neoplasms. In contrast, the localized variant manifests as a solitary, slow-growing, painless mass that frequently involves the tendon sheaths along the wrists and fingers; it is the most common mesenchymal neoplasm of the hand. Cortical erosion of adjacent bone occurs in approximately 15% of cases. Both types are amenable to surgical excision, but recurrence is common. Clinical trials using antagonists of M-CSF signaling have produced encouraging responses.

SOFT TISSUE

In terms of clinical and pathologic entities, soft tissue refers to non-epithelial tissue excluding the skeleton, joints, central nervous system, hematopoietic and lymphoid tissues. Although nonneoplastic conditions can involve soft tissue, they are seldom confined to this compartment so the area of soft tissue pathology is restricted to neoplasms. With the exception of skeletal muscle neoplasms, benign soft tissue tumors outnumber their malignant counterparts, the sarcomas, by 100 fold. In the United States, the incidence of soft tissue sarcomas is approximately 12,000 per year, which is less than 1% of all cancers. Sarcomas, however, cause 2% of all cancer mortality, reflecting their aggressive behavior. Most soft tissue tumors arise in the extremities, especially the thigh. Approximately 15% arise in children but the incidence increases with age.

Pathogenesis. The majority of sarcomas are sporadic and have no known predisposing cause. A small minority of soft tissue neoplasms are associated with germline mutations in tumor suppressor genes (neurofibromatosis 1, Gardner syndrome, Li-Fraumeni syndrome, Osler-Weber Rendu syndrome). A few tumors can be linked to known environmental exposures such as radiation, burns or toxins.

Unlike tumors such as colonic carcinoma that usually arises from easily recognized precursor lesions, the origin of sarcomas is unknown. The best guess is that the tumors arise from pluripotent mesenchymal stem cells, which acquire somatic "driver" mutations in oncogenes and tumor suppressor genes. Despite heterogeneous mechanisms of tumorigenesis among sarcomas, some generalizations can be made based on their karyotypic complexity:

- Simple karyotype (15% to 20%): Like many leukemias and lymphomas, sarcomas are often euploid tumors with a single, or limited number, of chromosomal changes (Table 26-8) that occur early in tumorigenesis and are specific enough to serve as diagnostic markers. Tumors with these features most commonly arise in younger patients and tend to have a monomorphic appearance microscopically. Examples include the Ewing sarcoma, described earlier, and synovial sarcoma. In some cases, the oncogenic effect of these rearrangements is reasonably well understood, but in other cases it remains unknown (Table 26-8).

- Complex karyotype (80% to 85%): These tumors are usually aneuploid or polyploid and demonstrate multiple, severe chromosomal gains and losses, none of which are recurrent, a feature that probably speaks to an underlying abnormality producing genomic instability. Examples include leiomyosarcomas and undifferentiated sarcomas. Such tumors are more common in adults and tend to be morphologically pleomorphic.

Classification of soft tissue tumors continues to evolve as new molecular genetic abnormalities are identified. Clinically, soft tissue tumors range from benign, self-limited lesions that require minimal treatment to intermediate grade, locally aggressive tumors with minimal metastatic risk to highly aggressive malignancies with significant metastatic risk and mortality. The term *sarcoma* is applied somewhat inconsistently such that some, but not all, locally aggressive tumors fall into this category. Tumors with significant metastatic potential are, of course, considered sarcomas. Pathologic classification integrates morphology (e.g., muscle differentiation), immunohistochemistry and molecular diagnostics (Table 26-9). In addition to accurate diagnosis, grade (degree of differentiation)

Table 26-8 Chromosomal Abnormalities in Soft tissue Tumors

Tumor	Cytogenetic Abnormality	Gene fusion	Proposed function
Ewing sarcoma family tumors	t(11;22)(q24;q12) t(21;22)(q22;q12	*EWS-FLI1* *EWS-ERG*	Disordered protein with multiple functions, including aberrant transcription, cell cycle regulation, RNA splicing and telomerase
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*EWS-CHN*	
Desmoplastic small round-cell tumor	t(11;22)(p13;q12)	*EWS-WT1*	
Clear-cell sarcoma	t(12;22)(q13;q12)	*EWS-ATF1*	
Liposarcoma—myxoid and round-cell type	t(12;16)(q13;p11)	*FUS-DDIT3*	Arrests adipocytic differentiation
Synovial sarcoma	t(x;18)(p11;q11)	*SS18-SSX1* *SS18-SSX2* *SS18-SSX4*	Chimeric transcription factors, interrupts cell cycle control
Rhabdomyosarcoma—alveolar type	t(2;13)(q35;q14) t(1;13)(p36;q14)	*PAX3-FOXO1* *PAX7-FOXO1*	Chimeric transcription factors, disrupt skeletal muscle differentiation
Dermatofibrosarcoma protuberans	t(17;22)(q22;q15)	*COLA1-PDGFB*	Promoter driven overexpression of PDGF-β, autocrine stimulation
Alveolar soft-part sarcoma	t(X;17)(p11.2;q25)	*TFE3-ASPL*	unknown
Infantile fibrosarcoma	t(12;15)(p13;q23)	*ETV6-NTRK3*	Chimeric tyrosine kinase leads to constitutively active Ras/MAPK pathway
Nodular fasciitis	t(22;17)	*MYH9-USP6*	Unknown