Chapter 12
Fibrosarcoma and Its Variants

Fibrosarcoma can occur at all ages (Fig. 12.1) and in all sites (Fig. 12.2). Before the era of immunohistochemistry, fibrosarcoma was a very fashionable diagnosis and represented one of the most common types of soft tissue sarcoma. With the development of immunohistochemical and molecular techniques, it is now rare for a sarcoma to be termed as fibrosarcoma, which by its name implies fibroblasts as the cell of origin. With increasing sophistication in diagnosis, more and more subtypes of fibroblastic sarcomas are now appreciated, all relatively rare tumors, but some show distinct molecular aberrations. While surgery for essentially all and radiation for some patients remain the standard of care for primary therapy for any of these soft tissue sarcomas, there has been less experience with each of these subtypes of tumors with respect to chemotherapy than with more common diagnoses. Beyond dermatofibrosarcoma protuberans, recommendations presented here are provisional and should be considered a starting point for prospective and hopefully multicenter clinical trials including patients with these diagnoses.

12.1 Outcome

Local recurrence for all primary fibrosarcomas is shown in Fig. 12.3 and disease-specific survival in Fig. 12.4 for those with primary presentation. Metastatic disease is recognized but affects only a minority of patients with primary disease, although some of these recurrences can be very late.

12.2 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is the most common of the fibrosarcomas overall. It presents in middle age (Fig. 12.5) and at essentially any anatomic site (Fig. 12.6). DFSP is a superficial sarcoma involving dermis and subcutis, with a

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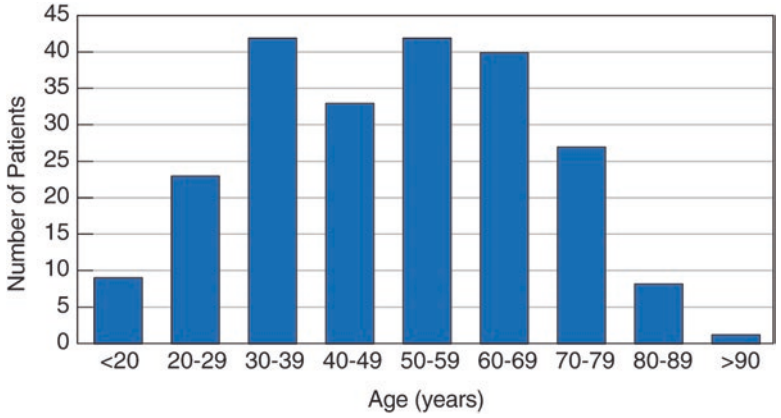

Fig. 12.1 Age distribution of adult patients with fibrosarcoma (all types except DFSP). MSKCC 7/1/1982–6/30/2010 $n = 225$

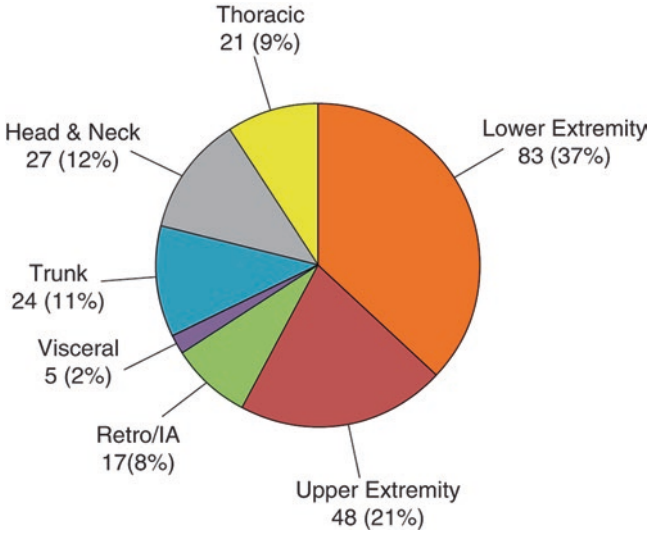

Fig. 12.2 Anatomic primary site distribution of adult patients with fibrosarcoma (all types except DFSP). MSKCC 7/1/1982–6/30/2010 $n = 225$. *Retro/IA* retroperitoneal/intra abdominal

distinctive horizontal rather than vertical growth and associated with a high rate of local recurrence. Rare DFSP will metastasize, usually after at least a decade of recurrences and degeneration to a fibrosarcomatous variant. Deaths from disease are uncommon and limited to those people with the development of metastatic disease.

DFSP is characterized by CD34 positivity and the presence of a recurrent t(17;22), resulting in a *COL1A1-PDGFB* fusion [1]. By FISH or karyotype, one can visualize the distinct amplification of the fusion gene, as a ring or marker chromosome,

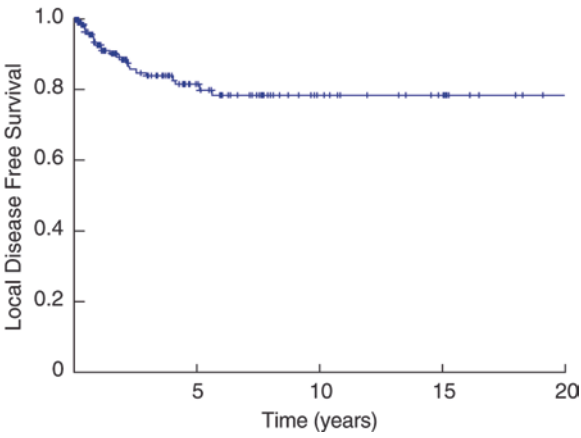

Fig. 12.3 Local disease-free survival for adult patients with primary fibrosarcomas (all types except DFSP). MSKCC 7/1/1982–6/30/2010 $n = 164$

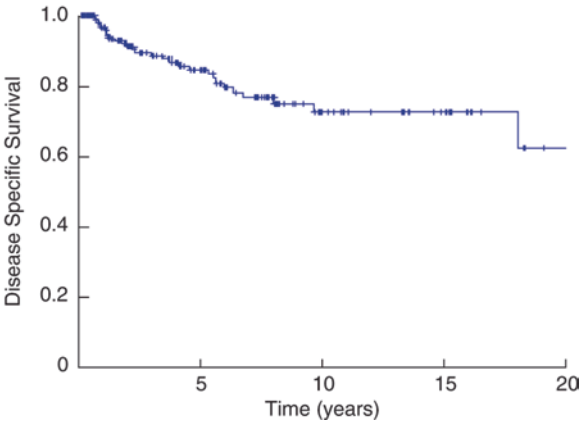

Fig. 12.4 Disease-specific survival for adult patients with primary fibrosarcomas (all types except DFSP). MSKCC 7/1/1982–6/30/2010 $n = 164$

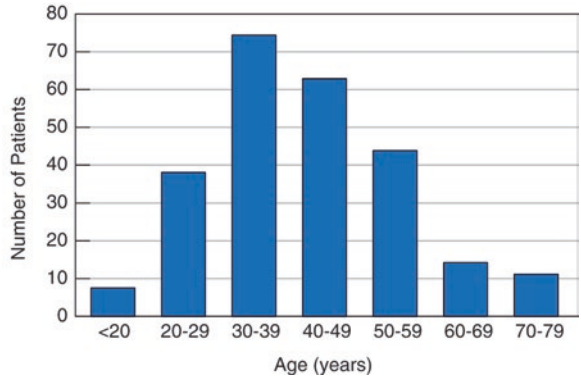

Fig. 12.5 Age distribution of adult patients with dermatofibrosarcoma protuberans. MSKCC 7/1/1982–6/30/2010 $n = 252$

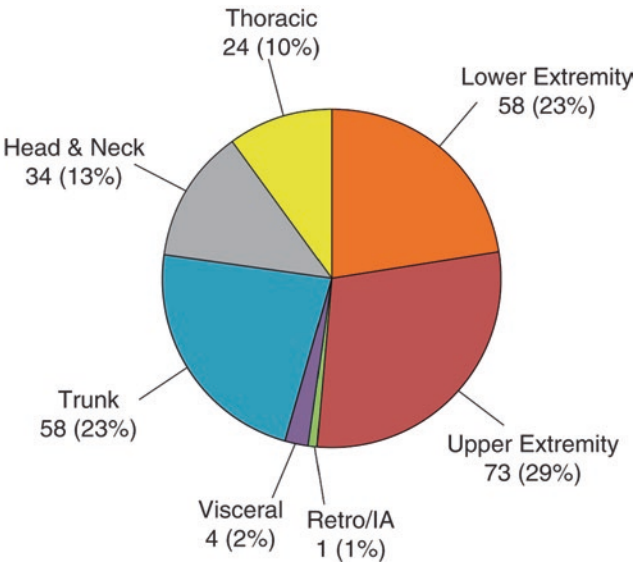

Fig. 12.6 Anatomic primary site distribution of adult patients with dermatofibrosarcoma protuberans. MSKCC 7/1/1982–6/30/2010 $n = 252$. *Retro/IA* retroperitoneal/intra abdominal

containing multiple copies of the translocation product [2]. Clinically it typically presents as a plaque-like lesion, and microscopically, the tumor is composed of monotonous spindle cells arranged in a storiform pattern. The transformation of DFSP to fibrosarcoma is seen in 10–15 % of cases, which increases the metastatic risk [3]. A pigmented form of disease (Bednar tumor) and a version found in children (giant cell fibroblastoma) are also characterized by the same translocation and behave similarly biologically [4]. For unclear reasons, multifocal DFSP is observed in some patients with adenosine deaminase deficiency (ADA) [5], whose gene locus is located on chromosome 20.

Primary surgery is the standard of care, without adjuvant radiation. There is a high risk of local recurrence of the tumor, and wide margins are generally advocated. One school of thought has led to use of Mohs micrographic surgery for this diagnosis, especially when the tumor occurs on the head and neck area as a primary site (Fig. 12.7); however, this surgical technique is inadequate and often accompanied by local recurrence. Adjuvant radiation, while not generally recommended for primary disease, should be considered for recurrent disease. Castle et al reported on 53 patients (45 % had 1 or more prior recurrence) treated with surgery and RT. With a median follow-up of 6.5 years, the 10-year local control was 93 % [6].

For recurrent disease, our experience is that standard doxorubicin and ifosfamide are strikingly ineffective. In contrast, as with gastrointestinal stromal tumor (GIST), imatinib can be very useful for disease recurrence [7–10]. In our experience the median time to progression is shorter than that seen for GIST but important palliation can be achieved with imatinib. We have observed some benefit from other tyrosine

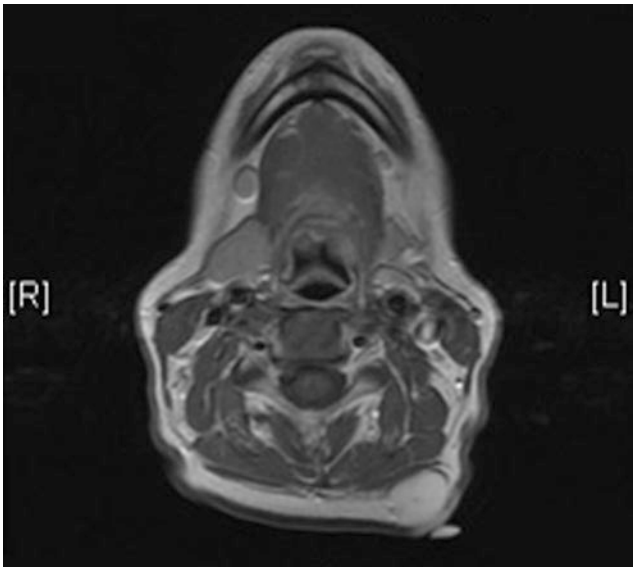

Fig. 12.7 T1-weighted contrast enhanced MRI image of a 2 cm dermatofibrosarcoma protuberans of the superficial posterior left neck

Table 12.1 Systemic therapy recommendations for patients with dermatofibrosarcoma protuberans

Clinical scenario		Comments
Neoadjuvant/ adjuvant systemic therapy		Not employed outside a clinical trial; the local–regional recurrence risk is low for patients who have adequate surgery
Recurrent or metastatic disease	First line	Imatinib
	Second line	Other tyrosine kinase inhibitor such as pazopanib. Clinical trials are appropriate. Immune checkpoint inhibitors are untested as of 2016 in DFSP. While interesting to consider, olaratumab is untested in this specific diagnosis as of 2016

kinase inhibitors in DFSP as well, but none that stands out as particularly meaningful in terms of durability of response (Tables 12.1 and 12.2). Given the surprising activity of PDGF receptor monoclonal antibody olaratumab in a clinical trial with doxorubicin in unselected sarcomas [11], the biology of DFSP begs the question of the utility of this agent in recurrent DFSP.

12.2.1 Outcome

Outcome is predicted based on fibrosarcomatous presentation, margin status, and depth of invasion. Local disease-free survival is shown in Fig. 12.8 and disease-specific survival for those presenting with primary lesions in Fig. 12.9.

Table 12.2 Patient and tumor characteristics of 240 patients treated for primary and recurrent dermatofibrosarcoma protuberans at MSKCC from 1982 to 2009

Characteristic	Primary ($n=196$)		Local recurrence ($n=44$)		P value[a]
	No.	%	No.	%	
Median age (years)	39		46		0.03
Gender					1.00
Male	95	48	21	47	
Female	101	52	23	53	
Primary site					0.66
Extremity	101	52	25	57	
Trunk/thorax	63	32	13	29	
Head and neck	29	15	4	10	
Other	3	1	2	4	
Tumor size					0.27
<5 cm	152	78	36	81	
5–10 cm	36	19	5	11	
>10 cm	6	2	3	7	
Unknown	2	1	0	0	
Tumor depth					0.42
Deep	42	21	12	27	
Superficial	154	79	31	70	
Unknown	0	0	1	3	
Tumor histology					0.64
"Classic" DFSP	166	68	39	88	
FS-DFSP	30	32	5	12	
Surgical margin					0.24
R0 (negative)	169	86	35	80	
R1 (microscopically positive)	26	14	9	20	
Unknown	1	<1	0	0	
Recurrence events					NE[b]
Local recurrence	9	4	5	11	
Distant recurrence	1[c]	<1	1	<1	
Vital status[d]					NE[b]
No evidence of disease	185	94	37	84	
Alive with disease	3	2	3	7	
Died of other causes	8	4	3	7	
Died of disease	0	0	1	2	

From: Fields RC, et al. Ann Surg Oncol 2011;18:328–336

DFSP Dermatofibrosarcoma protuberans, *FS-DFSP* fibrosarcomatous DFSP, *LR* locally recurrent, *MSKCC* Memorial Sloan-Kettering Cancer Center, *NE* not evaluable

[a]Fisher exact test for all variables (except age, which was analyzed using Wilcoxon rank sum test)

[b]Not evaluable. See text for explanation and Kaplan–Meir analysis for comparison of disease-free survival

[c]Synchronous distant and local recurrence

[d]As of July 2009

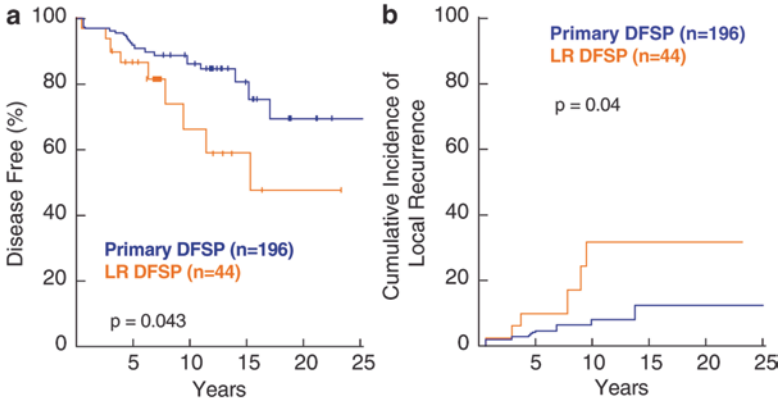

Fig. 12.8 (**a**) Disease-free survival and (**b**) cumulative incidence of local recurrence of DFSP in patients presenting with primary disease (*dark line*) or locally recurrent disease (*light line*). From: Fields RC, et al. Ann Surg Oncol 2011;18:328–336

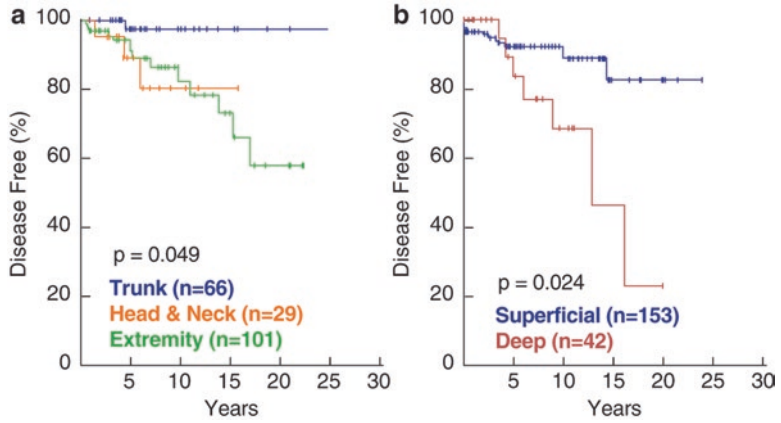

Fig. 12.9 Disease-free survival as a function of (**a**) anatomic primary site and (**b**) tumor depth at presentation. From: Fields RC, et al. Ann Surg Oncol 2011;18:328–336

12.3 Low-Grade Fibromyxoid Sarcoma (Also Termed Evans Tumor)

Evans tumor is uncommon and occurs in young patients, (Fig. 12.10) involving the deep soft tissues of limbs or head and neck area (Figs. 12.11 and 12.12). Low-grade fibromyxoid sarcoma (LGFMS) was first described by Dr. Harry Evans at MD Anderson in 1987, as a deceptively bland low-grade tumor that has the ability to

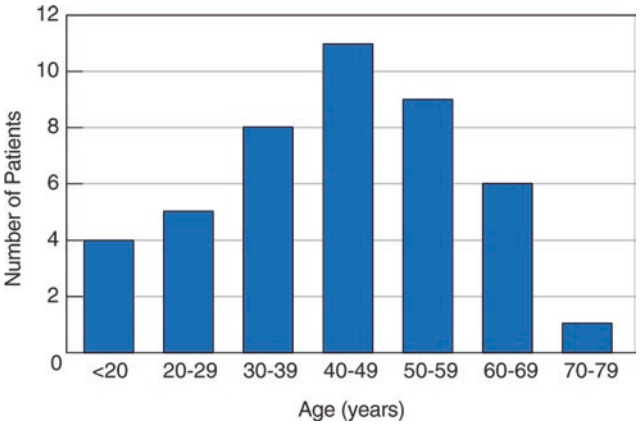

Fig. 12.10 Age distribution of adult patients with fibromyxoid sarcoma. MSKCC 7/1/1982–6/30/2010 $n=45$

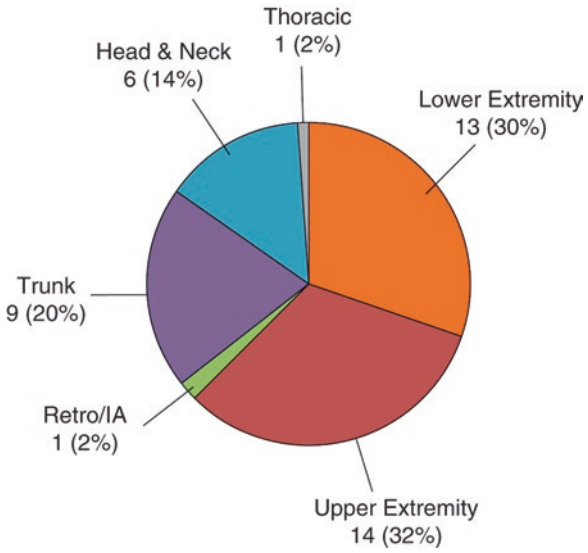

Fig. 12.11 Anatomic primary site distribution of adult patients with fibromyxoid sarcoma. MSKCC 7/1/1982–6/30/2010 $n=45$. *Retro/IA* retroperitoneal/intra abdominal

metastasize (Fig. 12.13). Metastases can be observed even decades after initial diagnosis. The diagnosis is often challenging due to its bland phenotype, which mimic benign conditions, such as desmoid, SFT, perineurioma. The diagnosis is confirmed by MUC4 immunoreactivity [12] and genetics, by demonstrating the characteristic t(7;16)(q34;p11) involving *FUS-CREB3L2* (or *CREB3L1* in isolated cases) [12–14]. There is some histologic and genetic overlap of these tumors with sclerosing epithelioid fibrosarcomas, see later [15].

Primary treatment is wide local excision with negative margins. Adjuvant radiation is reserved for positive margins or tumors with a high risk of local recurrence.

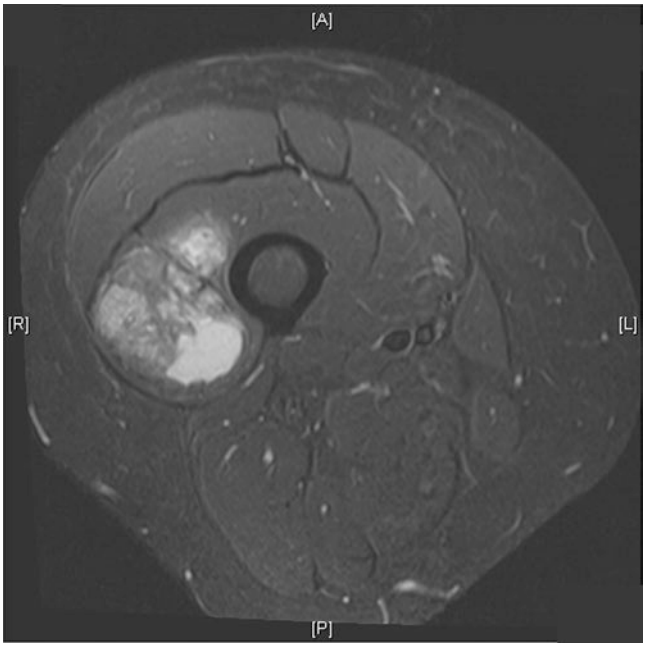

Fig. 12.12 T2-weighted MRI image of a 7 cm right thigh fibromyxoid sarcoma

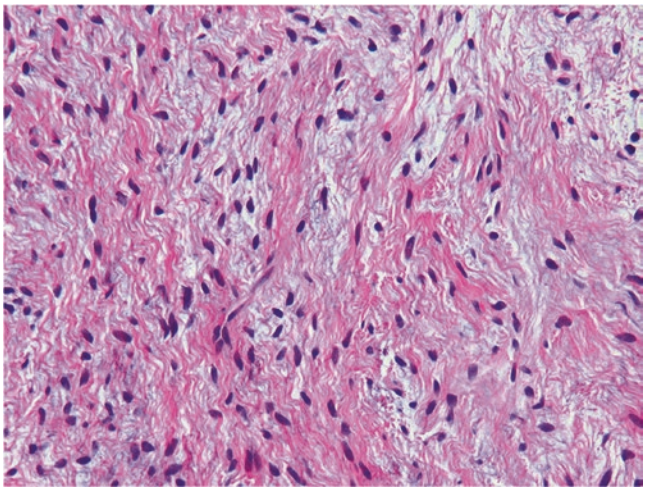

Fig. 12.13 Microscopic appearance of fibromyxoid sarcoma showing deceptively bland spindle cells embedded in a loose fibrous and myxoid stroma (H&E, ×200)

Table 12.3 Systemic therapy recommendations for patients with low-grade fibromyxoid sarcoma (Evans tumor)

Clinical scenario		Comments
Neoadjuvant/ adjuvant chemotherapy		Not utilized due to slow rate of tumor growth and only modest responses in the metastatic setting
Metastatic disease	First line	Pegylated liposomal doxorubicin, metronomic (low daily dose) oral agent such as cyclophosphamide; doxorubicin + olaratumab is also approved, though largely untested in this diagnosis
	Second line and greater	Pazopanib; clinical trial; immune checkpoint inhibitors are untested as of 2016 in this diagnosis

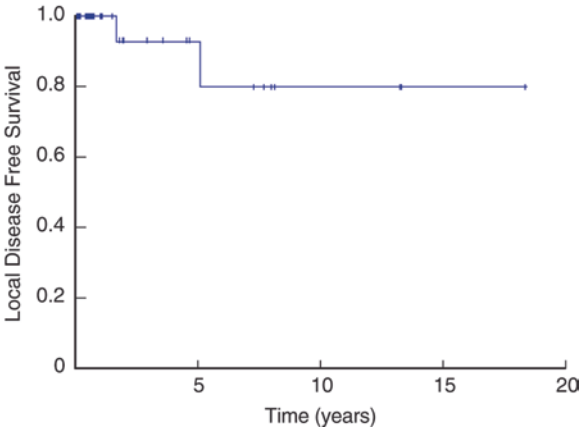

Fig. 12.14 Local disease-free survival for adult patients with primary fibromyxoid sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 36$

Regarding systemic therapy for metastatic disease, the long survival of even those with metastatic disease makes it difficult to recommend doxorubicin-based therapy (e.g., pegylated liposomal doxorubicin), although we have seen at least minor responses in treated patients. Hopefully systemic agents that are less toxic that can be administered for a long period time can help achieve meaningful palliation for patients (Table 12.3). As with other slowly progressing metastatic sarcomas, we suggest attempting to match toxicity of any proposed therapy to the aggressiveness of the metastatic disease. Given that Evans tumor and sclerosing epithelioid fibrosarcoma have distinct chromosomal rearrangements, it is hoped that epigenetic targets will have an impact on these diagnoses in the future. In the meantime, patients are prime candidates for clinical trials of novel agents.

12.3.1 Outcome

Local recurrence occurs (Fig. 12.14) but is uncommon and death from such tumors is relatively uncommon.

12.4 Sclerosing Epithelioid Fibrosarcoma

Sclerosing epithelioid fibrosarcoma (SEF) is another rare version of fibrosarcoma that falls in the same spectrum with low-grade fibromyxoid sarcoma (LGFMS) on the basis of shared chromosomal translocations in a subset of tumors, but follows a much more aggressive clinical course, with a significantly higher metastatic rate and disease-related mortality [16, 17].

SEF is usually a sarcoma of deep soft tissues of the extremities, but paraspinal and intracranial locations have been also reported [18]. Histology shows monotonous epithelioid cells with scant amphophilic cytoplasm, arranged in sheets or cords, separated by refractile collagenous columns (H&E, ×400) (Fig. 12.15).

SEFs are often MUC4(+), which appears to help in the differential diagnosis with other fibrosarcomas [19]. Two-thirds of sclerosing epithelioid fibrosarcomas harbor *EWSR1-CREB3L1* fusions, followed by *EWSR1-CREB3L2* in one-third of cases, with only rare examples of *FUS-CREBL1* [15, 20]. In contrast, hybrid tumors with both elements of Evans tumor and sclerosing epithelioid fibrosarcoma show mainly t(7;16) resulting in *FUS-CREB3L2* [15].

Primary therapy is surgery alone; radiation may be considered for larger primary tumors. Regarding systemic therapy for recurrent disease, we have observed minor responses to anthracycline-based therapy (again typically pegylated liposomal doxorubicin, given the slow changing nature of the tumor) (Table 12.4). A case report indicated activity of irinotecan in a patient with metastatic SEF [21], suggesting that agents active in refractory Ewing sarcoma, e.g., irinotecan–temozolomide

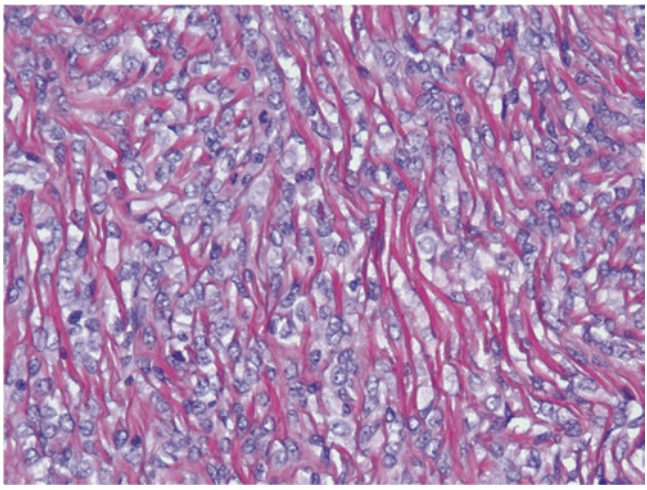

Fig. 12.15 Microscopic appearance of sclerosing epithelioid fibrosarcoma showing monotonous epithelioid cells with scant amphophilic cytoplasm arranged in cords, separated by refractile collagenous columns (H&E, ×400)

Table 12.4 Systemic therapy recommendations for patients with sclerosing epithelioid fibrosarcoma

Clinical scenario		Comments
Neoadjuvant/ adjuvant chemotherapy		Not administered (low response rate for people with metastatic disease)
Metastatic disease	First line	Anthracycline and/or alkylating-based therapy; doxorubicin + olaratumab is also approved in this setting, though there are no prospective data available
	Second line	Agents not used in first line; topoisomerase I inhibitor-based therapy (e.g., irinotecan, irinotecan–temozolomide, cyclophosphamide–topotecan), clinical trial; immune checkpoint inhibitors are untested as of 2016 in SEF

or cyclophosphamide–topotecan, could be considered for metastatic SEF. These data would be worth reporting even on a case-by-case basis at present, given the lack of any retrospective data on this issue.

12.5 Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is a distinctive neoplasm composed of myofibroblastic-type cells intimately associated with a lymphoplasmacytic inflammatory infiltrate. IMT can occur ubiquitously at any anatomic site, but show a predilection for lung, soft tissue, and viscera of children and young adults. Approximately half of the IMT harbor a clonal translocation involving the anaplastic lymphoma kinase (ALK)-receptor tyrosine kinase, resulting in ALK overexpression, which can be detected by IHC. In the most comprehensive analysis to date, Lovly et al showed 85 % of IMT contain translocations in *ALK*, *ROS1*, or *PDGFRB*, filling in the gap for many of the previously *ALK* translocation negative tumors. *RET* can also be translocated in some tumors [22, 23]. ALK expression by immunohistochemistry correlates often, but not always, with *ALK* translocation. Interestingly, 90 % of the *ALK* fusion-negative IMT occurred in adults, while the reverse was true in children [23].

Regarding systemic therapy, a case report of a patient with ALK(+) IMT responded to crizotinib, an inhibitor of ALK, MET, and ROS1, while a patient with an ALK(-) IMT did not respond, as proof of principle of the utility of ALK inhibitors in patients with this diagnosis [24]. Resistance in this responding patient to the ALK inhibitor crizotinib has already been identified in a manner similar to that seen with imatinib and KIT in GIST [25]. A patient with no *ALK* translocation had a *ROS1* translocation and had a radiological response to crizotinib. The presence of a *PDGFRB* translocation in one IMT suggests the use of multitargeted oral kinase inhibitors such as imatinib, though this has not been tested. Glucocorticoids may be useful for the inflammatory component of this tumor [26], but there are only case reports of systemic therapy for this diagnosis (Table 12.5).

Table 12.5 Systemic therapy recommendations for patients with inflammatory myofibroblastic tumor

Clinical scenario		Comments
Neoadjuvant/ adjuvant chemotherapy		Not administered due to lack of substantial benefit in metastatic or recurrent disease
Metastatic disease	First line	ALK/ROS1/MET inhibitors for ALK(+) tumors, e.g., crizotinib, crenolanib. Rare tumors have *PDGFRB* alterations and could respond to multitargeted kinase inhibitors, but this idea is untested. Doxorubicin + olaratumab is also untested in this situation
	Second line	Clinical trial

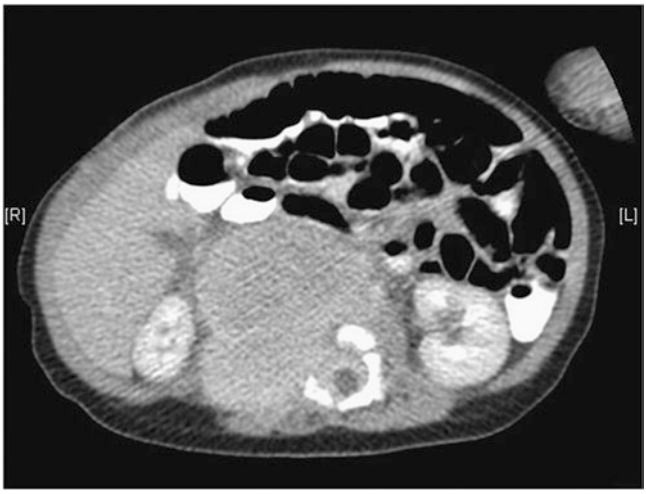

Fig. 12.16 Contrast-enhanced CT image of a patient with infantile fibrosarcoma of the right psoas musculature causing destruction of the spine and involvement of the spinal canal

12.6 Infantile Fibrosarcoma

Infantile fibrosarcoma most commonly occurs before age 1 (Fig. 12.16). Infantile fibrosarcoma carries a characteristic translocation, t(12;15)(p13;q25), encoding *ETV6-NTRK3*, which is also found in congenital mesoblastic nephroma [27, 28]. A recurrent *NCOA2* gene rearrangement has been reported in a pathologically and clinically similar tumor, infantile spindle cell rhabdomyosarcoma [29].

Despite its very rapid growth, children can do well with complete resection alone, avoiding radiation and chemotherapy. Chemotherapy can be considered if resection would be particularly morbid, with some positive results with an anthracycline- and alkylating-free regimen (Table 12.6) [30]. Chemotherapy for high-grade

Table 12.6 Systemic therapy recommendations for patients with infantile/congenital fibrosarcoma

Clinical scenario		Comments
Neoadjuvant/adjuvant chemotherapy		Vincristine/dactinomycin ± cyclophosphamide
Metastatic disease	First line	Agents for rhabdomyosarcoma or Ewing sarcoma; clinical trial as for second line
	Second line	Clinical trial (NTRK inhibitors are active in a case report, and the mechanism of action is compelling)

Table 12.7 Systemic therapy recommendations for patients with myxoinflammatory fibroblastic sarcoma/inflammatory myxohyaline tumor

Clinical scenario		Comments
Neoadjuvant/adjuvant chemotherapy		Not given, due to the low risk of recurrence
Metastatic disease	First line or greater	Undefined; clinical trials appropriate if available

pediatric sarcomas, as commonly used for Ewing sarcoma or rhabdomyosarcoma, may be employed as well. A child with an infantile fibrosarcoma with a *TRK3* translocation responded to a pan-TRK inhibitor [31], confirming the therapeutic relevance of this target in this rare pediatric tumor. Clinical trials will hopefully expand upon this hopeful initial result.

12.7 Myxoinflammatory Fibroblastic Sarcoma/Inflammatory Myxohyaline Tumor of Distal Extremities

Myxoinflammatory fibroblastic sarcoma is recognized as a separate entity based on both histology and anatomic location, nearly always found from the wrists and ankles distally [32, 33]. A characteristic t(1;10)(p22;q24) translocation, sometimes unbalanced, involving translocations of genes *MGEA5* and *TGFBR3* has been identified [34, 35], and is also seen in the unusual benign tumor hemosiderotic fibrolipomatous tumor [36, 37]. Both diagnoses also appear to have amplification of *VGLL3* and other genes from chromosome 3p12. Notably, the translocation attaches the genes head to head, so that they are not part of the same fusion gene product. Metastases are rare, so conservative management with complete resection is the standard of care (e.g., ray amputation). Tejwani et al reported on 16 patients with primary disease treated with surgery and radiation ($n = 13$), none developed local recurrence [38]. Chemotherapy remains an unknown in this tumor (Table 12.7).

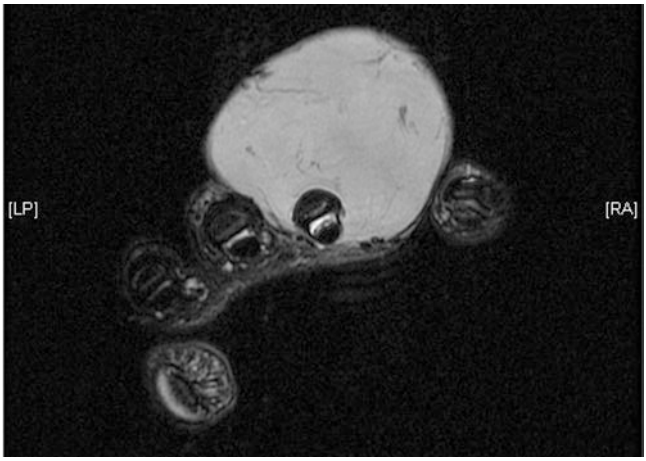

Fig. 12.17 T2-weighted MRI image of a 5 cm true fibrosarcoma of the fourth metatarsal soft tissues and extensor tendons of the right third, fourth, and fifth digits

Table 12.8 Systemic therapy recommendations for patients with (true) fibrosarcoma

Clinical scenario		Comments
Neoadjuvant/ adjuvant chemotherapy		Unknown; given the lack of perceived benefit for other types of fibrosarcoma adjuvant therapy is not generally recommended
Metastatic disease	First line	Anthracycline-based regimens e.g. doxorubicin + olaratumab
	Second line	Ifosfamide; pazopanib; clinical trial; immune checkpoint inhibitors are untested as of 2016 in fibrosarcoma

12.8 Adult-Type Fibrosarcoma

The adult-type fibrosarcoma is now a diagnosis of exclusion, after other immunohistochemical and/or molecular analyses have ruled out other sarcoma diagnoses (Fig. 12.17). Given the change in the diagnostic landscape for this tumor, it is hard to recommend adjuvant chemotherapy and anything other than standard chemotherapy agents or clinical trials for patients with metastatic disease (Table 12.8). More careful genomic analysis of this histology will hopefully identify molecular abnormalities to help us classify and better treat this sarcoma subset.

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