Adjuvant therapy with high-dose interferon may be considered for patients with a high risk of recurrence after complete resection—that is, those with a primary tumor larger than 4 mm or lymph node metastasis. Adjuvant interferon is administered over the course of 1 year; it has substantial morbidity. The improvement in outcome is modest, and the effect on overall survival remains unclear.

For patients with metastatic disease, new agents have been developed based on the molecular biology of the disease and the immune response to malignancy. Ipilimumab, for example, is a monoclonal antibody which targets cytotoxic T-lymphocyte antigen 4 (CTLA-4), an immune regulatory molecule that inhibits T cell activation. The immunomodulatory effects of ipilimumab result in an immune response against tumor antigens, improving the survival of patients with metastatic disease (level A evidence).

Approximately 45% of cutaneous melanomas have activating mutations of the proto-oncogene *BRAF*, a component of the mitogen-activated protein kinase (MAPK) signaling pathway. Vemurafenib and dabrafenib are oral BRAF inhibitors that improve the survival of patients with metastatic disease who harbor specific *BRAF* mutations (level A evidence). Trametinib is an orally active agent that targets MEK, another component of the MAPK pathway downstream of BRAF. This agent has also demonstrated activity in patients with *BRAF*-mutant metastatic melanoma.

SARCOMA

Definition and Epidemiology

Sarcomas are heterogeneous solid tumors of mesenchymal origin. These tumors are broadly categorized as sarcomas of bone or sarcomas of soft tissue, with several distinct clinicopathologic subtypes. There were expected to be 11,410 new diagnoses of soft tissue sarcoma and 3,010 new diagnoses of bone sarcoma in the United States in 2013. Overall, sarcomas account for fewer than 1% of all new cancer diagnoses.

Most sarcomas are sporadic, but risk factors include prior radiation exposure, chemical carcinogens, and genetic predisposition (familial adenomatous polyposis [FAP], Li-Fraumeni syndrome). Moreover, human herpesvirus 8 (HHV-8) infection is associated with the development of Kaposi's sarcoma.

Soft tissue sarcomas can be further classified by their anatomic site of origin: head and neck, visceral, retroperitoneal, intra-abdominal, and extremity. This categorization is useful for staging, assessing prognosis, and establishing a therapeutic approach. The most common soft tissue sarcomas are gastrointestinal stromal tumors (GISTs), pleomorphic sarcoma, liposarcoma, leiomyosarcoma, and synovial sarcoma. The most commonly encountered sarcomas of bone are the Ewing's family of sarcomas, chondrosarcomas, and osteosarcomas.

Clinical Presentation

Given the heterogeneity of this group of diseases, including differences in tumor biology and in anatomic site of origin, the clinical presentation is variable. Soft tissue sarcomas of the extremities and of the head and neck usually manifest as a progressively enlarging, often painless, mass. Visceral and intra-abdominal sarcomas including GISTs are often found incidentally and are not symptomatic until they are locally advanced. Symptoms are often nonspecific but may include early satiety, abdominal fullness, bloating, or discomfort.

Bone sarcomas, such as Ewing's sarcoma and osteosarcoma, typically manifest with pain. The most frequently involved locations are the femur, tibia, and humerus. The physical examination may reveal a palpable mass, which is often tender to palpation. Symptoms may be present for several months before diagnosis. Most patients have locally confined disease at diagnosis; the lungs and bone are the most common sites of metastatic spread.

Diagnosis and Differential Diagnosis

The diagnosis of sarcoma can be established only by obtaining histologic confirmation, for which a biopsy is required. This disease must be distinguished from more common malignancies such as lymphoma, melanoma, and poorly differentiated carcinoma. The diagnosis of sarcoma is based on characteristic morphology but may be aided by the use of immunohistochemical and molecular studies. For example, Ewing's sarcoma is often associated with a characteristic reciprocal translocation between chromosomes 11 and 22, t(11:22). Several other molecular derangements have been identified and are helpful in establishing the specific diagnosis.

For bone sarcomas, plain films often demonstrate a mixture of lytic and blastic components with associated soft tissue edema. For osteosarcoma, the periosteal reaction produces a "sunburst" appearance as new bone forms at right angles to the tumor, as opposed to the "onion peel" appearance caused by layering of reactive bone, which is more commonly associated with Ewing's sarcoma.

Treatment and Prognosis

Surgery is the primary therapy for locally confined disease. Radiotherapy before or after surgery may decrease the likelihood of local recurrence. Chemotherapy patients with certain histologic subtypes of sarcoma (Ewing's sarcoma, osteosarcoma) may improve local control, decrease the risk of distant recurrences, and improve overall survival.

Patients with metastatic sarcoma may occasionally benefit from surgical extirpation of their disease. However, once metastatic dissemination has been detected, the intent of therapy is palliative. Chemotherapy can reduce the overall tumor burden and minimize cancer-related symptoms; doxorubicin, ifosfamide, and gemcitabine are used.

Targeted therapies have revolutionized the management of GISTs. The small-molecule tyrosine kinase inhibitor, imatinib, is highly active in patients with GISTs. It rapidly reduces tumor burden with sustained benefit. Imatinib is currently administered to patients with GISTs in the perioperative and advanced/metastatic settings (level A evidence).

CANCER OF UNKNOWN PRIMARY SITE

Definition and Epidemiology

Malignancies for which there is no apparent site of origin after a thorough history, physical examination, imaging investigations, and appropriate diagnostic procedures are referred to as *cancers*