Molecular subtypes and imaging phenotypes of breast cancer

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During the last 15 years, traditional breast cancer classifications based on histopathology have been reorganized into the luminal A, luminal B, human epidermal growth factor receptor 2 (HER2), and basal-like subtypes based on gene expression profiling. Each molecular subtype has shown varying risk for progression, response to treatment, and survival outcomes. Research linking the imaging phenotype with the molecular subtype has revealed that non-calcified, relatively circumscribed masses with posterior acoustic enhancement are common in the basal-like subtype, spiculated masses with a poorly circumscribed margin and posterior acoustic shadowing in the luminal subtype, and pleomorphic calcifications in the HER2-enriched subtype. Understanding the clinical implications of the molecular subtypes and imaging phenotypes could help radiologists guide precision medicine, tailoring medical treatment to patients and their tumor characteristics.

Keywords: Breast neoplasms; Gene expression profiling; Ultrasonography; Diagnosis

Introduction

Tumor size, lymph node status, histologic type, histologic grade, and estrogen receptor (ER), or progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER2) expression status by immunohistochemistry (IHC) have been well established as prognostic and predictive factors for breast cancers. Yet the traditional classifications do not fully reflect the heterogeneity of breast cancer. For example, although women with ER-negative or HER2-negative tumors do not respond to endocrine or HER2-targeted therapy, respectively, women with ER-positive or HER2-positive tumors tend to show varying responses to each targeted treatment [1]. Thus, there has long been investigation into better classifications to predict outcomes for breast cancer patients.

During the last 15 years, a reshuffling of breast cancer classifications has been underway, from the histopathologic type to the molecular subtype determined by microarray-based gene expression profiling. Today, we recognize that ER-positive breast cancers and ER-negative breast cancers constitute different diseases [1]. In addition, the existence of the four intrinsic subtypes of “luminal A,” “luminal B,” “HER2-enriched,” and “basal-like” has been demonstrated by extensive profiling at the DNA, microRNA, and protein levels by The Cancer Genome Atlas (TCGA) Network [2]. The intrinsic subtype is similar to the subtype based on mRNA gene expression profiling alone [3].
Each subtype has shown different incidence, prognosis, response to treatment, preferential metastatic organs, and recurrence or disease-free survival outcomes [3, 4]. Since 2011, the St. Gallen International Expert Consensus panel has used the subtype-based recommendation for systemic therapies for breast cancer. As full genetic analysis of breast cancer is not easily available in clinical practice due to its high cost and the extensive resources required, surrogate definitions of the subtype based on semiquantitative IHC scoring of ER, PR, and in situ hybridization tests for HER2 overexpression have been proposed (Table 1) [5]. The most recent 2015 St. Gallen International Expert Consensus has suggested that discrimination between patients who will or will not benefit from particular therapies is the key question (Table 2) [6].

In this article, the clinical implications of breast cancer subtypes and the imaging phenotypes of each subtype are reviewed to help radiologists understand breast cancer biology and identify their roles in translational research.

**Basal-like Subtype**

Analysis based on TCGA has confirmed that the basal-like subtype is a unique subtype among breast cancers. Basal-like tumors have the worst prognosis, while luminal A tumors have the best. Possible explanations for the differentiation include distinct cell-of-origin (e.g., cancer stem cells) and tumor subtype-specific genetic and epigenetic events for each tumor subtype [7]. As the majority (86%) of triple negative breast cancers (TNBC)—those that show as ER-negative, PR-negative, and HER2-negative—correspond to the basal-like subtype [8], the terms TNBC and basal-like have been used interchangeably to refer to a tumor subtype. However, within the set of TNBC tumors, which make up 10%-20% of all breast cancers, all the intrinsic subtypes exist [9]. There are six molecular subtypes of TNBC, as follows: two basal-like (BL1 and BL2) subtypes, an immunomodulatory (IM) subtype, a mesenchymal (M) subtype, a mesenchymal stem-like subtype, and a luminal androgen receptor subtype [10]. The M group shows the worst outcomes and the IM group shows the best outcomes [8]. Rates of pathologic complete response (pCR) following anthracycline/taxane chemotherapy are 25%–35%, and patients achieving pCR have better outcomes from among those patients with TNBC [11]. The distinction between basal-like and non-basal-like subtypes within TNBC is important for the choice of chemotherapy, in that carboplatin is as effective as docetaxel in basal-like subtypes, but less so in other intrinsic subtypes in the metastatic setting [6].

Tumor infiltrating lymphocytes are most often found in TNBC or HER2-positive cancers, and other highly proliferative breast cancers are associated with increased pCR, longer disease-free survival, and improved overall survival outcomes [6]. It has also been suggested that genes involved in immune, inflammatory, and/or chemokine pathways might be related to the prognosis of hormone receptor (HR)-negative tumors, and that proliferation-associated genes are related to the prognosis of HR-positive tumors [1].

**Luminal Subtype**

Approximately 70% of breast cancers are HR-positive breast cancers, and they show a more favorable prognosis than HR-negative breast cancers. Within HR-positive/HER2-negative breast cancer, 90%–95% of tumors are luminal A and B subtypes [8]. Compared to luminal A tumors, the luminal B subtype tends to show higher expression of proliferation genes [3] and worse baseline distant recurrence-free survival at 5 years and 10 years, regardless
of adjuvant systemic therapy, although luminal B tumors do show a higher pCR rate following neoadjuvant chemotherapy [1,8]. In addition, at 5-year follow-up, basal-like tumors show a worse outcome than luminal B tumors, and at around 10-year follow-up, the survival curves of luminal B tumors tend to cross those of basal-like tumors [8]. Thus, stratification of luminal A and B tumors, combined with tumor size and nodal status, allow us to predict resistance to endocrine therapy or to decide the length of endocrine treatment (5 years vs. 10 years) [8]. Numerous studies have reported that there are 30% to 44% discordance rates between the classifications based on gene expression predictors and surrogate classifications using IHC scoring of monoclonal antibody Ki-67 and PR status [8,12]. Distinguishing between luminal A-like and luminal B-like tumors using conventional pathology has proven impractical, as it might not provide a clinically useful threshold [6].

Within HR-positive/HER2-negative tumors, occurrence rates of the non-luminal subtypes (HER2-enriched and basal-like tumors) by gene expression profiling are as follows: the HER2-enriched type exists in 5.5%-11.0% and the basal-like type in 1% to 5% of HR-positive/HER2-negative tumors [8]. The non-luminal subtypes of early breast cancers showed worse outcomes compared to the luminal A subtype when they were treated with 5 years of adjuvant tamoxifen-only [13]. This study suggests that tumors of the ER-positive but non-luminal subtype might not benefit from endocrine treatment. One study reported that 80% of ER-positive tumors with low expression (1%-9%) belonged to non-luminal subtypes [14].

The most influential contribution of microarray-based technology has been to the development of commercially available prognostic signatures, including the 70-gene MammaPrint microarray assay (Agenda, Amsterdam, The Netherlands), the 21-gene Oncotype DX assay (Genomic Health, Redwood City, CA, USA), and the 50-gene PAM50 assay (Prosigna, NanoString Technologies, Seattle, WA, USA) [1]. These signatures composed of different gene lists have been implemented to identify breast cancer patients with good or poor prognosis based on the expression levels of proliferation-associated genes [1]. All signatures show the highest discriminatory power for ER-positive tumors, but they have limited use for ER-negative tumors, since more than 95% of ER-negative tumors show high

Table 2. Treatment-oriented classification of subgroups of breast cancer from the St. Gallen Consensus 2015

| Clinical grouping | Note | Type of therapy |
|-------------------|------|-----------------|
| Triple-negative   | Negative ER, PR, and HER2 | Cytotoxic chemotherapy including anthracycline and taxane |
| HR (−) and HER2 (+) | ASCO/CAP guidelines | T1a node negative: no chemotherapy; T1b, c node negative: chemotherapy + trastuzumab |
| HR (+) and HER2 (+) | ASCO/CAP guidelines | Higher T or N stage: anthracycline → taxane with trastuzumab |
| HR (+) and HER2 (−) | ER and/or PR (+) ≥ 16% | As above + endocrine therapy |
| Luminal A-like    | High receptor, low proliferation, low tumor burden | Multiparameter molecular marker ‘favorable prognosis’ if available; High ER/PR and clearly low Ki-67; Low or absent nodal involvement (N 0-3), smaller T size (T1, T2) | Endocrine therapy alone according to menopausal status |
| Intermediate      | Multiparameter molecular marker ‘intermediate’ if available; Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies | – |
| Luminal B-like    | Low receptor, high proliferation, high tumor burden | Multiparameter molecular marker ‘unfavorable prognosis’ if available; lower ER/PR with clearly high Ki-67; more extensive nodal involvement, histological grade 3, extensive lymphovascular invasion, larger T size (T3) | Endocrine therapy + adjuvant cytotoxic chemotherapy in many cases |

Modified from Coates AS et al. Ann Oncol 2015;26:1533-1546 [6], according to the Creative Commons license.

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; IHC, immunohistochemistry.

aIHC of c-erbB-2 staining 3+ score was defined as HER2 positive, and the 0 or 1+ score was negative. For tumors with 2+ score, HER-2 gene copies to the centromeric region of chromosome 17 ratios of 2.2 or more on fluorescence in situ hybridization was interpreted as amplified. 5ER values between 1% and 9% were considered equivocal. Thus, endocrine therapy alone cannot be relied upon for patients with these values. ER (−), ER (+) (1%–10%) tumors were clinicopathologically more similar to ER (−) than ER (+) tumors, but they would be classified as ER (+). 6Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.
expression levels of proliferation-related genes [1,15].

**HER2-Enriched Subtype**

Tumors with HER2 overexpression are found in 15% to 25% of invasive breast cancers and they show a worse prognosis but respond well to HER2-targeted therapies [16]. Heterogeneous intrinsic subtypes exist within HER2-positive tumors, which indicates the potential for predicting the degree of a patient’s response to trastuzumab [6]. Within the HER2 subtype of breast cancer, HR-positive tumors were associated with increased disease-free survival and overall survival compared to HR-negative tumors—regardless of clinicopathologic factors—in the 4-year follow-up to the National Surgical Adjuvant Breast and Bowel Project B-31 trials [17]. In the first 5-year follow-up results from the National Comprehensive Cancer Network centers, more cancer recurrences were reported from the HR-negative tumor group than the HR-positive tumor group [14]. Women with HR-negative/HER2-positive tumors showed less first recurrence in bone and more recurrence in the brain [18].

In addition, women with HR-negative/HER2-positive tumors had a higher pCR rate than those with HR-positive/HER2-positive tumors [19]. The pCR rate could be increased to over 70% using a double-HER2 blockade treatment either with trastuzumab plus lapatinib or trastuzumab plus pertuzumab in addition to an anthracycline/taxane-based chemotherapy [6].

**Imaging Phenotype of Breast Cancer Subtypes**

A number of studies regarding imaging features according to the molecular subtypes have been published during the last 15 years. As commercially available microarray-based genetic analysis has been increasingly used, the definition of molecular subtype in the earlier imaging studies has changed from the alternate classification using IHC [20–29] to the intrinsic subtype classification using gene expression profiling techniques [30]. In addition, imaging parameters have changed from the Breast Imaging Reporting and Data System lexicon [20,24,26–29] to the quantitative parameters derived from texture analysis using computer-aided analysis software [30]. The primary outcome has also changed from distinguishing each subtype [20–29] to identifying an association between imaging parameters with response to a treatment [31,32] or recurrence-free survival outcomes [32].

Imaging phenotypes according to the molecular subtypes are summarized in Table 3. TNBC tends to present as a mass with a relatively circumscribed margin, without calcifications (Fig. 1A) [20]. Absence of associated calcifications and lower associated ductal carcinoma in situ suggest rapid progression of malignant transformation, bypassing the stage of in situ [20]. On ultrasonography (US), a distinct mass with a circumscribed margin and posterior acoustic enhancement is frequently reported in TNBC (Fig. 1B). TNBC showed greater stiffness than ER-positive tumors in one study [21], although such stiffness was not consistently found in other studies [22,23]. On magnetic resonance imaging (MRI), a mass with rim enhancement (Fig. 1C) and internal high signal intensity on T2-weighted MRI image (Fig. 1D) was frequently reported in TNBC [24–26]. For the prediction of response to a treatment or the survival outcome of TNBC, presence of intratumoral necrosis and irregular mass on MRI were reported to be associated with nonresponse to neoadjuvant chemotherapy [31] and peritumoral edema on T2-weighted MR image has also been reported to be associated with worse recurrence-free survival [32].

With regard to the HR-positive tumor, a poorly circumscribed...

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**Table 3. Imaging phenotypes according to the molecular subtypes**

| Clinical grouping         | Mammography                                      | Ultrasonography                                      | MRI                                      |
|---------------------------|--------------------------------------------------|------------------------------------------------------|------------------------------------------|
| Triple-negative           | A mass with a relatively circumscribed margin without calcifications | A distinct mass with a circumscribed margin and posterior acoustic enhancement | A mass with rim enhancement and internal high signal intensity on T2-weighted MRI Presence of intratumoral necrosis and irregular mass associated with nonresponse to neoadjuvant chemotherapy Peritumoral edema on T2-weighted MRI associated with worse recurrence free survival |
| HR(−) and HER2(+)         | Microcalcifications, branching or fine linear calcifications High suspicion for malignancy | Irregular mass with a not-circumscribed margin (circumscribed margin showing decreased possibility of HER2 type) High suspicion for malignancy | A washout or fast initial kinetics Multicentric and/or multifocal disease were more frequently found in HER2 type or luminal B type |
| HR(+) and HER2(−)         | A mass with a poorly circumscribed margin         | A mass with a poorly circumscribed margin and posterior acoustic shadowing | … |

MRI, magnetic resonance imaging; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.
margin, and posterior acoustic shadowing were associated with HR-positive tumors and lower-grade tumors (Fig. 2A, B), whereas a posterior enhancement and a circumscribed margin were associated with HR-negative or higher-grade tumors [29–31]. Recently, a study using the TCGA Imaging Archive reported that a higher enhancement ratio of lesion to background parenchyma on MRI was associated with the luminal B subtype [30].

According to a meta-analysis of the imaging features of tumors with HER2 overexpression, several imaging features were associated with HER2 overexpression, as follows: presence of

Fig. 1. A 59-year-old woman with a basal-like breast cancer.
A. Mammography shows an irregular mass with an indistinct margin without calcifications. B. Sonograms shows an irregular mass with a circumscribed margin and a posterior acoustic enhancement. C. Gadolinium-enhanced T1-weighted magnetic resonance (MR) image shows an irregular mass with rim-enhancement. D. T2-weighted MR image shows an irregular mass with internal high signal intensity. Histopathology revealed an invasive ductal carcinoma with high histologic grade. Immunohistochemistry analysis showed estrogen receptor—negative, progesterone receptor—negative, human epidermal growth factor receptor 2—negative, cytokeratin 5/6—positive, and Ki-67—30% positive.
microcalcifications, branching or fine linear calcifications, extremely dense breasts, high suspicion for malignancy on mammography or US, irregularly shaped masses on US (Fig. 3A, B) and a washout or fast initial kinetics on MRI [33]. A circumscribed margin showed a decreased probability of HER2 overexpression. Another study reported that multicentric and/or multifocal disease was more frequently found in the HER2 subtype or luminal B subtype than luminal A or basal-like subtype [34].

In addition, the multigene assays of MammaPrint, Oncotype DX, or PAM50 for predicting cancer recurrences have been used to evaluate associations between imaging phenotypes and recurrence scores [35–38]. Texture parameters on postcontrast MRI, vascularity or acoustic posterior enhancement on US, or pleomorphic microcalcifications on mammography were reported to be significant.
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radiomic signatures related to high recurrence scores [35–38].

The Role of Radiologists in Precision Medicine

Precision medicine is defined as tailoring medical treatment according to individual patients and their tumor characteristics [39]. Staging, grading, and classification of subtypes allow patients to be categorized into subpopulations that may benefit from a targeted treatment. Radiologists can play an important role in precision medicine, as follows. First, US and MR images are accurate in the quantification of the residual tumor burden and in determining response to systemic treatment. Second, they have advantages in repeated evaluation and depiction of the whole tumor, three-dimensionally [39], in contrast to percutaneous tissue sampling, which is not representative of the whole tumor, and repeated sequencings based on gene expression profiling, which are not always available. Finally, sophisticated texture analysis using imaging parameters including vascularity or stiffness would help physicians depict disease heterogeneity and identify mutations during treatment.

Conclusion

As breast cancer is a heterogeneous disease and evolves continuously following systemic treatment, refined knowledge of imaging phenotypes according to molecular subtypes could be helpful in realizing the goals of precision medicine.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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