Rare Mesenchymal Tumors

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Andrea Ferrari, Rita Alaggio, and Stefano Ferrari

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A. Ferrari (✉)
Pediatric Oncology Unit,
Fondazione IRCCS Istituto Nazionale Tumori,
Via G. Venezian 1, 20133, Milan, Italy
e-mail: andrea.ferrari@istitutotumori.mi.it

R. Alaggio
Pathology Department,
University Hospital of Padova, Padova, Italy

S. Ferrari
Division of Chemotherapy,
Istituto Ortopedico Rizzoli, Bologna, Italy

44.1 Non-rhabdomyosarcoma Soft Tissue Sarcomas

Andrea Ferrari and Rita Alaggio

While benign neoplasms of soft tissues (i.e., lipoma, fibroma, leiomyoma, hemangioma) are relatively frequent and outnumber by 100 times malignant cases (incidence of about 300 new cases per 100,000), soft tissue sarcomas are rare diseases. They account for <1% of all malignant tumors and 2% of all cancer-related deaths. Data from the Survival Epidemiology and End Result (SEER) registry indicated an overall incidence of 5.9/100,000 persons/year. The incidence rates increased with age, rising from 0.9/100,000 in children younger than age 10 years to 18.2 for individuals older than age 70 (Ferrari et al. 2011).

However, though their absolute number is lower than in adult age, in childhood and adolescence, soft part sarcomas encounter for about 8% of all malignancies and as a whole group represents the fifth most frequent childhood cancer. More than half of pediatric soft tissue sarcomas are represented by rhabdomyosarcoma, that is one of the most typical tumors of childhood. The remaining entities are usually grouped under the definition of "non-rhabdomyosarcoma soft tissue sarcomas" (NRSTS), a term that describes a heterogeneous group of mesenchymal extraskeletal malignant tumors: Some of them are peculiar of infants and small children, but most of the entities included in this group are really tumors more common in adults than in children (Fig. 44.1). The term "NRSTS" (currently in widespread use) reflects the fact that these tumors have been historically managed according to

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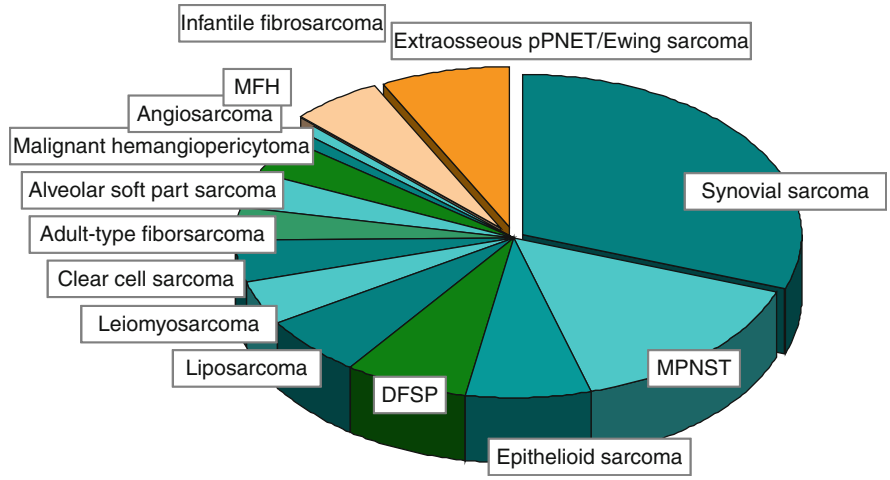

Fig. 44.1 Different non-rhabdomyosarcoma soft tissue sarcoma histotypes in the series from the Istituto Nazionale Tumori in Milan (Ferrari et al. 2005a). In *blue-green colors*, the "adult-type" subtypes. *pPNET* peripheral primitive neuroectodermal tumors, *MPNST* malignant peripheral nerve sheath tumors, *DFSP* dermatofibrosarcoma protuberans, *MFH* malignant fibrous histiocytoma

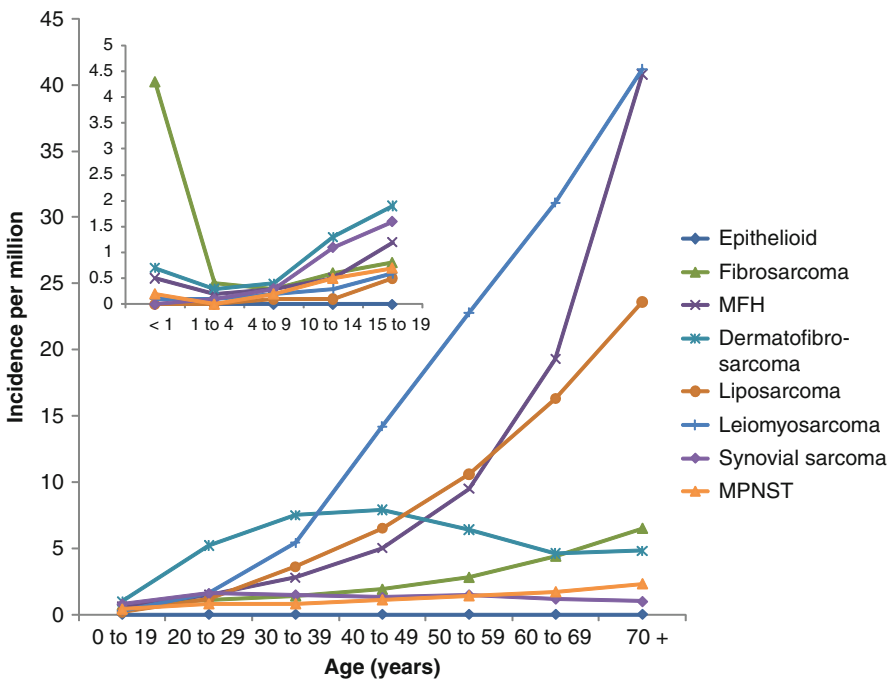

Fig. 44.2 Age-specific incidence of some non-rhabdomyosarcoma soft tissue sarcoma subtypes from the Survival Epidemiology and End Result (SEER) public-access database collected from various geographic areas in the United States (1973–2007) (www.seer.cancer.gov) (Courtesy Dr. Iyad Sultan, King Hussein Cancer Center, Amman, Jordan)

the principles adopted for rhabdomyosarcoma, but, though they share some clinical characteristics, NRSTS must be considered as clearly different entities. Each NRSTS histotype should be considered a very rare tumor in childhood. As examples, Fig. 44.2 shows the age-specific incidence of some subtypes from the SEER: synovial sarcoma, dermatofibrosarcoma protuberans, and malignant peripheral nerve sheath tumors (MPNST).

NRSTS can arise anywhere in the body, and can have a local invasiveness and a tendency to give distant metastases that is correlated to the different degrees of malignancy along histotype and tumor grade. As a general view, borderline and low-grade tumors may be locally aggressive, but unlikely to metastasize: The growth rate may be indolent and sometimes the diagnosis is done after removing a small swelling that has existed for several years. High-grade tumors are more aggressive and can have a strong propensity to metastasize, particularly to the lung. The clinical history may be very different among the different entities included under the NRSTS umbrella: e.g., MPNST are generally axial and aggressiveness disease, characterized by poor prognosis, particularly when associated to neurofibromatosis type 1 (NF1) (Ferrari et al. 2007a; Carli et al. 2005); epithelioid sarcomas present typical

features such as peculiar superficial distal location (i.e., hand, fingers), indolent growth and tendency for lymph node involvement (Casanova et al. 2006); infantile fibrosarcomas is a peculiar subtype that may have initial rapid growth and metastatic spread, but also indolent evolution (and also spontaneous regressions have been described) (Orbach et al. 2010); desmoplastic small round cell tumors (DSRCT) usually present as large abdominal masses generally disseminated at the time of diagnosis, with extensive spread to regional lymph nodes, peritoneal seeding, and distant metastases; the outcome is extremely poor despite intensive multimodality treatment approaches (Kushner et al. 1996; Bisogno et al. 2010).

As a preliminary statement, it could be said that the rarity and the heterogeneity of NRSTS would suggest that children and adolescents with these tumors should be referred to selected experienced institutions with multidisciplinary skills in enrolling patients in clinical trials. Tumors of intermediate malignancy are usually treated with surgery alone. For truly malignant tumors, and for high-grade sarcomas in particular, a multimodal therapy including surgery, radiotherapy, and chemotherapy needs to be considered the best approach. Most of NRSTS are usually considered scarcely chemosensitive tumors, but this is not true for all the histotypes, some of them requiring peculiar tailored approaches. In all the cases, the indication for the different treatment modalities and their intensity should be modulated according to the risk group, with the aim to give more intensive therapies to patients with less favorable prognostic factors, while avoiding overtreatment and side effects (without jeopardizing the outcome) in cases with more favorable clinical features (Ferrari and Casanova 2005).

The overall cure rate for NRSTS patients, in fact, is around 70%, but this data is strictly correlated to the presence of the different prognostic variables. For most NRSTS, and in particular for those entities typical of adult age (adult-type NRSTS), the variables known to have a prognostic role in adults are relevant also in children (Spunt et al. 1999; Ferrari et al. 2005b, 2007b): the disease extension at onset, the degree of the initial surgery, the grade of malignancy, the tumor site (Ferrari et al. 2008), the tumor size (though it should be considered that the risk associated with a given tumor size may not be the same in patients with the same tumor but of different age and body size) (Ferrari et al. 2009). Patient's age is often a prognostic factor (Hayes-Jordan et al. 2000) and for many NRSTS subtypes, treatment results reported in pediatric series are significantly better than those reported in adult cohorts (Sultan et al. 2009; Ferrari et al. 2004).

While in the past, children with NRSTS were often treated according to the guidelines defined for rhabdomyosarcoma, in the recent years, both the North-American Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG) and the European paediatric Soft tissue sarcoma Study Group (EpSSG) developed specific multimodal risk-adapted trials focused on pediatric NRSTS, the COG ARST0332 and the EpSSG NRSTS 2005.

44.1.1 The Pathological Characterization

The histologic classification of soft tissue tumors is based on their morphologic resemblance to one of the constituent mesenchymal tissues in the different developmental stages. Whether these tumors originate from a mesenchymal stem-cell or from a less primitive precursor committed to a differentiative lineage is still unknown. For a large and heterogeneous group of soft tissue tumors, the putative cell of origin remains a mystery.

The current WHO classification for soft tissue tumors (WHO 2002) recognizes three prognostic categories: benign tumors, malignant tumors, and tumors with intermediate prognosis (locally aggressive and rarely metastasizing). The clinical and histologic overlap between these forms make their diagnosis particularly challenging and complex for both clinicians and pathologists. In case of benign or intermediate tumors, it is important to avoid the risk of a mutilating surgery or overtreatment, and in case of sarcomas, the correct categorization allows the adequate treatment. Although the diagnosis is based on morphology, the widespread use of immunohistochemistry with specific lineage markers and the identification of cytogenetic and molecular genetic abnormalities have contributed to a more precise classification and to a better understanding of the mechanisms involved in tumor development, progression, and prognosis.

Genomic and expression profiling studies suggest that sarcomas can be divided into four major genetic groups: (a) sarcomas with specific translocation, (b) sarcomas with specific activating or inactivating mutations, (c) sarcomas with 12q13-15 amplification, and (d) sarcomas with a complex genomic profile (Chibon et al. 2009; Coindre and Chibon 2010). Most of sarcomas

Table 44.1 Clinicopathologic features of rare soft tissue tumors with intermediate prognosis in children

Differentiative lineage	Histotype	Site	Genetic alterations	Associated syndromes or malformations	Histologic key-features
Fibroblastic myofibroblastic	Superficial fibromatoses	Plantar, less frequently palmar	Autosomal dominant	Spine malformations, bifid uvula, geographic tongue, inflammatory bowel disease, and Ehlers–Danlos-like findings	Proliferation of fibroblasts and plump myofibroblasts in bundles
	Desmoid-type fibromatoses	Abdominal, extra-abdominal	Mutations in APC gene in FAP CTNNB1 (exon 3) in sporadic variants	FAP/Gardner syndrome	Uniform spindle cells in fascicle with thin-walled vessels running parallely, scattered mast cells
	Lipofibromatosis	Distal extremities, trunk, head	t (4;6;9)	–	Mature adipose tissue traversed by fascicles of fibroblasts
	Inflammatory myofibroblastic tumor	Lung, mesentery, omentum, retroperitoneum, liver, head, neck	ALK rearrangements with different partner genes	–	Fasciitis-like, fibrohistiocytoma-like, desmoid-like
	Infantile fibrosarcoma	Trunk, distal extremities	(12;15)(p13;q25)	–	Spindle cells with high nuclear/cytoplasm ratio and nuclear hyperchromasia, in fascicles with herringbone pattern
Vascular	Kaposiform hemangioendothelioma	Retroperitoneum, skin, head, and neck	–	Kasaback–Merrit syndrome	Nodules of capillary-sized vessels intermixed with spindle cells, glomeruloid nests of endothelial cells and dilated lymphatic vessels at periphery

FAP familial adenomatous polyposis

typical of childhood fall in the first group, whereas more than 50% of the adult-type sarcomas are encompassed in the last category, together with some sarcomas arising in the context of family cancer syndromes and those arising as second tumors after radiotherapy.

Tables 44.1 and 44.2 summarize the most frequent pediatric sarcomas other than rhabdomyosarcoma in children and adolescents, the chromosomal aberrations and the associated cancer syndromes.

44.1.2 Soft Tissue Tumors with Intermediate Prognosis

Soft part tumors with intermediate prognosis are mostly of fibroblastic-myofibroblastic origin and include some lesions occurring both in children and adults, such as fibromatoses and inflammatory myofibroblastic tumor, and others occurring exclusively in childhood, such as infantile fibrosarcoma. This group includes also tumors of fibrohistiocytic origin (plexiform fibrohistiocytic tumor), vascular origin (kaposiform hemangioendothelioma), or with unknown histogenesis (angiomatoid fibrous histiocytoma). *Plexiform fibrohistiocytic tumor*, *angiomatoid fibrous histiocytoma*, and *kaposiform hemangioendothelioma* are discussed in the chapter on "rare tumors of the skin and subcutaneous tissue."

These lesions of intermediate malignancy may display a worrisome morphology mimicking highly aggressive sarcomas, and clinical features of a poorly circumscribed mass with infiltrative margins may further support this possibility. They represent a therapeutic challenge for oncologists and surgeons, in particular

in case of large unresectable lesions. Historically, surgery had been generally considered the mainstay of treatment for these tumors. However, treatment strategies are currently changing to some degree, from a strategy of aggressive surgery to a multidisciplinary approach that includes also various potentially effective systemic therapies and takes the functional and cosmetic sequelae of treatments into account too.

44.1.2.1 Fibromatoses

The fibromatoses are benign or intermediate locally aggressive fibroblastic-myofibroblastic proliferations and may be sporadic or associated to syndromes or genetic disorders. Classically, they are divided into juvenile and adult-type fibromatoses (Allen 1977).

The great majority of *juvenile fibromatoses* are benign and include different clinicopathologic entities, some solitary and only occasionally multiple, like fibrous hamartoma of infancy, others frequently multicentric, like myofibromatosis. The clinical behavior may differ from spontaneous regression, either in solitary or multicentric variants, to lethal forms with visceral involvement (Chung and Enzinger 1981). Some other fibromatoses are hereditary, such as juvenile hyaline fibromatosis and gingival fibromatosis (Coffin and Boccon-Gibod 2004).

Lipofibromatosis is the only juvenile fibromatosis classified among the intermediate, soft tissue neoplasms, with recurrences or persistent growth observed after surgery in 72% of cases. It is typical of infants, congenital in 25% of cases, more frequent in males, and generally localized in the upper and lower distal extremities. In the past, many cases had been diagnosed as desmoid fibromatosis. The diagnostic key-feature is the presence of adipose tissue traversed by fibrous septa containing fascicles of bland fibroblasts. Risk of recurrence may be associated with congenital onset, male sex, hands and feet location, incomplete surgery, and a high mitotic activity (Fetsch et al. 2000).

The *adult fibromatoses* include the deep-seated *desmoid fibromatosis* (aggressive fibromatosis) and *superficial palmar/plantar fibromatosis*, both representing intermediate, locally recurring soft tissue neoplasms.

Although considered adult fibromatoses, *desmoid tumors* occur both in adults and children, with an incidence of 0.2–0.4/100,000 population/year. It account for up to 60% of fibrous tumors in childhood, where up to 30% occur in the first year of life, with a peak incidence around 4.5 years. A male predominance has been observed in pediatric series.

The pathogenesis of aggressive fibromatosis is most likely multifactorial and genetic predisposition, endocrine factors, and trauma, all seem to play an important part. This neoplasm can be sporadic or arise in the setting of Familial Adenomatous Polyposis (FAP) or the Gardner's variant of the syndrome, often characterized by intra-abdominal mesenteric lesions with aggressive behavior. Syndromic desmoid may be preceded or accompanied by fibrous, plaque-like lesions called Gardner Fibroma.

Histologically, the lesions vary in cellularity and amount of collagen matrix. Uniform spindle cells and subtle collagen bundles are arranged in long fascicles or sheets with thin-walled blood vessels parallel to the fascicles. Immunostains confirm the fibroblastic-myofibroblastic nature of desmoid fibromatoses, showing positive staining for vimentin and variable expressions of muscle-specific actin, desmin, and smooth muscle actin.

Cytogenetic investigation of desmoids in FAP has clarified the key role played by beta-catenin, a transcriptional activator involved in the promotion of mesenchymal cell proliferation. In FAP-related desmoids, germ-line mutations in APC gene inhibit its ability to induce the phosphorylation of beta-catenin necessary for its proteosomal degradation, and it accumulates in the cytoplasm and migrates to the nucleus with a permanent activation of genes involved in cell proliferation. In sporadic desmoids, mutations more frequently involve codons 41 (41A) and 45 (45F and 45P) of beta-catenin gene CTNNB1 resulting in a non-phosphorylated active beta-catenin. The mutated form of beta-catenin shows a positive nuclear immunostaining (Salas et al. 2010). Some studies indicate that increased nuclear expression of beta-catenin, especially if associated to p53 positivity, may be predictive of a high recurrence rate (wild-type beta-catenin tumors seem to have a better relapse-free survival) and may be potentially used as molecular biomarkers of local recurrence (Dômont et al. 2010; Lazar et al. 2008).

In children, desmoid fibromatosis may involve extremities, trunk, head, and neck. They have a strong tendency for local recurrence (ranging from 24% to 77%), but do not metastasize to other organs as truly malignant tumors do. (Overall survival is generally over 90% at 10 years.)

Table 44.2 Clinicopathologic features of rare malignant soft tissue tumors in children

Differentiative lineage	Histotype	Site	Genetic alterations	Associated syndromes or malformations, predisposing factors	Histologic key features
Fibroblastic myofibroblastic	Adult-type fibrosarcoma	Distal extremities, trunk, head, neck, and lung	–	Previous radiotherapy	Spindle cells with tapered nuclei, in herringbone pattern
	Myofibrosarcoma	Head and neck, rarely bone	Nonspecific alterations at 12p11, 12q13-q22, 1p gain	–	Myofibroblastic differentiation (with EM or IHC)
	Low-grade fibromyxoid sarcoma	Superficial, head and neck, lower extremities, and trunk	t(7;16)(q32-34;p11)	–	Biphasic tumor with myxoid/fibrous areas and bland spindle cells in myxoid stroma with prominent arciform vessels
	Sclerosing epithelioid fibrosarcoma	Deep, limb, trunk, shoulder, neck	t(7;16)(q32-34;p11) in mixed tumors with LGFMS areas	–	Carcinoma-like nests, sheets, or cords of epithelioid cells in a fibrous stroma
	Myxofibrosarcoma	Trunk, distal extremities	–	–	Low-grade: scattered spindle /stellate cells with hyperchromatic nuclei in myxoid matrix
					High grade: increase of cellularity and atypia
Smooth muscle	Leiomyosarcoma	Skin, superficial and deep soft tissue, bone, viscera (lung and GI tract)	Extra copies of chr 5, 18, 20, 21, 22 in infantile form, complex structural and numerical cytogenetic alterations in others		Spindle cells with elongated, blunt-ended nuclei in interlacing bundles; variants: inflammatory and myxoid leiomyosarcoma; epithelioid and pleomorphic leiomyosarcoma exceedingly rare
	Smooth muscle tumors with uncertain malignant potential	Multifocal	–	Immunocompromised patients (associated with Epstein–Barr virus infection)	Well-differentiated mitotic activity <18/10HPF
Adipose	Liposarcoma	Lower extremities, mediastinum	Myxoid liposarcoma: t(12;16) (q13;p11), MDM2 mutation in atypical lipomatous tumor	Li–Fraumeni syndrome	More than 90% myxoid LPS (including pleomorphic and spindle cell variants)
					<5% atypical lipomatous tumors
					<2% pleomorphic liposarcoma
Fibrohistiocytic tumors	Undifferentiated high-grade pleomorphic sarcoma			Family history of cancer previous radiotherapy	Spindle cells in fascicles or sheets and storiform pattern focal pleomorphism
Nerve sheath	MPNST		Mutation of NF1 gene in syndromic MPNST	NF1	Classic spindle cells with weavy nuclei, nuclear palisades
			TP53, p16INK4 mutations		Variants: epithelioid, glandular, triton tumor
Vascular tumors	Epithelioid hemangioendothelioma	Deep soft tissue of extremities, viscera	t(1;3)(p36.3;q25) in 2 cases		Epithelioid cells with cytoplasmic vacuoles in a myxoid stroma
	Angiosarcoma	Heart, mediastinum, breast, deep soft tissue	–	–	Malignant blood vessels, nests, sheets of spindle/epithelioid cells

Uncertain differentiation	Epithelioid sarcoma	Finger, hand, wrist, forearm, Lower extremities, trunk, head and neck, genital areas	INI mutation in 50%	–	Classic: nodules of large, eosinophilic cells, central necrosis, morphologic variants: fibroma-like, dermatofibroma-like, angiomatoid, proximal-type: s prominent epithelioid cells with rhabdoid cells
	Clear cell sarcoma of soft parts	Tendons aponeuroses distal extremities	t(12;22)(q13;q12)		Fascicles/nests of pale, elongated epithelioid cells
	Alveolar soft part sarcoma		ASPSCR1–TFE3		Epithelioid cells in nests. PAS-positive cytoplasmic rhomboid crystals
	Desmoplastic small round cell tumor	Abdominal, pelvic cavity, others sites	t (11; 22)(p13; q12),		Solid sheets, nests or cords of small cells in a desmoplastic stroma
	Extrarenal rhabdoid tumor	Somatic soft tissues, abdomen, pelvis, retroperitoneum, liver, heart, and GI tract	Deletion or mutation of hSNF5/SMARCB1/INI1	Syndrome of predisposition to rhabdoid tumor (germ-line mutation/ deletion of INI1 gene)	Epithelioid cells, large nuclei with prominent nucleoli, cytoplasmic juxtanuclear hyaline globules
	Synovial sarcoma	Any site	t(X;18)(p11.2;q11.2)	–	Monophasic fibrous or epithelial biphasic (spindle and epithelioid cells) poorly differentiated

IHC immunohistochemistry, *EM* electron microscopy, *GI tract* gastrointestinal tract, *Inf LMS* inflammatory leiomyosarcoma, *MPNST* malignant peripheral nerve sheath tumors, *NF1* neurofibromatosis type 1, *LGFMS* low-grade fibromyxoid sarcoma

Surgery had been generally considered the mainstay of treatment for these tumors; the goal should be a microscopically complete resection, but the influence of positive margins on local relapse is still debated, hence a mutilating surgery should be avoided. However, treatment strategies are currently changing: On the one hand, it is clear that surgery is not resolutive in many cases, and, moreover, it might be cause of fibromatosis growth and recurrence. On the other hand, various pharmacological treatments have proved to be relatively effective. Therapeutic options may be non-cytotoxic agents, including hormonal treatment (tamoxifene), nonsteroidal anti-inflammatory drugs and interferon-alpha, or cytotoxic agents, in particular the prolonged low-dose chemotherapy such as the weekly low-dose methotrexate plus vinca alkaloid (vinblastine or vinorelbine) combination. Interesting responses have been seen also using target therapy as imatinib (probably via a mechanism of action not involving c-kit and platelet-derived growth factor receptor [PDGFR]) (Heinrich et al. 2006). The response rate to the various systemic regimens is generally around 50% (or less) (Skapek et al. 2007). The goal of systemic therapy in this disease, however, is not only the tumor shrinkage to permit a subsequent resection (as in malignant tumors), but also the induction of growth arrest and tumor stabilization (Meazza et al. 2010).

Desmoid tumors can remain stable for a long time, with or without primary treatment, and this finding has prompted the suggestion that also a "wait-and-see" strategy (clinical-radiological monitoring alone) might be suitable in cases of non-evolving disease. A watchful waiting strategy is currently suggested by many experts: Therapies should be given only in the event of tumor growth (or in case of life-threatening tumors), and first therapeutic option might be a "minimal-morbidity systemic therapy" (being the combination of low-dose methotrexate plus vinblastine/vinorelbine the first choice) rather than a surgical resection (Bonvalot et al. 2008; Fiore et al. 2009).

Due to the potentially long-term cosmetic or functional morbidity in children, radiation therapy may have a role after failure to chemotherapy, in case of progression despite multiple surgeries, or as alternative to mutilating surgery.

The *superficial fibromatoses*, including *palmar and plantar fibromatosis*, usually affect adults over the age of 40 years and are rare in children (very uncommon before the age of 5 years) (Fetsch et al. 2005; Urban et al. 1996) [33–36]. Both these entities have a genetic predisposition. Palmar fibromatosis involves the ulnar aspect of the palm, whereas plantar fibromatosis affects the medial plantar arch. The tumors involve the aponeuroses and their morphology varies according to the stage of development. (Pediatric lesions are more cellular and show fibroblastic nodules and frequent mitoses; as the lesions evolve, they become hypocellular and collagenized.)

Differently from adults, in children, there is a prevalence of plantar fibromatosis with more frequent occurrence in females. Palmar and plantar fibromatoses may coexist in the same patient, may be bilateral, or may be associated with the involvement of the extensor surface of the finger joints (knuckle pads) and keloids. An association between palmar-plantar fibromatosis and fifth finger clinodactyly has been reported in about 13% of cases, as well as isolated cases of spine malformation, bifid uvula, "geographic" tongue, inflammatory bowel disease, and Ehlers–Danlos-like findings.

The recurrence rate is higher in children than in adults (about 80%). Surgery is essentially the only treatment and is recommended when the contracture is significant; however, recurrence after surgery is frequent. A wide or radical fasciectomy or dermofasciectomy is generally reserved for lesions determining functional impairment (Fetsch et al. 2005).

44.1.2.2 Inflammatory Pseudotumors

The umbrella term "inflammatory pseudotumors" includes reactive and neoplastic lesions characterized by a proliferation of fibroblasts and myofibroblasts with a prominent chronic inflammatory infiltrate (Gleason and Hornick 2008).

Inflammatory myofibroblastic tumor (IMT) is a distinctive neoplasm, observed mainly in children and young adults. It was originally described in the lung, but it involves also mesentery, omentum, retroperitoneum, abdominal soft tissues, liver, head, and neck. A palpable mass may be the clinical presentation, sometimes accompanied by an inflammatory syndrome, microcytic hypochromic anemia, thrombocytosis, polyclonal hyperglobulinemia (Coffin et al. 1995, 1998a).

Macroscopically, IMT are multinodular, non-encapsulated lesions, with a firm consistency, and may reach a large size, especially the intra-abdominal forms, that infiltrate the intestinal wall. Histologically,

IMT are composed of myofibroblasts with scattered large, ganglion-like cells and a prominent inflammatory infiltrate containing plasma cells, lymphocytes, and eosinophils. According to the degree of cellularity, inflammatory infiltrate, and prevalence of myxoid or fibrous stroma, IMT may display different patterns varying from fasciitis-like lesions, with prominent inflammatory infiltrate and myxoid stroma, to those highly cellular fibrohistiocytoma-like, or hypocellular, desmoid-like (Coffin et al. 1998b) (Fig. 44.5d). A round cell variant has been recently described (Chen and Lee 2008).

Immunohistochemistry shows reactivity for vimentin and variable staining for smooth muscle actin, muscle-specific actin, and desmin. In IMT, the ALK gene, located on chromosome 2p23, codifying for a tyrosine kinase receptor, rearranges with a variety of gene partners (TPM3, CLTC, RANBP2, and others) (Bridge et al. 2001), resulting in a persistently activated protein and a positive immunostaining for ALK-1 in approximately 50% (Cessna et al. 2002; Cook et al. 2001; Coffin et al. 2001). ALK-1 is more frequently positive in pediatric tumors and abdominal sites.

The recurrence rate varies according to the anatomical site. Extrapulmonary IMT lesions tend to recur more frequently, with a relapse rate of 25%. Distant metastases occur in <5% of cases, mostly in lung and brain. Tumor size and histologic features do not appear to influence the clinical behavior. However, aneuploidy may indicate a more aggressive potential (Hussong et al. 1999). A group of ALK-negative IMT might have a higher risk of metastasis and unfavorable prognosis (Coffin et al. 2007). Recent studies suggest that round cell IMT carry an ALK-RANBP2 fusion gene and behave aggressively (Chen and Lee 2008). Wide resection is the mainstay of treatment; radiotherapy and systemic treatments (corticosteroids, chemotherapy) have been variously used in high-risk situations, but their role remains to be established yet (Alaggio et al. 2010a).

44.1.2.3 Congenital Infantile Fibrosarcoma

Congenital infantile fibrosarcoma (CIFS) is the most common sarcoma under 1 year of age. It occurs in the first 2 years of life, and near 50% of cases are diagnosed at birth (or, occasionally, in utero) (Chung and Enzinger 1976; Coffin et al. 1994).

Histologically, CIFS display a wide morphologic spectrum. These tumors are generally highly cellular neoplasms, composed of spindle cells with hyperchromatic nuclei arranged in sheets, bands, or fascicles (Fig. 44.5c). A prominent hemangiopericytomatous vasculature is frequent. A focal herringbone pattern may simulate an adult fibrosarcoma. Mitoses are frequent. Immunostains are not specific and are important to exclude other spindle cell sarcomas: Smooth muscle actin, muscle-specific actin, and desmin are variously expressed. CIFS is characterized by the recurrent translocation t(12;15)(p13;q25) with the transcript ETV6-NTRK3, that is shared by cellular mesoblastic nephroma (Knezevich et al. 1998; Bourgeois et al. 2000). In addition, CIFS may have other cytogenetic abnormalities, including trisomy 11; random gains of chromosomes 8,11,17, and 20; and deletion of long arm of chromosome 17 (Bernstein et al. 1994; Dal Cin et al. 1991; Mandahl et al. 1989).

CIFS is generally located in deep soft tissues of distal extremities (and less frequently trunk). Tumors usually have rapid growth and huge size, while distant metastases are rare. However, the prognosis is favorable in the majority of cases, with survival rates between 80% and 100%. Surgery is the mainstay of treatment (Fig. 44.3), but chemotherapy is effective, also utilizing mild alkylating/anthracyclines-free regimens: The VA regimen (vincristine and actinomycin) is the chemotherapy of choice, and more intensive regimen should be considered only in the event of no response to VA chemotherapy (Orbach et al. 2010). Due to the young age of patients, radiotherapy must not be seen as an option.

The widespread use of molecular characterization has allowed the identification of a group of lesions previously classified as CIFS because of their occurrence in infants and their morphologic overlap with primitive forms of CIFS. These tumors, now identified as Primitive Myxoid Mesenchymal Tumor of Infancy (PMMTI), are characterized by a diffuse growth of primitive spindle, polygonal, and round cells embedded in a myxoid stroma with a characteristic prominent vascular network. The few cases studied by RT-PCR lack the ETV6-NTRK3 transcript. PMMTI may have an aggressive behavior: In the published cases, two out of five newborns with available follow-up died of disease and two experienced either distant metastases or local aggressive growth, not responding to chemotherapy. Surgery is the elective treatment, PMMTI being poorly responsive to chemotherapy (Alaggio et al. 2006).

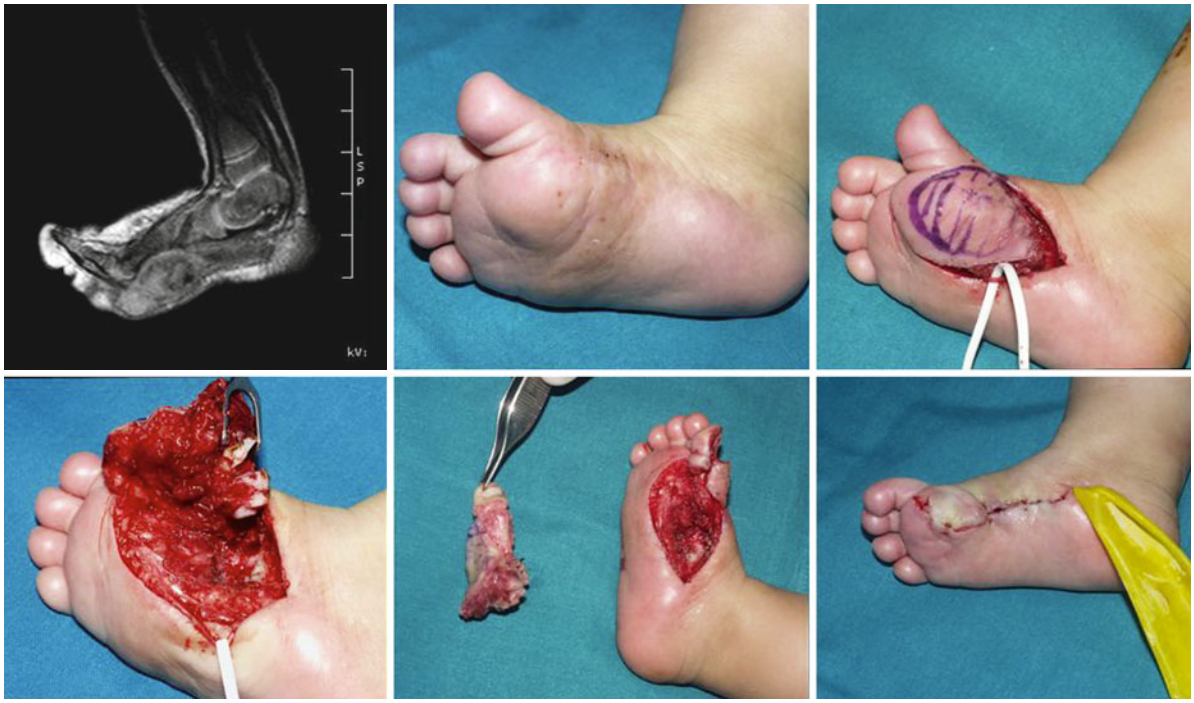

Fig. 44.3 Congenital infantile fibrosarcoma of the right foot. Wide surgical resection with amputation of the first finger (Courtesy Dr. Alessandro Gronchi, Melanoma Sarcoma Surgical Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy)

44.1.3 Malignant Soft Tissue Tumors

The large part of NRSTS represent the so-called adult-type sarcomas, tumor entities typically occurring in adults and elders and only occasionally in children. Most of them show an identifiable differentiative lineage and include adult fibrosarcomas, liposarcoma, leiomyosarcomas, and MPNST. A common denominator in this group of tumors (with the exclusion of MPNST) is the prognostic role of tumor grade. The two most widely used grading systems are the NCI (United States National Cancer Institute) system, which has been adapted for pediatric sarcomas in the POG (Pediatric Oncology Group) system (Parham et al. 1995) and the FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) system (Coindre et al. 1996; Guillou et al. 1997a). All have proven to be highly predictive of prognosis in this group of sarcomas. FNCLCC system identifies three grades, grade 1 the lowest, 2 intermediate, and 3 the highest, resulting from the addition of different scores given to tumor resemblance to its normal counterpart, mitotic activity, and necrosis. POG system takes into account the peculiarity of pediatric sarcomas which are considered by definition grade 1 or 3 according to histotype, whereas only adult-type sarcomas are graded according to mitotic rate and necrosis. Currently both FNCLCC and POG systems are being used in pediatric sarcomas.

Synovial sarcoma, alveolar soft part sarcoma, clear cell sarcoma of soft parts, epithelioid sarcoma, desmoplastic small round cell tumor, and rhabdoid tumor are characterized by the absence of a lineage differentiation or an identifiable normal cellular counterpart. With the partial exception of synovial sarcoma, their behavior is not influenced by tumor grade. All these tumors, but rhabdoid tumor, arise in young adults and adolescents and are less frequent in elders and children.

Dermatofibrosarcoma protuberans, *angiosarcoma*, and *epithelioid hemangioendothelioma* (this defined by the WHO as a malignant vascular tumor because of its metastatic risk) are discussed in the chapter on "rare tumors of the skin and subcutaneous tissue."

44.1.3.1 Treatment Strategy

The treatment management of adult-type NRSTS is complex and necessarily multidisciplinary (Table 44.3).

Table 44.3 A general view: practical diagnostic and therapeutic guidelines for pediatric soft tissue sarcomas

Physical examination	Soft tissue mass Signs of neurofibromatosis type 1, i.e., multiple café-au-lait spots, axillary or inguinal freckling, neurofibromas, Lisch nodules (iris hamartomas), plus learning disabilities
Laboratory assessment	No specific tumor markers available
Radiological assessment	
–First assessment	Ultrasonogram
–Local staging	Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the primary site is mandatory for local extension assessment before any treatment. MRI is usually considered superior in defining soft tissue extension
–Diagnostic work	Chest CT scan to identify lung metastases, in high-grade sarcomas Abdominal ultrasound, ultrasound of regional lymph nodes *Technetium bone scan and positron emission tomography* (*PET*) *are not considered a standard staging investigation* (*eventually in high-grade tumors*)
Pathological assessment	In the case of a large and deep soft tissue mass, biopsy should be always the initial surgical procedure, in order to avoid inadequate surgery. The initial biopsy (incisional biopsy or core needle biopsy) has the aim to define the diagnosis, but also should provide enough material for immunochemistry, cytogenetics, biological studies, and central pathology review for patients to be included in clinical trials Histological subtype Tumor grade
Staging systems for risk-adapted treatment strategy	*TNM classification* based on local invasiveness, *T1* and *T2*, and tumor size, *A* or *B*, i.e., less or more than 5 cm; *N0/N1* and *M0/M1*: absence or presence of nodal and distant involvement *Intergroup Rhabdomyosarcoma Study* (*IRS*) *postsurgical grouping systemgroup I* – completely excised tumors with negative microscopic margins; *group II* – grossly resected tumors with microscopic residual disease and/or regional lymph nodal spread; *group III* – gross residual disease after incomplete resection or biopsy; group IV – metastases at onset
General treatment guidelines	Need for multidisciplinary approach
–Surgery	Keystone of treatment Goal: complete and non-mutilating resection Importance of the referral to specialist centers
–Radiotherapy	Well-defined role in local control, after incomplete resection or after wide excision in case of high-grade and large tumor *Indication stricter in younger children due to the higher risk of severe late effects*
–Chemotherapy	Doxorubicin-/ifosfamide-based chemotherapy in unresected tumors Adjuvant chemotherapy in high-grade and large sized sarcomas (especially in synovial sarcomas)

These tumor types are usually considered scarcely sensitive to chemotherapy (tumor response in the range of 40% or less), and surgery thus remains the unquestionable keystone of treatment. Radiotherapy plays a well-defined role in local control, after incomplete resection and, according to adult experiences, also after wide excision, especially in case of large tumors. However, the indication for radiotherapy are usually stricter in children, given the higher risk of severe late effects (i.e., the risk of retardation or arrest of irradiated bone growth, the risk of functional impairment, and that of second post-irradiation tumor). Aggressiveness and intensity of surgery and radiotherapy should be discussed and customized for each patient (taking into account the anatomical site, tumor size, patient's age, response to initial chemotherapy), considering the need to maximize the chances of local control, but also containing the sequelae and preserve function (Ferrari and Casanova 2005).

The role of chemotherapy as part of the multidisciplinary approach in adult-type NRSTS remains uncertain. Chemotherapy is usually given in front-line treatment in patients with advanced unresectable disease (and also in all cases where the surgeon is unsure of being able to achieve a complete resection at the first attempt). Neo-adjuvant chemotherapy may have a role in converting these cases into conservative complete resections, but it may play an important role also in treating any micrometastases promptly (Ferrari et al. 2005b; Spunt et al. 2002; Pappo et al. 2005).

Recently, various international research groups pooled their series on unresected NRSTS in a joint

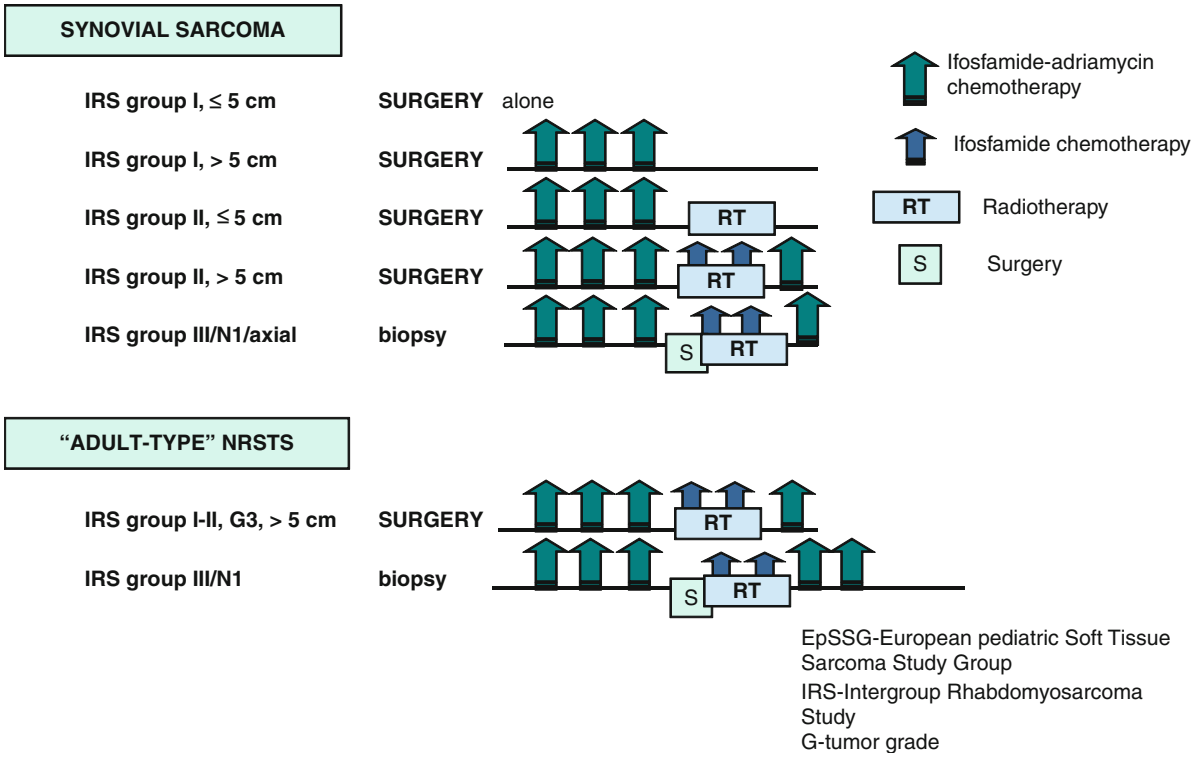

Fig. 44.4 Risk-adapted treatment strategy in the European pediatric Soft tissue sarcoma Study Group (EpSSG) NRSTS 2005 protocol for synovial sarcoma and adult-type NRSTS patients

study comprising 304 patients (Ferrari et al. 2011). Response rate to chemotherapy was 41% in terms of major responses, but also minor responses were seen (16%). Overall survival at 10 years was roughly 50%, and was associated with patient's age, histological subtype, and tumor site and size. MPNST was the tumor type with the worst rate of response to chemotherapy and the worst outcome. Patients who respond to chemotherapy have better chances of survival, as well as those who had a complete delayed surgical resection and those treated with radiotherapy, suggesting that intensive multimodal treatment should be recommended in these patients.

A major debate concern whether or not to provide adjuvant chemotherapy for adult-type soft tissue sarcomas, in order to prevent distant recurrences after initial surgery. Patients outcome after initial resection is good (survival rate up to 90%) in patients with small and low-grade tumor, but the prognosis for patients with high-grade and large invasive tumors is often unsatisfactory, when treated with local therapy alone, even after initial microscopically complete resection, because of a high risk of developing lung metastases (Ferrari et al. 2005a). Pediatric retrospective studies confirmed that in group I-II patients, the combination of two variables – high tumor grade plus large tumor size – gives rise to a very high risk of metastases (metastases-free survival around 30–40%), irrespective of the results of initial surgery, with better survival in those patients who received adjuvant chemotherapy, as compared to those who have not been given (Ferrari et al. 2005b).

This would suggest, in principle, the use of systemic chemotherapy to try to improve survival in those selected patients with high tumor grade and large tumor size (Ferrari 2008) (Fig. 44.4). The only randomized trial on adjuvant chemotherapy in pediatric age (conducted by the Pediatric Oncology Group POG between 1986 and 1992) failed to assess the benefits of adjuvant chemotherapy because the majority of patients refused randomization, showing how difficult it is to conduct prospective randomized studies in pediatric patients with such rare tumors, for which no standard therapy has been established (Pratt et al. 1999).

In adult oncology, the discussion on the role of adjuvant chemotherapy in soft tissue sarcomas has always been a point of controversy (Bramwell 2001): On the one hand, we know that most randomized trials performed by international collaborative groups showed no statistically significant benefit for patients given adjuvant chemotherapy (Santoro et al. 1995; Sarcoma Meta-analysis Collaboration 1997); on the other hand, it is emerging that some of these negative results need to be reconsidered since these trials did not use the combinations of drugs currently recognized as the most effective in soft tissue sarcomas (ifosfamide, in particular, was not included in most of these studies), nor had they selected patients most likely to respond to chemotherapy (tumors of diverse histology, grade, and size were grouped together). When these criteria were considered (targeting a selected group of high-risk patients and delivering a regimen of full-dose ifosfamide plus anthracyclines), a more significant beneficial impact emerged: The Italian Sarcoma Group (ISG) was closed in advance (after the enrollment of 104 patients) because an interim analysis showed a clear improvement in the survival of patients receiving adjuvant chemotherapy by comparison with those given local therapy alone (Frustaci et al. 2001).

44.1.3.2 The Fibrosarcoma Family

Until the 1960s, the diagnosis of fibrosarcoma was very common. The identification of specific sarcoma subtypes and the contribution of immunohistochemical and cytogenetic methods to define a more precise classification of spindle cell sarcomas determined a progressive disappearance of fibrosarcomas that became a rarity. In the last decade, the comprehension of the phenotypic plasticity of fibroblasts and the characterization of myofibroblasts have disclosed different subtypes of fibrosarcoma according to the predominance of fibroblasts or myofibroblasts, stromal patterns, recurrent chromosomal aberrations, and variable expression of immunohistochemical markers of myofibroblastic differentiation (fibronectin, desmin, a-SM actin).

Classic fibrosarcoma probably accounts for <1% of adult sarcomas and is most common between the second and sixth decade with equal sex distribution. It is extremely rare in children and may infrequently occur in adolescents, occasionally in association with a previous radiotherapy. The most common site is the distal parts of the extremities, but other uncommon localizations have been reported. Histologically, fibrosarcoma is characterized by spindle cells with tapered nuclei, small nucleoli, and scanty cytoplasm arranged in a typical herringbone pattern. Tumors with prominent myofibroblasts are classified as *myofibrosarcomas* (Fisher 2004; Montgomery et al. 2001).

Myofibrosarcomas are a controversial entity displaying a range of appearances from low-grade lesions, now recognized as an entity in the current WHO classification of soft tissue tumors, to high-grade forms resembling *storiform-pleomorphic malignant fibrous histiocytoma* included in the group of malignant high-grade pleomorphic sarcomas.

Less than 10% of *low-grade myofibrosarcomas* occur in children and privilege the deep soft tissues of head and neck (and rarely bone) (Smith et al. 1995; Keller et al. 2004). There is a slight male predominance with tumor size ranging from 1.5 to 17 cm. Tumors generally have an indolent clinical course, characterized by relapses in about 33% of cases and metastases, even after a long time, in 3–10% of cases, generally involving the lungs.

Low-grade fibromyxoid sarcoma (*LGFMS*) is a slow-growing mass, deeply located in soft tissues of lower extremities and trunk and occasionally head, neck, or spine (Evans 1987). In children, it is generally superficial and involves more frequently the head and neck (Billings et al. 2005). Histologically, the tumors display a typical biphasic pattern, with an abrupt or gradual transition from myxoid to fibrous, heavily collagenized areas. Spindle cells with bland nuclei, lacking pleomorphism are embedded in an abundant myxoid stroma, containing prominent vessels in an arcade-like configuration. Scattered giant rosettes, with a central zone of eosinophilic collagen surrounded by spindled and epithelioid cells, characterize the variant of LGFMS called hyalinizing spindle cell tumor with giant rosettes (Lane et al. 1997; Folpe et al. 2000a). LGFMS shows specific recurrent translocations involving the FUS gene: FUS-CREB3L2 transcript resulting from translocation t(7;16)(q32-34;p11), and the less frequent FUS-CREB3L1 from t(11;16)(p11;p11) (Mertens et al. 2005; Guillou et al. 2007). If completely excised, LGFMS has a relapse rate of 10%. Metastases may occur even many years after the initial diagnosis in 5–26% of cases. Superficial lesions have a more favorable prognosis (Folpe et al. 2000b).

Sclerosing epithelioid fibrosarcoma is probably a combination of different entities, some falling within

the spectrum of LGFMS and others not jet clearly defined (Meis-Kindblom et al. 1995). It is typical of adults and only 10% of patients are younger than 20 years. The tumors, often large in size, are deeply located in muscles in the lower limb, trunk, shoulder, and neck. Histologically, the tumors show epithelioid or fusiform cells with bland nuclei and clear cytoplasms arranged in carcinoma-like nests, sheets, or cords and embedded in a fibrous stroma or sclerotic matrix (Fig. 44.6d). Cytogenetic features of sclerosing epithelioid fibrosarcoma have been poorly investigated. Recently FUS-CREB3L2 transcripts typical of low-grade fibromyxoid sarcoma have been found in lesions with mixed features of sclerosing epithelioid fibrosarcomas and LGFMS (Guillou et al. 2007).

Due to the heterogeneity of tumors included in the category of sclerosing epithelioid fibrosarcoma, its prognosis remains controversial. An aggressive behavior with persistent disease or local recurrence has been reported in more than 50% of patients, with a metastatic rate between 43% and 86%, and a mortality rate between 25% and 57% (Antonescu et al. 2001).

Myxofibrosarcoma, previously considered a myxoid variant of malignant fibrous histiocytomas, has been included in the group of myofibroblastic lesions in the 2002 WHO classification. It is the commonest soft tissue sarcoma in limbs of older adults, whereas it is very rare under 20 years, with only few cases reported in children, mostly occurring in unusual sites (Denschlag et al. 2005). These tumors show a wide morphologic spectrum and include low- and high-grade forms, often coexisting. Scattered spindle or stellate tumor cells with atypical hyperchromatic nuclei embedded in an abundant myxoid matrix are found in low-grade tumors. Cellularity and atypias progressively increase in intermediate- and high-grade variants with evidence of sheets of pleomorphic cells and necrosis. The treatment is surgical resection, and myxofibrosarcoma can recur and metastasize.

Leiomyosarcoma

Smooth muscle tumors are rare in children and adolescents and include hamartomas, benign tumors (such as angioleiomyoma, leiomyoma, and leiomyomatosis), leiomyosarcoma, and smooth muscle tumors of uncertain malignant potential in immunocompromised individuals.

Leiomyosarcomas account for <4% of childhood soft tissue sarcomas; are more frequent in males; and involve skin, superficial and deep soft tissue, bone, and viscera, such as the lung and GI tract. The mean age at diagnosis is 8–11 years and may arise as a second malignancy in patients treated with radiotherapy. Their prognosis is better than that in adults with a survival rate bigger than 70%. Late metastases in unusual sites may be seen (De Saint Aubain Somerhausen and Fletcher 1999; Ferrari et al. 2001). Macroscopically, leiomyosarcomas are large, not encapsulated nodular masses ranging from 1 to 13 cm, with frequent foci of hemorrhage and necrosis. Histologically they are characterized by spindle cells with elongated, blunt-ended nuclei arranged in interlacing bundles. Morphologic variants include: *inflammatory leiomyosarcoma*, showing a prominent mixed inflammatory infiltrate, and *myxoid leiomyosarcoma*, a low-grade variant only rarely metastasizing, with more than 50% of tumor composed of myxoid stroma. *Pleomorphic* and *epithelioid leiomyosarcoma* are very rare in children. Immunohistochemistry shows reactivity for smooth muscle actin, muscle-specific actin, desmin, and h-caldesmon.

Smooth muscle tumors with uncertain malignant potential are less aggressive tumors, mostly occurring in immunocompromised patients. They are generally visceral, often multifocal. Epstein–Barr virus infection is involved in their pathogenesis. Compared to sporadic leiomyosarcoma, the tumors are well-differentiated, with minor cytologic atypia and mitotic activity ranging from 0 to 18 mitoses per 10 high power field (Mueller et al. 1992; Belarezo and Joshi 2002; Deyrup et al. 2006).

Liposarcoma

Liposarcoma is the most common malignant soft tissue tumor in adults. In children, the neoplasms of adipose tissue are relatively infrequent, and liposarcomas account for <3% of all pediatric sarcomas (Shmookler and Enzinger 1983; La Quaglia et al. 1993). While the anatomic distribution is similar in children and adults, the lower extremities, especially the thigh, being the most frequent site of involvement, the histotypes differ substantially. In adults, the *atypical lipomatous neoplasms* (*well-differentiated liposarcomas*) and their high-grade counterpart (*dedifferentiated liposarcoma*) account for approximately 60% of cases, the myxoid and round cell liposarcomas comprise about 35% of cases, and the *pleomorphic liposarcoma* the remaining 5%. In children, the conventional myxoid liposarcoma

is the most frequent histotype, including around 90% of cases (Ferrari et al. 1999; Alaggio et al. 2009). Atypical lipomatous tumors and pleomorphic liposarcoma are very rare, representing <5% and <2% of cases respectively.

Myxoid liposarcomas are characterized by a plexiform vascular pattern; abundant myxoid matrix; and uniform, bland, round cells with lipoblastic differentiation. Some tumors may display round cell areas, even if histologic progression to conventional round cell liposarcomas is very rare in this age group. As in older patients, the great majority of conventional myxoid liposarcomas show evidence of FUS-CHOP gene fusions, reflecting the presence of the t(12;16)(q13;p11). EWSR1-CHOP gene fusions is very rare, and its exact incidence in pediatric myxoid liposarcomas is unknown. Myxoid liposarcomas have a generally indolent clinical course. Round cell component does not necessarily appear to connote a worse prognosis in children; however, myxoid liposarcomas showing a round cell component bigger than 5% should be regarded as high-grade sarcomas in any age group, based on historical data.

Aggressive local growth and death have been reported in children affected by peculiar morphologic variant of myxoid liposarcoma displaying mixed features of conventional myxoid liposarcoma and pleomorphic liposarcoma. Whether it represents a different subtype of liposarcoma, typical of young patients, is still unknown. Spindle cell myxoid liposarcoma is another subtype of myxoid liposarcoma found in children. It behaves as a low-grade tumor, roughly similar to conventional myxoid liposarcoma (Alaggio et al. 2009).

So-called fibrohistiocytic tumors: *pleomorphic malignant fibrous histiocytoma/undifferentiated high-grade pleomorphic sarcoma*

Undifferentiated high-grade pleomorphic sarcoma (UHGPS), in the past called malignant fibrous histiocytoma (MFH), is a controversial entity characterized by pleomorphic spindle cells with fibroblastic and histiocytic differentiation. Its existence has been challenged, the morphologic features being common to a variety of poorly differentiated sarcomas (Fletcher 1992).

According to the 2002 WHO classification, MFH/UHGPS is a diagnosis of exclusion and should be reserved for those sarcomas without evidence of a specific lineage differentiation detected by available techniques. The diagnosis of MFH in childhood has always been rare, even in the pre-immunohistochemistry era; it comprised about 2–6% of all pediatric sarcomas, including angiomatoid fibrous histiocytoma (now classified separately as an intermediate soft tissue neoplasm of uncertain histogenesis) (Cole et al. 1993; Corpron et al. 1996). Like their adult counterpart, pediatric MFH can arise in sites previously irradiated or as second malignancies (especially after retinoblastoma) and may be associated with a family history of cancer. Histologically, pleomorphic lesions are composed of spindle cells arranged in fascicles or sheets, displaying a focal storiform pattern and scattered pleomorphic cells with hyperchromatic nuclei and atypical mitoses or multinucleated cells. Large aggregates of polygonal/epithelioid cells may be found in more aggressive tumors. Immunostains are helpful to exclude other diagnoses, the tumors being negative for lineage specific markers.

UHGPS are highly aggressive tumors with a high metastatic rate and an overall 5-year survival around 60–70%. Survival and metastases are related to tumor depth and size (Alaggio et al. 2010b).

44.1.3.3 Malignant Peripheral Nerve Sheath Tumors

Malignant peripheral nerve sheath tumors (MPNST) occur mainly in adults, and only 10–20% are diagnosed in the first two decades. Nevertheless, they represent one of the most frequent subtypes among pediatric NRSTS. In general MPNST are high-grade tumors, often arising in axial sites, characterized by uncertain prognosis. In about 21–67% of cases, MPNST arise in patients affected by neurofibromatosis type 1 (NF1), by malignant transformation of preexisting neurofibromas. The life-time risk of developing MPNST in NF1 patients has been estimated at 8–13%, as compared to 0.001% in the general population (Evans et al. 2002). The molecular mechanisms responsible for malignant transformation of neurofibromas and those involved in tumor progression in both sporadic and NF1-associated MPNST are largely unknown. NF1 is caused by mutation in the NF1 suppressor gene, located in chromosome band 17q11. It encodes the neurofibromin, a protein inhibiting p21-RAS. NF1 inactivation is not sufficient for malignant transformation and further genetic alterations are needed, most of them probably involving genes regulating cell cycle. In fact, several alterations in tumor suppressor genes playing a pivotal role in cell cycle, such as mutations

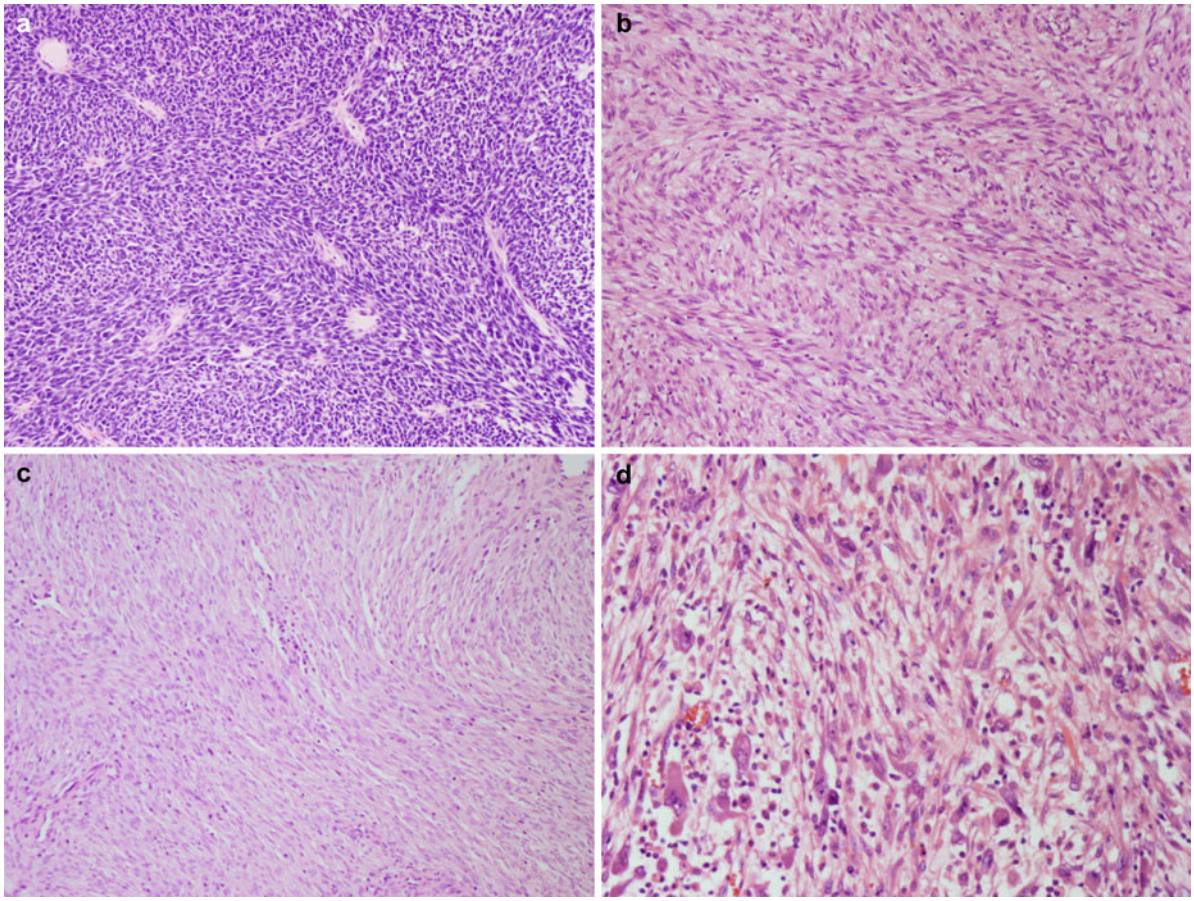

Fig. 44.5 Spindle cell sarcomas: (**a**) (HE staining, 100×) synovial sarcoma with the typical hemangiopericytomatous pattern; (**b**) (HE staining, 100×) malignant peripheral nerve sheath tumor (MPNST) showing fascicles of elongated cells with weavy nuclei; (**c**) (HE staining, 100×) congenital infantile fibrosarcoma with primitive elongated spindle cells; (**d**) (HE staining, 100×) inflammatory myofibroblastic tumor with elongated cells and scattered ganglion-like cells intermingled with lymphocytes and plasma cells

of TP53 and CDKN2A (p16INK4), have been reported in neurofibromas as they transform into MPNST (Ferrari et al. 2007a).

Histological diagnosis may be challenging, with the majority of MPNST highly cellular neoplasms mimicking other spindle cell sarcomas. At least focally the cells are arranged in sweeping fascicles, exhibit weavy nuclei typical of Schwann cells, and form palisades in about 10% of cases; other areas may be hypocellular with a myxoid stroma. Blood vessel shows a hyalinized wall, which is an important diagnostic tool. Criteria of malignancy are necrosis and mitotic activity. Immunostains show only rare S-100-positive cells (Fig. 44.5b). Morphologic variants of MPNST include epithelioid or glandular MPNST, respectively characterized by aggregates of epithelioid cells in solid nests or foci of glandular differentiation with mucin-secreting cells, rhabdoid MPNST, *triton tumor* (a MPNST with a rhabdomyosarcomatous component), and MPNST with a perineurioma-like component, showing a prominent perineurial differentiation. Unfortunately, in sporadic MPNST, there are no histologic markers predictive of clinical behavior and tumor grade does not appear to have a prognostic significance.

The Italian and German cooperative groups reported on a series of 167 pediatric MPNST cases (17% having NF1), with a 5-year overall survival and progression-free survival of 51% and 37%, respectively. Outcome was satisfactory only for the small group of resected and small tumors. NF1 patients have a peculiar poor outcome. That series confirmed the aggressiveness of MPNST, for which complete surgical resection is the mainstay of successful treatment. MPNST is generally regarded as a tumor with poor chemoresponsiveness, but in that series, an overall response rate to primary chemotherapy of 45% was recorded (Carli et al. 2005).

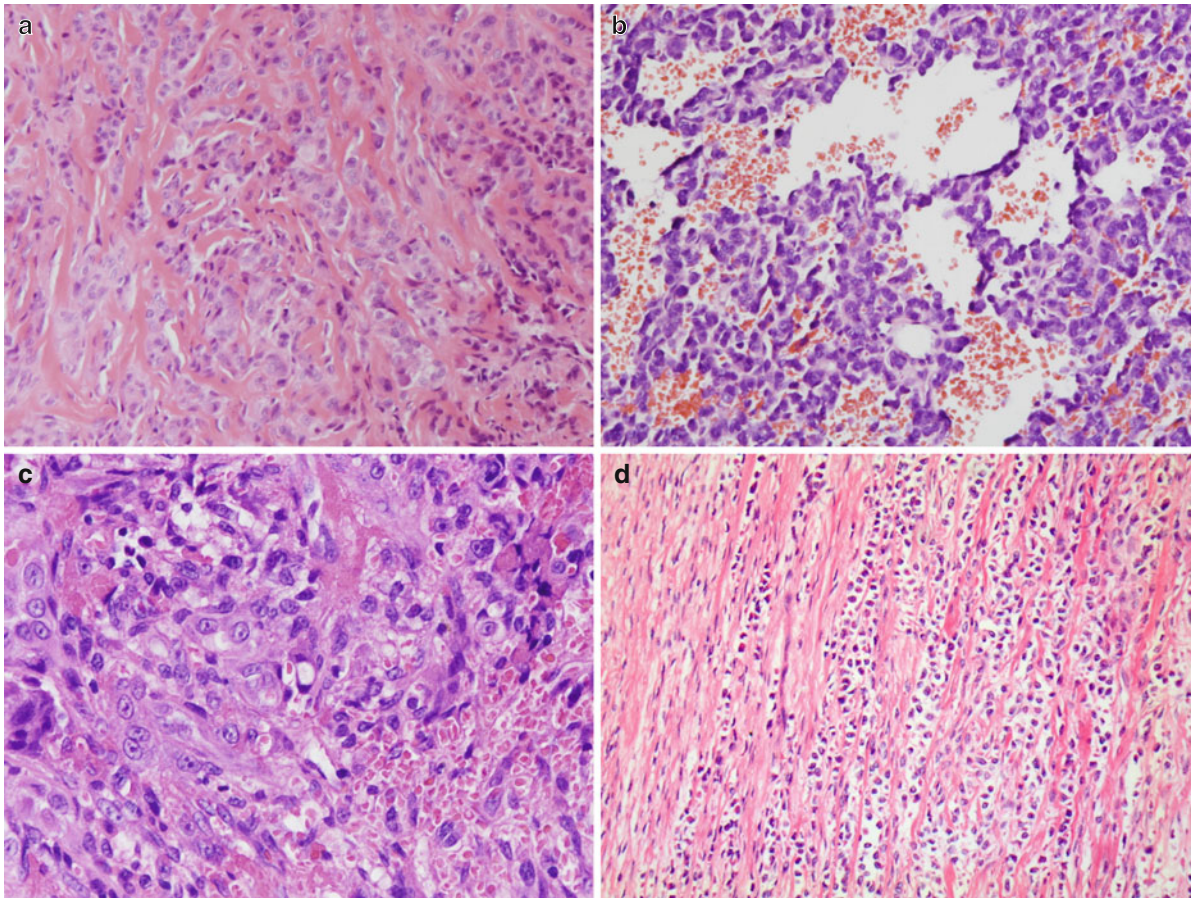

Fig. 44.6 Sarcomas with "epithelioid" cells: (**a**) (HE staining, 160×) epithelioid sarcoma showing large cells arranged in nests and cords embedded in a collagen stroma. (**b**) (HE staining, 100×) epithelioid sarcoma with vascular pattern mimicking epithelioid hemangioendothelioma. (**c**) (HE staining, 160×) epithelioid hemangioendothelioma with typical intracytoplasmic vacuoles, occasionally containing red cells. (**d**) (HE staining, 100×) Sclerosing epithelioid fibrosarcoma: cords of epithelioid in a collagen stroma. Fascicles of spindle cells with typical features of fibrosarcoma on the left

44.1.3.4 Malignant Tumors of Uncertain Differentiation

Epithelioid Sarcoma

Epithelioid sarcoma is a distinctive lesion, generally involving dermis or subcutaneous tissue, that may mimic clinically and morphologically a benign granulomatous process (Enzinger 1970). Peculiarly, it involves finger, hand, wrist, and forearm of adolescents and young adults. Lower extremities, shoulder, and less frequently trunk, head, and neck can be also involved. Epithelioid sarcoma may also occur in mucosal sites including the tongue and in genital areas (Casanova et al. 2006; Gross et al. 1996; Kodet et al. 1994). The tumors are slow-growing single or multiple ulcerating nodules of variable size. A particular tendency for lymph node involvement has been observed. The so-called proximal-type epithelioid sarcoma occurs in axial locations. It shares some morphological features with rhabdoid tumor and behaves more aggressively than conventional epithelioid sarcoma (Guillou et al. 1997b). Histologically, epithelioid sarcoma consists of nodular masses or large, eosinophilic polygonal cells imperceptibly merging with spindle cells. Cytologic atypia is minimal. Areas of central necrosis are frequent. Tumors may also show predominant spindle cells in a fibroma-like or dermatofibroma-like pattern or an angiomatoid angiosarcoma-like appearance with large epithelioid cells surrounding hemorrhagic spaces (Mirra et al. 1992; von Hochstetter et al. 1991) (Fig. 44.6a, b). Proximal-type epithelioid sarcoma shows prominent epithelioid cells with vesicular nuclei, prominent nucleoli, and eosinophilic cytoplasm.

Immunostains for low- and high-molecular-weight keratin, epithelial membrane antigen, and vimentin are generally positive. The majority of tumors express CD34 and CA 125. INI-1 negative staining in more than 50% of epithelioid sarcoma proximal-type supports a pathogenetic relationship with rhabdoid tumor (Chbani et al. 2009; Hornick et al. 2009).

Little information is available on clinical management in children. An Italian study reported on 30 patients <18 years old (19 classic-type and 11 proximal-type), suggesting a clinical course less aggressive than that generally observed in adults. In that series, 5-year event-free survival and overall survival rates were 62% and 92%, but overall survival dropped to 87% and 72% at 10 and 15 years, respectively. Local relapse was the major cause of treatment failure. The most significant finding influencing survival was tumor site (extremity location predicting a favorable outcome). A worse outcome was associated with the proximal-type variant. A response to chemotherapy was seen in 3/7 patients with measurable disease. The tendency for lymph nodal spread described in adults would be not clearly confirmed in pediatric cases (Casanova et al. 2006).

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) represents <1% of soft tissue sarcomas and occurs more frequently in patients younger than 40 years, often in the extremities and trunk (Folpe and Deyrup 2006). In children, it may arise in the head and neck (Casanova et al. 2000).

ASPS is characterized by a peculiar organoid pattern showing nests of epithelioid polygonal cells with eosinophilic cytoplasms, vesicular nuclei, and prominent nucleoli. PAS-positive intracytoplasmic rhomboid crystals are virtually diagnostic of ASPS. Immunostains are not helpful for diagnosis. The ASPSCR1–TFE3 fusion gene, deriving from chromosomal rearrangement at17q25 and Xp11.2, is typical of ASPS and is associated with a positive nuclear immunostaining for TFE3 (van Echten et al. 1995; Ladanyi et al. 2001; Argani et al. 2003).

Although tumor growth is slow and asymptomatic, ASPS is highly malignant with early vascular invasion and metastatic dissemination, more frequently to brain and lung. The elective treatment is a radical surgery, that generally allows a prolonged survival, but most of patients will ultimately succumb to disease. The role of chemotherapy is unclear; this entity is generally considered scarcely chemosensitive.

The ASPSCR1–TFE3 chimeric transcription factor induces the expression of numerous proteins that might represent therapeutic targets, including, among others, the Met, which is an angiogenetic factor, activating the downstream effectors AKT and MEK. A phase II clinical trial is currently accruing ASPS patients to evaluate the effect of a novel c-Met inhibitor, ARQ 197. Furthermore, several AKT and MEK inhibitors are also available, and using a multi-target therapeutic strategy might result in an improvement of prognosis. Overexpression of VEGF mRNA has also been identified in gene expression profiling of ASPS samples and may be a promising therapeutic target (Lazar et al. 2009; Tsuda et al. 2007).

Clear Cell Sarcoma of Tendons and Aponeuroses

Clear cell sarcoma (CCS), also called melanoma of soft parts, has a proclivity to involve tendons and aponeuroses of distal extremities of young individuals (Enzinger 1965). It has a close resemblance to melanoma and is characterized by fascicles and nests of pale, elongated, or epithelioid cells encased by delicate fibrous septa. The cells show clear cytoplasm frequently containing melanin, nuclei with prominent nucleoli. S-100 is generally positive. The cytogenetic hallmark is t(12;22)(q13;q12), resulting in a chimeric EWS/ATF1 gene, detected in about 75% of cases. The tumor has a prolonged clinical course with multiple local recurrences, late metastases, and a high rate of tumor deaths. Radical surgery is the elective treatment. Chemotherapy is generally considered ineffective. A series of 28 pediatric patients have been reported by the Italian and German Soft Tissue Sarcoma Cooperative Group, with survival rates around 60% (Ferrari et al. 2002). Gastrointestinal CCS-like tumor is a distinctive lesion morphologically resembling CCS, characterized by identical cytogenetic alterations, but lacking intracellular melanin and showing scattered osteoclast-like giant cells. The tumor is accompanied by prominent weight loss, anorexia, abdominal pain, bloody stools, and anemia. Although very few, pediatric gastrointestinal CCS behaves more aggressively. A prior history of acute lymphoblastic leukemia has been reported.

44.1.3.5 The PEComa Family Tumors

Perivascular-epithelioid cell tumors (PEComa) are a family of tumors sharing a common origin from a cell with an hybrid melanocytic and muscular phenotype,

lacking a normal counterpart. The different morphologic entities represented by angiomyolipomas, lymphangioleiomyomatosis, clear cell "sugar" tumor of the lung, clear cell myomelanocytic tumor of the falciform ligament/legamentum teres and abdomino-pelvic sarcoma of perivascular-epithelioid cells (PEC) show variation in their clinicopathologic features (Bonetti et al. 1992; Zamboni et al. 1996; Folpe et al. 2000b; Hornick and Fletcher 2006; Martignoni et al. 2007, 2008).

Angiomyolipomas may occur in the context of tuberous sclerosis complex (TSC) and arise in kidney, less frequently in liver (Goodman and Ishak 1984) or other sites (Hulbert and Graf 1983; Peh and Sivanesaratnam 1988; Castillenti and Bertin 1989; Watanabe and Suzuki 1999).

Classic angiomyolipomas are characterized by a variable combination of blood vessels with a hyalinized wall, smooth muscle and mature adipose tissue, whereas epithelioid AML display nests and sheets of large epithelioid cells (Eble et al. 1997; Mai et al. 1996; Martignoni et al. 1998). Lymphangioleiomyomatosis in children is exceptional (Nagy Nagy et al. 1998) and may occur in the context of TSC. It is characterized by multiple pulmonary nodules, composed of elongated cells surrounding small blood vessel, interstitial myoid cells, and ectatic lymphatics. Lymph nodes, retroperitoneum, and mediastinum may be also involved (Matsui et al. 2000; Torres et al. 1995). The nodules evolve into cystic lesions with destruction of the lung, pneumothorax, and pulmonary failure requiring lung transplant.

Only few "Sugar" tumors or clear cell tumors of the lung have been reported in children with identical clinical features as in adults. They generally occur as single benign nodules (Vijayabhaskar et al. 2010; Nehra et al. 2010; Kavunkal et al. 2007; Gora-Gebka et al. 2006), histologically composed of sheets or nests of large epithelioid cells with clear cytoplasm, and a prominent vascular network. Extrapulmonary sugar tumors have been also reported in children in breast, bone, and urethra. They differ from their pulmonary counterpart for the more frequent nuclear atypia, mitoses and necrosis.

Clear cell myomelanocytic tumor (CCMMT) is a variant of PEComa with a predilection for ligaments (ligamentum teres and falciform ligament) and extremities, characterized by fascicles of spindle cells with clear to eosinophilic cytoplasms (Folpe et al. 2000b). Abdominopelvic sarcoma is a malignant variant of PEComa, composed of sheets of epithelioid cells, with pleomorphism, necrosis, and vascular invasion (Bonetti et al. 2001). Immunohistochemistry plays a key role in the diagnostic work-up, disclosing the typical hybrid melanocytic (HMB45, Melan-A, tyrosinase, MiT family of transcription factors members, microphthalmia transcription factor-MiTF and TFE3), and muscular (smooth muscle actin, muscle-specific actin, sometimes calponin or h-caldesmon and less frequently Desmin) phenotype of cells (Pea et al. 1991).

Sporadic or TSC associated angiomyolipomas and other PEComas share common cytogenetic alterations. TSC is caused by malfunction of the TSC1/TSC2 complex, related to a somatic deletion in *TSC1 gene* (*on chromosome* 9q34) or inactivating mutations in *TSC1* or *TSC2* (on 16p13). In sporadic AML and PEComas, loss of heterozygosity of TSC2 gene is common (Pan et al. 2006, 2008). These genetic alterations activate the mTOR pathway promoting cell growth (Kenerson 2007; Wagner et al. 2010; Weinreb et al. 2007). Other genetic alterations include deletion of 1p, deletions on cr 19, chromosomal gain on 12q, 2q, 3q, 5 (Pan et al. 2006). Only a minority of PEComas carry a TFE3 gene fusion (Argani et al. 2010; Cho et al. 2008; Tanaka et al. 2009) and some of them have been reported in association with neuroblastoma.

The prognosis of PEComa is influenced by the histotypes. Classic angiomyolipomas are generally benign. Epithelioid angiomyolipomas of kidney metastasize in one-third of cases. The presence of at least three unfavorable prognostic features (atypical epithelioid cells representing at least 70% of the population, two or more mitotic figures/10 HPF, atypical mitoses or necrosis) appears to be predictive of a malignant behavior. Hepatic Epithelioid angiomyolipomas are generally benign. CCMMT showing a main diameter larger than 5 cm, infiltrative growth, hypercellularity, nuclear enlargement and hyperchromasia, high mitotic rate, atypical mitoses, and coagulative necrosis may have a more aggressive clinical behavior. PEComas are treated by complete surgical excision. Radiotherapy and chemotherapy are not effective. The use of the mTOR inhibitors, such as Sirolimus, may be an option in unresectable tumors (Subbiah et al. 2010).

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a rare neoplasm mainly affecting children and young adults with a male preponderance. Its classical histological

appearance, represented by solid sheets, nests, or cords of small cells in a desmoplastic stroma, can show many different morphological variations. Its specific immunohistochemical profile with divergent epithelial, muscular, and neural differentiation and the recurrent translocation t (11;22)(p13;q12), that gives rise to the fusion gene EWS-WT1, represent important diagnostic tools, especially when the typical clinicopathological features are lacking.

DSRCT occurs in the abdominal and pelvic cavity or in other sites in association with serosal surfaces such as paratesticular region and pleura. Rare examples of extra-serosal DSRCT involving parotid gland, posterior cranial fossa, bone and soft tissue, pancreas, and kidney have been also reported. In particular when arising in abdominal cavity, the tumor is often disseminated at onset, and is characterized by a dismal outcome, despite the various intensive multimodality treatment approaches (including aggressive surgery, intensive chemotherapy, and radiotherapy) attempted over the years (Kushner et al. 1996; Bisogno et al. 2010).

Extrarenal Rhabdoid Tumor

Malignant rhabdoid tumor is a highly aggressive neoplasm, mostly occurring in the central nervous system and kidney of infants and children. Less frequently, it may arise in somatic soft tissues, abdomen, pelvis, retroperitoneum, liver, heart, and gastrointestinal tract. The histologic diagnosis is generally straightforward when the tumor shows the typical morphology characterized by large epithelioid cells, with abundant eosinophilic or amphophilic cytoplasm containing juxtanuclear hyaline-like globules, large nuclei with prominent nucleoli and a polyphenotypic immunophenotype, with variable expression of Vimentin, EMA, cytokeratins, CD99, S-100, SMA. The identification of a recurrent genetic alteration in RT, in the region 11.2 of the long arm of chromosome 22 (22q11.2), characterized by the deletion or mutation of hSNF5/SMARCB1/INI1 gene resulting in the loss or reduced expression of INI protein, has contributed to enlarge the morphologic spectrum of rhabdoid tumor (Versteege et al. 1998; Weeks et al. 1989; Wick et al. 1995; Parham et al. 1994; Schofield et al. 1996). Rhabdoid tumors are very rare and very aggressive disease. These tumors are currently treated with intensive chemotherapeutic strategy (multidrug therapy with vincristine, ifosfamide, carboplatin, etoposide, doxorubicin, and cyclophosphamide), but improvements in genetic studies are strongly needed to cast light on their biology in order to think about new treatment approaches (Kodet et al. 1991).

Synovial Sarcoma

Synovial sarcoma is a tumor of uncertain histogenesis, accounting for 6–10% of adult soft tissue sarcomas and predominantly affecting children older than 10 years, adolescents, and young adults. It is the most frequent pediatric NRSTS (Sultan et al. 2009).

Histologically, this tumor is variously composed of spindle and epithelioid cells. Spindle cells are small, uniform, ovoid with pale nuclei, sparse cytoplasm, and inconspicuous cell borders. Epithelioid cells exhibit same nuclei and a more abundant cytoplasm (Fig. 44.5a). According to the different components, three major subtypes are recognized: the monophasic fibrous synovial sarcoma, composed of spindle cells with no evidence of epithelial component (the epithelial monophasic type is very rare and mimics an adenocarcinoma); the biphasic synovial sarcoma, containing spindle and epithelioid cells in variable proportions; the poorly differentiated synovial sarcoma, a highly cellular sarcoma resembling a small round cell tumor, whose diagnosis may be challenging. Synovial sarcoma express cytokeratins, in particular cytokeratins 7 and 19, which are not expressed in other sarcomas, epithelial membrane antigen, vimentin, CD99, and bcl2. Cytogenetic studies show chromosomal translocation t(X;18)(p11.2;q11.2). The SS18 (or SYT) gene from chromosome 18 is disrupted and juxtaposed to either SSX1, SSX2, or SSX4 on chromosome X, in a mutually exclusive manner. SYT-SSX1 may be associated with a biphasic histology and higher ki67 index. SYT-SSX2 is more frequently found in monophasic fibrous type (Mancuso et al. 2000; Mezzelani et al. 2001). Some studies suggest a better prognosis for tumors bearing the SYT-SSX1 transcript, but the prognostic significance of molecular findings is controversial (Guillou et al. 2004). The protein product of SMRRCB1/INI1 (INI1) gene, a tumor suppressor gene lost in malignant rhabdoid tumor, is reduced in the majority of synovial sarcoma. The specific molecular mechanism is not known and a post-transcriptional interaction of SS18-SSX transcript with the chromatin-remodeling pathway has been suggested. Moreover, gene expression studies are providing new insights into the molecular pathways involved in tumor progression in synovial sarcoma, including Wnt, IGF, ERBB2, HGF/MET, and beta-catenin pathways, disclosing new therapeutic

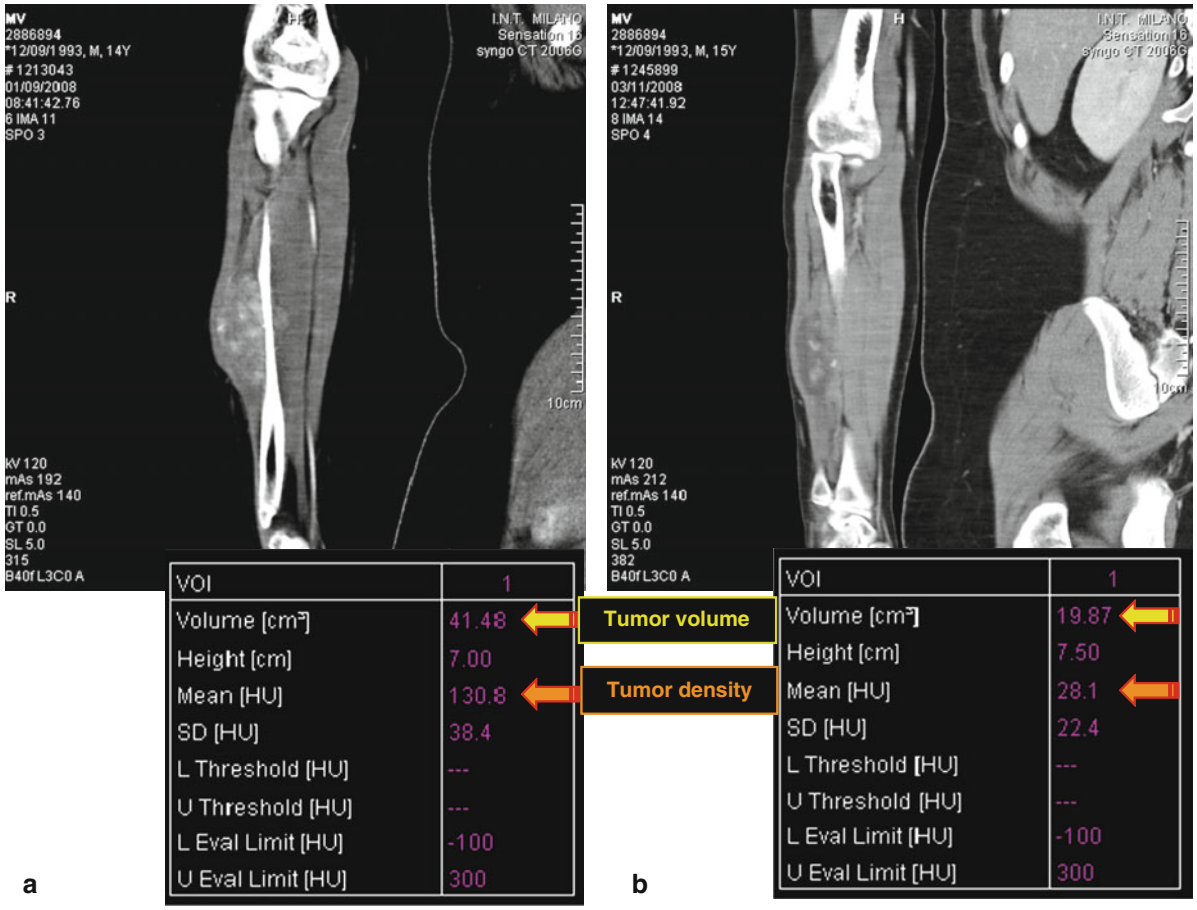

Fig. 44.7 Computed tomography scan of synovial sarcoma of the right forearm: (**a**) at onset, before chemotherapy; (**b**) after three courses of chemotherapy with ifosfamide and doxorubicin. Response to chemotherapy is shown by volume reduction as well as changes in tumor tissue characteristics (reduction of tumor density) (Courtesy Dr. Carlo Morosi, Radiology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy)

perspectives (Tamborini et al. 2004; Kawaguchi et al. 2005; Thomas et al. 2005).

Synovial sarcoma is the typical sarcoma subtype crosswise between the pediatric and adult age groups (Sultan et al. 2009). However, since up to recent times, different therapeutic strategies have been developed for pediatric and adult oncology protocols dealing with this tumor, in particular concerning the use of systemic therapy, though no published data describes a different biology of synovial sarcoma when arising in adults as opposed to children. Historically, relatively high rates of response to chemotherapy were recorded in pediatric series (i.e., an approximately 60% rate, that is higher than the response rate usually reported for other adult soft tissue sarcomas, but lower than that observed in rhabdomyosarcoma) (Fig. 44.7), and therefore, synovial sarcoma was traditionally considered as a "rhabdomyosarcoma-like" tumor by pediatric oncologists, particularly in Europe: Children were enrolled over the years in rhabdomyosarcoma protocols, thus receiving the same chemotherapy as for rhabdomyosarcoma patients, even in case of completely resected small tumors (Ferrari et al. 2008; Okcu et al. 2003; Brennan et al. 2010).

Differently, adult patients with synovial sarcoma were treated according to the same guidelines adopted for other soft tissue sarcomas; for instance, adjuvant chemotherapy was generally only used for those patients enrolled in randomized trials with a no-therapy control arm. Whether these different strategies produced differences in patient survival remains to be demonstrated; however, pediatric reported series showed 5-year survival rates of around 80%, which is higher than usually reported in

Table 44.4 Recent studies on pediatric synovial sarcoma

Pediatric synovial sarcoma series	
Okcu F, 2003 Multicenter study MDACC, SJCRH, INT Milan, CWS	219 pts <20 years 5-year OS 80% Rate of response to chemotherapy – 60%
Brecht IB, 2005 CWS, AIEOP-STSC	150 pts <18 years, IRS groups I-II (initial gross resection) Nearly all patients received chemotherapy 5-year OS 89% Identification of low-risk patients (group I, ≤5 cm) for which chemotherapy might be omitted
Ferrari A, 2009 AIEOP-STSC	115 patients <20 years 5-year OS 76.9%, worse outcome for non-extremity sites vs limbs (OS 55.1% vs 84.0%)
Brennan B, 2010 UK CCLG	77 patients <18 years 5-year EFS and OS 72% and 76% Prognostic factors: T stage and IRS group
Comparison pediatric vs adult series	
Ferrari A, 2004 INT Milan	271 patients of all ages (46 <17 years) 5-year OS 64% Role of adjuvant chemotherapy Age < 17 years: 78% received chemotherapy – 5-year EFS 66% Age ≥ 17 years: <20% received adjuvant CT – 5-year EFS ~ 35%
Sultan I, 2009 SEER (1983–2005)	1268 cases (213 ≤18 years) No major differences in stage distribution 5-year cancer-specific survival: 83% vs 62% (p<0.001) Multivariate analysis: significantly higher mortality for adults after adjusting for other variables

OS overall survival, *EFS* event-free survival, *IRS* Intergroup Rhabdomyosarcoma Study, *MDACC* M.D. Anderson Cancer Center, *SJCRH* St. Jude Children Research Hospital, *INT* Istituto Nazionale Tumori Milan, *CWS* Cooperative Weichteilsarkomen Studie (German Soft Tissue Sarcoma Cooperative Group), *AIEOP-STSC* Associazione Italiana Ematologia Oncologia Pediatrica – Soft Tissue Sarcoma Committee (Italian Cooperative Group), *UK CCLG* United Kingdom Children's Cancer and Leukaemia Group, *SEER* Surveillance, Epidemiology, and End Results

adult series (Lewis et al. 2000; Trassard et al. 2001). A recent study on the large cohort of synovial sarcoma cases registered in the SEER database (1983–2005) highlighted that the cancer-specific mortality was higher in adults than in children (34% vs 16%, respectively), and the outcome remained consistently worse for adults when the analysis was adjusted for the different prognostic variables (i.e., tumor size, site, and stage), suggesting that factors other than the possible difference in the incidence of unfavorable clinical variables might be involved in the unsatisfactory outcome for adult cases (Sultan et al. 2009). The hypothesis that the different treatment results might be related, at least in part, to the different treatment strategies adopted (i.e., the different use of chemotherapy) would be supported by the retrospective study of the Istituto Nazionale Tumori in Milan (on patients of all ages), in which adjuvant chemotherapy (administered to most of the children and to a minority of the older patients) seemed to improve patient outcome (Ferrari et al. 2004) (Table 44.4).

In recent years, the management of synovial sarcoma patients seems to be changing to some degree in both pediatric and adult cases, tending to converge toward a common strategy (Ferrari 2009). Pediatric oncologists have taken suggestions from adult experiences and moved toward a treatment concept partially similar to that adopted in the adult setting: The ifosfamide-doxorubicin chemotherapy is currently adopted as standard regimen, and its indication is given according to the patient's risk stratification, based on tumor size and site and surgical stage; in low-risk patients (completely resected tumors under 5 cm in size), chemotherapy is omitted (Brecht et al. 2006) (Fig. 44.2). On the other hand, adult oncologists seem to be recognizing that synovial sarcoma may be quite different from other adult

soft tissue sarcomas, particularly in the light of its higher chemosensitivity, probably standing midway between that of the most typical adult histotypes and that of pediatric small round cell tumors, such as rhabdomyosarcoma. Despite the absence of a published proof of its efficacy, in day-to-day clinical practice, many adult oncologists generally recommend chemotherapy for synovial sarcoma patients, not only in cases of advance disease, but also as an adjuvant treatment after surgery (Canter et al. 2008; Eilber et al. 2007).

44.1.3.6 Future Perspectives: Targeted Therapies

The management of adult soft tissue sarcomas (and therefore also of NRSTS) is currently entering the "histology-driven therapy era" (Ferrari 2008). Various drugs other than the classic ifosfamide-doxorubicin regimen have proved effective in particular histotypes, e.g., taxanes in angiosarcoma (Penel et al. 2008), gemcitabine and gemcitabine ± docetaxel in leiomyosarcoma (Hensley et al. 2002; Maki et al. 2007), and trabectidine in liposarcoma (Grosso et al. 2007). In particular, trabectidine has recently shown important activity in myxoid/round cell liposarcoma, possibly with a direct effect on the products of the histotype-specific FUS-CHOP translocation: After many years without any effective new drugs being registered, trabectidine has been officially approved by the European Agency for the Evaluation of Medicinal Products (EMEA) for the second-line treatment of adult soft tissue sarcomas.

The better understanding of the molecular pathways involved in tumor growth and progression is currently leading to the identification of new potential therapeutic targets: The product of the specific chromosomal translocations occurring in NRSTS may be perfect targets for new molecular agents specifically designed to influence the tumor's biology. New targets can be subdivided into signaling elements involved in cell cycle regulation and apoptosis, molecules responsible for tumor neoangiogenesis, and factors providing connective tissues disruption and tumor spread.

Several targeted therapies are currently under evaluation. Apart of GIST, imatinib has proven effective against dermatofibrosarcoma protuberans (possibly by deregulating the platelet-derived growth factor-B (PDGF-B) resulting from the specific t(17,22) translocation) (McArthur et al. 2003), chordoma (Casali et al. 2004), and desmoid-type fibromatosis (Heinrich et al. 2006).

Preliminary interesting data are available on the effects of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) inhibitors as pazopanib (an oral angiogenesis inhibitor), in particular, in vascular sarcomas, leiomyosarcoma, and synovial sarcoma (Sleijfer et al. 2009).

The activities of the mTOR inhibitor rapamycin (a macrolide antibiotic) and its synthetic derivatives sirolimus, temsirolimus, everolimus, and ridaforolimus have been variously explored, since the phosphatidylinositol-3 kinase (PI3K)-Akt-mTOR pathway has a central role in cell growth and has been shown to be activated at various levels in many sarcomas (Chawla et al. 2007; Mita et al. 2008; Blay 2011). Eribulin mesylate (a tubulin-targeting synthetic analogue of halichondrin B) showed promising activity in leiomyosarcoma and adipocytic sarcomas (Schoffski et al. 2010). Other promising agents are the recombinant human monoclonal antibodies to the insulin-like growth factor 1 receptor (IGF1R) (Patel et al. 2010).

44.2 Rare Bone Tumors

Stefano Ferrari and Andrea Ferrari

Less than 0.2% of the malignant tumors are primary bone neoplasms. Though they are rare tumors, osteosarcoma and Ewing sarcoma are tumor types typical of children and adolescents, and their clinical management is usually well known by pediatric oncologists. Chondrosarcoma is typically a tumor of the adulthood and is very rare in pediatric age.

A wide variety of benign or locally aggressive tumors may affect bone in children: These entities can be classified into different categories according to the matrix, or substance, that they produce: i.e., osteoid – or bone-forming tumors, cartilage-forming tumors, fibrous lesions. Many cases are discovered incidentally; in other cases, they present with localized pain, swelling, deformity, or pathologic fracture. These tumors have characteristic radiographic features (i.e., type of periosteal reaction, calcification, well-defined or sclerotic border, lack of destruction of the cortex, and soft tissue extension) and can be diagnosed with plain radiographs: The evaluation of expert radiologists may avoid in many cases unnecessary invasive diagnostic studies. It is important to refer these cases to experienced orthopedic surgeon: Most cases can be managed

with observation. Curettage and bone grafting or excision may be required in more aggressive cases (Yildiz et al. 2003; Wyers 2010).

However, it is very important to consider that patients with enchondromatoses or multiple osteochondromas have a higher risk of developing chondrosarcoma.

44.2.1 Chondromas

Enchondroma may be observed in children, young, and adults. It is usually asymptomatic and the diagnosis may be made after imaging investigation performed for other reasons. Most of the cases are observed in the tubular bones of the hand, where enchondroma is the most frequent bone tumor. Other preferred location are the long bones (especially the femur). Enchondroma can reach considerable extension in the major long bones and may cause pathologic fractures.

The neoplasm is frequently central, sometimes eccentric or intracortical. It is an osteolysis, with rounded, lobulated, well-defined edges with a thin rind of reactive sclerosis. Usually the lesion contains granular, popcorn, ring-like opacities that represent calcification and ossification at the periphery of the lobules. The computed tomography scan shows a radio-dense lobular or multi-islands lesion with sharp limits and a clear lack of permeative alterations of the cortex. The pathology appearance is characterized by lobules of cartilage with the typical aspect of hyaline cartilage. The calcified areas appear as granules white-opaque. The chondrocytes are sparse, with small, round, dense nuclei, of relatively uniform size. Diagnosis can usually be made on the basis of the clinico-radiographic features. The majority of enchondromas do not require biopsy nor surgical treatment, and patients should be followed up by means of standard radiography.

Periosteal chondroma is a benign hyaline cartilage neoplasm of bone surface that arises from the periosteum. It prefers the metaphyses of the long bones, particularly the proximal humerus. It may be painful and some swelling can be observed. The imaging shows a superficial erosion of the bone cortex with regular borders. Such erosion is caused by an hemispherical parosteal cartilaginous mass, usually of small-to-moderate size. In the largest chondromas, the tumor often contains granular or popcorn densities. Histologically, the tumor is very similar to enchondroma, but more frequently it displays features of cell proliferation (high cellularity, nuclear plumpness, and frequent double nucleated cells). Being somewhat painful and causing some swelling in most instances, it usually requires surgical management consisting of either en-bloc marginal excision or thorough curettage (Boriani et al. 1983).

44.2.1.1 Enchondromatoses (Ollier Disease, Maffucci Syndrome)

Enchondromatoses are rare; patients are younger than those with solitary tumors, the majority presenting during the first two decades of life. It has been reported that age at presentation is inversely related to the severity of the disease. *Ollier disease* is a developmental disorder characterized by failure of normal enchondral ossification and production of cartilaginous masses (enchondromas) leading to bone deformity. There is predominant unilateral involvement. *Maffucci syndrome* combines the features of Ollier disease associated with multiple soft tissue hemangiomas.

The most affected bones are the small tubular bones of the hand and foot, but the enchondromas may present everywhere in the skeleton. Swelling, deformities, and lower limb length discrepancy (even >10 cm) are the dominant symptoms.

Chondrosarcomas may develop in both syndromes (in approximately 25% of cases, after the age of 20–40 years), and there is an increased risk of extraskeletal malignancies, such as breast, liver, ovarian cancers and brain tumors.

Surgical treatment is aimed to relieve symptoms, rather than excise the enchondromas. Skeletal deformities and limb length discrepancy are addressed by osteotomies and/or lengthening procedures. Prognosis is burdened by the incidence of malignant change (Liu et al. 1987; Albregts and Rapini 1995; Altay, et al. 2007; Silve and Juppner 2006).

44.2.1.2 Multiple Osteochondromas

Osteochondroma (osteocartilaginous exostosis) is a cartilage-capped bony projection arising on the external surface of bone containing a marrow cavity that is continuous with that of the underlying bone. Osteochondroma is not a neoplasm, but, especially the poliostotic presentation, can go toward a malignant transformation. The diagnosis of osteochondroma is usually performed in the pediatric age with a prevalence for the male gender. The most frequent localization is in the metaphysic of long bones: distal femur, proximal humerus, and proximal tibia.

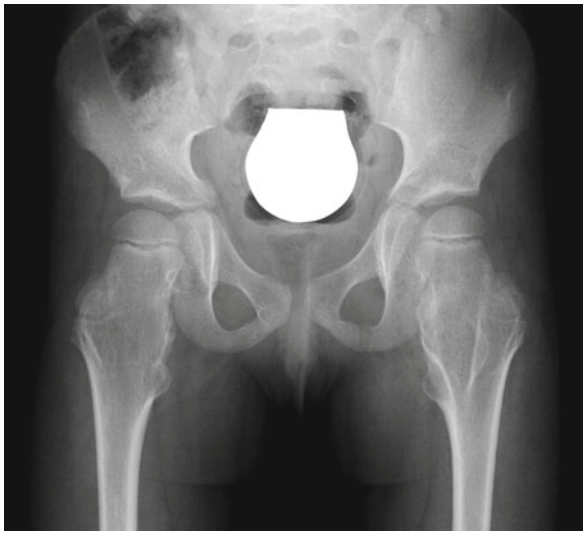

Fig. 44.8 Multiple osteochondromas in a 4-year-old girl (Courtesy Dr. Annette Schmitz-Stolbrink, Pediatric Radiology, Dortmund, Germany)

Multiple osteochondromas is an autosomal dominant condition. It is genetically heterogeneous and is caused by mutations in one of the exostosin (EXT) genes, tumor suppressor genes located respectively at 8q24 and 11p11-p12 (Fig. 44.8). The most important complication of this condition is the malignant transformation in chondrosarcoma. A cartilage cap >1.5 cm, as evaluated by means of magnetic resonance imaging, should be regarded with caution as a possible radiographic marker of malignant transformation (Bovee 2008; Ahmed et al. 2003).

44.2.1.3 Chondrosarcoma

Primary chondrosarcoma is a tumor of adulthood and old age. The majority of patients are older than 50 years with a peak incidence in the fifth to the seventh decades of life. Chondrosarcomas are graded on a scale of 1–3 (based on nuclear size, nuclear staining, and cellularity), from moderately cellular tumors similar to enchondroma to pleomorphic and atypical lesion with high mitotic rate. The majority of primary chondrosarcomas are grade 1 or 2.

Secondary chondrosarcoma arises from in a benign precursor, either osteochondroma or enchondroma. The risk of developing chondrosarcoma has been reported around 2% for solitary osteochondroma and 10–25% for multiple osteochondromas 5–25%. Patients with secondary chondrosarcoma are generally younger than patients with primary tumor. The pelvic and shoulder girdle bones are frequently affected. Changes in symptoms (sudden pain, increase in swelling) and radiological findings (increased thickness of the cartilage cap, destructive permeation of bone, development of soft tissue mass) in a patient with a known precursor lesion herald the development of chondrosarcoma. Secondary chondrosarcomas are generally low-grade tumors.

44.2.1.4 Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma (MCS) is a rare malignancy characterized by a biphasic histologic pattern of small undifferentiated round cells intermixed with islands of well-differentiated cartilaginous matrix. Because of its aggressive clinical behavior, MCS should be always regarded as a high-grade sarcoma.

MCS is a rare tumor. In comparison to the most frequent classic chondrosarcoma, generally affecting patients who are >50 years old, MCS typically occurs in young adults, it is highly malignant, and has a high proportion of extraskeletal tumors (about one-third of MCS occur in soft tissues, whereas extraosseous classic chondrosarcoma account for <1% of all cases). In the SEER database (1973–2006), only 24 children with MCS are recorded (and 142 adults). Tumor locations are bone and joints ($n=9$), soft tissue ($n=7$), nose/nasal cavity ($n=2$), eye/orbit (3), cranial nerves (1), lung (1), and kidney (1).

A German retrospective study reported on 15 cases aged 0–25 years, 4 osseous and 11 extraosseous. Tumor sites were head/neck (6 cases), paravertebral (3), pelvis (3), limbs (2), and kidney (1). Actuarial 10-year event-free and overall survival rates were 53% and 67%, respectively (Dantonello et al. 2008). Emerging cytogenetic data have raised the idea that this tumor may be closely related to extraskeletal Ewing's sarcoma/peripheral primitive neuroectodermal tumors (pPNET); patients with MCS should be probably treated with multimodal regimens, following Ewing's sarcoma protocols.

44.2.1.5 Chondroblastoma

Chondroblastoma is a benign rare tumor of the second decade of life, usually epiphyseal, located distally in long bones. Pain is usually present and, relatively common, also joint effusion. The radiographic appearance is characterized by a round or oval radiolucent lesion, small-to-moderate in size within the epiphysis or an apophysis or even extending across the plate. The

margins are sharp with a sclerotic rim. The cortex may be expanded but preserved in most cases. Usually no periosteal reaction can be detected. Calcification inside the defect is observed in 30–40% of cases.

Histologically, chondroblastoma shows a combination of mononuclear cells and giant cell. The typical cell is uniform, round to polygonal cell with well-defined cytoplasmic borders, clear to slightly eosinophilic cytoplasm, and a round to ovoid nucleus (chondroblasts). Chondroblasts are packed in pseudo-lobulated sheets often showing a pavement-like pattern.

Chondroblastoma has a slow course and may be surgically treated with curettage. The incidence of local recurrence is <20% and is related to the site of the tumor. Lung metastases can exceptionally complicate the course of the disease, but they can be effectively surgically removed.

44.2.1.6 Chondromyxoid Fibroma

Chondromyxoid fibroma is a benign tumor made by lobulated, fibromyxoid, and chondroid tissue, typical of the second and third decades of life, arising in the metaphysis of long bones (preferred sites are the proximal tibia). Mild-to-moderate pain is generally associated with local swelling. Radiographically, it appears as a small, metaphyseal and eccentric radiolucent defect, usually with the long axis parallel to the bone of origin, sharply marginated for a sclerotic rim. There may be cortical destruction with extension to the soft tissue with absent or minimal periosteal reaction (Fig. 44.9).

44.2.1.7 Osteoblastoma

Osteoblastoma is a benign tumor, made of osteoblasts producing osteoid and woven bone, arising in the second to third decades with an evident predilection for the posterior arch of the vertebral column and the sacrum. Signs of root compression may be present. Osteoblastoma is an osteolytic tumor well circumscribed and confined by a shell of reactive bone. Most of the tumors are of small size. In larger tumors, cystic spaces can be detected with radiographic appearance similar to an aneurismal bone cyst. Microscopically, the tumor consists of large osteoblasts producing osteoid and woven bone spicules and thin trabeculae. The surgical curettage is curative in most of the lesions. In selective cases, arterial embolization may be useful to reduce hemorrhage during surgery and postoperative radiation therapy can be added to improve the local control (Greenspan 1993).

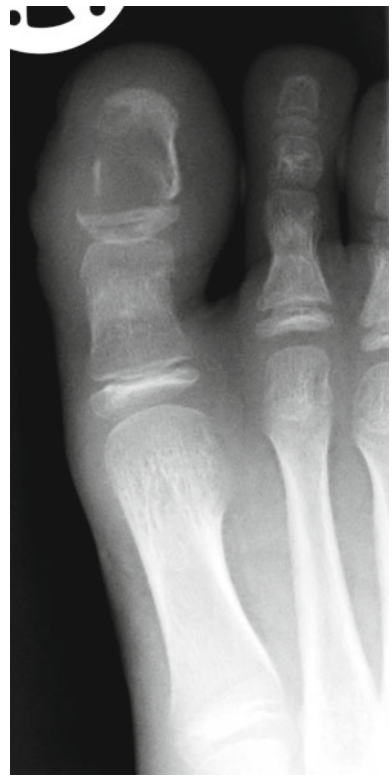

Fig. 44.9 X-ray of a chondromyxoid tumor of the toe in a 12-year-old boy (Courtesy Dr. Annette Schmitz-Stolbrink, Pediatric Radiology, Dortmund, Germany)

44.2.1.8 Osteoid Osteoma

Osteoid osteoma is a small benign tumor, made of osteoid and woven bone, surrounded by reactive bone. The tumor usually affects patients in the pediatric age. It mainly occurs in the appendicular skeleton (femur in particular), while it is rare in the trunk, with the exception of the spine (mostly localized in the posterior arch). The almost constant symptom is pain, with a typical tendency to increase during the night, relieved by nonsteroidal anti-inflammatory drugs. When localized near a joint, limited motion and chronic synovitis can be observed. In the spine, it may cause muscular spasm with stiff scoliosis. The basic radiographic element is a small (1–2 cm) rounded area of osteolysis ("nidus"), surrounded by a halo of bone sclerosis.

Left untreated it increases very slowly. Surgery, up to late 1990s, has been historically the mainstay of treatment. Nowadays computed tomography-guided percutaneous radiofrequency or laser ablation is considered the treatment choice. Success rate of this approach is usually more than 90% based on pain

relief. Surgery remains an option in cases refractory to percutaneous ablation (Kaweblum et al. 1993; Kneisl and Simon 1992).

44.2.2 Giant Cell Tumor of Bone

Giant cell tumor of bone is a relatively rare tumor (high incidence rates are reported in Asia) characterized by a benign but locally aggressive behavior. Rare cases of metastases are reported, as well as transformations to a malignant sarcoma phenotype. Giant cell tumor of bone usually affects young female, arising in long bones. The tumor presents as an osteolytic lesion, characterized by the presence of multinucleated giant cells (osteoclast-like cells) and stromal cells that express RANK ligand, a key mediator of osteoclastic activation. Radiologically, the tumor may show a non-sclerotic and sharply defined border, and a characteristic "soap bubble" appearance. Substantial skeletal morbidity may occur. Surgery is the treatment of choice. In unresectable cases, therapy with bisphosphonates may be used in order to induce apoptosis and prevent osteolysis. More recently, denosumab (a monoclonal antibody targeting the RANK ligand) showed to be significantly active (86% of tumor response was reported in a phase II trial on 37 patients with recurrent or unresectable disease) and may represent a potentially important treatment option (Thomas and Skubitz 2009; Thomas et al. 2010; Balke and Hardes 2010).

44.2.2.1 Adamantinoma

Adamantinoma is a slow-growing primary malignant tumor of long bone. The tumor may be characterized by a wide range of morphological patterns, the most common of which consists of circumscribed masses or tubular formations of what appear to be epithelial cells surrounded by spindle-celled fibrous tissue. Immunohistochemically, the epithelial cells show coexpressions of keratin, especially basal epithelial cell keratins (CKs 5, 14 and 19) and vimentin. The cells of origin and the pathogenesis of the disease are still unknown (Qureshi et al. 2000).

Adamantinoma is a very rare disease. Though the real number of cases may be underestimated in a cancer registry, only 15 cases under 20 years of age and 42 older cases are reported in the SEER database (1973–2006). A comprehensive literature review was able to identify 119 pediatric cases (Van Rijn et al. 2006).

The term "adamantinoma" derives from the Greek word "adamantinos," that means "very hard." The typical presentation of adamantinoma is a painless swelling on the anterior side of the tibia. On conventional imaging, adamantinoma initially appears as a cortical lytic lesion without significant periosteal reaction, but in advanced cases the tumor consists of a bubbly multiloculated sharply delineated lesion, with cortex disruption and soft tissue component.

Surgery is the mainstay of treatment. However, tumors may present in advanced stage and conservative wide resection with free margins is often unfeasible. Amputation might be required in more aggressive cases. Chemotherapy and radiotherapy do not have a role in the treatment of this tumor. The overall outcome is relatively good. In the pediatric review (Van Rijn et al. 2006), 13% of cases developed metastases (mainly in the lungs), and 10% of cases died of tumor. However, amputation was necessary in around 30% of cases.

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