Molecular Profiling of Breast Cancer

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KEYWORDS

• Breast cancer • Molecular profiling • Molecular diagnostics • Prognostication
• Genome

KEY POINTS

- Molecular profiling has identified at least 4 distinct subtypes of breast cancer: luminal, HER2-enriched, basal-like, and normal breast–like.
- Patients with ductal carcinoma in situ who have undergone surgical excision to margins of 3 mm or more and who have a low-risk 12-gene recurrence score may safely omit adjuvant radiation therapy.
- The 21-gene recurrence score, 70-gene signature, and PAM50 risk of recurrence score are all useful tools for determining prognosis beyond standard clinicopathologic features and in predicting response to chemotherapy for patients with ER-positive, node-negative, and node-positive invasive breast cancer.
- Molecular diagnostic tools should not replace standard clinicopathologic features but rather provide complementary information to aid in the complex decision-making process of adjuvant treatment recommendations in patients with breast cancer.
- Prospective clinical trials are needed to determine the impact of gene assays on outcomes for patients with breast cancer.

MOLECULAR PROFILING OF INTRINSIC SUBTYPES OF BREAST CANCER

Cluster Analysis and Subtypes

Molecular studies have demonstrated the great heterogeneity of breast cancer.[1–4] One of the first applications of microarray-based gene-expression profiling analysis in breast cancer was the landmark work by Perou and colleagues[5] and Sorlie and colleagues.[6] These studies were the first to demonstrate that estrogen receptor (ER)-positive and ER-negative breast cancers are biologically distinct diseases with respect to their molecular analysis.[6] In addition, cluster analysis of genes revealed that there are at least 4 molecular subtypes of breast cancer, including luminal, human

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epidermal growth factor receptor 2 (HER2)-enriched, basal-like, and normal breast–like.[5] Luminal A (~40% of all breast cancers) and luminal B (~20% of all breast cancers) are the most common subtypes, and are characterized by the expression of ER, progesterone receptor (PR), and other genes associated with ER activation. Although luminal A and luminal B constitute most ER-positive breast cancers, there are important molecular distinctions between the two. Luminal A tumors typically have high expression of ER-related genes, low expression of HER2 genes, and low expression of proliferation-related genes.[7,8] In comparison with luminal A tumors, luminal B tumors have lower expression of ER-related genes, variable expression of HER2 genes, and higher expression of the proliferation-related genes.[9] The HER2-enriched subtype (~10%–15% of all breast cancers) is characterized by high expression of the HER2 and proliferation-related genes, and low expression of the luminal and basal-like genes.[10] Importantly not all HER2-enriched subtypes translate to clinically HER2-positive breast cancer, and vice versa. Thus, not all HER2 mutations result in HER2 amplification and protein overexpression. Furthermore, approximately 50% of clinically HER2-positive breast cancers are not HER-enriched at a molecular level, but are characterized as HER2-positive luminal subtypes.[11] The basal-like subtype (~15%–20% of all breast cancers) is characterized by low expression of the luminal and HER2 genes and high expression of the proliferation cluster of genes.[12] Although most basal-like breast cancers are triple-negative (ER-negative, PR-negative, HER2-negative), not all triple-negative breast cancers are basal-like. Finally, the normal-like subtype is characterized by gene expression similar to that of normal breast tissue. It remains unclear whether this represents a separate subtype with clinical significance or a technical artifact of the molecular analysis.[11]

Subtype Prognostication and Treatment Recommendations

It must be borne in mind that the molecular analysis of intrinsic subtypes of breast cancer identifies relevant biology. These studies were not designed for prognostication. However, subtype analysis does correlate with prognosis in multiple large data sets.[10,11,13–15] Overall, patients with luminal A breast cancer have the best prognosis, followed by patients with luminal B breast cancer. Patients with either HER2-enriched or basal-like subtypes have the worst overall survival. However, more recent advances in targeted therapies (eg, trastuzumab) hold significant promise in the ability to alter that natural history.[16] A consensus conference was held to discuss the role of molecular subtype analysis in clinical decision making.[13] The panel concluded that ER/PR/HER2 measurements should not be used as surrogates for assigning patients into molecular groups, and that molecular subtype analysis was insufficient at present to incorporate into the decision-making algorithm for treatment recommendations.[13]

MOLECULAR PREDICTION AND PROGNOSTICATION FOR TREATMENT DECISION MAKING

Overview

Concurrent with the evolution of molecular subtype classification of breast cancers, several researchers and industry sponsors have developed multiple gene prognostic signatures, several of which have been validated and are in clinical use. The 3 most commonly used molecular prognostic profiles are the Recurrence Score (RS), derived from Oncotype Dx, the Amsterdam 70-gene signature (Mammaprint), and the Risk of Recurrence Score (ROR), derived from PAM50. The RS was validated in an independent data set from samples collected from node-negative, ER-positive patients treated with tamoxifen in the large multicenter National Surgical Adjuvant Breast