chips, with important differences in biology and response to treatment. Such testing requires that the tissue be handled properly (e.g., immunologic detection of proteins is more effective in fresh-frozen tissue rather than in formalin-fixed tissue). Coordination among the surgeon, pathologist, and primary care physician is essential to ensure that the amount of information learned from the biopsy material is maximized. These goals are best met by an *excisional biopsy* in which the entire tumor mass is removed with a small margin of normal tissue surrounding it. If an excisional biopsy cannot be performed, *incisional biopsy* is the procedure of second choice. A wedge of tissue is removed, and an effort is made to include the majority of the cross-sectional diameter of the tumor in the biopsy to minimize sampling error. Biopsy techniques that involve cutting into tumor carry with them a risk of facilitating the spread of the tumor, and consideration of whether the biopsy might be the prelude to a curative surgery if certain diagnoses are established should inform the actual approach taken. *Core-needle biopsy* usually obtains considerably less tissue, but this procedure often provides enough information to plan a definitive surgical procedure. *Fine-needle aspiration* generally obtains only a suspension of cells from within a mass. This procedure is minimally invasive, and if positive for cancer, it may allow inception of systemic treatment when metastatic disease is evident, or it can provide a basis for planning a more meticulous and extensive surgical procedure. However, a negative fine-needle aspiration for a neoplastic diagnosis cannot be taken as definitive evidence that a tumor is absent or make a definitive diagnosis in someone not known to have a cancer.

CANCER STAGING

An essential component of correct patient management in many cancer types is defining the extent of disease, because this information critically informs whether localized treatments, "combined-modality" approaches, or systemic treatments should initially be considered. Radiographic and other imaging tests can be helpful in defining the clinical stage; however, pathologic staging requires defining the extent of involvement by documenting the histologic presence of tumor in tissue biopsies obtained through a surgical procedure. Axillary lymph node sampling in breast cancer and lymph node sampling at laparotomy for testicular, colon, and other intraabdominal cancers may provide crucial information for treatment planning and may determine the extent and nature of primary cancer treatment.

For tumors associated with a potential "primary site," staging systems have evolved to define a "T" component related to the size of the tumor or its invasion into local structures, an "N" component related to the number and nature of lymph node groups adjacent to the tumor with evidence of tumor spread, and an "M" component, based on the presence of local or distant metastatic sites. The various "TNM" components are then aggregated to stages, usually stage I to III or IV, depending on the anatomic site. The numerical stages reflect similar long-term survival outcomes of the aggregated TNM groupings in a numeric stage after treatment tailored to the stage. In general, stage I tumors are T1 (reflecting small size), N0 or N1 (reflecting no or minimal node spread), and M0 (no metastases). Such early-stage tumors are amenable to curative approaches with local treatments. On the other hand, stage IV tumors usually have metastasized to distant sites or locally invaded viscera in a nonresectable way and are dealt with using techniques that have palliative intent, except for those diseases with exceptional sensitivity to systemic treatments such as chemotherapy or immunotherapy. Also, the TNM staging system is not useful in diseases such as leukemia, where bone marrow infiltration is never really localized, or central nervous system tumors, where tumor histology and the extent of anatomically feasible resection are more important in driving prognosis.

CANCER TREATMENT

The goal of cancer treatment is first to eradicate the cancer. If this primary goal cannot be accomplished, the goal of cancer treatment shifts to palliation, the amelioration of symptoms, and preservation of quality of life while striving to extend life. The dictum *primum non nocere* may not always be the guiding principle of cancer therapy. When cure of cancer is possible, cancer treatments may be considered despite the certainty of severe and perhaps life-threatening toxicities. Every cancer treatment has the potential to cause harm, and treatment may be given that produces toxicity with no benefit. The therapeutic index of many interventions may be quite narrow, with treatments given to the point of toxicity. Conversely, when the clinical goal is palliation, careful attention to minimizing the toxicity of potentially toxic treatments becomes a significant goal.

Cancer treatments are divided into two main types: local and systemic. Local treatments include surgery, radiation therapy (including photodynamic therapy), and ablative approaches, including radiofrequency and cryosurgical approaches. Systemic treatments include chemotherapy (including hormonal therapy and molecularly targeted therapy) and biologic therapy (including immunotherapy). The modalities are often used in combination, and agents in one category can act by several mechanisms. For example, cancer chemotherapy agents can induce differentiation, and antibodies (a form of immunotherapy) can be used to deliver radiation therapy. *Oncology*, the study of tumors including treatment approaches, is a multidisciplinary effort with surgical, radiation, and internal medicine–related areas of oncologic expertise. Treatments for patients with hematologic malignancies are often shared by hematologists and medical oncologists.

In many ways, cancer mimics an organ attempting to regulate its own growth. However, cancers have not set an appropriate limit on how much growth should be permitted. Normal organs and cancers share the property of having (1) a population of cells actively progressing through the cell cycle with their division providing a basis for tumor growth, and (2) a population of cells not in cycle. In cancers, cells that are not dividing are heterogeneous; some have sustained too much genetic damage to replicate but have defects in their death pathways that permit their survival, some are starving for nutrients and oxygen, and some are out of cycle but poised to be recruited back into cycle and expand if needed (i.e., reversibly growth-arrested). Severely damaged and starving cells are unlikely to kill the patient. The problem is that the cells that are reversibly not in cycle are capable of replenishing tumor cells physically removed or damaged by radiation and chemotherapy. These include *cancer stem cells*, whose properties are being elucidated, as they may serve as a basis for giving rise to tumor initiating or repopulating cells. The stem cell fraction may define new targets for therapies that will retard their ability to reenter the cell cycle.

Tumors follow a Gompertzian growth curve **(Fig. 103e-1)**, with the apparent growth fraction of a neoplasm being high with small tumor burdens and declining until, at the time of diagnosis, with a tumor burden of $1–5 \times 10^9$ tumor cells, the growth fraction is usually 1–4% for many solid tumors. By this view, the most rapid growth rate occurs before the tumor is detectable. An alternative explanation for such growth properties may also emerge from the ability of tumors at metastatic sites to recruit circulating tumor cells from the primary tumor or other metastases. An additional key feature of a successful tumor is the ability to stimulate the development of a new supporting stroma through angiogenesis and production of proteases to allow invasion through basement membranes and normal tissue barriers **(Chap. 102e)**. Specific cellular mechanisms promote entry or withdrawal of tumor cells from the cell cycle. For example, when a tumor recurs after surgery or chemotherapy, frequently its growth is accelerated and the growth fraction of the tumor is increased. This pattern is similar to that seen in regenerating organs. Partial resection of the liver results in the recruitment of cells into the cell cycle, and the resected liver volume is replaced. Similarly, chemotherapy-damaged bone marrow increases its growth to replace cells killed by chemotherapy. However, cancers do not recognize a limit on their expansion. Monoclonal gammopathy of uncertain significance may be an example of a clonal neoplasm with intrinsic features that stop its growth before a lethal tumor burden is reached. A fraction of patients with this disorder go on to develop fatal multiple myeloma, but probably this occurs because of the accumulation of additional genetic lesions. Elucidation of the mechanisms that regulate this "organ-like" behavior of tumors may provide additional clues to cancer control and treatment.