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Molecular Subtypes and Imaging Biomarkers in Breast Cancer: A Systemic Literature Review

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Background: Breast cancer ranks first in cancer incidence worldwide. As the leading cause of cancer death in women, breast cancer has become one of the major threats to human health. Approximately 20% of metastatic breast cancer patients only survive for 5 years. Molecular approaches refer to genetic analysis and specific biomarkers associated with breast cancer development. These include BRCA1 and BRCA2 gene mutations, as well as protein expression such as HER2, estrogen receptor (ER), and progesterone receptor (PR). Molecular testing is used to determine the cancer subtype (such as luminal A, luminal B, HER2+, or triple-negative breast cancer) which is important for determining the right therapy, such as hormone therapy or HER2-targeted therapy. Methods: Systematic Reviews, published between 2015 and 2024 worldwide were selected through searches of PubMed, Scopus, Embase, Web of Science, and the Cochrane Library. Conclusion: Breast cancer consists of heterogeneous subtypes and continues to develop after systemic therapy. Previous studies correlating imaging features and molecular subtypes have reported the presence of calcifications, margin or shape features, and enhancement features on dynamic contrast-enhanced MRI corresponding to each subtype. Recent studies using radiomic parameters, which are invisible to the human eye, have demonstrated high accuracy in differentiating molecular subtypes, predicting response to chemotherapy, and predicting survival outcomes. Imaging biomarkers may help in realizing better precision medicine due to the feasibility of repeated measurements across the entire tumor and the application of deep learning-based algorithms.

Keywords: breast cancer; molecular subtypes; BRCA mutations; Imaging biomarkers; Radiomics.

1. Introduction

Breast cancer ranks first in cancer incidence worldwide. As the leading cause of cancer death in women, breast cancer has become one of the major threats to human health.1 The prognosis of breast cancer has been significantly improved through targeted therapy, radiotherapy, and immunotherapy.2 However, some breast cancer patients still suffer from breast cancer. The prognosis is poor; about 20% of metastatic breast cancer patients survive only 5 years.3 Several randomized controlled trials have shown that mammography screening reduces breast cancer mortality in women over the age of 50 years.4 Breast lumps have been reported as the most common breast symptom in adult women in Western Nigeria and are benign in 60% of cases. In Southeast Nigeria, fibroadenoma is reported to be the most common breast disease (47.5%), followed by carcinoma (30.4%) and fibrocystic disease.5 Molecular approaches refer to genetic analysis and specific biomarkers associated with breast cancer development. These include mutations in the BRCA1 and BRCA2 genes, as well as the expression of proteins such as HER2, estrogen receptor (ER), and progesterone receptor (PR). Molecular testing is used to determine the subtype of cancer (such as luminal A, luminal B, HER2+, or triple-negative breast cancer) which is important for determining appropriate therapy, such as hormone therapy or HER2-targeted therapy.17,18 The purpose of this study was to identify and analyze the correlation between radiologic and pathologic findings in breast disease. Breast imaging radiologists are integral members of the multidisciplinary breast team that provides diagnostic screening and care. In this role, breast radiologists routinely perform image-guided biopsies of suspicious breast lesions and are tasked with determining radiologic-pathologic concordance. Determining concordance requires an understanding of breast anatomy, the histopathologic features of various breast diseases, and expected imaging findings. Gaining insight into how pathologists characterize and classify biopsy specimens may allow for more astute radiologic-pathologic correlation, thereby optimizing management.6

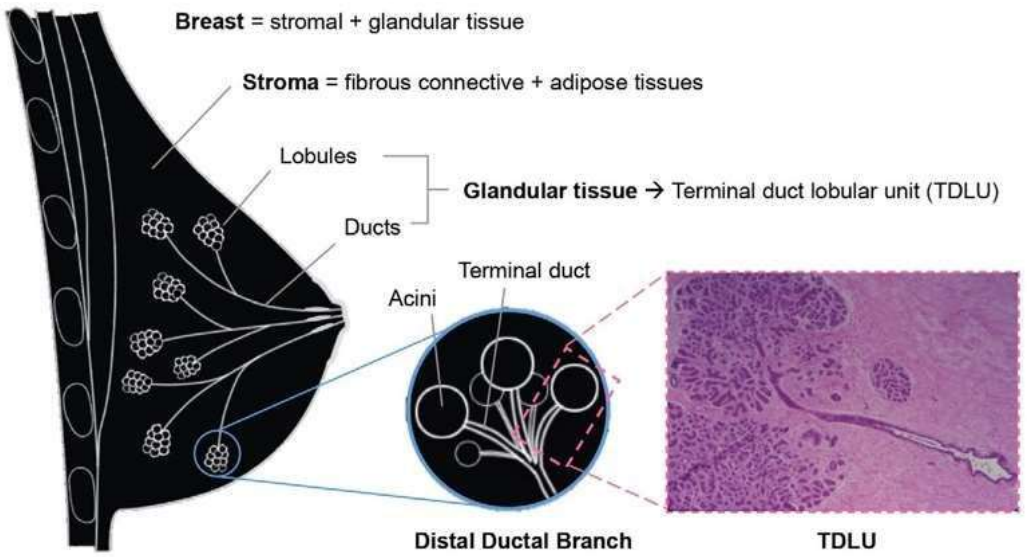

Figure 1. Schematic illustration depicts normal breast anatomy.6

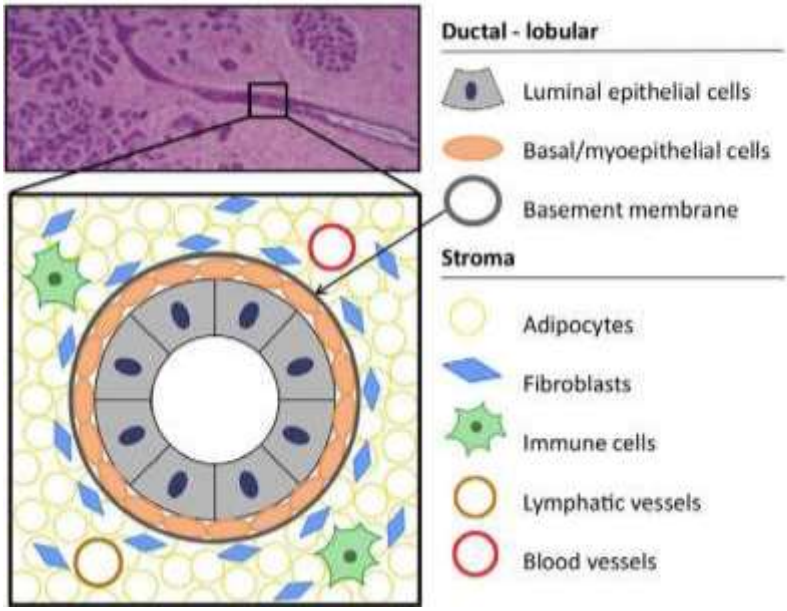

Figure 2. Schematic illustration depicts normal cellular anatomy of a breast TDLU (terminal duct lobular unit).6

The basic functional unit of the breast is the terminal ductal lobular unit (TDU). The TDU is the most important component because all major breast diseases originate from this functional unit. The development of fibrocystic disease is related to hormonal status, as studies have shown a positive relationship between estrogen and fibrocystic disease. Fibrocystic disease is the result of an aberration in the normal process of development and involution (ANDI) accompanied by hormonal irregularities. There is a high prevalence of FCC among patients with polycystic ovary disease (PCOD) and those undergoing hormone replacement therapy. ANDI results in apocrine metaplasia, clear cell change, eosinophilic change, and microcystic involution. These epithelial changes result in epithelial hyperplasia, and accumulation of secretions that cause duct dilatation, which in turn leads to cyst formation, causing calcification on mammography. Histologically, normal breast tissue may also show abnormalities, many of which are not detected clinically or by imaging. On ultrasound, lesions are usually bilateral. Focal lesions are less common than widespread lesions.8 Simple cysts (Figure 1a) are the most common imaging finding in FCC on US.10 These cysts are usually multiple and bilateral, either singly or in clusters. This group of lesions is categorized as BI-RADS 2 according to the ACR guidelines. The above two categories are usually followed up.9

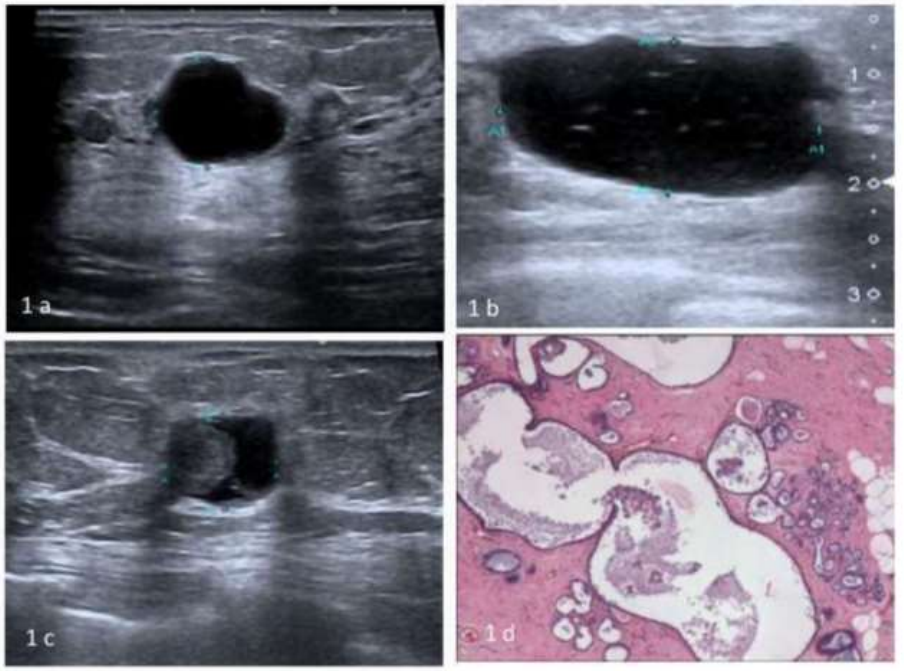

Figure 3.1a: USG shows a clear cyst with posterior acoustic enhancement. 1b: USG shows a complicated cyst with internal echoes and posterior acoustic enhancement. 1c: USG shows a complex solid cystic mass with solid components and eccentric septation. 1d: Light microscopy shows breast tissue with cystically dilated ducts, filled with secretions (H&Ex40).

Mammographic breast density, a strong risk factor for breast cancer associated with a 4- to 6-fold increased risk, is influenced by genetic and environmental factors, and familial correlations of breast density have been identified among twins and family members. Because some breast cancer risk factors show clustering or familial association, some studies have focused on the assumption that these factors may modify each other's influence on breast cancer risk. Breast density and its associated breast cancer risk were higher in women with a family history of breast cancer, suggesting an interaction between family history and breast density. In older women, the risk of breast cancer associated with first-degree family history varied by breast density and age group. Other studies have found no interaction between breast density and family history of breast cancer on breast cancer risk.7

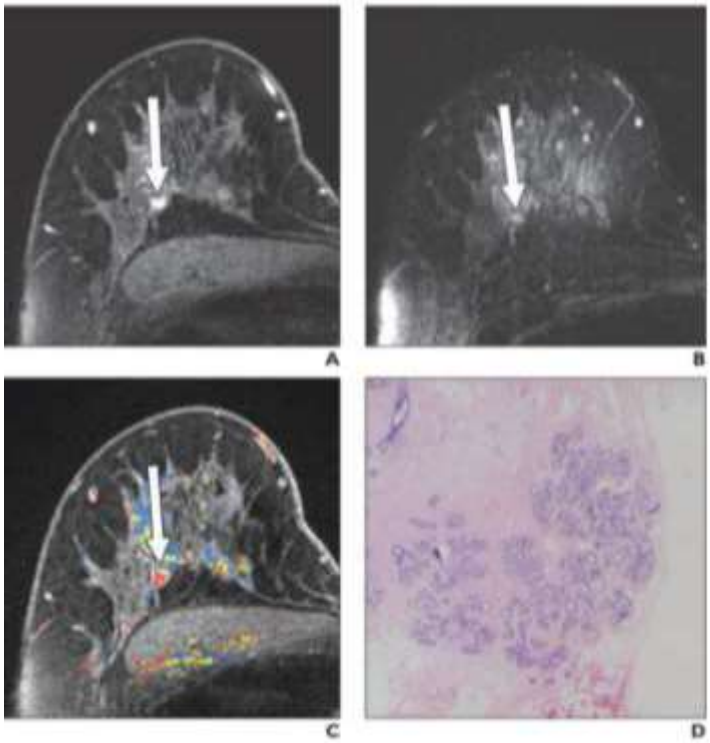

Figure 4.Fibroadenoma in a 49-year-old woman with a history of left breast cancer who underwent high-risk MRI. (A) Axial T1-weighted contrast-enhanced MR image shows a 7-mm oval mass (arrow) with partially circumscribed and partially irregular margins in the right breast. (B) Axial T2-weighted MR image shows that the lesion (arrow) is mildly hyperintense. (C) The lesion (arrow) shows rapid initial enhancement with delayed washout on dynamic contrast images. (D) Photomicrographs (H and E, x4) of pathologic specimens from MRI-guided core biopsy show fibroadenoma. Sections stained with H and E show a collection of dilated ducts lined by benign ductal cells and surrounded by distinctive stroma in a fibroadenoma pattern, pericannicular type.7

2. Methodology

Systematic Reviews, published between 2015 and 2024 worldwide were selected through PubMed, Scopus, Embase, Web of Science, and Cochrane Library searches. Keywords such as correlation, radiology, pathology and breast cancer and a combination of both were used in the search. The method used in this writing is a systematic literature review which is a systematic, explicit and reproducible method for identifying, evaluating and synthesizing research results. Literature reviews will provide an overview of the development of a particular topic. Systematic Review is a term commonly used for a methodology in certain research or studies, this development is carried out to collect and evaluate research related to a particular topic focus. The study uses descriptive analysis of the data obtained. The sources of literature used in compiling this systematic literature review are through National and

International Journal Websites such as Google Scholar, PubMeds, Proquest, Wiley, Science Direct, Scopus, and Elsevier. The articles obtained amounted to 20 articles published between the time span of 2015 - 2023 and will be analyzed using the systematic literature review method including the activities of collecting, evaluating, and developing research with a specific focus. The author seeks data or literature materials from journals or articles so that they can be used as a strong foundation in the content or discussion.

3. Results

Molecular Breast Cancer Imaging in the Era of Precision Medicine

Medicine today is moving towards precision medicine that rejects the old approach of one parameter for all diseases. There has been continuous evolution and development in the field of molecular imaging. Molecular imaging is defining its role in the era of precision medicine with improved techniques and instrumentation that can help in improving detection and characterization of breast lesions by providing specific cellular information including the presence of specific targets. This will not only help in diagnosis and management but will also help in tailoring therapy and predicting outcomes. Molecular imaging holds promise for precision medicine as specialized techniques are gradually being recognized as valid and useful tests for selected patient groups, particularly those underserved by currently available modalities.10

Current Histopathology Classification

The current WHO classification includes (i) adenosquamous carcinomas that are predominantly low-grade but have the potential to be high-grade (ii) pure squamous cell carcinomas (iii) pure spindle cell carcinomas (iv) fibromatosis-like metaplastic carcinomas, (iv) metaplastic carcinomas with mesenchymal differentiation that include chondroid (myxoid/cartilage), osseous (bone), rhabdomyoid (muscle), and neuroglial, and (v) mixed metaplastic carcinomas that may consist of multiple metaplastic elements or a mixture of epithelial and mesenchymal elements11. Examples of heterologous elements are shown in Figure 5.

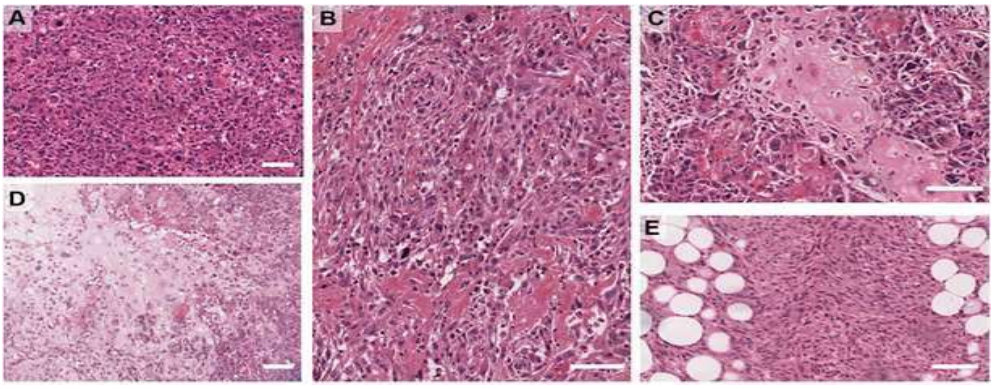

Figure 5. Examples of metaplastic breast cancer morphology. (A) High-grade pleomorphic differentiated carcinoma. (B) High-grade carcinoma with focal squamous differentiation. (C)

Osteoid differentiation. (D) Chondroid differentiation. (E) Spindle differentiation. Scale bar is 100 μm.

Why Molecular Techniques?

Conventional methods of breast cancer detection rely on morphological investigation of tissue changes by a pathologist. Breast tissue can be obtained by fine needle aspiration or surgical resection by a trained technician. The biopsy must undergo a complex technical procedure and the slide is ready to be observed by the pathologist under the microscope and interpreted for further decision making by the clinician. However, a review of the literature on the status of laboratory medicine in Africa shows a very high level of subjectivity in the interpretation of results which is partly due to the poor quality of reagents used to process the material, the quality of the tissue obtained, potential errors in the tissue processing steps and the technical skills of histotechnologists and pathologists.

In some cases, there are serious unavoidable errors observed in the pathological diagnosis of patient samples, even in advanced settings with state-of-the-art pathology services. This type of diagnostic subjectivity and error rate can be substantially minimized with the application of molecular technologies. Data on the error rate of pathological reports in Africa are not available in the literature. This may be due to the lack of commitment by public and professional authorities, the absence of health insurance investigations and poor awareness by patients. In addition, lawsuits for misdiagnosis of cancer are not filed when doctors fail to perform timely examinations, use outdated instruments and procedures, or fail to diagnose. However, based on the current status of pathology services on the continent, it is possible to speculate that there is a high rate of misdiagnosis of cancer. In addition to the financial and psychological costs, failure to diagnose cancer in a timely manner can delay potentially life-saving treatments and lead to premature death, along with painful and debilitating side effects.12 Detection of molecular alterations provides genetic identification of the presence of a particular tumor subtype and indications for drugs that target specific abnormal molecular functions. Currently, phenotypes and genotypes of different tumor subtypes can be performed to improve the accuracy and reproducibility of cancer diagnosis. Research findings also suggest that the use of clinically confirmed molecular biomarkers can help detect small numbers of malignant cells in cytology or biopsy specimens obtained through minimally invasive diagnostic techniques. Therefore, comprehensive cancer pathology should include a complete investigation of biological tissues through combined histological, immunohistochemical and molecular evaluations.12

Molecular Testing as a Prognostic and Predictive Tool in Breast Cancer

The assessment of predictive markers is mandatory in breast cancer diagnostics, as it allows to tailor specific adjuvant or neoadjuvant systemic therapies or targeted therapies in the regulation of metastatic tumors. Established markers are hormone receptors (ER, PR), Her2 status, and proliferation index through Ki67 labeling, which should be determined in all newly diagnosed breast cancers and should be retested in recurrent or metastatic lesions, if tissue is available. In addition, evidence of further sequencing-based alterations such as the PIK3CA pathway, BRCA1/2 mutations, NTRK fusions, microsatellite instability (MSI), or mutations in the ESR1 or ERBB2 genes are important tools to tailor individual targeted therapies.13

Hormone receptors (ER estrogen, PR progesterone)

Both ER and PR should be tested in every primary breast carcinoma and should be reassessed in every recurrent/metastatic lesion if tissue is available for testing, as differences in expression profiles can occur in up to 50% of cases. Positive ER status is a prerequisite for endocrine therapy (eg, aromatase inhibitors or selective estrogen receptor modulators) and is associated with a good prognosis. If PR is also positive, these tumors, classified as luminal-A tumors, show a good outcome. The methodology used is immunohistochemistry (according to internal and external quality assurance guidelines), which should provide a percentage of positively stained nuclei of the invasive tumor component (minimum limit of 1%, however, cases with positivity between 1 and 10% behave biologically similar to TNBC). Approximately 80% of BC are ER positive and up to 70% PR positive.13

Her2 status including Her2 low and Her2 mutation status

Her2 status is another mandatory marker, which should be tested in every primary breast carcinoma and should be reassessed in every recurrent/metastatic lesion if tissue is available for testing. Discrepancies in Her2 status are not very frequent; however, up to 30% of immunohistochemistry or ISH results may change during the course of the disease, possibly through clonal differentiation or clonal resistance to established therapy given to the primary tumor.13 Routine Her2 testing methods are immunohistochemistry alone with complementary ISH or ISH for Her2 alone. Both approaches are approved by ASCO/CAP guidelines. Her2 positivity, which qualifies a patient for anti-Her2 therapy, requires an immunohistochemistry score of 3+ or ERBB2 gene amplification on ISH regardless of IHC results. Approximately 10-15% of BC are Her2 positive.13 The newly described Her2-low category represents a subgroup of BC with an immunohistochemistry score of 1+ or 2+ without amplification on ISH. These cases are eligible for Trastuzumab-Derutexan (T-DXd) therapy for unresectable or metastatic breast carcinoma as second-line treatment. Her2 (ERBB2) activating point mutations are frequently detected in ER-positive carcinomas sequenced by NGS, especially in metastatic invasive lobular carcinoma (up to 8%). In these cases, a dual combination therapy regimen with an anti-hormonal and anti-Her2 regimen with Neratinib can be discussed.13

Intrinsic Molecular Classification

The pioneering molecular classification was performed by Perou et al2 in the early part of this century. Using complementary DNA microarrays representing 8102 human genes, they first characterized a set of 65 surgical specimens of breast tumors from 42 individuals, and found that tumors could be classified into distinct subtypes based on broad differences in gene expression profiles (GEPs). With further research and refinement, the authors proposed a classification scheme that divided breast cancers into 4 intrinsic molecular subtypes: luminal A, luminal B, v-erb-b2 (ERBB2)/human epithelial growth factor receptor 2 (HER2) gene overexpression (HER2þ), and basal-like. Luminal carcinomas characteristically express estrogen receptors (ERs) with variable cell proliferation. HER2 overexpression is a hallmark of ERBB2-overexpressing tumors that also lack ER and progesterone receptor (PR) expression. Basal-like carcinomas fail to express ER, PR, or HER2 (triple-negative carcinoma; TNBC), instead expressing basal cell markers, such as cytokeratin (CK) 5/6 and/or epidermal growth factor receptor (EGFR). This subtype exhibits distinct histologic

patterns, clinical features, and prognoses. Its development appears quite interesting. However, adoption of GEP testing by general pathology laboratories has been difficult due to its technical complexity and ineffectiveness. Therefore, alternative methods to simulate GEP results have been sought. Cheang et al5-7 identified a novel immunohistochemistry (IHC) panel, including 6 IHC markers, and found that it could recapitulate the biological subgroups of breast cancer derived from full GEP. Schnitt later summarized the IHC diagnostic criteria of the intrinsic classification as follows: (1) luminal A: ERþ and/or PRþ, HER2, and Ki-67 low (,14%); (2) luminal B: ERþ and/or PRþ, HER2þ or HER2, and high Ki-67 (,14%); (3) HER2þ: ER, PR, and HER2þ; and (4) basal-like (BLBC): ER, PR, HER2 (triple negative), plus CK 5/6þ, and/or EGFRþ. These criteria were adopted by the 2013 European St Gallen Consensus with slight modifications by increasing Ki-67 to 20% or more and reducing PR to 20% or less for better separation.14

Molecular imaging is a non-invasive medical imaging method that allows visualization, characterization, and measurement of biological processes at the molecular and cellular levels in tumors. In contrast to conventional imaging modalities that mainly depict differences in tissue or organ structure, molecular imaging reveals the physiological activity or expression status of specific molecules in tissues or organs using medical imaging modalities with or without tracers.15

Luminal Cancer

Luminal cancers have an immunophenotypic pattern similar to the epithelium, the luminal component of the milk ducts in normal mammary glands, mainly expressing low molecular weight luminal cytokeratins (CK7, CK8, CK18, etc.), E receptors and related genes (LIV1 and cyclin D1). They have a low association with proliferative genes. Three groups are distinguished from the IHC point of view: Luminal A, Luminal B and Luminal HER2.16

Luminal A subtype (E+, Pr+, HER2- and Ki-67 <14%)

This is the most common and least aggressive subtype, with a very good prognosis, with very low expression of proliferative genes. Here, the tumors are E receptor-positive, Pr-positive (at least 20%) and HER2-negative, with low Ki-67, less than 14%. By expressing E receptors, these carcinomas are susceptible to treatment with hormonal therapy (tamoxifen or aromatase inhibitors), in addition to surgical or radio/CT treatments that may be needed. It is worth noting that they show a low response to NACT, only 6% have a complete response.16

Luminal B subtype (E+, Pr+/-, HER2- and Ki-67: 14-30%)

Luminal B subtype cancers are E receptor positive, although usually expressed in lower amounts, can also be Pr-positive or negative, HER2-negative with an intermediate proliferation index, greater than 14%, but less than 25-30% and generally have an intermediate/high histological grade. Note that most BRCA2 cancers fall into this group. These tumors can benefit from hormone therapy together with chemotherapy (CT). Increased Ki-67 makes them grow faster than Luminal A and therefore have a worse prognosis.16

HER2 positive cancers

The HER2 proto-oncogene (or cerb-B-2) is found on chromosome 17 and is overexpressed in many epithelial tumors. This gene encodes a protein in the membrane of malignant cells

with tyrosine kinase activity. In HER2-positive breast cancers, which represent about 15-20% of breast carcinomas, tumor cells have an extra copy of the HER2 gene and are often associated with alterations in other genes such as TOP2A, GATA4, angiogenesis genes, and proteolysis19. Ki-67 is always high. They usually have a high histological grade and have a high proportion of mutations (40 to 80%) in p53 (a gene capable of detecting and repairing damaged DNA and causing cell death, mutations of which increase the likelihood of developing cancer). The above explains why this is a more aggressive and fast-growing subtype. They can be treated with specific drugs, which target the HER2/neu protein: anti-HER2 monoclonal antibodies (Trastuzumab or Herceptin, Pertuzumab) in addition to surgery and chemotherapy (CT) if necessary.16

Basal-Like Subtype Cancers

TNBCs comprise 10%-20% of all breast cancers. The terms TNBC and basal-like tumor are used interchangeably because 86% of TNBC are of the basal-like subtype. However, each intrinsic subtype exists within TNBC, and TNBC is a highly heterogeneous group of tumors based on genetic profile. The pCR rate after receiving an anthracycline/taxane regimen is 25%-35% and patients with pCR have better outcomes in TNBC patients. The recent St. Gallen Consensus Conference guidelines recommend that TILs should be routinely characterized for TNBC due to their prognostic value. Tumor programmed death-ligand 1 and immune-cell programmed death-1 expression are considered markers to predict the benefit of immunotherapy for advanced TNBC. In addition, in TNBC with residual disease after neoadjuvant chemotherapy, post-neoadjuvant treatment with capecitabine has shown a survival benefit.16

Radiological Features

Different radiological features have been associated with different molecular subtypes of breast cancer. Luminal A tumors have an irregular shape, spiculated margins, clustered calcifications, and are less than 2 cm in size. On MRI, luminal A tumors typically do not have peritumoral enhancement. The luminal B subtype exhibits an irregular shape, uncircumscribed margins, and extension to the skin or nipple on mammography and lower ADC values on MRI. Imaging findings associated with the HER2 subtype include an irregular or round shape, spiculated or uncircumscribed margins, higher ADC values, peritumoral edema, and persistent in-flow on delayed MRI. Branching or fine linear calcifications, microcalcifications, and increased breast density are also common in tumors overexpressing HER2. Basal-like or triple-negative tumors frequently harbor BRCA mutations. These tumors often appear as well-circumscribed round or oval lesions with smooth margins and no calcifications. Ultrasonography often shows a hypoechoic mass with microlobulated or angular margins in a parallel orientation, with one-third of cases showing posterior acoustic enhancement. On MRI, this cancer subtype typically shows high internal signal intensity on T2-weighted images, rim enhancement, higher ADC values than other subtypes, and peritumoral edema. When irregular margins and intratumoral necrosis are present, these features correlate with poor response to neoadjuvant chemotherapy. Peritumoral edema has also been associated with decreased disease-free survival. Kinetic curves for contrast enhancement and tumor size in basal-like tumors have been reported to be variable, so these indicators alone cannot reliably distinguish basal-like from other

subtypes. While imaging features are helpful in differentiating molecular or genetic subtypes of breast cancer, biopsy remains the primary diagnostic test.17

Table 1. Summary of Subtypes, MRI and USG Features

Subtype	MRI	USG
Luminal A	Heterogeneous stinging, irregular shape, spiculated margin. No rim enhancement, intralesional necrosis, peritumoral edema and axillary adenopathy were found. The smallest tumor compared to othersubtypes. Hypointensity images were found.	Distribution of calcifications that are clustered, size < 2 cm. Regular without parallel orientation accompanied by posterior acoustic shadow. Gives an image of a hypoechoic lesion with an irregular shape, surrounded by a desmoplastic reaction with a posterior shadow. Has a spiculated margin, high stiffness, and weak blood flow signal.
Luminal B	Rounded edges, poorly defined edges, and no rim enhancement, lower ADC values. Disease that has multicentric and/or multifocal characteristics. Has a slow/moderate initial enhancement pattern	Heterogeneous stinging, irregular shape, spiculated margins or ill-defined borders, extension to skin or nipple. Irregular shape without desmoplastic reaction. Associated with low tumor stiffness.
HER2 positive	The edges are not clearly defined, heterogeneous enhancement and accompanied by peritumoral edema, higher ADC values. Persistent inflow type enhancement in the delayed phase. Disease that has multicentric and/or multifocal characteristics. The largest tumor compared to other subtypes. Tends to appear as a non-mass enhancing lesion with rapid absorption in the early post-contrast phase. Perilesional and prepectoral edema are found. Most are oval/round with smooth contours.	Heterogeneous stinging, irregular or round shape, spiculated margins or ill-defined borders. Usually appears as an irregular mass and is accompanied by posterior acoustic enhancement. Has an irregular shape with lobulated edges and is not accompanied by desmoplastic reaction. Microlobulated tumor edges, isoechoic pattern, and high blood flow signal
Basal Like	Rim enhancement, round or oval shape, regular margin, intralesional necrosis, high signal intensity on sequence, high ADC value, and accompanied by peritumoral edema. Associated with unifocal lesions and hyperintensity. Most are oval/round with smooth contours and axillary lymphadenopathy is found.	Parallel orientation with a round/more oval shape on USG, with one third of cases showing posterior enhancement. It has an oval shape with a bordered edge by a benign-appearing malignant lesion that has the worst prognosis. It is accompanied by posterior acoustic enhancement and high blood flow signal.

Tumor Size

The median size of invasive BC on MRI was 53 mm (range 6-100 mm); 44% of lesions were <2 cm in size, while 56% were ≥2 cm in size. There was a significant association between lesion size <2 cm and luminal A-like tumors. No statistical association was found between tumor size and other molecular subtypes, even if luminal B and triple negative were larger than others.18

MRI Morphological Features Grouped by Molecular Subtypes

According to a study by Temerik et al (2023), there was no significant difference between different mass shapes and different molecular subtypes (P>0.05); 100% of TNBCs were round, 46.7% of HR-positive tumors were irregular, 40% were round, and only 6.7% were oval. Forty-one and seven-tenths of HER-2-positive tumors were round and irregular, while 6.7% were oval. There were statistically significant differences between the various

molecular subtypes and hypothesized mass margins (P = 0.023). Post hoc testing using Bonferroni correction was performed to determine the nature of the differences between the subtypes. This analysis showed that the percentage of HR-positive breast cancers with spiculated margins (80%) was greater than that of TNBC (0%); however, there was a large difference (P = 0.044). There were no significant differences between the molecular subtypes and tumor size (P = 0.602), lymph node (P = 0.283), multicentricity (P = 0.386) (Figs. 8, 9), and curve type (P = 0.107).19

Table 2. MRI morphological features are grouped according to molecular subtypes.

Gambaran Morfologi	Subtipe Molekular				P Value
	Luminal A (n=15)	Luminal B (n=7)	HER-2 Positif (n=5)	TNBC (n=3)	
	N (%)	N (%)	N (%)	N (%)	
Bentuk massa					
Round	6 (40%)	4 (57,1%)	1 (20%)	3 (100%)	0,093
Oval	1 (14,3%)	1 (14,3%)	1 (20%)	0 (0%)	0,345
Ireguler	7 (46,7%)	2 (28,6%)	3 (60%)	0 (0%)	0,112
Peningkatan non-massa	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1,00
Batas massa					
Spiculated	12 (80%)	3 (42,9%)	4 (80%)	0 (0%)	0,023*
Ireguler	2 (13,3%)	3 (42,9%)	1 (20%)	2 (66,7%)	0,188
Angulated	1 (6,7%)	0 (0%)	0 (0%)	1 (33,3%)	0,161
Batas tegas	0 (0%)	1 (14,3%)	0 (0%)	0 (0%)	1,00
Multisenstrisitas					
Unisentris	4 (26,7%)	2 (28,6%)	2 (66,7%)	3 (60%)	0,386
Multisentris	11 (73,3%)	5 (71,4%)	1 (33,3%)	2 (40%)	
Ukuran Tumor					
T1	0 (0%)	1 (14,3%)	1 (20%)	0 (0%)	0,602
T2	9 (60%)	3 (42,9%)	3 (60%)	1 (33,3%)	
T3	3 (20%)	0 (0%)	0 (0%)	1 (33,3%)	
T4	3 (20%)	3 (42,9%)	1 (20%)	1 (33,3%)	
Limfonodus					
Positif	4 (26,7%)	0 (0%)	0 (0%)	1 (33,3%)	0,283
Negatif	11 (73,3%)	7 (100%)	5 (100%)	2 (66,7%)	

*chi-square test—one way ANOVA

Prediction of Molecular Subtypes of Breast Cancer using Synthetic Mammography Radiomic Identification from Digital Breast Tomosynthesis (DBT)

According to Son Jinwoo's research (2020), a significant relationship was found between radiomic identification based on synthetic mammography reconstructed from digital breast tomosynthesis (DBT) images and molecular subtypes of breast cancer. Radiomic identification is able to distinguish triple negative (TN) subtypes of breast cancer with high accuracy. Since DBT is an imaging modality that can be performed on almost all patients, radiomic identification can be used as a potential biomarker for clinical diagnosis and treatment of breast cancer patients.20

Relationship between Radiological Findings and Molecular Subtypes

Based on Wang Simin's research (2022), compared to luminal subtype lesions, non-luminal subtype lesions showed larger lesion sizes, higher lesion densities, and lower CNR/lesion size values. Compared to subtype lesions that are not enriched with HER2, HER2 subtype lesions showed higher lesion densities. Although neither RDE nor CNR values showed significant differences among different molecular subtype groups, TNBC subtype lesions

showed lower RDE/lesion size values than non-TNBC subtype lesions.21 When molecular variables were used as dichotomous variables, HER2-amplified subtypes showed a significantly higher proportion of lesions with calcification than HER2-non-amplified subtypes. The proportion of lesions presenting with AD in the luminal subtype group was significantly higher than that in the non-luminal subtype group. Likewise, the proportion of lesions presenting with AD in the TNBC group was significantly lower than that in the non-TNBC group. However, the presence of mass or asymmetry did not show statistically significant correlation with molecular subtype. For HER2-amplified lesions, non-mass enhancement was present, while this proportion was present for HER2-non-amplified lesions. The type of enhancement showed a weak correlation with HER2 subtype while the degree of enhancement did not correlate.21

4. Discussions

Breast cancer is a heterogeneous disease, with different molecular subtypes having prognostic and predictive value. In this context, precision medicine involves the use of biomarkers to create personalized treatments. Furthermore, the possibility of drawing reliable correlations between molecular subtypes and breast cancer imaging features is considered to improve patient care. Consequently, imaging currently aims to offer a complementary non-invasive method to obtain biological information about breast cancer, in addition to biomarkers derived from conventional tissue sampling.18

Breast MRI is considered a more promising technique to differentiate tumor subtypes non-invasively. Contrast-enhanced sequences are the backbone of breast MRI protocols, providing information on the morphological and kinetic features of breast cancer. To overcome the suboptimal specificity of contrast-enhanced MRI, functional techniques, such as MR spectroscopy and DWI, have been widely investigated and are progressively introduced into routine clinical practice. Currently, the basic mpMRI protocol includes an unenhanced sequence (T2-weighted and DWI) followed by a series of T1-weighted acquisitions before and after contrast, as it has been shown that mpMRI including contrast-enhanced sequences and DWI improves the diagnostic accuracy in the diagnosis of BC. In addition, magnetic resonance spectroscopy improves the diagnostic accuracy of breast MRI. However, technical challenges and operator dependency have limited the large-scale application of these techniques.18

Gene expression profiling has revealed that there are four major subtypes of breast cancer: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-amplified, and basal-like tumors. Each subtype has a different prognosis, risk of progression, response to treatment, and survival. In general, basal-like tumors have the worst prognosis, while luminal A tumors have the best prognosis. However, because complete genomic analysis is expensive and time-consuming in clinical practice, the St. Gallen has suggested surrogate subtypes based on semiquantitative immunohistochemistry (IHC) assessment of estrogen receptor (ER), progesterone receptor (PR), and in situ hybridization assays for HER2 overexpression as follows: luminal A (ER and/or PR positive, HER2 negative), luminal B (ER and/or PR positive and HER2 positive or Ki67 $\geq$ 14%), HER2-enriched (HER2 amplified, ER and PR negative), and triple-negative breast cancer (TNBC; ER, PR, and

HER2 negative). Staging by percutaneous image-guided biopsy is the first step in managing systemic therapy strategies for breast cancer, as traditional prognostic factors including tumor size, histologic grade, and lymph node status do not fully reflect the heterogeneity of breast cancer, and treatment guidelines are no longer based solely on anatomic stage. The biological diversity of tumors requires ongoing refinement of treatment algorithms, which are increasingly outlined in Consensus Guidelines. Enhancements include longer duration of anti-estrogen therapy, suppression of ovarian function, dual blockade with anti-HER2 therapy, and treatment of residual tumor after neoadjuvant chemotherapy. De-escalation strategies include omission of adjuvant chemotherapy, shortening of radiation therapy, and avoidance of axillary dissection. However, percutaneous biopsy sampling does not represent the topographic heterogeneity of the entire tumor. Furthermore, because breast cancer continues to grow after systemic therapy, spatio-longitudinal monitoring of the entire tumor using imaging modalities during systemic therapy is essential.22,23

Early imaging studies have reported that triple-negative subtypes have uncalcified and circumscribed margins, luminal subtype masses have irregular, jagged margins, and HER2-positive subtype masses have pleomorphic calcifications. Although repeated voxel-based signal intensity measurements of the entire tumor are possible, with breast magnetic resonance imaging (MRI) there have been few studies correlating imaging phenotypes using radiomic analysis with breast cancer molecular subtypes.22,23

Luminal A cancers often present as irregularly shaped mass lesions with bordered enhancement margins, whereas Luminal B cancers often present with spiculated margins, irregular shapes, and hyperechoic internal septa. TN masses show a round shape, smooth margins, and enhanced margins. In contrast, non-mass enhancement is more predominant in Her2neu lesions.24

Several studies have suggested that TN subtypes of breast cancer can be distinguished by radiomic analysis of synthetic mammograms reconstructed from DBT. Radiomic models have shown good performance in identifying TN subtypes in a temporally independent validation cohort. In addition, the combined clinical and radiomic identification models showed significantly higher performance compared to the clinical model alone. This means that radiomic identification has added value to the clinical model, which consists of patient age, tumor size, and qualitative imaging findings. 20 The combination of DBT and digital mammography showed higher sensitivity for breast cancer than digital mammography alone in the screening setting. However, patients undergoing mammography and DBT at the same time were exposed to higher radiation doses. Therefore, efforts have been made to replace digital mammography with synthetic mammography from DBT. Because synthetic mammography from DBT has shown comparable sensitivity to digital mammography, efforts have been made to use DBT alone as a screening modality in North America. As the role of DBT increases, more and more research is actively being conducted to apply radiomics to DBT.20

5. Conclusion

Breast cancer consists of heterogeneous subtypes and continues to evolve after systemic

therapy. Previous studies correlating imaging features and molecular subtypes have reported the presence of calcifications, margin or shape features, and enhancement features on dynamic contrast-enhanced MRI corresponding to each subtype. Recent studies using radiomic parameters, which are invisible to the human eye, have demonstrated high accuracy in differentiating molecular subtypes, predicting response to chemotherapy, and predicting survival outcomes. Imaging biomarkers may help in realizing better precision medicine due to the feasibility of repeated measurements for the entire tumor and the application of deep learning-based algorithms.

6. Limitations and Future Studies

The studies included in this review were drawn from various regions and clinical settings, leading to variability in imaging technologies, patient populations, and methodologies. This limits the ability to generalize the findings across all breast cancer cases. Many of the studies reviewed did not provide long-term follow-up data, making it challenging to assess the predictive value of imaging biomarkers in the context of disease progression and survival outcomes. Certain breast cancer molecular subtypes, particularly rare ones, were underrepresented in the available literature, potentially skewing the overall conclusions regarding imaging characteristics and treatment responsiveness. Rapid advances in imaging technologies may have led to older studies using outdated methods, limiting the relevance of their findings to current clinical practice. Future research should focus on long-term, multi-center studies to evaluate the efficacy of imaging biomarkers in predicting patient outcomes, treatment response, and survival. Further studies should explore the use of emerging imaging technologies, such as molecular imaging and artificial intelligence, to enhance the precision of breast cancer diagnosis and prognosis. Research should investigate the imaging characteristics of less common breast cancer subtypes to develop more comprehensive and personalized imaging strategies. Studies should explore the integration of imaging biomarkers with genomic data to improve the accuracy of breast cancer molecular subtyping and provide more targeted treatment options.

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