

## Retrospective Study

# Mammographic correlation with molecular subtypes of breast carcinoma

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## Abstract

**Aim:** To determine the correlation between mammographic features of breast cancer with molecular subtypes and to calculate the predictive value of these features.

**Materials and method:** This is a retrospective study of breast cancer patients presenting between January 2017 and December 2021, who underwent mammography of the breast followed by true cut biopsy and immunohistochemical staining of the tissue sample. Breast carcinoma patients without preoperative mammograms, those unable to undergo histopathological and IHC examinations and h/o prior cancer treatment were excluded. On mammography, size, shape, margins, density, the presence or absence of suspicious calcifications and associated features were noted.

**Results:** Irregular-shaped tumors with spiculated margins were likely to be luminal A/B subtypes of breast cancer. Tumors with a round or oval shape with circumscribed margins were highly suggestive of Triple negative breast cancer. Tumors with suspicious calcifications were likely to be HER2 enriched.

**Conclusion:** Mammographic features such as irregular or round shape, circumscribed or noncircumscribed margins and suspicious calcifications are strongly correlated in predicting the molecular subtypes of breast cancer and thus may further expand the role of conventional breast imaging.

## Introduction

Breast cancer is the leading cause of death due to cancer in women worldwide and the incidence has been increasing [1]. The molecular subtyping of breast cancer has become an essential requirement for treatment planning disease prognosis and avoiding overtreatment [2]. The St Galen International Expert Consensus recently classified breast cancer into five different molecular subtypes based on gene expression patterns: luminal A (LA), luminal B [(LB; HER2-), LB (HER2+)], human epidermal growth factor receptor 2 (HER2)-enriched, and basal-like (triple-negative). Pathologically, these molecular subtypes are categorized based on tumor markers' expression status: estrogen receptor (ER), progesterone receptor (PR), HER2neu overexpression, and Ki-67 index. Invasive breast cancer with ER and/or PR positive, HER2 negative and low Ki-67 index (Ki-67 <14%) are considered LA type, ER and/or PR positive with high Ki-67 index (Ki-67 ≥14%) and HER2 negative are LB(HER2-)

subtype, ER and/or PR positive with HER2 positive are LB (HER2+) subtype, ER and PR negative with HER2neu overexpression are HER2-enriched type, and breast cancer with all three receptors (ER/PR/HER2neu) negative are basal or triple-negative type [3-8].

Immunohistochemistry (IHC) is the gold standard for detecting hormone receptor (ER/PR), HER2 overexpression and Ki-67 expression status, but it is an invasive method, an expensive test and not readily available in many developing and underdeveloped countries.

The aim of the present study was to investigate the association between mammographic image features and molecular subtypes of breast carcinoma. Molecular classification by immunohistochemistry is necessary for therapeutic decision and prognosis of breast carcinoma since luminal A subtype is associated with favorable biological characteristics and a better prognosis than triple negative tumors that are associated with a poor prognosis.

## More Information

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## Materials and methods

This is a retrospective study conducted at Max Super Specialty Hospital, Saket, New Delhi. The study sample consisted of 119 known cases of breast carcinoma patients presenting between January 2017 and December 2021 who were evaluated with mammography and underwent ultrasound-guided true cut biopsy followed by histopathological and IHC examination of the sample.

The clinical and pathological results and mammography reports of 119 patients were retrospectively analyzed. The mammographic appearances were assessed according to the analytical criteria of the Breast Imaging Reporting and Data System from the database of Max Super Specialty Hospital, Saket, New Delhi.

**Inclusion criteria:** K/C/O breast cancer who underwent true cut biopsy with IHC staining. Equivocal HER2 neu cases followed by FISH.

**Exclusion criteria:** K/C/O breast carcinoma without preoperative mammograms, Patient without detailed pathological information, History of prior neoadjuvant chemotherapy, Prior cancer treatment and those unable to undergo histopathological and IHC examinations.

### Mammography interpretation

Two standard imaging views (craniocaudal and mediolateral oblique) were used for mammography, with additional views if necessary. Using the American College of Radiology (ACR) Breast Imaging-Reporting and Data System (BI-RADS) lexicon, we retrospectively examined breast density (fatty, scattered fibro glandular, heterogeneously dense, or dense) and the presence of lesions. Lesions were described as masses reporting size, shape (oval, round, or irregular) and margins (circumscribed, micro lobulated, obscured, indistinct, or spiculated); microcalcifications; masses with microcalcifications, asymmetric focal densities or architectural distortions and associated features like nipple retraction or skin thickening.

### Tissue sampling and analysis

Percutaneous imaging-guided core biopsy or surgical excision was performed to acquire a tumor sample. Specimens underwent immunohistochemistry to detect the levels of ER, PR, HER2 oncogene overexpression, and Ki-67. Stained slides were evaluated for nuclear ER or PR expression according to the College of American Pathologists guidelines ( $\geq 1\%$  cutoff for positive) by pathologists. Ki-67 index  $< 14\%$  was considered as low expression and  $\geq 14\%$  was considered high expression. HER2 expression on IHC was based on the cell membrane staining pattern with grade 2+ considered equivocal, grade 3+ considered positive, and grade 1+ or 0 considered negative. All the equivocal samples were further analyzed with fluorescence in situ hybridization where a

FISH ratio higher than 2.2 or HER2 gene copy greater than 6.0 was considered positive. Based on ER/PR/HER2 and Ki-67 expression status, breast cancers were categorized into four molecular subtypes in accordance with St. Gallen 2011 consensus surrogate definitions of the molecular subtypes:

- LA subtype: ER- and/or PR-positive, HER2-negative, and Ki-67  $< 14\%$
- LB subtype: either ER- and/or PR-positive, HER2-negative, and Ki-67  $\geq 14\%$  Or ER- and/or PR-positive and HER2-positive
- HER2-enriched type (HER2): ER- and PR-negative and HER2-positive ? Triple-negative type (TN): ER, PR, and HER2-negative [9]
- As Ki -67 was not available in all data, in our study we have kept LA and LB subtypes into one category- Luminal types. Thus, breast cancer was categorized into three molecular subtypes
- Luminal A/B
- HER2-enriched
- Triple-negative

### Statistical analysis

Our data was collected on Microsoft Office Excel 2010 and statistical analysis was performed using IBM SPSS version 20. The imaging features of different molecular subtypes were compared using univariate and multivariate analyses of data. Pearson chi-square test was used. For all the tests, statistical significance was assumed when the  $p$  value  $< 0.05$ .

## Results

Our study consisted of 119 patients with a mean age of 53.14. Out of 119 patients, 84 (70.6%) were luminal A/B 23 were TNC (19.3%) and 12 were HER 2 enriched (10.1%) molecular subtypes. Most breast cancers had irregular shapes 84 (70.6%). The irregular shape was most common in luminal A/B types 66 (78.6%). The round or oval shape was most commonly seen in TNC 12 (52%). HER2 enrich cancer mostly had irregular shapes 7 (58.3%). There was a significant association between shape and breast cancer ( $p$  - value = 0.048).

Circumscribed margins were more common in TNC 6 (85.7%). Circumscribed margins were uncommon in luminal types 1 (1.1%) and none in Her 2 enrich 0(0). Spiculated margins were the most common margins in breast cancer patients 71 (59.7%), followed by indistinct margins 24 (20.2%), micro lobulated 16 (13.4%), circumscribed 7 (5.9%), and the least common was obscured margin 1 (0.8%). Spiculated margins were more commonly seen in luminal A/B 58 (81.7%) followed by TNC 8 (11.3%) and HER2 enrich 5 (7%). Indistinct margins were most common

in luminal A/B 15 (62.5%) followed by TNC 6 (25%) and Her 2 enrich 3 (12.5%). Micro lobulated margins were most commonly seen in luminal A/B 9 (56.2%) followed by Her 2 enrich 4 (25%) and TNC 3 (18.8%).

There was a significant association between margins and breast cancer ( $p$  value < 0.001).

High-density masses in mammograms were the most common 74 (62.2%) of which luminal A/B was the most common molecular type 54 (73%) followed by TNC 16 (21.6%) and HER2 enrich 4 (5.4%). 42 (35.3%) of breast cancer presented as isodense masses. Isodense masses were most common in luminal types 27 (64.3%) followed by Her 2 enrich 8 (19%) and TNC 7 (16.7%). Hypodense masses were the least common 3 (2.5%). There was no significant association between density and breast cancer.

Out of 119 patients, 48 (40.3%) had calcifications. The most common type of breast cancer associated with calcifications was the HER2 enrich subtype (50%) followed by luminal A/B subtypes (42%) In TNC, calcifications were not so common (26%). The most common type of calcification seen in HER2 enrich patients was pleomorphic (41.7%). The most common type of calcification seen in Luminal A/B subtypes was pleomorphic (44.5%). There is no significant association between calcifications and breast cancer ( $p$  - value = 0.658).

Architectural distortion was seen in a small number of cases 8 (6.7%) and was most common in luminal A/B 5 (62.5%). Only 24 (20.2%) out of 119 patients had associated features among which 19 (16%) had nipple retraction and 15 (12.6%) had skin thickening. Luminal A/B was the most common type of breast cancer associated with nipple retraction 16 (84.2) and skin thickening 12 (80.0%) (Figures 1, 2).

## Discussion

In this study, we analyzed the associations between mammographic features with molecular subtypes of breast cancer categorized based on receptor status (ER, PR, HER2+, and Ki67) determined by IHC.

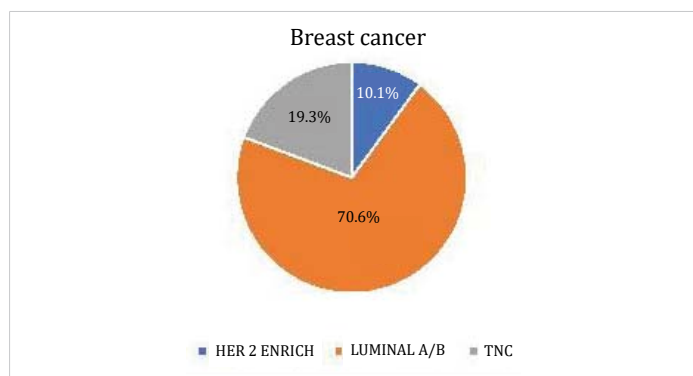


Figure 1: Pie chart showing the distribution of 3 molecular subtypes.

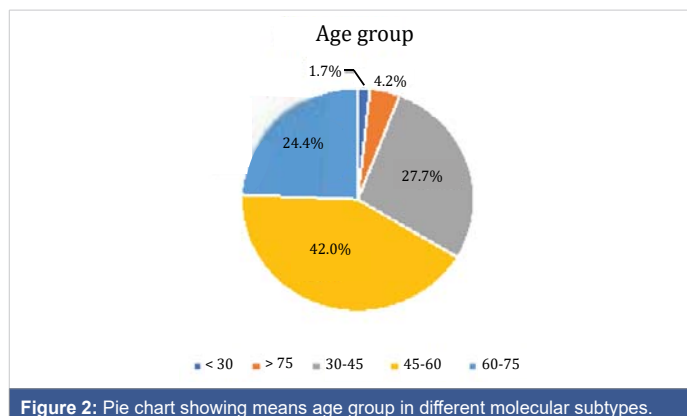


Figure 2: Pie chart showing means age group in different molecular subtypes.

In our study, luminal A/B subtypes showed a significant positive association between having irregular shapes and spiculated margins in a mammogram ( $p$  value = 0.048 and < 0.001 respectively). These findings were similar to a study done by Anupama, et al. who reported that tumors with noncircumscribed margins had 9.5 times higher chances of having hormone receptor positivity [10]. Similarly, Celebi, et al. found that tumors with combined findings of non-circumscribed margins and posterior shadowing were found to have a 10.58 times higher association with luminal subtypes [11]. In our study, 52% of TNC were seen as round or oval, masses with circumscribed margins. TNC reportedly has associated microcalcifications less frequently than other phenotypes [12-14]. In our study, only 26% of TNC had calcifications. Our report supports previous reports where TNCs were mistaken for benign lesions due to their benign appearing features.

In our study most common type of breast cancer associated with calcifications was HER2 enrich followed by Luminal A/B. In a study done by Seo, et al. and Zhang, et al, tumors detected to have microcalcifications on mammograms were strongly associated with HER2 overexpression [15,16]. Sun, et al. reported malignant calcification to be more frequent in HER2/ neu-positive tumors [17].

Boisserie-Lacroix, et al. stated that the presence of calcifications in the mammogram may predict a HER2/neu-positive status when the HER2 score is equivocally 2+ in immunohistochemistry [18].

In our study, pleomorphic calcifications were the most common type seen in HER2 enrich subtypes. Cen, et al. and Patel, et al. also found that HER2-enriched tumors were more likely to have heterogeneous and pleomorphic microcalcifications on a mammogram [19,20]. HER 2 enrich had irregular shapes with spiculated margins.

Most breast cancers presented as high-density mass followed by isodense mass.

Also, there was no significant difference in the diagnosis of nipple retraction by mammography in 3 different subtypes ( $p$  = 0.788) which was consistent with Jiang, et al. study [21].



Architectural distortion with nipple retraction and skin thickening was most common in luminal types.

## Conclusion

Tumor shapes, margins and the presence of suspicious calcifications on mammography can be correlated in predicting the molecular subtype of breast cancer, and thus may further expand the role of conventional breast imaging for a more precise diagnosis of breast cancer. Tumors with irregular shapes and non-circumscribed margins are predicted to be LA or LB subtypes. Tumors with suspicious calcifications are strongly predicted to be HER2 subtypes. Oval or round shape tumors with circumscribed margins with absent calcifications are predicted to be triple-negative types of breast cancer. IHC-based classification of breast tumors can be helpful since the predictive power of IHC criteria appears to be similar to that of gene expression analysis, this information can be used to improve therapeutic decisions, mainly for luminal B, HER2-overexpressing and basal-like subtypes. The luminal A subtype is associated with favorable biological characteristics and a better prognosis than triple negative tumors which is associated with a poor prognosis and unfavorable clinicopathological characteristics. Our results should be confirmed by large studies conducted in other institutions and hospitals.

### Supplementary tables

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