Prognostic and predictive markers for breast carcinoma

Breast carcinoma is the most common malignancy and the leading cause of cancer death in women. In this country, there has been a sharp increase in its detection, largely due to the widespread use of mammography. Despite detection of smaller (and presumably earlier) disease, the survival rate has improved very little since the 1930’s.

Major prognostic and predictive factors can be important in choosing appropriate treatment, determining the risk of recurrence and classifying patients for clinical trials. Below is a review of markers routinely offered by most reference laboratories.

**Estrogen Receptors (ERs) and Progesterone Receptors (PRs):** Expression of ERs and/or PRs within tumors correlates well with low histologic grade and responsiveness to hormonal manipulation, especially in postmenopausal women. ERs and PRs are evaluated with immunohistochemistry (IHC) on paraffin embedded tissue, where staining of cell nuclei is considered positive. The percentage of cells staining and strength of the stain needed for a positive test is controversial, so most labs will report the actual percentage of positive cells.

While many agree that ≥5% is considered positive, tumors with a lower percentage (1-4%), or even no staining, may show a borderline response to hormonal therapy. The American Society of Clinical Oncology (ASCO) Tumor Marker Panel of 1995 concluded: (1) ER and PR should be measured on every primary breast cancer (and metastatic lesions if it would influence treatment planning), (2) in metastatic disease, ER and PR positivity supports use of hormonal therapy, (3) regardless of menopausal status, ER and PR positivity helps to identify patients likely to benefit from adjuvant hormonal therapy and (4) ER and PR receptors are weak prognostic indicators and should not be used to determine whether to treat a patient with adjuvant therapy.

**HER2/neu (Immunohistochemistry [IHC] and Fluorescence In-Situ Hybridization [FISH]):** HER2/neu is a proto-oncogene that encodes the production of HER2, a cell surface protein important in cell regulation. Abnormalities of HER2/neu occur in 25-30% of breast carcinomas, especially those that are poorly differentiated, lymph node positive, hormone receptor negative, flow aneuploid and/or show high proliferation rates.

HER2/neu amplification and protein overexpression can be detected with FISH and IHC, respectively, both of which can be performed on paraffin-embedded tissue. Maximum sensitivity can be achieved by using both methods. HER2 status is used as an eligibility criterion for anti-HER2 immunotherapies, such as Herceptin™. While some studies have shown a positive dose-response effect with adjuvant chemotherapy for tumors showing gene amplification, elevated HER2 may actually be a negative predictor of response to Adriamycin-based chemotherapy.

**Measures of Tumor Cell Proliferation Rate:** Proliferation can be measured by flow cytometry (S-phase fraction), thymidine labeling index, mitotic counts or IHC detection of cellular proteins (e.g. Ki-67/MIB-1). Most evidence supports that tumors with a high proliferation rate have a worse prognosis. Manual mitotic counts have shown to be an important part of the standard grading system (Scarff-Bloom-Richardson).
Nonetheless, the best technique to use remains unclear as it has not been determined which can be most accurately measured and will provide results that correlate well with overall survival.

**DNA Ploidy:** DNA content in cells can be determined by flow cytometry, image analysis or laser scanning cytometry. Aneuploid DNA content has been shown to be associated with a worse prognosis, but it is uncertain whether this parameter adds *independent* information of prognostic value.

**Other Molecular Markers:** Mutation of p53, an oncosuppressor gene, causes variant p53 proteins to have an increased half-life, thus accumulating in the cell. These excess proteins can be detected with IHC in about 90% of cases by increased nuclear staining. Although over accumulation of p53 protein has been associated with shortened survival in breast carcinoma patients, it also correlates with cell proliferation and thus may not be an independent prognostic factor.

Epidermal growth factor receptor (EGFR) is related to HER2/neu and can be detected with IHC. The expression of EGFR is associated with shorter survival, but there is very little evidence to support its routine use at this time.

At a minimum, hormone receptor and HER2 status should be determined for every new breast cancer diagnosis. These tests are, of course, in addition to major prognostic factors such as axillary lymph node status, tumor size and distant metastasis (the basis of clinical staging), as well as tumor grade and lymph vascular invasion.