Molecular Subtypes and Local-Regional Control of Breast Cancer

Simona Maria Fragomeni, MD[a], Andrew Sciallis, MD[b], Jacqueline S. Jeruss, MD, PhD[b,c,*]

KEYWORDS

• Breast cancer • Molecular subtypes • Local-regional recurrence • Gene signatures • Immunohistochemical surrogates

KEY POINTS

- The analysis of cancer gene expression patterns expands the understanding of breast cancer as a heterogeneous group of diseases.
- The presence or absence of estrogen, progesterone, and HER2/neu receptor (ER/PR/HER2) expression is key to molecular subtype stratification.
- Immunohistochemical techniques are widely applied to identify the markers of the different molecular subtypes.
- Gene expression profiling techniques, including commercially available tools such as Oncotype DX and MammaPrint, are considered complementary to the known prognostic factors.
- According to the currently available data, the different molecular subtypes are associated with different patterns of local-regional recurrence and response to treatment.

INTRODUCTION

Breast cancer is a heterogeneous disease that affects one anatomic site, yet is phenotypically variable.[1,2] The identification of different biological subtypes occurs primarily through the use of techniques including immunohistochemistry[3] and gene expression profiling.[1] To date, several studies have shown that the different biological subtypes are associated with variations in treatment response and disease-specific

Conflicts of Interest: The authors have nothing to disclose.
Funded by National Institutes of Health grant R01GM097220.
[a] Division of Gynecologic Oncology, Multidisciplinary Breast Center, Catholic University of the Sacred Heart of Rome, L.go Agostino Gemelli 8, 00168 Rome, Italy; [b] Division of Anatomic Pathology, Department of Pathology, University of Michigan, Ann Arbor, MI 48105, USA; [c] Division of Surgical Oncology, Department of Surgery, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48105, USA
* Corresponding author. Department of Surgery, University of Michigan, 3303 Cancer Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5932.
E-mail address: jjeruss@med.umich.edu

Surg Oncol Clin N Am 27 (2018) 95–120
http://dx.doi.org/10.1016/j.soc.2017.08.005 surgonc.theclinics.com

outcomes.[4–10] Currently, decision-making for individual patients is based on several factors, including tumor morphology and grade classification, tumor size, presence of lymph node metastases, and expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)/neu (HER2). Although knowledge of these factors aids in treatment planning, there is a clear need to enhance the understanding of both prognostic and predictive markers that will facilitate customized treatment. The advent of novel technologies to aid in the identification of new markers also will be critical.

Through molecular analysis of breast cancers with gene expression profiling, both Perou and colleagues[1] and Sorlie and colleagues[2] showed that breast cancer could be subclassified into different subtypes. Broadly, these subtypes include luminal ER-positive (luminal A and luminal B), HER2 enriched, and basal-like (**Table 1**). Gene expression profiling can be costly, time-consuming, and, depending on the platform, may require a fresh tumor biopsy sample that has not been fixed in formalin.[11,12] Given these constraints, gene expression profiling can be difficult to implement on a broad scale. Nevertheless, several groups including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the St Gallen Group have issued guidelines and recommendations supporting the implementation of molecular analysis as useful for risk stratification and for treatment planning.[13–15]

To facilitate the implementation of breast cancer subtype classification, efforts have been made to use immunohistochemical analysis to create approximated subtypes. Although taking this approach may enable stratification of breast cancers into subgroups that have outcomes comparable to those defined by gene expression profiling, there is not precise overlap.[16] Furthermore, in addition to the evaluation of standard biomarkers that can be assessed with immunohistochemistry (ER, PR, and HER2), the contribution of other factors, such as proliferative rate and expression of cytokeratins, also may be important. For example, the St Gallen 2013 classification included the evaluation of Ki67 (a marker of cell proliferation)[17] and a cutoff of PR of less than 20% as factors associated with the luminal B, HER2-negative subtype.[15]

The different molecular subtypes reflect the biological diversity of breast cancer. In a time in which medicine is moving toward a personalized approach, a critical goal is the correlation of the different disease subtypes with clinical outcomes and targeted therapeutics. Several studies have evaluated the variance in systemic disease recurrence and survival among the intrinsic subtypes.[18–21] To this end, additional work has pointed toward the growing significance of molecular subtypes in the risk of local-regional recurrence along with clinical and pathologic features.[5]

Table 1
Classification of molecular subtypes and correlation with biomarker staining on immunohistochemistry

Molecular Subtype	ER		PR	HER 2
Luminal A	Positive	and/or	Positive	Negative
Luminal B	Positive	and/or	Positive or negative[a]	Negative
Luminal B	Positive	and/or	Positive or negative [b]	Positive
HER2	Negative		Negative	Positive
Triple negative or basal-like	Negative		Negative	Negative

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

[a] (PR <20% + Ki 67 >14%).

[b] (Any PR + any Ki 67).