

SPECIAL BREAST CANCER STUDIES

The treatment of breast cancer patients is based on the stage of the tumor at diagnosis, number of axillary lymph nodes with metastatic disease, and the status of hormone (estrogen and progesterone) receptors. A major goal of breast cancer research is the identification of biomarkers that would identify patients who might benefit for adjuvant therapy. In addition to hormone receptors, promising markers include HER-2/neu and ki-67 determinations. We employ immunohistochemical assays to identify these biomarkers. The assays are performed on routine formalin fixed paraffin embedded tissue. It is important to fix the tissue in formalin immediately. This immunohistochemical method can be performed on current or on archived tumors as long as paraffin blocks are available.

Estrogen and Progesterone Receptor Immunohistochemistry

Approximately 55-65% of primary breast carcinomas and 45-55% of the metastases from the breast carcinomas have been found to be estrogen receptor positive (ER+). Studies have shown that 55-60% of women with ER+ tumors respond to additive or ablative hormone therapy compared to about 8% of women with ER- tumors. ER- carcinomas show a better response to cytotoxic chemotherapy. Tumors that are better differentiated are more likely to be ER+, and ER+ carcinomas have a relatively better prognosis.

Approximately 45-60% of primary and metastatic breast cancers contain progesterone receptors (PR). The presence of both ER and PR in the tumor increases the likelihood of response to endocrine therapy from 55% (ER+ only) to 75-80%. The loss of PR by tumor cells is associated with a worse prognosis.

Hormone receptor analysis is also occasionally useful in evaluating endometrial and ovarian carcinomas.

HER-2/neu (c-erbB-2, HER2) Oncogene Immunohistochemistry

A semi-quantitative immunohistochemical assay is used to determine HER-2/neu overexpression in breast carcinoma. HER-2/neu (also known as c-erbB-2 and HER2) is an oncogene which encodes a transmembrane glycoprotein with tyrosine kinase activity. The protein is a normal component expressed by a number of epithelial cell types, when the gene is amplified. In breast cancer the gene is overexpressed with multiple copies appearing in the nucleus.

Amplification of HER-2 is seen in almost all cases of comedo-type duct carcinoma in situ, in 10-40% of invasive duct carcinomas and in only a few cases of invasive lobular carcinoma. The expression of this protein has been associated with poor histologic grade, spread to axillary nodes, and number of nodes involved. A negative association between HER-2 expression and ER and PR has been noted. No significant association has been found between HER-2 expression and ploidy. In axillary node-positive

patients, there is significant correlation between amplification of HER-2 and shorter disease-free and overall survival. It has also been claimed that patients with overexpression of HER-2 show a better response to Adriamycin-based chemotherapy and less likely to respond to hormonal therapy (even if ER+). Interest in HER-2 status has increased with the arrival of FDA approved Herceptin (Trastuzumab), a monoclonal antibody of HER-2. The antibody binds to the HER-2 membrane protein inhibiting the proliferation of tumor cells that overexpress HER-2. Herceptin is reported to help prevent the spread of metastasis from breast cancer.

If the immunohistochemical assay for HER-2/neu is inconclusive, fluorescence in situ hybridization (FISH) is available on deparaffinized formalin fixed material. This method directly visualizes the amplification of the HER-2/neu gene in tumor nuclei.

Ki-67

Ki-67 is a monoclonal antibody that reacts with an undefined nuclear antigen present in all non-G0 cells of the cell cycle, identifying proliferating cells within a tumor. Since cells from any phase of the cycle can enter the G0 phase regardless of their DNA content, determination of the Ki-67 fraction could reflect more significant information regarding the proliferating cell component of a tumor compared with the DNA content. Using immunohistochemistry, the Ki-67 fraction "growth fraction" reflects the percentage of positively stained cells in a tumor. The higher the Ki-67 growth fraction, the more aggressive the tumor.