Breast Carcinoma
Updates in Molecular Profiling 2018

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KEYWORDS

• Carcinoma • Breast • Molecular subtyping • Genetic alterations

KEY POINTS

- Understanding the molecular heterogeneity underlying the clinical heterogeneity of breast cancer.
- Molecular and genetic variations in breast cancer with impact on treatment and prognosis.
- Correlation of the histologic variants of breast cancer and their molecular correlates.
- Introduction to progression of in situ carcinoma to invasive carcinoma.

Breast carcinoma is the most common malignancy affecting women in the United States, comprising almost 29% of all cancers occurring in women. Moreover, it is the second most common cause of mortality, responsible for 14% of cancer-related mortality.[1] It is estimated to increase both in this country and globally.

Traditionally, this tumor is classified based on morphologic features.[2] The most common subtype is invasive ductal carcinoma (IDC), not otherwise specified (NOS). This type accounts for approximately 60% to 75% of all breast carcinomas. Established prognostic factors associated with survival in breast cancer are clinicopathologic factors such as tumor size and grade, lymph node involvement, margin status, and lymph vascular invasion.[3] Predictive biological markers that are in use clinically are estrogen and progesterone receptors and Her-2/neu receptor status. Predictive markers are used to determine subsequent treatment options and estimate response to treatment.[4] Receptor expression is determined using validated immunohistochemical methods. In the case of Her-2/neu, fluorescence in situ hybridization assay is performed to evaluate gene amplification, in the event of equivocal Her-2/neu protein expression by immunohistochemistry. The testing methodology and protocols, cutoff values and reporting guidelines are based on College of American Pathologists/American Society of Clinical Oncology guidelines.[5]

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Over the past decades, the heterogeneity of breast carcinomas has been acknowledged and studied. Observations regarding variable outcome in patients with breast cancer have supported these theories. A landmark study by Perou and colleagues[6] showed that the heterogeneity of breast carcinoma was reflected in the molecular makeup of these tumors. Using complementary DNA technology, the investigators analyzed 65 tumors from 42 individuals, including 20 paired samples before and after chemotherapy. For the purpose of this study, 496 genes, nominated as the intrinsic gene subset, were included for analysis. Differences in specific signaling pathways, cellular components, and proliferation gene expressions were identified as variations in expression of different subsets of genes. Using hierarchical clustering to analyze these tumors, 2 main groups of tumors were identified based on the estrogen receptor status: estrogen-positive tumors and estrogen-negative tumors.[6–8] Estrogen-positive tumors corresponded with the luminal subtype, whereas the estrogen-negative group included the Her-2/neu-enriched and the basal groups.[6]

Also identified as a separate group was the normal breast subtype, which is characterized by genes normally characterizing adipose tissue and basal cell genes, with a low expression of genes characterizing luminal cells. It is thought that this group may represent contamination by the normal breast parenchyma and need further investigation.

A subsequent study by Sorlie and colleagues[7] extended the cohort to include 38 additional tumors (total of 78 cases). From the initial gene subset, 456 genes were selected for analysis. Expanding the size of the cohort allowed for identification of subclasses within the estrogen receptor–positive group.

Based on these molecular studies, breast carcinomas can be classified as follows:

a. Estrogen positive
   1. Luminal A
   2. Luminal B
b. Estrogen negative
   3. Her-2/neu
   4. Triple negative
   5. Normal breast–like

LUMINAL A

This subtype is characterized by upregulation of the estrogen receptor gene (ESR-1) and related genes such as GATA 3, FOX A1, and LIV 1. Her-2/neu gene amplification is not seen. By immunohistochemistry, these tumors are characterized as estrogen receptor positive (ER+) and Her-2/neu negative. They are positive for luminal cytokeratins such as CK8/18.

These tumors are generally well differentiated, more likely to be low stage (T1), with increased expression of progesterone receptor, low proliferation index, and negative Her-2/neu expression compared with luminal B tumors. These tumors are also associated with a significantly better recurrence-free survival and superior overall survival.[3,8–11] In addition, the level of progesterone receptor expression seems to be a significant prognosticator in luminal A tumors, in which levels higher than 20% are associated with a better survival,[9] compared with luminal B tumors. In the study by Sotirou and colleagues,[8] the 10-year relapse-free survival for luminal A tumors was 80%. Similarly, this subtype constitutes the largest group, comprising approximately 60% of all breast cancers and also shows a lower relapse rate (9% within 5 years).[3] Endocrine therapy alone is considered sufficient for this group of tumors.[12]