Breast cancer is the most common malignant tumor in American women and is second only to lung cancer as a cause of cancer-related mortality. During the past two decades the mortality rate has declined significantly, primarily due to the early use of adjuvant systemic therapy as well as detection of earlier stage tumors due to increased screening. The mainstay of treatment for patients with localized disease is surgical excision and staging axillary lymph node evaluation with or without radiation therapy. Some patients receive neoadjuvant chemotherapy or hormonal therapy prior to definitive excision of the tumor. Other treatment options include adjuvant chemotherapy, hormonal therapy or monoclonal antibody therapy with a primary goal of eliminating or delaying the subsequent appearance of clinically occult micrometastases.

Prognostic and predictive factors are universally utilized in the management of breast cancer and can be used to stratify patients into two groups: (1) those who are expected to derive the most benefit from adjuvant systemic therapy, which includes all patients with lymph node metastases and a subset of node-negative patients, and (2) those for which the risks and costs of adjuvant therapy outweigh the expected benefit. In this context, prognostic factors should be distinguished from predictive factors. A prognostic factor may be defined as a measurable variable that correlates with the natural history of the disease. In contrast, a predictive factor is one that is associated with response to a given therapy. Some factors, such as estrogen receptor/progesterone receptor status and Her2/neu gene amplification and/or overexpression, can serve as both prognostic and predictive factors.
receptor/progesterone receptor (ER/PR) status and HER2/neu gene amplification and/or overexpression, are both prognostic and predictive.

The most significant prognostic factor in breast cancer is the presence or absence of axillary lymph node involvement, which is usually assessed at the time of surgery using sentinel lymph node biopsy or axillary dissection. Macrometastases (>0.2 cm in size) have clearly been shown to have prognostic significance. Smaller metastases (i.e., micrometastases and isolated tumor cells) have not been shown to have prognostic significance when the initial processing of lymph nodes has been controlled and all macrometastases detected. The value of serial sections and/or immunohistochemistry to detect these small metastases remains under investigation.

The vast majority of patients found to have lymph node metastases are candidates for adjuvant systemic therapy. However, determining which node-negative patients should receive adjuvant therapy is challenging, particularly because the majority are cured by surgical excision alone. The benefit to those patients who are destined to relapse is minimal, and the costs and toxicities of the treatments are significant. Thus, node-negative patients require further stratification using additional prognostic and predictive factors.

Tumor size has long been recognized as an independent prognostic factor and as a predictor of axillary node status, with larger tumors being associated with a worse prognosis and an increased likelihood of nodal metastasis. Additional established prognostic factors include lymphatic/vascular invasion, patient age and histologic grade of the tumor. Certain histologic subtypes of breast cancer are generally associated with a favorable prognosis, including tubular, colloid (mucinous) and papillary carcinoma. The proliferation rate of the tumor as determined by the mitotic count is also of prognostic importance, but this information is included as a component of the tumor grade. Other methods for determining tumor proliferation (e.g., thymidine labeling index, Ki-67 immunostaining or determination of the S-phase fraction by flow cytometry) likely do not add additional prognostic information. Response to neoadjuvant chemotherapy and hormonal therapy has been shown to be a strong prognostic factor, and has the added benefit of providing a short-term endpoint for the rapid evaluation of treatment protocols. Determining patient response to neoadjuvant therapy is best achieved using pathologic evaluation of the post-treatment specimen. Multiple scoring systems have been devised to evaluate tumor response.

Factors that may have prognostic impact but are not routinely used in clinical practice include overexpression of urokinase plasminogen activator (uPA) and its inhibitor PAI-1, detection of bone marrow micrometastases at the time of diagnosis, p53 gene analysis, markers of invasion (e.g., levels of the proteolytic enzyme cathepsin D), markers of angiogenesis (e.g., microvessel density as detected by immunohistochemistry) and DNA ploidy analysis. Another newly
identified potential prognostic factor is the tumor gene expression profile. Molecular assays have been developed to analyze patterns of gene expression by individual tumors, and this has been shown to be useful both as a predictor of response to chemotherapy and as a prognostic factor for clinical outcome, particularly in patients with early stage, node-negative disease.\textsuperscript{11,12}

All cases of invasive breast carcinoma are evaluated for ER/PR status using immunohistochemistry, which has both predictive and prognostic value. The presence of hormone receptors is a powerful predictive factor for the likelihood of benefit from adjuvant hormonal therapy including aromatase inhibitors (e.g., anastrozole, letrozole) and tamoxifen, an oral selective estrogen receptor modulator.\textsuperscript{13-15} As a prognostic factor, ER and/or PR positivity is associated with reduced mortality compared to women with ER and/or PR negative disease.\textsuperscript{16} However, the percentage of immunohistochemically positive tumor cells used to classify a tumor as ER or PR positive varies among institutions. Studies support that carcinomas with >1\% ER positive cells have better survival rates compared to carcinomas that are completely devoid of ER.\textsuperscript{17,18}

The HER2/neu (ERBB2) oncogene is amplified and/or overexpressed in approximately 20\% of breast cancers, and is a strong prognostic factor for relapse and poor overall survival, particularly in node-positive patients.\textsuperscript{19,20} Amplification and/or overexpression of the HER2/neu gene is routinely evaluated, using immunohistochemistry and/or fluorescence in-situ hybridization (FISH), in all cases of invasive breast carcinoma, although variability in testing remains a major issue with both methodologies. The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) recently published a clinical practice guideline on improving the accuracy of HER2 testing for breast cancer patients.\textsuperscript{21} As a predictive factor, HER2/neu status strongly predicts response to treatment with the anti-HER2 monoclonal antibody trastuzumab,\textsuperscript{22} and may be predictive of resistance to alkylator-based chemotherapy, the need for higher dose chemotherapy, benefit from adjuvant anthracyclines and tamoxifen resistance.\textsuperscript{3}

In summary, several well-established prognostic and predictive factors are universally used to guide the clinical management of women with breast cancer. Despite the success of these markers, difficulties remain in accurately identifying those patients who are best suited for adjuvant systemic therapy, particularly among women with early stage disease. Numerous additional factors are currently under investigation, and some show great promise in improving our ability to predict patient prognosis and response to therapy.

\textbf{Acknowledgement:}
I would like to thank Susan C. Lester, MD, PhD, for reviewing this article and providing excellent suggestions for improvement.
References


