mastectomy. Thus, a great many women still undergo mastectomy who could safely avoid this procedure and probably would if appropriately counseled.

Sentinel lymph node biopsy (SLNB) is generally the standard of care for women with localized breast cancer and clinically negative axilla. If SLNB is negative, more extensive axillary surgery is not required, avoiding much of the risk of lymphedema following more extensive axillary dissections. In the presence of minimal involvement of a sentinel lymph node, further axillary surgery is not required.

An extensive intraductal component is a predictor of recurrence in the breast, and so are several clinical variables. Both axillary lymph node involvement and involvement of vascular or lymphatic channels by metastatic tumor in the breast are associated with a higher risk of relapse in the breast but are not contraindications to breast-conserving treatment. When these patients are excluded, and when lumpectomy with negative tumor margins is achieved, breast conservation is associated with a recurrence rate in the breast of 5% or less. The survival of patients who have recurrence in the breast is somewhat worse than that of women who do not. Thus, recurrence in the breast is a negative prognostic variable for long-term survival. However, recurrence in the breast is not the *cause* of distant metastasis. If recurrence in the breast caused metastatic disease, then women treated with lumpectomy, who have a higher rate of recurrence in the breast, should have poorer survival than women treated with mastectomy, and they do not. Most patients should consult with a radiation oncologist before making a final decision concerning local therapy. However, a multimodality clinic in which the surgeon, radiation oncologist, medical oncologist, and other caregivers cooperate to evaluate the patient and develop a treatment plan is usually considered a major advantage by patients.

Adjuvant Therapy The use of systemic therapy after local management of breast cancer substantially improves survival. More than half of the women who would otherwise die of metastatic breast cancer remain disease-free when treated with the appropriate systemic regimen. These data have grown more and more impressive with longer follow-up and more effective regimens.

PROGNOSTIC VARIABLES The most important prognostic variables are provided by *tumor staging*. The size of the tumor and the status of the axillary lymph nodes provide reasonably accurate information on the likelihood of tumor relapse. The relation of pathologic stage to 5-year survival is shown in **Table 108-2**. For most women, the need for adjuvant therapy can be readily defined on this basis alone. In the absence of lymph node involvement, involvement of microvessels (either capillaries or lymphatic channels) in tumors is nearly equivalent to lymph node involvement. The greatest controversy concerns women with intermediate prognoses. *There is rarely justification for adjuvant chemotherapy in most women with tumors <1 cm in size whose axillary lymph nodes are negative. HER2-positive tumors are a potential exception*. Detection of breast cancer cells either in the circulation or bone marrow is associated with an increased relapse rate. The most exciting development in this area is the use of gene expression arrays to analyze patterns of tumor gene expression. Several groups have independently defined gene sets that reliably predict disease-free and overall survival far more accurately than any single prognostic variable including the Oncotype DX® analysis of 21 genes. Also, the use of such standardized risk assessment tools such as Adjuvant! Online (*www.adjuvantonline.com*) is very helpful. These tools are highly recommended in otherwise ambiguous circumstances.

TABLE 108-2 5-YEAR SURVIVAL RATE FOR BREAST CANCER BY STAGE

Stage	5-Year Survival, %
0	99
I	92
IIA	82
IIB	65
IIIA	47
IIIB	44
IV	14

Source: Modified from data of the National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER).

Estrogen receptor status and progesterone receptor status are of prognostic significance. Tumors that lack either or both of these receptors are more likely to recur than tumors that have them.

Several *measures of tumor growth rate* correlate with early relapse. S-phase analysis using flow cytometry is the most accurate measure. Indirect S-phase assessments using antigens associated with the cell cycle, such as PCNA (Ki67), are also valuable. Tumors with a high proportion (more than the median) of cells in S-phase pose a greater risk of relapse; chemotherapy offers the greatest survival benefit for these tumors. Assessment of DNA content in the form of ploidy is of modest value, with nondiploid tumors having a somewhat worse prognosis.

Histologic classification of the tumor has also been used as a prognostic factor. Tumors with a poor nuclear grade have a higher risk of recurrence than tumors with a good nuclear grade. Semiquantitative measures such as the Elston score improve the reproducibility of this measurement.

Molecular changes in the tumor are also useful. Tumors that overexpress *erbB2* (HER2/neu) or have a mutated *p53* gene have a worse prognosis. Particular interest has centered on *erbB2* overexpression as measured by immunohistochemistry or fluorescence in situ hybridization. Tumors that overexpress *erbB2* are more likely to respond to doxorubicin-containing regimens; *erbB2* overexpression also predicts those tumors that will respond to HER2/neu antibodies (trastuzumab) (Herceptin) and HER2/neu kinase inhibitors.

Other variables that have also been used to evaluate prognosis include proteins associated with invasiveness, such as type IV collagenase, cathepsin D, plasminogen activator, plasminogen activator receptor, and the metastasis-suppressor gene *nm23*. None of these has been widely accepted as a prognostic variable for therapeutic decision-making. One problem in interpreting these prognostic variables is that most of them have not been examined in a study using a large cohort of patients.

ADJUVANT REGIMENS Adjuvant therapy is the use of systemic therapies in patients whose known disease has received local therapy but who are at risk of relapse. Selection of appropriate adjuvant chemotherapy or hormone therapy is highly controversial in some situations. Meta-analyses have helped to define broad limits for therapy but do not help in choosing optimal regimens or in choosing a regimen for certain subgroups of patients. A summary of recommendations is shown in **Table 108-3**. In general, premenopausal women for whom any form of adjuvant systemic therapy is indicated should receive multidrug chemotherapy. Antihormone therapy improves survival in premenopausal patients who are estrogen receptor positive and should be added following completion of chemotherapy. Prophylactic surgical or medically induced castration may also be associated with a substantial survival benefit (primarily in estrogen receptor–positive patients) but is not widely used in this country.

Data on postmenopausal women are also controversial. The impact of adjuvant chemotherapy is quantitatively less clear-cut than in premenopausal patients, particularly in estrogen receptor–positive cases, although survival advantages have been shown. The first decision is whether chemotherapy or endocrine therapy should be used. While adjuvant endocrine therapy (aromatase inhibitors and tamoxifen) improves survival regardless of axillary lymph node status, the improvement in survival is modest for patients in whom multiple lymph nodes are involved. For this reason, it has been usual to give chemotherapy to postmenopausal patients who have no medical contraindications and who have more than one positive lymph node; hormone therapy is commonly given subsequently. For postmenopausal women for whom systemic therapy is warranted but who have a more favorable prognosis (based more commonly on analysis such as the Oncotype DX methodology), hormone therapy may be used alone. Large clinical trials have