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Lamba N et al: Epidemiology of brain metastases and leptomeningeal disease. Neuro Oncol 23:1447, 2021. Louis DN et al: The 2021 WHO classification of tumors of the central nervous system: A summary. Neuro-Oncology 23:1231, 2021. Mellinghoff IK et al: Vorasidenib in IDH1- or IDH2-mutant lowgrade glioma. N Engl J Med 389:589, 2023. Ostrom QT et al: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2016-2020. Neuro Oncol 25:iv1-iv99, 2023. Schiff D et al: Recent developments and future directions in adult lower-grade gliomas: Society for Neuro-Oncology (SNO) and Euro pean Association of Neuro-Oncology (EANO) consensus. Neuro Oncol 21:837, 2019. Wen PY et al: Glioblastoma in adults: A Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol 22:1073, 2020. Shreyaskumar R. Patel

Soft Tissue and Bone

Sarcomas and Bone

Metastases Sarcomas are rare (<1% of all malignancies) mesenchymal neoplasms that arise in bone and soft tissues. These tumors are usually of meso dermal origin, although a few are derived from neuroectoderm, and they are biologically distinct from the more common epithelial malig nancies. Sarcomas affect all age groups; 15% are found in children <15 years of age, and 40% occur after age 55 years. Sarcomas are one of the most common solid tumors of childhood and are the fifth most common cause of cancer deaths in children. Sarcomas may be divided into two groups, those derived from bone and those derived from soft tissues. SOFT TISSUE SARCOMAS Soft tissues include muscles, tendons, fat, fibrous tissue, synovial tissue, vessels, and nerves. Approximately 60% of soft tissue sarcomas arise in the extremities, with the lower extremities involved three times as often as the upper extremities. Thirty percent arise in the trunk, with the ret roperitoneum accounting for 40% of all trunk lesions. The remaining 10% arise in the head and

neck. ■ ■INCIDENCE Approximately 13,400 new cases of soft tissue sarcomas occurred in the United States in 2023. The annual age-adjusted incidence is 3 per 100,000 population, but the incidence varies with age. Soft tissue sarco mas constitute 0.7% of all cancers in the general population and 6.5% of all cancers in children. ■ ■EPIDEMIOLOGY Malignant transformation of a benign soft tissue tumor is extremely rare, with the exception that malignant peripheral nerve sheath tumors (neurofibrosarcoma, malignant schwannoma) can arise from neuro fibromas in patients with neurofibromatosis. Several etiologic factors have been implicated in soft tissue sarcomas. Environmental Factors Trauma or previous injury is rarely involved, but sarcomas can arise in scar tissue resulting from a prior operation, burn, fracture, or foreign body implantation. Chemical car cinogens such as polycyclic hydrocarbons, asbestos, and dioxin may be involved in the pathogenesis.

Iatrogenic Factors Sarcomas in bone or soft tissues occur in patients who are treated with radiation therapy. The tumor nearly always arises in the irradiated field. The risk increases with time.

Viruses Kaposi’s sarcoma (KS) in patients with HIV type 1, classic KS, and KS in HIV-negative homosexual men is caused by human herpesvirus (HHV) 8 (Chap. 200). No other sarcomas are associated with viruses. Immunologic Factors Congenital or acquired immunodefi ciency, including therapeutic immunosuppression, increases the risk of sarcoma. ■ ■GENETIC CONSIDERATIONS Li-Fraumeni syndrome is a familial cancer syndrome in which affected individuals have germline abnormalities of the tumorsuppressor gene p53 and an increased incidence of soft tissue sarcomas and other malignancies, including breast cancer, osteosar coma, brain tumor, leukemia, and adrenal carcinoma (Chap. 76). Neurofibromatosis 1 (NF-1; peripheral form, von Recklinghausen’s disease) is characterized by multiple neurofibromas and café-au-lait spots. Neurofibromas occasionally undergo malignant degeneration to become malignant peripheral nerve sheath tumors. The gene for NF1 is located in the pericentromeric region of chromosome 17 and encodes neurofibromin, a tumor-suppressor protein with guanosine 5′-triphosphate (GTP)ase-activating activity that inhibits ras function (Chap. 95). Germline mutation of the RB1 locus (chromosome 13q14) in patients with inherited retinoblastoma is associated with the devel opment of osteosarcoma in those who survive the retinoblastoma and of soft tissue sarcomas unrelated to radiation therapy. Other soft tissue tumors, including desmoid tumors, lipomas, leiomyomas, neuroblasto mas, and paragangliomas, occasionally show a familial predisposition. CHAPTER 96 Soft Tissue and Bone Sarcomas and Bone Metastases
Insulin-like growth factor (IGF) type II is produced by some sarco mas and may act as an autocrine growth factor and as a motility factor that promotes metastatic spread. IGF-II stimulates growth through IGF-I receptors, but its effects on motility are through different recep tors. If secreted in large amounts, IGF-II may produce hypoglycemia (Chaps. 98 and 418). A large international sarcoma kindred study including 1162 patients and 6545 Caucasian controls revealed that about half the patients with sarcoma have putatively pathogenic mono genic and polygenic variation in previously reported and new cancer genes, some of them representing therapeutically actionable targets. These patients were diagnosed with sarcoma at an earlier age compared to controls. ■ ■CLASSIFICATION Approximately 20 different groups of sarcomas are recognized on the basis of the pattern of differentiation toward normal tissue. For example, rhabdomyosarcoma shows evidence of skeletal muscle fibers with cross-striations; leiomyosarcomas contain interlacing fascicles of spindle cells resembling smooth muscle; and liposarcomas contain adipocytes. When precise characterization of the group is not possible, the tumors are called unclassified sarcomas.

All of the primary bone sarcomas can also arise from soft tissues (e.g., extraskeletal osteosar coma). The entity malignant fibrous histiocytoma (MFH) includes many tumors previously classified as fibrosarcomas or as pleomorphic variants of other sarcomas and is characterized by a mixture of spindle (fibrous) cells and round (histiocytic) cells arranged in a storiform pattern with frequent giant cells and areas of pleomorphism. As immu nohistochemical suggestion of differentiation, particularly myogenic differentiation, may be found in a significant fraction of these patients, many are now characterized as poorly differentiated leiomyosarcomas, and the terms undifferentiated pleomorphic sarcoma (UPS) and myxofi brosarcoma are replacing MFH and myxoid MFH. For purposes of treatment, most soft tissue sarcomas can be consid ered together. However, some specific tumors have distinct features. For example, liposarcoma can have a spectrum of behaviors. Pleomor phic liposarcomas and dedifferentiated liposarcomas behave like other high-grade sarcomas; in contrast, well-differentiated liposarcomas (better termed atypical lipomatous tumors) lack metastatic potential,

and myxoid liposarcomas metastasize infrequently, but, when they do, they have a predilection for unusual metastatic sites containing fat, such as the retroperitoneum, mediastinum, and subcutaneous tissue. Rhabdomyosarcomas, Ewing’s sarcoma, and other small-cell sarcomas tend to be more aggressive and are more responsive to chemotherapy than other soft tissue sarcomas.

Approximately a third of all soft tissue sarcomas have a translocation that may have diagnostic and prognostic relevance; for example, 90% of synovial sarcomas contain a characteristic chromosomal translocation t(X;18)(p11;q11) involving a nuclear transcription factor on chromo some 18 called SYT and two breakpoints on X. Patients with transloca tions to the second X breakpoint (SSX2) may have longer survival than those with translocations involving SSX1. Targeting these transloca tions for therapy is an area of ongoing investigation. Gastrointestinal stromal tumors (GISTs), previously classified as gastrointestinal leiomyosarcomas, are now recognized as a distinct entity within soft tissue sarcomas. Its cell of origin resembles the interstitial cell of Cajal, which controls peristalsis. The majority of malignant GISTs have activating mutations of the c-kit gene that result in ligand-independent phosphorylation and activation of the KIT receptor tyrosine kinase, leading to tumorigenesis. Approximately 5–10% of tumors will have a mutation in the platelet-derived growth factor receptor α (PDGFRA). GISTs that are wild type for both KIT and PDGFRA mutations may show mutations in SDH B, C, or D and may be driven by the IGF-I pathway. PART 4 Oncology and Hematology ■ ■DIAGNOSIS The most common presentation is an asymptomatic mass. Mechanical symptoms referable to pressure, traction, or entrapment of nerves or muscles may be present. All new and persistent or growing masses should be biopsied, either by a small incision or by a cutting needle (core-needle biopsy) placed so that it can be encompassed in the subsequent excision without compromising a definitive resection. Lymph node metastases occur in 5%, except in synovial and epithelioid sarcomas, clear cell sarcoma (melanoma of the soft parts), angiosarcoma, and rhabdomyo sarcoma, where nodal spread may be seen in 17%. The pulmonary paren chyma is the most common site of metastases. Exceptions are GISTs, which metastasize to the liver; myxoid liposarcomas, which seek fatty tissue; and clear cell sarcomas, which may metastasize to bones. Central nervous system metastases are rare, except in alveolar soft part sarcoma. Radiographic Evaluation Imaging of the primary tumor is best with plain radiographs and magnetic resonance imaging (MRI) for tumors of the extremities or head and neck and by computed tomog raphy (CT) for tumors of the chest, abdomen, or retroperitoneal cavity. A radiograph and CT scan of the chest are important for the detection of lung metastases. Other imaging studies may be indicated,

depending on the symptoms, signs, or histology. ■ ■STAGING AND PROGNOSIS The histologic grade and size of the primary tumor are the most important prognostic factors. The current American Joint Committee on Cancer (AJCC) staging system is shown in Table 96-1. Prognosis is related to the stage. Cure is common in the absence of metastatic disease, but a small number of patients with metastases can also be cured. Historically, most patients with stage IV disease used to die within 12 months, but with availability of multiple lines of treatments, median survival in second-line and beyond ranges from 13 to 18 months, and some patients may live with stable or slowly progressive disease for many years. TREATMENT Soft Tissue Sarcomas AJCC stage I patients are adequately treated with surgery alone. Stage II patients are considered for adjuvant radiation therapy. Stage III patients may benefit from neoadjuvant or adjuvant che motherapy. Stage IV patients are managed primarily with systemic therapy, with or without other modalities.

TABLE 96-1 American Joint Commission on Cancer Staging System for Sarcomas, Eighth Edition T1 Tumor ≤5 cm in greatest dimension T2 Tumor >5 cm and ≤10 cm in greatest dimension T3 Tumor >10 cm and ≤15 cm in greatest dimension T4 Tumor >15 cm in greatest dimension N0 No regional lymph node metastasis or unknown lymph node status N1 Regional lymph node metastasis M0 No distant metastasis M1 Distant metastasis Stage Groups Stage IA T1; N0; M0; G1 Stage IB T2, T3, T4; N0; M0; G1 Stage II T1; N0; M0; G2/3 Stage IIIA T1A, T2; N0; M0; G2/3 Stage IIIB T3, T4; N0; M0; G2/3 Stage IV Any T; N1; M0; any G Any T; any N; M1; any G SURGERY Soft tissue sarcomas tend to grow along fascial planes, with the surrounding soft tissues compressed to form a pseudocapsule that gives the sarcoma the appearance of a well-encapsulated lesion. This is invariably deceptive because “shelling out,” or marginal exci sion, of such lesions results in a 50–90% probability of local recur rence. Wide excision with a negative margin, incorporating the biopsy site, is the standard surgical procedure for local disease. The adjuvant use of radiation therapy and/or chemotherapy improves the local control rate and permits the use of limb-sparing surgery with a local control rate (85–90%) comparable to that achieved by radical excisions and amputations. Limb-sparing approaches are indicated except when negative margins are not obtainable, when the risks of radiation are prohibitive, or when neurovascular struc tures are involved so that resection will result in serious functional consequences to the limb. RADIATION THERAPY External-beam radiation therapy is an adjuvant to limb-sparing surgery for improved local control. Preoperative radiation therapy allows the use of smaller fields and smaller doses but results in a higher rate of wound complications. Postoperative radiation therapy must be given to larger fields, because the entire surgical bed must be encompassed, and in higher doses to compensate for hypoxia in the operated field. This results in a higher rate of late complications. Brachytherapy or interstitial therapy, in which the radiation source is inserted into the tumor bed, is comparable in efficacy (except in low-grade lesions), less time consuming, and less expensive. With the advent of stereotactic body radiotherapy (SBRT), the role of radiation therapy in oligometastatic disease in various vis ceral sites is evolving. ADJUVANT CHEMOTHERAPY Chemotherapy is the mainstay of treatment for Ewing’s sarcomas/ primitive neuroectodermal tumors (PNETs) and rhabdomyosar comas. Meta-analysis of 14 randomized trials in non-small-cell sarcomas revealed a significant improvement in local control and disease-free survival in favor of doxorubicin-based chemotherapy. Overall survival improvement was 4% for all sites and 7% for the extremity site. An updated meta-analysis including four additional trials with doxorubicin and ifosfamide combination reported a statistically significant 6% survival advantage in favor of chemo therapy. A chemotherapy regimen including an anthracycline and ifosfamide with growth factor support improved overall survival by 19% for high-risk (high-grade, ≥5 cm primary, or locally recurrent)

extremity soft tissue sarcomas. Long-term follow-up of a trial evaluating neoadjuvant use of the same combination confirms survival advantage and reports a 10-year survival of 61%. A more contemporary randomized trial compared the standard anthra cycline and ifosfamide combination to specific histology-tailored chemotherapy as an active control and confirmed superiority of the standard regimen. ADVANCED DISEASE Metastatic soft tissue sarcomas are largely incurable, but up to 20% of patients who achieve a complete response become long-term sur vivors. The therapeutic intent, therefore, is to produce a complete remission with chemotherapy (<10%) and/or surgery (30–40%). Surgical resection of metastases, whenever possible, is an integral part of the management. Some patients benefit from repeated surgi cal excision of metastases. The two most active chemotherapeutic agents are doxorubicin and ifosfamide. These drugs show a steep dose-response relationship in sarcomas. Gemcitabine with or with out docetaxel has become an established second-line regimen and is particularly active in patients with UPS and leiomyosarcomas. Dacarbazine also has some modest activity. Taxanes have selective activity in angiosarcomas, and vincristine, etoposide, and irino tecan are effective in rhabdomyosarcomas and Ewing's sarcomas. Pazopanib, an inhibitor of the vascular endothelial growth factor, platelet-derived growth factor (PDGF), and c-kit, is approved for patients with advanced soft tissue sarcomas excluding liposarcomas after failure of chemotherapy. Two additional chemotherapy drugs have gained approval from the U.S. Food and Drug Administration (FDA). Trabectedin was compared to dacarbazine in a large phase 3 randomized study in advanced leiomyosarcomas and liposarcomas after failure of an anthracycline and resulted in significant improve ment in progression-free survival. Eribulin was also tested in a similar trial and showed improvement in survival, predominantly in the liposarcoma subgroup, and is therefore now approved for that subset. Tazemetostat, an EZH2 inhibitor, is now approved for use in metastatic epithelioid sarcomas characterized by loss of tumorsuppressor gene INI1, resulting in activation of the EZH2 pathway. Nab-sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR) pathway, is now approved for treatment of metastatic perivascular epithelioid cell tumors (PEComas). The FDA granted approval for nirogacestat, a γ-secretase inhibitor, for the treatment of desmoid tumors. Imatinib targets KIT and PDGF tyrosine kinase activity and is standard therapy for advanced/metastatic GISTs and dermatofibrosarcoma protuberans. Imatinib is also indicated as adjuvant therapy for completely resected primary GISTs. Three years of adjuvant imatinib appear to be superior to 1 year of therapy for high-risk GISTs, although the optimal treatment dura tion remains unknown. Sunitinib and regorafenib are approved for second- and third-line use, respectively, in metastatic GIST after failure of or intolerance to imatinib. Ripretinib, an inhibitor of c-kit and PDGFRA, was approved for fourth-line use in metastatic GIST based on a placebo-controlled randomized trial reporting an improved median progression-free and overall survival. Avapritinib also received approval for use in the specific molecular subset of PDGFRA D842V–mutant metastatic GIST. Immune checkpoint inhibitors have generally been ineffective in most forms of sarcoma, but atezolizumab, an anti-PD-L1 antibody, has produced responses in about one-third of patients with alveolar soft part sarcoma. BONE SARCOMAS ■ ■INCIDENCE AND EPIDEMIOLOGY Bone sarcomas are rarer than soft tissue sarcomas; they accounted for only 0.2% of all new malignancies and 3970 new cases in the United States in 2023. Several benign bone lesions have the potential for malignant transformation. Enchondromas and osteochondromas can transform into chondrosarcoma; fibrous dysplasia, bone infarcts, and Paget's disease of bone can transform into either UPS or osteosarcoma.

■ ■CLASSIFICATION

Benign Tumors The common benign bone tumors include enchondroma, osteochondroma, chondroblastoma, and chondromyx oid fibroma, of cartilage origin; osteoid osteoma and osteoblastoma, of bone origin; fibroma and desmoplastic fibroma, of fibrous tissue ori gin; hemangioma, of vascular origin; and giant cell tumor, of unknown origin. Malignant Tumors The most common malignant tumors of bone are plasma cell tumors (Chap. 116). The four most common malignant nonhematopoietic bone tumors are osteosarcoma, chondrosarcoma, Ewing's sarcoma, and UPS. Rare malignant tumors include chordoma (of notochordal origin), malignant giant cell tumor, adamantinoma (of unknown origin), and hemangioendothelioma (of vascular origin). Musculoskeletal Tumor Society Staging System Sarcomas of bone are staged according to the Musculoskeletal Tumor Society stag ing system based on grade and compartmental localization. A Roman numeral reflects the tumor grade: stage I is low grade, stage II is high grade, and stage III includes tumors of any grade that have lymph node or distant metastases. In addition, the tumor is given a letter reflecting its compartmental localization. Tumors designated A are intracom partmental (i.e., confined to the same soft tissue compartment as the initial tumor), and tumors designated B are extracompartmental (i.e., extending into the adjacent soft tissue compartment or into bone). The tumor-node-metastasis (TNM) staging system is shown in Table 96-2. CHAPTER 96 ■ ■OSTEOSARCOMA Osteosarcoma, accounting for almost 45% of all bone sarcomas, is a spindle cell neoplasm that produces osteoid (unmineralized bone) or bone. Approximately 60% of all osteosarcomas occur in children and Soft Tissue and Bone Sarcomas and Bone Metastases

TABLE 96-2 Staging System for Bone Sarcomas Primary tumor (T) TX Primary tumor cannot be assessed T0 No evidence of primary tumor T1 Tumor ≤8 cm in greatest dimension T2 Tumor >8 cm in greatest dimension T3 Discontinuous tumors in the primary bone site Regional lymph nodes (N) NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Regional lymph node metastasis Distant metastasis (M) MX Distant metastasis cannot be assessed M0 No distant metastasis M1 Distant metastasis M1a Lung M1b Other distant sites Histologic grade (G) GX Grade cannot be assessed G1 Well differentiated—low grade G2 Moderately differentiated—low grade G3 Poorly differentiated—high grade G4 Undifferentiated—high grade (Ewing's is always classed G4) Stage Grouping Stage IA T1 N0 M0 G1,2 low grade Stage IB T2 N0 M0 G1,2 low grade Stage IIA T1 N0 M0 G3,4 high grade Stage IIB T2 N0 M0 G3,4 high grade Stage III T3 N0 M0 Any G Stage IVA Any T N0 M1a Any G Stage IVB Any T N1 Any M Any G Any T Any N M1b Any G

adolescents in the second decade of life, and ~10% occur in the third decade of life. Osteosarcomas in the fifth and sixth decades of life are frequently secondary to either radiation therapy or transformation in a preexisting benign condition, such as Paget's disease. Males are affected 1.5–2 times as often as females. Osteosarcoma has a predilection for metaphyses of long bones; the most common sites of involvement are the distal femur, proximal tibia, and proximal humerus. The classifica tion of osteosarcoma is complex, but 75% of osteosarcomas fall into the "classic" category, which includes osteoblastic, chondroblastic, and fibroblastic osteosarcomas. The remaining 25% are classified as "variants" on the basis of (1) clinical characteristics, as in the case of osteosarcoma of the jaw, postradiation osteosarcoma, or Paget's osteo sarcoma; (2) morphologic characteristics, as in the case of telangiectatic osteosarcoma, small-cell osteosarcoma, or epithelioid osteosarcoma; or (3) location, as in parosteal or periosteal osteosarcoma. Diagnosis usu ally requires a synthesis of clinical, radiologic, and pathologic features. Patients typically present with pain and swelling of the affected area. A plain radiograph reveals a destructive lesion

with a moth-eaten appear ance, a spiculated periosteal reaction (sunburst appearance), and a cuff of periosteal new bone formation at the margin of the soft tissue mass (Codman's triangle). A CT scan of the primary tumor is best for defin ing bone destruction and the pattern of calcification, whereas MRI is better for defining intramedullary and soft tissue extension. A chest radiograph and CT scan are used to detect lung metastases. Metastases to the bony skeleton should be imaged by a bone scan or by fluoro deoxyglucose positron emission tomography (FDG-PET). Almost all osteosarcomas are hypervascular and PET-avid. Pathologic diagnosis is established either with a core-needle biopsy, where feasible, or with an open biopsy with an appropriately placed incision that does not com promise future limb-sparing resection. Most osteosarcomas are high grade. The most important predictive factor for long-term survival is response to chemotherapy. Preoperative chemotherapy followed by limb-sparing surgery (which can be accomplished in >80% of patients) followed by postoperative chemotherapy is standard management. The effective drugs are doxorubicin, ifosfamide, cisplatin, and high-dose methotrexate with leucovorin rescue. The various combinations of these agents that have been used have all been about equally success ful. Long-term survival rates in extremity osteosarcoma range from 60 to 80%. Osteosarcoma is radioresistant; radiation therapy has no role in the routine management. UPS is considered a part of the spectrum of osteosarcoma and is managed similarly. A randomized trial has shown improved progression-free survival with regorafenib compared to placebo.

PART 4 Oncology and Hematology ■ ■CHONDROSARCOMA Chondrosarcoma, which constitutes ~20–25% of all bone sarcomas, is a tumor of adulthood and old age, with a peak incidence in the fourth to sixth decades of life. It has a predilection for the flat bones, especially the shoulder and pelvic girdles, but can also affect the diaphyseal por tions of long bones. Chondrosarcomas can arise de novo or as a malig nant transformation of an enchondroma or, rarely, of the cartilaginous cap of an osteochondroma. Chondrosarcomas have an indolent natural history and typically present as pain and swelling. Radiographically, the lesion may have a lobular appearance with mottled or punctate or annular calcification of the cartilaginous matrix. It is difficult to distinguish low-grade chondrosarcoma from benign lesions by x-ray or histologic examination. The diagnosis is therefore influenced by clinical history and physical examination. A new onset of pain, signs of inflammation, and progressive increase in the size of the mass sug gest malignancy. The histologic classification is complex, but most tumors fall within the classic category. Like other bone sarcomas, highgrade chondrosarcomas spread to the lungs. Most chondrosarcomas are resistant to chemotherapy, and surgical resection of primary or recurrent tumors, including pulmonary metastases, is the mainstay of therapy with the exception of two histologic variants. Dedifferentiated chondrosarcoma has a high-grade osteosarcoma or a UPS component that responds to chemotherapy. Mesenchymal chondrosarcoma, a rare variant composed of a small-cell element, also is responsive to systemic chemotherapy and is treated like Ewing's sarcoma.

■ ■EWING'S SARCOMA Ewing's sarcoma, which constitutes ~10–15% of all bone sarcomas, is common in adolescence and has a peak incidence in the second decade of life. It typically involves the diaphyseal region of long bones and also has an affinity for flat bones. The plain radiograph may show a charac teristic "onion peel" periosteal reaction with a generous soft tissue mass, which is better demonstrated by CT or MRI. This mass is composed of sheets of monotonous, small, round, blue cells and can be confused with lymphoma, embryonal rhabdomyosarcoma, and small-cell carcinoma. The presence of p30/32, the product of the mic-2 gene (which maps to the pseudoautosomal region of the X and Y chromosomes), is a cell-sur face marker for Ewing's sarcoma (and other members of the Ewing fam ily of tumors, previously also called PNETs). Most

PNETs arise in soft tissues; they include peripheral neuroepithelioma, Askin's tumor (chest wall), and esthesioneuroblastoma. The classic cytogenetic abnormality associated with this disease is a reciprocal translocation of the long arms of chromosomes 11 and 22, t(11;22), which creates a chimeric gene product of unknown function with components from the fli-1 gene on chromosome 11 and ews on chromosome 22. This disease is very aggres sive, and it is therefore considered a systemic disease. Common sites of metastases are lung, bones, and bone marrow. Systemic chemotherapy is the mainstay of therapy, often being used before surgery. Doxoru bicin, cyclophosphamide or ifosfamide, etoposide, and vincristine are active drugs. Topotecan or irinotecan in combination with an alkylating agent is often used in relapsed patients. Local treatment for the primary tumor includes surgical resection, usually with limb salvage or radiation therapy. Overall cure rates approach 60–70% for localized tumors. TUMORS METASTATIC TO BONE Bone is a common site of metastasis for carcinomas of the prostate, breast, lung, kidney, bladder, and thyroid and for lymphomas and sarcomas. Prostate, breast, and lung primaries account for 80% of all bone metastases. Metastatic tumors of bone are more common than primary bone tumors. Tumors usually spread to bone hematogenously, but local invasion from soft tissue masses also occurs. In descending order of frequency, the sites most often involved are the vertebrae, proximal femur, pelvis, ribs, sternum, proximal humerus, and skull. Bone metastases may be asymptomatic or may produce pain, swelling, nerve root or spinal cord compression, pathologic fracture, or myelo phthisis (replacement of the marrow). Symptoms of hypercalcemia may be noted in cases of bony destruction. Pain is the most frequent symptom. It usually develops gradually over weeks, is usually localized, and often is more severe at night. When patients with back pain develop neurologic signs or symptoms, emergency evaluation for spinal cord compression is indicated (Chap. 80). Bone metastases exert a major adverse effect on quality of life in cancer patients. Cancer in the bone may produce osteolysis, osteogenesis, or both. Osteolytic lesions result when the tumor produces substances that can directly elicit bone resorption (vitamin D–like steroids, prostaglan dins, or parathyroid hormone–related peptide) or cytokines that can induce the formation of osteoclasts (interleukin 1 and tumor necrosis factor). Osteoblastic lesions result when the tumor produces cytokines that activate osteoblasts. In general, purely osteolytic lesions are best detected by plain radiography, but they may not be apparent until they are >1 cm. These lesions are more commonly associated with hyper calcemia and with the excretion of hydroxyproline-containing peptides indicative of matrix destruction. When osteoblastic activity is promi nent, the lesions may be readily detected using radionuclide bone scan ning (which is sensitive to new bone formation), and the radiographic appearance may show increased bone density or sclerosis. Osteoblastic lesions are associated with higher serum levels of alkaline phosphatase and, if extensive, may produce hypocalcemia. Although some tumors may produce mainly osteolytic lesions (e.g., kidney cancer) and oth ers mainly osteoblastic lesions (e.g., prostate cancer), most metastatic lesions produce both types of lesion and may go through stages where one or the other predominates. In older patients, particularly women, it may be necessary to distinguish metastatic disease of the spine from osteoporosis. In

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