantitative measurement of diffusion derived from DWI. Values are expressed in 10^{-3} mm^2/s. Because of the hampered diffusion in carcinomas, mean ADC is generally low (range: $0.8–1.3\times10^{-3}$ mm^2/s) compared with to that of benign lesions (range: $1.2–2.0\times10^{-3}$ mm^2/s). As a result, tumours have low signal intensity on ADC maps that are generated.[74]

Dynamic Evaluation with Time–Signal Intensity Curves

The permeability of vessels that will supply a lesion is investigated using dynamic analysis.[60] It is accomplished by taking a series of T1W images between 5 to 7 minutes after administration of contrast.[75,76] Benign and malignant masses have different enhancement patterns based on type of lesion (Fig 21 & 22).[75] The peak of contrast material accumulation has passed in the event of leaky vessels, and contrast is being evacuated from the lesion. The contrast gradient over the vessel wall will yet be positive in lesions with less-permeable vasculature, so the lesion will be enhanced. This is

evident in the shape of the time–signal intensity curves; benign lesions tend to have a continuous increase, whereas malignant lesions tend to have a reduction in the late phase. [60]

The most suspicious curve found- 'washout > plateau > persistent', inside a tiny region of interest (ROI) in the lesion is utilised to enhance lesion classification. A washout curve is present in approximately 85% of malignancies. Persistent curve is uncommon in cancers, but they might appear in ductal carcinoma in situ (DCIS) and more invasive tumours with are growing diffusely, such as lobular breast cancers. Reading with visual assessment of full tumor's enhancing behaviour can replace ROI-based measurement of time intensity curves. Additionally, software applications that generate colour map overlays with that of the kinetic enhancement curve distribution within lesion are available, which can be used instead of placing ROIs and generating time–signal/ kinetic intensity curves.[60]

MRI images of "benign and malignant breast lesions"[75]

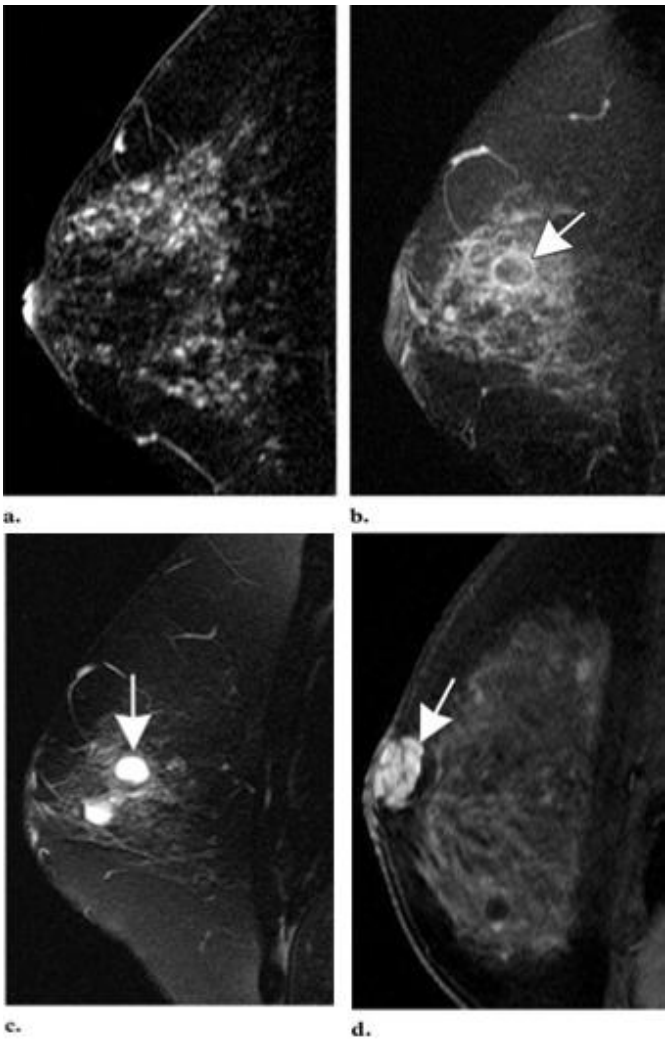


Figure 21: Benign features. **(a, b**) Contrast-enhanced T1-weighted fat-saturated gradient-echo (GRE) images from a 51-year-old woman show regional micro nodular (<5 mm stippled or punctate) enhancement in fibrocystic breast tissue **(a)** and rim like enhancement around a cyst (arrow in **b**) within a region of fibrocystic breast tissue. **(c)** T2-weighted fat-saturated image shows the cyst (arrow). **(d)** Contrast-enhanced T1-weighted GRE subtraction image from a 44-year-old woman shows an oval mass with smooth and lobular margins and enhancement with dark internal septa, typical of a fibroadenoma (arrow).

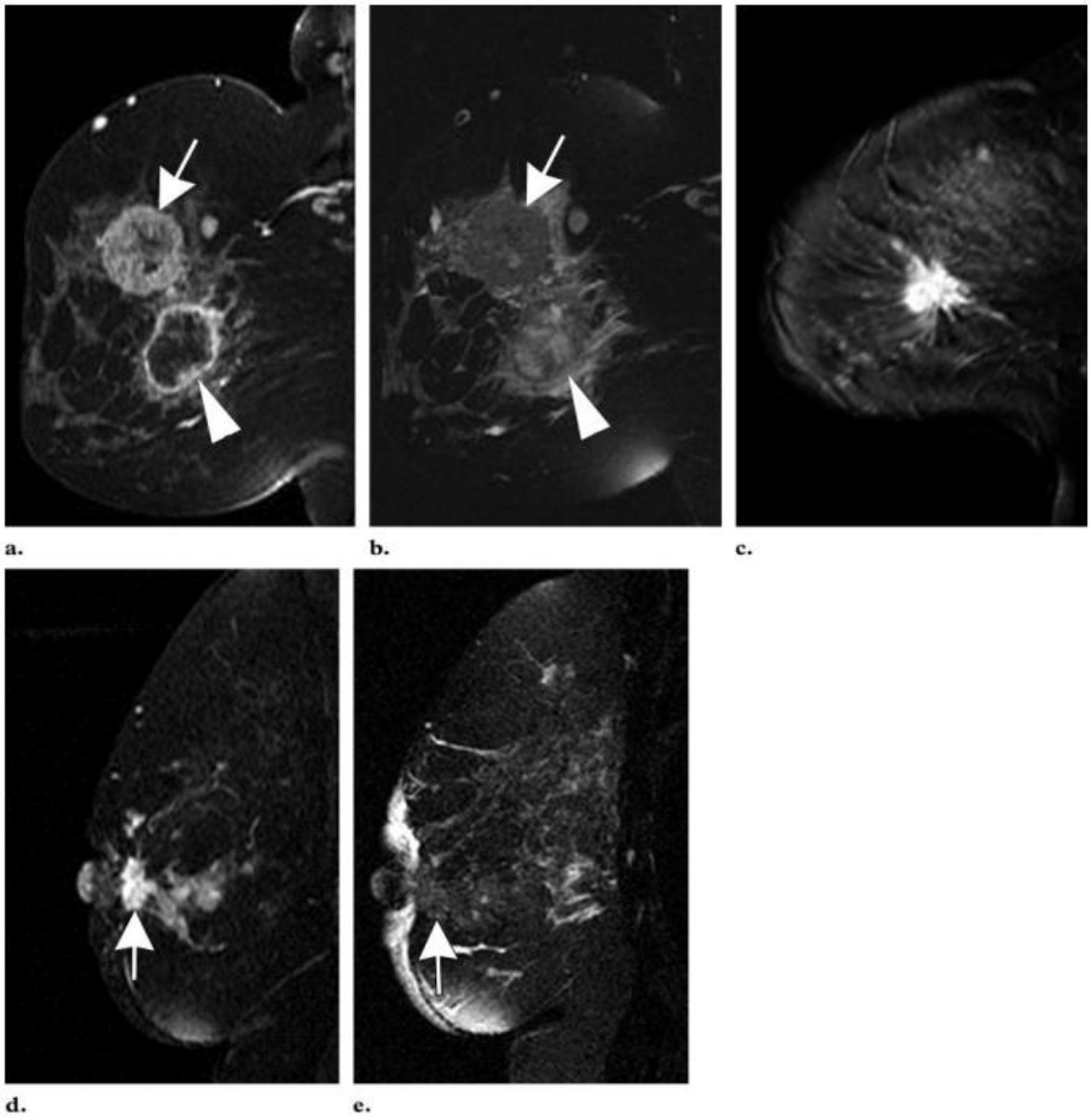


Figure 22. Malignant features. (a) Contrast-enhanced T1-weighted fat-saturated GRE image shows two masses in left breast of a 44-year-old woman, one with thin rim like enhancement at the 4-o'clock position (arrowhead) and the other with heterogeneous enhancement and enhanced internal septa at the 2-o'clock position (arrow). (b) T2-weighted fat-saturated image shows low signal intensity in the portions of the masses that appeared enhanced in a. A central region of necrosis in the mass at the 4-o'clock position shows increased internal T2-weighted signal intensity. The masses proved to be poorly differentiated ductal carcinoma with necrosis and signet ring cell features. (c) Contrast-enhanced T1-weighted subtraction image from a 42-year-old woman

shows a spiculated margin in an infiltrating carcinoma with ductal and lobular features. (d) Contrast-enhanced T1-weighted fat-saturated GRE image from a 52-year-old woman shows a retroareolar mass (arrow) with an irregular margin and heterogeneous enhancement. The results of histologic analysis indicated infiltrating ductal carcinoma. (e) T2-weighted fat-saturated image (same patient as in d) shows the mass (arrow) with low signal intensity. Note the focal skin thickening and nipple retraction.

Kinetic curves types[77]

There are three different types of kinetic curves. Early enhancement (2 minutes after agent injection), when the augmented curve's initial increase can be classified as moderate, medium, or rapid. Rapid enhancement is characterised as a >90% increase in initial peak signal strength within 90 seconds, which is highly predictive of malignancy. The "delayed phase" is defined as the signal strength 2 minutes after contrast injection, which is categorised into "persistent" (type I), "plateau" (type II), and "washout" (type III) (type III). The signal intensity reached a peak 2 minutes after contrast medium injection, followed by a flattening during the delayed phase; washout (type 3) - an initial increase and subsequent reduction in signal intensity 2 minutes after contrast medium injection. The first rise usually indicates the extent of tumour angiogenesis, whereas the subsequent rise usually reflects the extent of tumour angiogenesis.

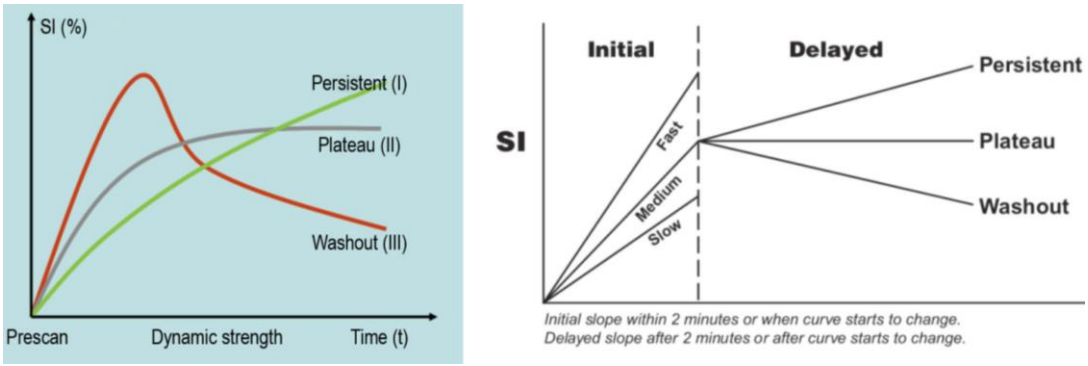


Figure 23: The initial slope and delayed phase of the kinetic curve are separated. The initial slope refers to the first two minutes after the contrast medium is injected or when the curve begins to alter.

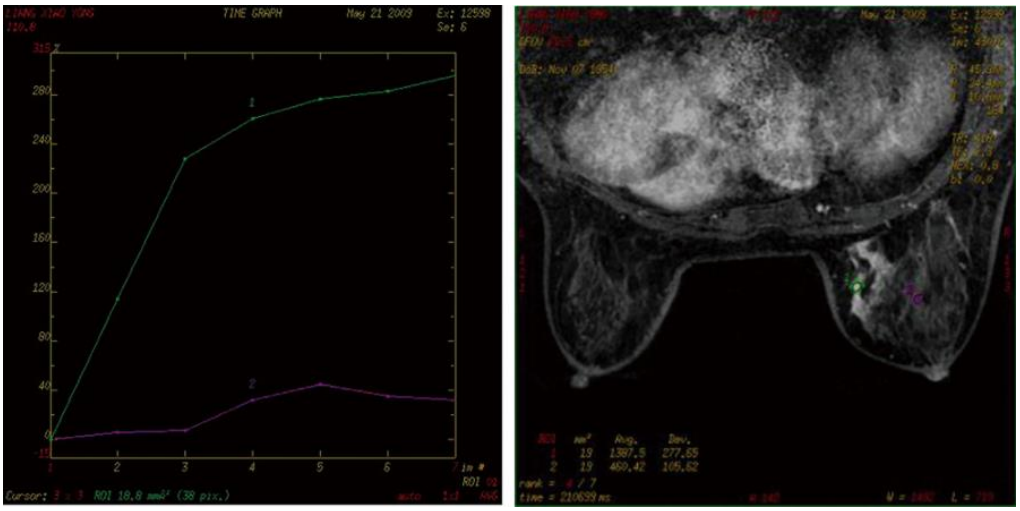


Figure 24(i): Non-mass lesion in the medial quadrant of right breast with a persistent (type 1) curve. An inflow curve can be seen in ROI 1. Breast adenosis has been established pathologically as the lesion. The increased curve of typical breast glands is ROI 2.

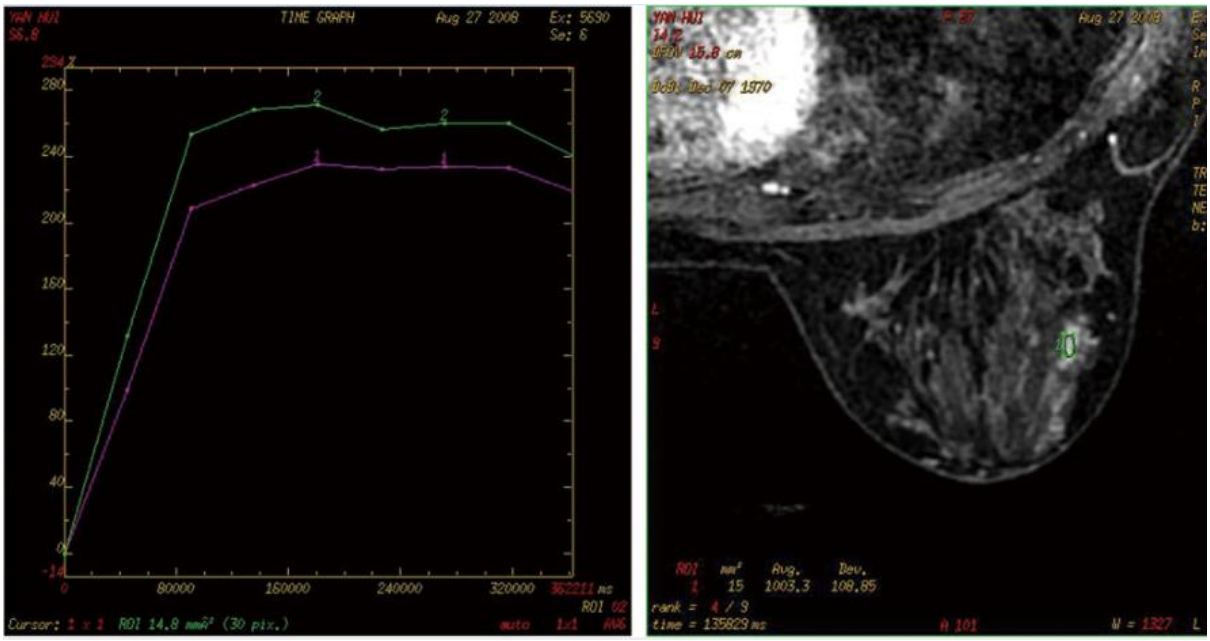


Figure 24(ii): "Plateau (type 2) curve: the curve reaches a peak during the arterial phase 91-180 seconds after contrast medium injection, followed by a flattening during the delayed phase".

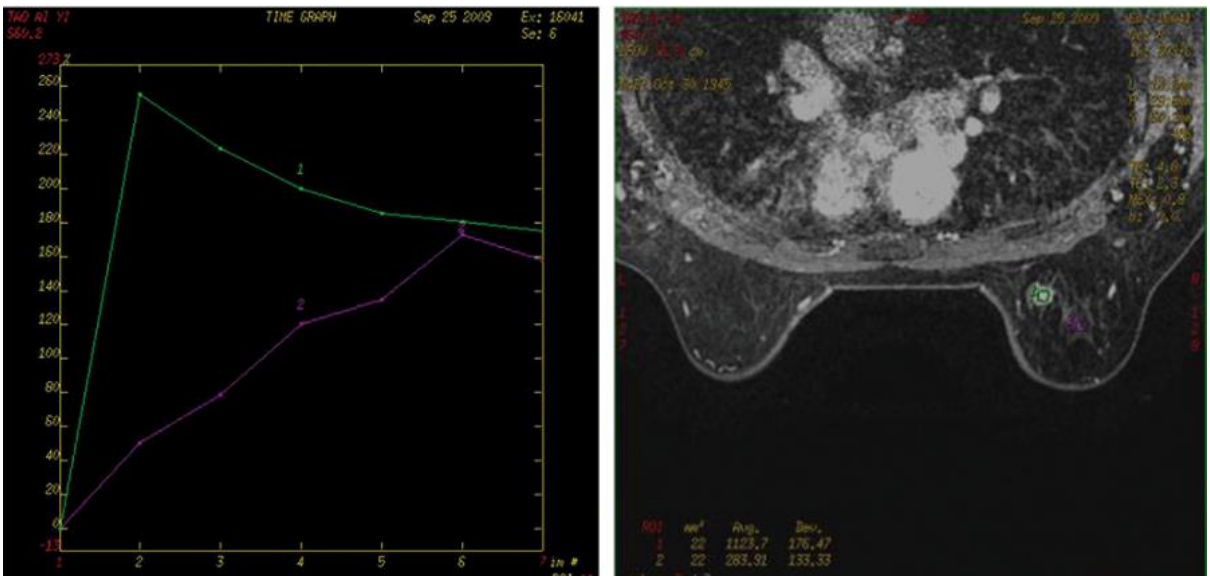


Figure 24(iii): "Washout (type 3) curve: the curve reaches its peak within 90 seconds during the arterial phase, and then begins to wash out".

MR SPECTROSCOPY:

MRS is a non-invasive diagnostic technique that measures chemical information from a specific location within a tissue.[78] MRS can be used to obtain a chemical spectrum from a specific tissue location, which can then be translated into chemical data that can be used in the therapeutic environment. The spectra generated by MRS represent all observable metabolites in the region of interest, along with their individual chemical profiles; the underlying chemical formulae determine the position and characteristics of each metabolite peak, and the area under each metabolite peak represents metabolite concentration. The compounds that are measured, as well as the methods that are commonly employed to measure them, are usually disease-specific. Different chemical compounds, such as phospoethanolamine, choline, phosphocholine, and glycerophosphocholine (the latter three together are simply referred to as total choline (tCho), and non-choline compounds, have been ascribed to the presence of a compound resonance about 3.23 ppm. (Fig 25)**.**[79]

In the diagnostic situation, MRS is now used to distinguish malignant from benign lesions based on higher tCho levels in malignant lesions. Using absolute tCho concentrations,Baek[80] and Sah et al,[81] found a sensitivity of 66 percent and 92 percent, respectively, and a specificity of 76 percent and 75 percent. The mean tCho concentrations in malignant lesions ranged from 2.7 to 5.3 mmol/kg, while benign lesions had mean tCho concentrations of 0.1 to 1.6 mmol/kg.

Enhanced tCho levels have been found in malignant tumours, which have been linked to increased cellular membrane turnover.[82] As a result, tCho has been employed as a diagnostic test in the workup of malignant breast lesions assessed in vivo using either

a qualitative or quantitative technique. In fact, investigations have shown that an aberrant choline and phospholipid metabolism linked to oncogenesis and tumor growth is a metabolic hallmark of cancer.

MR spectroscopy of breast lesions images

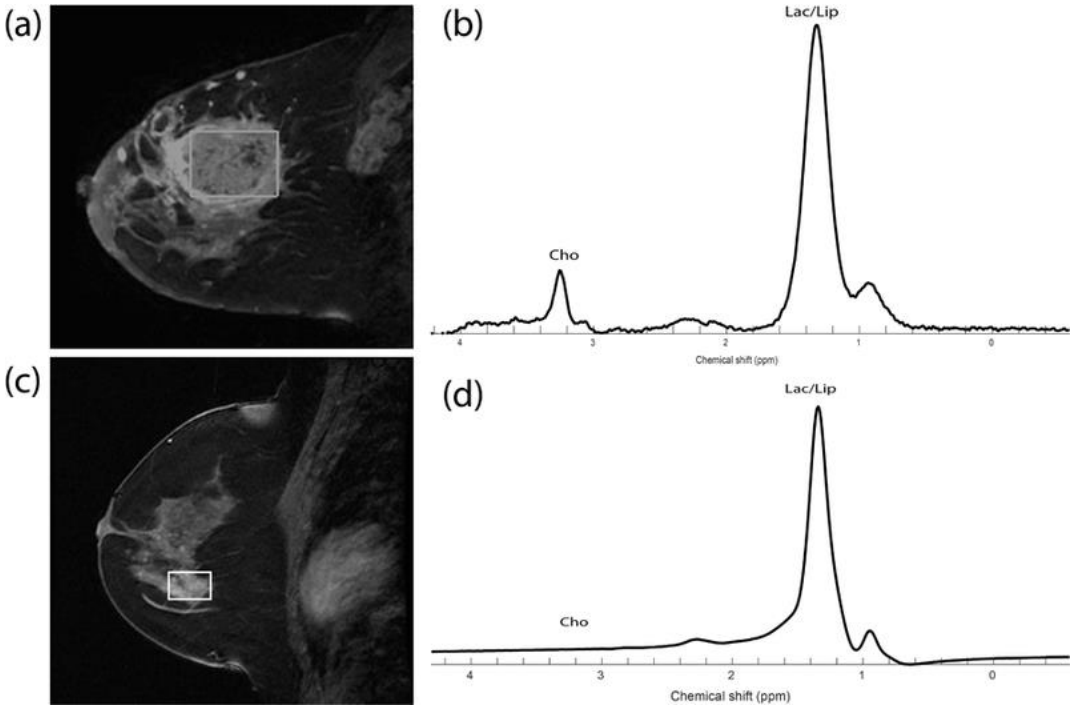


Figure 25: (a-b) Biopsy-proved invasive ductal cancer in left breast of 34-year-old woman. (a) Sagittal T1-weighted MR image immediately after intravenous injection (b) Spectrum demonstrates a choline (Cho) peak at a frequency of 3.2 ppm. This is a true-positive finding. (c–d). Mass in right breast of 59-year-old woman. MR imaging–guided biopsy yielded benign papillomas, fibrocystic changes and stromal fibrosis. (c) Postcontrast sagittal T1-weighted MR image demonstrates an irregular mass. (d) Spectrum did not demonstrate a choline (Cho) peak at a frequency of 3.2 ppm. This is a true-negative finding. Lac = lactate, Lip = lipid.

Ultrafast Breast MRI:

The early entry of contrast into a lesion is documented using ultrafast breast imaging. 60 Malignancies progress more quickly and earlier than benign lesions. [60] As a result, the lesion in the breast visualised initially will increase in size and it is most suspicious. Most malignancies begin to enhance within 10 sec of the contrast entering into the main arteries, but benign lesions take longer (>15 sec) to enhance. A steeper upslope of the first half of the kinetic curve corresponds to faster enhancement.

"Breast Lesion Evaluation at Breast MRI"

'The American College of Radiology Breast Imaging Reporting and Data System' standardises breast MRI reporting (BI-RADS).[85] In clinical indications, MRI sequences and post-processing procedures employed, the amount and type of contrast agent administered are all included in a standard report. Following that, the breast composition and the quantity of background parenchymal enhancement (BPE) should be specified. Higher proportion of it is related with a higher chance of malignant etiology in both metrics. But, the correlation between the amount of BPE, amount of fibroglandular tissue, and breast cancer risk in its future is not completely understood. Higher fraction of the BPE will usually lead to a higher risk of false-positive finding. BI-RADS lexicon is used in characterizing morphologic and kinetic characteristics of discovered pathologies. Focuses (less than 5 mm of enhancement/ too small to define or characterize any further), masses, and non-mass enhancement (NME) are the three types of lesions. The shape, borders, and internal enhancing pattern of masses are also used to classify them. NME area is further classified according on its distribution & pattern of internal enhancement. Initial & delayed phases of enhancement are discussed for both types of lesions to aid in differential diagnosis.[60]

- Approximately 2/3rd to 3/4th of cancers will manifest as mass lesion, including invasive ductal cancers;[84] rest will be visible as area of NME, together with the majority of subjects with DCIS.
- Typical malignant tumours have an uneven size and/or margin, show washout, and will have heterogeneous/ rim enhancing patterns.
- The classic malignant regions of NME usually have a segmental distribution and internal enhancement ring pattern that is either clumped or crowded.
- While most tumours can be identified solely by their morphologic features, assessing small lesion is more difficult.
- Characteristics of NME is less specific than those of masses in general. A focus has 2.9 percent–6% chance of becoming cancerous.[85]

Lexicon criteria for breast lesions on MRI[86]

a. Breast composition

The morphology and enhancement kinetics descriptors in the ACR BI-RADS MRI lexicon are the two major types of descriptors. Lesions can be classified morphologically as focus/foci, mass, and non-mass-like improvements. A focus is a breast lesion that is less than 5 mm in diameter. Mass is a three-dimensional lesion with characteristics such as shape (round, oval, lobulated, irregular), edge (smooth, uneven, spiculated), and interior mass enhancement (homogeneous, heterogeneous, rim enhancement, dark internal septations, enhancing internal septations, and central enhancement). The distribution pattern characterises non-mass-like amplification (focal, linear, ductal, segmental, regional, multiple regions, and diffuse). Internal characteristics (homogeneous, heterogeneous, stippled/punctate,

clumped, reticular/dendritic) and whether the enhancement is symmetric or asymmetric between both breasts might further identify the distribution pattern of non-mass-like enhancement. Other symptoms such as lymphadenopathy and pectoralis muscle invasion have also been described.

Breast composition

The four categories of breast composition (Table 2) are defined by the visually estimated content of fibroglandular tissue (FGT) within the breasts. If the breasts are not of apparently equal amounts of FGT the breast with the most FGT should be used in categorizing breast composition. Although there may be considerable variation in visually estimating breast composition, categorizing based on percentages (and specifically into quartiles) is not recommended. We recognize that quantification of breast FGT volume on MRI may be feasible in the future, but we await publication of robust data before endorsing percentage recommendations. We urge the use of BI-RADS® terminology instead of numbers to classify breast FGT in order to eliminate any possible confusion with the BI-RADS® assessment categories, which are numbered.

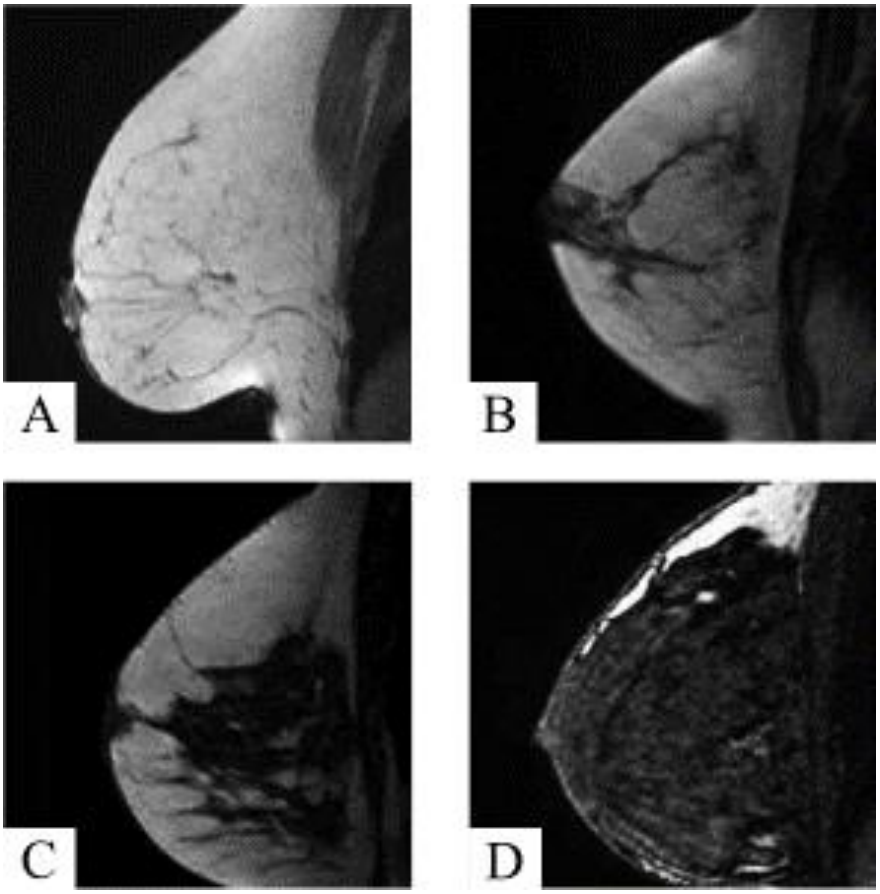


Figure 26: Composition of breast based on the "fibroglandular tissue" (A) Almost entirely fat (B) "Scattered fibroglandular tissue" (C) Heterogeneous fibroglandular (D) Extreme fibroglandular tissue

b. "The amount of background parenchymal enhancement"(BPE)

a. Minimal

b. Mild

c. Moderate

d. Marked

The 4 categories of BPE are defined by the visually estimated augmentation of the FGT of the breast(s). If the breasts are not of an apparently equal amounts of BPE, the breast

with the most BPE must be used to categorize BPE. In the event that treatment has altered BPE in one or both breasts, this can be reported. Although there may be considerable variation in visually estimating BPE, categorizing based on percentages (and specifically into quartiles) is not recommended. Quantification of BPE volume and intensity on MRI may be feasible in the future, but we await publication of robust data on that topic before endorsing percentage recommendations. We recognize that there are variations in BPE distribution and morphology. However, we defer on recommending descriptions of distribution or morphology until additional data are available. Currently, BPE refers to the volume of enhancement & intensity of enhancement. For consistency, BPE should be included for all patients, using the categories mentioned above.

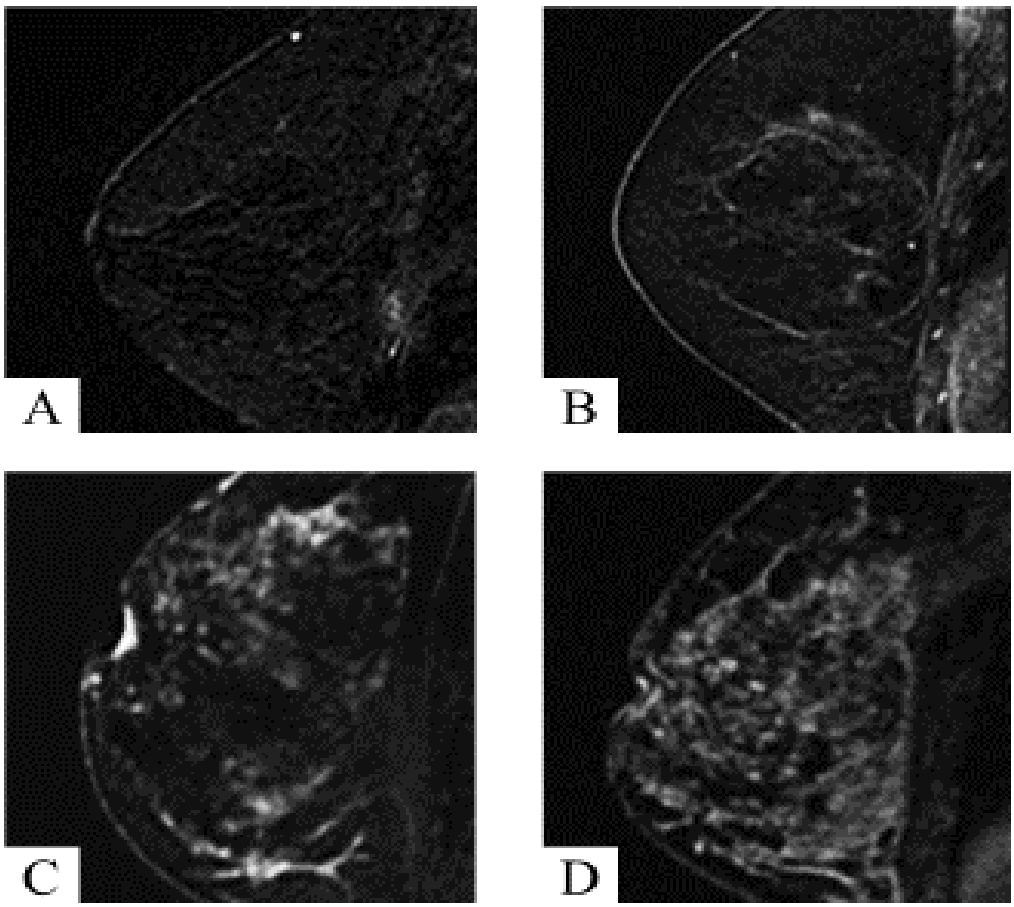


Figure 27: "Amount of background parenchymal enhancement

(A) Minimal (B) Mild (C) Moderate (D) Marked"

c. Whether implants are present

If an implant is present, it should be so stated in the report. Information should include its composition (saline, silicone, or other) and the number of lumens (single or multiple).

d. Clear description of any important findings

Abnormal enhancement is unique and separate from BPE. Its description should indicate the breast in which the abnormal enhancement occurs, the lesion type, and modifiers.

The clinical location of the abnormality as extrapolated from the MRI location (based on clock-face position and quadrant location) should be reported. A more consistent measurement is the distance from the nipple. It is encouraged that distance from the nipple for a lesion be reported, although it should be understood that one should expect some difference in distance from the nipple among the breast imaging modalities.

For bilateral axial examinations, the breasts should be pointing up, following the cross-sectional imaging convention.

The descriptors should include:

a. Size

b. **Location**

i. Right or left

ii. Breast quadrant and clock-face position (or central, retroareolar, and axillary tail descriptors)

iii. Distance from nipple, skin, or chest wall in centimeters (if applicable)

Descriptors for abnormal enhancement:

c. **Findings associated with abnormal enhancement include:**

i. Artifacts that affect interpretation

ii. Focus: a tiny dot of enhancement that does not clearly represent a space-occupying lesion or mass and does not clearly show a mass on precontrast imaging.

iii. Masses: space-occupying lesions, usually spherical or ball-like, may displace or retract surrounding breast tissue.

Descriptors used for describing a breast lesion on MR Mammography is as explained in Table 1. Such as breast composition; background parenchymal enhancement; shape, margin, internal enhancement of the lesion; non-mass enhancement; intramammary lymph node; other associated features and kinetic curve enhancement patterns.

Findings from other techniques, such as DWI or MR spectroscopy, should be reported if clinically important.

Table 1: "BI-RADS and Supplemental Descriptors for the Evaluation of Lesions at Breast MRI" [86]

Breast composition	Amount of fibroglandular tissue A) Almost entirely fat B) Scattered fibroglandular tissue C) Heterogeneous fibroglandular tissue D) Extreme fibroglandular tissue
Background parenchymal enhancement	A) Minimal B) Mild C) Moderate D) Marked
Shape: describes the overall morphology of the enhancement	▪ Oval (includes lobulated) ▪ Round ▪ Irregular
Margin: describes the borders	▪ Circumscribed ▪ Not circumscribed - Irregular - Spiculated
Internal enhancement characteristics	Now under masses: internal enhancement characteristics (A) Homogeneous (B) Heterogeneous enhancement (C) Rim enhancement (D) Dark internal septations

Non-mass enhancement (NME): modifiers describing enhancement patterns with a specific MRI pattern	(a) Distribution - Focal - Linear - Segmental - Regional - Multiple regions - Diffuse (b) Internal enhancement patterns (for all other types) - Homogeneous - Heterogeneous - Clumped - Clustered ring
New finding categories	New finding categories A) Intramammary lymph node B) Skin lesion
Associated features	(a) Nipple retraction (b) Nipple invasion shape (c) Skin retraction (d) Skin thickening (e) Skin invasion (f) Axillary adenopathy (g) Pectoralis muscle invasion (h) Chest wall invasion (i) Architectural distortion

Kinetic curve assessment	Signal intensity/time curve ▪ Initial enhancement phase – depicts the enhancing pattern in the first two minutes, or when the curve begins to shift. - Slow - Medium - Fast ▪ Delayed phase – describes the enhancement pattern after 2 minutes or after the curve starts to change - Persistent - Plateau - Washout

Associated features

These are things that are seen in association with suspicious findings like masses, asymmetries and calcifications.

Associated features play a role in the final assessment.

For instance a BI-RADS 4-mass could get a BI-RADS 5 assessment if seen in association with skin retraction.

Benign breast lesions on MR mammography

They are usually well-defined lesions with smooth margins, no restricted diffusion and are seen to have no enhancement or homogenous enhancement on post-contrast study. They show type 1 kinetic enhancement curve.

Simple cyst is the most common benign lesion of the breast. On X ray mammography both simple cyst and other benign and malignant lesions appear radio-opaque making it difficult to rule out the possibility of malignancy. On MRI they are seen as well-defined round or ovoid homogenously T1 hypointense, T2 hyperintense lesions showing no enhancement on post-contrast study.

Fibroadenomas are the second most common benign lesions of the breast. MRM shows a well-defined T1 hyperintense lesion with smooth margins. They show homogenous enhancement and few of the lesions shows dark internal septations. The lesions do not show choline peak on MR spectroscopy adding extra information in diagnosing the neoplasticity of the lesions.

Few of the benign lesions that can be misdiagnosed on MRM to be malignant are papillomas, adenosis, atypical hyperplasia and benign Phyllodes tumor. It will also be difficult to characterise the lesions when they are too small and hence can be misdiagnosed to be malignant.[87]

Malignant breast lesions on MR mammography

Malignancy is the most frequent indication for MRM. These lesions are commonly known to have irregular or spiculated margins, showing restricted diffusion, heterogeneous or rim enhancement on post-contrast study with type 2 or 3 kinetic enhancement curves. They show choline peak on MR spectroscopy. It also gives information about involvement of the adjacent breast parenchyma in which they show enhancement of the surrounding breast parenchyma on post-contrast study.[87] Mucinous carcinoma is one of the malignant condition which can be misdiagnosed to

be harmless as these lesions show few of the characteristics of benign lesions on MRM like smooth margins, no restricted diffusion and sometimes these lesions do not enhance.

BIRADS[86]

BI-RADS (Breast Imaging-Reporting and Data System) is a risk assessment and quality assurance tool developed by American College of Radiology that provides a widely accepted lexicon and reporting schema for imaging of the breast. It applies to mammography, ultrasound and MRI.

"Category 0: Incomplete — Need Additional Imaging Evaluation"

Use this for a finding that needs additional imaging evaluation. This may be used for a technically unsatisfactory scan or when more information is needed to interpret the scan. A reference for extra imaging evaluation might involve a repeat MRI with satisfactory technique or obtaining information with other imaging modalities (mammographic views, US, etc.).

All effort must be made not to use category 0. The reason for this is that almost always there is enough information on the initial breast MRI examination to provide a management recommendation. In general, the decision to biopsy or not may be made on the basis of the existing MRI study. A situation in which a final assessment of 0 may be helpful is when a finding on MRI is suspicious, but demonstration that the finding is characteristically benign on an additional study would avert biopsy. For example, if a small mass is suspicious on MRI but there is a possibility that it may represent a

benign finding, such as an intramammary lymph node, then a category 0 assessment may be made, with the recommendation for targeted US (that might demonstrate characteristically benign features) to possibly avert biopsy. Another example would be a suspicious finding at MRI that may represent fat necrosis, with the recommendation for diagnostic mammography (that might demonstrate characteristically benign features) to possibly avert biopsy. If a category 0 assessment is rendered at MRI, detailed recommendations should describe the subsequent diagnostic imaging workup and level of suspicion (pertinent in case the additional imaging does not establish benignity).

When additional studies are completed, a final assessment is rendered. If the additional studies are described in the same report, separate paragraphs indicating the pertinent findings from each imaging study will contribute to the final integrated assessment that takes all the findings into consideration.

2. FINAL ASSESSMENT CATEGORIES (ASSESSMENT IS COMPLETE)

Category 1: Negative

- There isn't anything to say about it. This is a routine check-up.
- No abnormal enhancement was found; routine follow-up is advised. There is nothing to comment on. The breasts are symmetric, and no enhancing masses, architectural distortion, or suspicious areas of enhancement are present.

Category 1: includes a normal description of breast composition (amount of FGT) and the degree of BPE. It should be emphasized that BPE is a normal finding, and short-term follow-up is not necessary to assess BPE for stability.

Category 2: Benign

- This is a typical evaluation, same like category 1, but the interpreter decides to convey a benign finding in the breast MRI result.
- The interpreter may describe a benign finding such as: intramammary lymph node, implants, metallic foreign bodies (such as core biopsy and surgical clips), enhancing and non-enhancing fibroadenomas, cysts, old non-enhancing scars or recent scars; postoperative collections, fat-containing lesions (such as oil cysts, lipomas, galactoceles, and hamartomas).
- This is a standard evaluation, similar to category 1, except the interpreter chooses to communicate a benign finding in the breast MRI report.
- There isn't any evidence of malignancy in both the category 1 and 2 examinations. When describing one or more particular benign MRI findings in the report, category 2 should be utilised, whereas category 1 should be used when no such results are provided (even if such findings are present).
- The committee supports a directive for annual follow-up MRI and mammography after either a category 1 or 2 screening MRI assessment, in line with established guidelines for high-risk screening.

Category 3: Probably Benign

A discovery evaluated in this category should have a $\leq 2\%$ likelihood of malignancy, which is higher than the virtually 0% likelihood of malignant etiology of a typically benign result. Although a likely benign finding is unlikely to alter over the recommended duration of imaging monitoring, the interpreting physician likes to establish the finding's stability before prescribing routine breast screening.

Follow-up of Foci

Foci are defined as small dots of enhancement that are unique and stand out from the BPE. They are too small to be accurately assessed with respect to margin or internal enhancement. Indeed, if margin or internal enhancement can be assessed, the finding should be considered a small mass and not a focus. New foci or foci that have increased in size should be viewed with suspicion and carefully evaluated.

Correlation with bright-fluid imaging (T2W imaging or STIR imaging) will be helpful in evaluation of a focus. If a correlate is uniformly very high in signal intensity or if cyst-like features are identified, the focus may be assessed as benign. (Most of these foci represent lymph nodes or small myxomatous fibroadenomas.) However, if the focus does not have a very high signal correlate on bright-fluid imaging, then the focus may or may not be benign. These foci may be followed or biopsied. In certain cases (if the finding is new or increased in size) the focus always should be biopsied. Note that malignant foci may be brighter than the surrounding FGT, although they do not usually appear cyst-like.

Category 4: Suspicious

This category is for results that do not have the conventional appearance of malignancy but are suspicious enough to warrant a biopsy suggestion. A 2 percent risk of malignancy is the ceiling for a category 3 assessment, and a 95 percent likelihood of malignancy is the floor for a category 5 assessment, so category 4 assessments encompass the entire range of likelihood of malignancy in between. As a result, practically all breast interventional procedure suggestions will come from assessments performed using this assessment category. In breast MRI, assessment category 4 is not currently divided into subcategories 4A, 4B, and 4C.

Category 4 is used for the majority of findings prompting breast intervention, which can be performed by percutaneous biopsy, by US or stereotactic guidance, or by MRI guidance for lesions not visible at either US or mammography. As cysts rarely pose a problem in interpretation at MRI, diagnostic aspiration is not commonly performed. In many patients with a suspicious abnormality at MRI, targeted US will identify a corresponding abnormality so that US-guided biopsy can be performed.

"Category 5: Highly Suggestive of Malignancy"

These examinations have a very high probability of malignancy (≥95 percent). In an era when preoperative wire localization was the primary breast interventional procedure, this group was created to cover lesions for which 1-stage surgical therapy was considered without prior biopsy. The current rationale for using category 5 assessment is to identify lesions for which any non-malignant percutaneous tissue diagnosis is considered discordant, resulting in a recommendation for reiteration (frequently surgical) biopsy.

No single MRI descriptor is sufficiently predictive of malignancy to produce the ≥ 95% likelihood required for a category 5 assessment. Just as in mammography and US, an appropriate combination of suspicious findings is needed to justify a category 5 assessment at MRI. It is recommended that category 5 assessments be audited separately to verify a ≥ 95% PPV, thereby validating that the assessment is not being overused.

"Category 6: Known Biopsy-Proven Malignancy"

This category is for tests performed following biopsy evidence of malignancy (imaging after percutaneous biopsy) but before surgical excision, in which no abnormalities other than the known cancer require further assessment. That is, a cancer diagnosis has

already been established, a lesion is depicted at MRI, and this lesion corresponds to the previously biopsied cancer.

A category 6 is not appropriate following successful lumpectomy or mastectomy (margin of resection free of tumor). The rationale for establishing category 6 is exclusion of these cases from auditing, because additional malignancy is frequently found such that auditing these cases would inappropriately skew overall outcomes. In the event that the breast with known cancer has a separate suspicious MRI finding that requires biopsy for diagnosis, the appropriate category 4 or 5 assessment should be rendered, and this would be the overall assessment because it leads to more prompt intervention.

BI-RADS Assessment Categories[86]

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

Table 2: BIRADS classification of breast lesions

Unknown primary

In case of a carcinoma of unknown primary, metastases are diagnosed, but a primary tumor site cannot be identified. These metastases may either present in axillary lymph nodes, supraclavicular lymph nodes, bones, liver, brain or lungs. When the mammogram does not show any abnormality, reports in the literature show, in about 50% of the cases, an abnormal MRI. In case of metastatic axillary lymph nodes, MRI is even able to detect a primary breast tumor in 75–85% of patients. MRI thus can subsequently be used to plan the most appropriate treatment as the size of these lesions on MRI is usually concordant with the size at pathology, thus MRI may prevent gratuitous mastectomies or assign patients with large tumours to neoadjuvant protocols.[59]

MRI anatomy of lymph nodes

Normal intramammary lymph node (IMLN) are usually described in all the imaging modalities as a well-circumscribed mass, normally is smaller than 10 mm along its short axis, which is oval or reniform in shape with hilar fat, it is usually at peripheral location (figure 28(i)). Upper outer quadrant is its most common location (about 70%); but it can be located anywhere within the breast. They will be usually stable over time in comparison to its previous studies. On MRM, IMLN cortex will show high signal intensity at T2WI, post-contrast homogeneous enhancement & they may show suspicious findings on assessment of kinetic curve, such as washout type in delayed phases.[88]

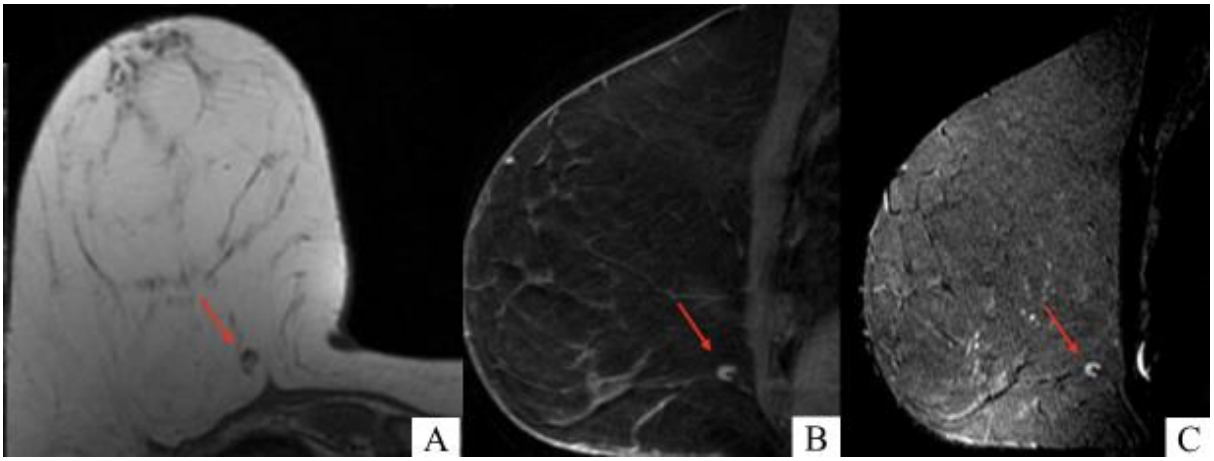


Figure 28(i): Normal IMLN MRI imaging features (A) T_1 weighted images demonstrates a circumscribed reniform mass with hilar fat signal. (B) IMLN cortex showing homogeneous enhancement on T1 post-contrast study and, (C) high signal at T_2 weighted images

Metastatic IMLN

IMLN is a potential site for locoregional spread from an ipsilateral breast carcinoma. The incidence of these nodal metastases ranges between 1 - 34% and they are usually found in same quadrant as that of the primary tumor in nearly half of the cases.

IMLN should be carefully evaluated in patients with carcinoma breast. "Low suspicion" imaging features like diffuse/eccentric cortex thickening ≥ 3 mm, should be used as threshold to biopsy. In contrast, due to low prevalence of malignancy in imaging-detected suspected abnormal IMLN in females without concurrent breast cancer, only "high suspicion" features, like eccentric/diffuse cortex thickening ≥ 5 mm or loss of fatty hilum, must be used for threshold for taking biopsy (Figure 28).[88]

Metastatic IMLN may mimic a synchronous benign mass in a patient with breast cancer; however, its location and proximity of an artery or vein should alert the radiologist to the possibility of a metastatic IMLN (figures below).[89]

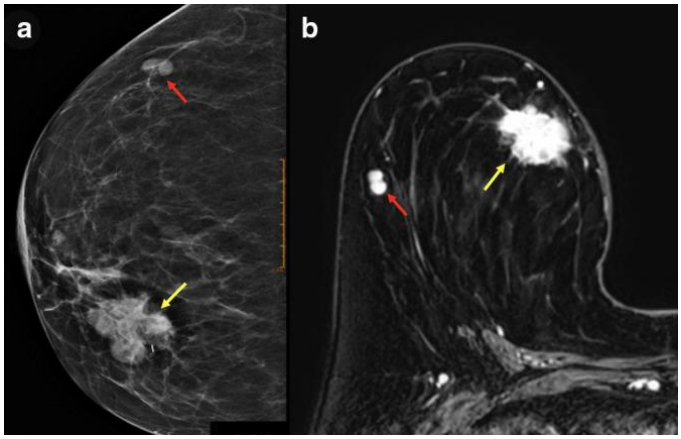


Figure 28(ii): (A) Mammography (craniocaudal view) (B) T1 FS post contrast study of right breast showing invasive breast carcinoma in the inner quadrants of right breast (yellow arrow) associated to an atypical IMLN in the outer quadrants (red arrow), which was confirmed to be metastatic.

Role of MRI in assessing metastasis to axillary lymph nodes

The identification of lymph node metastases has a substantial impact on the staging, therapy, and prognosis of patients with initial breast cancer. Axillary lymph node dissection (ALND) in clinically positive axilla was once upon a gold standard for determining staging and achieving regional control in breast cancer patients.

Preoperative imaging of the axilla and sampling of suspicious lymph nodes are critical tasks for the radiologist. The goal is to evaluate and detect the existence of metastatic disease in non-palpable axillary lymph nodes (low or high tumor load) with a high enough positive predictive value to select patients for ALND up front. Mammography, CT, and MRI can reveal imaging characteristics that indicate axillary lymph node metastatic involvement.[90]

Cortical thickness, loss of fatty hilum, round form, or a long axis to short axis ratio of less than 2 are all MRI characteristics that are suggestive for cancer. Perifocal edema, defined as a region of marked T2 prolongation in the fat around a node, has been demonstrated to have the best positive predictive value (100 percent) for malignancy among predefined quantitative and qualitative descriptors.[90]

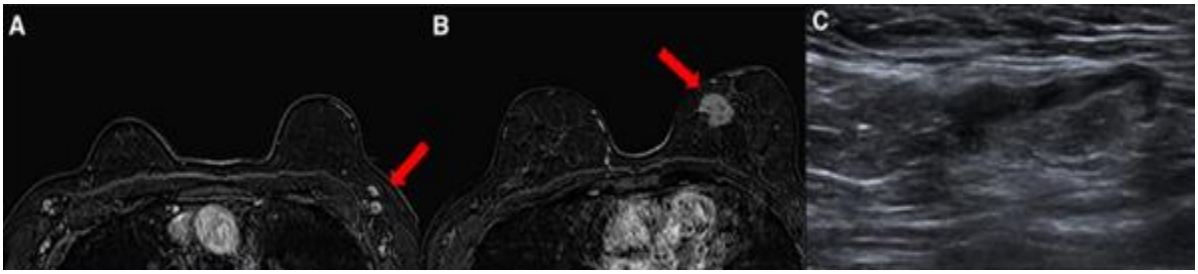


Figure 29: (A) T1 fat-saturated magnetic resonance imaging, (red arrow) showing bilateral enlarged nodes with central fatty hilum (B) Suspicious mass (red arrow) was seen in median-inner quadrant of left breast (C) Ultrasound showed normal appearance of axillary lymph node.

ROLE OF DWI AND ADC VALUES IN ASSESSMENT OF METASTASIS TO AXILLARY LYMPH NODES

In differentiation of malignant and benign lymph nodes, measurement of ADC obtained from DWI added to conventional MR increases specificity and provides more accurate differentiation. In order to obtain an ADC map two imaging with and without diffusion gradient are performed. The value of maximum diffusion is assessed. When there is restriction to diffusion the ADC value decreases.[91]

In most of the studies conducted, patients with diagnosis of invasive breast carcinoma were taken as a study group and by comparing ADC values of axillary lymph nodes, its contribution to differentiation of malignant and benign lymph nodes was

investigated.[92,93] In the study conducted by Kim *et al*[92] The ADC value for metastatic lymph nodes was 0.91 × 10^{-3} mm^2/s and it was 1.27 × 10^{-3} mm^2/s for benign lymph nodes; in the study of Razek *et al*[94] the ADC value for metastatic lymph nodes was 1.08 × 10^{-3} mm^2/s and it was 1.15 × 10^{-3} mm^2/s for benign lymph nodes; in the study of Chung *et al*[93] the ADC value for metastatic lymph nodes was 0.69 × 10^{-3} mm^2/s (Fig 30(i)) and it was 1.04 × 10^{-3} mm^2/s for benign lymph nodes (Fig 30(ii)); and in the study conducted by Hazanzadeh *et al*[95] the value for metastatic lymph nodes was 0.824 × 10^{-3} mm^2/s and it was 1.098 × 10^{-3} mm^2/s for benign lymph nodes. In these studies, the ADC values were significantly lower in metastatic lymph nodes.

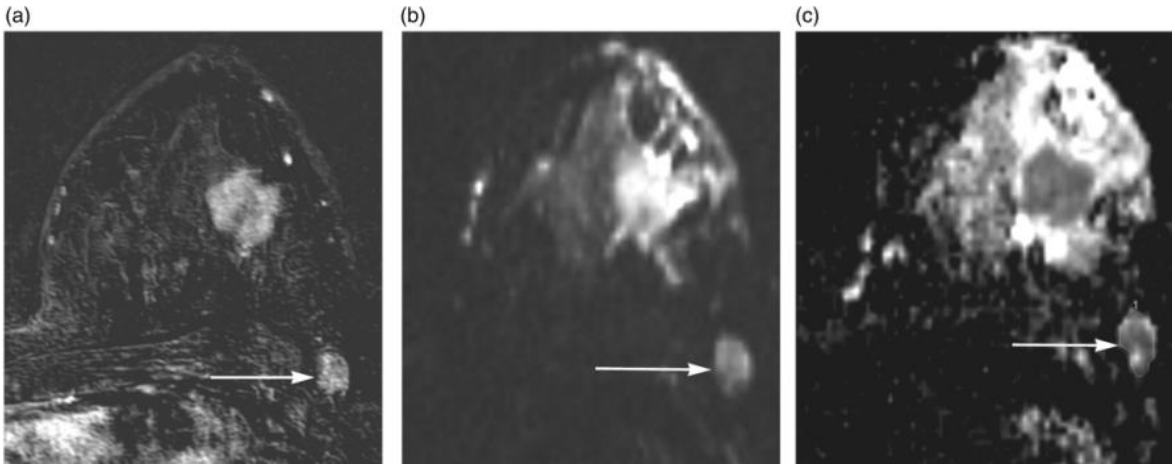


Figure 30(i): 40-year-old woman with a surgically verified metastatic lymph node. (a) Axial early DCE 3D T1-weighted subtraction of the left axilla shows an enhancing lymph node (arrow). (b) Axial single shot-spin-echo planar DWI high signal intensity of the lymph node (arrow). (c) Axial ADC map (b values, 1000 mm^2/s) shows the same lesion with restricted diffusion (arrow), the mean ADC of the lesion was 0.69 x $10^{-3}mm^2/s$.

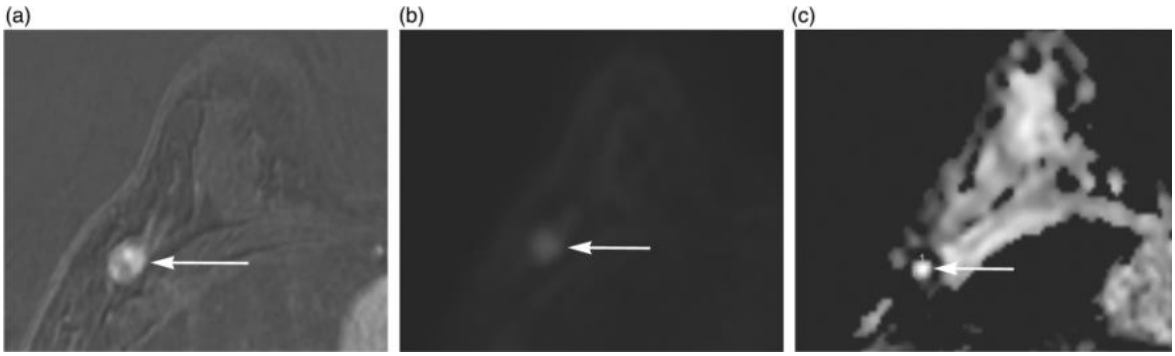


Figure 30(ii): A 57-year-old woman with a surgically verified benign lymph node. (a) Axial early DCE 3D T1-weighted subtraction 3.0-T MR image of the right axilla shows a enhancing lymph node (arrow). (b) Axial single shot-spin-echo planar DWI high signal intensity of the lymph node. (c) Axial ADC map (b value, 1000 mm^2/s) shows unrestricted diffusion (arrow), the mean ADC of the lesion was 1.26 x $10^{-3}mm^2/s$.

"Breast MRI in Clinical Practice"

"Staging in Women with Known Breast Cancer"

A common but contentious indication is preoperative MRM for local staging of the known breast cancer. More illness detection during MRI hasn't translated into better outcomes. As a result, guidelines varied greatly in their recommendations for pre-operative MRM in women with new breast cancer diagnosis.[60]

Females who are diagnosed at a young age, have an initial cancer that manifests as interval cancer, have hormone receptor–negative tumours or thick breasts, and have breast conservation without radiation therapy are all linked to have a higher risk of invasive interval cancers in the postoperative term. Women who have any of these characteristics should get an MRI examination prior to surgery. Furthermore, because performance of the traditional imaging modalities & breast examination clinically is

limited, most guidelines advocate MRM for the staging of invasive lobular malignancies.[110]

***Quality of preoperative diagnosis* —** Approximately 75% of tumours are measured within 1cm of their pathologic size using MRM, with similar levels of over- and underestimation. For invasive lobular carcinomas, the benefit of using MRI in estimating tumour size is quite substantial. Similarly, MRI's depiction of DCIS related to invasive tumours is far superior to mammography's, with the latter missing more than half of all lesions while MRI's sensitivity for big DCIS components approaches 100%.[96] Also, MRM is more accurate in depicting DCIS (pure type) lesions, especially high-grade lesions; nevertheless, minor DCIS lesions found on mammography due to calcifications may be occult on MRI.[96]

"Using MRI findings in surgery"

MRI-guided localization and/or MRI-guided bracketing of extent of the bigger tumour or DCIS, aids surgeons in making use of the data provided by MRI. Corroboration definitely points to decrease in the rate of re-excisions without an increase in number of mastectomies in lobular malignancies.[97]

Detection of breast cancer on contralateral side—

MRM reveals covert contralateral illness in nearly 5.5–9.3% of patients with known breast cancer on ipsilateral side; 37–48% of these findings were malignant (2–4%). If the tumors found are tiny (< 1 cm), and roughly one third of them will be DCIS. Detection of contralateral cancer is essentially a sort of high-risk screening, with a cancer identification that exceeds that of BRCA mutation carriers. No factors, such as

breast density, have been linked to the likelihood of identifying contralateral cancer to yet.[98]

A) Cyto-Histopathology:

Fine Needle Aspiration Cytology (FNAC)/ Core Biopsy:

Two types of needle biopsies are used to diagnose breast cancer: fine-needle aspiration cytology (FNAC) and core needle biopsy (CNB).[48] FNAC is the least invasive, can be conducted rapidly and easily, and quick smears can be used to assess the adequacy of the tissue sample. CNB removes a small cylinder of tissue (a core) about the size of a grain of rice. About three to five cores are usually removed, although more may be taken. The core tissue samples are then analysed for malignant cells.[99]

Breast biopsy/ Resected specimen of breast:

The only definitive method for diagnosing breast cancer is with a breast biopsy. To increase diagnostic accuracy and eliminate as many false-negative results as possible, clinical breast examination, breast imaging, and biopsy are performed simultaneously (triple test).

Immunohistochemistry (IHC): IHC is a technique that uses antibodies as a tool to detect protein expression. Monoclonal or polyclonal antibodies complementary to the antigen of interest are labelled with a marker (either visible by light microscopy or fluorescence), allowing detection of the antibodies bound to regions of protein expression in a tissue sample. Diagnostic IHC is widely used, for example, to detect tissue markers associated with specific cancer. The most common immunohistochemical breast carcinoma prognostic and therapeutic markers used

include ER, HER2, Ki-67, PR, and p53. In addition markers of angiogenesis and apoptosis are used.[100]

CLINICAL STUDIES:

A retrospective study by Naranjo I, et al 2021,[101] aimed to evaluate radiomics analysis coupled with machine learning (ML) of DCE and DWI radiomics models separately and combined as multiparametric MRI for improved breast cancer detection. In 93 patients (mean age: 49 years ± 12 years; 100%women), there were 104 lesions (mean size: 22.8 mm; range: 7–99 mm), 46 malignant and 58 benign. Radiomics features were calculated. Subsequently, the five most significant features were fitted into multivariable modelling to produce a robust ML model for discriminating between malignant and benign lesions. A medium Gaussian support vector machine (SVM) model with five-fold cross validation was developed for each modality. A model based on DWI-extracted features achieved an AUC of 0.79 (95% CI: 0.70–0.88), whereas a model based on DCE-extracted features yielded an AUC of 0.83 (95%CI: 0.75–0.91). A multiparametric radiomics model combining DCE- and DWI-extracted features showed the best AUC (0.85; 95% CI: 0.77–0.92) and diagnostic accuracy (81.7%; 95% CI: 73.0–88.6). In conclusion, radiomics analysis coupled with ML of multiparametric MRI allows an improved evaluation of suspicious enhancing breast tumors recommended for biopsy on clinical breast MRI, facilitating accurate breast cancer diagnosis while reducing unnecessary benign breast biopsies.

A retrospective study by Choi B, et al 2021,[102] aimed to evaluate the association between LVI and pre-operative features of DCE-MRI and DWI in node-negative invasive breast cancer. Data were collected retrospectively from 132 cases who had undergone pre-operative MRI and had invasive breast carcinoma confirmed on the last

surgical pathology report. Pathologic tumor size, mass margin, internal enhancement pattern, kinetic enhancement curve, DWI rim sign, and the difference between maximum and minimum ADC were significantly in correlation with LVI ($p < 0.05$). This study suggested that DCE-MRI with DWI would assist in predicting LVI status in node-negative invasive breast cancer patients.

A meta-analysis by Wielema M, et al 2020,[103] aimed to assess the impact of ADC in the discrimination of malignant from benign breast lesions in DWI in terms of specificity, sensitivity and area under the curve (AUC). A 61 studies, with 65 study subsets with benign or malignant primary breast lesions (6291 lesions) were assessed. Pooled sensitivity, specificity and AUC were calculated. None of the breast tissue selection (BTTS) methodologies outperformed in differentiating benign from malignant breast lesions. The high heterogeneity of ADC data acquisition demands further standardization, such as DWI acquisition parameters and tumor tissue selection to substantially increase the reliability of DWI of the breast.

Kamal, R et al 2020,[104] aimed was to assess the feasibility of replacing DCE-MRI by Contrast enhanced mammography (CEM) in the assessment of sonomammographic indeterminate lesions (BIRADS 3 and 4). The study included 82 patients with 171 breast lesions. CEM and DCE-MRI was performed in all the subjects. DCE-MRI sensitivity and NPV were significantly higher than those of CEM. The overall accuracy of MRI was better than that of CEM; however, no statistically significant difference could be detected. CEM and DC-MRI improved the characterization of breast lesions. CEM showed slightly lower sensitivity and accuracy compared to MRI; however, because of being relatively easy, available, cheap, and acceptable by women, CEM can

replace DC-MRI as a problem-solving tool in the characterization of indeterminate breast lesions.

A cross-sectional study by Hardas V, et al 2019,[105] aimed to assess whether glandular tissue-normalised Apparent Diffusion Coefficient (nADC) could further improve the diagnostic accuracy of MRI, in characterising benign versus malignant breast masses. This study included 39 patients with 51 focal breast masses. These patients underwent CE-MRI and DWI, on a 3T MR system. Absolute ADC values and glandular tissue-normalised ADC values were measured in breast masses satisfying the inclusion criteria. Twenty- six (51%) of the 51 breast masses were benign and 25 (49%) were malignant. The mean nADC value (0.619+0.21×10−3 mm2 /sec) obtained from malignant breast masses was significantly lower than the mean nADC value (0.98+0.26×10−3 mm2 /sec) measured from benign breast mass ($p<0.05$). Adding, nADC to CE-MRI, increased the specificity of MRM in differentiating malignant from benign breast masses, from 88.5% to 92.3% and improved its kappa score of agreement with HPE or follow-up results, from 0.883 to 0.960. Receiver Operating Characteristic (ROC) curve analysis indicated that AUC for nADC (0.870) was higher than the AUC for absolute ADC (0.809). Quantitative DWI with glandular tissue-normalised ADC mapping at 3T, improves the diagnostic performance of MRM in characterising breast masses; especially in a subset of masses with borderline CE-MRI findings and absolute ADC.

Tezcan, Ş et al, 2019,[106] aimed to evaluate relationship between ADC values with pathologic prognostic factors in breast carcinoma (BC). A total of 83 patients were enrolled in this study. There was no significant difference between ADC and prognostic

factors, including age, tumor size, ER, HER2 and histologic type. The PR- positive tumors (p=0.03) and axillary lymph node involvement (p=0.000) showed a significant association with lower ADC values. The ADC values were significantly lower in high-grade tumors than low-grade tumors (p=0.000). ROC analysis showed an optimal ADC threshold of 0.66 (×10-3 mm2/s) for differentiating low-grade tumors from high-grade tumors (sensitivity, 85.5%; specificity, 81%; area under curve, 0.90). Conclusion: The lower ADC values of BC were significantly associated with positive expression of PR, LN positivity and high-grade tumor.

Hammad A, et al 2015,[107] aimed the role of conventional and functional MRM in evaluation and diagnosis of breast mass. The study had included 34 female patients who had presented breast mass by clinically and/or who had abnormal sonomammography findings. MRM results were correlated with pathological findings for all cases. They were classified pathologically into 21 patients with benign lesions (61.8% - 21/34), 10 patients with malignant lesions (29.4%) and remaining 3 with high-risk lesion (8.8%). Type III intensity kinetic curve was most depicted type amongst the malignant lesions (60%), while type Ia curve was the most depicted type among benign lesions (61.8%). Out of 25 subjects without RD; 19 of them had benign lesions and out of 9 with RD; 6 patients showed malignant lesion. Out of 17 with choline trace; 9 were malignant, 5 were benign and 3 were with high risk lesion. DCE-MRM had higher sensitivity for carcinoma breast detection and more accurate in the delineation of disease extension. The MRM with three parameters (DCE-MRI, DWI, and MRS) increased the diagnostic accuracy of carcinoma breast.

A retrospective study by Raikhlin A, et al, 2015,[108] aimed to evaluate the diagnostic performance of screening breast MRI. This study identified 650 eligible high-risk women who underwent screening breast MRI and mammography between July 2011 and January 2013. Results of 806 screening rounds (comprising both MRI and mammography) were reviewed. Malignancy was diagnosed in 13 patients. Of the 13 cancers, 12 (92.3%) were detected by MRI and four (30.8%) by mammography. In nine of these patients, the cancer was diagnosed by MRI only, resulting in an incremental cancer detection rate of 10 cancers per 1000 women screened. MRI screening had significantly higher sensitivity than mammography (92.3% vs 30.8%) but lower specificity (85.9% vs 96.8%). MRI also resulted in a higher call back rate for a 6-month follow-up study (BI-RADS category 3 assessment) than mammography (119 [14.8%] vs 13 [1.6%]) and more image-guided biopsies than mammography (95 [11.8%] vs 19 [2.4%]). MRI is a useful adjunct to mammography for screening in high-risk women, resulting in a significantly higher rate of cancer detection.

MATERIALS AND METHODS

Source of data

The study was conducted over a period of eighteen months from January 2020 to June 2021 on 41 patients with 54 clinically palpable breast lumps and/or who underwent sonomammography or X-ray mammography at the Department of Radiodiagnosis at R. L. Jalappa Hospital and Research Center attached to SDUMC, Kolar. Prior informed consent was taken from the patients for their willingness to participate in the study.

Study design: Prospective observational study

Sample size: A sample size of 41 patients with 54 masses were selected using n masters' software.

Sample size estimated by using the specificity of MR Mammography (85 %) on benign and malignant breast masses detected by MR mammography according to a study: The Role of MR Mammography in Differentiating Benign from Malignant in Suspicious Breast Masses, conducted by Balasubramanian P[1] using the formula

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

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

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

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

p = 85 or 0.85

q = 15 or 0.15

d = 12% or 0.12

Using the above values at 95% Confidence level a sample size of 34 subjects with breast mass will be included in the study and evaluated for different stages of carcinoma. Considering 10% Nonresponse a sample size of $34 + 3.4 \approx 38$ subjects were planned to be included in the study. A total of 41 patients with 54 breast masses were included in the final analysis. The patients were included in the study if they fulfilled the inclusion/exclusion criteria listed below:

Inclusion criteria:

- Patients with breast lump.
- Patients with inconclusive mammography and sonomammography findings.

Exclusion criteria:

- Patients undergoing chemotherapy or radiotherapy for carcinoma breast.
- Recurrent breast carcinoma.
- Patients who have undergone FNAC or biopsy within 3 weeks.

Method of collection of data:

Baseline data of the patients participating in the study were recorded. Individuals having clinically palpable breast mass or diagnosed on ultrasonography and/or X-ray mammography. MR Mammography was performed on 1.5 Tesla, 18 channel, MR Scanner (Siemens® Magnetom Avanto®) using dedicated double breast coil. To avoid motion artefacts while performing MR mammography, cushions of varying sizes were used to hold breasts firmly. The patients were made to lie down in prone position and following sequences was performed:

- T1 FS and T2 axial images.

- DWI at 50, 400 and 800 s/mm^2 b values with corresponding ADC values.
- Dynamic contrast enhancement study & kinetic curves.
- MR Spectroscopy

Morphological changes seen on MR mammography were interpreted based on BIRADS lexicon, which included the imaging characteristics; DWI along with its ADC values and MR spectroscopy findings were assessed. DWI and ADC sequences were also used in assessing enlarged axillary lymph nodes and their corresponding ADC values were calculated.

Initially, axial T1 sequences is performed, after 2 minutes of start of study, 10 ml of Gadolinium MRI contrast is injected to the patient, followed by 20 ml of saline is injected. 3 separate T1 FS contrast enhancement sequences are of equal number of sections as that of plain study are acquired within a total time of 5-7 minutes. Enhancement of the lesion after contrast administration is assessed. Kinetic curves are derived and their pattern of enhancement on initial and late phases are assessed.

Next DWI sequences at 50, 400 and 800 s/mm^2 b values are taken followed by its ADC sequence is acquired. Both the sequences; i.e. DWI at 800 s/mm^2 b value and ADC sequence are compared to assess the presence or absence of restricted diffusion within the breast mass. For derived ADC values, in case of malignant lesions, multiple oval shaped region of interest (ROI) each measuring ~25 mm^2 are drawn over the areas of restricted diffusion. Value of each ROI is measured and mean of all the ROIs is taken as the final ADC value of the breast mass. In case of benign breast mass, multiple ROIs each measuring ~25 mm^2 are drawn throughout the lesion and the lesions show no restricted diffusion. Mean of all the ROIs are taken as final ADC value for benign

lesion. Proton MR Spectroscopy is derived over the lesion and presence or absence of the choline peak is assessed and tabulated.

Axilla of all the patients was assessed for any enlarged lymph nodes. These lymph nodes were compared on DWI sequence of 800 s/mm^2 b value with that of ADC sequence. Restricted diffusion of these lymph nodes were assessed and for calculating its corresponding ADC value a single oval shaped ROI which almost includes the entire axillary lymph node is drawn and the value derived is taken as the ADC value of the lymph node.

Figure 31: 1.5 Tesla, 18 channel, MR Scanner (Siemens® Magnetom Avanto®)

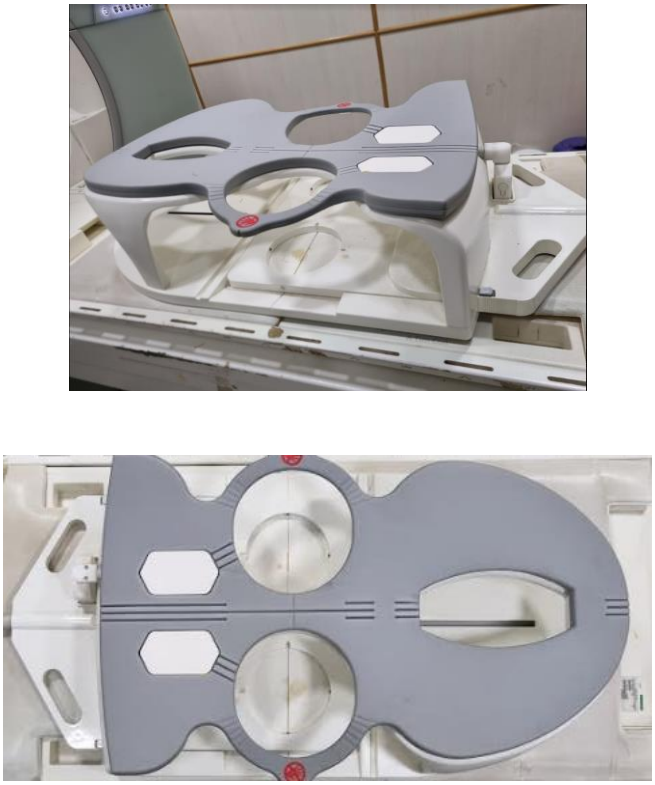


Figure 32: Dedicated double breast coil

Data analysis

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

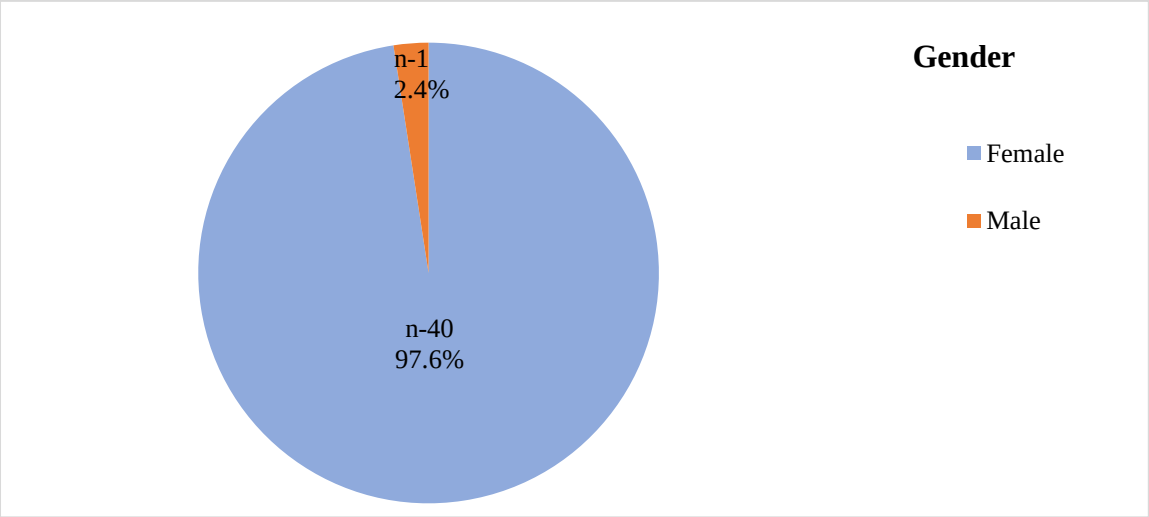
RESULTS

In the study 54 breast lesions from 41 patients were included, amongst the study population, 40 (97.6%) participants were female and only 1 (2.44%) participant was male patient (Figure 33; Table 3).

Table 3: Descriptive analysis of gender wise distribution in the study population (N=41)

Gender	Frequency	Percentages
Female	40	97.56%
Male	1	2.44%

Figure 33: Pie chart of gender wise distribution in the study population (N=41)



Total number of patients – 41 were included in the final analysis (number of lesions assessed – 54)

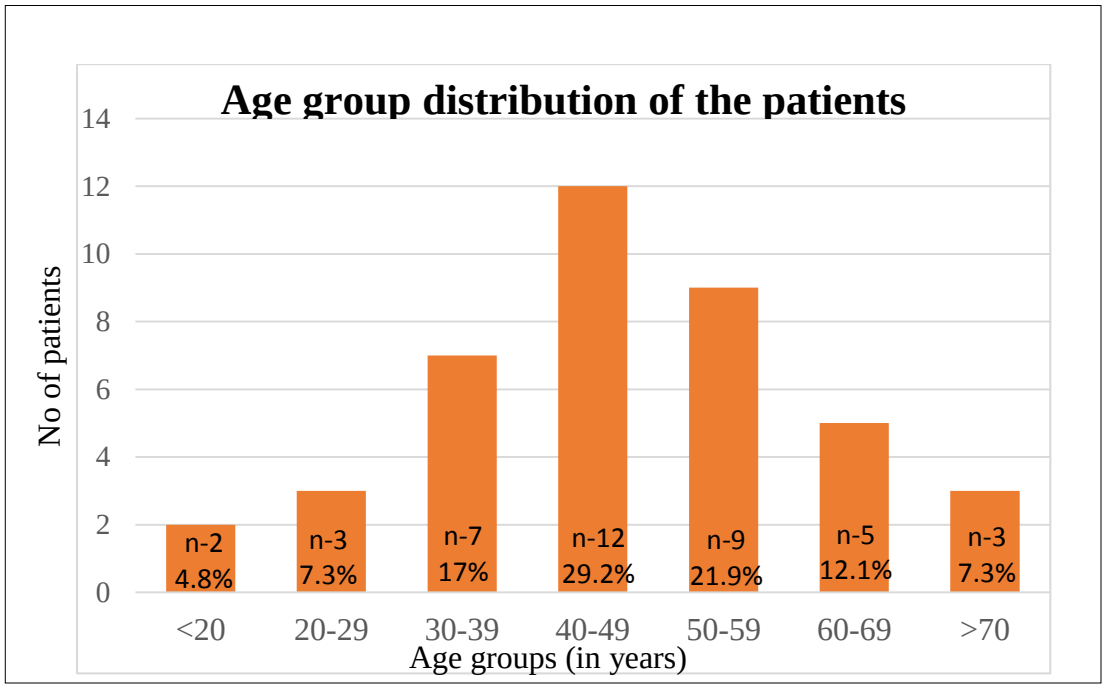
Age group distribution

Commonest age group in our study was 40-59 years (n = 14; 34.1%), followed by 50-59 years (n = 13; 31.7%). Patients with age group of > 70 years and above were 4.8% (n = 2) and there was only one patient with age < 20 years and below constituting 2.4% (n = 1) (Figure 34; Table 4). The mean age of the patients was 47.1 ± 14.7 years (mean ± SD) with range of 16 to 75 years in the study population.

Table 4. Age Group Distribution

Age group (in years)	Number of patients	Percentages
< 20	2	4.8%
20-29	3	7.3%
30-39	7	17.0%
40-49	12	29.2%
50-59	9	21.9%
60-69	5	12.1%
> 70	3	7.3%

Figure 34: Age group distribution



Laterality of the breast lesions present in the patients

Table 5: Descriptive analysis of no. of lesions in the patient totally on both sides in the study population (N=41)

No. of lesions in the patient totally on both sides	Frequency	Percentages
1	32	78.05%
2	6	14.63%
3	2	4.88%
4	1	2.44%

Out of 41 participants, majority of the patients were reported to have only one breast lesion 32 (78.05%); 6 patients (14.63%) were reported to have 2 breast lesions 2; 2 participants had (4.88%) 3 breast lesions in total and only 1 (2.44%) patients was reported to have 4 lesions in total including both sides (Table 5).

Assessment of the breast tissue and breast lesions based on ACR-BIRADS MRI LEXICON

Breast tissue was assessed for fibroglandular tissue on plain study and the amount of background parenchymal enhancement (BPE) on post-contrast study

1. **Breast tissue- Fibroglandular tissue-**

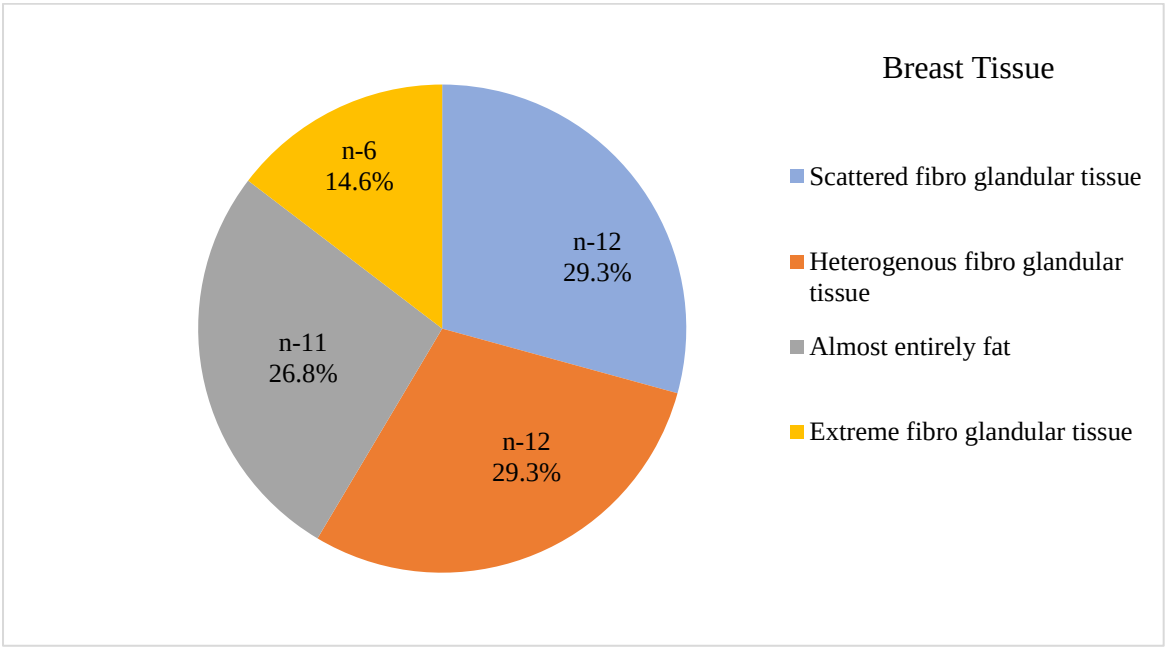
Among the study population, of the 4 categories of breast composition 12 (29.27%) were reported to have scattered fibroglandular tissue and heterogenous fibroglandular tissue for each respectively; 11 (26.83%) patients were reported to have almost entirely fat content within the breast with minimal or absent fibroglandular

tissue and rest 6 (14.63%) of them were reported to have breast with extreme fibroglandular tissue within (Table 6 & Figure 35).

Table 6: Descriptive analysis of type of breast tissue in the study population (N=41)

Breast Tissue	Frequency	Percentages
Almost entirely fat	11	26.83%
Scattered fibroglandular tissue	12	29.27%
Heterogenous fibroglandular tissue	12	29.27%
Extreme fibroglandular tissue	6	14.63%

Figure 35: Pie chart of type of breast tissue in the study population (N=41)



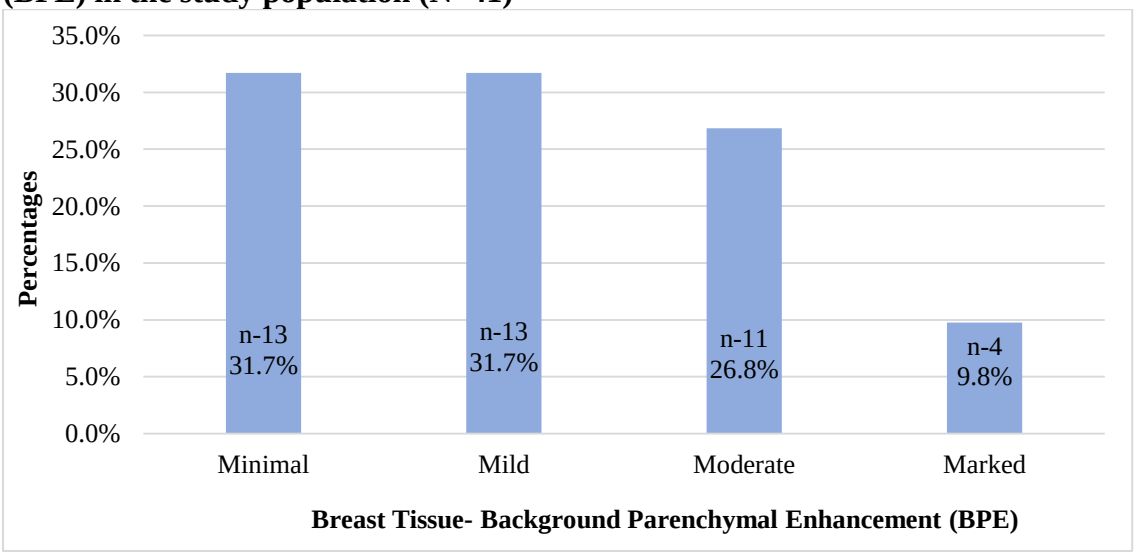
2. **Breast tissue- Background parenchymal enhancement (BPE)**

Based on the amount of enhancement of the fibroglandular tissue of breast after contrast administration BPE is broadly divided into 4 categories as minimal, mild, moderate or marked enhancement of the breast tissue. We observed 13 (31.71%) participants to have minimal BPE and mild BPE for each respectively, 11 (26.83%) were reported as having moderate BPE and only 4 (9.76%) patients had marked BPE (Table 7 & Figure 36).

Table 7: Descriptive analysis of breast tissue- background parenchymal enhancement (BPE) in the study population (N=41)

Breast Tissue- Background Parenchymal Enhancement (BPE)	Frequency	Percentages
Minimal	13	31.71%
Mild	13	31.71%
Moderate	11	26.83%
Marked	4	9.76%

Figure 36: Bar chart of breast tissue- background parenchymal enhancement (BPE) in the study population (N=41)



Descriptors – modifiers describing a mass:

Following identification of the breast mass on MRM, shape, margins, enhancement pattern and kinetic curves of the breast masses were assessed.

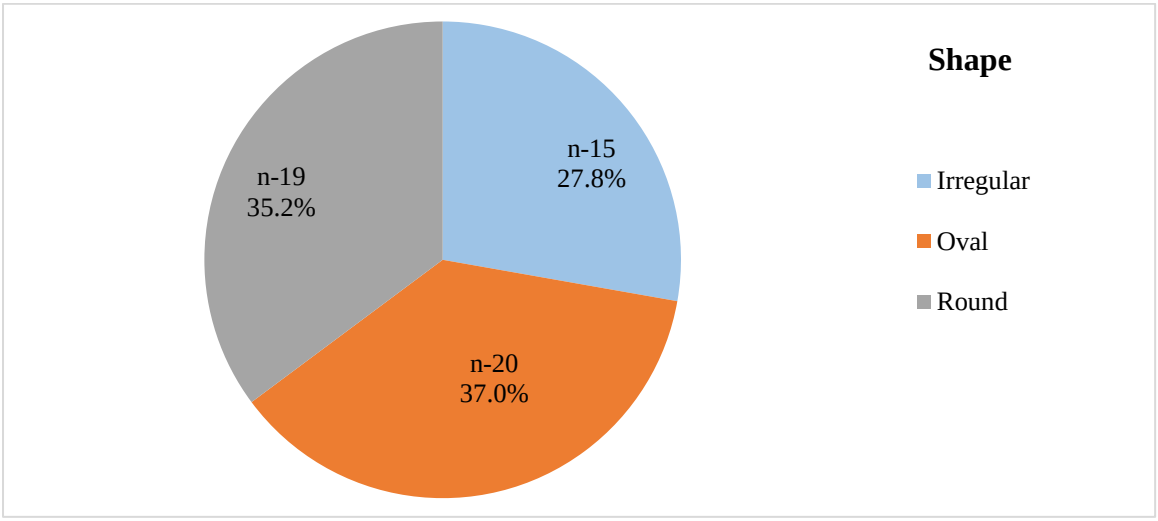
1. **Shape of the lesion:**

As per morphology of the enhancement breast lesion studied, out of all the 54 lesions assessed, 15 (27.78%) lesions had irregular shape, 20 (37.04%) were oval in shape and 19 (35.19%) lesions were round in shape (Table 8 & Figure 37).

Table 8: Descriptive analysis of shape: describes the overall morphology of the enhancement in the lesions studied (N=54)

Shape: describes the overall morphology of the enhancement	Frequency	Percentages
Irregular	15	27.78%
Oval	20	37.04%
Round	19	35.19%

Figure 37: Pie chart of shape: describes the overall morphology of the enhancement in the lesions studied (N=54)



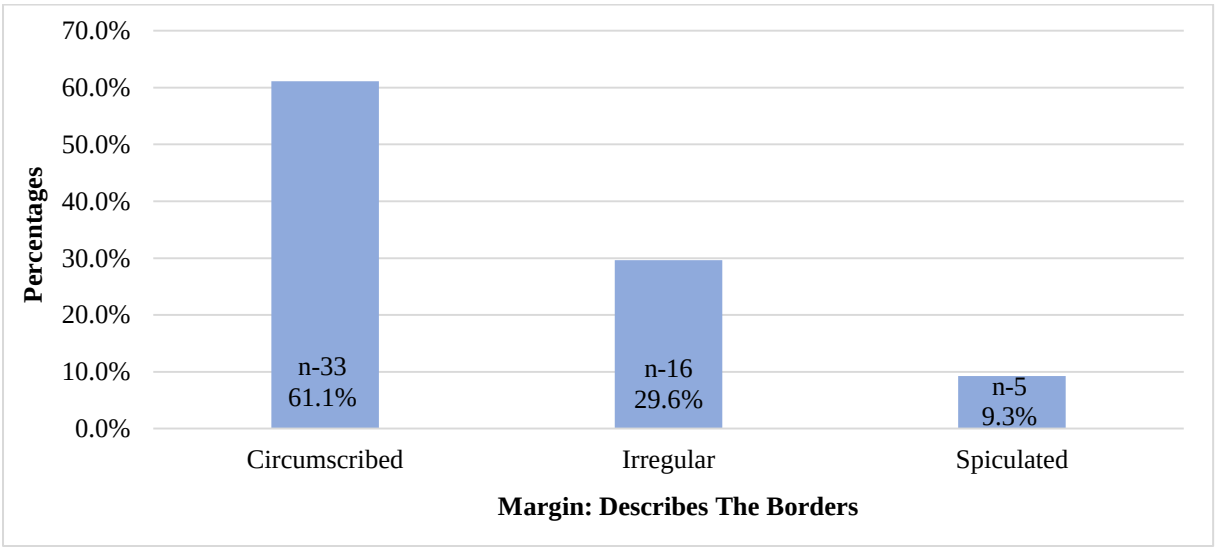
2. Margins of the lesion:

Margins of the lesions describe the border and extent of the lesion. The lesions were broadly divided as circumscribed or not circumscribed. The lesions which were not circumscribed were subdivided into two categories as lesions having irregular margins or spiculated margins. As we observed, most of them, i.e. 33 lesions (61.11%) were circumscribed. 21 lesions had margins which were not circumscribed, out of which 16 (29.63%) lesions had irregular margins and rest 5 (9.26%) were found to have spiculated borders (Table 9 & Figure 38).

Table 9: Descriptive analysis of margin: describes the borders in the lesions studied (N=54)

Margin: describes the borders	Frequency	Percentages
Circumscribed	33	61.11%
Irregular	16	29.63%
Spiculated	5	9.26%

Figure 38: Bar chart of margin: describes the borders in the lesions studied (N=54)



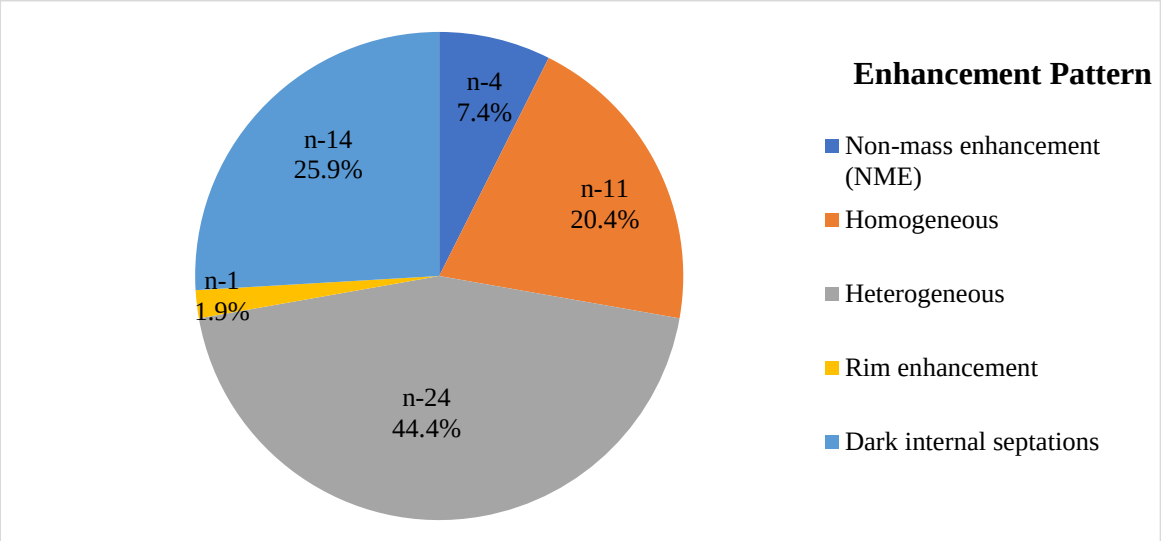
3. Internal enhancement characteristics:

Lesions were identified to enhancement either as a mass or if they show non-mass like enhancement. All the masses were observed to have either of the 4 types of enhancement- homogenous, heterogenous, rim enhancement or enhancement with dark internal septations. In our study, majority of the mass [24 (44.44%)] showed heterogeneous type of enhancement, followed by enhancement with dark internal septations was noted in 14 (25.93%) mass and homogeneous type of enhancement was seen in 11 (20.37%) lesions. 4 of the lesions showed non-mass like enhancement constituting 7.4% of the total study population (Table 10 & Figure 39).

Table 10: Descriptive analysis of enhancement pattern in the lesions studied (N=54)

Enhancement Pattern	Frequency	Percentages
Non-mass enhancement (NME)	4	7.41%
Homogeneous	11	20.37%
Heterogeneous	24	44.44%
Rim enhancement	1	1.85%
Dark internal septations	14	25.93%

Figure 39: Pie chart of enhancement pattern in the lesions studied (N=54)



Kinetic curve assessment

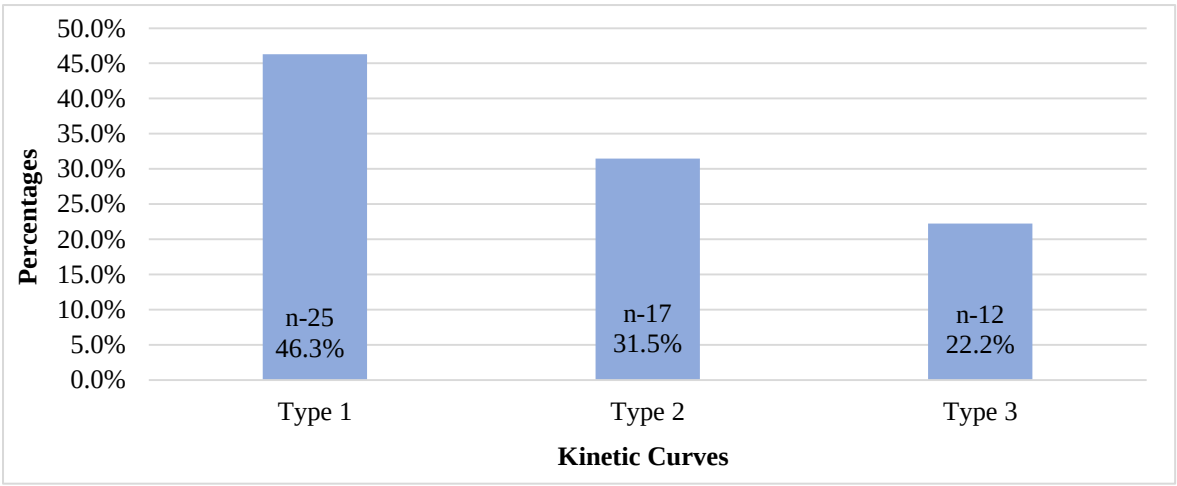
Enhancement curves of the breast lesions following contrast administration was divided into type I, II or III following assessment of the signal intensity/ time curve on both initial and delayed phase.

As per lesions studied, 25 (46.30%) were found to show type 1 enhancement curve, 17 (31.48%) of them had type 2 and 12 (22.22%) had type 3 Kinetic Curves (Table 11 & Figure 40).

Table 11: Descriptive analysis of kinetic curves in the lesions studied (N=54)

Kinetic Curves	Frequency	Percentages
Type 1	25	46.30%
Type 2	17	31.48%
Type 3	12	22.22%

Figure 40: Bar chart of kinetic curves in the lesions studied (N=54)



Diffusion weighted imaging (DWI) and Apparent diffusion coefficient (ADC)

All the lesions were assessed for restricted of diffusion if present or not by comparing DWI sequence at 800s/mm^2 with its corresponding ADC sequence. 29 (53.7%) out of the 54 lesions showed restricted diffusion and all were diagnosed to be malignant mass on histopathology. 25 46.3% lesions showed no restricted diffusion. 20 of them were confirmed to be benign lesions but 5 lesions on HPE were diagnosed to be malignant (Table 12).

Table 12: Descriptive analysis of DWI in the lesions studied (N=54)

Restricted diffusion on DWI	Frequency	Percentages
Present	29	53.7%
Absent	25	46.3%

Apparent diffusion coefficient of all the breast masses were assessed. 30 (55.56%) lesions had ADC value < 1.3 × 10^{-3} mm^2/s and 24 (44.44%) had ADC value >1.3 × 10^{-3} mm^2/s (Table 13).

Table 13: Descriptive analysis of ADC values in the lesions studied (N=54)

ADC values (× 10^{-3} mm^2/s)	Frequency	Percentages
ADC value < 1.3	30	55.56%
ADC value >1.3	24	44.44%

MR spectroscopy (MRS)

As per MRS of the lesions studied, 28 (51.85%) showed Choline Peak and the rest 26 showed no choline peak (Table 14 & figure 41).

Table 14: Descriptive analysis of choline peak on MR spectroscopy in the lesions studied (N=54)

MR Spectroscopy- Choline Peak	Frequency	Percentages
Yes	28	51.85%
No	26	48.15%

Figure 41: Pie chart of MR spectroscopy- choline peak in the lesions studied (N=54)

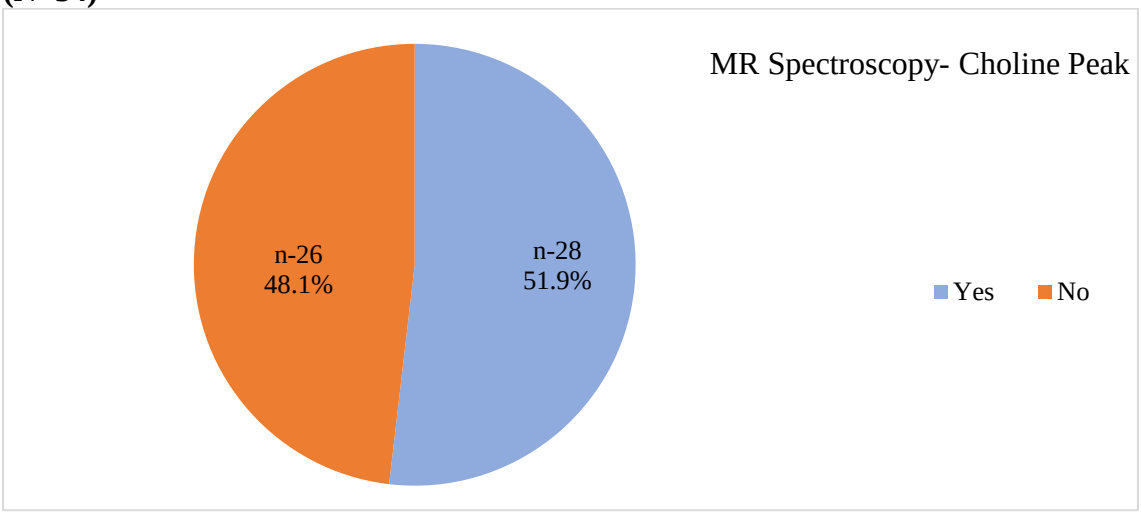


Table 15: Descriptive analysis of MRI final diagnosis in the lesions studied (N=54)

MRI final diagnosis	Frequency	Percentages
Malignant	29	53.70%
Benign	25	46.30%

As per MRI final diagnosis, 29 (53.70%) lesions were diagnosed as malignant and 25 (46.30%) as benign (Table 15).

Table 16: Descriptive analysis of histopathological diagnosis in the lesions studied (N=54)

Histopathological diagnosis	Frequency	Percentages
Fibroadenoma	18	33.33%
Infiltrating ductal carcinoma	17	31.48%
Pure Mucinous carcinoma	5	9.26%
Ductal carcinoma	4	7.41%
Squamous cell carcinoma	3	5.56%
Benign Phyllodes tumor	1	1.85%
Ductal carcinoma insitu	1	1.85%
Intracystic papillary carcinoma	1	1.85%
Liponecrosis	1	1.85%
Lobular carcinoma insitu	1	1.85%
Medullary carcinoma	1	1.85%
Secretory carcinoma	1	1.85%
TOTAL	54	100%

The histopathological type of the breast lesion was assessed, fibroadenomas were most common benign breast mass and infiltrating ductal carcinoma was most common malignant breast mass (Table 16).

Table 17: Descriptive analysis of HPE in the lesions studied (N=54)

HPE	Frequency	Percentages
Malignant	34	62.96%
Benign	20	37.04%

As per HPE report, 34 (62.96%) were malignant and 20 (37.04%) were benign in etiology. (Table 17)

Table 18: Comparison of restricted diffusion on DWI with HPE (N=54)

Restricted diffusion on DWI	HPE	
	Benign (N=20)	Malignant (N=34)
Present	0 (0%)	29 (85.29%)
Absent	20 (100%)	5 (14.71%)

No statistical test was applied- due to 0 subjects in the cells

Out of 34 malignant lesions on HPE, 29 (85.29%) showed restricted diffusion on DWI and findings were consistent. But 5 mucinous carcinomas showed no restricted diffusion which gave false negative results on MRI (Table 18).

Table 19: Comparison of ADC value with HPE (N=54)

ADC values	HPE		Chi square	P value
	Benign (N=20)	Malignant (N=34)		
ADC Value <1.3	1 (5%)	29 (85.29%)	32.880	<0.001
ADC Value >1.3	19 (95%)	5 (14.71%)		

Out of 20 benign on HPE, only 1 (5%) had ADC value $<1.3 \times 10^{-3}$ mm^2/s and rest 19 (95%) had ADC value $>1.3 \times 10^{-3}$ mm^2/s. Out of 34 malignant mass in HPE, 29 (85.29%) had ADC value $<1.3 \times 10^{-3}$ mm^2/s and 5 (14.71%) had ADC value $>1.3 \times 10^{-3}$ mm^2/s. The difference in the proportion of ADC value between HPE status was statistically significant (P value <0.001) (Table 19).

Table 20: Comparison of MRI final diagnosis (malignant/benign) with HPE (N=54)

MRI final diagnosis (malignant/benign)	HPE	
	Benign (N=20)	Malignant (N=34)
Benign	20 (100%)	5 (14.71%)
Malignant	0 (0%)	29 (85.29%)

No statistical test was applied- due to 0 subjects in the cells

Out of 20 benign in HPE, 20 (100%) were labelled as benign by MRI. Out of 34 malignant in HPE, 5 (14.71%) were labelled as benign by MRI and 29 (85.29%) were labelled as malignant by MRI. (Table 20).

Axillary lymph nodes

Restricted diffusion of the enlarged axillary lymph nodes were assessed and its corresponding ADC values were calculated. As we observed, 16 (51.85%) axillary lymph nodes showed restricted diffusion with ADC value < 1.4 x 10-3 (Table 21).

Table 21: Descriptive analysis of restricted diffusion in axillary lymph nodes (N = 24)

Axillary Lymph Nodes – Restricted Diffusion	Frequency	ADC values of the lymph nodes
Present	16	$< 1.4 \times 10^{-3}$
Absent	8	$> 1.4 \times 10^{-3}$

IMAGES

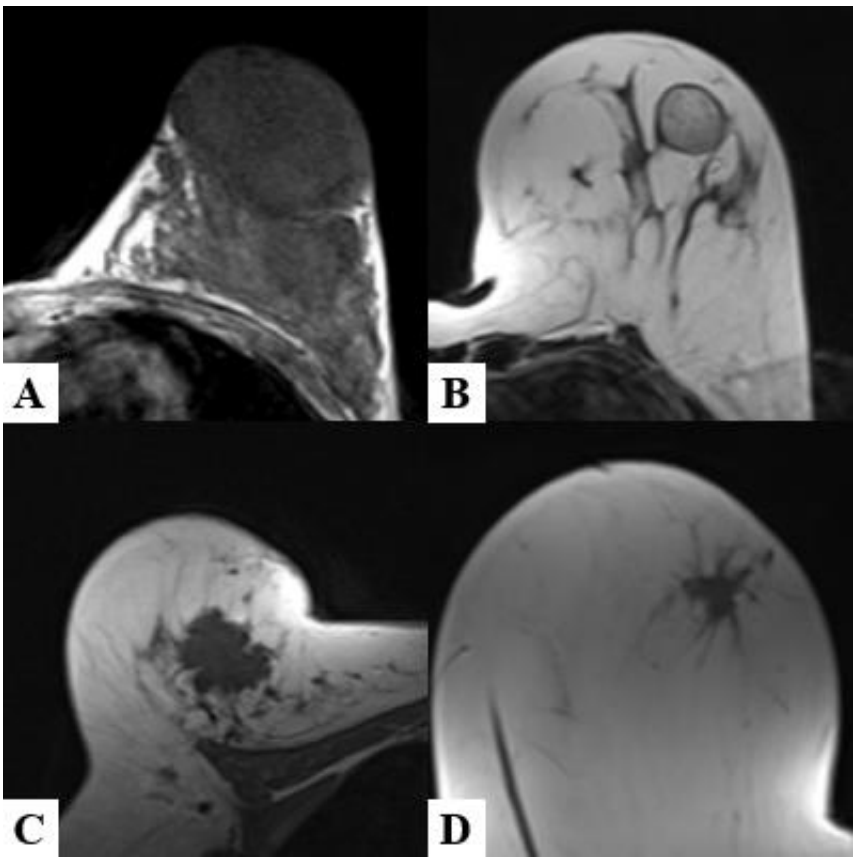


Figure 42: Shape of breast lesions:

(A) Oval (B) Round (C) Lobulated (D) Spiculated

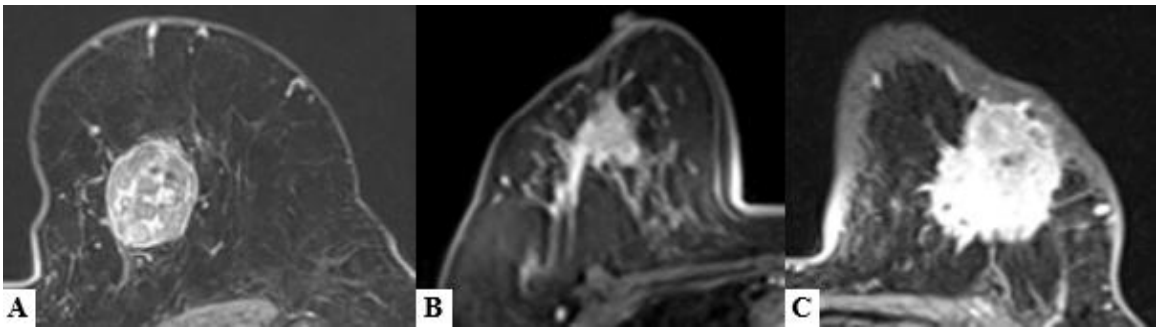


Figure 43: Margin of breast lesion on T1 weighted post-contrast images:
(A) Circumscribed (B) Irregular (C) Spiculated

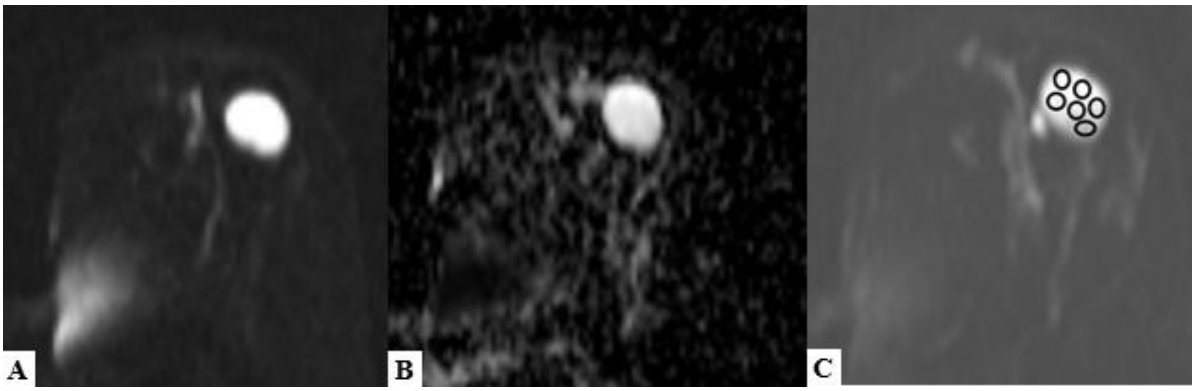


Figure 44: DWI & ADC sequences of a patient with fibroadenoma: (A) DWI and (B) corresponding ADC images showing no restriction of diffusion within the lesion present in left breast – suggestive of benign etiology (C) DWI image demonstrating the method of placing multiple ovoid ROIs (each measuring ~ 25 mm^2) throughout the benign lesion for calculation of mean ADC value.

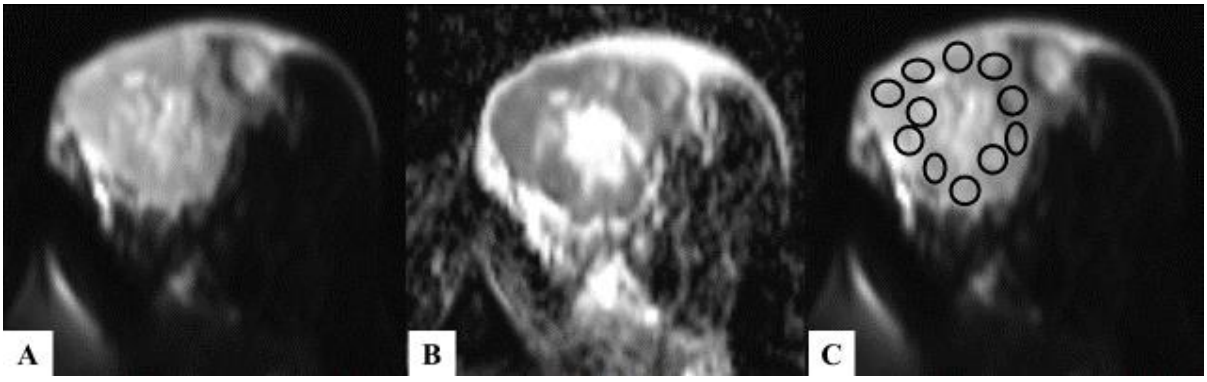


Figure 45: DWI & ADC sequences of a patient with infiltrative ductal carcinoma: (A) DWI and (B) corresponding ADC images showing peripheral area of restriction of diffusion within the lesion present in left breast- suggestive of malignant etiology (C) DWI image demonstrating the method of placing multiple ovoid ROIs (each measuring ~ 25 mm^2) in the areas of restricted diffusion for calculation of mean ADC value.

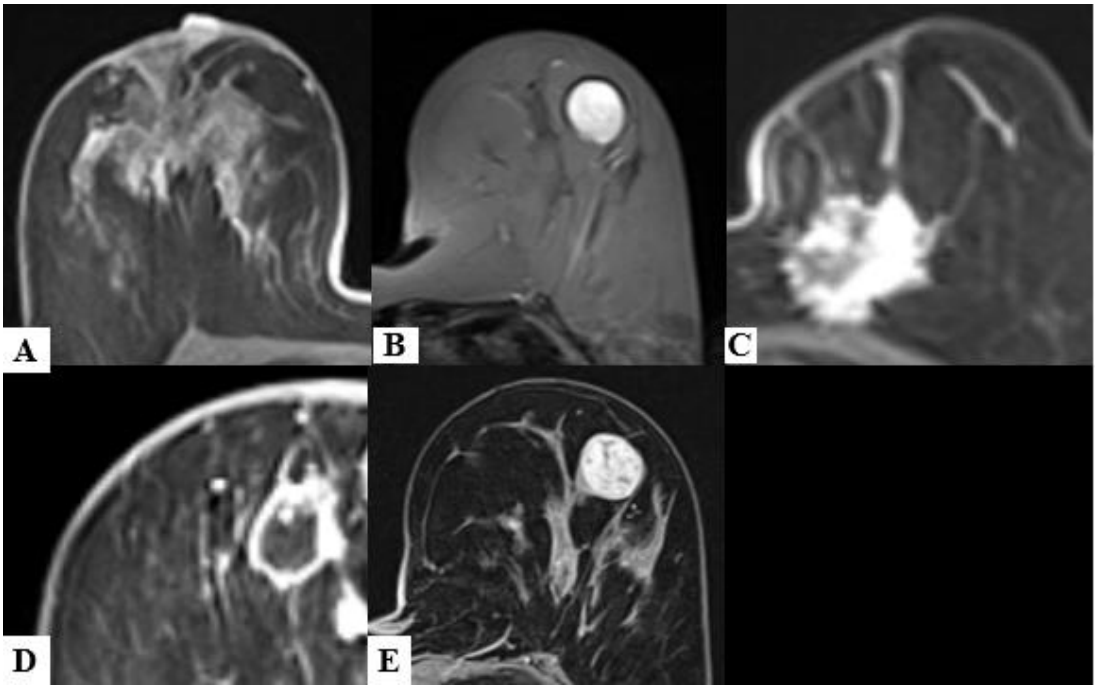


Figure 46: Five patterns of post-contrast enhancement of breast lesions on contrast enhanced T1 fat saturated MR images: (A) Non-mass like enhancement (B) Homogenous enhancement (C) Heterogenous enhancement (D) Rim enhancement (E) Enhancement of the lesion with dark internal septations.

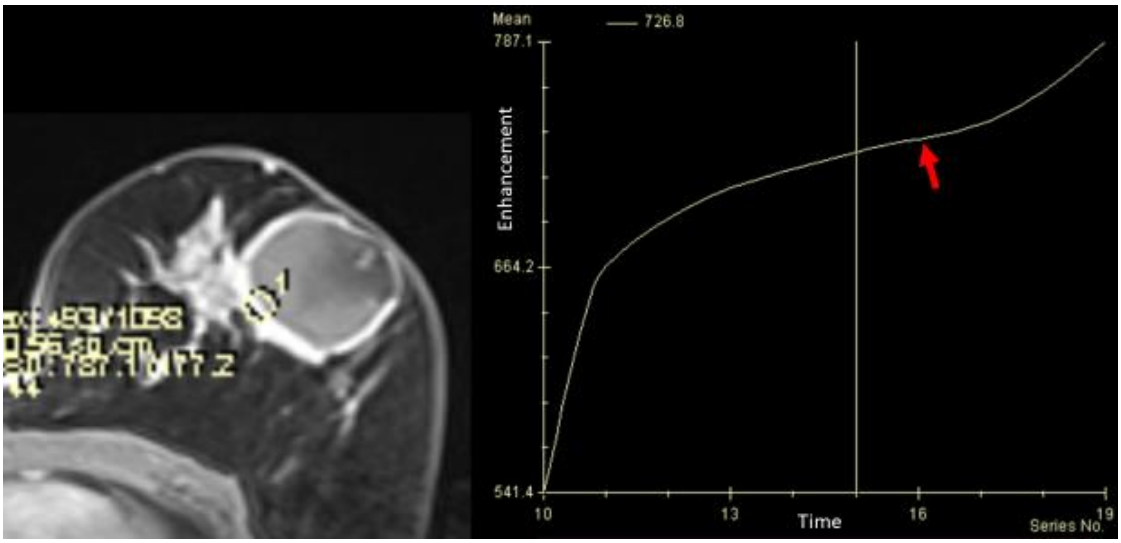


Figure 47: Fibroadenoma in left breast showing type I kinetic enhancement curve.

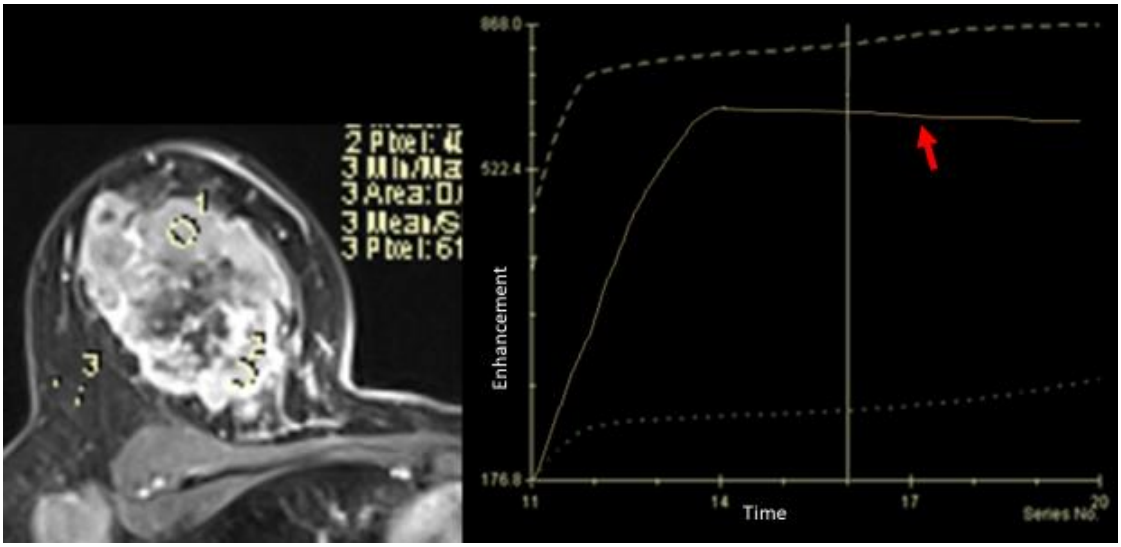


Figure 48: Infiltrative ductal carcinoma in right breast showing type II kinetic enhancement curve.

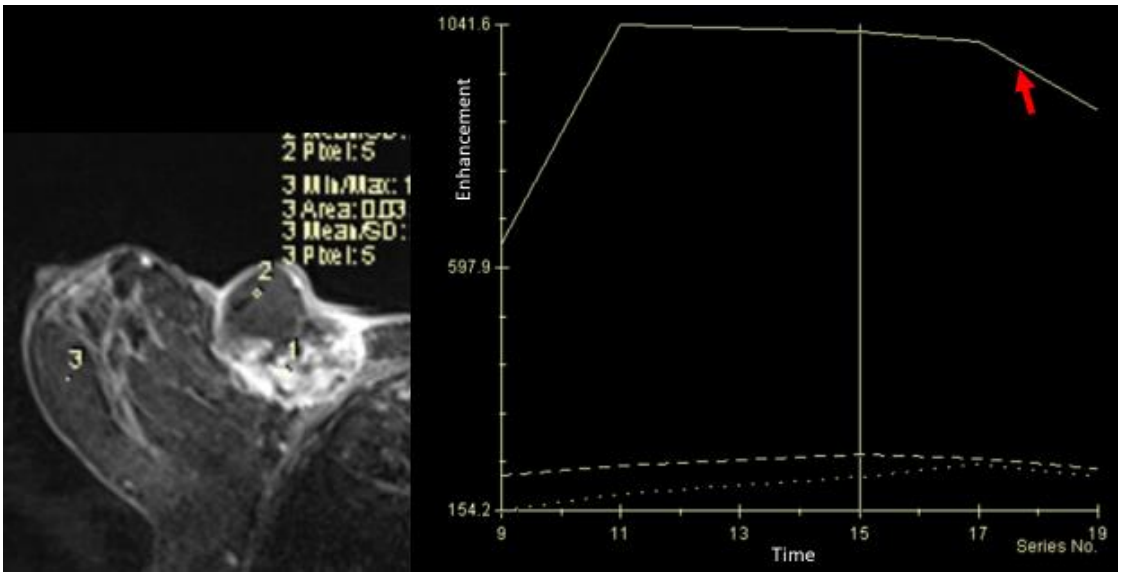


Figure 49: Squamous cell carcinoma in right breast showing type III kinetic enhancement curve.

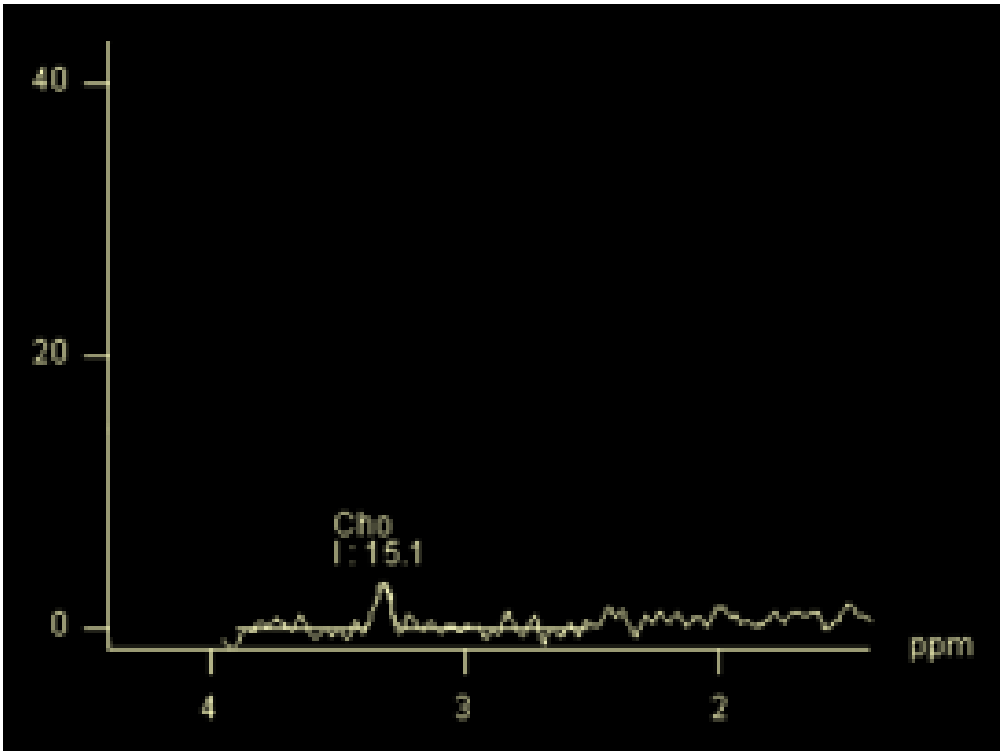


Figure 50: MR spectroscopy image of a malignant breast lesion showing tCho peak at 3.2ppm.

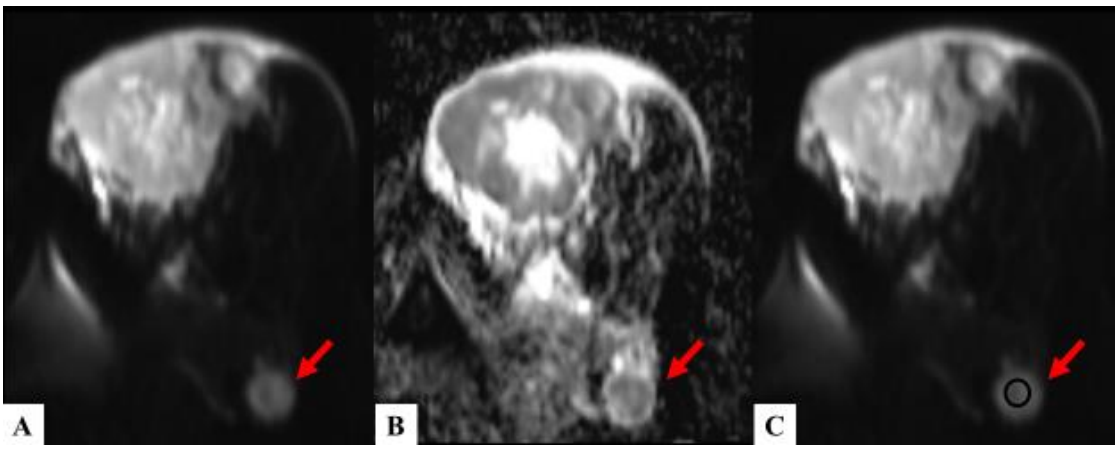


Figure 51: DWI & ADC sequences of axillary lymph node in a patient with infiltrative ductal carcinoma in left breast:
(A) DWI and (B) corresponding ADC images showing a lymph node in left axilla with restriction of diffusion (C) DWI image demonstrating method placing a single ovoid ROI on the lymph node for calculation of ADC value.

DISCUSSION

The DCE and DWI both techniques of MRI are the most sensitive imaging technique used detecting breast cancer. In recent years, these techniques have out-performed the traditional ultrasonography and mammography. The DCE -MRI has several indications in the lesions of breast, as it has good sensitivity and specificity for detection of breast cancer.[109] We analysed the role of the discrete BI-RADS descriptors for DCE-MRI (shape, type of enhancement, internal enhancement pattern/ characteristics, margin and enhancement kinetics) and ADC values on DWI and correlated these findings with the histopathology of the lesions. Very few studies,[110,111] have developed a multiparametric MRI models in diagnosing breast cancer. These models have proven to be very valuable in characterization of lesion and staging.

The present study involved 41 subjects and a total of 54 lesion were studied. The mean age of the study population was 47.1 ± 14.76 years. There was only one male participant (2.44%) in our study (female-97.56%). Majority of our study participants had only one lesion in number (78.05%) followed by 2 lesions in 14.43% and 3 lesions in only 2.44% on both the sides of the breast. A retrospective study by Zang M et al,[110] found 74 benign and 136 malignant lesions in 188 subjects with mean age of 51.6 years. Out of the total 188 subjects 16 of them had multiple and or bilateral lesions, of their total 210 lesion, masses were present in 182 subjects where, 66 where benign and 116 were malignant. Based on the MRI- BIRADS lexicon in 28 NME masses 8 were benign and 20 were malignant.[110] Similar findings were found in our study with malignant lesions in majority 62.96% and benign in 37.04%. The present study found scattered fibro glandular tissue and heterogenous fibro glandular tissue in 29.27% of the study population for each respectively followed by entirely fat in 26.83%, extreme

fibroglandular tissue in 14.63%. Out of total study population 31.71% each represented minimal and mild BPE and 26.83% had moderate BPE. In another similar study by Naranjo, I et al,[109] analysed 93 subjects with mean age of 49 years ± 12 years and benign lesion in 55.8% and malignant in 44.2%. they studied 104 lesions in total and found Fibroadenoma or fibroadenomatoid change (histopathological finding) in majority of the subjects (51.8%) followed by Adenosis, stromal fibrosis, ductal ectasia, or normal breast in 17.3% among the benign lesions; and invasive ductal carcinoma in 91.6% and followed by invasive lobular carcinoma; ductal carcinoma in situ in 4.3% each.[109]

As per lesion studied, out of 54 no. of lession, 15 (27.78%) lesions had irregular shape, 20 (37.04%) had oval shape and 19 (35.19%) had round shape. Majority of the lesions had circumscribed margin in 61.11%, irregular margins in 29.63% and irregular margin in 9.26%. Heterogenous lesions were found in majority of the participants (44.44%) followed by Dark internal septations in 25.93% and homogeneous was 20.37%. A study by Zhang M et al,[110] On DCE-MRI, DCE morphological features associated with breast cancer presented as masses having irregular shape, irregular/spiculated margin, and heterogeneous/rim internal enhancement pattern ($P < 0.0001$). The significant morphological features presenting in benign lesions was masses with round/ oval shape, with circumscribed margins and dark/homogenous septations internal enhancement pattern ($P < 0.0001$). For benign breast lesions presenting as NME, the significant features were focal distribution and homogenous internal enhancement pattern ($P < 0.0001$).[110] Although, in our study we found all these features, these descriptions for benign and malignant lesion was not studied and hence such correlation was not possible.

Restricted diffusion on DWI was found in 53.70% and 55.56% had ADC value <1.3 and 44.44% had ADC values has >1.3. The kinetic curves studied among the study population found type 1 in 46.30%, type 2 in 31.48%, and type 3 in 22.22%. Nearly half (51.85%) of the study population showed MR Spectroscopy- Choline Peak. In a study by Zhang M et al,[110] when they incluced the kinetic curves in their mpMRI model 2 they found that Lesions with plateau or washout kinetic curves had a 3.7-fold risk of being malignant than lesions with persistent enhancement. From the past literature it is found the presence of a tCho peak to be a reliable marker for detection of malignancy and threshold of tCho greater than 2 is frequently used in detecting malignancy.[112,113] A MRI -spectroscopic study by Shin et al found choline measures greater in invasive carcinoma and had well correlating with prognostic factors such as histoligicand nuclear grade and estrogen receptor status.

In our study, almost 51.85% had axillary lymph nodes with ADC value < 1.4 x 10^{-3}. In study by Razek, A et al,[114] found the mean ADC value in metastatic axillary lymph node to be $1.08 \pm 0.21 \times 10^{-3}$ mm^2/s and in benign lymph nodes was $1.58 \pm 0.14 \times 10^{-3}$ mm^2/s. There was statistically difference in mean ADC values between metastatic and of benign axillary lymph nodes ($P = 0.001$). Metastatic nodes were associated with low ADC ≤ 1.3. In comparison to our study results we have found lesser ADC value in half of the subjects with axillary lymph nodes suggesting metastatic.

From the MRI final diagnosis, majority(53.70%) was diagnosed as malignant and 46.30% as benign. Out of 34 malignant in HPE, majority (85.29%) displayed restricted diffusion on DWI present. Out of 20 benign in HPE, only 5% had ADC value <1.3 and

majority 95% had ADC value >1.3. Out of 34 malignant in HPE, majority (85.29%) had ADC value <1.3 and 14.71% had ADC value >1.3. The difference in the proportion of ADC value between HPE status was statistically significant (P value <0.001). A study by Zhang M et al,[110] found, malignant lesions having significant lower average ADC mean (0.90×10^{-3} mm^2/sec) compared with benign lesions (1.43×10^{-3} mm^2/sec) (P < 0.0001). In the literature, different ADC cut-off values has been projected to distinguish malignant from benign lesions, ranging from 0.9–1.76 × 10−3 mm2/sec, while a meta-analysis of 12 articles suggested a threshold of 1.23×10^{-3} mm^2/sec.[115] In our study we found majority of the study population with benign lesions having ADC value >1.3 and malignant lesions having ADC < 1.3, which is in line with the literature. Further, the conceptualization of identifying malignancy by diffusion imaging is that malignancy shows significant lower ADC value compared to benign lesions.[116] The reason behind this is that malignancy possess increased amount of cellularity which restricts diffusion displaying as bright signal on diffusion on weighted images and dark signal on a ADC map.[117]

A study by Naranjo, I et al,[109] found that their model constructed on mpMRI inclined to have the best diagnostic accuracy of 81.7% at AUC of 0.85. Similar study by Parekh et al,[118] found that there was differences in the radiomics map curves for malignant and benign breast lesion, where an increased entropy was significant in malignant tumours. Their model found perfusion and ADC reached at an AUC of 0.91 having good sensitivity and specificity of 93 % and 85%. Another study by Zhang Q et al,[119] inspected T1, T2 weighted imaging, diffusion kurtosis imaging (DKI), quantitative pharmacokinetic parameters of DCE-MRI, with ADC mapping to build models for the differentiation of breast lesions based on each sequence or combinations

of sequences. They found that the model constructed on radiomics topographies from T_2WI, DKI, and quantitative DCE pharmacokinetic parameter maps had a high discriminatory ability for benign and malignant breast lesions.[119] These studies have included BI-RADS 2 to 6 lesions against suspicious lesions only and has well established a good categorizing accuracy. In addition, the extra information got by DWI with ADC mapping used while MRI can be used for targeting the most appropriate site for biopsy as it depicts the most aggressive site of lesion and hence diminishing an error in sampling.[110]

Out of 20 benign in HPE, 20 (100%) were labelled as benign by MRI. Out of 34 malignant in HPE, 5 (14.71%) were labelled as benign by MRI and 29 (85.29%) were labelled as malignant by MRI.

LIMITATIONS AND RECOMMENDATIONS

The present single center study was performed on a relatively small study population. Increasing the sample size would improve the statistical power of the results. This study included only breast mass and did not evaluate the diagnostic performance of DWI in diffuse inflammatory/infective conditions such as mastitis.

Multicentric studies involving larger groups of patients are needed for evaluating the feasibility and utility of nADC, in further improving the diagnostic accuracy and specificity of breast MRI.

CONCLUSION

Breast cancer is the leading cause for mortality and morbidity among women. Early Screening of breast lesions become important to determine good prognosis. Ultrasound mammography is the most widely accepted and traditional tool used in screening breast lesions. At present DCE-MRM along with advanced technique such as DWI and ADC makes more appropriate and precise diagnosis of breast lesions. Hence the present study aimed to assess the morphology of breast mass using multiparametric MR mammography along with ADC values.

This study was an observational study of 41 subjects and a total of 54 breast mass were studied. The mean age of the study population was 47.1 ± 14.76 years. From the MRI final diagnosis, majority (53.70%) was diagnosed as malignant and 46.30% as benign. Of the 54 lesions, 29 lesions were reported as malignant breast mass and remaining as benign 25 masses as benign. Most of the malignant breast lesions had irregular/ spiculated margins, heterogeneous post-contrast enhancement and type 2 or 3 kinetic enhancement curve. All these lesions showed restricted diffusion on DWI with a corresponding ADC value of $<1.3\times10^{-3}$ mm^2/s and had choline peak on MR spectroscopy.

Most of the benign breast masses were more circumscribed, showed homogenous enhancement or enhancement with dark internal septations. They showed no restricted diffusion on DWI with their corresponding ADC value $>1.3\times10^{-3}$ mm^2/s and showed no choline peak on MR spectroscopy. Only one lesion (5% of all the benign lesions), benign Phyllodes tumor had an ADC value of 1.2×10^{-3} mm^2/s, suggesting malignant; rest of the findings was that of benign breast lesions.

On histopathology, malignant lesions was found in majority (34 lesions, 62.96%) and benign in rest 37.04% of them. 5 lesions (14.71% of malignant lesion on HPE) were misdiagnosed as benign on MRM which on HPE were mucinous carcinomas. These lesions showed no restricted diffusion and had a high ADC value that of a benign lesion; i.e, $>1.3\times10^{-3}$ mm^2/s.

SUMMARY

This study was prospective observational study on 41 subjects with a total of 54 lesions studied. The mean age of the study population was 47.1 ± 14.76 years. There was only one male participant (2.44%) in our study rest were females (97.56%).

Majority of our study participants had only one lesion in number (78.05%) followed by 2 lesions in 14.43% and 3 lesions in only 2.44% on both the sides of the breast.

This study found malignant lesions in majority 62.96% of the patients and benign lesions in 37.04% of them.

Scattered fibroglandular tissue and heterogenous fibroglandular tissue was found in 29.27% of the study population for each respectively followed by entirely fat in 26.83%, extreme fibroglandular tissue in 14.63%.

As per morphology of the lesions studied, out of 54 number of lesions, 15 (27.78%) lesions had irregular shape, 20 (37.04%) had oval shape and 19 (35.19%) had round shape. Majority of the lesions had circumscribed margins in 61.11%, irregular margins in 29.63% and spiculated margins in 9.26%.

On post-contrast study, out of total study population 31.71% each represented minimal and mild BPE and 26.83% had moderate BPE.

Heterogenous internal enhancement of the breast lesions were found in majority of the participants (44.44%), followed by dark internal septations in 25.93% and homogeneous enhancement was seen in 20.37%. Only one lesion showed rim enhancement and remaining 7.41% lesions showed non-mass enhancement.

The kinetic curves studied among the study population found type 1 in 46.30%, type 2 in 31.48%, and type 3 in 22.22%.

Restricted diffusion of the lesions on DWI was found in 53.70% and 55.56% had ADC value $<1.3\times10^{-3}$ mm^2/s and 44.44% had ADC values $>1.3\times10^{-3}$ mm^2/s.
Nearly half (51.85%) of the study population showed Choline peak on MR Spectroscopy, which were malignant.

From the final MRI diagnosis, majority (53.70%) were diagnosed as malignant and 46.30% as benign. Out of 34 malignant lesions on HPE, only 5 lesions showed false negative findings of absent restricted diffusion on DWI rest of the majority malignant lesions (85.29%) displayed restricted diffusion on DWI. All 29 lesions also had an ADC value of $<1.3\times10^{-3}$ mm^2/s. 20 lesions were benign on HPE, only 5% (1 lesion) had ADC value $<1.3\times10^{-3}$ mm^2/s which was diagnosed to be benign Phyllodes tumor and rest had ADC value $>1.3\times10^{-3}$ mm^2/s. The difference in the proportion of ADC value between HPE status was statistically significant (P value <0.001).

Therefore, 20 benign were diagnosed as benign on both HPE as well as on MRI. Out of 34 malignant lesions diagnosed on HPE, 5 (14.71%) Mucinous carcinomas were labelled as benign by MRM and rest 29 (85.29%) were labelled as malignant by MRM.

Nearly 51.85% of the assessed axillary lymph nodes had an ADC value $< 1.4\times10^{-3}$ mm^2/s which is suggestive of malignant/ metastatic lymph nodes.

BIBLIOGRAPHY

1. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast cancer 2019;11:151–64.
2. Zendehdel M, Niakan B, Keshtkar A, Rafiei E, Salamat F. Subtypes of Benign Breast Disease as a Risk Factor for Breast Cancer: A Systematic Review and Meta-Analysis Protocol. Iran J Med Sci 2018;43:1–8.
3. Mavaddat N, Pharoah PDP, Michailidou K, Tyrer J, Brook MN, Bolla MK, et al. Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst 2015;107:1-15.
4. https://www.who.int/acessed on 6-7-21.
5. Rahbar H, Partridge SC. Multiparametric Breast MRI of Breast Cancer. Magn Reson Imaging Clin North Am 2016;24:223–38.
6. Kriege M, Brekelmans CTM, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, et al. Efficacy of MRI & mammography for breast-cancer screening in women with familial or genetic predisposition. N Engl J Med 2004;351:427–37
7. Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004;292:1317–25.
8. Lehman CD, Isaacs C, Schnall MD, Pisano ED, Ascher SM, Weatherall PT, et al. Cancer yield of mammography, MR and US in high-risk women: prospective multi-institution breast cancer screening study. Radiology 2007;244:381–8.
9. Schnall MD, Blume J, Bluemke DA, Deangelis GA, Debruhl N, Harms S, et al. MRI detection of distinct incidental cancer in women with primary breast cancer

studied in IBMC 6883. J Surg Oncol 2005;92:32–8.

10. Elmore JG, Armstrong K, Lehman CD, Fletcher SW. Screening for breast cancer. JAMA 2005;293:1245–56.
11. Martincich L, Montemurro F, De Rosa G, Marra V, Ponzone R, Cirillo S, et al. Monitoring response to primary chemotherapy in breast cancer using dynamic contrast-enhanced magnetic resonance imaging. Breast Cancer Res Treat 2004;83:67–76.
12. Rosen EL, Blackwell KL, Baker JA, Soo MS, Bentley RC, Yu D, et al. Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy. Am J Roentgenol 2003;181:1275–82.
13. Weatherall PT, Evans GF, Metzger GJ, Saborrian MH, Leitch AM. MRI vs. histologic measurement of breast cancer following chemotherapy: comparison with x-ray mammography and palpation. J Magn Res Imaging 2001;13:868–75
14. Hylton NM, Blume JD, Bernreuter WK, Pisano ED, Rosen MA, Morris EA, et al. Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy--results from ACRIN 6657/I-SPY TRIAL. Radiology 2012;263:663–72.
15. Sardanelli F, Boetes C, Borisch B, Decker T, Federico M, Gilbert FJ, et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 2010;46:1296–316.
16. Pinker K, Grabner G, Bogner W, Gruber S, Szomolanyi P, Trattnig S, et al. A combined high temporal and high spatial resolution 3 T MR imaging protocol for assessment of breast lesions: initial results. Invest Radiol 2009;44:553–8.
17. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57–70.
18. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell

2011;144:646–74.

19. Pinker K, Bickel H, Helbich TH, Gruber S, Dubsky P, Pluschnig U, et al. Combined contrast-enhanced magnetic resonance and diffusion-weighted imaging reading adapted to the "Breast Imaging Reporting and Data System" for multiparametric 3-T imaging of breast lesions. Eur Radiol 2013;23:1791–802.

20. Pinker K, Bogner W, Baltzer P, Trattnig S, Gruber S, Abeyakoon O, et al. Clinical application of bilateral high temporal and spatial resolution dynamic contrast-enhanced magnetic resonance imaging of the breast at 7 T. Eur Radiol 2014;24:913–20.

21. Pooja Gupta, Samar Chatterjee, Vivek Sharma, Kamlesh Kumar Singh DG. Efficacy of X-Ray Mammography , Sonomammography and Mr Mammography for Evaluation of Breast Lesions in Women. Indian J Appl Res 2017;7:26–30.

22. Hassan HHM, Mahmoud Zahran MH, El-Prince Hassan H, Mohamed Abdel-Hamid A-E, Abdel Shafy Fadaly G. Diffusion magnetic resonance imaging of breast lesions: Initial experience at Alexandria University. Alexandria J Med 2013;49:265–72.

23. Yilmaz E, Sari O, Yilmaz A, Ucar N, Aslan A, Inan I, et al. Diffusion-weighted imaging for the discrimination of benign and malignant breast masses; utility of adc and relative adc. J Belgian Soc Radiol 2018;102:1–6.

24. Bickelhaupt S, Jaeger PF, Laun FB, Lederer W, Daniel H, Kuder TA, et al. Radiomics Based on Adapted Diffusion Kurtosis Imaging Helps to Clarify Most Mammographic Findings Suspicious for Cancer. Radiology 2018;287:761–70.

25. Bickelhaupt S, Paech D, Kickingereder P, Steudle F, Lederer W, Daniel H, et al. Prediction of malignancy by a radiomic signature from contrast agent-free

diffusion MRI in suspicious breast lesions found on screening mammography. J Magn Reson Imaging 2017;46:604–16.

26. Cai H, Peng Y, Ou C, Chen M, Li L. Diagnosis of breast masses from dynamic contrast-enhanced and diffusion-weighted MR: a machine learning approach. PLoS One 2014;9:e87387.

27. Howard BA, Gusterson BA. Human Breast Development. J Mammary Gland Biol Neoplasia 2000;5:119–37.

28. Javed A, Lteif A. Development of the human breast. Semin Plast Surg 2013;27:5–12.

29. Sternlicht MD. Key stages in mammary gland development: the cues that regulate ductal branching morphogenesis. Breast Cancer Res 2006;8:201.

30. Turashvili G, Bouchal J, Burkadze G, Kolar Z. Mammary gland development and cancer. Cesk Patol 2005;41:94–101.

31. Jolicoeur F. Intrauterine Breast Development and the Mammary Myoepithelial Lineage. J Mammary Gland Biol Neoplasia 2005;10:199–210.

32. Moore KL, Persod TVN TM. Moore KL, Persod TVN, Torchia MG.The Developing Human. Clinically Oriented Embryology. 9th ed. Philadelphia: Elsevier Saunders; 2011;560.

33. MC J. Anatomy and Physiology of the Breast [Internet]. Springer. 2010 [cited 2020 Nov 20]. p. 1–36. Available from: https://link.springer.com/chapter/10.1007%2F978-3-540-69743-5_1#citeas

34. MC J. Anatomy and Physiology of the Breast. Springer 2010;1:1–36.

35. Lategan B. Histology. Breast General Histology [Internet]. 2015 PathologyOutlines.com. [Update: 2020 sep 14, Cited 2020 Nov 12]. Available from: http://www.pathologyoutlines.com/topic/breastnormal.html.

36. Kumar V, Abbas AK, Aster JC. The Breast. In: Lester SC, editor. Robbins and Cotran: Pathologic basis of disease. 10th ed. Philadelphia: Elsevier Saunders; 2020;1:1037.

37. Arthur M. Institute for Health Metrics and Evaluation. Nurs Stand 2014;28:32.

38. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global Cancer in Women: Burden and Trends. Cancer Epidemiol Biomarkers Prev 2017;26:444–57.

39. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2017;3:524–48.

40. Denny L, de Sanjose S, Mutebi M, Anderson BO, Kim J, Jeronimo J, et al. Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. Lancet 2017;389:861–70.

41. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:359–86.

42. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–917.

43. Anonymous. Three Year Report of Population Based Cancer Registries 2012–2014. Indian Council of Medical Research (ICMR), Bangalore, India 2016.

44. Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, Zhu ZY, et al. Risk factors and preventions of breast cancer. Int J Biol Sci 2017;13:1387–97.

45. Masciadri N, Ferranti C. Benign breast lesions: Ultrasound. J Ultrasound [Internet]. 2011/04/20. 2011;14:55–65. Available from: https://pubmed.ncbi.nlm.nih.gov/23396888

46. Jafari SH, Saadatpour Z, Salmaninejad A, Momeni F, Mokhtari M, Nahand JS, et al. Breast cancer diagnosis: Imaging techniques and biochemical markers. J Cell Physiol 2018;233:5200–13.

47. Iranmakani S, Mortezazadeh T, Sajadian F, Ghaziani MF, Ghafari A, Khezerloo D, et al. A review of various modalities in breast imaging: technical aspects and clinical outcomes. Egypt J Radiol Nucl Med [Internet]. 2020;51:57. Available from: https://doi.org/10.1186/s43055-020-00175-5

48. Kerlikowske K, Hubbard RA, Miglioretti DL, Geller BM, Yankaskas BC, Lehman CD, et al. Comparative effectiveness of digital versus film-screen mammography in community practice in the United States: a cohort study. Ann Intern Med 2011;155:493–502.

49. Khan MD, Banerjee S, Tarafdar S, Kundu D. Role of sonomammography and its diagnostic accuracy for evaluating benign and malignant breast lesions. Int J Res Med Sci 2021;9:1448.

50. Xu H, Rao M, Varghese T, Sommer A, Baker S, Hall TJ, et al. Axial-Shear Strain Imaging for Differentiating Benign and Malignant Breast Masses. Ultrasound Med Biol 2010;36:1813–24.

51. Balleyguier C, Ciolovan L, Ammari S, Canale S, Sethom S, Al Rouhbane R, et al. Breast elastography: The technical process and its applications. Diagn Interv Imaging 2013;94:503–13.

52. Barr RG. Real-time ultrasound elasticity of the breast: initial clinical results.

Ultrasound Q 2010;26:61–6.

53. Gruber S, Minarikova L, Pinker K, Zaric O, Chmelik M, Strasser B, et al. Diffusion-weighted imaging of breast tumours at 3 Tesla and 7 Tesla: a comparison. Eur Radiol 2016;26:1466–73.

54. Zhou JQ, Zhan WW, Chang C, Zhang XX, Jia Y, Dong YJ, et al. Breast lesions: Evaluation with shear wave elastography, with special emphasis on the "stiff rim" sign. Radiology 2014;272:63–72.

55. Lin Y-P, Hsu H-H, Ko K-H, Chu C-M, Chou Y-C, Chang W-C, et al. Differentiation of Malignant and Benign Incidental Breast Lesions Detected by Chest Multidetector-Row Computed Tomography: Added Value of Quantitative Enhancement Analysis. PLoS One [Internet]. 2016 29;11:e0154569–e0154569. Available from: https://pubmed.ncbi.nlm.nih.gov/27128524

56. Prionas ND, Lindfors KK, Ray S, Huang S-Y, Beckett LA, Monsky WL, et al. Contrast-enhanced dedicated breast CT: initial clinical experience. Radiology 2010;256:714–23.

57. Geethanath S, Vaughan JT. Accessible magnetic resonance imaging: A review. J Magn Reson Imaging 2019;49:65–77.

58. Warner E, Causer PA, Wong JW-N, Wright FC, Jong RA, Hill KA, et al. Improvement in DCIS detection rates by MRI over time in a high-risk breast screening study. Breast J 2011;17:9–17.

59. Mann RM, Kuhl CK, Kinkel K, Boetes C. Breast MRI: Guidelines from the European Society of Breast Imaging. Eur Radiol 2008;18:1307–18.

60. Mann RM, Cho N, Moy L. Breast MRI: State of the art. Radiology 2019;292:520–36.

61. Ferré R, Ianculescu V, Ciolovan L, Mathieu M-C, Uzan C, Canale S, et al.

Diagnostic Performance of MR-guided Vacuum-Assisted Breast Biopsy: 8 Years of Experience. Breast J 2016;22:83–9.

62. Konyer NB, Ramsay EA, Bronskill MJ, Plewes DB. Comparison of MR Imaging Breast Coils. Radiology 2002;222:830–4.

63. Nnewihe AN, Grafendorfer T, Daniel BL, Calderon P, Alley MT, Robb F, et al. Custom-fitted 16-channel bilateral breast coil for bidirectional parallel imaging. Magn Reson Med 2011;66:281–9.

64. Heywang-Köbrunner SH, Bick U, Bradley WGJ, Boné B, Casselman J, Coulthard A, et al. International investigation of breast MRI: results of a multicentre study (11 sites) concerning diagnostic parameters for contrast-enhanced MRI based on 519 histopathologically correlated lesions. Eur Radiol 2001;11:531–46.

65. Schnall M, Orel S. Breast MR imaging in the diagnostic setting. Magn Reson Imaging Clin N Am 2006;14:329–37.

66. Petralia G, Bonello L, Priolo F, Summers P, Bellomi M. Breast MR with special focus on DW-MRI and DCE-MRI. Cancer Imaging 2011;11:76–90.

67. Lyons D, Wahab RA, Vijapura C, Mahoney MC. The nipple–areolar complex: comprehensive imaging review. Clin Radiol 2021;76:172–84.

68. Martaindale SR. Breast MR Imaging: Atlas of Anatomy, Physiology, Pathophysiology, and Breast Imaging Reporting and Data Systems Lexicon. Magn Reson Imaging Clin N Am 2018;26:179–90.

69. Carbonaro LA, Pediconi F, Verardi N, Trimboli RM, Calabrese M, Sardanelli F. Breast MRI using a high-relaxivity contrast agent: an overview. Am J Roentgenol 2011;196:942–55.

70. Westra C, Dialani V, Mehta TS, Eisenberg RL. Using T2-weighted sequences

to more accurately characterize breast masses seen on MRI. Am J Roentgenol 2014;202:183-90.

71. Ballesio L, Savelli S, Angeletti M, Porfiri LM, D'Ambrosio I, Maggi C, et al. Breast MRI: Are T2 IR sequences useful in the evaluation of breast lesions? Eur J Radiol 2009;71:96–101.

72. Arponen O, Masarwah A, Sutela A, Taina M, Könönen M, Sironen R, et al. Incidentally detected enhancing lesions found in breast MRI: analysis of apparent diffusion coefficient and T2 signal intensity significantly improves specificity. Eur Radiol 2016;26:4361–70.

73. Partridge SC, McDonald ES. Diffusion weighted magnetic resonance imaging of the breast: protocol optimization, interpretation, and clinical applications. Magn Reson Imaging Clin N Am 2013;21:601–24.

74. Shi R-Y, Yao Q-Y, Wu L-M, Xu J-R. Breast Lesions: Diagnosis Using Diffusion Weighted Imaging at 1.5T and 3.0T-Systematic Review and Meta-analysis. Clin Breast Cancer 2018;18:305–20.

75. Macura KJ, Ouwerkerk R, Jacobs MA, Bluemke DA. Patterns of enhancement on breast MR images: interpretation and imaging pitfalls. Radiographics 2006;26:1719.

76. Partridge SC, Stone KM, Strigel RM, DeMartini WB, Peacock S, Lehman CD. Breast DCE-MRI: influence of postcontrast timing on automated lesion kinetics assessments and discrimination of benign and malignant lesions. Acad Radiol 2014;21:1195–203.

77. Cheng L, Li X. Breast magnetic resonance imaging: kinetic curve assessment.

Gland Surg 2013;2:50–3.

78. Thakur SB, Brennan SB, Ishill NM, Morris EA, Liberman L, Dershaw DD, et al. Diagnostic usefulness of water-to-fat ratio and choline concentration in malignant and benign breast lesions and normal breast parenchyma: an in vivo (1) H MRS study. J Magn Reson Imaging 2011;33:855–63.

79. Fardanesh R, Marino MA, Avendano D, Leithner D, Pinker K, Thakur SB. Proton MR spectroscopy in the breast: Technical innovations and clinical applications. J Magn Reson Imaging 2019;50:1033–46.

80. Baek H-M. Diagnostic value of breast proton magnetic resonance spectroscopy at 1.5T in different histopathological types. ScientificWorldJournal 2012;2012:508295.

81. Sah RG, Sharma U, Parshad R, Seenu V, Mathur SR, Jagannathan NR. Association of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status with total choline concentration and tumor volume in breast cancer patients: an MRI and in vivo proton MRS study. Magn Reson Med 2012;68:1039–47.

82. Baltzer PAT, Benndorf M, Dietzel M, Gajda M, Runnebaum IB, Kaiser WA. False-positive findings at contrast-enhanced breast MRI: a BI-RADS descriptor study. Am J Roentgenol 2010;194:1658–63.

83. American College of Radiology. BI-RADS atlas. 5th ed. Reston, Va: American College of Radiology, 2013.

84. Gutierrez RL, DeMartini WB, Eby PR, Kurland BF, Peacock S, Lehman CD. BI-RADS lesion characteristics predict likelihood of malignancy in breast MRI for masses but not for nonmasslike enhancement. Am J Roentgenol

2009;193:994–1000.

85. Machida Y, Shimauchi A, Kuroki Y, Tozaki M, Kato Y, Hoshi K, et al. Single focus on breast magnetic resonance imaging: diagnosis based on kinetic pattern and patient age. Acta Radiol 2017;58:652–9.

86. Bi-rads ACR, Mri B. ACR Bi-Rads® Atlas — Breast MRI. Am Coll Radiol [Internet]. 2013;125–43. Available from: https://www.acr.org/-/media/ACR/Files/RADS/BI-RADS/MRI-Reporting.pdf

87. Pediconi F, Catalano C, Padula S, Roselli A, Dominelli V, Cagioli S, et al. Contrast-enhanced MR mammography: Improved lesion detection and differentiation with gadobenate dimeglumine. Am J Roentgenol 2008;191:1339–46.

88. Bitencourt AG, Ferreira EV, Bastos DC, Sperandio VA, Graziano L, Guatelli CS, et al. Intramammary lymph nodes: normal and abnormal multimodality imaging features. Br J Radiol 2019;92:20190517.

89. Solorzano S, Seidler M, Mesurolle B. Metastatic intramammary lymph node as a synchronous benign-appearing breast nodule detected in a patient with breast cancer. Vol. 192. American journal of roentgenology. United States; 2009.349.

90. Marino MA, Avendano D, Zapata P, Riedl CC, Pinker K. Lymph Node Imaging in Patients with Primary Breast Cancer: Concurrent Diagnostic Tools. Oncologist 2020;25.

91. Yılmaz E, Erok B, Atca A. Measurement of apparent diffusion coefficient in discrimination of benign and malignant axillary lymph nodes. Polish J Radiol 2019;84:592–7.

92. Kim EJ, Kim SH, Kang BJ, Choi BG, Song BJ, Choi JJ. Diagnostic value of breast MRI for predicting metastatic axillary lymph nodes in breast cancer

patients: diffusion-weighted MRI and conventional MRI. Magn Reson Imaging 2014;32:1230–6.

93. Chung J, Youk JH, Kim J-A, Gweon HM, Kim E-K, Ryu YH, et al. Role of diffusion-weighted MRI: predicting axillary lymph node metastases in breast cancer. Acta Radiol 2014;55:909–16.

94. Razek AAKA, Lattif MA, Denewer A, Farouk O, Nada N. Assessment of axillary lymph nodes in patients with breast cancer with diffusion-weighted MR imaging in combination with routine and dynamic contrast MR imaging. Breast Cancer 2016;23:525–32.

95. Hasanzadeh F, Faeghi F, Valizadeh A, Bayani L. Diagnostic Value of Diffusion Weighted Magnetic Resonance Imaging in Evaluation of Metastatic Axillary Lymph Nodes in a Sample of Iranian Women with Breast Cancer. Asian Pac J Cancer Prev 2017;18:1265–70.

96. Kuhl CK, Strobel K, Bieling H, Wardelmann E, Kuhn W, Maass N, et al. Impact of Preoperative Breast MR Imaging and MR-guided Surgery on Diagnosis and Surgical Outcome of Women with Invasive Breast Cancer with and without DCIS Component. Radiology 2017;284:645–55.

97. Lobbes MBI, Vriens IJH, van Bommel ACM, Nieuwenhuijzen GAP, Smidt ML, Boersma LJ, et al. Breast MRI increases the number of mastectomies for

ductal cancers, but decreases them for lobular cancers. Breast Cancer Res Treat 2017;162:353–64.

98. Brennan ME, Houssami N, Lord S, Macaskill P, Irwig L, Dixon JM, et al. Magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer: systematic review and meta-analysis of

incremental cancer detection and impact on surgical management. J Clin Oncol Off J Am Soc Clin Oncol 2009;27:5640–9.

99. Chaiwun B, Thorner P. Fine needle aspiration for evaluation of breast masses. Curr Opin Obstet Gynecol 2007;19:48–55.

100. Kroese M, Zimmern RL, Pinder SE. HER2 status in breast cancer--an example of pharmacogenetic testing. J R Soc Med 2007;100:326–9.

101. Naranjo ID, Gibbs P, Reiner JS, Lo Gullo R, Sooknanan C, Thakur SB, et al. Radiomics and machine learning with multiparametric breast mri for improved diagnostic accuracy in breast cancer diagnosis. Diagnostics 2021;11:1–13.

102. Choi BB. Dynamic contrast enhanced-MRI and diffusion-weighted image as predictors of lymphovascular invasion in node-negative invasive breast cancer. World J Surg Oncol 2021;1–10.

103. Wielema M, Dorrius MD, Pijnappel RM, Bock GH De, Baltzer PAT, Oudkerk M, et al. Diagnostic performance of breast tumor tissue selection in diffusion weighted imaging : A systematic review and meta-analysis. Plos one 2020;82:1–23.

104. Kamal RM, Hanafy MM, Mansour SM, Hassan M, Gomaa MM. Can contrast-enhanced mammography replace dynamic contrast-enhanced MRI in the assessment of sonomammographic indeterminate breast lesions? Egypt J Radiol Nucl Med 2020;51:1-8.

105. Hardas VS, Chandorkar AH, Atre AA. Does Normalised Apparent Diffusion Coefficient Further Improve the Diagnostic Accuracy of Diffusion-Weighted MRI at 3T in Characterising Breast Masses? J Clin Diagn Res 2019;10–5.

106. Tezcan Ş, Öztürk FU. Diffusion-Weighted Imaging of Breast Cancer : Correlation of the Apparent Diffusion Coefficient Value with Pathologic

Prognostic Factors 2019;15:262–7.

107. Hammad A, Hassanien OA, Ahmed H. The role of conventional and functional MRI in diagnosis of breast masses. Egy J of Radiol and Nuc Med 2015;1215–30.

108. Raikhlin A, Curpen B, Warner E, Betel C, Wright B, Jong R. Breast MRI as an adjunct to mammography for breast cancer screening in high-risk patients: retrospective review. Am J Roentgenol 2015;204:889–97.

109. Naranjo ID, Gibbs P, Reiner JS, et al. Radiomics and machine learning with multiparametric breast mri for improved diagnostic accuracy in breast cancer diagnosis. Diagnostics. 2021;11(6):1-13. doi:10.3390/diagnostics11060919

110. Zhang M, Horvat J V., Bernard-Davila B, et al. Multiparametric MRI model with dynamic contrast-enhanced and diffusion-weighted imaging enables breast cancer diagnosis with high accuracy. J Magn Reson Imaging. 2019;49(3):864-874. doi:10.1002/jmri.26285

111. Rahbar H, Partridge SC, DeMartini WB, et al. In vivo assessment of ductal carcinoma in situ grade: A model incorporating dynamic contrast-enhanced and diffusion-weighted breast MR imaging parameters. Radiology. 2012;263(2):374-382. doi:10.1148/radiol.12111368

112. Kwock L, Smith JK, Castillo M, et al. Clinical role of proton magnetic resonance spectroscopy in oncology: brain, breast, and prostate cancer. Lancet Oncol. 2006;7(10):859-868. doi:10.1016/S1470-2045(06)70905-6

113. Zhao C, Bolan PJ, Royce M, et al. Quantitative mapping of total choline in healthy human breast using proton echo planar spectroscopic imaging (PEPSI) at 3 Tesla. J Magn Reson Imaging. 2012;36(5):1113-1123. doi:10.1002/jmri.23748

114. Razek AAKA, Lattif MA, Denewer A, Farouk O, Nada N. Assessment of axillary lymph nodes in patients with breast cancer with diffusion-weighted MR imaging in combination with routine and dynamic contrast MR imaging. Breast Cancer. 2016;23(3):525-532. doi:10.1007/s12282-015-0598-7

115. Partridge SC, McDonald ES. Diffusion Weighted Magnetic Resonance Imaging of the Breast: Protocol Optimization, Interpretation, and Clinical Applications. Magn Reson Imaging Clin N Am. 2013;21(3):601-624. doi:10.1016/j.mric.2013.04.007

116. Mi JP, Eun SC, Bong JK, Yon KI, Jun HB. The role of diffusion-weighted imaging and the apparent diffusion coefficient (ADC) values for breast tumors. Korean J Radiol. 2007;8(5):390-396. doi:10.3348/kjr.2007.8.5.390

117. Woodhams R, Matsunaga K, Kan S, et al. ADC mapping of benign and malignant breast tumors. Magn Reson Med Sci MRMS an Off J Japan Soc Magn Reson Med. 2005;4(1):35-42. doi:10.2463/mrms.4.35

118. Parekh VS, Jacobs MA. Integrated radiomic framework for breast cancer and tumor biology using advanced machine learning and multiparametric MRI. npj Breast Cancer. 2017;3(1):1-8. doi:10.1038/s41523-017-0045-3

119. Zhang Q, Peng Y, Liu W, et al. Radiomics Based on Multimodal MRI for the Differential Diagnosis of Benign and Malignant Breast Lesions. J Magn Reson Imaging. 2020;52(2):596-607. doi:https://doi.org/10.1002/jmri.27098

ANNEXURE I

PROFORMA FOR DISSERTATION

Demographic details:
Name: Age/ Sex:
Patient Hospital ID: Address:
Chief complaints:
History:
Local examination:

MRI FINDINGS		
	RIGHT BREAST	**LEFT BREAST**
CONVENTIONAL MRI 1. Number of lesions 2. Fatty tissue in the breast		
CONTRAST ENHANCED MRI 1. Background parenchymal enhancement 2. Shape 3. Margins 4. Enhancement pattern of the lesion 5. Type of kinetic curve		
Restricted diffusion on DWI sequence		
ADC value		
Choline peak on MR SPECTROSCOPY		
AXILLARY LYMPH NODES 1. Number of axillary lymph nodes 2. Restricted diffusion on DWI sequence 3. ADC values		

OTHER FINDINGS		

MRI diagnosis:

Histopathological Diagnosis:

Conclusion:

Chief Researcher signature Guide signature

ANNEXURE II

PATIENT CONSENT FORM

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

Principal investigator: Dr. VARSHITHA G. R.

Name of the subject:

Age :

Gender :

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

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

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

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

e. I confirm that Dr. Varshitha G. R. / 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 signature/Guide signature **Date:**

ANNEXURE II

PATIENT INFORMATION SHEET

Principal Investigator: Dr. VARSHITHA G. R. / Dr. ANIL KUMAR SAKALECHA

I, Dr. Varshitha G. R.**,** post-graduate student in Department of Radio-Diagnosis at Sri Devaraj Urs Medical College. I will be conducting a study titled "Multiparametric magnetic resonance imaging in evaluation of benign from malignant breast masses with pathological correlation" for my dissertation under the guidance of Dr. Anil Kumar Sakalecha, Professor & HOD, Department of Radio-Diagnosis. In this study, we will assess the role of MR mammography in differentiating benign from malignant breast mass. You will not be paid any financial compensation for participating in this research project.

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

Name and Signature of the Principal Investigator

Signature of the Guide

Date:

I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	XVIII	XIX
	HOSPITAL NO.	AGE	SEX	NO. OF LESION IN RIGHT BREAST	NO. OF LESION IN LEFT BREAST	TOTAL NO. OF LESIONS	BREAST TISSUE	BREAST TISSUE - BPE	SHAPE	MARGIN	ENHANCEMENT PATTERN OF THE LESION	TYPE OF KINETIC CURVE	RESTRICTED DIFFUSION ON DWI	ADC values (x 10^{-3})	CHOLINE PEAK ON MR SPECTROSCOPY- (ppm)	AXILLARY LYMPH NODES	MRI FINAL DIAGNOSIS	HISTOPATHOLOGICAL DIAGNOSIS
1	782974	45	F	x	1	1	b	Mod	Oval	Cir	c	3	P	0.86	P	x	M	Squamous cell carcinoma
2	789840	28	F	1	x	1	c	Mod	Oval	Cir	c	2	P	1.1	P	2- 1 RD, 1 NRD	M	Infiltrating ductal carcinoma
3	767363	54	F	x	1	1	d	Mod	Oval	Cir	c	2	P	0.8	P	1- RD	M	Ductal carcinoma
4	782593	28	F	x	1	1	a	Mild	Round	Cir	e	1	Ab	1.8	Ab	x	B	Fibroadenoma
5	797271	42	F	1	x	1	c	Mild	Irregular	Irr	c	2	P	0.9	P	x	M	Infiltrating ductal carcinoma
6	815426	53	F	2	1	2	b	Min	Irregular	Irr	c	2	P	0.9, 1.0	P	3 -RD	M	Infiltrating ductal carcinoma
7	401616	55	M	1	x	1	b	Min	Irregular	Irr	c	1	Ab	1.4	Ab	x	B	Liponecrosis
8	857344	59	F	x	1	1	a	Min	Oval	Spi	c	2	P	0.9	P	x	M	Ductal carcinoma
9	852425	38	F	1	x	1	c	Ext	Irregular	Spi	c	3	P	1.1	P	x	M	Infiltrating ductal carcinoma
10	864285	45	F	1	x	1	c	Mod	Irregular	Irr	d	3	P	0.9	P	1 - RD	M	Medullary carcinoma
11	876189	58	F	1	x	1	b	Mild	Irregular	Irr	c	2	P	1.2	P	2 - NRD	M	Infiltrating ductal carcinoma
12	869668	55	F	x	1	1	b	Min	Irregular	Spi	b	3	P	0.7	P	1 - RD	M	Ductal carcinoma
13	865098	45	F	1	x	1	c	Min	Oval	Cir	c	2	P	0.6	P	x	M	Secretory carcinoma
14	883719	75	F	x	1	1	d	Min	Irregular	Irr	a	2	P	1	P	x	M	Infiltrating ductal carcinoma
15	869126	50	F	x	1	1	b	Mild	Oval	Cir	c	3	P	0.8	P	3 -RD	M	Infiltrating ductal carcinoma
16	876159	48	F	1	1	2	a	Mild	Oval	Cir	e	1	Ab	1.5, 1.3	Ab	1 - NRD	B	Fibroadenoma
17	879823	67	F	1	x	1	a	Min	Oval	Cir	c	2	P	0.8	P	1 - RD	M	Lobular carcinoma insitu
18	887897	55	F	x	2	2	a	Mild	Oval	Irr	c	3	P	0.8, 0.9	P	x	M	Infiltrating ductal carcinoma
19	889092	46	F	1	x	1	b	Mod	Irregular	Irr	a	2	P	1.1	P	x	M	Infiltrating ductal carcinoma
20	891674	70	F	1	x	1	b	Mild	Round	Cir	c	2	P	1.1	P	x	M	Squamous cell carcinoma
21	891520	41	F	1	x	1	b	Min	Oval	Irr	c	3	P	1.2	P	x	M	Ductal carcinoma insitu
22	876123	46	F	x	1	1	c	Mild	Irregular	Irr	c	2	P	0.9	P	x	M	Infiltrating ductal carcinoma
23	889092	35	F	2	x	2	a	Mod	Round	Cir	e	1	Ab	1.4, 1.4	Ab	1 - NRD	B	Fibroadenoma
24	898269	19	F	1	1	2	a	Ext	Oval	Cir	b	1	Ab	1.6,1.5	Ab	x	B	Fibroadenoma
25	795938	49	F	x	3	3	c	Mild	Round	Cir	e	1	Ab	1.32, 1.5, 1.6	Ab	x	B	Fibroadenoma
30	883719	75	F	x	3	3	a	Min	Round	Cir	b	1	Ab	1.7	Ab	x	B	Pure Mucinous carcinoma
27	852475	31	F	1	x	1	c	Mod	Oval	Irr	c	2	P	1.1	P	x	M	Infiltrating ductal carcinoma
28	903840	30	F	1	x	1	c	Mod	Irregular	Spi	a	3	P	0.8	P	1 - RD, 2- NRD	M	Infiltrating ductal carcinoma
29	920033	67	F	1	x	1	d	Min	Oval	Cir	c	3	P	0.8	P	1 - RD	M	Ductal carcinoma
30	925795	60	F	x	1	1	b	Mild	Oval	Cir	c	2	P	1	P	2 - RD	M	Squamous cell carcinoma
31	926208	55	F	1	x	1	b	Mild	Irregular	Irr	c	3	P	1.1	P	x	M	Intracystic papillary carcinoma
32	882674	40	F	x	1	1	c	Mild	Irregular	Irr	a	2	P	0.8	Ab	1 - RD	M	Infiltrating ductal carcinoma
8	789495	40	F	1	x	1	c	Mod	Oval	Cir	c	1	Ab	1.2	Ab	x	B	Benign Phyllodes tumor
34	827804	68	F	1	x	1	a	Min	Irregular	Spi	b	3	P	1	P	x	M	Infiltrating ductal carcinoma
17	848610	63	F	2		2	a	Min	Round	Cir	b	1	Ab	1.8	Ab	x	M	Pure Mucinous carcinoma
36	848407	24	F	x	1	1	d	Ext	Oval	Cir	e	1	Ab	2	Ab	x	B	Fibroadenoma
37	852812	32	F	x	1	1	d	Mod	Round	Cir	b	1	Ab	1.4	Ab	x	B	Fibroadenoma
38	788475	16	F	x	4	4	d	Mod	Round	Cir	e	1	Ab	1.9, 1.4, 1.5, 1.5	Ab	x	B	Fibroadenoma
39	871420	38	F	x	1	1	c	Ext	Round	Cir	e	1	Ab	1.5	Ab	x	B	Fibroadenoma
40	725146	38	F	1	x	1	b	Mild	Round	Cir	b	1	Ab	1.7	Ab	x	B	Fibroadenoma
41	955721	48	F	1	x	1	a	Min	Oval	Irr	c	2	P	0.7	P	1 - RD	M	Infiltrating ductal carcinoma

COLUMN NUMBER	TITLE	
I	Serial Number	
II	Hospital Number	
III	Age	
IV	Sex	
V	Number of lesions in right breast	
VI	Number of lesions in left breast	
VII	Total number of lesions on both sides in the patient	
VIII	Breast tissue	a - Almost entirely fat b - Scattered fibroglandular tissue c - Heterogenous fibroglandular tissue d - Extreme fibroglandular tissue
IX	Background parenchymal enhancement (BPE) of the breast tissue	a -Minimal b -Mild c - Moderate d - Extreme
X	Shape	Oval Round Irregular
XI	Margin	Cir – Circumscribed Irr- Irregular Spi- spiculated
XII	Enhancement pattern of the lesion	a-Non-mass enhancement b- Homogenous enhancement c- heterogenous enhancement d- Rim enhancement e- Dark internal septations
XIII	Type of Kinetic curve	
XIV	Restricted diffusion on DWI	P- Present Ab- Absent
XV	ADC values (x 10^{-3})	
XVI	Choline peak on MR spectroscopy- (ppm)	P-Present Ab- Absent
XVII	Axillary lymph nodes	x – absent RD - Restricted diffusion present NRD - No restricted diffusion)
XVIII	MRI Final diagnosis	M – Malignant B - Benign
XIX	Histopathological examination	