A pictorial review of breast cancer's radiogenomic

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Authors: B. Mannato¹, C. V. Castro², M. S. Dantas do Amaral Campos³, M. A. longo galvao da silva³, D. Roveda⁴, G. Badan², R. OLIVEIRA SELETI², B. Maragno², ¹São Paulo, SP/BR, ²São Paulo/BR, ³SÃO PAULO/BR, ⁴05410002, Sa/BR
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Learning objectives

The main objective of this pictorial review is to show the most prevalent imaging patterns of the different molecular subtypes of breast cancer (Luminal A/B, Her2, Basal-Like Intrinsic (triple negative)) in the mammography (MMG), ultrasound (US) and magnetic resonance (MR).
Background

Breast cancer is the most common cancer in women and a leading cause of cancer death worldwide. It is a genetically and clinically heterogeneous disease, and can be broadly categorized into in situ carcinoma and invasive (infiltrating) carcinoma. [1,2,4]

Traditional classification of breast cancer is based on the clinicopathologic analysis of tumors, with classes of breast cancer defined by histopathologic features, including the pattern of architectural growth and the nuclear grade (low, intermediate, or high). Invasive breast carcinoma can be defined by the extension of tumor cells through basement membrane and loss of myoepithelial cell layer, being categorized by histomorphological criteria into invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and other less common subtypes. IDC is the most common subtype accounting for 70-80% of all invasive lesions. [1,4,5]

This model for breast cancer classification offers limited prognostic value, with patients at the same stage of disease having markedly different clinical courses and clinical outcomes. [3,4]

Immunohistochemical techniques, utilized to measure expression of estrogen receptor (ER), progesterone receptor (PR) and overexpression of human epidermal growth factor receptor 2 (HER2/neu), has allowed a new classification that offers prognostic value, with predictive categories of disease aggressiveness. [1-5]

This classification subdivides breast cancer intro three main molecular subtypes:

- **Luminal Intrinsic Subtype**

The luminal intrinsic subtype represent up to 70% of breast carcinomas and are characterized by expression of ERs and PRs. It is the breast cancer carries the best prognosis of all intrinsic subtypes. There are two subtypes within luminal-like tumors, luminal A and luminal B. [1,3,4]

1. Luminal A cancers are usually low-grade tumors, with a low Ki-67 proliferative index. Overall, luminal A breast cancer is associated with the most favorable prognosis, with a 5-year survival rate of more than 80%. [1,3-5]
2. Luminal B breast cancers have higher Ki-67 levels, showing greater proliferative activity. These cancers are usually mid- to high-grade tumors. [1,3-5]

- **HER2-Enriched Intrinsic Subtype**

  Represents 15-20% of invasive breast cancers. Is defined by overexpression of the HER2/neu gene and a lack of expression of genes characteristic of the luminal subtypes. Are generally intermediate to high grade tumors, with an aggressive course and higher incidence of local recurrence. [4,5]

- **Basal-Like Intrinsic Subtype**

  Basal-like breast cancer is more common in BRCA1 mutation carriers and in young black women. It is estimated that 12%-17% of women diagnosed with breast cancer have triple-negative cancer. The most common basal-type gene signature is the triple-negative (ER-negative, PR-negative, and HER2-negative) type. Patients with triple negative breast cancers have been shown to carry a poorer prognosis when compared with patients that have non-triple negative tumors. [2,4,5]

  The imaging aspects of tumors correlate with molecular subgroups, as well as other pathologic features such as nuclear grade. [2,4,5]
Findings and procedure details

A review of breast biopsies performed in our institution over the last two years composed the primary data for this study, followed by the selection of the biopsies that had undergone molecular analysis and finally their classification into the three classical molecular subtypes - Luminal (A and B), HER2 and Basal-Like Intrinsic (triple negative). Then, a retrospective analysis was conducted for each group, in order to determine the most prevalent findings within the distinct imaging tests available (mammography, breast ultrasound and magnetic resonance imaging), based on the ACR-BIRADS descriptors.

A literature survey was accomplished by using the "Web of Science" and "PUBMED" online databases, and the descriptors were defined based on their Medical Subject Headings (MeSH), namely the terms and variations related to mammography, ultrasound, magnetic resonance imaging and breast cancer molecular subtypes. The search time frame included the last ten years, and only articles in the languages english, spanish or portuguese were selected. No other criteria was applied, other than the inclusion of articles that discussed mainly the correlation between the molecular subtypes of breast cancer and their imaging findings, as long as they presented relevant bibliographic sources and scientific rigour.

IMAGING FINDINGS OF THE MOLECULAR SUBTYPES OF BREAST CANCER

• LUMINAL INTRINSIC SUBTYPE

Mammography

In our institution and in agreement with the relevant literature, the most frequent presentation was the irregular mass with spiculated margins. (Fig. 1 on page 9) [4,6] Secondly, microcalcifications (generally pleomorphic) have certain significance and are frequently associated with masses. (Fig. 2 on page 9)

Ultrasound

This study is also in accordance with the literature with regards to the most common ultrasonographic finding: the irregular, hypoechoic, non-circumscribed mass. (Fig. 3 on page 10) [4,7,8]

Magnetic Resonance Imaging
As in the previous methods, the present study agrees with the literature in reference to magnetic resonance imaging results. The mass with irregular shape and margins with an early and heterogeneous enhancement peak in the dynamic phases was the most prevalent finding. (Fig. 4 on page 10) [4,9,10]

Despite being divided into luminal A and B, up to the present study there has been no consensus regarding differences in imaging between the two histological subtypes. Therefore, the image findings were similar for both.

- **HER2 - ENRICHED INTRINSIC SUBTYPE**

**Mammography**

A review of the literature shows that microcalcifications are the most common image findings, as well as predictors of the likelihood of this subtype, particularly the fine linear and/or fine linear branching microcalcifications. (Fig. 5 on page 11) The distribution and association with masses varies, but some meta-analysis have shown no statistical significance. [7, 8, 11, 12]

In our institution, the most frequent presentation was the irregular mass with indistinct or spiculated margins, some of which were associated with pleomorphic microcalcifications. (Fig. 6 on page 11)

**Ultrasound**

The literature sets forth various imaging findings, which are in most cases, not evidentiated by this method. When visible, the most common findings are the hypoechoic, non-circumscribed masses with posterior acoustic shadowing. [7, 8, 11]

Within our institution, the irregular, non-circumscribed, hypoechoic mass with posterior acoustic shadowing was frequently found. (Fig. 7 on page 12)

**Magnetic Resonance Imaging**

A review of the literature demonstrated a great discrepancy of results amongst the published studies. However, Elias SG et al, in his meta-analysis, showed that the irregular mass with spiculated margins, a fast initial kinetic curve and washout is highly correlated to the HER2 subtype. [11,13,14]

The data collected in our institution, corroborates the aforementioned researcher's work, the most common finding being the irregular shaped mass with irregular margins, early and heterogeneous enhancement with washout. (Fig. 8 on page 13)
BASAL-LIKE_INTRINSIC_SUBTYPE

Mammography

Data from the literature on mammographic findings are very diverse, with histology as the main independent variable at the moment of diagnosis. Thus, when an early diagnosis is made, most articles describe masses with characteristics leaning towards benignity (oval or round, with circumscribed margins and absence of calcification), as the major finding. However, when diagnosed late, the irregular masses, with indistinct or microlobulated margins are the leading findings. [15 - 17]

In our institution, the most frequent presentation was the irregular mass, with indistinct margins and high density. (Fig. 9 on page 13) In second place, round or oval masses, mainly with indistinct margins are somewhat representative. (Fig. 10 on page 14)

Ultrasound

Similarly to the mammography, the relevant literature places the mass with a tendency towards benignity as the most common, especially when diagnosed in the early stages. (Fig. 11 on page 15) [8,15 - 17]

In our institution, the most frequent finding was the irregular, hypoechoic non-circumscribed mass, without posterior acoustic findings. (Fig. 12 on page 15)

Magnetic Resonance Imaging

Most of the literature describes as the most frequent finding, masses that are generally oval or round, with well defined margins, hypersignal on the T2-weighted sequences and ring enhancement. (Fig. 13 on page 16) [9, 18 - 20]

In our institution, the masses with irregular shape and margins and early, heterogeneous enhancement was the most common finding. (Fig. 14 on page 17)

Given the above, the present study has demonstrated a few differences between the findings found in the literature and those from our institution, which we account mainly to the hypothesis of late diagnosis, especially since our service is focused predominantly on the public health service, which further delays the diagnosis.

Among the limitations of this study are the short period of data collection, thus limiting the available "N". Furthermore, the choice of a simple analysis of the most prevalent findings rather than a systematic review and meta-analysis, may well have contributed to some
of the divergences observed. Therefore, further studies with a more detailed statistical analysis may provide more reliable results.
**Fig. 1:** Bilateral mediolateral oblique (MLO) and compression view mammogram show irregular mass with spiculated margins of the left breast (arrow).

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**Fig. 2:** Bilateral MLO and compression view mammogram shows irregular mass with spiculated margins of the left breast, with fine pleomorphic calcifications within the mass (circles).
Fig. 3: Ultrasound (US) image shows hypoechoic, irregular shaped mass, with indistinct margins.
**Fig. 4:** Axial T2 (A) and post-contrast (B) Magnetic Resonance (MR) images show irregular shaped mass (arrow) with irregular margins of the left breast, showing early and heterogeneous enhancement.

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![Axial T2 and post-contrast MR images showing irregular shaped mass with irregular margins.](image)

**Fig. 5:** Bilateral MLO and magnification view mammogram show pleomorphic calcifications with linear distribution of the right breast (circles). Additional findings: oval, isodense mass, with indistinct margins in retroareolar right breast.

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![Bilateral MLO and magnification view mammogram showing pleomorphic calcifications.](image)
Fig. 6: Bilateral MLO and compression view mammogram show irregular mass with spiculated margins (arrow) of the left breast.

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**Fig. 7:** US image shows hypoechoic, irregular shaped mass, with indistinct margins.

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**Fig. 8:** Axial T2 (A) and post-contrast MR images (B) show irregular shaped mass with irregular margins of the left breast, showing early and heterogeneous enhancement (arrow).

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**Fig. 9:** Bilateral MLO and compression view mammogram show irregular mass (arrow) of high density with indistinct margins in left breast.

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**Fig. 10:** Bilateral MLO and compression view mammogram show oval mass (arrow) of equal density with indistinct margins in right breast.

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**Fig. 11**: US image shows oval mass, hypoechoic with microlobulated margins, orientation parallel and discreet shadowing posterior in right breast.

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Fig. 12: US image shows irregular mass, hypoechoic with spiculated margins, orientation not parallel and without posterior acoustic features in left breast.

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**Fig. 13:** Axial T2 (A) and dynamic contrast-enhanced (B) MR images show an oval mass with circumscribed margins and with heterogeneous internal enhancement in left breast (arrow).

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**Fig. 14:** Axial T2 (A) and dynamic contrast-enhanced (B) MR images show an irregular mass with irregular margins and with heterogeneous internal enhancement in left breast (arrow).

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Conclusion

The advent of gene expression analysis has shown that tumor cell response to treatment is not determined by anatomical prognostic factors but rather intrinsic molecular characteristics, therefore, breast cancer molecular signatures open the door to personalized therapeutic options.

The molecular subtypes of breast cancer have been shown to translate into specific imaging phenotypes and it is important to the radiologist do acknowledge those patterns.
References


