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Principles of Cancer Therapy

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INTRODUCTION

The treatment of cancer is evolving rapidly. Chemotherapy is the mainstay of systemic treatment, but the explosive increase in knowledge of cancer biology has allowed research efforts to focus on the development of more specific "targeted" agents. The annual number of new drugs approved for cancer treatment has increased several-fold since the 1990s. In addition, almost 400 anticancer agents are in clinical trials, more than for any other class of medicine. Surgery and radiation therapy are safe and effective treatments for localized cancers, and techniques continue to be refined. However, cancer remains the second leading cause of death in the United States, requiring that resources be devoted to palliative care as well. The treatment of cancer requires various specialists, including surgeons and medical and radiation oncologists, to work in an integrated fashion to deliver optimal care to the patient. This chapter reviews the principles of surgical, radiation, and medical approaches to cancer treatment; it also considers diagnosis and staging as well as supportive care interventions that are integral to the care of patients with cancer.

DIAGNOSIS AND STAGING

Definitive treatment for cancer usually requires an adequate histologic diagnosis. This typically involves performance of an invasive biopsy to obtain sufficient material to evaluate the morphology and invasiveness of the tumor and the expression of various molecular markers. Noninvasive tests such as radiologic imaging are seldom substitutes for tissue diagnosis. There are some exceptions, such as an elevated α-fetoprotein level along with imaging evidence, which can be used to make a diagnosis of hepatocellular carcinoma.

Once the diagnosis of cancer has been made, the next step is to systematically determine the extent of tumor spread, a process called *staging.* Tumor staging can be clinical or pathologic. *Clinical staging* involves physical examination and imaging studies, including targeted ultrasound, computed tomography scans, magnetic resonance imaging, whole-body positron-emission tomography scans, radionuclide scans, or a combination thereof. The choice of studies for particular tumors depends on their propensity to spread to particular organs. *Pathologic staging* is more definitive and follows the tumor-node-metastasis (TNM) method developed by the American Joint Committee on Cancer and the International Union against Cancer. This system requires a careful evaluation of the primary resection specimen for three measurements: (1) the size and extent of invasion of the primary tumor (the T score), (2) the number and location of histologically involved regional lymph nodes (the N score), and (3) the presence or absence of distant metastases (the M score). The M score is based on information derived from both clinical and pathologic staging. TNM scores are then grouped into a pathologic stage, from I through IV, reflecting an increasing burden of disease. The final TNM stage has both prognostic and therapeutic implications. For instance, a resected colon cancer that invades the muscularis propria, involves 2 of 16 lymph nodes, but shows no evidence of distant metastases is staged as a T2 N1 M0 (stage III) colon cancer. The likelihood of tumor recurrence is 40% to 50%; a patient receives 6 months of chemotherapy after surgery. On the other hand, if no lymph nodes are involved (T2 N0 M0, stage I), the likelihood of recurrence is less than 10%, and chemotherapy is not recommended.

Biomarkers provide additional prognostic information, such as the absence of hormone receptors or expression of HER2 in breast cancer, which are indicative of a poor prognosis. Such markers can also be predictive; for instance, overexpression of HER2 in breast cancer predicts response to trastuzumab. Similarly, *KRAS* mutations in colorectal cancer predict lack of response to antibodies (e.g., cetuximab, panitumumab) that are directed against the epidermal growth factor receptor (EGFR). Both prognostic and predictive biomarkers provide important information in addition to the formal TNM stage. Gene expression signatures also provide additional prognostic or predictive information. A 21-gene signature is commonly used for clinical decision making regarding adjuvant therapy in patients with certain estrogen receptor–positive breast cancers. For certain tumors, measurement of serum levels of tumor markers (e.g., carcinoembryonic antigen in colon cancer, α-fetoprotein in testicular and liver cancers) can also be of prognostic importance. All of this information is compiled into a final assessment of whether the cancer is curable or not.

The next step is to evaluate the patient's overall clinical condition with respect to comorbidities affecting major organ function and the patient's functional ability, termed *performance status*. Performance status is assessed with the use of various history-based methods, such as the Eastern Cooperative Oncology Group or Karnofsky performance score. Patients with poor performance status or major comorbid conditions may not derive a benefit from cancer-directed therapy and are at greater risk for adverse events. This comprehensive assessment—diagnosis, stage, prognostic and predictive markers, and patient condition—dictates the management plan: either curative or palliative.

PRINCIPLES OF CANCER SURGERY

Surgery can prevent cancer by removal of precancerous lesions or organs that are at high risk for cancer (e.g., bilateral