Chapter 7
Undifferentiated Pleomorphic Sarcoma (UPS) (Malignant Fibrous Histiocytoma (MFH) and Myxofibrosarcoma)

The most common term for a generic high-grade sarcoma has evolved over the years from fibrosarcoma to malignant fibrous histiocytoma (MFH), and now to high-grade undifferentiated pleomorphic sarcoma (UPS), as of the writing of the 2013 WHO sarcoma fascicle. The new nomenclature is utilized to differentiate from tumors that are truly histiocytic, i.e., histiocytic sarcoma, recognizing that their microscopic morphology is not specific for this sarcoma subtype. Specific varieties of what was called MFH in the past have proved to be unique entities. For example, myxofibrosarcoma is now a clearly defined sarcoma subtype that was formerly termed myxoid MFH. Myxofibrosarcoma occurs more frequently in the subcutaneous tissue and has infiltrating pattern (Fig. 7.1). Angiomatoid MFH was reclassified as angiomatoid fibrous histiocytoma, having mostly a benign clinical course and occurring in children and young adults. The situation is further complicated since the term MFH is still sometimes employed as a term for a high-grade bone sarcoma that lacks osteoblastic or chondroblastic differentiation (and treated most commonly as osteogenic sarcoma in children). Increasingly, the term UPS of bone is used instead of MFH of bone.

The age distribution for adult myxofibrosarcoma is shown in Fig. 7.2. The summary of the various sites now identified as having myxofibrosarcoma is seen in Fig. 7.3.

7.1 Imaging

There are no unique characteristics that discern UPS/myxofibrosarcoma from other sarcomas radiologically (Fig. 7.4). The lungs are the most common site of metastasis and should be monitored by x-ray or CT.

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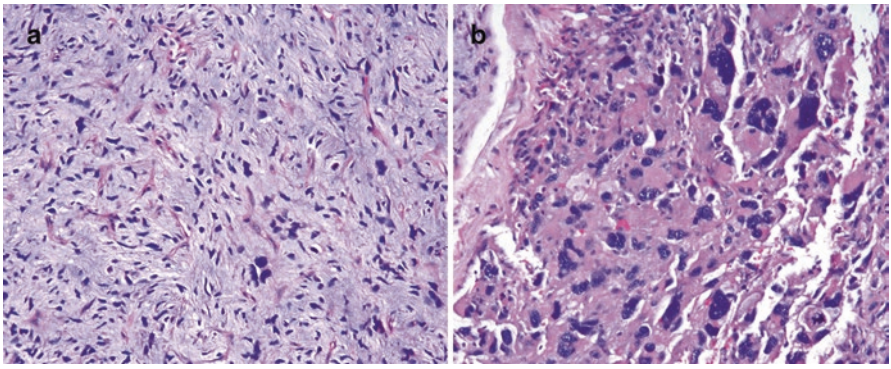

Fig. 7.1 (**a**) Myxofibrosarcoma: spindle and pleomorphic cells embedded in a predominantly myxoid stroma and associated with a rich vascular network. (**b**) High-grade pleomorphic type UPS (undifferentiated pleomorphic sarcoma) bizarre, multinucleated cells, with hyperchromasia and anaplasia

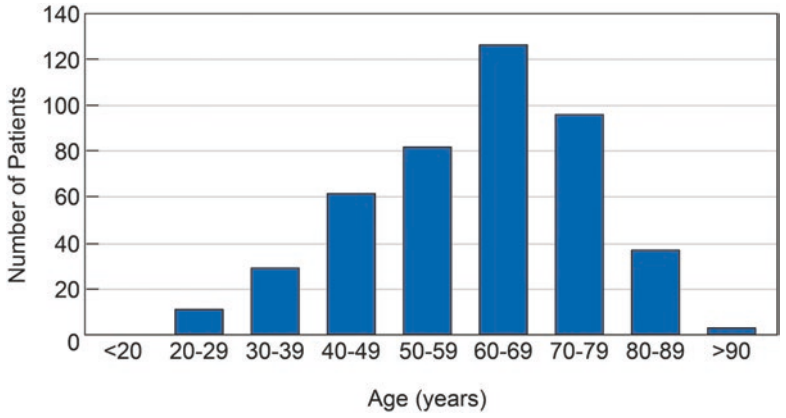

Fig. 7.2 Distribution by age for adult patients with myxofibrosarcoma, all sites. MSKCC 7/1/1982 – 6/30/2010, $n = 445$

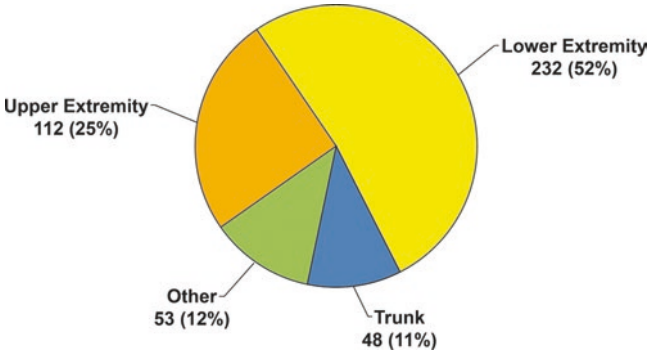

Fig. 7.3 Distribution by site for adult patients with myxofibrosarcoma. MSKCC 7/1/1982 – 6/30/2010, $n = 445$

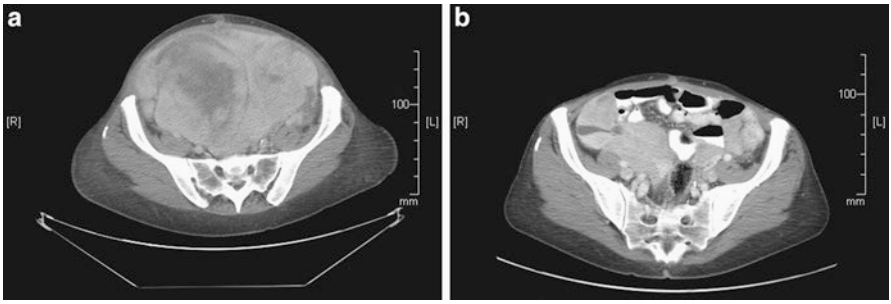

Fig. 7.4 CT of malignant fibrous histiocytoma /undifferentiated pleomorphic sarcoma of abdomen (**a**), and response to treatment at 4 months (**b**)

7.2 Diagnosis, Molecular Pathology

The cells in UPS appear to be fibroblastic or myofibroblastic, but by definition should not show a more specific line of differentiation. The differential diagnosis will depend on the anatomic site of the body in which the tumor is identified. For example, in the retroperitoneum, most (if not all) lesions with pleomorphic morphology represent dedifferentiated liposarcoma; MDM2 (HDM2) is overexpressed in such tumors. Cytogenetically, UPS are aneuploid tumors without recurrent or characteristic genetic abnormalities. Conversely, angiomatoid fibrous histiocytoma is characterized by a t(2;22) resulting in *EWSR1-CREB1* in most cases, and rarely by a t(12;22) or t(12;16) secondary to *EWSR1-ATF1* or *FUS-ATF1* [1–4]. Finding such a translocation rules out the diagnosis of UPS. Myxofibrosarcomas have a characteristic light microscopic pattern, but like UPS have no specific characteristic genetic abnormality. Interestingly, a spectrum of tumors ranging from embryonal rhabdomyosarcoma and UPS has been defined in an elegant series of mouse model experiments, suggesting the primitive nature of UPS may be from their derivation from muscular satellite cells, in which tumor suppressor *Rb1* is lost [5].

Not mentioned in this section are the rarer diagnoses that also appear to be related to fibroblastic or myofibroblastic cells, such as low-grade fibromyxoid sarcoma (Evans tumor), sclerosing epithelioid fibrosarcoma, dermatofibrosarcoma protuberans, or even rarer inflammatory myofibroblastic tumor, or acral myxoinflammatory fibroblastic sarcoma (see Chap. 12). These diagnoses have only become evident with the careful application of immunohistochemical and molecular techniques for a group of sarcomas that are otherwise relatively rare and difficult to subclassify.

7.3 Natural History

A major concern with myxofibrosarcoma, even when compared to UPS, is local recurrence. The margins of myxofibrosarcoma are often difficult to appreciate and difficult to manage.

Patterns of failure of myxofibrosarcoma are both local and distant. Local recurrence is related to the diffuse growth pattern and the infiltrative nature. The lung is the most common site for distant metastasis, but satellite lesions can be identified in the area of the primary lesion, particularly in low-grade myxofibrosarcoma of the extremity. Grade is a factor in outcome and low-grade lesions, having a reasonably good prognosis; high-grade lesions have a substantial rate of both local recurrence and distant metastasis.

7.4 Treatment

Primary treatment is surgical. The ability to gain negative margins in these lesions is often most challenging. Only rarely is skin involved and so skin grafts should be uncommon.

7.5 Radiation Therapy

In the MSKCC brachytherapy randomized trial, 3/19 MFH patients recurred locally in the BRT arm as opposed to 6/20 in the no BRT arm [6]. Data on external beam radiation therapy from MSKCC showed a 5-year local control rate of 85% in 117 patients with primary extremity MFH [7]. We note that the data on the specific role of radiation therapy for UPS is somewhat limited, since most reports included both UPS and myxofibrosarcomas under the old term MFH. In a report on the role of IMRT in primary extremity sarcoma, the local control rate for patients with UPS ($n=35$) was 87.5%, which was similar to the myxofibrosarcomas ($n=33$) 88.1% [8].

The notion that myxofibrosarcomas might be radioresistant needs some clarification. Mutter et al. compared 88 primary high-grade leiomyosarcoma of the extremity to 144 high-grade myxofibrosarcomas [9]. The 5-year rates of local control were similar (86.8% vs. 85.4%, respectively, $p=0.5$). What was different in terms of local recurrence was the pattern; 47% of local recurrences in the myxofibrosarcomas were out of field as opposed to only 8% in the leiomyosarcomas group ($p=0.04$). Furthermore, once local recurrence developed, the chances of subsequent local recurrences were significantly higher with myxofibrosarcomas (35% vs. 0%, $p=0.05$). All these give the impression that the rate of local recurrence in myxofibrosarcomas is higher.

7.6 Metastatic Disease

Agents to consider for UPS/MFH as of 2016 include anthracyclines, ifosfamide, gemcitabine-docetaxel (or gemcitabine alone or in combination with vinorelbine), and pazopanib, at least in the United States. Doxorubicin and olaratumab, approved

in 1st line, is appropriate for UPS/MFH as well as other anthracycline sensitive soft tissue sarcomas.

Regarding traditional cytotoxic chemotherapy agents UPS can respond to doxorubicin or ifosfamide, but rarely to dacarbazine. Thanks to a careful analysis of patients treated prospectively in EORTC studies, it appears both ifosfamide and doxorubicin are useful systemic agents for metastatic sarcoma [10]. As a byproduct of a randomized study of gemcitabine-docetaxel vs. gemcitabine for patients with recurrent/metastatic soft tissue sarcomas [11], we learned that UPS/MFH is sensitive to gemcitabine-docetaxel, and to gemcitabine to a lesser degree, with sensitivity perhaps even greater than that of leiomyosarcoma (Fig. 7.4). In a study of neo/adjuvant gemcitabine-docetaxel vs. doxorubicin-ifosfamide in over 80 patients with primary soft tissue sarcomas, in which the predominant diagnosis enrolled was UPS, PFS was numerically superior, though overall survival was no different. The primary endpoint was hospitalization rate and was not statistically different between the arms. These data suggest that gemcitabine-docetaxel may be superior in primary UPS, but require a larger study to determine the relative efficacy [12].

While clinical trials have been performed generally examining gemcitabine on day 1 and day 8, and docetaxel at a large dose on day 8, with the randomized study noted above, as many as 50 % of patients had to stop therapy for toxicity within 6 months of treatment [11]. Gemcitabine and docetaxel can both be given on a low dose weekly schedule, with gemcitabine 600–900 mg/m^2 day 1 and day 8, docetaxel 20–35 mg/m^2 d1, d8, with or without growth factors, q 21 days, a variation of a 3 week out of four treatment schedule used for treatment of other cancers [13, 14]. Whether this schedule is as effective as the high-dose docetaxel regimen is to be seen, but provides another treatment option for patients who are more frail or with poor performance status to tolerate the admitted toxic day 8 docetaxel at 100 (or 75) mg/m^2. Of course, gemcitabine alone is also an option for poor performance status patients.

Gemcitabine with either vinorelbine or dacarbazine are other options for combination therapy [15, 16]. Eribulin is not well-examined in UPS specifically and was not included in the large phase III study vs. dacarbazine [17]. Gemcitabine-docetaxel was studied with bevacizumab in a phase II trial of a variety of sarcomas, featuring UPS. The relatively favorable PFS observed in the study could in principle be an effect of bevacizumab, but in the authors' estimation comes in large part from choosing the subtypes of sarcoma that respond best to the gemcitabine-docetaxel backbone, such as UPS [18].

Small molecule oral kinase inhibitors such as imatinib, sorafenib, and sunitinib do not appear to have significant activity in UPS/MFH, though there are relatively sparse data specifically testing sunitinib against UPS/MFH [19–22]. Pazopanib may have at least minor activity in UPS/MFH and is one of the diagnoses for which the agent is approved [22]. It is hoped that agents that inhibit the tumor cell cycle, immune checkpoints, or agents impacting epigenetic factors within the aneuploid tumor cell may prove a more useful approach than kinase inhibitors, as may combinations of chemotherapeutic agents. The first data regarding immune checkpoint inhibitors in STS (in this case pembrolizumab) indicates that UPS may be relatively sensitive among sarcomas. The initial results of the SARC28 study indicated 4/9 evaluable patients had a partial response to treatment. It is unclear if myxofibrosarcomas will be as sensitive as UPS per se [23].

Table 7.1 Recommendations for systemic therapy for patients with UPS[a]

Clinical scenario		Comments[a]
Neoadjuvant Adjuvant chemotherapy		Remains controversial and should be discussed on a case-by-case basis; the authors often opt for treating fit patients based on meta-analysis data, employing doxorubicin + ifosfamide
Metastatic disease	1st line	Anthracycline + olaratumab[b] or gemcitabine alone or in combination (with docetaxel or vinorelbine) in poorer performance status patients; doxorubicin-ifosfamide has been used historically in symptomatic patients
	2nd line	Ifosfamide or other agent(s) not used in 1st line
	3rd line	Pazopanib; immune checkpoint inhibitors, such as PD1 inhibitor pembrolizumab, appear to have activity. It is not clear if myxofibrosarcoma is similarly sensitive to immune checkpoint inhibitors

[a]Clinical trials are always appropriate if available
[b]PEGylated liposomal doxorubicin (Doxil®/Caelyx®) if poor KPS or elderly

7.7 Adjuvant Chemotherapy

Given the sensitivity of some patients with UPS/MFH to doxorubicin/ifosfamide in the metastatic setting, consideration can be given to the use of these agents in the adjuvant setting. While most of these individual studies are negative [24, 25], a few of these studies are positive for overall survival benefit [26, 27], and the most recent meta-analysis of adjuvant therapy studies, which unfortunately excludes a large but negative study from EORTC [25], indicates benefit of adjuvant therapy for patients who receive doxorubicin-ifosfamide-based therapy [28]. Given the relatively high risk of larger tumors (e.g., those over 10 cm), consideration can be given to adjuvant chemotherapy with the understanding of the conflicting data, knowing that a high percentage of such patients will require the use of chemotherapy at some point in their course of treatment (Table 7.1).

7.8 Outcome

Local disease-free survival (Fig. 7.5) for patients with UPS is approximately 75 % at 10 years with a local recurrence uncommon. Patients have a substantial risk of metastatic disease, with disease-specific survival of approximately 60 % (Fig. 7.6) at 10 years and late metastatic recurrence possible but most uncommon. In contrast, myxofibrosarcoma has a higher local relapse rate of at least 40 % at 10 years (Fig. 7.7), while the metastatic risk is similar between the myxofibrosarcoma group and patients who have UPS. There are perhaps more patients with late relapses and death from myxofibrosarcoma compared to UPS (Fig. 7.8) [9]. A recent review of extremity myxofibrosarcoma suggests that, despite more adverse clinical features, myxofibrosarcoma recurred less frequently than leiomyosarcoma. Radiation appeared to decrease local recurrence. (Fig. 7.9)

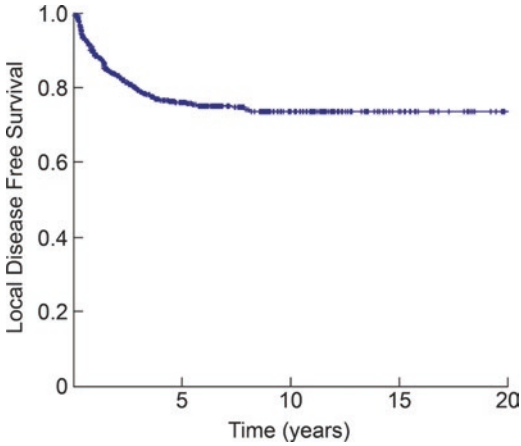

Fig. 7.5 Local disease-free survival for adult patients with primary malignant fibrous histiocytoma/ undifferentiated pleomorphic sarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 772$

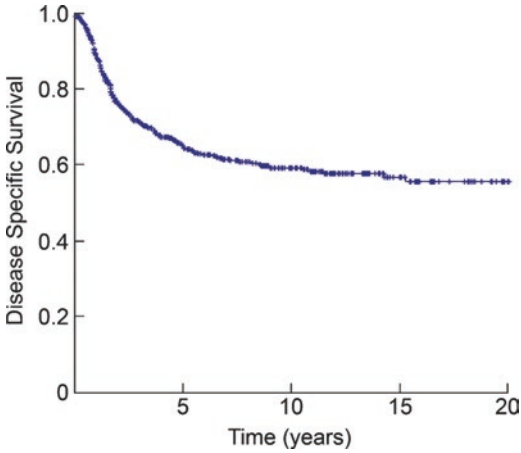

Fig. 7.6 Disease-specific survival for adult patients with primary malignant fibrous histiocytoma/ undifferentiated pleomorphic sarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 772$

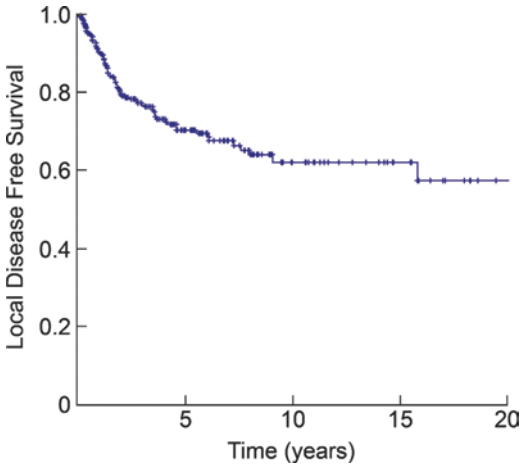

Fig. 7.7 Local recurrence-free survival for adult patients with primary myxofibrosarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 361$

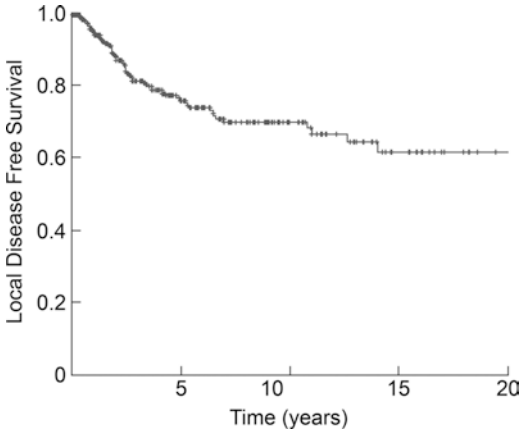

Fig. 7.8 Disease-specific survival for adult patients with primary myxofibrosarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 361$

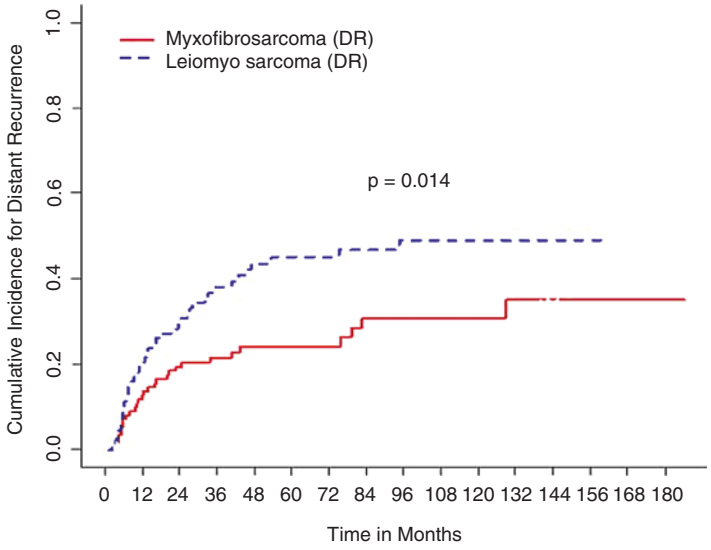

Fig. 7.9 The cumulative incidence of distant recurrence (DR) is illustrated according to histologic subtype. With permission from : *Mutter RW, et al. Cancer 118(2):518-527, 2012*

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