without axillary lymph node metastases recur with distant metastasis. In these patients, metastasis may occur via the internal mammary lymph nodes or hematogenously. Up until recently, nodal status has been a major determinant of treatment choice. As this decision shifts to being based on the molecular type of carcinoma (discussed below), the information gained from nodal status is becoming less important. It is likely that in the future many women will not undergo node sampling.

- ***Tumor size.*** The risk of axillary lymph node metastases increases with the size of the primary tumor, but both are independent prognostic factors. Women with node-negative carcinomas less than 1 cm in size have a 10-year survival rate of more than 90%, whereas survival drops to 77% for cancers greater than 2 cm. Size is less important for HER2-positive and ER-negative carcinomas, as these carcinomas can metastasize even when quite small.
- ***Locally advanced disease.*** Carcinomas invading into skin or skeletal muscle are usually large and may be difficult to treat surgically. With increased awareness of breast cancer detection, such cases have fortunately decreased in frequency and are now rare at presentation.
- ***Inflammatory carcinoma.*** Breast cancers presenting with breast erythema and skin thickening have a very poor prognosis, as most patients prove to have distant metastases. The edematous skin is tethered to the breast by Cooper ligaments and mimics the surface of an orange peel, an appearance referred to as *peau d'orange*. These clinical signs are caused by dermal lymphatics filled with metastatic carcinoma that blocks lymphatic drainage. The 3-year survival rate is only 3% to 10%. Fewer than 3% of cancers are in this group, but the incidence is higher in African American women and younger women. The underlying carcinoma is usually diffusely infiltrative and typically does not form a discrete palpable mass. The presentation of a swollen breast without a mass can be confused with a breast infection, leading to delayed diagnosis. These carcinomas are not of a uniform specific histologic or molecular type, and thus are classified as "inflammatory" based on the clinical presentation. More than half (60%) are ER-negative and 40% to 50% overexpress HER2.
- ***Lymphovascular invasion.*** Tumor cells are present within vascular spaces (either lymphatics or small capillaries) in about half of all invasive carcinomas. This finding is strongly associated with the presence of lymph node metastases. It is a poor prognostic factor for overall survival in women without lymph node metastases and a risk factor for local recurrence. As already mentioned, extensive plugging of the lymphovascular spaces of the dermis with carcinoma cells (inflammatory carcinoma) bodes a very poor prognosis.

Other prognostic factors are related to tumor biology, as follows:

- ***Molecular subtype.*** The molecular subtype, determined by expression of ER and HER2 and proliferation, is an important prognostic factor
- ***Special histologic types.*** The survival rate of women with some special types of invasive carcinomas (tubular, mucinous, lobular, papillary, adenoid cystic) is greater than that of women with cancers of no special type. Alternatively, women with metaplastic carcinoma or micropapillary carcinoma have a poorer prognosis. In other special subtypes, particularly adenoid cystic carcinoma, low-grade adenosquamous carcinoma, and secretory carcinoma in young women, the histologic

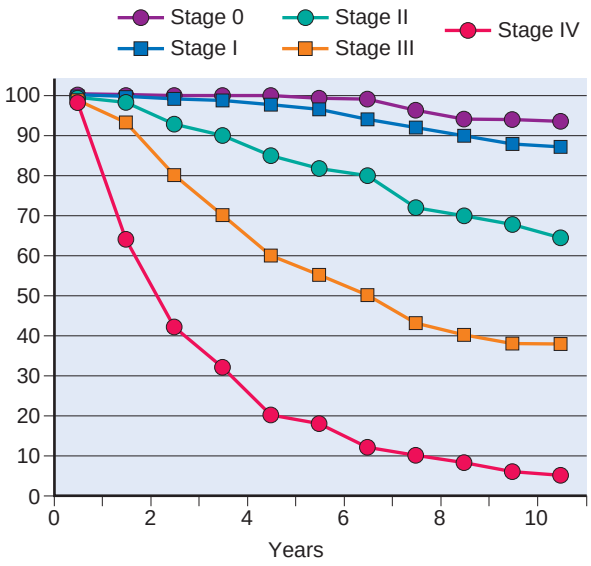

Figure 23-25 Ten-year survival according to AJCC/UICC stage (Table 23-4). Survival is strongly correlated with the extent of disease at the time of diagnosis.

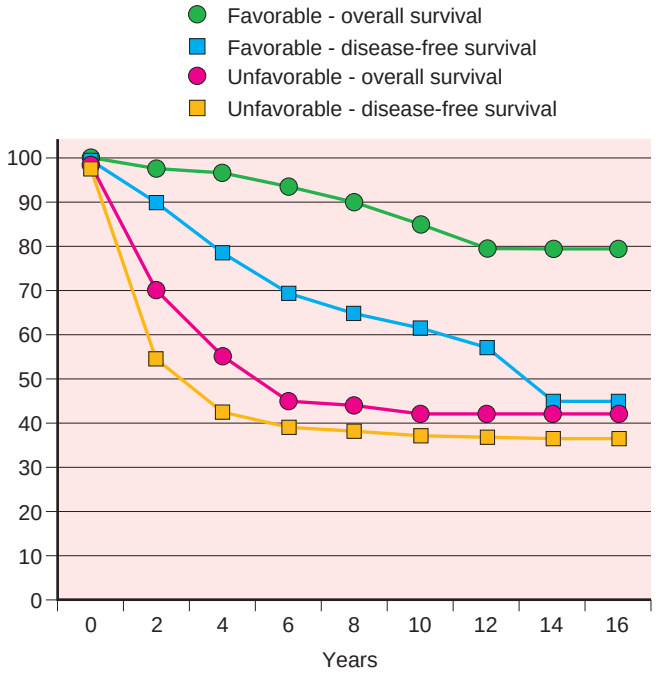

Figure 23-26 Biologic (intrinsic) breast cancer type predicts clinical outcome. Overall survival and disease-free survival are shown for the most favorable biologic type (well-differentiated, ER-positive, HER2-negative, low proliferation) and least favorable biologic type (poorly differentiated, ER-negative and/or HER2-positive). See text for other details.