Management of Soft Tissue Sarcoma

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Preface

The authors were approached some time ago to write a text regarding the management of soft tissue sarcomas. There are several existing texts in the literature, and before embarking on such a project, it was necessary to identify what could be added that was unique to the existing literature.

We note that although there have been several texts that discuss management of sarcomas, there are few that discuss subtypes individually, given the rare nature of any one of these diagnoses. The prospectively accrued soft tissue sarcoma database initiated by Dr. Brennan in 1982 represents the largest single collection of individual soft tissue sarcoma patient data, allowing characterization of subtype by prevalence, age, and site. This is a unique resource for patient care and management and for outlining the clinical outcomes and management for each sarcoma subtype and has inspired other groups to collect information on an institutional, local, or national level in the intervening decades.

There are also relatively comprehensive resources regarding systemic therapy for different sarcoma diagnoses. For example, there have been a large number of phase II studies and retrospective analyses of outcomes with specific agents; there has not been a consistent place to refer for subtype-specific data. Despite issues regarding recall bias and other well-recognized weaknesses of retrospective analyses, we endeavored to collect at least some of those data herein. Until better data are accumulated, we have resorted to anecdote and case reports regarding treatments for rarer subtypes.

Since the publication of the first edition of our book, the most dramatic developments in cancer have been in molecular genomics and in immunotherapy. The molecular genomics of cancer have undergone a seismic shift in the past 5 years. While gene mutation panels have not led to revelatory changes in the treatment of sarcoma subtypes, such testing helps secure the diagnosis with certainty, when applied correctly. As of 2016, engineered T cells are being used to treat synovial sarcoma and myxoid-round cell liposarcoma, and we are learning in what context immune checkpoint inhibitors may be useful.

Other advances in sarcoma management involve the greater reporting of clinical experience over time. The recognition of second cancers even 30–40 years after initial therapy also makes one take pause as to treating patients with new diagnoses today. There are agents approved in the past 5 years that impact treatment as well. Investigators are accumulating data on chemotherapy responses on a sarcoma subtype-specific basis, which continues to affect the choice of treatments.

While a book becomes out of date the day it is published, it is clear that the principles of treatment of sarcoma remain consistent. It is in that light that we provide the readers with our contribution. We hope this book will help clinicians to better identify, characterize, treat, and perhaps even someday prevent these unusual and varied forms of cancer.

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Acknowledgments

Limited author texts such as this are a great challenge. They cannot be completed without the help of many people. Over the 30 years of the MSKCC database, we have been fortunate to have outstanding support, particularly from our colleagues in Pathology, Medicine, Surgery, and Radiation Therapy. The accumulation and maintenance of such a prospective database, reviewed and updated on a weekly basis, has been the province of many committed data managers.

As we review a database of more than 10,000 treated patients, it is hard to accept that each one is an individual patient with individual defining characteristics. We thank those individuals for the ability to use the data generated during their course of illness to create information valuable for the treatment of those yet undiagnosed patients.

The synthesis of the text would not have happened but for the efforts of Ms. Victoria Frohnhoefer. Her tireless commitment to the project and meticulous oversight of the authors are what brought this project to fruition. We cannot thank her enough.

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Introduction

Chapter 1
General Description

1.1 Introduction

Soft tissue sarcomas are an unusual group of tumors deriving their name from the Greek term for a fleshy excrescence. As early as Galen (130–200 C.E.), it was suggested they were a cancerous tumor and caution advised against any surgical intervention [1]. Early reports of myxoid liposarcoma by Severinius (1580–1637) and retroperitoneal liposarcoma by Morgagni (1682–1771) have been recorded [2]. Wardrop (1782–1869), an Edinburgh surgeon who had studied in Vienna, introduced the term soft cancer. In his book *Surgical Observations*, published in 1816, Charles Bell (1772–1842) has been credited with the utilization of the term soft tissue sarcoma to differentiate it from carcinoma [3]. The first classification of sarcoma has been attributed to Abernethy in 1804. Johannes Müller (1801–1858) has been credited with coining the term desmoid in 1838 [3]. Stout (1885–1967) published a seminal monograph in 1932 on the pathology and treatment of sarcomas [4].

Important contributions to the description and classification of sarcomas have been made at the Memorial Sloan Kettering Cancer Center starting with Dr. James Ewing (1866–1943). Ewing was the first Professor of Pathology at Cornell and the Clinical Director at Memorial Sloan Kettering Cancer Center. He was Chief of Pathology at Memorial in 1899 at the age of 33 and published the first edition of his classic monograph, *Neoplastic Diseases*, in 1919. His original description of soft tissue sarcoma, "sarcoma is a malignant tumor composed of cells of the connective tissue type…" was based on the morphology of tumor cells and on their histogenesis. Ewing was one of the first to list benign and malignant counterparts of tumors arising in the soft tissues. The most recognized contribution of Ewing was the description in 1920 of the tumor that bears his name [5].

M.F. Brennan et al., *Management of Soft Tissue Sarcoma*,
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Sarcoma has played a major contribution in the Memorial Sloan Kettering Cancer Center's history. William Coley in 1889 treated the 17-year-old Elizabeth Dashiell at the hospital for an extremity sarcoma. This young woman, a friend of J.D. Rockefeller, Jr., died of her disease in June of 1890, and it was said to have influenced Coley's willingness to study sarcoma. Rockefeller contributed as a consequence of this experience with continued financial and endowment support of the Memorial Sloan Kettering Cancer Center (MSKCC). Coley was recognized for his first attempts at what we would now call immunotherapy based on the utilization of Coley's toxins. He made the observation that a patient's sarcoma resolved after an episode of postoperative erysipelas infection, although it is not clear that the involved lesion was a sarcoma.

The first description of liposarcomas in 1944 has been attributed to Stout, also at Memorial Sloan Kettering, as was the description with Ackerman of leiomyosarcoma of soft tissue in 1947. Dr. Stout's comprehensive listing of the sarcomas was described in an Armed Forces Institute of Pathology (AFIP) *Atlas of Tumor Pathology* in 1953 [6]. One of the classical sarcoma syndromes, the Stewart–Treves syndrome, was described by Fred W. Stewart and Norman Treves (Figs. 1.1 and 1.2) in the first issue of Cancer in 1948. Stewart, the Chairman of Pathology at MSKCC and Treves, a member of the MSKCC Breast Service, described the highly malignant lymphangiosarcoma occurring in post mastectomy patients with chronic lymphedema [7].

Fig. 1.1 Fred W. Stewart, MD, PhD, 1894–1991, Pathologist, Memorial Sloan Kettering Cancer Center. From: Brennan MF, Lewis JJ. Diagnosis and Management of Soft Tissue Sarcoma. London: Martin Dunitz Ltd., 1998

Fig. 1.2 Norman Treves, MD, 1894–1964, Breast Surgeon, Memorial Sloan Kettering Cancer Center. From: Brennan MF, Lewis JJ. Diagnosis and Management of Soft Tissue Sarcoma. London: Martin Dunitz Ltd., 1998

1.2 Incidence and Prevalence

It is difficult to determine the true incidence of soft tissue sarcoma in the United States. It has previously been suggested to be between 10,000 and 14,000 new cases a year, but difficulties in classification, the inclusion of metastasis from sarcoma with other pathologies, and the relatively increased identification of gastrointestinal stromal tumors suggest that this number is considerably higher.

Current estimates [8] suggest 12,310 new cases in the United States in 2016, with 5330 deaths. This is almost certainly an underestimate, as gastrointestinal stromal tumors (GISTs) are often counted as GI cancers and metastatic sarcomas are often coded by site, rather than origin. The increasing diagnosis of GIST, many of which may never be a risk of metastasis or death, further obfuscates the problem. A Swedish-based population study [9] suggests an incidence of 14.5 per million and a prevalence of 129 per million, which would translate into at least 4000 new cases of GIST per year in the US. GISTs under 1 cm in size are found in over 20 % of patients in autopsy series of elderly patients.

There does appear to be a significant increase in survival from sarcomas in children (birth to 14 years) from 61 % in the mid-1970s to 80 % in the mid-2000s. This has not been confirmed in adults when corrected for stage of presentation.

Much of the data presented in this book is derived from a prospective database of patients being admitted over the age of 16 to the Memorial Sloan Kettering Cancer Center beginning in July of 1982. A review from this database of over 10,000 patients suggests that gender is equally distributed (Fig. 1.3). Distribution by site is shown in Fig. 1.4, and distribution within the extremities is shown in Fig. 1.5. Distribution of tumors by age and site is found for each relevant histology in individual chapters, where sufficient numbers exist. The overall distribution by histology is given in Fig. 1.6. The distribution of dominant histology type by site is provided in Fig. 1.7.

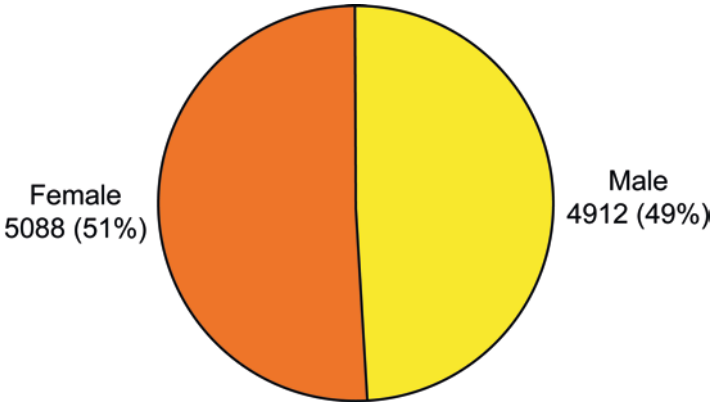

Fig. 1.3 Distribution by gender for adult patients with soft tissue sarcoma, all sites. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$

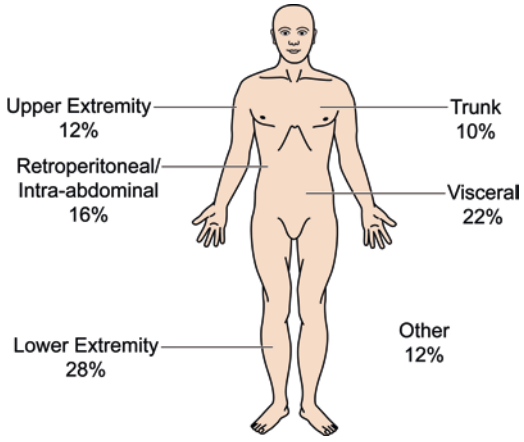

Fig. 1.4 Distribution by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$

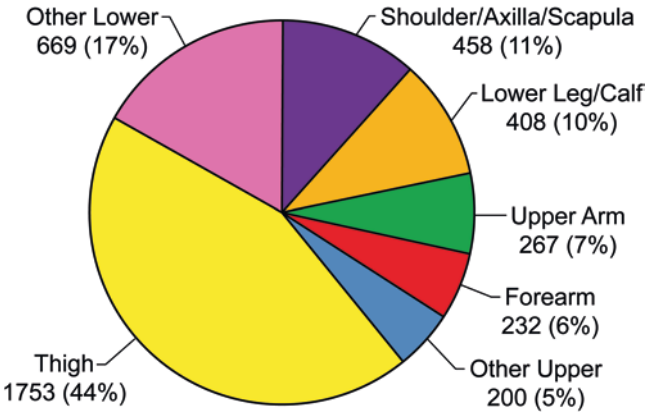

Fig. 1.5 Distribution by site within the extremities for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 3987$. With permission from: Brennan MF, et al. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. Ann Surg 260(3):416–422, 2014

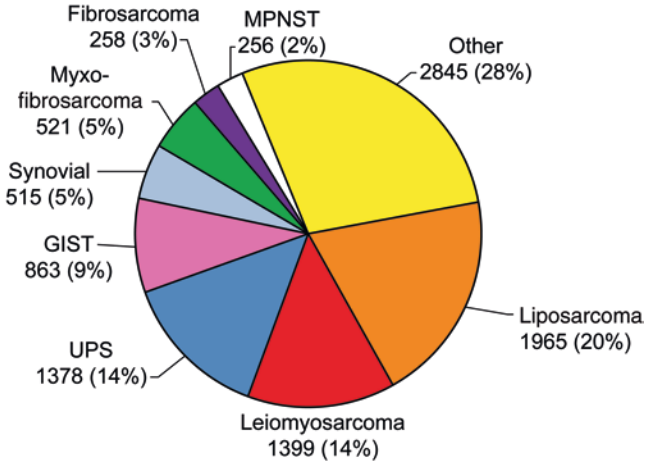

Fig. 1.6 Distribution by histology for adult patients with soft tissue sarcoma, all sites. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$. *MPNST* malignant peripheral nerve sheath tumor, *GIST* gastrointestinal stromal tumor, *UPS* undifferentiated pleomorphic sarcoma

Grade (Fig. 1.8), depth (Fig. 1.9), and primary size (Fig. 1.10) are covered and their relevance to prognosis is suggested in the appropriate sections.

The breakdown of site within extremity is included for lower and upper limb (Figs. 1.11 and 1.12). Size of extremity primary tumors, a widely recognized variable for outcome, is included in Fig. 1.13.

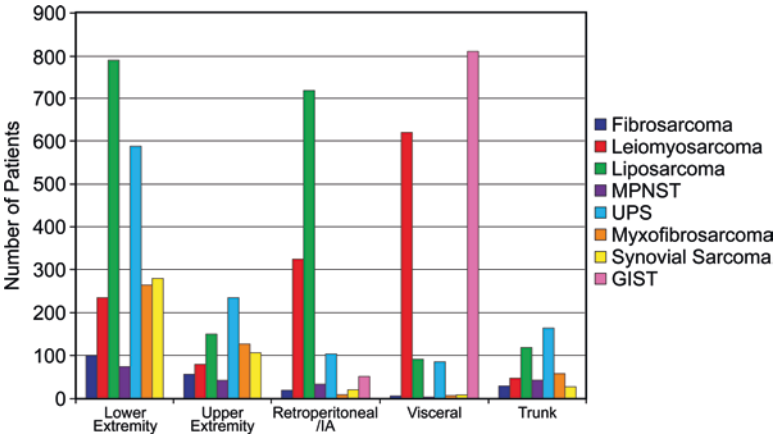

Fig. 1.7 Predominant histopathology by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 6536$. *MPNST* malignant peripheral nerve sheath tumor; *GIST* gastrointestinal stromal tumor; *UPS* undifferentiated pleomorphic sarcoma; *IA* intra-abdominal. With permission from: Brennan MF, et al. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. Ann Surg 260(3):416–422, 2014

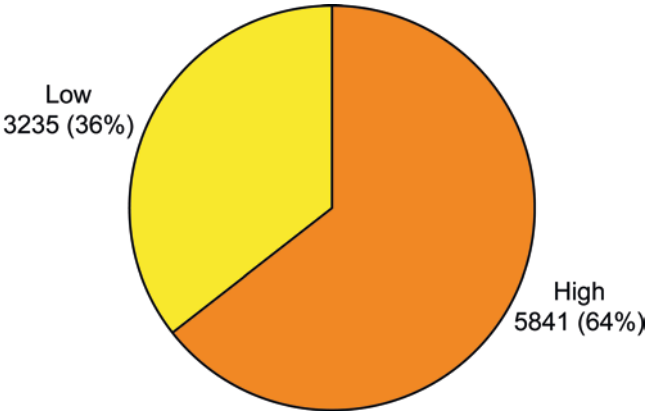

Fig. 1.8 Distribution by grade for adult patients with soft tissue sarcoma (excludes GIST), all sites. MSKCC 7/1/1982–5/31/2013 $n = 9076$

1.3 Predisposing and Genetic Factors

Predisposing and genetic factors have been identified and include the genetic predisposition in the patients with neurofibromatosis (Fig. 1.14), familial adenomatous polyposis coli (FAP), the Li–Fraumeni syndrome, and retinoblastoma, although the majority of soft tissue sarcomas have no clear identified cause. There are two distinct genetic groups of sarcomas. The first group contains specific

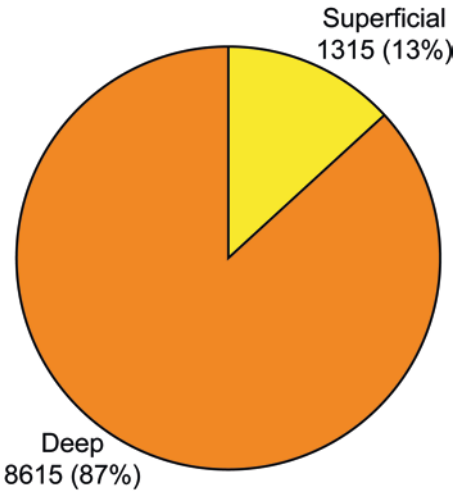

Fig. 1.9 Distribution of primary lesion by depth for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 9930$

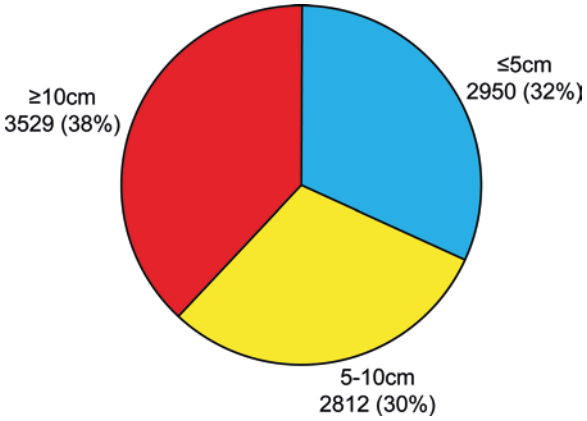

Fig. 1.10 Distribution by size for adult patients with soft tissue sarcoma, all primary sites. MSKCC 7/1/1982–5/31/2013 $n = 9291$

genetic alterations (Table 1.1), including fusion genes, and specific mutations, such as those seen for *KIT* or *PDGFRA* in GIST and the *APC* loss or *CTNNB1* mutations seen in desmoid tumors. Although advances in molecular characterization are changing our view of the genetics of many cancers, including sarcomas, most sarcomas have nonspecific genetic alterations, which are often complex, multiple, and represent variable chromosomal gains or losses. This second group often has a high prevalence of *TP53* and *RB1* mutations or deletion. *TP53* mutations have been associated with the Li–Fraumeni syndrome [10]. In addition to *TP53*, various genes that modulate the activity of p53, such as *CDKN2A* and *HDM2*, are also observed to be altered in some way in sarcomas. These cell cycle-regulating genes have been incriminated in the high incidence of germ line mutation as is seen in hereditary retinoblastoma and suggested to be casually associated with the genetic

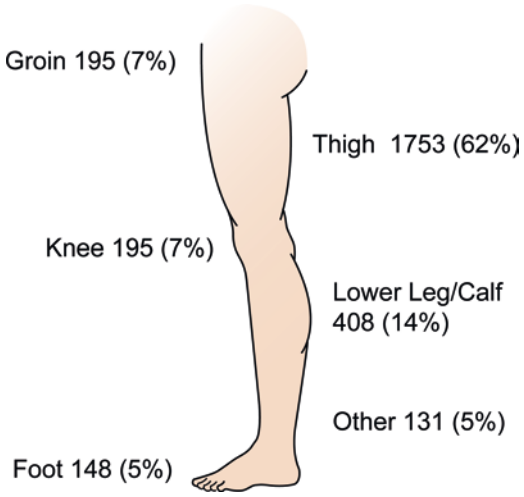

Fig. 1.11 Distribution within the lower extremity by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 2830$

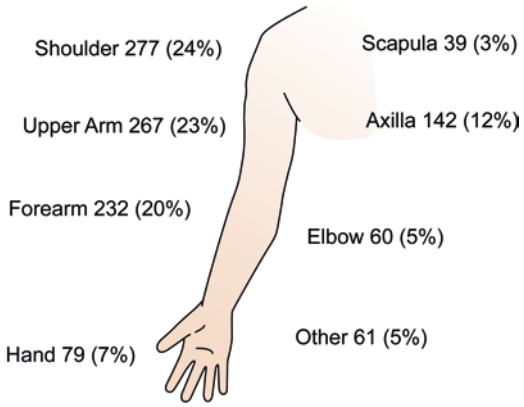

Fig. 1.12 Distribution within the upper extremity by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 1157$

predisposition to soft tissue sarcoma as has been seen in neurofibromatosis [11] and familial adenomatous polyposis [12]. These genetic aberrations have been suggested to be responsible for the increased susceptibility to second malignancy in such patients undergoing radiation therapy.

In neurofibromatosis, there is a high prevalence of malignant tumors, with almost 45 % of such patients developing malignant tumor in a lifetime [13]. Patients who have had retinoblastoma have an increased risk of development of nonocular tumors [14]. A review of the data suggests that 211 of 1506 patients with retinoblastoma developed a second tumor, 142 died before any malignancy developed, and 28 devel-

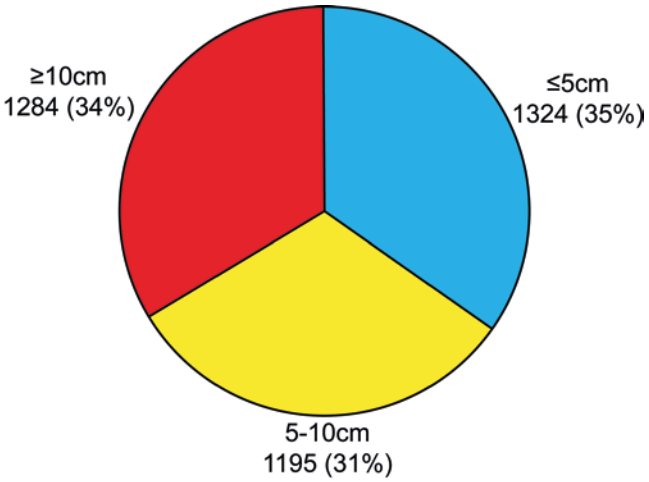

Fig. 1.13 Distribution within extremities by size for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 3803$

oped a third tumor at a median of 5–8 years. This is an important finding as pertains to this book, since the predominant tumors were soft tissue sarcomas. The relative risk of developing a second tumor after treatment for retinoblastoma is radiation dose dependent, and has spurred the rise of intra-arterial chemotherapy as primary treatment for retinoblastoma [15].

Patients with familial adenomatous polyposis (FAP) often develop desmoid tumors which are intra-abdominal or in the abdominal wall. Although debate exists as to whether desmoid tumors are benign or malignant, they behave as low grade soft tissue sarcomas, with invasion of local structures and significant potential for morbidity and mortality.

Radiation therapy is a causative agent for soft tissue sarcoma, although the mechanism is unknown. Patients undergoing radiation therapy for common diseases such as breast, prostate, lymphoma, and cervical cancer, and for pediatric cancers are at increased risk of subsequent soft tissue sarcoma and other cancers. Often these soft tissue sarcomas develop at the edge of the radiation field, suggesting incomplete repair of normal tissue that ultimately results in malignant transformation. Whether it is radiation that is causative or requires the underlying genetic defect that initiated the initial tumor is unclear. Almost 20 years ago, we reviewed our experience with radiation-associated sarcomas [16] suggesting that these tumors usually have a poor prognosis as they are often high grade and large at the time of diagnosis. Common soft tissue sarcomas that develop following radiation are undifferentiated pleomorphic sarcoma (UPS, formerly termed malignant fibrous histiocytoma, MFH) or myxofibrosarcoma (see below), angiosarcoma, and osteogenic sarcoma. It is rare for such patients to have low grade tumors or

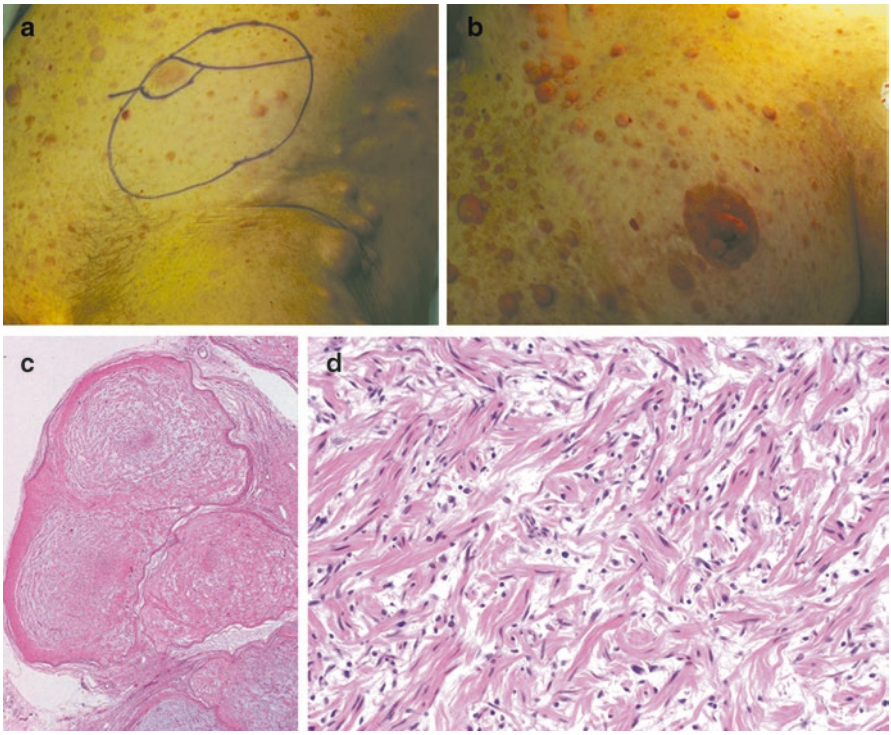

Fig. 1.14 Neurofibromatosis—neurofibroma left abdominal wall: (**a** and **b**) Gross appearance of multiple neurofibromas and café au lait spots; (**c**) whole mount low power microscopic appearance (H&E) and (**d**) high power

translocation-associated sarcomas. We have great concern that as use of radiation therapy as a primary treatment for ductal carcinoma in situ or early stage breast cancer increases we can expect a greater prevalence of lethal radiation-induced sarcomas. Many studies have examined this risk, and it would appear that the risk of developing soft tissue sarcoma approaches 5 in 1000 at 15 years [17]. This risk of second cancers increases with time. Studies performed from the Scandinavian data sets show a greater prevalence of sarcoma following radiation than would be expected in the absence of radiation therapy. An updated review of our experience has been reported [18]. Radiation-associated sarcomas are described more fully under Chap. 16.

We also have had a longstanding interest in the association of lymphedema with the development of soft tissue sarcoma since the earliest report by Stewart and Treves from our institution [7]. While often the lymphedema is associated with extent of operation and radiation therapy, it is not a radiation-induced sarcoma per

Table 1.1 More common molecular events that characterize a number of soft tissue sarcomas and related entities

Sarcoma subtype	Genetic alteration	Affected gene(s)	Frequency (%)
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FOXO1A*	70
	t(1;13)(p36;q14)	*PAX7-FOXO1A*	15
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	*ASPSCR1-TFE3*	>95
Angiomatoid fibrous histiocytoma	t(2;22)(q34;q12)	*EWSR1-CREB1*	>90
	t(12;22)(q13;q12)	*EWSR1-ATF1*	<5
Clear cell sarcoma (melanoma of soft parts)	t(12;22)(q13;q12)	*EWSR1-ATF1*	>90
	t(2;22)(q34;q12)	*EWSR1-CREB1*	<5
Ewing sarcoma-like tumors	t(4;19)(q35;q13.1)	*CIC-DUX4*	unk
	t(10;19)(q26.3;q13.1)		
	inv(X)(p11.4;p11.22)	*BCOR-CCNB3*	unk
Congenital (infantile) fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*	>80
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	*COL1A1-PDGFB*	>60
Desmoid tumor (deep fibromatosis)	*CTNNB1* exon 3 mut		>90
		T41A	60
		S45F	25
		S45P, S45C	5–10
	APC loss		Rare, except in FAP
Desmoplastic round cell tumor	t(11;22)(p13;q12)	*EWSR1-EWSR1*	>90
Endometrial stromal sarcoma	t(7;17)(p15;q11)	*JAZF1-SUZ12*	>65
	t(6;7)(p21;p15)	*JAZF1-PHF1*	unk
	t(6;10)(p21;p11)	*EPC1-PHF1*	unk
Undifferentiated endometrial sarcoma/"high grade endometrial stromal sarcoma"	t(10;17)(q22;p13); others	*YWHAE-FAM22A/B,* other partners	unk
Epithelioid hemangioendothelioma	t(1;3)(p36.3;q25)	*WWTR1-CAMTA1*	>90

(continued)

Table 1.1 (continued)

Sarcoma subtype	Genetic alteration	Affected gene(s)	Frequency (%)
Epithelioid sarcoma (distal, proximal)	*INI1* inactivation [22(q11.2)]	*hSNF5/INI1*	>80
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*EWSR1-NR4A3*	>80
	t(9;17)(q22;q11)	*TAF15-NR4A3*	unk
	t(9;15)(q22;q21)	*TCF12-NR4A3*	unk
Ewing sarcoma/PNET[a]	t(11;22)(q24;q12)	*EWSR1-FLI1*	85
	t(21;22)(q22;q12)	*EWSR1-ERG*	5–10
Fibromyxoid sarcoma (Evans' tumor)	t(7;16)(q33;p11)	*FUS-CREB3L2*	>70
	t(11;16)(p11;p11)	*FUS-CREB3L1*	<20
Sclerosing epithelioid fibrosarcoma	t(11;22)(p11;q12)	*EWSR1-CREB3L1*	60
	t(7;22)(q33;q12)	*EWSR1-CREB3L2*	30
	t(11;16)(p11;p11)	*FUS-CREB3L1*	10
Hybrid sclerosing epithelioid fibrosarcoma/ fibromyxoid sarcoma	t(7;16)(q33;p11)	*FUS-CREB3L2*	>95
Gastrointestinal stromal tumor	4q	*KIT* exon 11 mut	65
	4q	*KIT e*xon 9 mut	10
	4q	*PDGFRA* mut	10
		Other alteration (e.g., *BRAF* V600E,*SDHA/B/C/D* loss)	15
Giant cell tumor of tendon sheath	t(1;2)(p13;q37)	*COL6A3-CSF1*	>75
Glomus tumors (benign, malignant)	t(1;5)(p13;q32)	*MIR143-NOTCH2*	50
		MIR143-NOTCH3	9
		MIR143-NOTCH1	rare
Inflammatory myofibroblastic tumor[a]	t(2;19)(p23;p13.1)	*TPM4-ALK*	unk
	inv2(2)(p21p23)	*EML4-ALK*	
	t(3;6)(q12;q22)	*TFG-ROS1*	
	t(1;2)(q22-23;p23)	*TPM3-ALK*	unk

Sarcoma subtype	Genetic alteration	Affected gene(s)	Frequency (%)
Myoepithelial tumors	t(6;22)(p21;q12)	*EWSR1-POU5F1*	10
	t(1;22)(q23;q12)	*EWSR1-PBX1*	5
	t(1;16)(p34;p11)	*FUS-KLF17*	unk
Myxoid–round cell liposarcoma	t(12;16)(q13;p11)	*FUS-DDIT3*	>90
	t(12;22)(q13;q12)	*EWSR1-DDIT3*	<5
Pericytoma with t(7;12)	t(7;12)(p22;q13)	*ACTB-GLI*	unk
(Extrarenal) rhabdoid tumor	del 22(q11.2)	*hSNF5/INI1*	~50
Synovial sarcoma	t(X;18)(p11;q11)	*SS18-SSX1/SSX2*	>95
		SS18-SSX4	<5
Well-differentiated/dedifferentiated liposarcoma	12q amplification	*CDK4, MDM2*, others	>80

[a]Other fusion partners or alterations are known; *mut* mutation, *unk* unknown, *FAP* familial adenomatous polyposis

se, as the sarcoma develops in the lymphedematous extremity outside the radiation field. Such (lymph)angiosarcomas also develop after chronic lymphedema, such as that seen with filarial infection [19].

It is difficult to identify whether trauma is a causative agent in soft tissue sarcoma as often an antecedent injury draws attention to the presence of a mass rather than being causative of the mass. This remains unproven although it does appear that the development of the desmoid tumor, which may be considered a fibroblastic hyperproliferation in response to injury, is more common in athletes.

Lastly, various chemical agents have long been utilized in the laboratory to develop sarcomas in murine models and have been implicated in the etiology of soft tissue sarcoma. The relationship between phenoxyacetic acids found in various herbicides is controversial and was highlighted because of the concern that dioxins were the active agents in "Agent Orange" utilized during the Vietnam War. While not proved, these data were suggestive of a relationship to chemical exposure. Chemical carcinogens are known to be associated with the development of hepatic angiosarcoma although rare. Thorotrast, vinyl chloride, and arsenic have all been incriminated, but more vigilant avoidance of these agents makes this diagnosis much less likely at the present time.

A recent summary of available data [20] concluded that strong associations were indentified for (1) HIV and the HHV8 infection associated with Kaposi sarcoma, (2) radiation therapy and development of soft tissue and bone sarcomas, and (3) suggestive evidence for hernias or craniofacial abnormalities in children such as cleft lip and their association with Ewing sarcoma, (4) occupational exposure to herbicides and chlorophenols and soft tissue sarcoma, and (5) an association of bone sarcomas with an occupation of blacksmiths, toolmakers, or machine-tool operators. Many of these associations require further validation.

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Chapter 2
Natural History: Importance of Size, Site, Histopathology

2.1 Natural History

The natural history of soft tissue sarcoma is highly influenced by the site of the primary lesion, tumor histopathology, and tumor size. Multiple approaches have been developed to define outcome variables based on these factors, and as data accumulate with sufficient numbers, progressively more refined staging or predictive systems can be provided for rare tumors with multiple variables.

2.2 Influence of Site

The anatomic site of the primary lesion is clearly a determinant of outcome. This is most dramatically illustrated when one looks at the risk of local recurrence at various sites (Fig. 2.1). Retroperitoneal and intra-abdominal lesions have a significant risk of local recurrence, whereas extremity lesions have a much lower risk. When one considers disease-specific survival (Fig. 2.2), it is clear that disease-specific survival in retroperitoneal lesions is associated with similar prevalence to local recurrence, whereas for visceral lesions, systemic disease is the cause of death as local recurrence is relatively infrequent. This emphasizes the value of prospective, long-term databases in determining aspects of biology as well as outcome.

2.3 Staging

Staging of soft tissue sarcoma continues to evolve. Most staging systems depend on the grade and presence or absence of metastasis. The original soft tissue sarcoma staging system was based on data from 1977 (Fig. 2.3). Stage was subdivided based

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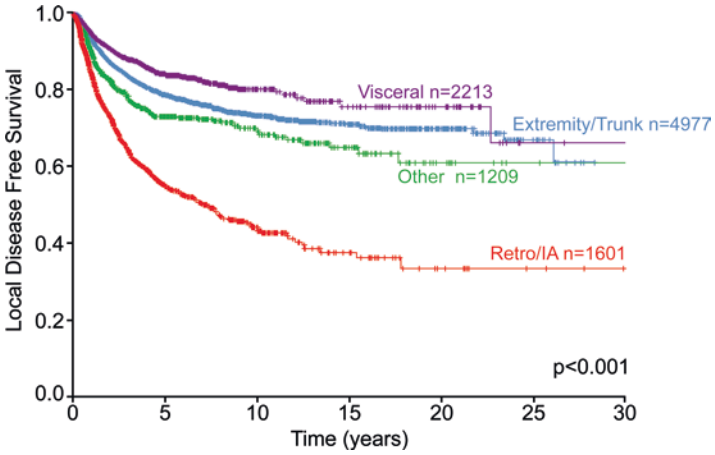

Fig. 2.1 All adult sarcomas, local disease-free survival by site. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$

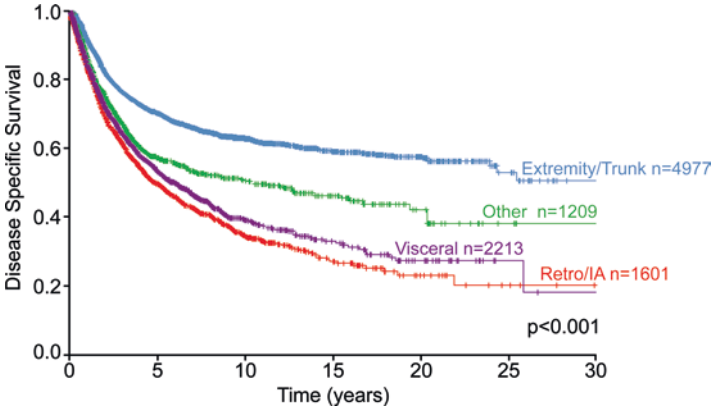

Fig. 2.2 All adult sarcomas, disease-specific survival by site. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$

on the primary size of the initial tumor, into categories of <5 and >5 cm (T1/T2). By 1992, the absence or presence of nodal metastasis was included (N0/N1).

It became progressively clear that tumors of very small size have a much better prognosis than was predicted by the initial AJCC staging system. Small (<5 cm) high-grade lesions (Fig. 2.4) have a favorable local recurrence-free survival similar to low-grade lesions. Small, low-grade tumors have a negligible risk of death from sarcoma, and small high-grade tumors have a 10-year disease-specific survival of approximately 80 % (Fig. 2.5) [1]. We have shown that grade, depth, and size are independent predictors of outcome, and most systems base the risk of developing distant metastases giving each factor equal weight. However, tumor grade is dominant

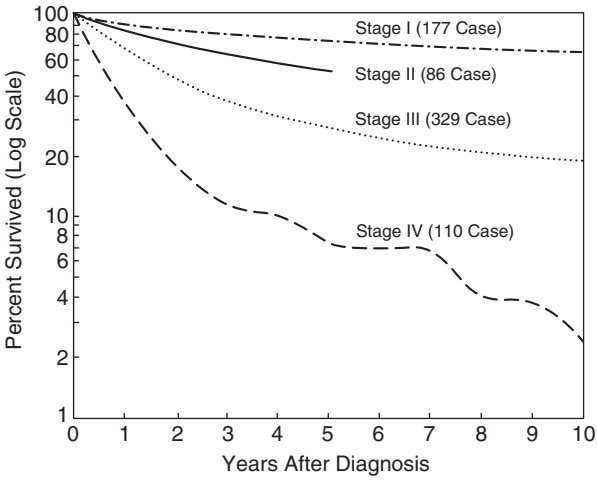

Fig. 2.3 1977 AJCC staging system. From: Russell WO, et al. Cancer 40:1562–1570, 1977

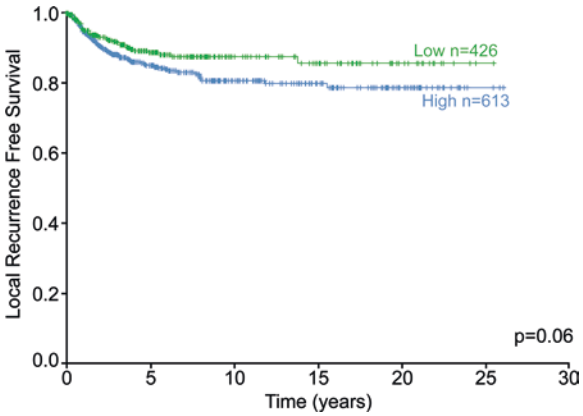

Fig. 2.4 Local recurrence-free survival, primary extremity ≤5 cm, by grade. MSKCC 7/1/1982–5/31/2013 $n = 1039$

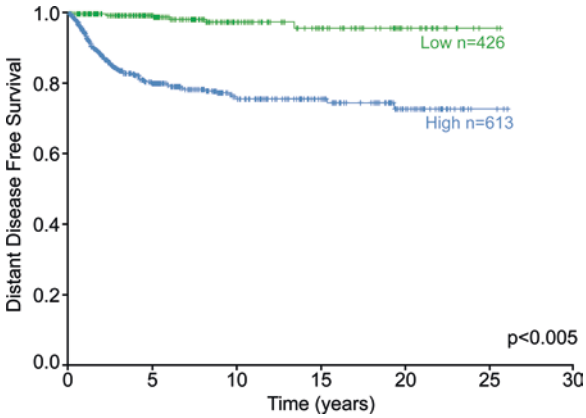

Fig. 2.5 Distant disease-free survival, primary extremity ≤5 cm, by grade. MSKCC 7/1/1982–5/31/2013 $n = 1039$

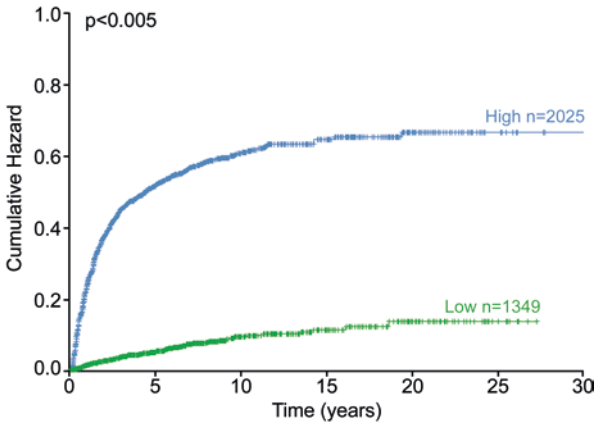

Fig. 2.6 Distant metastasis, extremity primary and local recurrent by grade. MSKCC 7/1/1982–5/31/2013 $n = 3374$

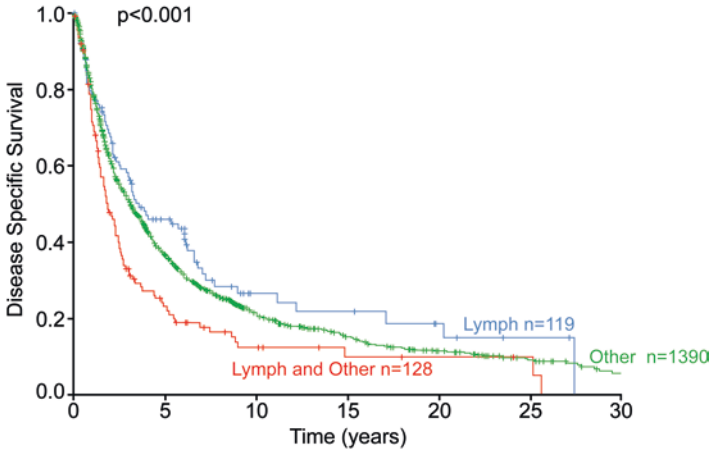

Fig. 2.7 Disease-specific survival by lymph node metastases alone or with other metastasis and other metastasis MSKCC 7/1/1982–5/31/2013 $n = 1637$

in the initial presentation, where patients with high-grade lesions are more likely to have an early distant metastasis, whereas patients with lower grade but large tumors have progressive and prolonged risk of metastatic recurrence (Fig. 2.6) [2, 3]. Early metastatic disease is dominated by the grade of the tumor.

The outcome for patients with lymph node metastasis is similar, but not identical, to patients with other metastases (Fig. 2.7). It is important to emphasize that lymph node metastasis is infrequent in soft tissue sarcoma (Table 2.1) with an overall prevalence of <5 % for all sarcomas and occurring predominantly in those having epithelioid features. There clearly are patients with limited nodal metastasis who are salvaged by resection and such patients tend to do better than those with metastasis to other sites (Fig. 2.7).

Table 2.1 Histologic type of sarcomas and lymph node metastasis

	No of nodal metastases/all sarcoma patients			% of all lesions		
Histologic findings	Weingrad[a]	Mazeron[b]	This study[c]	Weingrad	Mazeron	This study
Fibrosarcoma	55/1083	54/215	0/162	5.1	4.4	0
Malignant fibrous histiocytoma	1/30	84/823	8/316	3.3	10.2	2.6
Undifferentiated spindle cell	–	–	0/42	–	0	–
Rhabdomyosarcoma (all types)	108/888	201/1354	–	12.2	14.8	–
Rhabdomyosarcoma (non embryonal)	–	–	1/35	–	–	2.9
Embryonal rhabdomyosarcoma	–	–	12/88	–	–	13.6
Leiomyosarcoma	10/94	21/524	9/328	10.6	4.0	2.7
Malignant peripheral nerve sheath tumor	0/60	3/476	2/96	0	0.6	2.1
Vascular	–	43/376	–	–	11.4	–
Angiosarcoma	–	–	5/37	–	–	13.5
Hemangiopericytoma	3/23	–	0/21	13.0	–	0
Lymphangiosarcoma	–	–	1/4	–	–	25.0
Osteosarcoma	20/327	–	0/11	6.1	–	0
Chondrosarcoma	–	–	1/46	–	–	2.2
Synovial sarcoma	91/535	117/851	2/145	19.1	13.7	1.4
Epithelioid sarcoma	–	14/70	2/12	–	20	16.7
Liposarcoma	15/288	16/504	3/403	5.7	3.2	0.7
Alveolar soft part sarcoma	6/62	3/24	0/13	9.7	12.5	0
Clear cell sarcoma	–	11/40	–	–	27.5	–
Other	11/125	–	0/27	8.8	–	0
Total	320/3515	567/5257	47/1772	9.1	10.8	2.6

MPNST malignant peripheral nerve sheath tumor

Adapted from: Fong Y, Coit DG, Woodruff JM, Brennan MF. Ann Surg 218:72–77, 1993

Review of past studies of nodal metastasis from sarcomas and current study

[a]Adapted from a review by Weingrad and Rosenberg summary of 47 studies (Weingrad DN, et al. Surgery 1978; 84:231–240)

[b]Adapted from a review of Mazeron and Suit summary of 122 studies (Mazeron JJ, Suit HD. Cancer 1987; 60:1800–1808)

[c]Database only includes extraskeletal osteo- and chondrosarcomas

Table 2.2 Cox proportional hazard regression analysis for disease-specific survival including all database patients

Variable	Categories	*p* value	HR	95 % CI for HR
Age	<54.4, ≥54.4 years (median)	<0.001	0.749	0.641–0.874
Gender	Male, female	0.914	–	–
Anatomic primary site	Other site, retroperitoneal and visceral, extremity	0.005	1.221	1.061–1.405
Primary tumor size (cm)	>15, >10–15, >5–10, <5	<0.001	1.198	1.106–1.299
Depth	Superficial, deep	0.166	–	–
Grade	Low, high	0.042	0.556	0.316–0.978
Metastatic disease	None, nodal metastases (N1M0), other metastases (N0M1), both nodal and other metastases (N1M1)	<0.001		
	N0M0 vs. N1M0	0.011	0.392	0.190–0.807
	N1M0 vs. N0M1	<0.001	0.197	0.109–0.353
	N1M0 vs. N1M1	0.613	–	–

With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–83
Tumors >10 cm were excluded if their exact sizes were not specified
HR hazard ratio; *95 % CI* 95 % confidence interval—omitted since not statistically significant

A study comparing three different staging systems [4] was published in 2000. At that time, the authors found that depth, grade, and size were significant prognostic indicators and that inclusion of these criteria could better define patients who might benefit from systemic therapy. This was in contradistinction to the Musculoskeletal Tumor Society study [5], which employed a staging system based on extra compartmental extension (which is itself influenced by size).

Disease-specific survival including all patients from our database (Table 2.2) suggests age, site, size, grade, nodal metastases alone and systemic metastases alone, but not N1 M1, to all be independent predictors of survival (Fig. 2.8). All categories, local disease-free survival, recurrence-free survival, and disease-specific survival, are shown in Fig. 2.9. In the AJCC Staging Manual, 8th edition, depth was removed as a stratification factor, given its lesser role in recurrence compared to grade and primary tumor size. However, disease-specific survival is still influenced by both size and depth in our own analyses (Fig. 2.10 and Table 2.2).

Grade has historically been a dominant factor in outcome for soft tissue sarcoma. Previous AJCC systems used four grade levels, but this has been effectively functioning as a two grade system, i.e., grades I and II as low grade, and grades III and IV as high grade. This was the system employed at Memorial Sloan Kettering for many years with good discrimination. Grade is interpreted not only by differentiation, but also by specific histological subtype, mitotic rate, and degree of necrosis.

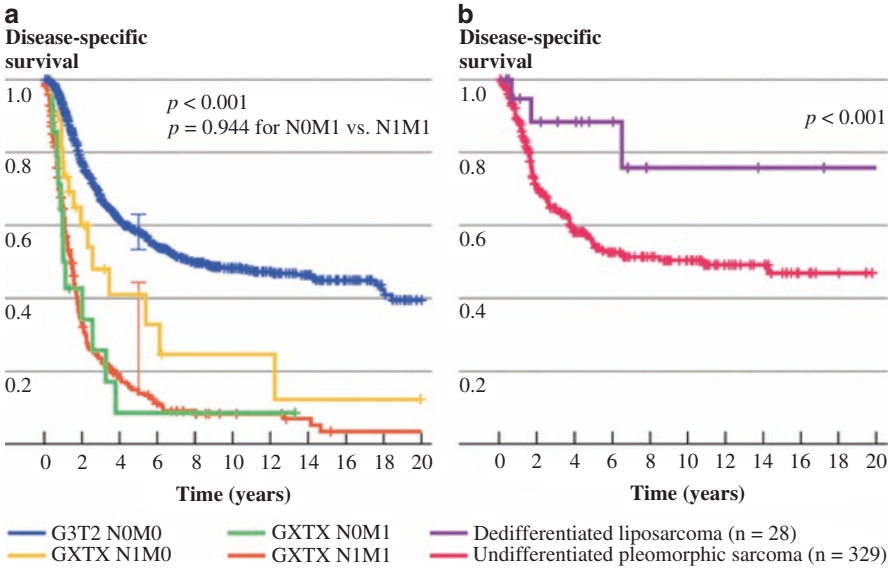

Fig. 2.8 (**a**) Disease-specific survival comparing G3T2N0M0 primary STS to GXTXN1M0 and GXTXN1M1 STS, $n=1440$ total; G3T2N0M0 disease ($n=1123$), GXTXN1M0 ($n=33$), GXTXN1M1 ($n=15$), and GXTXN0M1 disease ($n=269$); log rank, $p<0.001$. Comparing GXTXN0M1 and GXTXN1M1 patients; log rank, $p=0.944$. 95 % confidence intervals are noted at 5 years for the two largest groups; they are not meaningful for the smallest groups with so few events. (**b**) Disease-specific survival comparing extremity dedifferentiated liposarcoma ($n=28$) and undifferentiated pleomorphic sarcoma ($n=329$); log rank, $p<0.001$. With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–3383

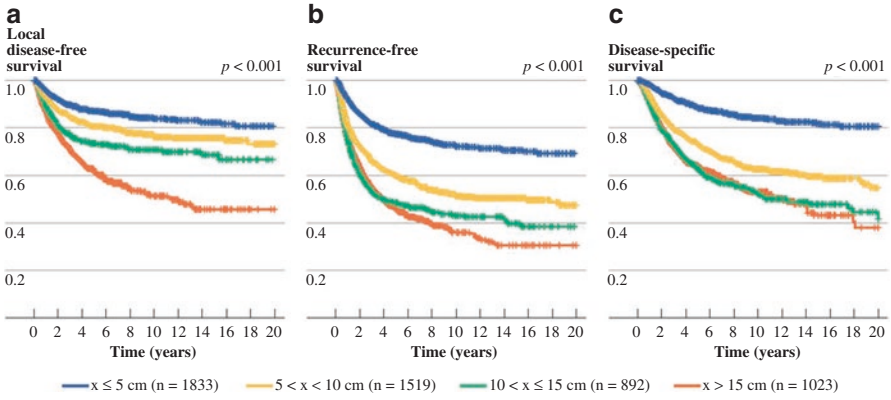

Fig. 2.9 Local recurrence-free survival (RFS), overall recurrence-free survival, and disease-specific survival (DSS) by size category, ≤5, 5–10, 10–15, and >15 cm. (**a**) Local recurrence-free survival (time from primary surgery to first local recurrence), $n=5267$ patients, excludes 75 patients with unknown size categories; log rank, $p<0.001$. (**b**) Recurrence-free survival (time from primary surgery to first local or distant recurrence), $n=5267$, excludes 75 patients with unknown size categories; log rank, $p<0.001$. (**c**) Disease-specific survival (time from primary surgery to death from disease), $n=5267$, excludes 75 patients with unknown size categories; log rank, $p<0.001$; log rank, p value $=0.91$ comparing >10–15 and >15 cm groups. With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–3383

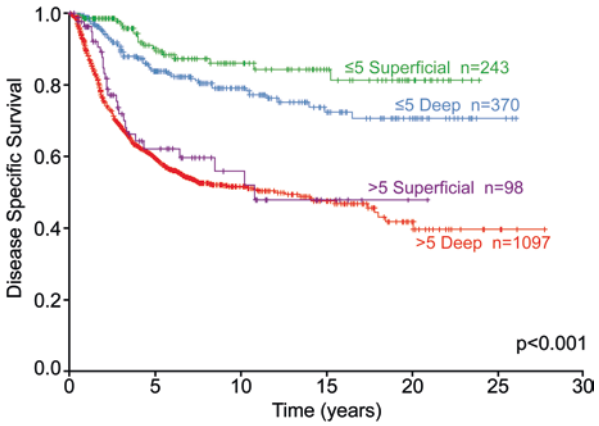

Fig. 2.10 Disease-specific survival, primary extremity high grade, by size and depth. MSKCC 7/1/1982–5/31/2013 $n = 1808$

The AJCC staging system, 8th edition, continues to incorporate the FNCLCC three-tier grading system, though the 8th edition of the AJCC system for extremity and trunk tumors still has a dichotomy in that both grade 2 and 3 tumors are considered higher-risk tumors.

The FNCLCC grading system (Fédération Nationale des Centres de Lutte Contre le Cancer) is determined by three different parameters, specifically differentiation, mitotic activity, and extent of necrosis. Each parameter is then scored and the sum yields score used to assign grade. Specifically, differentiation is scored 1–3, mitotic activity scored 1–3, and necrosis scored 0–2. Summation then makes grade I (2 or 3 points), grade II (4 or 5 points), and grade III (6–8 points). Most encouraging is the attempt to place measurable numbers on the mitotic count, i.e., a score of 1 for 0–9 mitoses per 10 high-powered fields, score 2 for 10–19 mitoses per 10 high-powered fields, and score 3, 20 or more mitoses per 10 high-powered fields. A score of 2 is defined by histologic type, much as some sarcomas are automatically classified as high grade by their cellular subtype. The functional outcome of this grading system is that grade I—II tumors are tumors of defined histological types with less than 10 mitoses per 10 high-powered fields and no tumor necrosis, whereas grade III tumors require lack of differentiation and greater than 10 mitoses and some tumor necrosis. All others then become intermediate lesions.

For trunk, extremity, head, and neck primary alone, local disease-free survival, recurrence-free survival, and disease-specific survival are illustrated in Fig. 2.11. These differences in outcome were a significant reason in justifying separating soft tissue sarcoma staging systems by anatomic site. As more variables are added, staging systems become exponentially more complex, an argument that relies on new tools such as nomograms or Bayesian belief networks for risk estimation.

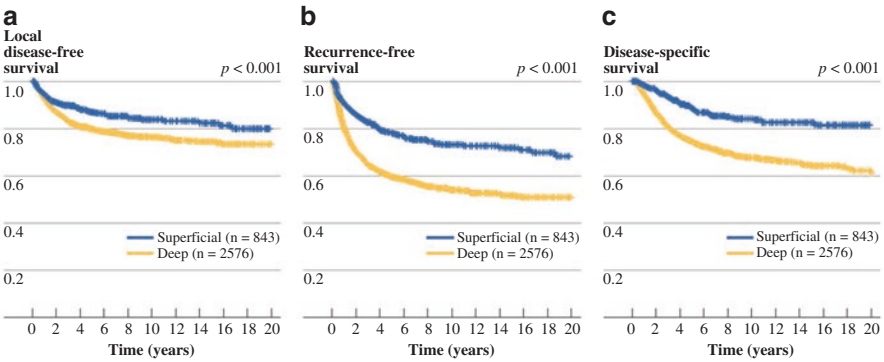

Fig. 2.11 (**a**) Local relapse-free survival (time from primary surgery to first local relapse, trunk/extremity/head-neck primary sites only). $n = 3419$, excludes six patients with unknown size categories; (**b**) Recurrence-free survival (time from primary surgery to first local or distant relapse, trunk/extremity/head-neck primary sites only), $n = 3419$, excludes six patients with unknown size categories; (**c**) Disease-specific survival (time from primary surgery to death from disease, trunk/extremity/head-neck primary sites only), $n = 3419$, excludes six patients with unknown size categories. With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–3383

(see Prognostic Factors—Nomograms below) In principle, single histology staging systems should provide the most accuracy in prognostication. While difficult to achieve, GIST and rhabdomyosarcoma stand out as two histologies in which histology-specific staging systems exist; the AJCC version 8 staging system is the first to reference a nomogram to aid in staging, in the case of retroperitoneal sarcomas.

Neurovascular and bone invasion are negative prognostic factors, but are not included in current staging systems. Molecular markers are currently being evaluated as determinants of outcome, but are not part of traditional staging systems; *KIT* or *PDGFRA* mutation will likely be incorporated in future iterations of the staging system for GIST, but no such markers have been found with such impact in other soft tissue sarcomas. Given their importance in defining characteristics of a variety of soft tissue sarcomas, molecular markers are discussed in the histology-specific sections that follow.

2.4 Staging of Retroperitoneal and Visceral Sarcoma

As noted immediately above, it is important to emphasize that no adequate staging system to date has specifically addressed retroperitoneal or visceral sarcomas; this was the impetus behind changes to the AJCC version 8 staging system for soft tissue sarcomas, which now employs a nomogram to stage retroperitoneal sarcomas, based on development and validation of a nomogram across multiple large volume institutions. In addition, there is a separate staging system for visceral soft tissue sarcomas.

These nomogram data highlight the data that while death from local recurrence is possible with a large, low-grade tumor, death from visceral lesions is usually from systemic disease. This emphasizes the importance of approaches to therapy, as the predominant factor in outcome for retroperitoneal sarcoma is the adequacy of the initial resection. Without complete gross resection, essentially all patients recur regardless of grade. Only following complete resection does grade become a factor for outcome, i.e., high that are completely resected. This finding is consistent with the fact that many of the high-grade lesions have a risk of metastatic spread.

We have previously described the factors that influence outcome for primary retroperitoneal patients [6]. Local recurrence-free survival for such lesions is summarized in Table 2.3 and distant metastasis-free survival in Table 2.4. Important

Table 2.3 Analysis of local recurrence-free survival in 231 primary retroperitoneal sarcoma patients with resectable disease

	N	*p* value* (univariate)	*p* value (multivariate)	Relative risk[a] (95 % CI)
Sex		0.06		
Male	140			
Female	91			
Age		0.9		
>50 years	156			
<50 years	75			
Grade		0.05		
High	134		0.01	2.1 (1.2–3.4)
Low	97			
Size		0.07		
>10 cm	170			
≤10 cm	59			
Histologic subtype		0.02		
Liposarcoma	109		0.01	2.6 (1.5–4.6)
Others	58			
Leiomyosarcoma	48			
Fibrosarcoma	16			
Surgical resection margins		0.2		
Negative micro and gross margins	136			
Positive micro and negative gross margins	49			
Positive micro and gross margins	46			

95 % CI 95 percent confidence interval
From: Lewis JJ, Leung D, Woodruff JM, Brennan MF. Ann Surg 228:355–365, 1998
*Univariate p refers to log rank test of no difference vs. any difference between categories
[a]Relative risk to other categories of the same factor

Table 2.4 Analysis of distant metastasis-free survival in 231 primary retroperitoneal sarcoma patients with resectable disease

	N	*p* value* (univariate)	*p* value (multivariate)	Relative risk[a] (95 % CI)
Sex		0.8		
Male	140			
Female	91			
Age		0.8		
>50 years	156			
<50 years	75			
Grade		0.01		
High	134		0.01	5.0 (1.7–15)
Low	97			
Size		0.06		
>10 cm	170			
≤10 cm	59			
Histologic subtype		0.01		
Liposarcoma	109		0.01	0.2 (0.07–0.7)
Others	58			
Leiomyosarcoma	48			
Fibrosarcoma	16			
Surgical resection margins		0.01		
Negative micro and gross margins	136			
Positive micro and negative gross margins	49			
Positive micro and gross margins	46		0.01	3.9 (1.6–9.5)

95 % CI 95 percent confidence interval
From: Lewis JJ, Leung D, Woodruff JM, Brennan MF. Ann Surg 228:355–365, 1998
*Univariate p refers to log rank test of no difference vs. any difference between categories
[a]Relative risk to other categories of the same factor

sites of metastasis include the lung and liver. Once metastasis develops, survival is poor, at a median of 13 months (Fig. 2.12). It is important to emphasize that recurrence is common in retroperitoneal tumors, such primary sarcomas can occur late, and that many patients can undergo further resection, which is associated with prolonged survival (Figs. 2.2 and 2.1). The complete resection rate diminishes with each subsequent local recurrence (Fig. 2.13). If one looks at multivariate analysis of disease-specific survival of patients who undergo complete resection, the important factors for overall survival include grade and size, as emphasized previously (Table 2.5). These and other data have directly impacted upon the AJCC version 8 sarcoma staging systems.

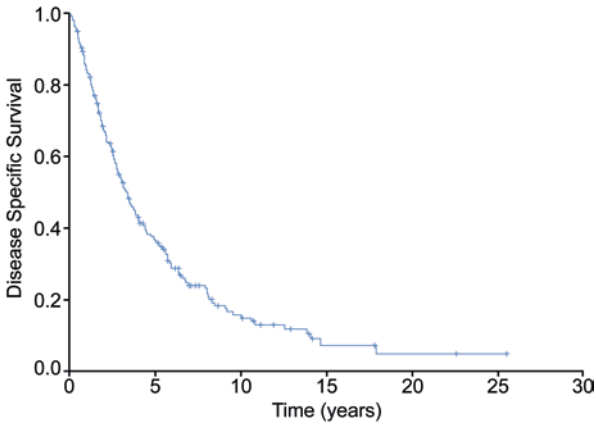

Fig. 2.12 Disease-specific survival for retroperitoneal sarcoma who had operation at MSKCC ($n = 899$) and then developed metastases ($n = 196$). MSKCC 7/1/1982–5/31/2013

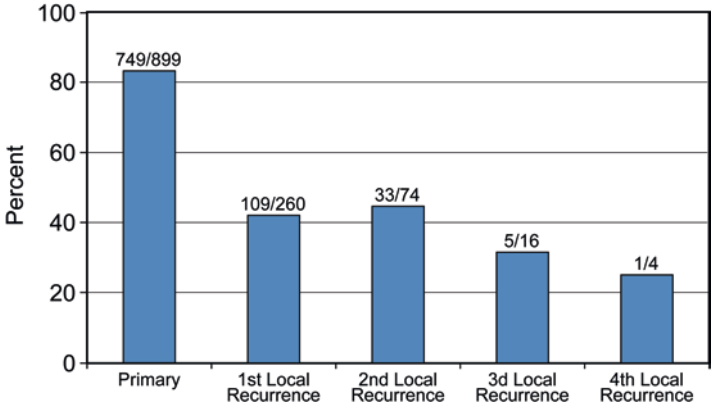

Fig. 2.13 Complete resection rate at primary operation and then following recurrence. MSKCC 7/1/1982–5/31/2013

2.5 Prognostic Factors for Extremity and Superficial Soft Tissue Sarcoma

Highlighting outcomes that eventually were incorporated into sarcoma staging systems, we published [7] an analysis of a single institution study of over 1000 patients with extremity soft tissue sarcoma treated between 1982 and 1994. In this analysis, patient, tumor, and pathological factors were all analyzed by univariate and multivariate analysis to better define prognostic factors for local recurrence, metastatic recurrence, death from sarcoma, and post-metastasis survival. Prognostic factors identified are illustrated in Table 2.6. It was clear that age >50, recurrent presentation, positive initial microscopic margin, and the histopathological subtype of fibrosarcoma or malignant peripheral nerve tumor were all factors in multivariate

Table 2.5 Analysis of disease-specific survival in 278 primary retroperitoneal sarcoma patients

	`	*p* value* (univariate)	*p*-value (multivariate)	Relative risk[a] (95 % CI)
Sex		0.6		
Male	170			
Female	108			
Age		0.08		
>50 years	183			
<50 years	95			
Grade		0.001		
High	168			
Low	119		0.001	3.2 (2.0–5.0)
Size		0.2		
>10 cm	196			
≤10 cm	170		0.02	1.7 (1.1–2.7)
Histological subtype		0.08		
Liposarcoma	116			
Other	87			
Leiomyosarcoma	109			
Fibrosarcoma	22			
Surgical resection margins		0.001		
Negative micro and gross margins	136			
Positive micro and negative gross margins	49		0.001	4.7 (2.9–7.5)
Positive micro and gross margins	46		0.001	4.0 (2.5–6.5)

From: Lewis JJ, Leung D, Woodruff JM, Brennan MF. Ann Surg 228:355–365, 1998
*Univariate p refers to log rank test of no difference vs. any difference between categories
[a]Relative risk to other categories of the same factor

analysis and were associated with a higher risk of local recurrence. Local recurrence is not grade-dependent, and an analysis of extremity lesions is shown in (Fig. 2.14). Local recurrence for all is approximately 25 %. Local recurrence by size is illustrated (Fig. 2.15), emphasizing the progressive increase in local recurrence as the lesion increases in size, whether low grade (Fig. 2.16) or high grade (Fig. 2.17).

2.6 Disease-Specific Survival

Disease-specific survival or death from disease can be characterized by grade, size, and location, presence of positive margins, and local recurrence at presentation (Table 2.6). As with all of these issues, many of these factors are not arbitrary, but interdependent and continuous. For example in size, increase in size (Fig. 2.18) shows an increasing risk of disease-specific death.

Table 2.6 Prognostic factors in extremity soft tissue sarcoma—summary of significant adverse prognostic factors

Local recurrence	Distant recurrence	Post-metastasis survival	Disease-specific survival
LR at presentation	High grade	Size >10 cm	High grade
Positive margins	Size >5 cm		Size >10 cm
MPNST	Size >10 cm		Deep location
Age >50	Deep location		Positive margins
	LR at presentation		LR at presentation
			Lower extremity site
			MPNST
			Leiomyosarcoma

MSKCC 1982–1994 $n=1041$
MPNST malignant peripheral nerve sheath tumor
Adapted from: Pisters P, Leung D, Woodruff J, Shi W, Brennan MF. J Clin Oncol 14:1679–1689, 1996

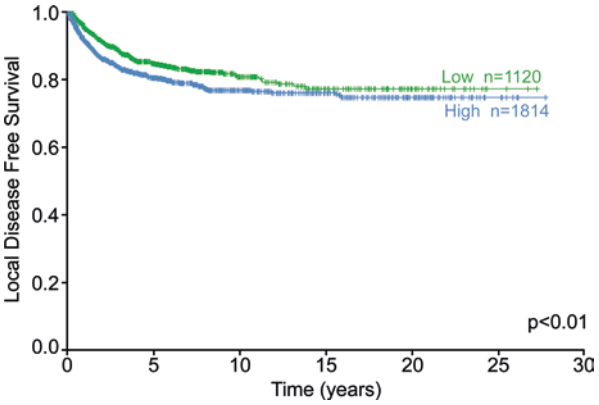

Fig. 2.14 Local disease-free survival for all primary extremity, by grade. MSKCC 7/1/1982–5/31/2013 $n=2934$

2.7 Prognostic Factors for Survival Following Local Recurrence of Extremity Sarcoma

Prognostic factors for outcome after a patient has developed a local recurrence have been defined [8]. We found that the median time to local recurrence was 19 months; 65 % of patients had developed local recurrence by 2 years and 90 % of all patients who will recur will do so within 4 years. Transition from low to high grade is uncommon and independent predictors for disease-specific survival after recurrence are high grade, the local recurrence tumor size, and the recurrence-free interval. Patients who developed a local recurrence >5 cm in less than 16 months had a

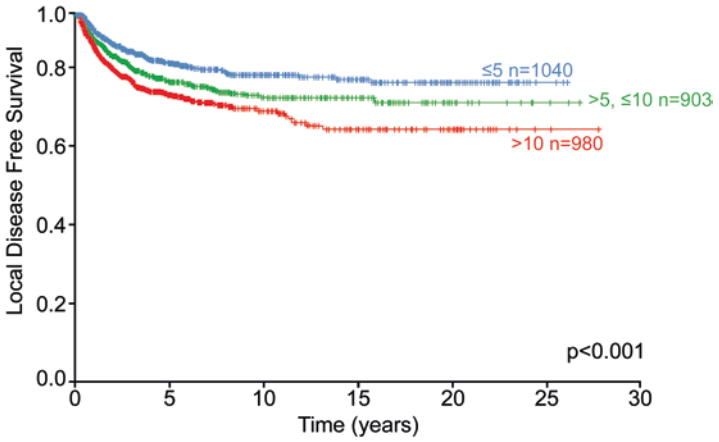

Fig. 2.15 Local disease- free survival for all primary extremity, by size. MSKCC 7/1/1982–5/31/2013 $n = 2923$

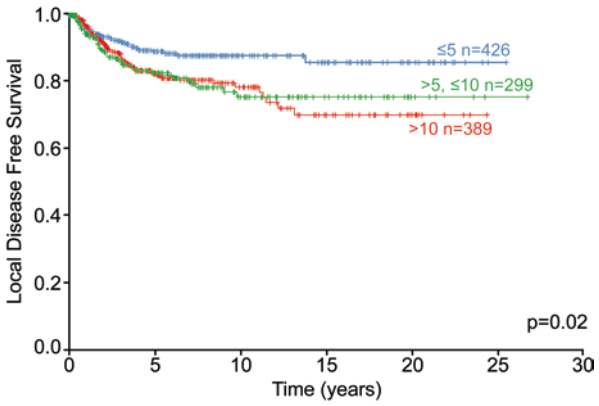

Fig. 2.16 Local recurrence-free survival primary extremity low grade, by size. MSKCC 7/1/1982–5/31/2013 $n = 1114$

4-year disease-specific survival of 18 % compared to 81 % for patients who developed a local recurrence less than or equal to 5 cm in greater than 16 months. These data are reflected in Figs. 2.19 and 2.20.

2.8 AJCC Staging

The 8th edition of the American Joint Commission on Cancer soft tissue sarcoma staging system is expanded from prior editions with a greater emphasis on site-specific staging than in previous editions. For example, from prior editions of the staging manual, since all retroperitoneal tumors are deep, the designation of superficial or deep is meaningless and is removed from the staging system(s) in the 8th edition. We will emphasize here the staging of extremity and trunk tumors, the most common primary

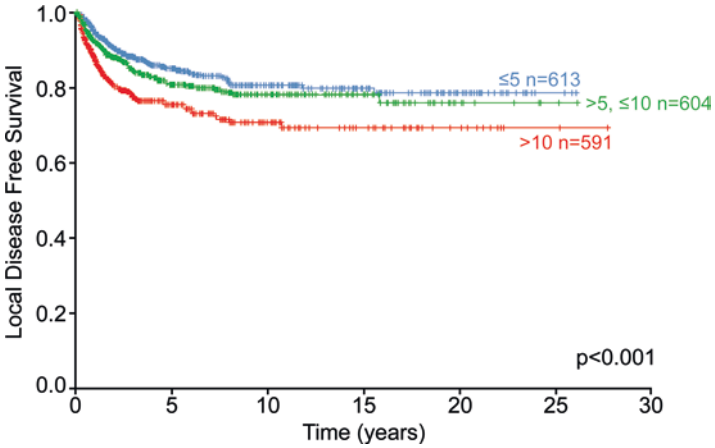

Fig. 2.17 Local recurrence-free survival for primary high-grade extremity, by size. MSKCC 7/1/1982–5/31/2013 $n = 1808$

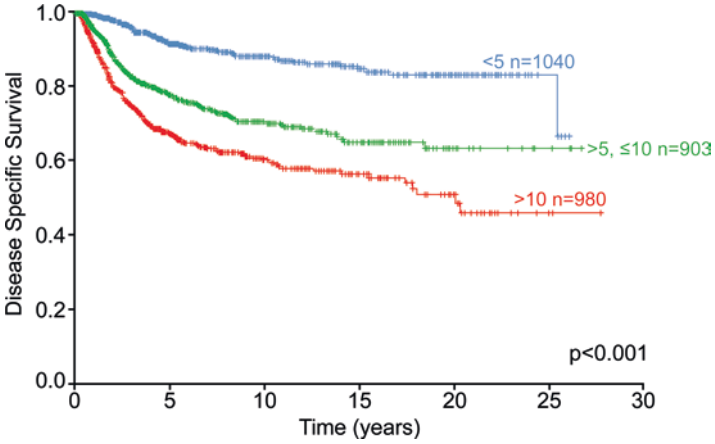

Fig. 2.18 Disease-specific survival all primary extremity, by size. MSKCC 7/1/1982–5/31/2013 $n = 2923$

site, and refer to the staging manual for a more detailed discussion of other anatomic sites, all of which are staged differently from extremity/trunk tumors.

Desmoid tumors and Kaposi sarcoma continue to be excluded from the staging system, given their very different biology compared to other soft tissue sarcomas. Nodal disease, included as stage IV in older editions, is considered stage IIIb in the 7th and 8th edition, although the differences in outcome between patients with nodal and other metastases are small (Fig. 2.7). This reclassification highlights the ability to cure some patients with lymph node metastasis alone with further treatment, usually surgical resection. Anatomic stage and prognostic groups for extremity and truncal

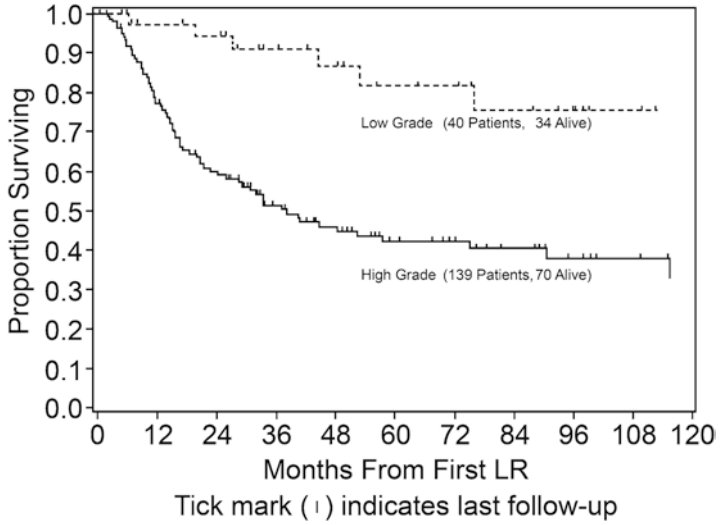

Fig. 2.19 Disease-specific survival extremity by primary tumor grade from time of local recurrence. From: Eilber FC, Brennan MF, Riedel E, et al. Ann Surg Oncol 12:228–236, 2005

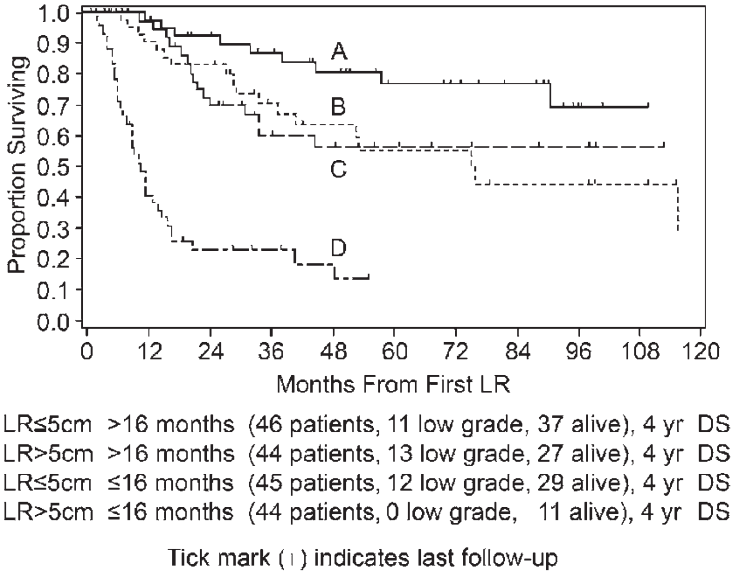

Fig. 2.20 Disease-specific survival extremity by local recurrence-free interval and size of local recurrence. From: Eilber FC, Brennan MF, Riedel E, et al. Ann Surg Oncol 12:228–236, 2005

Table 2.7 AJCC 8 staging system for extremity and trunk sarcoma (in press 2017)

T category	*T criteria*
Definition of primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension

N category	*N criteria*
Definition of regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M category	*M criteria*
Definition of distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

G	*G Definition*
Definition of grade (G)	
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3

Modified from Amin, M.B., Edge, S., Greene, F.L., et al. (Eds.) (2017) *AJCC Cancer Staging Manual*
Proposed for 8th Edition:
Stage Ia: T1; N0; M0; G1; GX
Stage Ib: T2;T3;T4; N0; M0; G1; GX
Stage II: T1; N0; M0; G2; G3
Stage IIIa: T2; N0; M0; G2; G3
Stage IIIb: T3; T4; N0; M0; G2; G3; Any T: N1; M0; Any G
Stage IV: Any T; Any N; M1; Any G

primary tumors are defined in Table 2.7. Prognostic groups are defined by T stage as 5 cm or less (T1), over 5 and up to 10 cm (T2), over 10 and up to 15 cm (T3), and over 15 cm in greatest dimension (T4), in keeping with data that metastasis and recurrence continue to increase in frequency in primary tumors larger than 5 cm, as we had shown previously [9]. (Figs. 2.21 and 2.22). T3 and T4 lesions are distinguished from one another by the increased local recurrence risk of T4 vs. T3 tumors, though the metastatic potential appears to plateau and is similar for both T3 and T4 tumors. It should

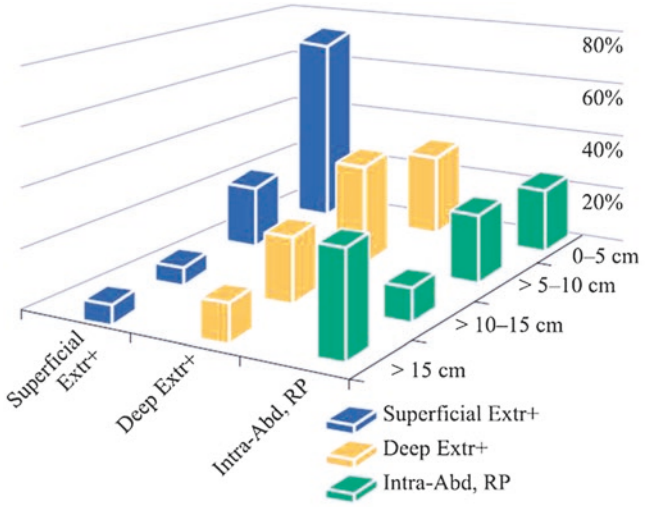

Fig. 2.21 Frequency of different size categories by superficial or deep site. All intra-abdominal, retroperitoneal, and visceral tumors are deep and are noted separately. Percentages of each tumor class by size are indicated. Extr + = extremity and head and neck, Intra-abd, RP = intra-abdominal, retroperitoneal, and visceral. With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–3383

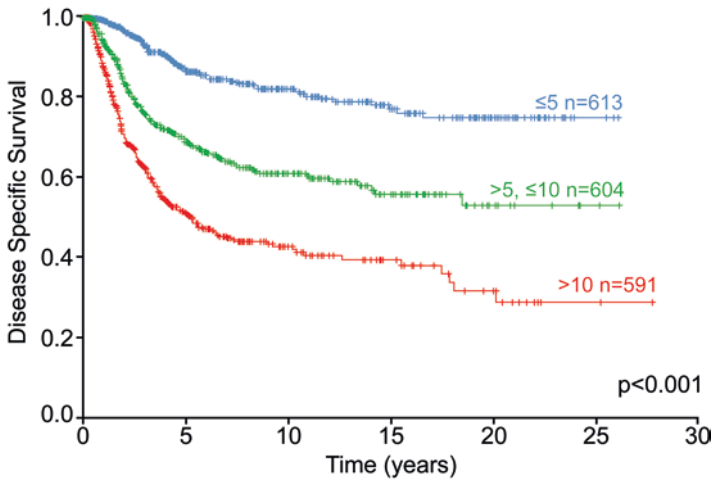

Fig. 2.22 Disease-specific survival, primary extremity high grade, by size. MSKCC 7/1/1982–5/31/2013 $n = 1808$. With permission from: Brennan MF, et al. Ann Surg 260(3):416–422, 2014

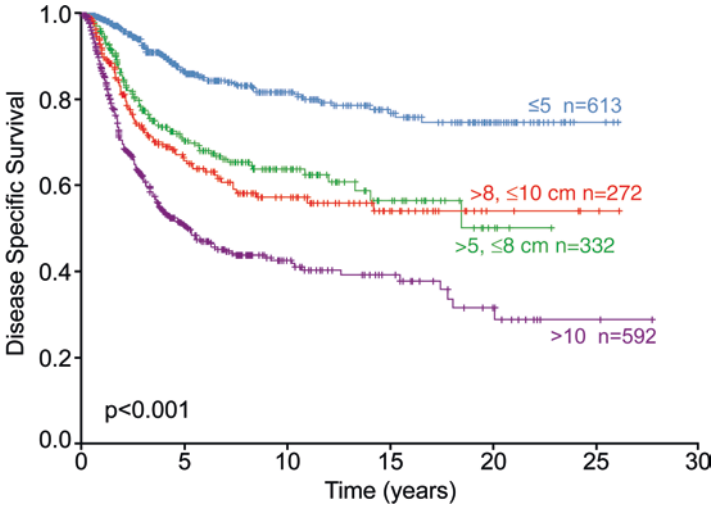

Fig. 2.23 Disease-specific survival, primary extremity high grade, by size. MSKCC 7/1/1982–5/31/2013 $n = 1808$

be emphasized that superficial lesions >5 cm are rare (< 1 %) in the extremity. Wherever possible, size should be recorded three dimensionally, since future efforts will be made to examine risk based on tumor volume (Fig. 2.23).

2.9 Prognostic Factors—Nomograms

Nomograms provide a powerful means to yield improved specificity of a given clinical outcome for an individual patient, but at the present time are available for a limited number of histological types and subtypes, e.g., liposarcoma and GIST, as well as for specific anatomic sites, such as retroperitoneum.

Nomograms are graphical representations of statistical models that provide the probability of outcome based on patient-specific covariates following specific treatment. They are usually expressed as time to a specific event, such as local recurrence or survival. They require large datasets in which there are a significant number of both negative and positive events and they require extended length of follow-up. We have been actively involved in defining nomograms for prediction of sarcoma outcome. As we have a defined population with defined outcomes, known risk factors, and selected covariates, we are able to construct such nomograms in a meaningful way.

Our initial attempt was a postoperative nomogram for 12-year sarcoma-specific death [10]. In that study, we were clearly able to utilize the multiple known factors of our large dataset to predict outcome. As there were only sufficient data for six defined histologies, i.e., fibrosarcoma, liposarcoma, leiomyosarcoma, synovial sar-

coma, undifferentiated pleomorphic sarcoma (UPS), and malignant peripheral nerve sheath tumor (MPNST), outcomes were only defined for these categories. Other barriers to defining outcomes better using nomograms include the knowledge that different liposarcoma subtypes each has distinct recurrence risk or chance of death and the definition of myxofibrosarcoma as a unique sarcoma subtype, differing from malignant fibrous histiocytoma, which is now itself called undifferentiated pleomorphic sarcoma (UPS) [10]. The original sarcoma nomogram subsequently has been validated using an independent dataset [11] and has been further validated by others [12].

Because of the multiple subtypes of liposarcoma, we developed a specific liposarcoma nomogram for disease-specific survival [13]. With larger data sets, nomograms can be developed to be site- or histology-specific, can be considered to develop in time-altered sequence, and have the potential to add biological variables. We further developed nomograms for probability of death from sarcoma following a local recurrence [14].

The use of nomograms has spread to other specific soft tissue tumor subtypes. Nomograms have been described for local recurrence of a soft tissue sarcoma without radiation, which will hopefully identify populations appropriate for a closer examination of radiation therapy [15]. More recently, a nomogram specific for uterine leiomyosarcoma has been developed [16]. An important nomogram has now been developed for the desmoid tumor, demonstrating the importance of size, site, and age, but not microscopic margin [17].

Nomograms have the potential to be utilized as a tool for evaluating the effects of treatment. While this requires validation by testing in a randomized trial, it has been suggestive [18] in our study of ifosfamide-based chemotherapy in adults with synovial sarcoma. Similar nomograms have been developed for predicting local recurrence both for all histologies and for desmoid tumors and can provide useful tools in patient management.

An alternative approach to yield better clinical prognostication is the development of Bayesian Belief Networks [19] where dominant factors in predication of survival and recurrence can be identified. Such networks can also identify within the network primary/dependent relationships.

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Chapter 3
General Statement as to Efficacy of Surgery, Chemotherapy, Radiation Therapy, and Immunotherapy

3.1 Extent of Primary Surgery

The principal management of primary soft tissue sarcoma is surgical resection. The clinical goal is resection with negative margins, preferably that extend 2 cm from the grossly determined border. This can be difficult to assess and is often limited by the presence of major neurovascular and bony structures. The majority of soft tissue sarcomas do not invade into bone unless there has been previous injury to bone or the lesion has an epithelioid component, such as synovial sarcoma.

When major arteries or nerves are involved, a decision must be made as to whether the morbidity of the procedure justifies the resection of an often negative vascular structure just because of proximity. We have been liberal in the resection of major veins, often not reconstructing them. The inferior vena cava can be resected without being replaced, and an excellent postoperative functional result obtained [1, 2]. The majority of soft tissue sarcomas do not invade into arterial structures but when they do, limited resection is possible. However, arterial invasion is rarely the primary determinant of outcome and there is usually a secondary component that limits the adequacy of the procedure. In the retroperitoneum, vascular structures can be surrounded by low grade liposarcoma (Fig. 3.1), often with ureteric encasement. In those situations, a judgment must be made as to function preservation vs. subsequent persistence or recurrence. When soft tissue tumors abut the periosteum, we have been liberal in removing the periosteum without further damage to the cortical bone. This can weaken the bone and increase the risk of subsequent fracture, especially in those receiving adjuvant radiation (Table 3.1).

The most extensive resection for extremity lesions is amputation. At present, this is only rarely indicated as the majority of extremity sarcomas can undergo a limb sparing operation with or without radiation therapy. The experience of our institution is illustrated in Fig. 3.2 showing that the 50% amputation in the late 1960s and 1970s is now less than 10%. It is important to understand that on occasion, amputa-

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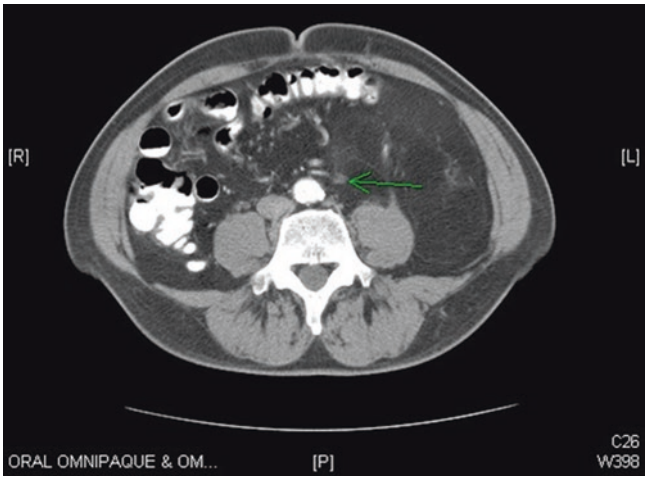

Fig. 3.1 CT of low grade liposarcoma surrounding superior and inferior mesenteric vessels, green arrow shows encased mesenteric artery

Table 3.1 Risk of bone fracture in soft tissue sarcomas of the extremity after radiation therapy

	n	Radiation therapy type	% Fracture
MSKCC [33]	369	Brachytherapy	4
University of Florida [76]	285	Preoperative	4
National Cancer Institute [77]	145	Postoperative	6
Princess Margaret Hospital [80]	364	Preoperative and postoperative	6

MSKCC Memorial Sloan Kettering Cancer Center

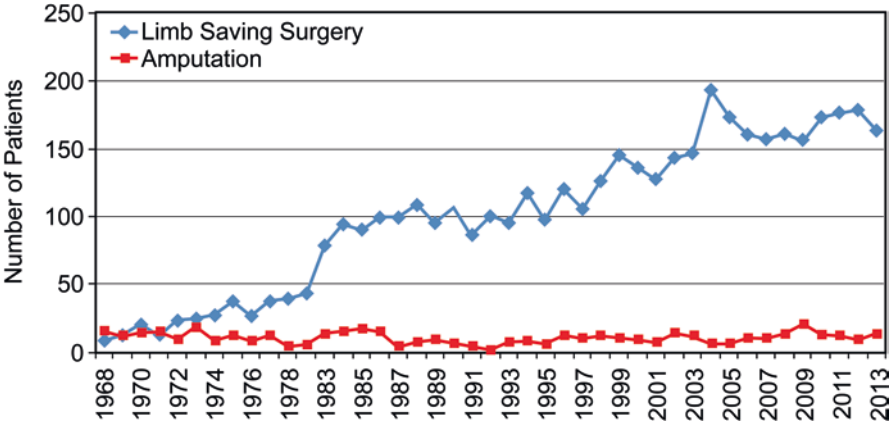

Fig. 3.2 Change in frequency of the need for amputation by time. MSKCC 1968–2013

tion is still indicated. In patients with large low grade tumors with no evidence of metastasis who present with fungating or painful extremities, amputation can be lifesaving.

We have examined the benefit of extending resections to take further organs, particularly intra-abdominally. This has not proven to be of benefit as the kidney parenchyma is rarely invaded by soft tissue sarcoma unless there has been a prior operation. In those situations where adherence to the capsule is obtained, the capsule of the kidney can be resected to improve the margin [3]. The resection of an organ just because it approximates the lesion to improve margin in one direction when the defining margin is limited in another does not make sense, in particular in sarcomas where local regional recurrence risk is already very high. Often in retroperitoneal tumors, the bowel is displaced and can be salvaged, but once an operation has taken place followed by recurrence, there is often serosal adherence and invasion, which is more difficult to manage without intestinal resection. Others [4–6] have argued strongly for extended resections. Drs. Gronchi, Bonvalot, and colleagues argue for more extended resection. In a series of 288 patients [7], while overall survival was not changed, the authors claim a decrease in local recurrence by more extended, liberal visceral resection. Interestingly, in the latter group with less local recurrence, metastases were more frequent. Unfortunately this question cannot be answered by any retrospective study. We believe that one should consider the concept of the least definitive margin as the margin that determines the ultimate outcome, rather than the extension of resection to normal organs such as bowel or kidney which can be resected, because function remains. The oncological concept that removing uninvolved organs, i.e., the "R0+ resection," can improve survival or freedom from recurrence is difficult to comprehend.

The extent of surgical resection and the uncommon major ablative resection, such as forequarter amputation and hindquarter resection, are described in greater detail in dedicated surgical texts [8].

3.2 Surgical Treatment of Local Recurrence

The treatment of local recurrence after a limb sparing operation is often technically feasible. Unfortunately, there is limited impact on long-term survival. We do know that early local recurrence of a high grade lesion is a very poor prognostic event. This is summarized in a paper from Eilber et al. [9]. Chapter 2, Fig. 2.20 shows the outcome of patients who have a late small recurrence vs. those with a large high grade recurrence. As anticipated, a large, high grade recurrence is associated with poor survival.

3.3 Diagnostic Imaging

Diagnostic imaging is presented along with the definitive pathologies in the text as they are encountered in turn. Imaging of the primary tumor is obtained from computerized tomography (CT) and magnetic resonance imaging (MRI). Both are

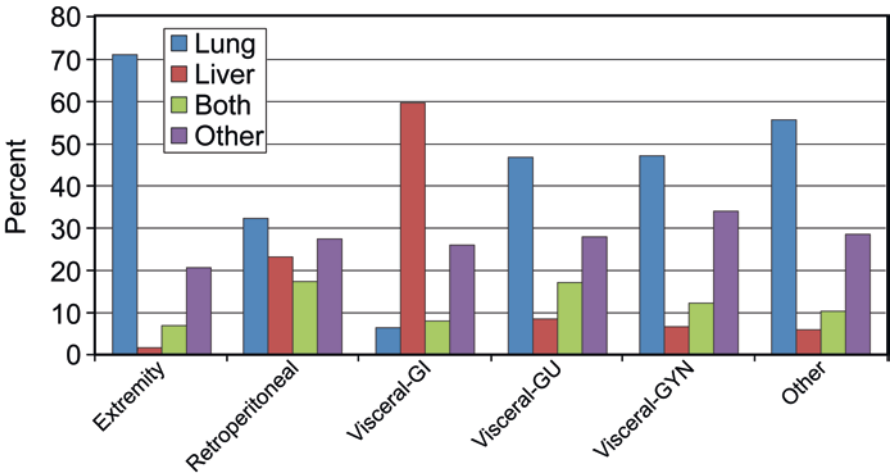

Fig. 3.3 Commonest sites of metastasis based on primary site. MSKCC 7/1/1982–5/31/2013, $n = 3802$, *GI* gastrointestinal, *GU* genitourinary, *GYN* gynecologic. With permission from: Brennan MF, et al. Ann Surg 260(3):416-422, 2014

reliable and provide varying information. As discussed below, addition of 18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) to CT imaging, and now MRI imaging, has added little in the evaluation of the primary sarcoma site, perhaps since nodal spread of disease is uncommon in most soft tissue sarcoma subtypes.

Comparative value of MRI vs. CT was studied by the Radiological Diagnostic Oncology Group (RDOG) where 367 patients were examined with both modalities, less than 4 weeks from operation [10]. When comparing the imaging characteristics both prior to the operation and in alternate institutions, similar information was obtained. No one modality was better than the other in determining whether or not the tumor involved bone, joint, or neurovascular structures. There was consistent but definite variability between individual reviewers. As this study was done in the early 1990s and CT and MRI imaging have markedly improved since then, one assumes the findings would be the same, although certainly the resolution in both modalities has markedly improved. Initially, MRI had the advantage of multiplanar imaging, but this result can now be achieved with CT reconstruction [10]. Currently, with the concerns over the radiation dose obtained from repeated CT imaging [11], many clinicians are moving progressively more to the utilization of MRI of the primary site.

Imaging is important in determining the extent of disease at primary presentation. We now know the sites of primary metastasis for most soft tissue sarcoma histologies. For example, 80 % of people with extremity lesions develop metastasis in the lung, often as the only site of metastatic disease. On the other hand, visceral lesions commonly result in liver metastasis (Fig. 3.3). FDG-PET is utilized, but has

not been as valuable as one initially hoped. It is possible to differentiate high vs. low grade primary sarcomas by FDG-PET, although there are false negatives and false positives in our experience [12]. FDG-PET may be used as a predictor of response to cytotoxic treatment in high grade lesions [13, 14] but in terms of imaging distant metastatic disease, it has been less valuable. Much of this is due to the fact that low grade liposarcoma has limited FDG-PET avidity and so the distinction between a low grade sarcoma and a lipoma is not able to be made. Conversely, high grade sarcomas are usually FDG-PET avid and this can help evaluate the extent of the disease and the presence or absence of metastasis from a high grade lesion.

Newer modalities for imaging remain investigational, e.g., FLT-PET and volumetric imaging. It is clear that existing radiological staging systems such as RECIST (Response Evaluation Criteria in Solid Tumors) do not capture the response to treatment well. RECIST uses the longest dimension of the tumor for response purposes, while it is clear that patients may have response (and thus benefit) in a dimension perpendicular to the long axis of the tumor, which is termed stable disease. Lesions can also change density with treatment, best demonstrated in the response of gastrointestinal stromal tumor (GIST) to tyrosine kinase inhibitors (the so-called Choi criteria), with the density changes (and not size changes) correlating best with responses by FDG-PET scans [15, 16].

3.4 Surgery for Metastatic Disease

3.4.1 Pulmonary Metastasis

The lung is the primary site of extremity sarcoma metastasis. It is much more common in high grade lesions, and on occasion development can be most rapid. An example is given in Fig. 3.4a, on the chest X-ray taken prior to resection of a high grade leiomyosarcoma of the left groin. Within 4 weeks (Fig. 3.4b) pulmonary metastases are identifiable in a chest X-ray, and a CT scan shows extensive pleural effusion and widespread metastasis with rapid progression and death within 6 weeks.

3.4.1.1 The Role of Pulmonary Metastatic Resection

Patients with high grade soft tissue sarcoma are at risk of metastatic disease. The dominant and often only first site of metastasis from extremity lesions is the lung. It has been previously proposed [17] that pulmonary metastatic resection is a valuable modality. Early reports [18] emphasized the important role of pulmonary resection.

Our initial report of 716 adult patients admitted with primary or local recurrence of extremity soft tissue sarcoma, 135 (19 %) patients had pulmonary metastasis as the initial or only site of distant recurrence [17]. At that time, the indications for pulmonary resection were: (1) the absence of or presence of a controllable primary

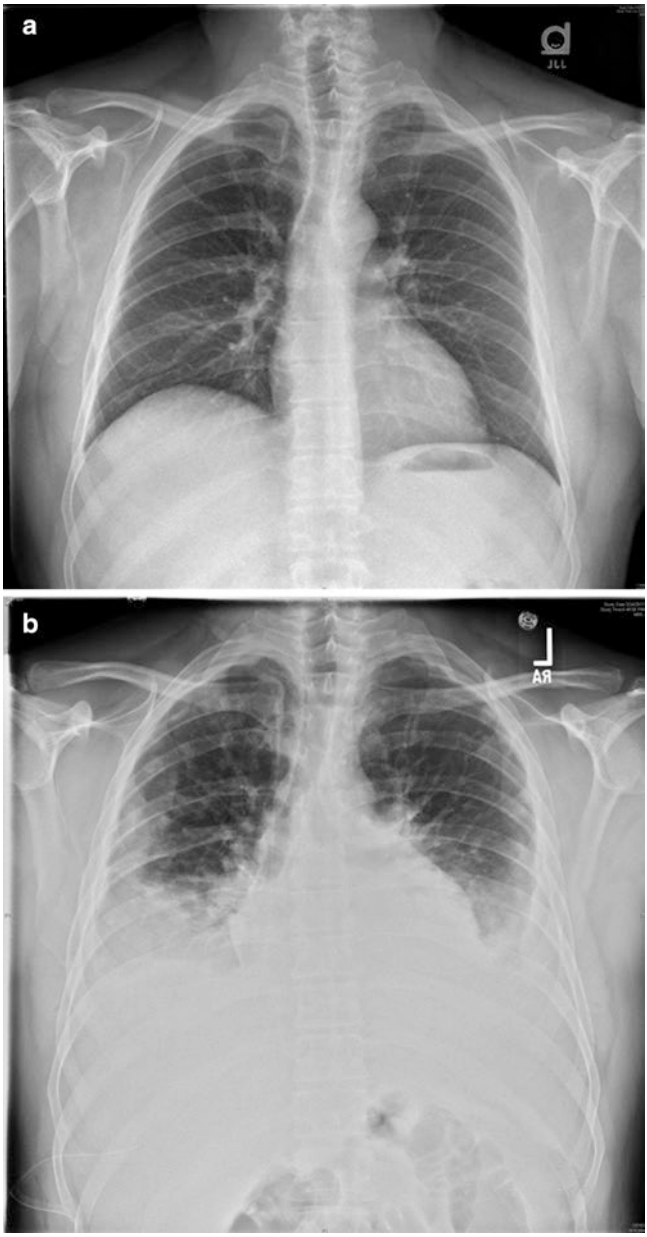

Fig. 3.4 Chest X-rays of rapid development of pulmonary metastases in a high grade leiomyosarcoma of the left groin, (**a**) pre resection, and (**b**) 6 weeks post resection

recurrence, (2) no known simultaneous distant metastases, (3) the ability, based on radiologic assessment, to anticipate complete removal of all metastasis, and (4) adequate pulmonary function to tolerate resection. Aggressive approaches with unilateral, bilateral, thoracotomy and mediastinotomy were performed.

Of the 135 patients, 112 were admitted for pulmonary tumor management and 23 for local resection of recurrent disease. Thirty percent of the patients presented with synchronous disease. Primary histological types when contrasted to the overall database suggested that pulmonary metastases were more common than their initially presenting prevalence in synovial sarcoma, spindle cell sarcoma (i.e., leiomyosarcoma and undifferentiated pleomorphic sarcoma) and less common in liposarcoma. Pulmonary metastasis was more likely to develop from large, high grade tumors. Of the 135 patients, 78 were treated with pulmonary resection, and 65 (or 83 %) could be completely resected. Resectability rate was not affected by age, sex, disease-free interval, presentation, size, or grade. The overall median survival for the 135 patients was 12 months with a 7 % 3-year survival rate. Of the 65 patients who were completely resected, the median survival was 19 months and the 3-year survival was 23 %. However, two-thirds of the patients who had completely resected pulmonary metastases had a second pulmonary recurrence with a median disease-free interval of 4 months. So if we consider the 135 patients who had pulmonary metastases as the initial and only identified site of recurrence, 86 % of those were treated and 78 were treated surgically (58 %). Of the 78, 65 (83 %) underwent a complete resection and of those 23 % were alive at 3 years. So of the initial 135 patients, 15 (11 %) of the original presenting cohort with pulmonary or lung disease were alive at 3 years.

A follow-up study [19] examined over 3000 patients with soft tissue sarcoma admitted and treated at Memorial Sloan Kettering Cancer Center, of which 719 developed or presented with lung metastases. The prevalence of lung metastasis from soft tissue sarcoma is highly dependent on the original site of the lesion. The most dominant primary site of those developing pulmonary metastasis is the extremity (Table 3.2). In addition, lung metastasis from soft tissue sarcoma varies according to the original histopathology with leiomyosarcoma and synovial sarcoma the most common (Table 3.3). Overall disease-specific survival has a median of 15 months. In 719 examined patients, the value of resection is outlined in Fig. 3.5. An aggressive approach to resection was taken. Median survival from diagnosis of pulmonary metastasis for all patients was 15 months with a 3-year actuarial survival of 25 %. Patients treated with complete resection had a median survival of 33 months and 3-year actuarial survival of 46 %. Negative factors for survival included liposarcoma, malignant peripheral nerve tumors, and patients over the age of 50. Patients who did not undergo a complete resection had only marginal survival benefit over those who did not have any resection. Of the 138 patients evaluable for 5-year survival, 14 % were alive. That analysis showed disease-free interval greater than 12 months was a favorable factor for prolonged survival. Patients who underwent complete resection had a median survival of 33 months. However, of the total presenting with pulmonary metastasis, only 161 could undergo complete resection (22 %).

Table 3.2 Lung metastases from soft tissue sarcoma: incidence by primary site for all patients with pulmonary metastases

Primary Site	Total no. of patients (%)	Patients with lung metastases (% of total)	% of All lung metastases
Extremity/trunk	1837 (58)	474 (26)	65
Retroperitoneal	466 (15)	63 (14)	9
Thoracic	193 (6)	44 (23)	6
Visceral-GI	206 (7)	12 (6)	2
Visceral-GYN	172 (6)	65 (38)	9
Visceral-GU	101 (3)	23 (23)	3
Head and neck	141 (5)	25 (18)	4
Skin/Others	33 (1)	13 (36)	2
TOTAL	3149	719	100

From: Billingsley KG et al. Ann Surg 229 (5):602-612, 1999

Outcomes for patients who had more than one resection for metastatic disease have been examined [20]. Two hundred and forty-eight patients were studied having undergone at least one resection of pulmonary metastasis, and 86 of those (35 %) underwent re-exploration. Of those patients able to have complete re-resection, median disease-free survival was 51 months. Factors predictive of a poor outcome at the time of re-resection included greater than three nodules, any metastasis larger than 2 cm, and high grade tumor histology. Patients with three of these prognostic factors had a median disease-free specific survival of 10 months whereas patients with 0 or 1 of these poor factors had a median disease-specific survival of greater than 65 months. The role of metastasis surgery has been summarized in more detail elsewhere [21].

The use of perioperative chemotherapy in patients undergoing pulmonary resection for metastatic disease was examined in a study reviewing the MSKCC database [22]. The study was comprised of 508 patients (27 % of 1897 patients) with extremity soft tissue sarcoma who developed lung metastasis as the first site of distant disease. Of those, 138 (27 %) patients underwent pulmonary resection. Of those 138, 53 (38 %) received perioperative chemotherapy. While some factors were similar, i.e., sex, grade, size, primary tumor, depth, histology, and number and size of lung metastasis, there was a significant difference between the patients who received perioperative chemotherapy in terms of disease-free interval. The rate of complete resection was the same. Complete resection was the only factor shown to be associated with prolonged survival. Those data suggested that the median post-metastasis disease-specific survival was 24 months in those patients treated with surgery and chemotherapy compared to 33 months in patients who were treated with surgery alone. Treatment outcome is highly influenced by patient selection, and it is thus not possible to evaluate the benefit of chemotherapy directly. Given the lack of substantial benefit in patients who were treated

Table 3.3 Lung metastases from soft tissue sarcoma: distribution by histologic type and grade

Histology	Overall (% overall)	High-grade histology	% High-grade	Patients with lung metastases	% Patients with lung metastases	% of all patients with lung metastases
Alveolar soft part sarcoma	22 (0.7)	22	100	13	59	2
Embryonal rhabdomyosarcoma	97 (3.0)	97	100	25	26	3
Synovial sarcoma	225 (7.0)	215	96	98	44	14
Epithelioid	21 (1.0)	20	95	8	38	1
Spindle cell (without specific lineage assigned)	56 (1.7)	51	91	20	36	3
Undifferentiated (sarcoma not otherwise specified)	25 (0.7)	22	88	15	60	2
Others[a]	221 (7.0)	190	86	65	29	9
Malignant peripheral nerve sheath tumor	130 (4.0)	111	85	36	28	5
Leiomyosarcoma	590 (18.7)	492	83	149	25	21
Angiosarcoma	124 (3.9)	97	78	33	27	5
Undifferentiated pleomorphic sarcoma	559 (18.0)	376	67	132	24	18
Extraskeletal chondrosarcoma	57 (2.0)	32	56	18	32	2
Liposarcoma	657 (20.8)	329	50	86	13	12
Fibrosarcoma	314 (10.0)	15	16	19	6	3
Gastrointestinal stromal tumor	51 (2.0)	5	10	2	4	<1

From: Billingsley KG et al. Ann Surg 229(5):602–612, 1999

[a]Includes adenosarcoma, anaplastic sarcoma, clear cell sarcoma, cystosarcoma phyllodes, and desmoplastic sarcoma

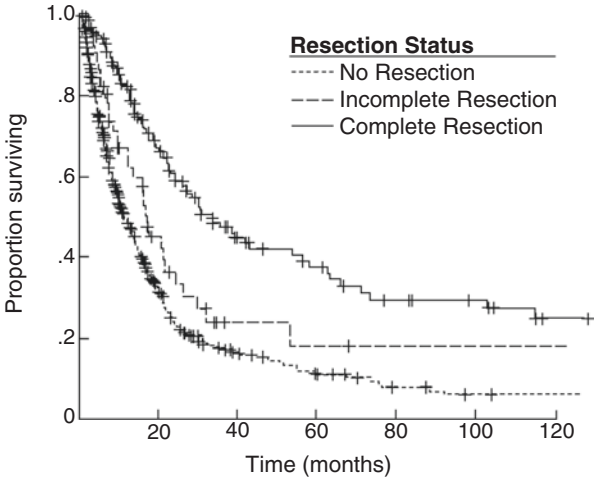

Fig. 3.5 Disease-specific survival for patients with pulmonary metastases undergoing thoracotomy, by treatment. Incomplete gross resection is only minimally better than operation with no resection. From: Billingsley KG et al. Ann Surg 229(5):602-612, 1999

with chemotherapy, systemic chemotherapy before or after pulmonary resection appears to be of limited value. A randomized clinical trial to test this hypothesis has failed for lack of accrual.

3.4.2 Surgery and Management of Sarcoma Liver Metastasis

The liver is a rare site of metastasis from extremity soft tissue sarcoma, but much more common for gastrointestinal primary sarcomas such as GIST. Standard treatment for sarcomas other than GIST metastatic to the liver usually entails chemotherapy or supportive care. Very few reports of resection exist for metastatic sarcoma, whereas hepatectomy for other types of metastatic disease is well established. We analyzed 331 patients from a database of 4270 (8 %) who developed liver metastases. Of those 331 patients, 56 (17 %) underwent complete resection of all gross liver disease. There was considerable patient selection based on the absence of disease elsewhere, the physical status of the patient, and the distribution of the metastases. Of the patients who had metastases to the liver from sarcoma, 40 % were patients with GISTs [23]. Prior to 1993, GISTs were often considered leiomyosarcoma and approximately one-fourth had extraintestinal leiomyosarcoma. Many of these patients would now be treated as metastatic GIST with first-line imatinib, but even these patients may come to liver resection. Of the group studied,

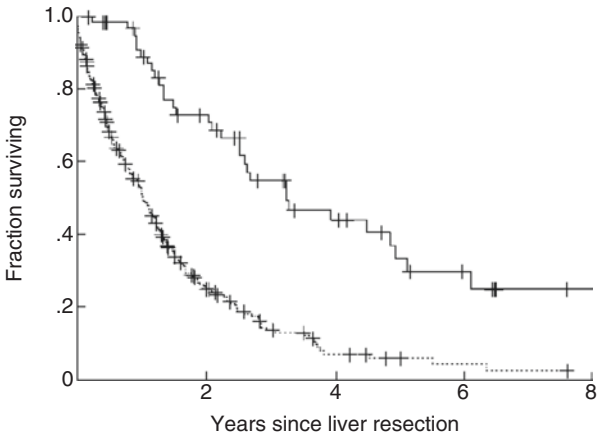

Fig. 3.6 Disease-specific survival for patients with liver metastases who had complete gross resection ($n=56$) (*upper line*) of all metastases was associated with improved survival compared to similar patients (275) treated without gross complete resection (*lower line*) of all liver lesions. From: DeMatteo RP, Shah A, Fong Y, et al. *Ann Surg* 2001; 234(4):540–547

the ability to undergo a liver resection was associated with improved survival (Fig. 3.6). This association with a survival benefit was histology independent. The only factor predicting improved survival was a disease-free interval of greater than 2 years. In those patients undergoing resection, there was no perioperative death. However, there were three perioperative deaths in patients who had incomplete resection. Given the ability to perform liver resection with low morbidity and mortality, surgical resection of liver metastatic disease should be considered in selected patients with apparent liver only disease, with reasonable possibility for complete gross resection, although recurrence is common (Fig. 3.7). With present imaging techniques, the likelihood of complete resection can now be much more adequately predicted; however on rare occasions, palliative resection is performed for the seriously symptomatic patient (Fig. 3.8). The role of liver resection for GIST in the age of imatinib remains investigational.

3.5 Radiation Therapy

Radiation therapy may be given in the adjuvant setting following or preceding surgical resection or on occasions as a definitive treatment of inoperable lesions. In addition, radiation therapy could be used for palliation of spinal and pulmonary metastasis.

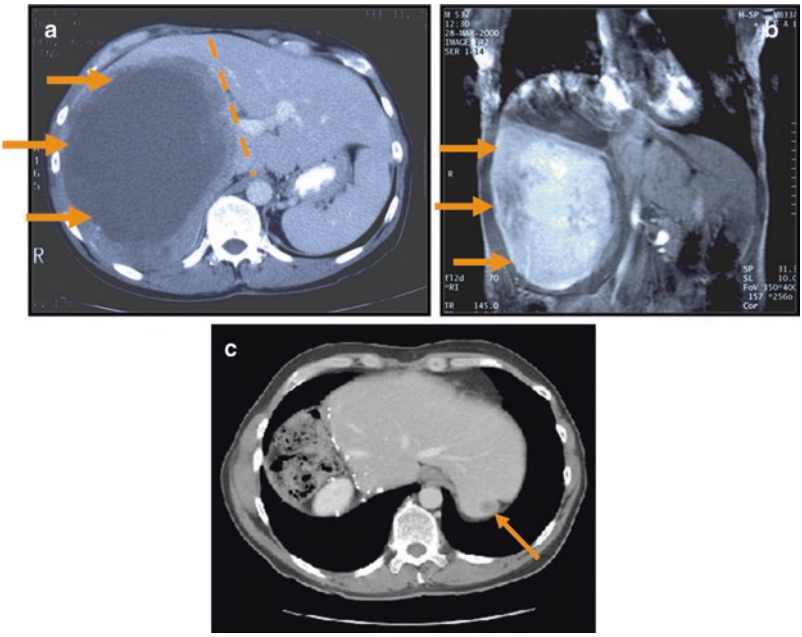

Fig. 3.7 Preoperative CT scan of liver metastases from GIST (**a**, **b**). Contralateral recurrence at 6 months (**c**)

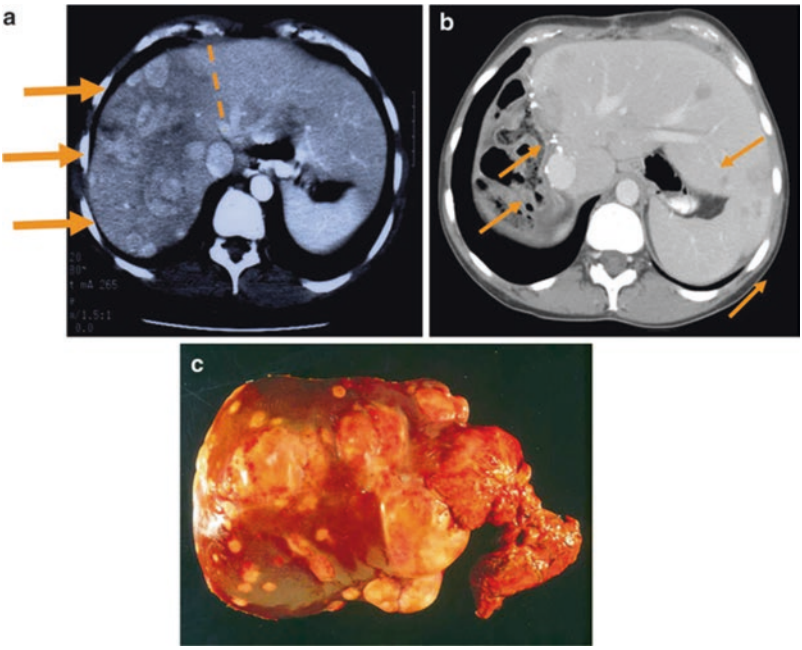

Fig. 3.8 CT of large symptomatic GIST, asymptomatic progression. (**a**) preoperative, (**b**) postoperative, (**c**) gross specimen

3.5.1 *Adjuvant Radiation Therapy*

The goal of utilizing adjuvant radiation therapy is to limit local recurrence, avoid amputation, and contribute to tissue preservation by limiting the extent of resection. In the absence of an adequate margin of 1–2 cm following a surgical procedure, or the presence of microscopic wound positivity, local recurrence is increased. This local recurrence can be limited by the judicious use of radiation therapy. Most of the data on the role of adjuvant radiation are derived from extremity lesions and to some extent superficial trunk. Two randomized trials have examined the benefit of adjuvant radiation therapy to limit local recurrence following conservative, especially limb sparing surgical resection. One trial used external beam radiation therapy (EBRT) and the other brachytherapy [24, 25]. An update of the brachytherapy trial performed at our institution sustaining the long-term ability to improve local control by adjuvant radiation therapy (Fig. 3.9). This benefit is most marked for high grade lesions (Fig. 3.10). Unfortunately, this is not translated into a survival benefit and does not limit metastasis (Fig. 3.11). There are limited if any local control benefits using brachytherapy for low grade tumors, but marked increase in local control with external beam radiation therapy as demonstrated by the National Cancer Institute (NCI) trial [25]. Attempts at performing evaluable trials of preoperative radiation therapy for large intra-abdominal lesions, an approach favored by many, have unfortunately not been possible.

Exact indications for radiation therapy remain uncertain and are often arbitrary. The majority of surgeons prefer to avoid radiation therapy particularly for lesions that are less than 5 cm who have adequate tissue margins, following complete resection [26]. At MSK, a nomogram was developed to assist in predicting the risk of local recurrence for primary soft tissue sarcoma of the extremity treated with definitive surgery alone, based on patient's age, tumor size, grade, margin status, and histology (Fig. 3.12) [27].

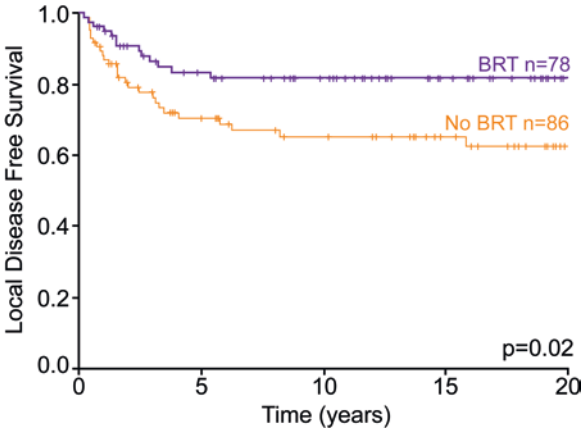

Fig. 3.9 Local disease-free survival for adult patients with extremity soft tissue sarcoma excluding desmoids: a prospective randomized trial of adjuvant brachytherapy vs. observation. MSKCC 7/1/1982–6/30/1992, follow-up to 7/15/2013, $n = 164$

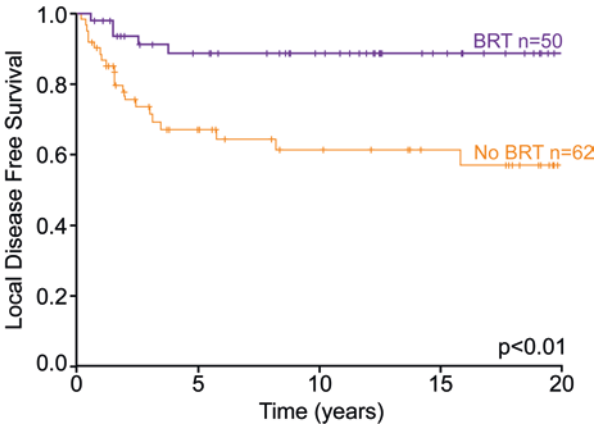

Fig. 3.10 Local disease-free survival for adult patients with extremity soft tissue sarcoma, high grade only: a prospective randomized trial of adjuvant brachytherapy vs. observation. MSKCC 7/1/1982–6/30/1992, follow-up to 7/15/2013, $n=112$

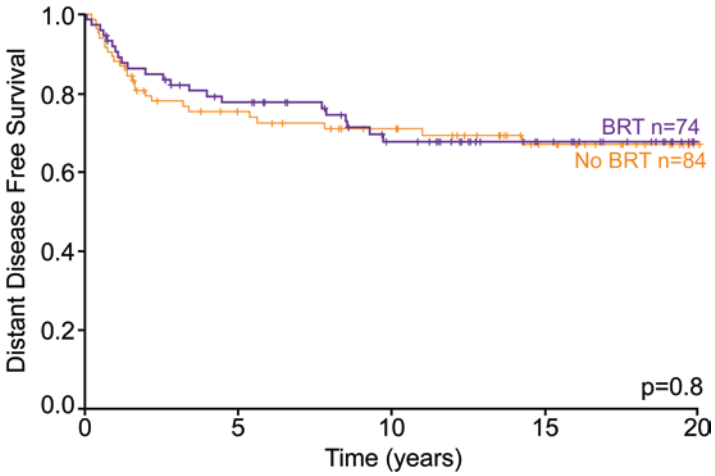

Fig. 3.11 Disease-specific survival for adult patients with extremity soft tissue sarcoma excluding desmoids: a prospective randomized trial of adjuvant brachytherapy vs. observation. MSKCC 7/1/1982–6/30/1992, follow-up to 7/15/2013, $n=158$

3.5.2 Types of Radiation Therapy

Conventional external beam radiation therapy is the most widely used adjuvant approach without requiring the sophistication of catheter replacement for brachytherapy. The issue of whether it is preferable to use preoperative radiation therapy or postoperative radiation therapy is also uncertain. A prospective randomized control trial by the National Cancer Institute of Canada (NCIC) [28] demonstrated equivalence in terms of local control by either preoperative or postoperative radiation therapy but with a greater complication rate in terms of wound healing (35 % vs. 17 %, $p=0.01$) and early postoperative diminution of function with the

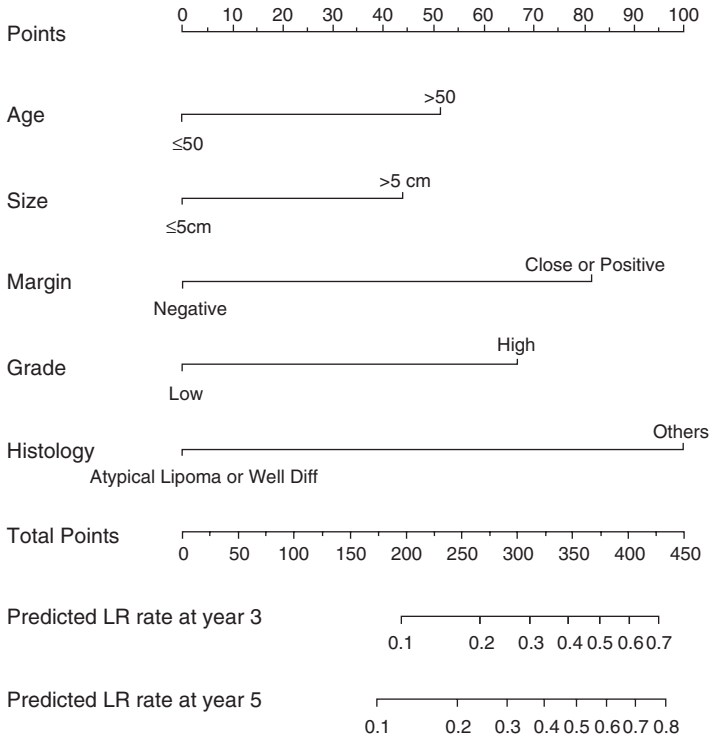

Fig. 3.12 Nomogram to predict the rate of local recurrence at 3 and 5 years. With permission from: Cahlon, O, et al. Ann Surg 255(2):343-347, 2012

preoperative treatment. Postoperative radiation therapy is also accompanied by late tissue complications such as lymphedema, fibrosis, and scarring [29]. As radiation therapy and techniques improve and *intensity modulated radiation therapy (IMRT)* is more widely utilized, complications and side effects can be expected to continue to diminish. Certainly advances have been achieved with the utilization of IMRT [30]. In a non-randomized comparison of brachytherapy and IMRT, IMRT appeared to be associated with superior local control despite higher risk factors (close margins, larger size, and nerve stripping) [31]. In a similar comparison of conventional external beam radiation and IMRT, IMRT was associated with improved local control (92.4 % vs. 84.9 %, $p = 0.05$) and less acute dermatitis (grade $\geq$ 2: 31.5 % vs. 48.7 %, $p = 0.002$), and edema (grade $\geq$ 2: 7.9 % vs. 14.9 %, $p = 0.05$) [32].

Brachytherapy (BRT) is an attractive approach which we have utilized over many years especially in high grade lesions [33], although with the advent of IMRT that utilization is diminishing. The attractiveness of brachytherapy is that a completed course can be delivered in 5–7 days as opposed to the 5–7 weeks required for external beam radiation therapy. The other attraction for BRT is that less normal tissue is

damaged or more normal tissue is protected. Usual doses are 45 Gy given over 4–6 days. We have shown that it is very important that this dose does not begin before the sixth postoperative day to avoid potential wound problems [34, 35]. The majority utilize ^{192}Ir although ^{125}I has been utilized in lesions that are close to reproductive structures. Our original trial of adjuvant brachytherapy showed a clear benefit in local control to the group receiving radiation therapy. This has been maintained over years (Fig. 3.9). It does appear that external beam radiation therapy is preferable to brachytherapy for patients with low grade lesions [25]. As the local control in the external beam randomized trial was much improved over the local control in low grade lesions with the brachytherapy technique. On rare occasions, both external beam radiation therapy and brachytherapy can be combined, usually when there are issues about the geometry of the BRT implant or difficulties with surgical margins. Importantly, brachytherapy can be given to patients who have received previous external beam radiation therapy providing that reconstructive techniques are taken to preserve tissue coverage [36].

3.5.3 Dose/Volume of Radiation Therapy

The recommended doses of radiation therapy in the NCIC trial (24) for extremity sarcoma were 50 Gy in daily fractions of 2 Gy over 5 weeks preoperatively and 66 Gy in 33 daily fractions over 7 weeks postoperatively. In general, patients with positive margins tend to have lower rate of local control than those with negative margins, but the addition of radiation still impacts local control in a positive way [37]. One area of controversy is whether patients treated with preoperative EBRT who later were found to have positive margins need to receive additional radiation. In the NCIC trial, such patients were given additional 16 Gy postoperatively, but recent data from Princes Margret Hospital (PMH) raises some question about the need for such boost [38]. The dose of postoperative radiation therapy in the NCI trial [25] was 63 Gy in 1.8 Gy per fraction, which is also the typical dose utilized with IMRT. The dose of BRT is usually 45 Gy with LDR Ir-192 given over 5 days, based on the MSK randomized trial [24]. When BRT is combined with external beam radiation therapy (45–50 Gy), the dose is 15–20 Gy.

The volume to encompass with preoperative radiation therapy includes the gross tumor volume plus 5 cm margin expansion longitudinally and 1–1.5 cm axially (Fig. 3.13). In the postoperative setting, the volume encompassed is significantly larger than that for preoperative treatment. While the amount of expansion is similar, the starting point is the tumor bed rather than the gross tumor volume, which is by definition larger. With BRT the volume is the tumor bed plus a 2 expansion longitudinally and 1 cm axially.

For non-extremity sites, the amount of expansion beyond gross tumor/tumor bed is less, in order to minimize the amount of critical intrathoracic and intra-abdominal organs/structures included in the radiation field. In addition, the pattern of local spread along the long axis of major muscles is less critical than in extremity lesions.

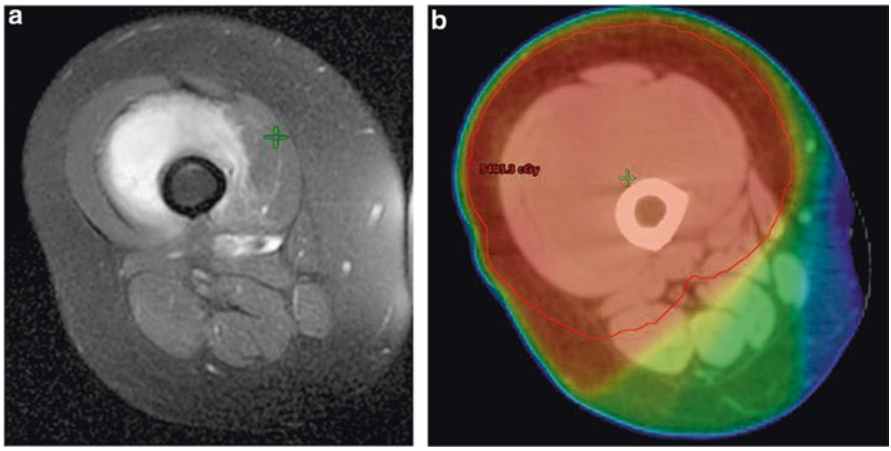

Fig. 3.13 Preoperative IMRT dose distribution: (**a**) Axial MRI demonstrating anterior thigh STS. (**b**) Axial view demonstrating the conformal dose distribution of IMRT

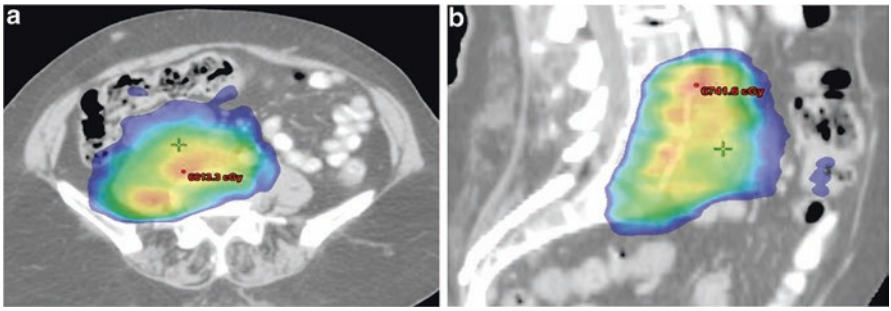

Fig. 3.14 Retroperitoneal STS: Dose-painting preoperative IMRT: (**a**) axial view demonstrating high dose (*red*) juxtaposed to posterior structures. (**b**) Sagittal view demonstrating low dose of radiation (*blue*) juxtaposed to bowel

The dose of radiation therapy for intra-abdominal sarcomas is usually 50.4/60.2 Gy using preoperative dose-painting IMRT (Fig. 3.14). For truncal lesions, the doses are similar to extremity sites.

3.5.4 Morbidity of Adjuvant Radiation Therapy

Most patients undergoing external beam radiation will experience some degree of *radiation dermatitis*. In the NCIC trial comparing preoperative to postoperative RT (24), the rate of grade ≥ 2 skin desquamation was higher in the postoperative arm (68 % vs. 36 %, $p < 0.0001$). As mentioned earlier, the rate of dermatitis was less

with IMRT than conventional EBRT [32]. *Wound complications* are also common irrespective of the type of radiation used. Previous studies have been performed [39] and a further study looking at the morbidity of adjuvant radiation therapy has been described [37]. A review of our morbidity contained within the randomized trial of brachytherapy vs. no brachytherapy [37] suggested an increase in significant wound complications in those undergoing brachytherapy (24 % vs. 14 %, $p=0.13$), with complications requiring reoperation being significantly higher (10 % vs. 0 %, $p=0.006$). It is clear based on prior wound healing studies [34, 35] that there is a definitive point following placement of catheters at which time radiation can be loaded. Any interval less than 5 days from the time of operation results in increased wound complications such that we load brachytherapy catheters more than 5 days from the time of operation. The timing of external beam radiation therapy in relationship to surgery also influences the rate of significant wound complications as demonstrated by the NCIC trial [26], 35 % for preoperative EBRT vs. 17 % for postoperative RT.

It is important to note that the rate of wound complications is not the same across extremity sites. In a report from MSK comparing upper vs. lower extremity STS, the rate of wound complications requiring reoperation was 1 % for upper extremity vs. 11 % for lower extremity, $p=0.002$ [40]. In the NCIC trial, the largest number of significant wound complications was also seen in thigh lesions [26]. In some extremity sarcomas, tissue transfer in the form of skin graft or myocutaneous flap is required. Data indicate that once the tissue transfer is healed, it tolerates postoperative RT well [41].

Some of late complications of adjuvant radiation include subcutaneous fibrosis, joint stiffness, edema, fracture, and peripheral neuropathy. In the NCIC trial [29], the rate of ≥ grade 2 *fibrosis* was 31.5 % in the preoperative RT arm compared to 48.2 % for the postoperative arm. The corresponding rates for *joint stiffness* were 17.8 % in the preoperative RT arm and 23.2 %, respectively, and for *edema* 15.1 % of patients treated with preoperative RT compared to 23.3 % for those treated postoperatively. For patients with medial thigh sarcoma, a site rich with lymphatic vessels, the rate of edema is significantly higher than anterior or posterior compartment lesions (25.7 % vs. 9 %, $p=0.005$) [42]. IMRT [32] seems to be associated with less edema than conventional EBRT (rate of ≥ grade 2 edema 7.9 % vs. 14.9 %, $p=0.05$. The overall rate of bone *fracture* is about 4–5 % in all extremity sites, but lower extremity site and thigh in specific account for most of these fractures. Investigators from PMH developed a nomogram for predicting the risk of femoral fracture utilizing gender, age, compartment location, extent of periosteal stripping, tumor size, and the dose of radiation [43]. In a separate report from PMH, dose constrains such as V40 < 64 %, mean dose <37 Gy, or D-max anywhere along the length of bone was <59 Gy were associated with reduced risk of fracture [44]. The technique of radiation may influence the risk of fracture; IMRT may provide a dosimetric advantage in reducing the dose to the femur when treating thigh sarcomas.

Peripheral neuropathy could be seen in about 7 % of patients treated with BRT [37] and 2.6 % with external beam radiation therapy [32]. An important predictor of neuropathy is neurolysis at the time of resection. For patients with thigh sarcoma,

the rate was 27 % for patients who had neurolysis as opposed to 5.2 % for those who didn't, $p = 0.0003$ [42].

3.5.5 *Definitive Radiation Therapy*

Definitive radiation therapy is occasionally utilized in patients with unresectable disease or severe medical comorbidities preventing operation [45]. In one study, 112 patients underwent radiation therapy for gross residual primary disease. Local control was achieved at the 50 % level at 5 years for small lesions and less than 10 % for large, greater than 10 cm lesions. Complications increase as dose increased, but there does appear to be a range, i.e., 63–68 Gy where complications are minimized and local control maximized. Treatment with high dose limited fraction IMRT remains a topic of investigation in this clinical setting.

There is increasing interest in using stereotactic body radiation therapy (SBRT) for the treatment of metastatic sarcoma. Several investigators reported local control rate of 85–96 % in selected patients with pulmonary metastasis treated with SBRT [46, 47]. Data on spinal metastasis are also encouraging. In a report from our institution on 88 patients, the 1-year local control was 87.9 % [48].

3.6 Adjuvant and Neoadjuvant Chemotherapy for Soft Tissue Sarcomas

The question of adjuvant chemotherapy for soft tissue sarcomas remains important since up to half of high risk, predominantly high grade patients with adequate local control of disease develop distant metastasis, usually to the lungs (extremity, trunk, and uterus primaries) and/or liver (GIST, other abdominal primaries). Given the increasing appreciation of the different biologies of each type of sarcoma, a blanket discussion of adjuvant chemotherapy for soft tissue sarcomas is difficult. The development of imatinib for GIST is the best example of the importance of choosing therapy appropriate to specific soft tissue sarcoma histology. Nonetheless, a number of principles are germane to adjuvant therapy and can be grouped into discussions of GIST, sarcomas more common in pediatric populations, and sarcomas more common in adult populations.

3.6.1 *Sarcomas More Common in Adults*

Nearly 20 studies of adjuvant therapy for soft tissue sarcoma have been conducted. Because anthracyclines are the most active agents in sarcoma therapy in the metastatic setting, they have been used in nearly all of the adjuvant trials, alone or in

combination. More recent studies have included ifosfamide in the treatment regimen. Most of the studies have been small and lack statistical power to detect small changes in overall survival. Meta-analyses have been performed on the randomized trials for adjuvant chemotherapy in soft tissue sarcoma. After the Sarcoma Meta-analysis Collaboration (SMAC) of 1997 [49], five studies involving ifosfamide have been performed, one of which is positive. All but the largest of these studies were included as part of a new meta-analysis, which did not examine individual patient data like the SMAC meta-analysis, but now shows a survival advantage for adjuvant chemotherapy, not observed in prior meta-analyses (or in most randomized clinical trials). Some of the data of the individual trials involved are discussed below, followed by a discussion of the meta-analyses of 1997 and 2008.

3.6.2 Larger Randomized Studies

The Gynecologic Oncology Group (GOG) performed one of the few adjuvant studies for patients with non-extremity (specifically uterine) sarcomas [50]. Two hundred and twenty-five patients with stage I or II uterine sarcomas (any subtype) were treated with surgery for local control, adding radiation at the discretion of the treating physician. Patients were randomly assigned to receive doxorubicin 60 mg/m [2] every 3 weeks for eight cycles or to observation. For the 156 evaluable patients, disease-free survival was no different between the two groups, nor was there a statistically significant difference in overall survival (73.7 months [doxorubicin] vs. 55.0 months [control]). The addition of radiation therapy did not affect survival although there was a lower rate of vaginal relapse in the radiation group.

A more aggressive treatment regimen was examined in women with uterine sarcomas in study that closed early for lack of accrual ($n=81$). Treatment consisted of pelvic irradiation vs pelvic irradiation with adjuvant chemotherapy with doxorubicin-ifosfamide-cisplatin. While there was a statistically significant improvement in progression-free survival (55 % with chemotherapy, 41 % without), there was no improvement in overall survival. This study, which included both sarcomas and carcinosarcomas, highlights the need to examine individual histologies with respect to adjuvant therapy [51].

The GOG and SARC (Sarcoma Alliance for Research through Collaboration) have followed up on the utility of the gemcitabine-docetaxel combination in metastatic disease with phase II studies of four cycles of adjuvant gemcitabine-docetaxel (GOG) [52] or four cycles of adjuvant gemcitabine-docetaxel followed by four cycles of doxorubicin (SARC) [53] in patients with uterine leiomyosarcoma [54]. A total of 46 women were treated and evaluable for outcome. While there were promising data initially, 3-year RFS was 57 % (95 % confidence interval 44–74 %), not significantly different from historical controls. As a result, we still consider the use of adjuvant therapy for uterine leiomyosarcoma investigational.

The Scandinavian Sarcoma Group performed the largest adjuvant study of doxorubicin [55]. After surgery and optional radiation, 240 patients were randomly assigned to receive doxorubicin 60 mg/m [2] every 4 weeks for nine cycles or no

chemotherapy. One hundred and eighty-one patients were evaluable. With a median 40 months of follow-up, there was no difference in local control, disease-free survival, or overall survival. Survival data were also assessed for the entire 240-patient cohort; there was no difference among treatment groups in disease-free or overall survival.

The largest single study of adjuvant combination chemotherapy in soft tissue sarcoma was performed by the European Organisation for Research and Treatment of Cancer (EORTC) [56]. Four hundred and sixty-eight patients (excluding those with "very low grade" sarcomas) were treated with surgery for their primary sarcoma and adjuvant radiation if surgical margins were under 1 cm. Patients then randomly assigned combination chemotherapy with cyclophosphamide, vincristine, doxorubicin, and dacarbazine (CyVADIC) given every 4 weeks for eight cycles. While disease-free survival and local control were both better in the chemotherapy arm, overall survival was not significantly different between the two arms. Criticism has been raised as to the 11-year accrual time, the inability of nearly half the patients to complete all eight cycles, and the relatively large number of patients ineligible for analysis, most commonly due to radiation therapy outside that defined by the study.

The first large study to incorporate ifosfamide as part of adjuvant therapy for truncal and extremity soft tissue sarcomas is that from the Italian Sarcoma Study Group [57]. After surgery with or without local radiation, 104 patients received either no chemotherapy or receive ifosfamide (9 g/m [2] split over 5 days) and epirubicin (120 mg/m [2] split over 2 days), with filgrastim. Interim analysis in 1996 led to early termination of the trial for meeting the primary endpoint of improved disease-free survival. With median 36-month follow-up, overall survival in the chemotherapy arm was 72 % vs. 55 % in the control arm ($p = 0.002$). Interpretation of the study is made somewhat more difficult by the finding of equal rates of distant or local recurrence or both at 4 years as well as by subtle imbalances in the distribution of patients on the control and treatment arms of the study. With longer follow-up, overall and disease-free survival no longer reach a statistical significance level of $p = 0.05$, but 5-year overall survival was still significantly better with chemotherapy. These data indicate that chemotherapy may delay, but may not ultimately eliminate, metastatic disease for most patients, but is the first study with a survival advantage for chemotherapy with modern ifosfamide-anthracycline-based therapy. Three smaller studies of adjuvant or neoadjuvant chemotherapy were negative, but were underpowered to determine small differences in overall survival [58, 59].

The largest randomized study of adjuvant ifosfamide and an anthracycline (doxorubicin) was performed by the EORTC (study 62029). A total of 351 patients were recruited over 8 years. Patient characteristics were evenly distributed between the two arms with 47 % of patients older than 50; 54 % were male. Histologies included leiomyosarcoma 15 %, liposarcoma 13 %, MFH 11 %, synovial 11 %, with 60 % of tumors grade III, and two-thirds with an extremity primary. 88 % of patients received radiation. Estimated 5-year relapse-free survival was 52 % in both arms and overall survival was 69 % (observation) and 64 % (chemotherapy) [60].

Recent data from ESMO 2016 indicated that neoadjuvant chemotherapy tailored for sarcoma histology did not prove beneficial compared to three cycles of neoadjuvant

epirubicin-ifosfamide. A futility boundary of the study triggered study closure, showing better relapse-free and overall survival for the epirubicin-ifosfamide study arm. While formally a negative trial, these data showed better outcomes of standard therapy against an active control arm. Pending publication of the final data, like the other adjuvant studies, these data affect the choice of neoadjuvant chemotherapy or not for a given patient [61].

3.6.3 Selected Meta-analyses of Randomized Trials of Adjuvant Chemotherapy

Given the lack of statistical power of many of the existing randomized trials, it was hoped that combining data from individual studies of adjuvant chemotherapy would reveal improvement in overall survival undetectable in smaller studies. The most rigorous meta-analysis regarding adjuvant chemotherapy for soft tissue sarcoma to date was published in 1997 [62]. In this analysis, 23 potential studies were considered and 14 ultimately included. Tumor histology for each patient was recorded, but pathology review was not centralized. Median follow-up was 9.4 years. Analyses were stratified by trial, and hazard ratios were calculated for each trial and combined, which allowed for an assessment of the risk of death or recurrence in comparison to control patients. Disease-free survival at 10 years was superior with chemotherapy (55 % vs. 45 %, $p=0.0001$). Local disease-free survival at 10 years also favored chemotherapy, 81 % vs. 75 %, $p=0.016$. Although overall survival was superior with chemotherapy at 10 years (54 % vs. 50 %), this difference was not statistically significant ($p=0.12$). Notably, the largest difference in overall survival was found in a subgroup analysis of the 886 patients with extremity sarcomas; overall survival was 46 % for patients receiving chemotherapy vs. 39 % for those who did not ($p=0.029$).

More recent studies using ifosfamide as part of adjuvant or neoadjuvant therapy were added to the SMAC meta-analysis in a 2008 meta-analysis [63]. Approximately 95 % of the patients had had primary sites in the extremity or trunk, patients in whom adequate surgical margins are most likely achieved. Considering the ifosfamide-anthracycline containing studies alone or in combination with the older doxorubicin-based studies (without ifosfamide) yielded similar results. Local, distant, and overall recurrence risks were lower with chemotherapy, and survival was statistically improved for patients receiving chemotherapy vs. those who did not. Considering all trials together, there was an absolute risk reduction of death of 6 % (95 % CI 2–11 %; $p=0.003$), or 5-year survival of 46 % for patients receiving chemotherapy and 40 % for those who did not.

As has been seen with large studies of patients receiving chemotherapy for non-small cell lung cancer, as the large size of the recent meta-analysis supports the use of chemotherapy in the adjuvant setting for patients with soft tissue sarcoma, with some caveats. Most individual clinical trials of adjuvant chemotherapy are negative,

though most are small by modern standards. One is thus left to balance the individual studies (such as the two large negative EORTC studies of adjuvant chemotherapy) with the meta-analysis data. Further analysis is hampered to some degree by the quality of the data reported in individual studies [64]. It is safe to say that if there is a benefit to chemotherapy, it remains a small one. With the advent of newer agents, it may well be that we readdress the question of adjuvant therapy in the near future.

The issue of histological sensitivity is also lost in meta-analyses and individual trials alike, since no subtype represents a majority in any of these studies. Since synovial sarcoma and myxoid-round cell liposarcoma are more sensitive to chemotherapy in the metastatic setting than other subtypes, one could argue that these are the best potential candidates for adjuvant therapy. The best data in this respect may be combined data from two EORTC randomized trials of adjuvant therapy. In this study of 819 patients, no histology (liposarcoma, leiomyosarcoma, synovial sarcoma) stood out as one that responded better to adjuvant therapy than others. For unclear reasons, men appeared to benefit more than women, and patients under age 40 fared worse than older patients, which is surprising, since patients under age 40 are enriched in chemotherapy-sensitive diagnoses such as synovial sarcoma and myxoid liposarcoma [65].

Based on these data and data from randomized trials, we consider adjuvant chemotherapy most seriously for patients with undifferentiated pleomorphic sarcoma and chemotherapy-sensitive histologies, with the caveats of the EORTC data above. We note the benefit, if any, is a small one, with significant short-term and potential long-term toxicity to face for anyone who receives such treatment. It is also worth noting that the retroperitoneal, visceral, and head/neck locations are often those in which a good margin cannot be achieved and that it is less likely that chemotherapy itself will provide a survival advantage, borne out to some degree from the negative data from multiple studies with doxorubicin that included patients with retroperitoneal, abdominal, and visceral disease (noting that some of these sarcomas would be today called GIST). Uterine leiomyosarcoma is one example of active research in an organ- and histology-specific manner, and hopefully will yield results that can be applied to other sites with the same histology.

3.6.4 Adjuvant Therapy for GIST

While GIST is impervious to standard cytotoxic chemotherapy, it is very sensitive to imatinib, begging the question of the utility of imatinib in the adjuvant setting. With the improvement in disease-free survival observed in the American College of Surgeons Oncology Group (ACOSOG) Z9001 randomized study described below [66], the FDA (Food and Drug Administration) and EMA (European Medicines Agency) approved imatinib in the adjuvant setting.

The first study examining adjuvant imatinib for high-risk GIST (i.e., >10-cm disease, ruptured tumor, or satellite implants near a primary tumor) was completed

by the American College of Surgeons Oncology Group (ACOSOG) [66]. More than 100 evaluable patients were accrued on study Z9000 from September 2001 to September 2003. Patients received imatinib at a starting dose of 400 mg orally daily for 48 weeks and were then followed for recurrence. The data of Z9000 are consistent with the high-risk cohort of Z9001 discussed below.

The Z9000 study was followed by ACOSOG study Z9001, examining imatinib 400 mg daily vs. placebo for 48 weeks for any GIST more than 3 cm in greatest dimension [67]. This study completed accrual in 2007, and showed a very significant difference in progression-free survival at the end of 1 year of therapy (3 % vs. 17 % for those on or not on imatinib). This difference did not translate to a survival advantage, although median follow-up was brief, less than 2 years at the time of publication. A delay in the progression-free survival curve of patients who received imatinib for 1 year toward that of the patients receiving placebo alone suggests that the cure rate is not improved with one year of imatinib [66].

The American studies were followed by other studies that ultimately confirmed the survival benefit of adjuvant imatinib for higher risk primary GIST. A study of the EORTC demonstrated superiority in PFS and OS with 2 years of imatinib vs. placebo [68]. However, the key study that dictates adjuvant therapy in 2015 was conducted by the SSG and AIO, examining 1 vs. 3 years of imatinib in patients with higher risk GIST i.e., (a) tumor size >10 cm, (b) tumor mitosis count >10/50 HPF, or (c) primary tumor size >5 cm and mitosis count >5/50 HPFs or (d) tumor rupture spontaneously or at surgery. PFS and OS were superior on 3 years adjuvant therapy, and thus became a standard of care for higher risk GIST as of 2011 [69].

As noted in the GIST chapter (Chap. 4.1), and incorporating the SSG XVII data with data from Corless et al. [70], the authors suggest that if adjuvant therapy be used, it should be employed for patients with higher risk tumors (≥5 cm *and* >5/50 HPF mitoses [gastric]; ≥5 cm *or* >5/50 HPF mitoses [non-gastric that can be assumed to have a high risk of metastasis]). These include high-risk tumors with *KIT* exon 11 mutations or *PDGFRA* mutations other than D842V. These data suggest patients with *KIT* exon 9 and "wild-type" GIST will not benefit from adjuvant therapy, though this remains a controversial topic [70]. For the time being, the authors suggest therapy for 3 years, the longest exposure employed in a randomized study. A phase II study of imatinib for 5 years of adjuvant therapy for high-risk patients has completed accrual, and a follow-up study from the SSG is examining 5 vs. 10 years of imatinib for highest risk GIST.

3.6.5 Sarcomas More Common in the Pediatric Setting

Without reviewing the positive studies performed in the past, the present standard of care for Ewing sarcoma is 9–15 weeks of systemic chemotherapy before local control (surgery, radiation, or both). A consensus standard of care in the United States, based on a large randomized clinical trial (more details can be found in Chap. 15 on pediatric sarcomas), is 5-drug therapy with ifosfamide and etoposide (IE) alternating with

vincristine, doxorubicin, and cyclophosphamide (VAdrC), which is superior to 3-drug VAdrC therapy for patients with localized tumors [71]. In children, a compressed schedule, attempting to give therapy every 2 weeks instead of every 3 weeks, is the standard of care [72]. However, in data only presented in a meeting and not published as of 2016, adults did not benefit from the 2 week schedule, though the number treated on the trial was relatively small. A four drug regimen, VIDE (vincristine, ifosfamide, doxorubicin, etoposide) is more commonly employed in Europe. Interestingly, increasing the dose per cycle of chemotherapy, while maintaining the same total cumulative dose of drugs administered, did not lead to an improvement in survival [73].

The most recent randomized data from randomized studies (IRS-IV) for most aggressive embryonal and alveolar rhabdomyosarcomas indicate that the combination of vincristine, dactinomycin, and cyclophosphamide is as active as two other combinations (vincristine, dactinomycin, ifosfamide and vincristine, ifosfamide, etoposide) and less myelotoxic than the other two regimens, and thus a good standard of care for higher risk embryonal and alveolar rhabdomyosarcomas [74]. Notably, the vincristine dosing needed in pediatric patients with rhabdomyosarcoma cannot be delivered to most adults. Also in rhabdomyosarcomas in adults, the cure rate is lower than in children, even on a histology-by-histology basis (embryonal, alveolar, and pleomorphic rhabdomyosarcomas). As a result, some physicians opt for the same VAC/IE chemotherapy employed in Ewing sarcoma. Other centers have used the MAID combination effectively in metastatic disease, raising it as a possible treatment for primary disease as well. However, there are no adjuvant data to support its use [75].

3.7 Brief Comments Regarding Chemotherapy for Metastatic Soft Tissue Sarcoma

It is well appreciated that different sarcoma subtypes have different patterns of sensitivity to a cytotoxic chemotherapy. We have attempted to address the histology-specific issues in each subtype-specific section of this book. It is worth noting that agents not used in the adjuvant setting, namely doxorubicin or ifosfamide, remain the best agents for a number of the sarcomas that require treatment. Certain systemic agents or combinations show predilection for one or more subtypes as well, such as dacarbazine or temozolomide in leiomyosarcoma [76–78] (and perhaps in solitary fibrous tumor), taxanes for angiosarcoma [79–81], or ifosfamide for synovial sarcoma [82, 83]. To date, few agents have achieved positive results in randomized clinical trials to be considered good drugs in a generic sense for metastatic sarcoma. For example, a study of doxorubicin ± palifosfamide demonstrated no survival advantage to the combination in first-line metastatic disease [84]. Per a 2015 company press release, a different alkylating agent (evofosfamide, TH-302) did no better in combination with doxorubicin; patients treated with evofosfamide and doxorubicin did not demonstrate a statistically significant improvement in overall survival compared with doxorubicin alone (HR: 1.06; 95 % CI: 0.88–1.29).

The combination gemcitabine and docetaxel is active in leiomyosarcoma and undifferentiated pleomorphic sarcoma, as well as pleomorphic liposarcoma [85, 86]. Trabectedin, shown active in a 3-week schedule in comparison to a weekly schedule, was initially approved in Europe but not in the United States based largely on a randomized phase II study. A follow-up phase III trial of trabectedin vs dacarbazine in liposarcoma and leiomyosarcoma showed statistically superior PFS for trabectedin (approximately 4 months vs. 2 months), but no survival advantage [87]. Because of these data, trabectedin was approved in 2015 for leiomyosarcoma and liposarcoma in the U.S. Conversely, the microtubule poison eribulin, in its study vs dacarbazine in liposarcoma and leiomyosarcoma, demonstrated a statistically significant 2-month overall survival advantage but no PFS advantage, in particular in liposarcoma; it was also approved late in 2015 for liposarcoma specifically [88]. Pazopanib was approved in 2012 for advanced sarcomas, but was found to have a progression-free survival advantage only in its pivotal phase III randomized study, and did not meet statistical significance for overall or disease-specific survival [89]. A TOR inhibitor was tested in a large phase III study in the maintenance setting, but the PFS benefit was too small for regulatory agencies to consider appropriate for approval. There continues to be a need of new agents with generic activity in sarcomas as well as those agents with specificity for particular sarcoma subtypes.

Newer agents other than immunotherapy: Newer agents in mid to late phase clinical trials show activity and may provide newer options for treatment in the next few years. Aldoxorubicin, an albumin-bound version of doxorubicin, may have greater activity than other anthracyclines [90]. A novel alkylating agent, evofosfamide, completed phase II [91], but the phase III with doxorubicin vs doxorubicin alone was a negative trial, and halted development of the evofosfamide in sarcoma. A monoclonal antibody against platelet-derived growth factor receptor alpha receptor, olaratumab (IMC-3G3), shows activity in sarcomas in a randomized phase II trial; [92] a phase III trial is fully accrued and led to accelerated approval of olaratumab in Europe and the United States in 2016. The combination of doxorubicin and olaratumab is a good first line standard of care for anthracycline-sensitive soft tissue sarcomas.

Lastly, agents impacting metabolic circuits or epigenetics of sarcomas are just now being studied presently. A few comments on these novel pathways are made in the sections on specific sarcoma subtypes.

3.8 Special Techniques for Primary and Locally Recurrent Disease

3.8.1 Intra-arterial Chemotherapy

A number of studies have examined the role of intra-arterial chemotherapy with doxorubicin, cisplatin, or both (among other drugs) for primary sarcomas [93]. The infusional approach is to be differentiated from local limb perfusion [94, 95].

Intra-arterial chemotherapy has the potential benefit of providing higher doses of chemotherapy to the limb in a first-pass effect. It remains a technique used at some centers and not used at others, perhaps due to the lack of compelling randomized data to support its use. Intra-arterial chemotherapy has been used in conjunction with radiation. In these studies, some patients have been able to avoid amputation. Infusional chemotherapy has its attendant complications, including arterial thromboembolism, infection, gangrene, and problems with wound healing, requiring amputation. Pathologic fractures have been reported in patients receiving chemotherapy and relatively large doses of radiation. Although there are situations in which such therapy could be considered, intra-arterial chemotherapy has a limited role at most institutions in the treatment of extremity sarcomas, given the technical expertise required, and the questionable benefits.

3.8.2 Limb Perfusion and Hyperthermia

In contrast to systemic intra-arterial chemotherapy infusion as noted above, perfusion of limbs requires isolating the arterial and venous system of the limb by means of a tourniquet, obtaining access to arteries and veins supplying the limb [94, 95]. The arterial and venous supply of the limb is connected to an external circulator to isolate the limb from the rest of the body. Blood from the limb is reoxygenated using a heart–lung machine. Radioactively tagged albumin is injected into the circuit and a probe is used to insure isolation of the bypass circuit. Because mild hyperthermia may make chemotherapy more effective in some clinical settings (as mentioned later in this section), the blood of the circuit is often warmed to 39–40 °C.

A number of chemotherapeutic agents have been used for limb perfusion, such as doxorubicin, melphalan, and dactinomycin. The most effective agent to date has been melphalan when given with tumor necrosis factor (TNF). The greatest experience with this technique comes from Eggermont et al. [94, 95]. After isolation of the extremity, 246 patients with unresectable sarcomas had melphalan perfused into the limb with TNF under mild hyperthermic conditions. Both components of the regimen appeared important; the omission of TNF led to a decrease in tissue dose of melphalan, probably from its effects on the tumor vasculature. Surgery to remove residual tumor was performed 2–4 months after limb perfusion. With a median follow-up of 3 years, 71 % of patients had successful limb salvage. A recent 20 year experience has been reported by Hoven-Gondre et al. [96] using isolated limb perfusion with TNF and melphalan followed by surgical resection and radiation therapy. A total of 113 patients were reported; after a median follow-up of 8 weeks, 107 tumors were resected, and 81 or 76 % had tumor-free margins. At a median follow-up of 51 months, the limb was spared in 88 patients, or 78 %. Ten-year disease-specific survival was 54 %. TNF remains unavailable in the United States, but is approved for use in Europe and elsewhere for this setting. It is important to note that isolated limb perfusion requires substantial expertise and specialized dedicated

equipment, which has led to a decrease in the incidence and severity of complications over time. Isolated limb perfusion does appear to hold promise for at least a subset of patients who would otherwise require amputation for local control.

Hyperthermia can potentially enhance the effects of chemotherapy in patients with locally advanced disease. Regional hyperthermia provided through an external electromagnetic field (phased array) has been examined in combination with ifosfamide and etoposide as well as other combinations of chemotherapy [97–99]. In a series of studies, partial and complete responses in patients with locally advanced and metastatic soft tissue sarcoma have been noted. Randomized data also support the superior local control rate with chemotherapy given with hyperthermia vs. chemotherapy [100], which has led to the approval of hyperthermia in Germany in this setting. Hyperthermia with chemotherapy remains investigational in the United States. The recent publications in melanoma, of the use of infusion rather than perfusion, suggest that the former technique may well be preferable, and with less technical challenge in the absence of a need for a recirculation circuit.

3.9 Immunotherapy for Sarcomas

While discussed to a greater extent in specific sections of the text, a few comments on immunotherapy for sarcoma are relevant here. Note was already made on the historical relevance of bacterial toxins as a potential therapy for sarcoma from the days of Coley at MSKCC. It is worth noting that immunotherapy has already been approved for sarcomas in some countries, in the form of muramyl tripeptide as an adjuvant for therapy of osteogenic sarcoma [101]. More specific immunotherapeutic agents are being tested in sarcomas, now that an increasing number of agents are approved for more common cancers. Key among these are immune checkpoint inhibitors, monoclonal antibodies targeting the immune synapse between tumor and T lymphocyte, which are attractive as they are off the shelf agents that can be relatively easily administered, although the side effects for some patients can be harrowing. In the first presentation regarding a PD1 inhibitor in sarcomas, pembrolizumab showed activity in undifferentiated pleomorphic sarcomas more than other histologies [102]. At least for PD1 inhibitors alone, the concept of mutational burden predicting response does not appear to hold, as the response rate appears much lower for leiomyosarcoma, another aneuploid tumor like UPS; osteosarcomas also showed relatively low response rates to single agent pembrolizumab in the SARC28 trial. There are anecdotes of responses of immune checkpoint inhibitors in bone and soft tissue sarcoma histologies that provide hints of activity for clinical trials underway or not reported as of 2016 [103].

Chimeric antigen receptor T cell therapy and similar cellular therapies targeted specific antigens in hematopoietic malignancies are attractive as well for at least two forms of soft tissue sarcoma; both synovial sarcoma and myxoid-round cell sarcoma consistently express cancer-germline antigen NY-ESO-1, and cellular therapeutics against NY-ESO-1 have already demonstrated evidence of activity [104].

Whether these approaches can be expanded more broadly remains to be seen, but the attractiveness of the immune system to combat a genetically heterogeneous and evolving foe is very clear, and will undoubtedly be a larger topic in future editions of this fascicle.

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Part II
Management by Histopathology

Chapter 4
Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GIST) were defined as a distinct biological entity in 1998, with the finding of its strong association with mutations in the oncogenes KIT or PDGFRA. Previously, GISTs were considered to be smooth muscle neoplasms often classified as leiomyosarcoma or gastrointestinal autonomic nerve tumors (GANT), or combinations of both. Definition and cellular origin appears to be the interstitial cell of Cajal or a precursor [1]. They commonly present as mass lesions, intra-abdominally, often of large size and with rupture and/or metastatic disease. GISTs make up one third of all visceral sarcomas (Fig. 4.1). Our original report [2] described 200 gastrointestinal stromal tumors, which was approximately 6 % of the 3500 patients with sarcoma admitted to our institution. Age and sex distribution are shown in Fig. 4.2, and lesions are distributed in the stomach, more than the small intestine, and more than other sites (Fig. 4.3). An example of a GIST of the stomach is demonstrated in Fig. 4.4.

4.1 Imaging

Imaging is usually by computed tomography or MRI, designed to examine the primary lesion, site of origin, as well as the presence or absence of metastasis (Figs. 4.5 and 4.6). ^{18}F-FDG PET-CT has been used to identify occult metastatic disease before primary surgery is conducted and can in principle be used to follow the response to metastatic disease. However, in the latter case, routine anatomic imaging with contrast yields nearly identical data with much lower cost and with lower exposure to radioactive agents.

M.F. Brennan et al., *Management of Soft Tissue Sarcoma*,
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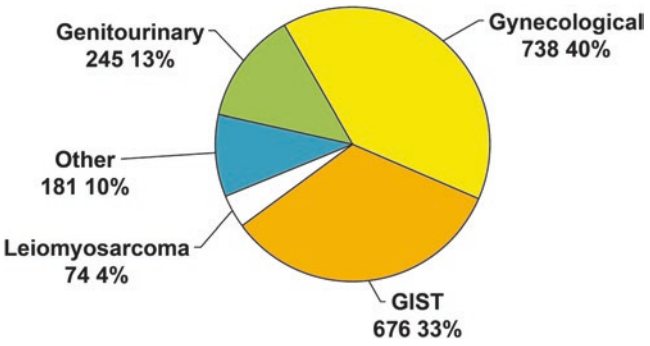

Fig. 4.1 Distribution by site for adult patients with visceral sarcomas. MSKCC 7/1/1982–6/30/2010, $n = 1864$. *GIST* gastrointestinal stromal tumor

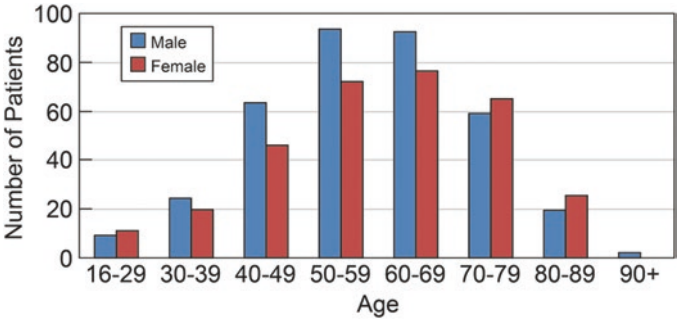

Fig. 4.2 Distribution by age and gender for adult patients with gastrointestinal stromal tumors (GIST). MSKCC 7/1/1982–6/30/2010, $n = 676$

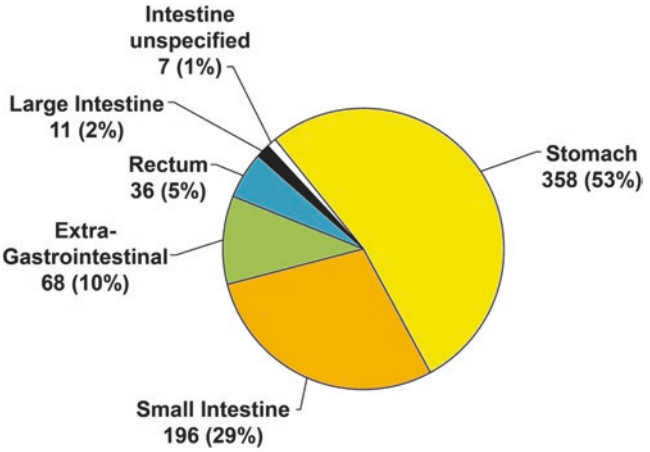

Fig. 4.3 Distribution by visceral site of adult patients with GIST. MSKCC 7/1/1982–6/30/2010, $n = 676$

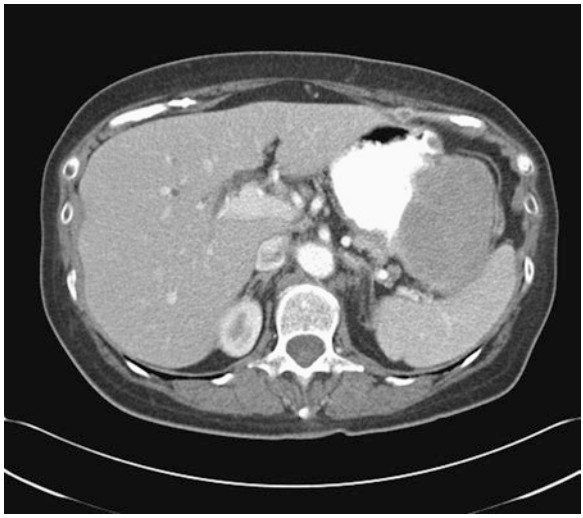

Fig. 4.4 Contrast-enhanced axial CT of a primary large gastric GIST arising from the greater curvature, showing a large gastric wall mass, likely hypodense to spleen owing to central tumor necrosis

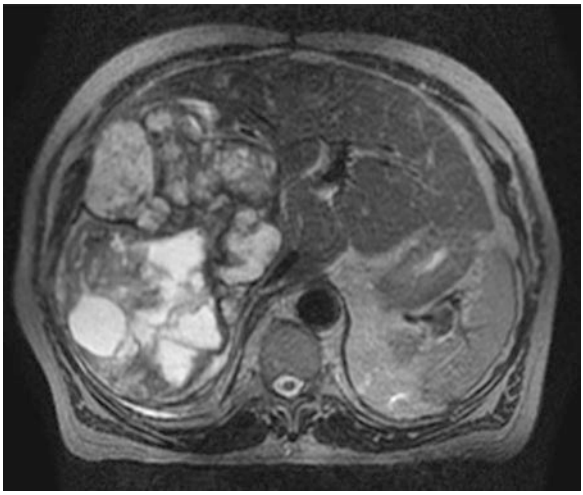

Fig. 4.5 Axial T2 weighted MRI with contrast showing metastatic GIST to liver

4.2 Familial GIST

Familial GIST is a rare hereditary predisposition to develop GIST due to a germ line mutation. Various kindreds have been described; patients typically have multiple tumors involving both stomach and jejunum and occasionally develop bowel diverticuli. In familial GIST, the mean age at diagnosis was 53 [3]. The majority of

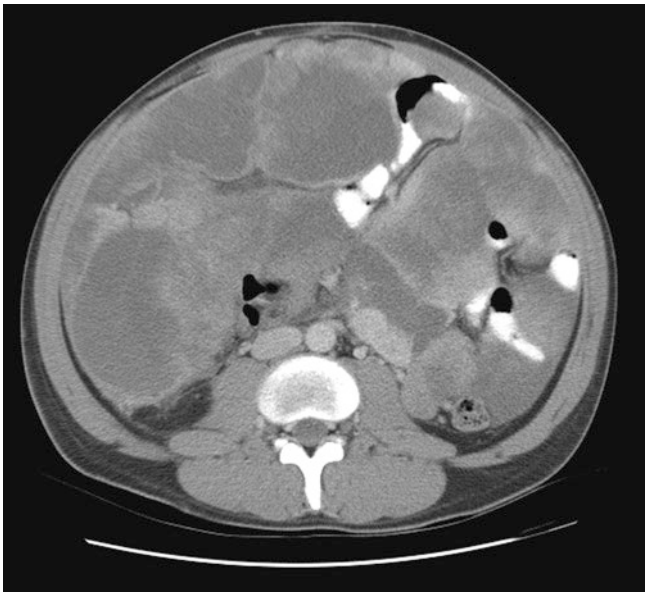

Fig. 4.6 Axial contrast-enhanced CT of extensive peritoneal metastases from GIST

tumors have a low mitotic rate. Mutations may affect *KIT* or rarely *PDGFRA* in these kindreds. Altered pigmentation patterns are common, with increased pigment on the hands, feet, axilla, or groin (Fig. 4.7), and symptoms similar to irritable bowel syndrome from GI dysmotility are common, from hypertrophy of their myenteric plexus. The observation that *KIT* mutations may be inherited was used to develop murine models harboring a germ line gain of function mutation [4].

Interestingly, multiple GIST also have been observed in patients with type I neurofibromatosis [5]; however, they often lack the presence of *KIT* or *PDGFRA* mutations. GIST is also characteristic of Carney-Stratakis dyad, along with paragangliomas, and these tumors characteristically harbor loss of function mutations in the succinate dehydrogenase complex (SDH), e.g., mutation of the gene encoding subunit B of this citric acid cycle enzyme (*SDHB*), though *SDHA* or *SDHC* can be affected instead.

Treatment of familial GIST is directed at removal of the largest or symptomatic lesion when feasible. Resection should be as conservative as possible, since all sites along the GI tract are at risk for development of GIST. Continuous long-term follow-up with symptomatic treatment appears appropriate. Imatinib is an effective treatment for unresectable or metastatic disease; however, long-term therapy in a preventative, other than in an adjuvant setting, is unlikely to be tested.

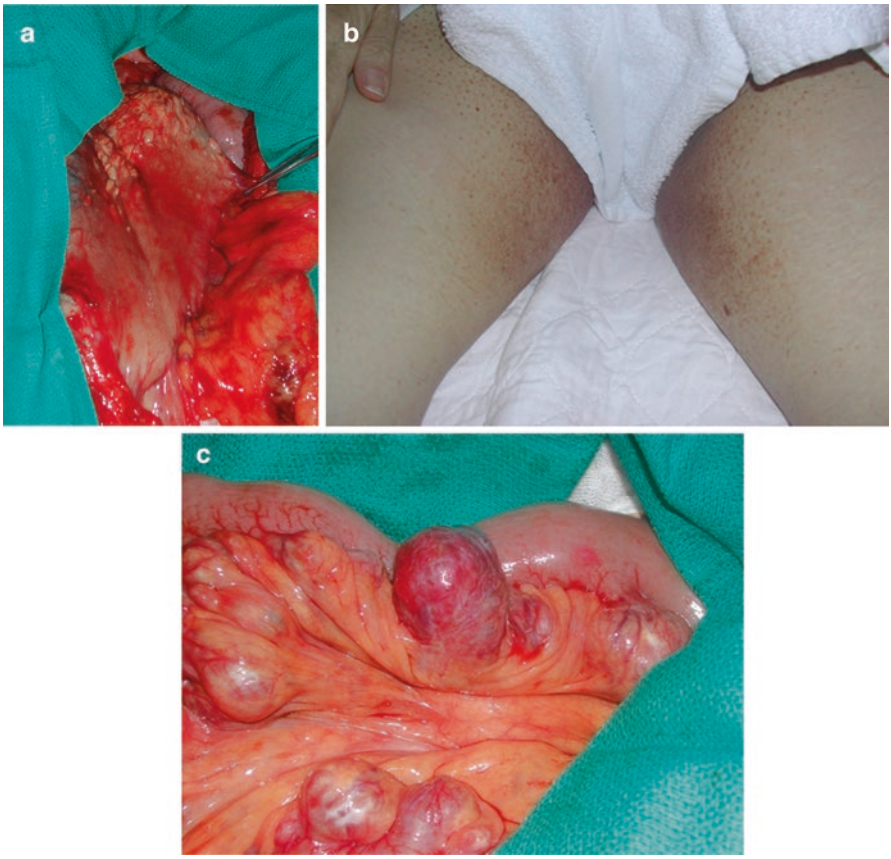

Fig. 4.7 Familial GIST with multifocal gastric and small bowel lesions (**a**), with characteristic inner thigh pigmentation (**c**) and small bowel diverticula (**b**)

4.3 Natural History

Prior to the availability of tyrosine kinase inhibitors (TKI) [6], GIST patients had a 2-year survival of 40 % and a <25 % 5-year survival. Outcome for primary completely resected tumors was more favorable, especially for stomach and small intestine rather than for colon and rectum (Fig. 4.8) [7]. Primary tumor site, size, mitotic rate <5 mitosis per 50 high-powered fields, disease-free interval, and surgical resection were all independent predictors of improved survival. Mutational status did not predict outcome independently. It is recognized that *KIT* genetic alterations, such as deletion in exons 557-558, is a poor prognostic marker for recurrence.

With the advent of TKI, improvement in survival was clear for patients with metastatic disease. In an effort to define the role of adjuvant tyrosine kinase inhibitor, we developed a nomogram to predict relapse-free survival after operation in the absence of adjuvant therapy. This was based on the examination of 127 patients and validated

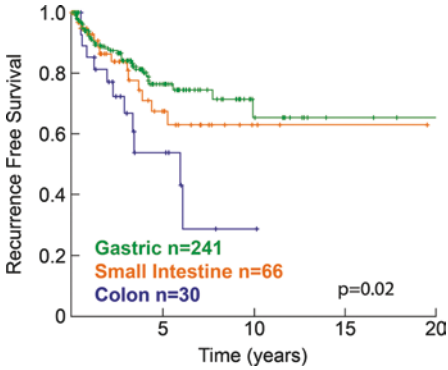

Fig. 4.8 Recurrence-free survival for adult patients with complete resection of localized (GIST) by tumor location. MSKCC 7/1/1982–6/30/2010, $n=337$

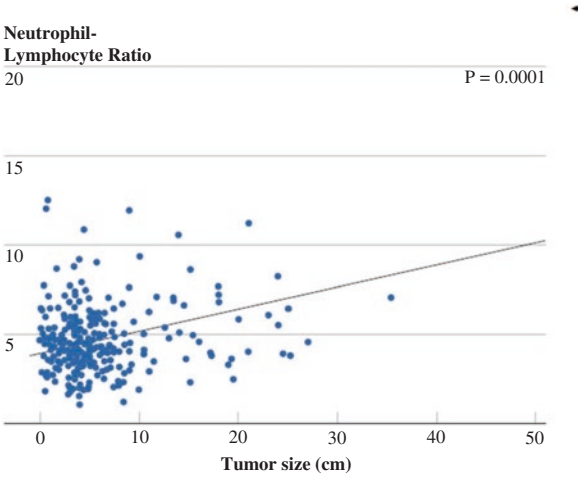

Fig. 4.9 Tumor size is significantly (P<0.01, Pearson correlation coefficient +36) associated with blood NLR ($n=271$). Patients with large tumors have high NLR. Lymphocytes. With permission from: Perez DR, et al. Ann Surg Oncol. 20(2):593–599, 2013

utilizing an additional independent cohort. This nomogram had a concordance probability of 0.78 in the Memorial Sloan Kettering Cancer Center dataset and 0.80 in the validation cohort. We were not able to show that inclusion of mutation status in the nomogram improved discriminatory ability of the nomogram. Utilizing this pre-tyrosine kinase dataset, we were able to show that mitotic rate, size, and location all independently predicted recurrence after resection of primary GIST. Newer versions of GIST nomograms have improved discrimination of outcome based on mitotic rate, which is a binary variable in the original nomogram [8]. In terms of risk stratification, gene expression profiling, examining for genes involved in cell checkpoints and chromosomal instability, seems to show a substantial ability to discern between people who will fare well vs. those who do not [9]. Lastly, an interesting observation is that the blood neutrophil to lymphocytic ratio can be prognostic for outcomes [10]. (Fig. 4.9)

Stratification of risk by anatomic site, size, mitotic rate, and tumor rupture has been captured for patients with primary GIST using heat maps, which allow determination of risk of primary GISTs across multiple continuous variables, and is presently more

effective than currently existing staging systems for discussing risk with patients [11]. Taking advantage of the SSG XVIII study data, discussed above and below, it is possible to assign a risk score for recurrence after use of adjuvant imatinib as well [12].

4.4 Diagnosis, Molecular Pathology

Based on autopsy series, GIST are the most common sarcoma if 'sarcomalets', such as microscopic GIST and incidentally noted GIST, are included. Without such caveats, GIST are the most common mesenchymal neoplasms of the gastrointestinal tract. Nearly all GIST express the receptor tyrosine kinase KIT, and most have a mutation in the *KIT* gene. Microscopic imaging of an epithelioid GIST with KIT staining is shown in Fig. 4.10. Chi et al. demonstrated oncogene *ETV1* is overexpressed in GIST and also characteristic of its neoplastic phenotype [13]. Less commonly, GIST bears mutations in *PDGFRA*. Five to seven percent of GIST do not have detectable *KIT* or *PDGFRA* and were generally termed "wild type" (WT) GIST, although rare mutations seen in *BRAF* are the exception to the rule. Many wild-type GISTs express insulin-like growth factor 1 receptor (IGF1R) [14], though IGFR1 is itself not mutated in GIST. A number of *KIT* and *PDGFRA* non-mutated GIST show loss of expression of the subunit B of succinate dehydrogenase (SDHB) [15]. SDHB expression is also lost in patients with Carney-Stratakis dyad, in whom paragangliomas are the defining tumor, due to mutations in one of the subunits of the SDH complex. [16] GIST, paraganglioma, and pulmonary chondromas are observed in Carney triad, which also lack SDHB expression in the absence of a known genetic abnormality [17]. Germline *SDHA* mutations have been identified in a significant subset of young adults with *KIT* and *PDGFRA* non-mutated GIST. [18] SDH-deficient GIST

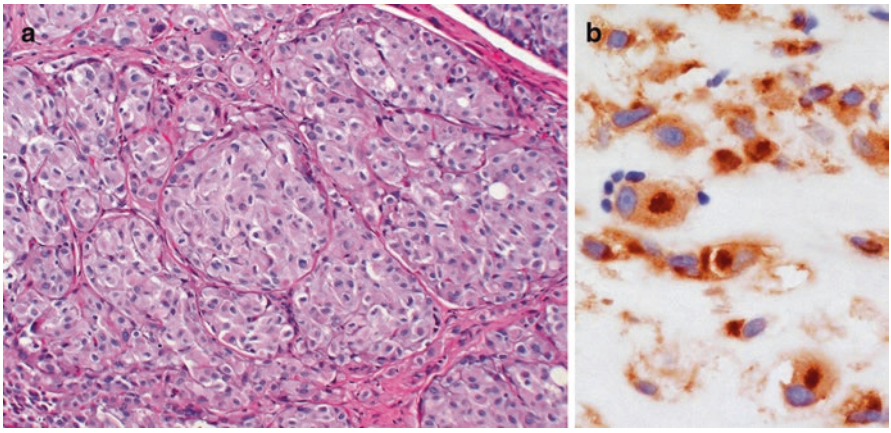

Fig. 4.10 Small bowel epithelioid GIST (**a**) with KIT positivity (**b**)

is associated with characteristic hypermethylation profile compared to *KIT*-mutated GIST, implicating the metabolic derangement of increased succinate levels with alterations in epigenetic targets [19]; the same study showed the Carney-Stratakis dyad GISTs formed a separate group by methylation analysis as well. It is important to be aware that there are other sarcomas that may show variable immunoreactivity for KIT, such as Ewing sarcoma, small cell carcinomas, and desmoid tumors, but such tumors do not carry activating *KIT* mutations and do not respond to imatinib. When other markers are needed to discern GIST from other tumors, *DOG1*, immunohistochemistry can be applied for a more definitive diagnosis [20, 21].

4.5 Treatment

The primary modality for higher risk tumors is surgical resection followed by 3-year adjuvant imatinib as standard of care (see below). Complete resection without encroachment of the pseudocapsule is a dominant factor in survival. The presence of metastatic disease and/or high-risk tumors is a clear indication for tyrosine kinase inhibitor treatment. Radiation has a limited role in the management of these tumors largely due to anatomic constraints and its relative radio-resistance.

4.6 Adjuvant Imatinib for Primary GIST

Adjuvant therapy was tested in a phase II trial before moving to phase III trials that now define the standard of care for primary GIST therapy. Long-term results of the initial Z9000 phase II trial of adjuvant imatinib in high risk (>10 cm, intraperitoneal tumor rupture or up to four intraperitoneal implants) have now been reported [22]. After a median follow-up of 7.7 years, the 1-, 3-, and 5-year overall survival rates were 99, 97 , and 83 %, respectively (Fig. 4.11a). This can be compared to historical 5-year survival of 35 % recurrence-free survival; RFS in the treatment population at 1, 3, and 5 years was 96, 60, and 40 %, respectively. The RFS was lower with increasing tumor size, small bowel site high mitotic rate, *KIT* exon 9 mutation, and older age (Fig. 4.11b).

The issue of adjuvant TKI in the treatment of GIST post-resection was further examined in prospective randomized trials. The first was designed under the aegis of the American College of Surgeons Oncology Group (ACOSOG). Patients with primary gastrointestinal stromal tumors ≥3 cm were randomized following complete gross resection and confirmation of KIT positivity to receive a placebo or imatinib for 1 year. This was a double blind trial with crossover allowed if recurrence was identified. Three hundred twenty-five patients were randomized to imatinib, 319 to placebo, and there were 21 events in the imatinib group and 62 in the placebo group. This trial was positive (Fig. 4.12) with a highly significant recurrence-free survival identified and a hazard ratio of 0.33. Overall survival (Fig. 4.13) has not reached statistical significance [23]. The most dramatic

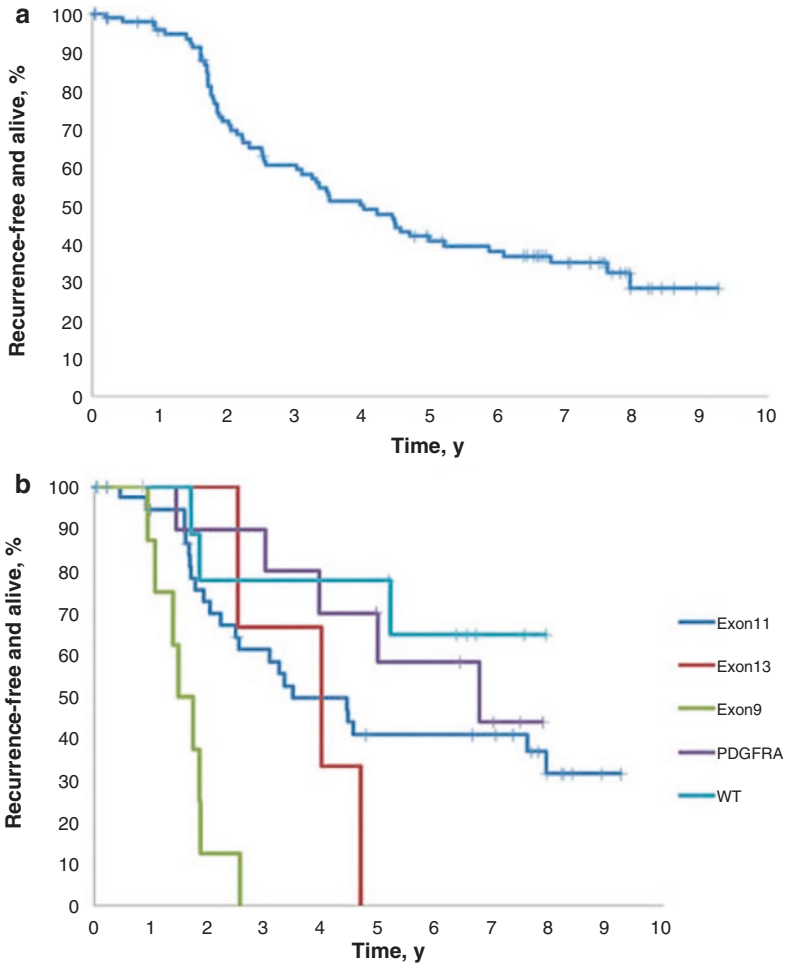

Fig. 4.11 Recurrence-free survival. (**a**) Entire population. (**b**) Mutation status. With permission from: DeMatteo R, et al. Ann. Surg. 258(3):422–429, 2013

effect was seen in patients with tumor size >10 cm (Fig. 4.14). However, 1 year of imatinib does not appear sufficient to eliminate microscopic metastatic disease in most patients.

Recurrence-free survival by type of mutation was also examined [24] showing that patients with *KIT* exon 11 mutant GIST had improved recurrence-free survival over those patients with *KIT* exon 9 and *KIT* exon 11 with a deletion affecting amino acids 557 or 558 (Fig. 4.15). These initial data suggest that 1 year of adjuvant imatinib only delays recurrence but does not prevent it. The FDA and EMA approved use of imatinib in the adjuvant setting. The data from the Z9001 trial were corroborated by an independent trial from the EORTC, examining 0 years vs. 2 years

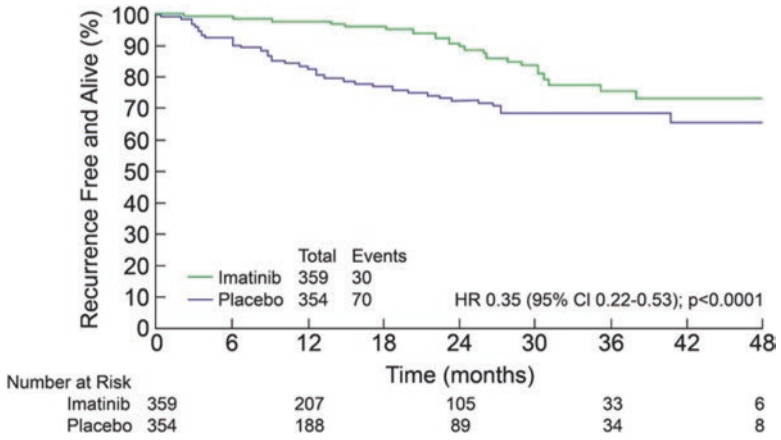

Fig. 4.12 Recurrence-free survival, randomized controlled trial of adjuvant imatinib vs. placebo. From: DeMatteo RP, et al. Lancet. 2009;373:1097–1104

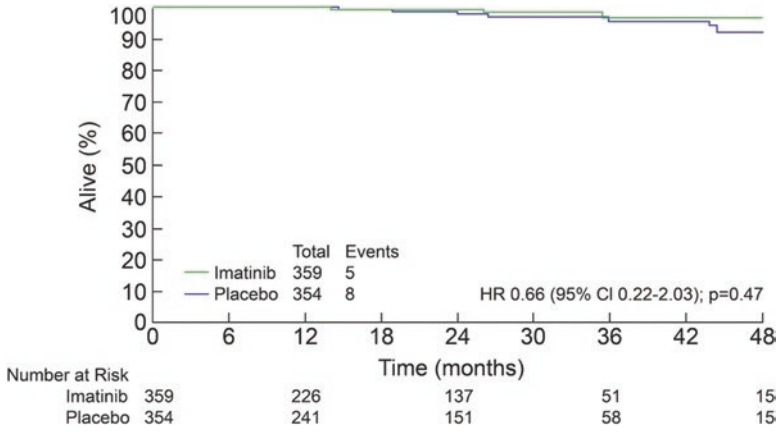

Fig. 4.13 Overall survival, randomized controlled trial of adjuvant imatinib vs. placebo, size ≤5 cm. From: DeMatteo RP, et al. Lancet. 2009;373:1097–1104

imatinib in the adjuvant setting. In this study, PFS and a new metric, "imatinib relapse free survival", were improved with 2 years of therapy vs. none [25].

The defining study for present day adjuvant therapy is the SSG XVIII trial, which compared 3 vs. 1 year of imatinib with overall survival as a primary endpoint. Adjuvant imatinib for 3 years improved recurrence-free survival (RFS) and overall survival (OS) compared with 1 year of adjuvant treatment for GIST patients who had a high risk of recurrence after surgery. Patients assigned 3

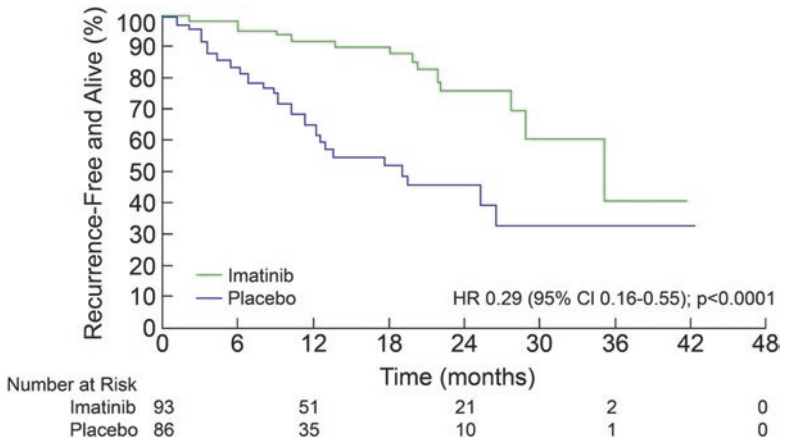

Fig. 4.14 Recurrence-free survival, randomized controlled trial of adjuvant imatinib vs. placebo, size >10 cm. From: DeMatteo RP, et al. Lancet. 2009;373:1097–1104

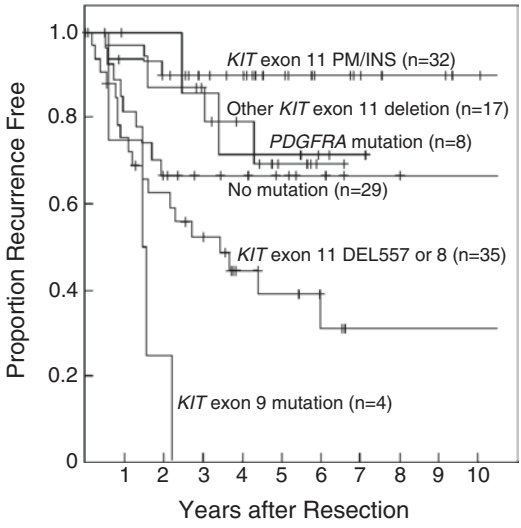

Fig. 4.15 Recurrence-free survival in 127 patients with completely resected localized gastrointestinal stromal tumor (GIST) based on the type of mutation. From: DeMatteo, R.P., et al. Cancer, 2008;112(3):608–15.

years of imatinib had statistically superior relapse-free survival (RFS) compared with those assigned 1 year (5-year RFS 66 % vs. 48 %) and longer OS (5-year OS 92 % vs. 82 %), despite 13 and 26 % of people assigned 1 year vs. 3 years imatinib stopping therapy for reasons other than GIST recurrence. With 7.5 years median follow-up, a 2015 update of these data indicated 5-year RFS was 71 % vs. 52 % for 3 year vs. 1 years of imatinib, and 5 year OS was 92 % vs. 85 %, both statistically significant [26].

The overall survival results were unexpected. Improved survival had not been observed in the 1 year study of adjuvant imatinib nor in the BFR 14 study from France, in which patients with metastatic GIST stopped or continued imatinib after 1, 3, or 5 years of stable disease or better. In the latter case, there was improved PFS for those patients who continued imatinib versus those who interrupted imatinib therapy. However, OS was identical in both groups in BFR14, indicating that even in the setting of metastatic disease one is not penalized by a break-in therapy in terms of survival. However, given that the survival curves are ultimately coming together over time, it is not clear that in the long run if imatinib can be truly curative for a fraction of patients, or if delay of recurrence is all that can be expected from 3 years' treatment with imatinib.

With the understanding that longer exposure may be necessary to achieve the best possible RFS and OS for higher-risk tumors, a subsequent phase II trial looking at 5 years of imatinib has completed accrual and awaits maturation of the data. The SSG have also initiated a 5-year vs. 10-year imatinib study in the adjuvant setting for people with the highest-risk GIST.

Further mutation data have become available regarding adjuvant therapy from the ACOSOG Z9000 and Z9001 studies. These data will help discriminate which patients should receive therapy [27]. In particular, people had better RFS with 1 year of imatinib vs. placebo if they had deletions in KIT, as opposed to insertions or point mutations. Patients with *PDGFRA* D842V mutation did not appear to benefit from 1 year of imatinib, nor did patients with *KIT* exon 9 mutations or no mutation in *KIT* or *PDGFRA*. There was the suggestion of benefit in patients who had *PDGFRA* mutations that were not D842V. These data help select patients who will not benefit from imatinib, by virtue of the lower risk of their tumors. However, questions around the use of adjuvant therapy for exon 9 *KIT* mutated GIST or GIST without *KIT* or *PDGFRA* mutation remain. Assuming a clinical trial is not available, our general approach is to opt for a trial of adjuvant therapy in these borderline cases, understanding there may be a lower threshold to stop treatment for toxicity in these patients.

4.7 Neoadjuvant Therapy for Primary Disease Not Amenable to Surgery

Patients with clinically unresectable primary GIST provide an opportunity for neoadjuvant therapy prior to resection. In such a situation, an unresectable or marginally resectable tumor can be rendered resectable in difficult anatomical locations

such as the rectum [28]. It is generally advocated that patients continue imatinib after such surgery, given the high frequency of relapse off imatinib in such patients. In the setting of resectable disease, it is not clear at this time whether it will be better to consider imatinib with surgery as an "adjuvant" to imatinib, or imatinib as an adjuvant to surgery [29, 30]. Two studies of neoadjuvant imatinib for resectable disease indicate that such an approach is both feasible and effective [29, 30]. The long-term implications of such therapy will require longer follow-up.

4.8 Treatment of Recurrence

In terms of risk factors for local-regional recurrence, the influence of positive microscopic margin on tumor recurrence has been examined [31]. Approximately 9 % of 819 GIST patients had an R1 resection. Significant factors associated with R1 resection include tumor size ≥10 cm, location, and rupture. The difference in recurrence-free survival with or without imatinib therapy in those undergoing an R1 vs. R0 resection was not statistically significant at a median follow-up of 4 years. (Fig. 4.16)

The primary management of metastatic disease remains tyrosine kinase inhibitors, while the role of surgery in the treatment of recurrent disease is unclear. It does appear that there is a role for surgery or other interventions, such as radiofrequency ablation (RFA) or cryotherapy, particularly in the presence of non-responding lesions or lesions that develop resistance to tyrosine kinase inhibitor therapy. Studies to examine early vs. later surgery for metastatic GIST have failed to accrue and were closed.

4.9 First line Imatinib For Metastatic GIST

The initial demonstration of imatinib-induced KIT inhibition and apoptosis in a GIST cell line [32] led to the first treatment of a patient with GIST with imatinib. [33] The activity of imatinib was most remarkable, given the resistance of GIST to standard cytotoxic chemotherapy. The response of the first patient rapidly led to phase I [34], randomized phase II [35], and confirmatory phase II studies [36], demonstrating activity of imatinib in successively larger cohorts of patients.

Patients with bulky disease showed improved symptoms within days of starting therapy, eventually prompting two randomized studies of 400 mg daily versus 400 mg twice daily imatinib in patients with metastatic GIST. [37, 38] The studies showed consistent ~50 % RECIST (Response Evaluation Criteria in Solid Tumors) response rates in patients with metastatic disease, with survival being no different in the 400 mg and 800 mg arms, and allowed registration of imatinib at 400 mg oral daily as a first line standard of care for metastatic GIST.

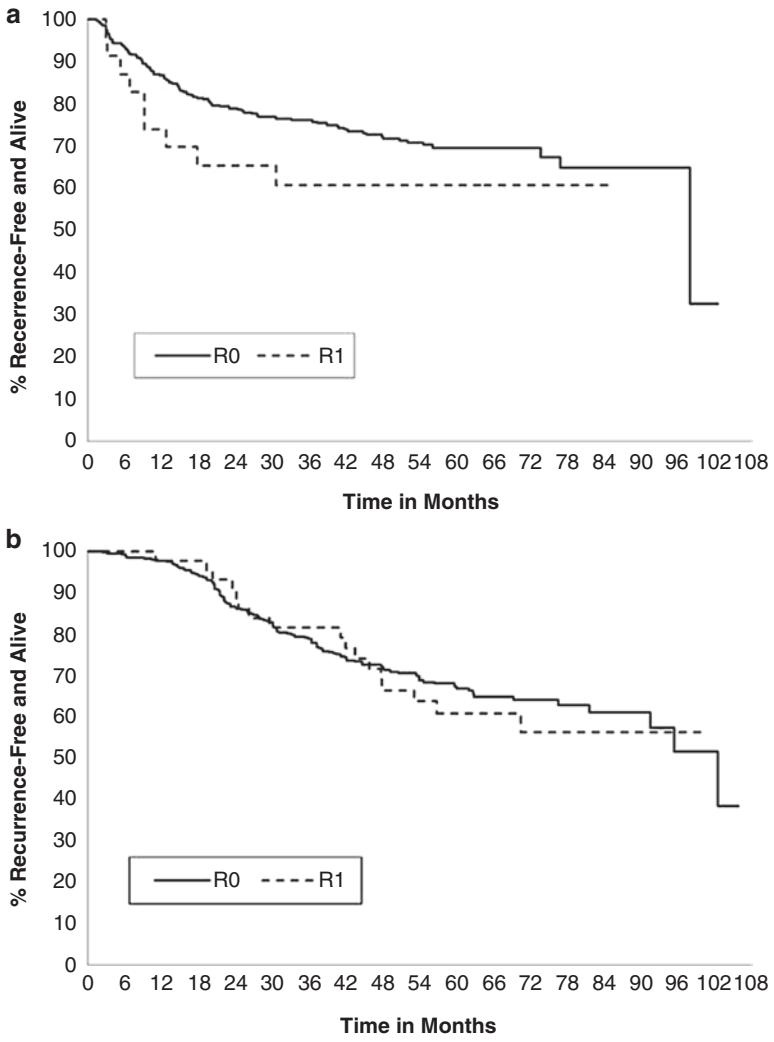

Fig. 4.16 (**a**) Recurrence-free survival (RFS) by margin status for patients in the placebo arm ($n=330$ for R0 and 23 for R1); hazard ratio 1.5; 95 % CI 0.76, 2.99; $p=0.24$. (**b**) Recurrence-free survival by margin status for patients in the imatinib arm ($n=415$ for R0 and 49 for R1); hazard ratio 1.1; 95 % CI 0.66, 1.83; $p=0.73$. With permission from: McCarter MD, et al. J Am Coll Surg. 215:53–60, 2012

Overall survival of patients with metastatic GIST in the first published phase III study of imatinib ($n=946$) is shown (Fig. 4.17). The third, non-randomized comparator arm was a group of patients with gastrointestinal leiomyosarcoma/GIST treated with doxorubicin in older clinical trials, giving a sense of the improvement in survival achieved in patients with metastatic disease. The United States-randomized study B2222 gave similar results, with median overall survival of 58

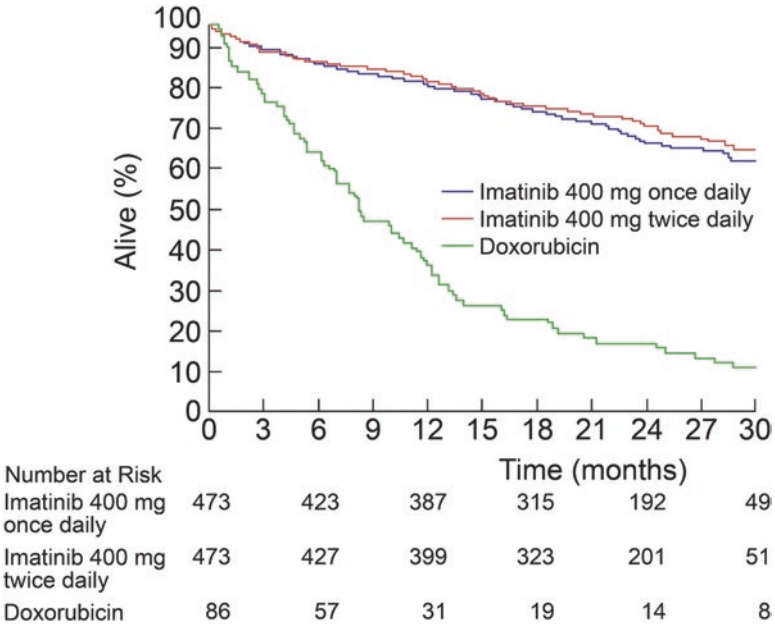

Fig. 4.17 Overall survival for patients receiving imatinib for metastatic GIST, 400 mg vs. 800 mg oral daily, European/Australasian randomized study, $n = 946$. From: Verweij J, et al. Lancet 2004;364:1127–1134

months for all patients treated in this 746 patient study [37]. Patients with RECIST stable disease survived just as long as patients with an overt RECIST partial or complete response, confirming that RECIST is inadequate for determining clinical outcomes for patients receiving imatinib for GIST. [39, 40] The lack of progression thus is the most important radiologic finding suggesting clinical benefit. PET scans can also track response of GIST to imatinib and other TKI, but add little to contrast-enhanced CT scans (Figs. 4.18 and 4.19).

Data from France indicated that patients with metastatic disease need to be treated on a lifelong basis. The basis of this recommendation is the first portion of the French BFR14 study, in which patients received 12 months of imatinib. Patients doing well were randomized to continue or stop imatinib. Those stopping imatinib progressed with a median time of 6 months, compared to 28 months for those who continued imatinib. [41] Nearly all patients responded again when re-challenged with imatinib. Overall survival for the two groups was not different. These data show imatinib can be interrupted for periods of time without a negative impact on survival. Nonetheless, as in patients with HIV receiving antiretroviral therapy, the general consensus among medical oncologists is that patients tolerating imatinib well should continue imatinib unless there is intolerance despite dose reduction or disease progression. These data were confirmed in a similar study, in this case using 3 years of imatinib before randomization. A 5-year follow-up study has also been reported, with similar findings [42].

Although the overall survival was not different between patients receiving 400 mg vs. 800 mg imatinib daily for metastatic disease, progression-free survival (PFS) was superior for patients taking 800 mg daily, with a hazard ratio of 0.89 at 3 years in favor of the higher dose, $p = 0.04$ [43]. It has become clear that the group of patients with largest difference in PFS by dose is that with exon 9 *KIT* mutations [43]. In this group, PFS was 6 months at the 400 mg daily dose, versus 17 months for those taking 800 mg oral daily ($p = 0.017$). There is also a trend to improved

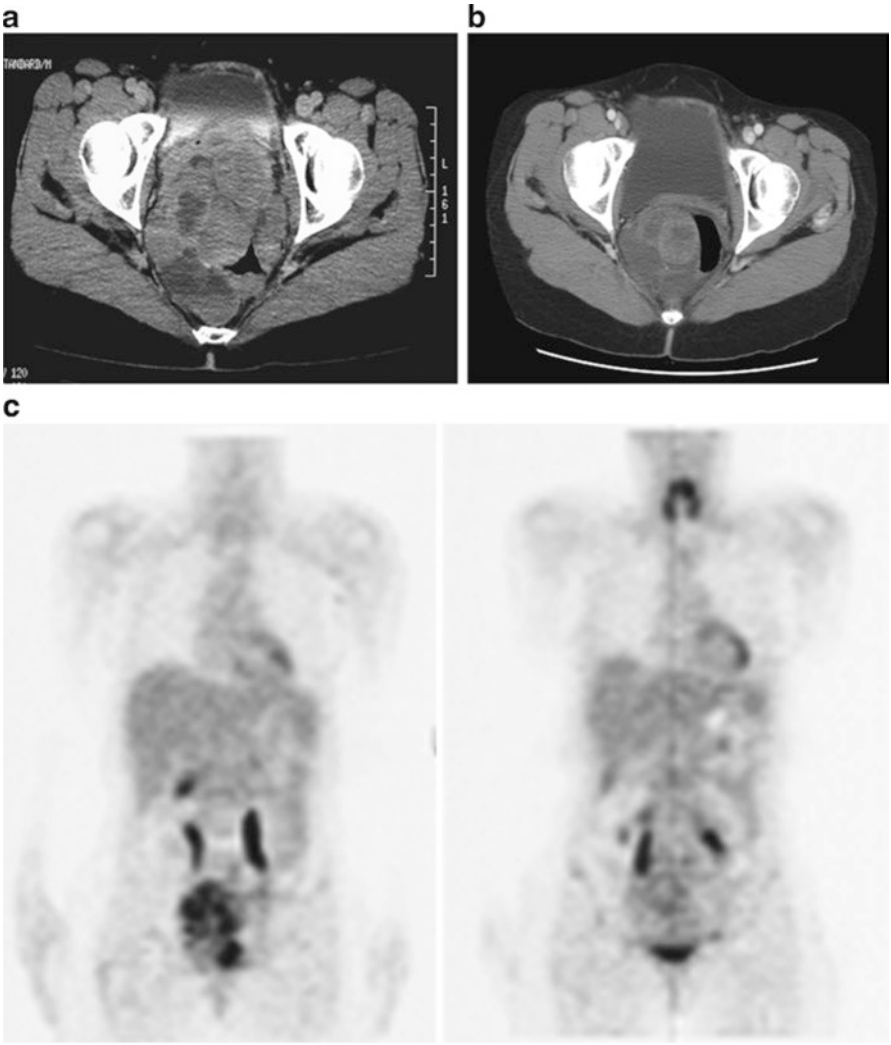

Fig. 4.18 CT and PET scan showing response to imatinib (exon 11 KIT mutation) (**a** and **b**) CT at 0 and 2 months, (**c**) PET at 0 and 2 weeks

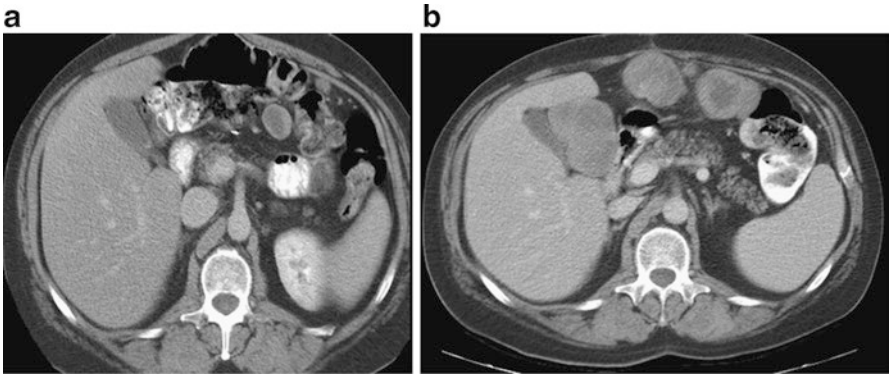

Fig. 4.19 CT and PET showing progression in response to imatinib (exon 9 *KIT* mutation), (**a** and **b**) CT before therapy and 2 months after starting therapy

survival for patients receiving the higher dose. Because of this subset analysis, NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) guidelines for GIST incorporate imatinib dose based on mutation status, specifically 400 mg oral BID for people with exon 9 *KIT* mutations, and 400 mg oral daily for other patients [42]. *KIT* mutation testing is now commercially available and can also be used to guide this decision.

Who should have mutation testing for their GIST? Arguably, this test should be a standard of care for people with high enough risk disease to potentially merit adjuvant therapy. While testing every 1 cm GIST has no clinical import, since the risk of recurrence is so low, it is useful to know which genomic subtype of GIST is being treated in order to tailor adjuvant therapy, and in several instances metastatic disease. For example, in *KIT* exon 9 mutant GIST, there are retrospective data that show that people have superior progression-free survival on higher (800 mg oral daily) rather than lower doses of imatinib, thus it makes sense to ascertain these data if they have not been collected previously [44]. Notably, the vast majority of exon 9 *KIT* mutation GISTs arise in the small bowel, thus consideration can be given to testing this subgroup. Of note, exon 9 KIT mutation GISTs are still the minority, even in the small bowel. Similarly, *PDGFRA* mutations are most commonly found in the stomach.

We remain somewhat skeptical of the use of higher-dose imatinib for patients with *KIT* exon 9 mutations since the benefit is modest in the existing randomized clinical trials data in the two large randomized studies of metastatic disease [37, 45]. Specifically, the response rate after increasing the imatinib dose is 2–3 % and disease stabilization rate 27–28 % in the two randomized studies, with a median PFS of 2.5–5 months, and a 1-year PFS of ~20 %. Other people have significant adverse events at 400 mg oral daily that only worsen at 800 mg daily. Nonetheless, if a patient can tolerate the higher dose, a higher dose for exon 9 *KIT* mutant GIST remains a worthy goal, given that there remain so few options beyond imatinib for metastatic disease.

4.10 Dose Intensity Over Time

The first patient with GIST being treated with imatinib was in March, 2000 [33]. It is worthwhile reviewing the dosing of this remarkable drug. Specifically, why is a flat dose of imatinib typically given to GIST patients, i.e., 400 mg oral daily? To a first approximation, in the five phase I–II–III studies, there appears to be no improvement in RECIST response rate or survival in patient who receive 400, 600, or 800 mg oral daily [34–38, 46]. What we do not know with this patient population is whether there will be long-term survival benefits in patients who receive lower or higher doses of imatinib. A more detailed analysis of data from the EORTC 62005 intergroup study of 400 mg vs. 800 mg imatinib daily for patients with metastatic GIST [36] showed that a higher dose of imatinib was associated with improved response rate and survival in metastatic GIST patients who had exon 9 mutations in the *KIT* gene in their GIST. [47] Patients with exon 9 mutations fared poorly overall compared to other patients on this study.

A variety of factors that lead to imatinib resistance may be a function of dose, while others are not. Compliance, treatment interruptions, and variability of the pharmacokinetics of imatinib distribution in the body all affect the dose intensity of imatinib. However, secondary *KIT* mutations, *KIT* amplification, loss of *KIT* expression, or other factors such as OCT-1 or ABCB1 channel proteins responsible for influx and efflux of imatinib into the tumor cell are not likely so affected by dose intensity.

Reanalysis of the first large scale randomized phase II data of patients treated with 400 mg vs. 600 mg oral imatinib daily for GIST (B2222) showed that those patients in the lowest quartile of plasma drug concentration had the shortest time to progression, in comparison to all other patients [48]. These data are consistent with data from chronic myelogenous leukemia (CML), in which those patients with major molecular responses to therapy had a higher median trough level in comparison to patient who did not have a major molecular response; [49] however, other data do not support this contention [50].

The assessment of plasma levels of imatinib in patients with hematological malignancies is becoming a standard of care, and imatinib trough level testing should be considered in GIST in at least some clinical scenarios, though data are limited. For example, a 120 kg patient without side effects who has radiological progression on imatinib 400 mg daily could have trough level testing to indicate if dose escalation is appropriate to try and achieve a better result. These data also highlight a problem with oral therapy. It is difficult to monitor treatment on an ongoing basis when administering oral therapy, while it is much easier to document treatment compliance with intravenous agents. In examining patients with CML on imatinib, only lack of compliance was associated with failure to achieve a major molecular response [51].

Actual dose (as opposed to assigned dose) received can thus be an important indicator of benefit of imatinib therapy. In the EORTC 62005 400 mg vs. 800 mg phase III study, patients with lower actual administered dose fared less well than

those maintaining the full assigned dose. Furthermore, those patients crossed over in the 62005 study and the S0033 (US 400 mg vs. 800 mg) study showed that about one third of patients had benefit when their dose was increased, i.e., stable disease or partial response as best outcome [45]. While some of this effect could be due to the well-recognized increased clearance of imatinib over time, a compliance effect was likely also important with more patients continuing the higher dose of therapy understanding their tumor was getting worse.

Does surgery impact upon time to progression? Patients with resectable disease after imatinib therapy have a longer time to progression than those who did not have surgery. While these data are not randomized, these data suggest that resection for remaining residual disease is a way to eliminate disease that will become resistant later [52–55]. Unfortunately, studies in Europe and the US have failed to ask this question owing to lack of accrual.

4.11 Imatinib Pharmacokinetics

Regarding imatinib pharmacokinetics, imatinib has an excellent oral bioavailability exceeding 95 %, unaffected by food intake [56]. It is thought that ATP-binding cassette (ABC) pumps such as P-glycoprotein and Breast Cancer Resistance protein (BCP) mediate absorption of imatinib from the lining of the bowel into the circulation. ABC pumps, which are expressed in the gastrointestinal tract, are thought to pump imatinib back to the gastrointestinal lumen, thereby decreasing the absorption of imatinib. [57] As only the unbound fraction of imatinib is active, binding of imatinib to blood components also plays a major role in the activity of imatinib. The most important blood protein to which imatinib binds is alpha1-acid glycoprotein (AAG) [58].

Imatinib is converted into several metabolites. CPG74588, an N-demethylated piperazine derivate, is the most important. CPG74588 exhibits similar anti-tumor activity as imatinib in vitro and has an area under the curve (AUC) approximately 10 % of that of imatinib. [56] The main metabolizing enzymes include the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, though others contribute [56]. Elimination of imatinib and its metabolites occurs mainly via the bile. ABC transporters are also involved in this process, pumping imatinib and the metabolites into the bile. The remaining 15–20 % is excreted by the kidneys [56]. Surprisingly, imatinib pharmacokinetics is not affected by severe hepatic dysfunction [59], and no dose modifications are required even in the case of moderate renal impairment (creatinine clearance of 20–39 mL/min) [60].

It appears that there are decreased imatinib plasma levels over time. In patients who used imatinib over approximately 12 months, the AUC after prolonged imatinib use was approximately 40 % of that shortly after treatment initiation [61]. Two mechanisms have been suggested to underlie this phenomenon of decreasing imatinib levels over time. The first is increased expression of ABC transporters in the gut wall causing decreased absorption; [57] the other is increased uptake by erythrocytes [62]. Compliance and other factors may be involved.

One expects that there is a certain threshold blood level required for imatinib activity against GIST. Given the IC50 of different *KIT* isoforms, this threshold appears to differ by *KIT* or *PDGFRA* mutation status, with the highest levels required for *KIT* exon 9 mutated tumors and the lowest levels for patients with *KIT* exon 11 mutated tumors, consistent with the observed clinical data. Imatinib trough level testing may eventually become important in this setting, as a result.

4.12 Second Line Sunitinib for Imatinib-Resistant Metastatic GIST

Sunitinib was given regulatory approval based on a single phase III study, where imatinib-resistant (400 mg daily) or intolerant patients were randomized (2:1) to sunitinib (50 mg, 4 on, 2 off) or placebo with an option to crossover at progression. In this trial, 310 patients were randomized and received sunitinib ($n=205$) or placebo ($n=105$). Partial responses and stable disease was seen in 7 and 58 % of patients in the sunitinib arm, and no responses were seen with placebo. Median PFS in the treatment arm was 6.3 and 1.5 months on placebo (Fig. 4.20) [63]. Interestingly, changes in serum KIT levels and other correlates of KIT and VEGF receptor blockade were observed in the sunitinib arm when compared to placebo [64, 65]. Specifically, a rising serum KIT level after 12 weeks of treatment was correlated with inferior outcome compared to those without such a rise. Responding patients tended to have either exon 9 mutations in GIST or wild-type GIST.

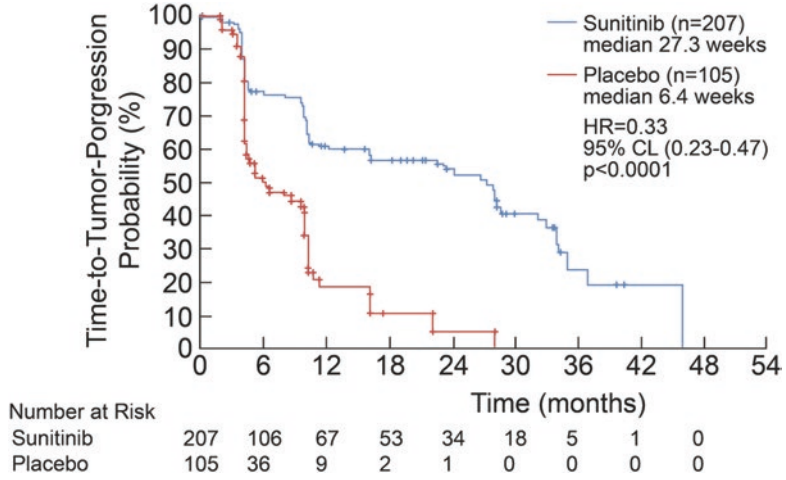

Fig. 4.20 Time to progression on sunitinib vs. placebo in GIST patients failing or intolerant of imatinib. From: Demetri GD, et al. Lancet 2006;368:1329–1338

Those patients with imatinib resistance and exon 11 *KIT* mutations often had secondary mutations that rendered the masses resistant to imatinib. [66]

In retrospect, an appropriate control group may have been to continue imatinib. It is now clear to medical oncologists that there can be an acceleration of symptoms for patients with metastatic disease when tyrosine kinase inhibitors are stopped. These data contribute to the concept that imatinib or sunitinib should be continued even in the setting of radiological or clinical progression, since treatment may still limit tumor growth and be associated with longer survival.

In a study of schedule, 60 patients were treated on a phase II trial of with imatinib-resistant or -intolerant GIST with daily continuous dosing of sunitinib at 37.5 mg; PFS and OS were 8.5 and 28 months, respectively [67]. This study indicated that with treatment, serum VEGF levels increased, while soluble KIT and VEGFR2 and VEGFR3 decreased. While there was a trend toward improvement in PFS and OS in patients whose serum KIT levels dropped from baseline, this was not significant until cycle 6 of treatment or later.

4.13 Regorafenib in Third Line for Metastatic GIST

As a practical matter, after failure of sunitinib, regorafenib has wide regulatory approved, by virtue of a placebo controlled randomized trial, the "GRID" trial. In this study patients were randomized to regorafenib 160 mg oral daily 3 weeks on 1 off or placebo, with crossover to regorafenib allowed if there was worsening of disease on placebo. In this study people with any primary genomic subtype had benefit (*KIT* or *PDGFRA* or no mutation in either) [75]. Median PFS was 4.8 months in the treatment group and 0.9 months in the control group. Patients crossed over from placebo experienced similar benefit.

After failure of all tyrosine kinase inhibitors, systemic treatment is better than no treatment. In a small randomized trial, imatinib was compared to placebo for patients who failed other lines of systemic therapy. Median PFS was 0.9 months on placebo vs. 1.8 months on imatinib. Thus, imatinib may slow progression, even though resistant clones may continue to grow. These data support the clinical finding of people doing worse when on breaks from their tyrosine kinase inhibitor [76].

4.14 Other Tyrosine Kinase Inhibitors for Metastatic GIST Failing Imatinib and Sunitinib

Of the other existing tyrosine kinase inhibitors, sorafenib [68], nilotinib [69], vatalanib [70], and others appear to have activity greater than observation alone. Masitinib has activity in first line metastatic GIST patients [72] and thus may be useful in later lines as well, as may be pazopanib. [73]. Dasatinib appears to have activity specifically in *PDGFRA* D842V mutation-positive GIST [74]. Activity of

these agents in later lines of therapy [69] suggests examination of these drugs as an earlier line of treatment during a patient's clinical course.

4.15 Newer Agents for GIST

It appears that at least three quarters of *KIT* mutant GIST patients progressing on imatinib develop secondary mutations in *KIT* that render the molecule insensitive to imatinib and often to other tyrosine kinase inhibitors. The heterogeneity of secondary mutations in one tumor limits the utility of tyrosine kinase inhibitors in this setting. How can these multiple resistant clones be managed medically? After imatinib, sunitinib, and regorafenib, other TKI appear [77] to have some activity, as noted above, but by and large responses are limited, as is the duration of response.

It is clear that resistant GISTs are genetically heterogeneous, even within one tumor or anatomical site [52, 66, 78–81]. Resistant clones can be identified by polymerase chain reaction, indicating selection of clones as a reason for imatinib resistance [82]. Other than differences in mitotic rate, it is not at all clear why some patients develop resistance more rapidly than others. Regardless, patients need a therapy with a different mechanism for activity against a wide spectrum of evolving mutations.

One approach to imatinib- and/or sunitinib-refractory GIST is to "vertically" target multiple steps in *KIT* signaling. The recent availability of new inhibitors of downstream target TOR (target of rapamycin) and more recently the PI3K (phosphatidylinositol 3-kinase) family of proteins makes combinations with receptor tyrosine kinase inhibitors natural combinations to examine [83].

Drugs targeting the molecular chaperone hsp90 (heat shock protein of 90kD molecular mass) may provide an avenue to pursue for tyrosine kinase inhibitor-resistant GIST. The hsp90 family of proteins (two proteins in humans, termed hsp84 and hsp86) are "chaperone" proteins, in that they are responsible for proper folding and function of oncogenic and normal proteins alike. It is hypothesized that proteins expressed from mutated genes are more structurally unstable, and thus more dependent upon the re-folding function of hsp90 family members than their wild-type counterparts [84]. Interestingly, both imatinib-sensitive and -resistant GIST cell lines are sensitive to the effects of hsp90 inhibitors such as retaspimycin (IPI504), a more soluble version of the classic geldanamycin analogue 17-AAG. It is also notable that a *PDGFRA* mutant GIST cell line is sensitive to IPI504.

These translational data informed a clinical trial of retaspimycin in patients with GIST. Decreased activity by PET (positron emission tomography) scan was observed in 16 of 22 evaluable patients, although only 1 of 36 had a RECIST response to therapy (as did 1 of 11 patients with other sarcomas treated with retaspimycin) [85]. Thus, like in CML and BCR-ABL, these findings provide some support for the contention that GIST remains dependent upon *KIT* expression and signaling even after the development of multiple mutations. However, a phase III

Table 4.1 Recommendations for systemic therapy for patients with GIST[a]

Clinical scenario		Comments
Adjuvant setting		PFS and overall survival are improved with 3 years of imatinib in the adjuvant setting for higher risk tumors. The use of imatinib in patients with GIST bearing exon 9 *KIT* mutations is controversial. Based on available data, patients with WT *KIT* and *PDGFRA* or D842V *PDGFRA* mutant GIST should not receive adjuvant imatinib, although patients with *PDGFRA* mutation other than D842V may benefit
Metastatic disease	First line	Imatinib 400 mg daily; consider increase to 800 mg oral daily if exon 9 *KIT* mutant. Patients with recurrent *PDGFRA* mutant or WT *KIT*/*PDGFR* GIST should be considered for alternative clinical studies given the low response rate with imatinib
	Second line	Sunitinib; we favor dosing at 37.5 mg oral daily without interruption instead of the 50 mg oral daily 4 weeks on, 2 weeks off schedule
	Third line	Regorafenib; since most patients require a dose reduction, starting at a lower than regulator-approved doses may be appropriate
	Fourth line and beyond	Continuing or recycling an approved inhibitor. Some clinicians will try pazopanib or other RTK inhibitors

[a]Clinical trials are always appropriate if available

study of retaspimycin against best supportive care was stopped early owing to early deaths on the treatment arm. These data will be important in planning future studies of other agents in third and greater line of treatment.

The biology of GIST continues to fascinate biologists and clinicians alike, looking for a means to treat patients with this difficult clinical problem. Rational combinations of existing agents and new drugs targeted against non-kinase portions of *KIT* or components of the downstream signaling cascade may become increasingly important, and it will be important to rigorously prove benefit so that GIST remains an effective proof-of-concept disease for innovative drug development. For example, IGF1R (insulin-like growth factor 1 receptor) antagonists administration caused stable disease in at least some GIST patients without *KIT* or *PDGFRA* mutations [86, 87]. Perhaps, *KIT* inhibitors will have to be administered with IGF1R, EGFR (epidermal growth factor), or other inhibitors to block activation of parallel kinase pathways usurped by GIST to maintain AKT signaling. This example is one in which horizontal blockade of signaling pathways may prove as important as the vertical blockade of one pathway at different steps. Thanks to new basic and translational science, the near future will be exciting for GIST research, in particular as the signaling pathway and dependence of GIST upon *KIT* signaling are unraveled (Table 4.1). As noted above as a general concept for sarcomas in general, immunotherapy, metabolic therapy, and epigenetic agents remain largely untested in GIST.

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Chapter 5
Liposarcoma

Liposarcoma is primarily a tumor that occurs with peak incidence between ages 50 and 70 and equal gender distribution (Fig. 5.1). As described previously (see Chap. 1, Fig. 1.6), liposarcomas account for approximately 20 % of all soft tissue sarcomas in adults. Anatomic distribution of liposarcoma is wide (Fig. 5.2) and is usually considered to manifest in three biological subtypes. The most common type is well-differentiated liposarcoma (sometimes called atypical lipomatous tumor [ALT]), and its high-grade variant dedifferentiated liposarcoma. The second most common is myxoid (low grade) and round cell (high-grade) liposarcoma. The least common is (high-grade) pleomorphic liposarcoma. Each subtype has a very distinctive morphology, natural history, and genetic changes utilized in diagnosis.

Well-differentiated (WD) liposarcoma or ALT is used to describe non-metastasizing low-grade lipomatous neoplasms that have a propensity for local recurrence. The term ALT is applied to extremity lesions, while WD liposarcoma is the preferred term for retroperitoneal and truncal lesions. It is important to realize that ALT recurs much more commonly than lipomas and is considered to have malignant potential due to the higher incidence of local recurrence. Both ALT and WD liposarcoma show similar ring, giant and marker chromosomes in the 12q13-15 region, resulting in amplifications of *HDM2*, *CDK4* and *HMGIC*, in keeping with a single pathologic entity, as suggested by the ALT/WD liposarcoma in the World Health Organization Classification. On our review of 800 patients with a histological diagnosis of liposarcoma [1]. ALT rarely recurred, whereas WD liposarcoma, particularly of sclerosing type, was more likely to recur.

WD liposarcoma is locally aggressive, non-metastasizing, composed of mature adipocytes of variable size and scattered stromal atypical cells. These tumors present as deep-seated enlarging masses often of very large size. They have been subdivided into adipocytic or lipoma-like, sclerosing-type, and inflammatory. The high-grade counterpart of WD is dedifferentiated liposarcoma which occurs much more frequently in the retroperitoneum compared to extremities. In the retroperitoneum, it more often presents de novo rather than subsequently present in recurrences

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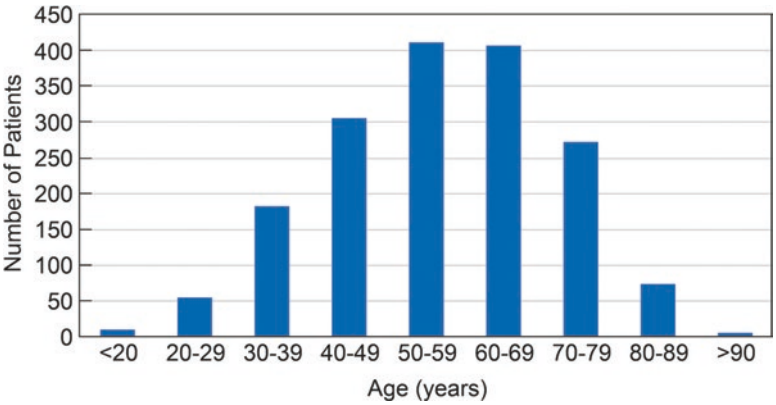

Fig. 5.1 Age distribution for adult patients with liposarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 1713$

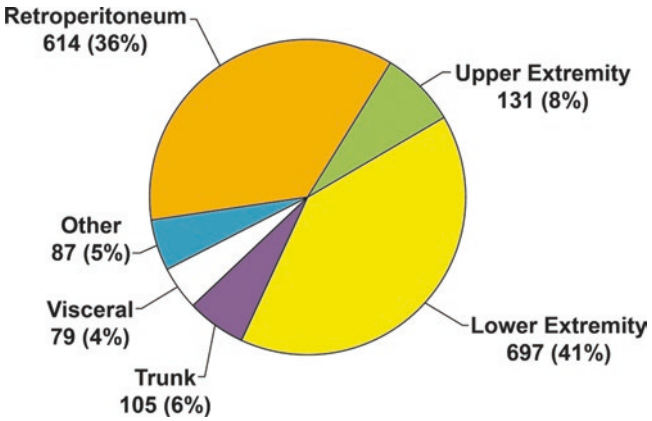

Fig. 5.2 Site distribution for adult patients with liposarcoma, all patients. MSKCC 7/1/1982–6/30/2010, $n = 1713$

(Fig. 5.3). The kidney is often surrounded, and adherence to the capsule is seen, usually without parenchymal invasion (see Treatment, below). The most frequent morphology of the non-lipogenic component includes myxofibrosarcoma or undifferentiated pleomorphic sarcoma (formerly termed malignant fibrous histiocytoma) although other histologies such as osteogenic sarcoma or rhabdomyosarcoma are not infrequently observed as well. Notably, these secondary histologies do not predict for a more aggressive course than the dedifferentiated liposarcoma component itself.

Myxoid liposarcoma (Fig. 5.4), and its high-grade counterpart round cell liposarcoma, account for up to 40 % of all liposarcomas. They are often large at time of presentation (Fig. 5.5). The histologic picture is composed of uniform, round, or

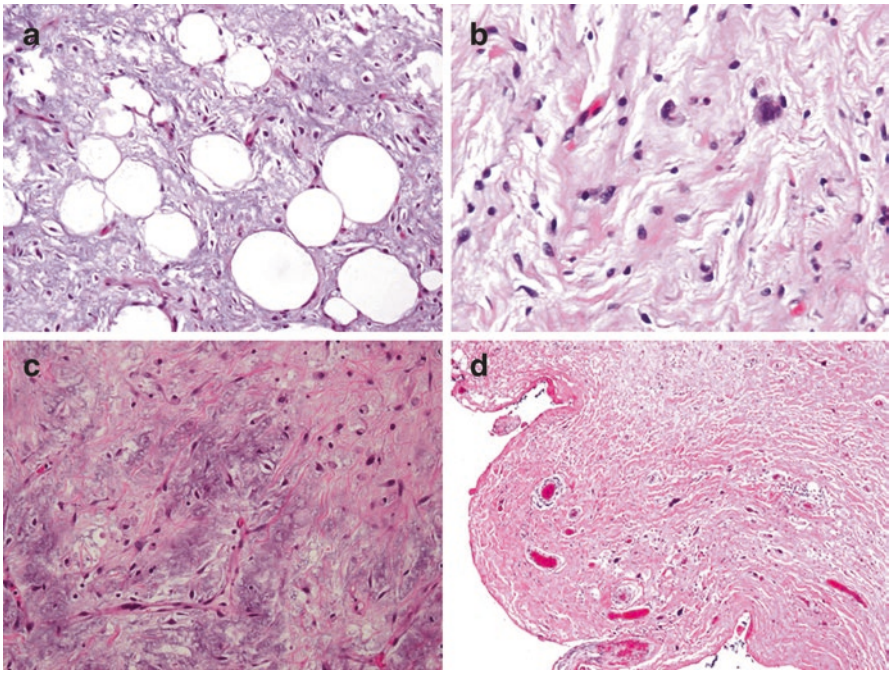

Fig. 5.3 Liposarcoma: (**a**) WD-myxoid areas, (**b**) other component non-lipogenic low grade, (**c**) dedifferentiated high grade, (**d**) renal capsule adherence

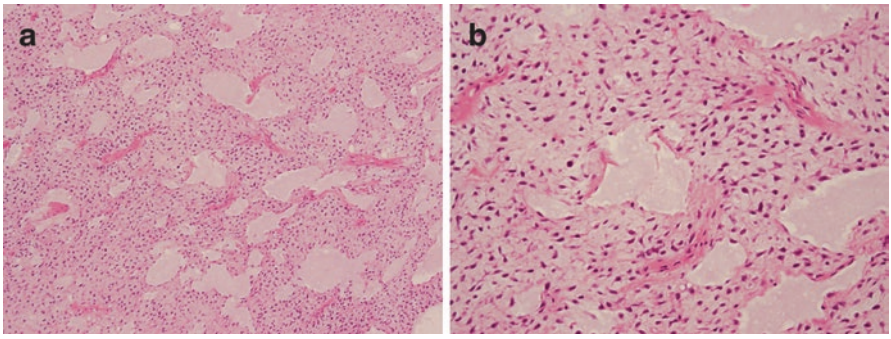

Fig. 5.4 Low-grade liposarcoma, without round cell component (**a** and **b**)

oval primitive non-lipogenic mesenchymal cells with a variable number of small signet ring lipoblasts, all in a prominent myxoid stroma. A characteristic branching vascular pattern described as "chicken wire" is commonly seen. Studies have shown that >5% of round cell define the high-grade variant with significant risk of metastatic disease. Most commonly, the myxoid/round cell subtype occurs in the deep tissues of the extremities, usually the proximal thigh.

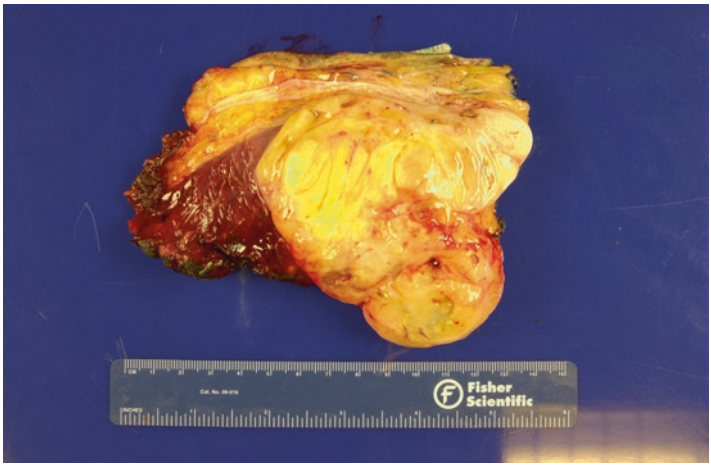

Fig. 5.5 Gross resection of low-grade myxoid liposarcoma left posterior thigh, 15.2 × 10.1 × 6.3 cm

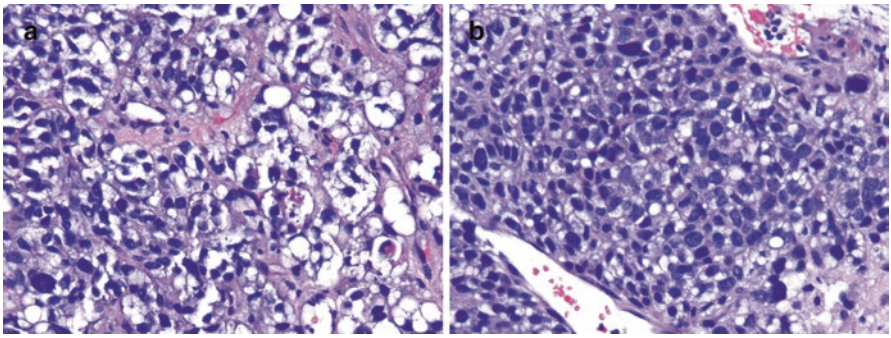

Fig. 5.6 Pleomorphic liposarcoma, needle biopsy

Pleomorphic liposarcoma (Fig. 5.6) is a highly malignant sarcoma, which accounts for fewer than 5 % of all liposarcomas, being commonly present in an older age group, usually in the deep soft tissue of the extremities. The diagnostic microscopic features is the presence of pleomorphic lipoblasts. Mitotic activity is always high, and hemorrhage and necrosis very common. Early metastasis is common, almost always to the lung. Distribution of the various histologic subtypes of liposarcoma is seen in Fig. 5.7 and by subtype by site, Fig. 5.8.

Outcome is site dependent with lower risk of local recurrence in extremity lesions. Those tumors that did recur in our institution occurred late, often after 5 years [1]. WD liposarcoma situated in the retroperitoneum and mediastinum recurs

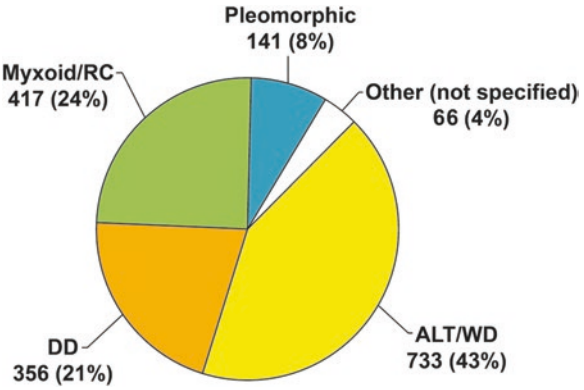

Fig. 5.7 Distribution of adult patients with liposarcoma by histology, all sites. MSKCC 7/1/1982–6/30/2010, $n = 1713$, *DD* dedifferentiated, *ALT/WD* atypical lipomatous tumor/well differentiated

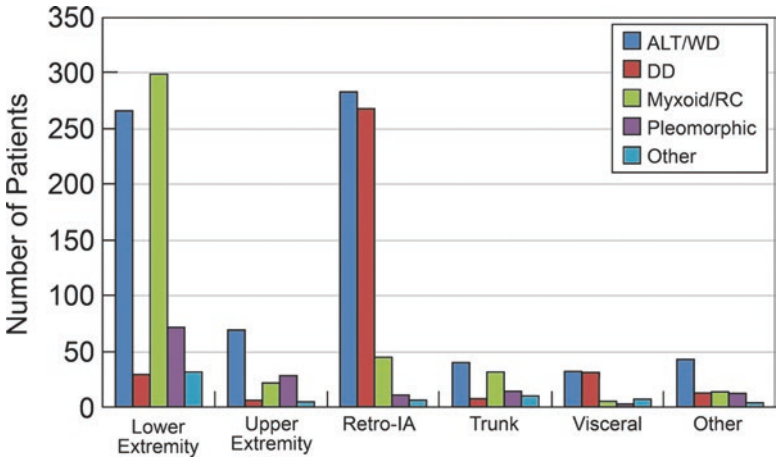

Fig. 5.8 Distribution of adult patients with liposarcoma by site and histology. MSKCC 7/1/1982–6/30/2010, $n = 1713$, *DD* dedifferentiated, *ALT/WD* atypical lipomatous tumor/well differentiated, *RC* round cell, *IA* intra-abdominal

consistently, often accompanied by dedifferentiation and ultimately metastasis in some. It is difficult to determine how frequent dedifferentiation occurs, but it is certainly greater than 10 % and probably in a lifetime approaches 40 %.

5.1 Imaging

Imaging is characteristic, particularly in the retroperitoneum, where well-differentiated components can be readily identified and often accompanied by subsequent dedifferentiation. On CT imaging, this portion of the tumor has fat density, typically Hounsfield units (HU). The dedifferentiated component has more variable

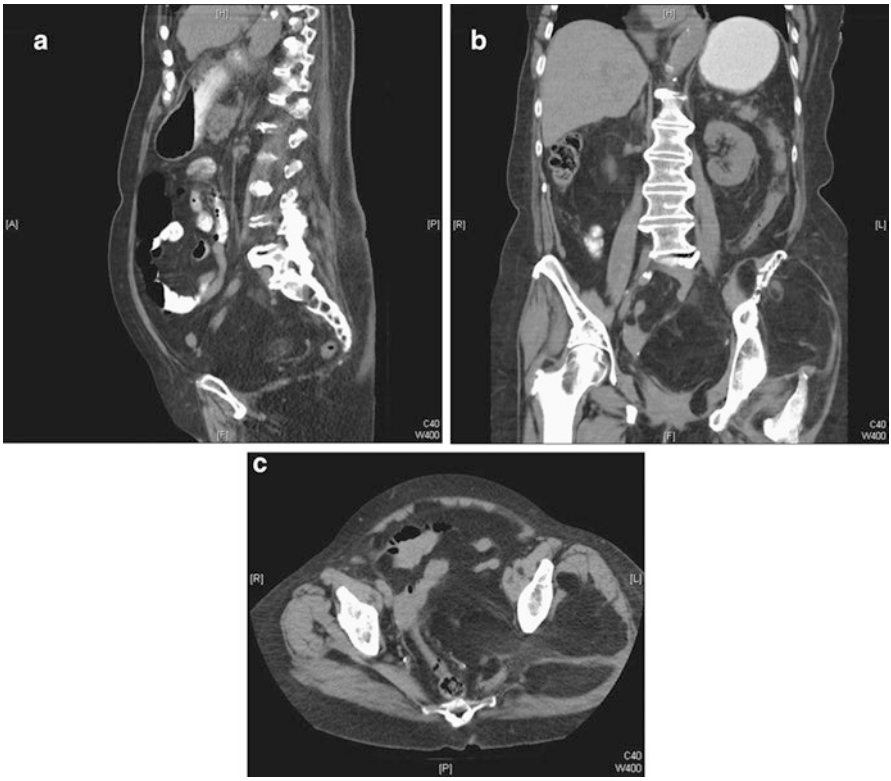

Fig. 5.9 CT scan (**a**–**c**) of extensive well-differentiated liposarcoma, extending through the pelvis into the buttock. The sarcoma has nearly the same radiological density as normal fat

but higher density by HU; a minimum of 0 HU for defining the dedifferentiated component may be useful in characterizing these tumors, but this concept has not been examined prospectively. Once a recurrence has occurred, the lesions are often multifocal and unlikely to be cured by further operative procedures. In the retroperitoneum, lesions are large, often with a well-differentiated component that can be present for years (Figs. 5.9 and 5.10). The majority usually develops a dedifferentiated component, and it is this higher grade component that increases the risk of progression with displacement, but not invasion of intra-abdominal organs (Fig. 5.11). The largest of these tumors can reach large size and extend into the buttock and thigh (Figs. 5.12 and 5.13). Pleomorphic liposarcoma has a relatively high risk of metastasis to multiple sites including lung, soft tissue, bone, and liver (Fig. 5.14). Myxoid/round cell liposarcoma has an unusual predilection for unusual sites of soft tissue metastasis (Fig. 5.15) and subsequent death, making surveillance for metastases a challenge, as noted below in the section on radiation therapy.

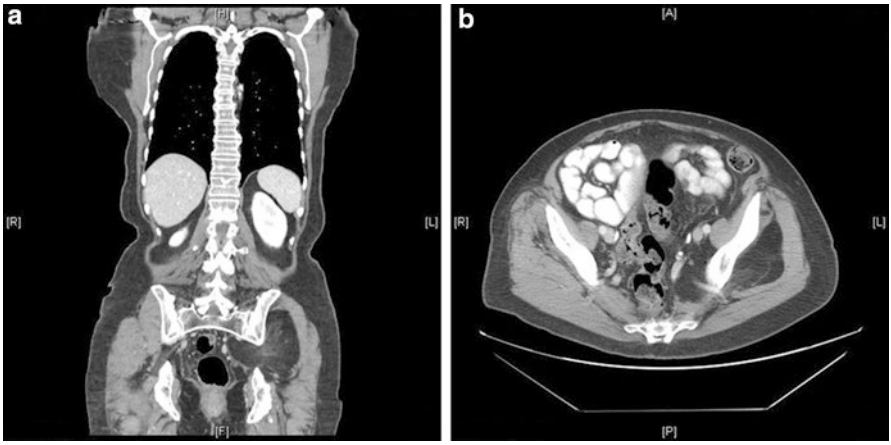

Fig. 5.10 Well-differentiated liposarcoma of pelvis and buttock with encasement of L5 nerve root and superior gluteal vessels (**a**, **b**)

5.2 Diagnosis

The genetics of each type of liposarcoma makes them as distinct from one another as breast adenocarcinoma is from renal cell carcinoma, and their biology and the results of treatment vary substantially. WD and dedifferentiated liposarcomas have characteristic amplifications of chromosome 12q, giant chromosomes, ring and marker chromosomes, in particular loci around genes encoding *CDK4* and *HDM2* (the human version of *MDM2*). Myxoid/round cell liposarcomas usually contain t(12;16) with *FUS-DDIT3* (genes formerly termed *TLS* and *CHOP*, respectively), and occasionally t(12;22) *EWSR1-DDIT3* (see Chap. 1, Table 1.1). Both are distinct from pleomorphic liposarcoma, which has genetic characteristics more in common with undifferentiated pleomorphic sarcoma (UPS, formerly termed malignant fibrous histiocytoma [MFH]) than the other forms of liposarcoma. Myoxid/round cell liposarcoma, in comparison to aneuploid sarcomas like pleomorphic liposarcoma, contain very few secondary mutations; perhaps, the most common are mutations in *PIK3CA* found in 10–15 % of myxoid/round cell liposarcomas to date. The implications for therapy for this mutation are unknown.

5.3 Treatment

The dominant treatment of all liposarcoma subtypes remains surgical resection. The extent of surgical resection is dependent both on the site of the lesion and the underlying histopathology. As with all sarcomas, complete gross resection is essential. The extent of the resection beyond complete gross resection will vary by site and by type. ALT often presents late as a large lesion and have a somewhat tenuous

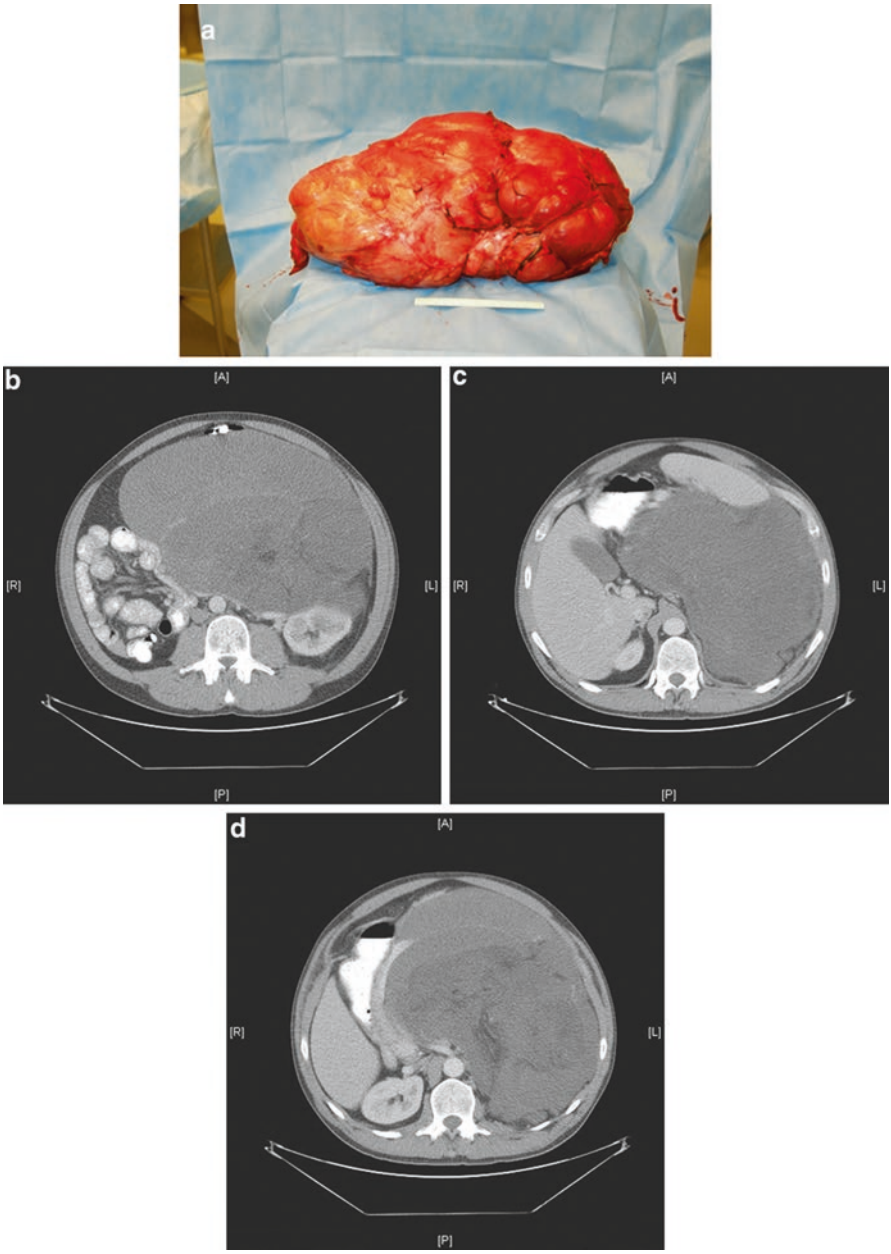

Fig. 5.11 Gross specimen (**a**) and CT of well-differentiated low-grade liposarcoma with dedifferentiated elements, showing displacement of (**b**) kidney, (**c**) spleen, and (**d**) pancreas

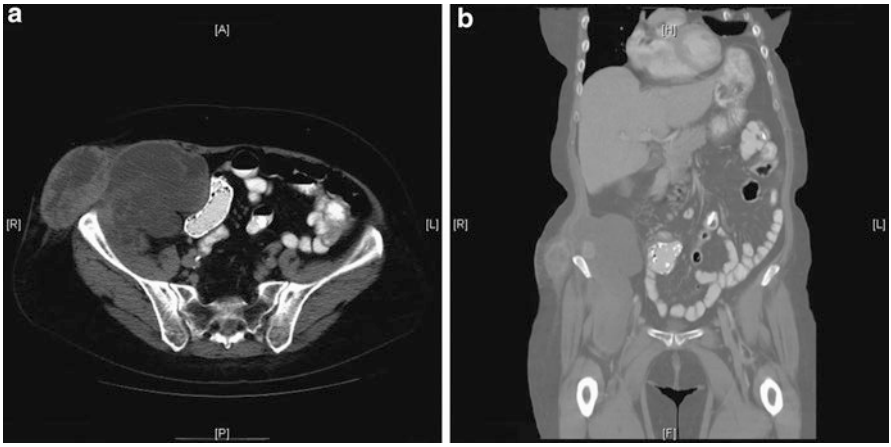

Fig. 5.12 CT of dedifferentiated liposarcoma with retroperitoneal trans pelvic extension into thigh (**a**, **b**)

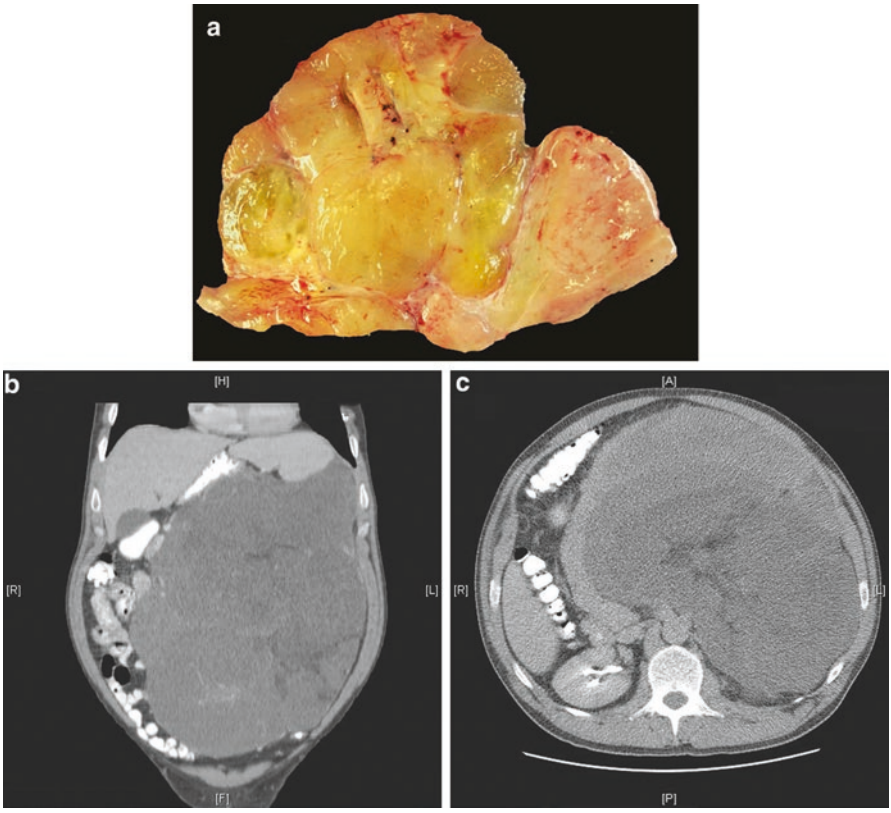

Fig. 5.13 Gross specimen (**a**) and CT (**b**, **c**) of 31 lb, 44×31×23 cm. well-differentiated and dedifferentiated liposarcoma

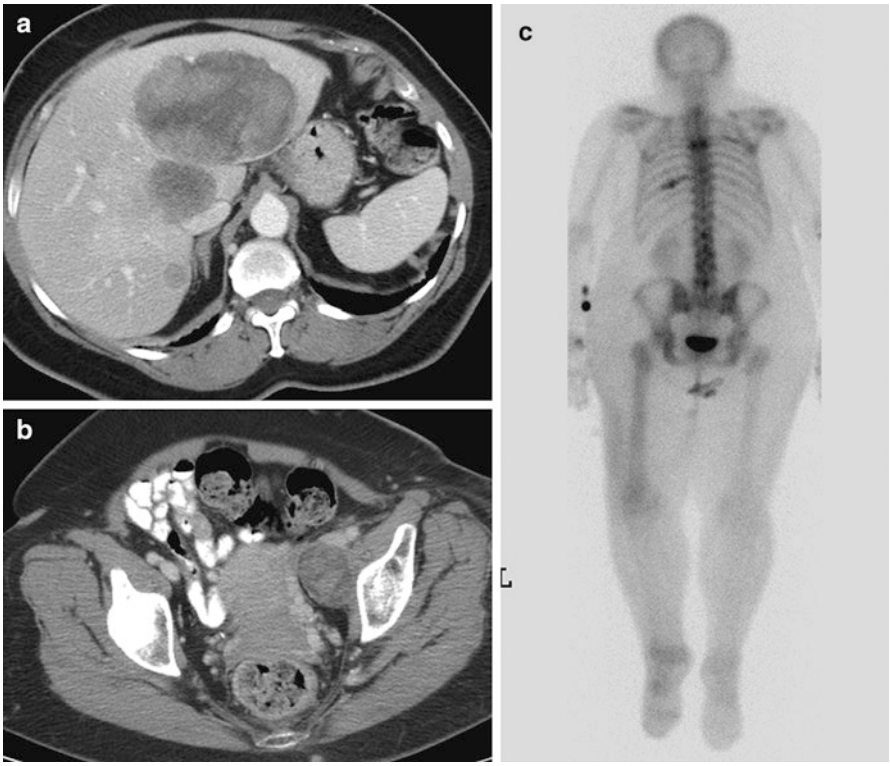

Fig. 5.14 Axial CT (**a**, **b**) and PET scan (**c**) of metastatic pleomorphic liposarcoma to liver, retroperitoneum, and bone

membrane or pseudocapsule at the time of initial dissection and simple but large excision is adequate. High-grade sarcomas require a more extensive resection with a 2 cm margin of normal tissue but limited by adjacent neurovascular structures. The focus on the extremity is continued preservation of function as local recurrence has only limited, if any, effect on long-term survival.

The object at the first operation in the retroperitoneum is complete gross resection. We have not shown a benefit to more extended resections to involve adjacent but uninvolved organs [2]. It is important to appreciate that the kidney is rarely involved by parenchymal invasion and capsular adherence can be treated by capsular excision (Fig. 5.3). Recurrence is common and multifocal recurrence very common. On the majority of occasions when there is no identifiable high-grade or dedifferentiated recurrence, low-grade recurrence can be followed symptomatically. Aggressive use of chemotherapy or radiation in this situation is not justified.

Where the patient is symptomatic, reoperation can be advised with some evidence that even an incomplete resection can palliate symptoms and be associated with prolonged survival [3]. In the extremity, bone invasion is very uncommon but

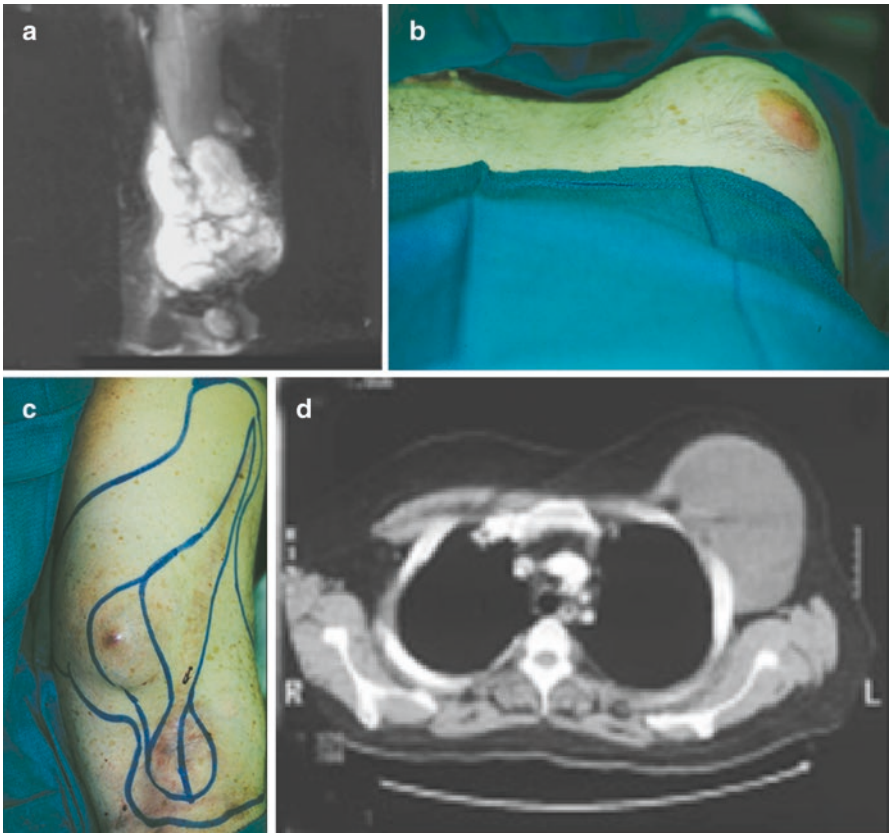

Fig. 5.15 Primary myxoid liposarcoma posterior thigh (**a**) with metastases to the left breast (**b**–**d**)

periosteal adherence is possible and requires periosteal stripping. The latter is associated with increased risk of fracture if adjuvant radiation is employed [4]. In the retroperitoneum, recurrent lesions, in contradistinction to primary lesions, can often invade or involve previously dissected tissue especially viscera and mesentery. This can often present in solvable local problems with great morbidity (Fig. 5.16).

5.4 Radiation Therapy for Liposarcoma

Many groups have utilized radiation therapy more aggressively than we do, but the data to support such an approach is limited and the potential complications significant.

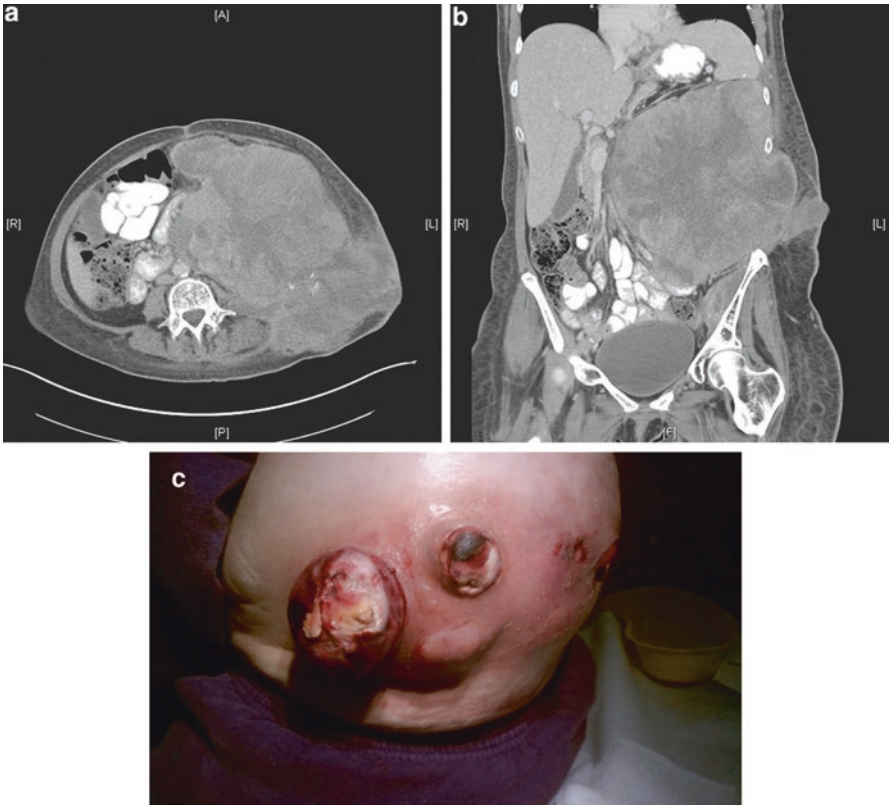

Fig. 5.16 (**a**, **b**) Locally recurrent dedifferentiated liposarcoma with visceral, bony, and abdominal wall invasion (**c**) clinical picture

Perhaps, the role of radiation therapy for liposarcomas should be more dependent on the specific subtype as well as site. Generally for atypical lipomatous tumors and well differentiated liposarcoma, the role remains a matter of controversy. For primary extremity lesions, the risk of local recurrence is low even for large lesions with positive margins as shown in the MSK nomogram [5]. For retroperitoneal lesions, a WD liposarcoma can exist for many years without symptoms or progression, making routine utilization of radiation therapy in these patients not justified. Dedifferentiated liposarcomas are less indolent with higher rate of relapse. In a report from Brigham & Women Hospital, 119 primary dedifferentiated liposarcoma of the retroperitoneum were evaluated. There was recurrence or progression in 84 % of patients with 92 % of the recurrence in the retroperitoneum6 making the use of radiation therapy attractive. This, however, has to be balanced with the potential morbidity associated with radiation therapy. Myxoid liposarcomas are considered exquisitely radiosensitive. In a report from Princess Margaret Hospital on 88 patients, the 5-year local control rate was 97.7 % with this histology [6]. As noted

above, myxoid liposarcoma is one of the sarcomas that commonly recur in non-pulmonary sites in comparison to other soft tissue sarcomas of the extremity, such as soft tissue, spine and bony pelvis [7], and radiation therapy can be effective in palliation of disease in this and other sites (Fig. 5.15). It is also notable that such bony metastases of myxoid liposarcoma are often not observed with CT scan, PET or bone scan, but only visible by MRI [7, 8]. For pleomorphic liposarcomas, the indications for radiation therapy are similar to other high grade histologies.

5.5 Systemic Therapy: General Considerations

It is particularly important to recall the three major forms of liposarcoma when deciding upon systemic therapy for patients with metastatic disease [9–20]. The recurrence patterns of these tumors differ substantially, with retroperitoneal WD and dedifferentiated liposarcoma recurring much more commonly in the abdomen than metastasizing. Sites for the unusual dedifferentiated–well-differentiated liposarcoma that do metastasize include other fatty sites of the body or bone as frequently as lung. Myxoid/round cell liposarcoma particularly metastasizes to other fatty sites of the body (e.g., mediastinum, bone marrow of the spine/pelvis) [7, 8], making assessment of response as challenging as identifying the key metastatic sites of disease in the first place.

5.6 Adjuvant Therapy

Given the 0 % response rate for WD and very low response rate for dedifferentiated liposarcoma to doxorubicin–ifosfamide [21], it is clear that existing agents as adjuvant chemotherapy are not indicated for this diagnosis. Given the resemblance of pleomorphic liposarcoma to UPS (see Chap. 7, UPS) and sensitivity to doxorubicin–ifosfamide, use of adjuvant therapy for this diagnosis should be discussed on a case-by-case basis for those patients with high-risk disease. The Royal Marsden database summary [21] and two studies including patients receiving adjuvant or neoadjuvant therapy for myxoid liposarcoma [22, 23] indicate the relative sensitivity to chemotherapy of myxoid/round cell liposarcoma. However, data regarding adjuvant chemotherapy are conflicting when considering extremity sarcomas, with many negative and few positive studies of patients with an array of histologies [24]. The Pervaiz 2008 meta-analysis suggests a clinically meaningful effect of chemotherapy on overall survival [25].

If there is an “adult” sarcoma histology in which chemotherapy may be helpful (along with synovial sarcoma), it is myxoid/round cell liposarcoma, and for young patients with higher risk disease we will offer systemic adjuvant or neoadjuvant chemotherapy for high-risk tumors based on the liposarcoma nomogram [26]. This recommendation may be an over-reading or under-reading of the literature, and treating physicians are encouraged to review the primary data.

5.7 Treatment of Metastatic Disease

Subsets of liposarcoma and their response to chemotherapy in the recurrent or metastatic setting were not well defined before the publication from the Royal Marsden group of the results of chemotherapy for patients with metastatic liposarcoma, grouped by liposarcoma subtype [21]. This has been the most instructive paper in highlighting the differences in doxorubicin–ifosfamide therapy for each of the diagnoses. In this study of 88 patients receiving chemotherapy for recurrent or metastatic liposarcoma, Jones et al. found patients with myxoid liposarcoma had a significantly higher response rate compared to all other liposarcoma patients, 48 % (95%CI; 28–69) and 18 % (95%CI; 8–31). Fourteen percent of patients had received adjuvant therapy, typically with doxorubicin–ifosfamide. Despite the higher response rate for the lower grade tumor, there was a longer time to progression for the high-grade version of the tumor (round cell liposarcoma) in comparison to myxoid liposarcoma, 16 months vs. 4 months (with wide and overlapping confidence intervals), indicating at least some activity of chemotherapy in both myxoid and round cell liposarcoma. Notably, the response rate (largely using RECIST [Response Evaluation Criteria In Solid Tumors]) for patients with WD liposarcoma was 0. No data were provided on the specific utility of trabectedin, known to be active in myxoid/round cell liposarcoma [27].

Other studies examining patients with primary and metastatic liposarcoma demonstrate [23] or deduce [22] that myxoid/round cell liposarcoma is relatively sensitive to doxorubicin- or ifosfamide-based chemotherapy. The recently approved agent olaratumab along with doxorubicin provides a new option for first line therapy for metastatic liposarcoma, since this is one histology that has at least some doxorubicin sensitivity.

Patients with myxoid and round cell liposarcoma demonstrate significant sensitivity to the minor groove binding agent trabectedin (ET743, Yondelis®), approved for clinical use in Europe, the United States, and elsewhere [27, 28].Although real and reproducible activity was seen in a number of phase II studies with trabectedin in myxoid/round cell liposarcoma, the randomized phase II study of patients with all forms of leiomyosarcoma and liposarcoma treated with trabectedin as a 24 h infusion vs. 1 h infusion showed RECIST 1.0 response rates of 6 % and 2 %, respectively [28]. Of note, trabectedin was active in both schedules, though median progression-free survival was only modestly different, at 3.7 months for the 24 h arm q 3 week vs. 2.3 months for the 3 h weekly infusion arm ($p < 0.02$ after multivariate adjustment) [28] (Fig. 5.17). Although the data on time to progression as a function of sarcoma subtype were not published, in the authors' experience the responses to trabectedin were in patients with myxoid/round cell liposarcoma, and largely only stable disease for patients with leiomyosarcoma or well-differentiated or dedifferentiated liposarcoma.

As part of the trabectedin vs. dacarbazine later line study [28], liposarcoma patients fared better with trabectedin than with dacarbazine. A total of 518 patients with metastatic/recurrent liposarcomas (all types) and leiomyosarcomas were randomized 2:1 between trabectedin:dacarbazine. Median PFS was 4.2 mo in the trabectedin group and 1.5 mo in the dacarbazine group, HR=0.55, p<0.001; overall survival was not significantly different between the two arms (12.4 mo for trabect-

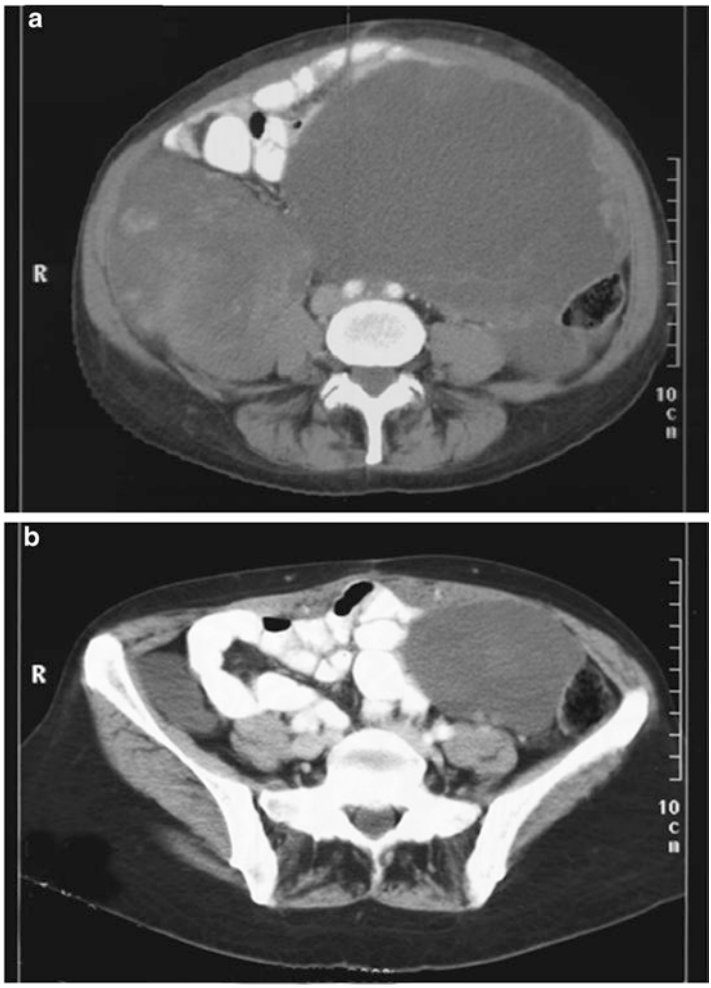

Fig. 5.17 Axial CT scan of response of myxoid/round cell liposarcoma to trabectedin (ET743)—(**a**) at diagnosis (**b**) after 7 months of treatment

edin, 12.9 mo for DTIC). These data are somewhat unsurprising given the known lack of activity of dacarbazine in liposarcoma, but underscores the idea that trabectedin is active in liposarcoma.

In a similar manner, eribulin demonstrated superior overall survival than dacarbazine in liposarcoma and leiomyosarcoma patients in a phase III trial. A total of 452 patients were randomized 1:1 between eribulin and dacarbazine. Overall survival was superior for the eribulin patients vs patients treated with dacarbazine (13.5 mo vs 11.5 mo, HR 0.77, $p<0.017$). In a subset analysis, the principal benefit was observed in liposarcoma patients, and thus is a valid option for therapy where the drug is approved [29]. While the paper by Jones et al. noted activity of doxorubicin–ifosfamide in pleomorphic liposarcoma [21], there are only anecdotal data that pleomor-

Table 5.1 Recommendations for systemic therapy for patients with well-differentiated/dedifferentiated liposarcoma[a]

Clinical scenario		Comments
Neoadjuvant/ Adjuvant chemotherapy		Not employed
Metastatic/recurrent disease[a]	1st line	Anthracycline[b] or anthracycline–olaratumab; anthracycline-ifosfamide can be considered, but nephrectiomy conducted in many patients with this diagnosis makes its administration more challenging
	2nd line	Eribulin (in countries where the agent is approved)
		Trabectedin (in countries where the agent is approved)
		Gemcitabine alone or in combination with docetaxel or vinorelbine
	3rd line	Ifosfamide; CDK4 inhibitors, if available; pazopanib clinical trial; supportive care. There appears to be at least minor activity of immune checkpoint inhibitors

[a]Only the dedifferentiated component may respond
[b]PEGylated liposomal doxorubicin (Doxil®/Caelyx®) if poor KPS or elderly

Table 5.2 Recommendations for systemic therapy for patients with myxoid/round cell liposarcoma

Clinical scenario		Comments[b]
Neoadjuvant Adjuvant chemotherapy		Anthracycline–ifosfamide for 3–6 cycles in patients with high-risk myxoid/round cell liposarcoma
Metastatic disease	1st line	Anthracycline[a], anthracycline and olaratumab, or anthracycline–ifosfamide
	2nd line	Ifosfamide, if not used in 1st line
		Eribulin (in countries where approved)
		Trabectedin (in countries where approved)
		Gemcitabine–docetaxel appears inactive; pazopanib has little activity
	3rd line	As of 2016, patients are eligible for engineered T cells against NY-ESO-1 if they are HLA-A2(+)
		Clinical trial; supportive care

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

phic liposarcoma can respond to gemcitabine–docetaxel, with two of three patients on a randomized study responding to gemcitabine-based therapy [30], suggesting a unique sensitivity of this form of liposarcoma, which we have seen in patients treated off study. Similarly, gemcitabine–docetaxel has occasionally been associated with minor responses of the dedifferentiated form of liposarcoma although we have not observed responses of WD liposarcoma to any form of systemic therapy to date.

Similarly, responses of any of these forms of liposarcoma to kinase directed agents has been rare to date [31–34], indicating the need to focus more on the activity seen with trabectedin in these sarcomas as well as the role by which these largely aneuploid tumors (save myxoid/round cell liposarcoma) maintain their aneuploidy without undergoing apoptosis (Tables 5.1, 5.2, 5.3).

Table 5.3 Recommendations for systemic therapy for patients with pleomorphic liposarcoma

Clinical scenario		Comments[b]
Neoadjuvant/ Adjuvant chemotherapy		Remains controversial, to be discussed on a case-by-case basis; anthracycline–ifosfamide is the combination to consider in this scenario
Metastatic disease	1st line	Anthracycline ± olaratumab[a] ; alternate options include gemcitabine alone or in combination with docetaxel or vinorelbine
	2nd line	Ifosfamide or other agent not used in 1st line
		Eribulin (in countries where approved)
		Trabectedin (in countries where approved)
	3rd line	The effectiveness of immunotherapy is unknown. Pazopanib has only minor activity Clinical trial; supportive care

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

Other clear targets for therapy among liposarcomas are CDK4 and MDM2 in WD/differentiated liposarcomas by virtue of their genomics. Unfortunately, despite large-scale amplification of both genes in most WD/dedifferentiated liposarcoma, response rates to either MDM2 or CDK4 inhibitors in clinical trials is under 10 % and probably under 5 % [35]. Given the bone marrow toxicity of MDM2 inhibitors seen to date (late and long lasting thrombocytopenia), it is not clear that these agents will be combinable. CDK4/6 inhibitors with their lesser toxicity may end up being agents more amenable to combination therapy. It is not clear what the role of epigenetic or metabolic regulators may be in liposarcoma. In terms of immunotherapy, response rates are low but not zero for dedifferentiated liposarcoma from the SARC 28 trial, but further exploration of subtypes is needed [36].

5.8 Outcomes

Mortality rates for liposarcoma vary widely depending on the underlying histopathology and have been reported to vary from 1 to 90 %, firmly establishing the importance of histological subtyping. Recurrence is common and depending on site and histopathology, has equal wide range. In addition to the histological subtype, histological grade remains a dominant factor in outcome, often reflecting the extent of differentiation or dedifferentiation. We have recently described a subtype-specific nomogram for patients with primary liposarcoma [26], which allows better characterization of outcome. The clear delineation between the subtypes is seen (Fig. 5.18), and a nomogram has been established based on over 800 patients presenting with primary liposarcoma to our institution. The break down by histological subtype was 46 % WD, 18 % dedifferentiated, 18 % myxoid, 10 % round cell, and pleomorphic 8 %.

Outcome is also dependent on site (Fig. 5.19) and the ability to obtain a complete gross resection. Once a complete gross resection has been achieved, a negative microscopic margin contributes a small but limited benefit. In the retroperitoneum,

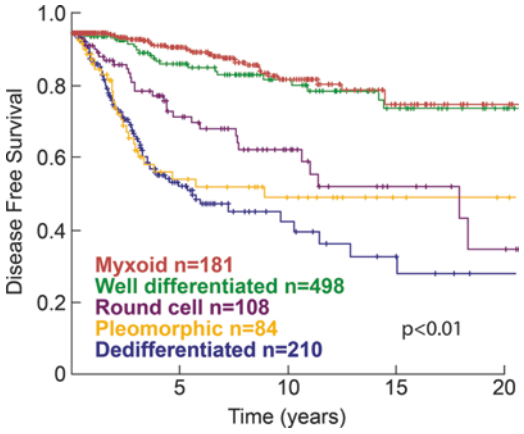

Fig. 5.18 Disease-specific survival of adult patients with primary liposarcoma by histology. MSKCC 7/1/1982–6/30/2010, $n = 1081$

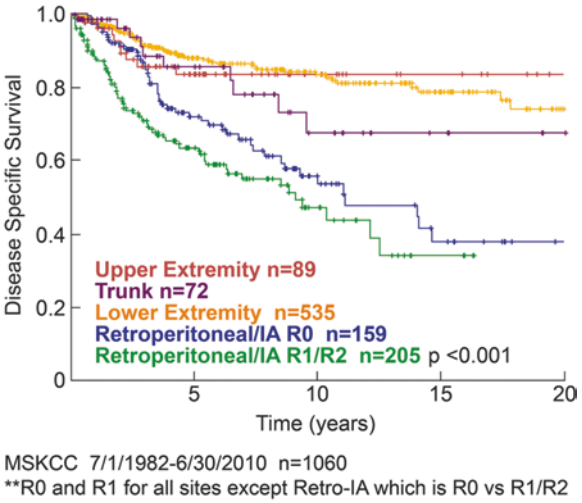

Fig. 5.19 Disease-specific survival of adult patients with primary liposarcoma by site. MSKCC 7/1/1982–6/30/2010, $n = 1060$

microscopic margin has not been identified as an important issue for recurrence or survival.

5.9 Outcome Following Metastasis

While there can be patients with responses to trabectedin for 3 or more years, responses to systemic therapy are not durable for the majority of patients. As an upper boundary, a European summary of 51 patients treated with trabectedin noted their myxoid/round cell liposarcoma population had a median progression-free survival of 14 months [37], while the Jones paper from Royal Marsden noted better survival for patients with lower grade liposarcomas, despite a lower response rate [21]. WD/DD liposarcoma remains a frustrating disease for patients, surgeons, radiation oncologists, and medical oncologists alike. It is hoped that the genomics of

pleomorphic liposarcoma and perhaps dedifferentiated liposarcoma will allow for responses to immune checkpoint inhibitors, in which a relationship to tumor mutational burden has been established in other cancers.

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Chapter 6
Leiomyosarcoma

Leiomyosarcoma (LMS) is one of the most common forms of soft tissue sarcoma, with approximately 2500 cases per year in the United States in 2015. The age distribution of adult leiomyosarcoma is presented in Fig. 6.1.

Leiomyosarcoma occurs at multiple different sites of the body (Fig. 6.2). Approximately half are located in the retroperitoneum or intra-abdominal sites, most commonly in the uterus. Leiomyosarcoma can arise in major vessels including the inferior vena cava (Figs. 6.3, 6.4, and 6.5). It is important to recognize that leiomyosarcomas are excellent examples of the difference in tumor biology based on their anatomic site of origin. For example, cutaneous leiomyosarcoma are lesions mostly lacking metastatic potential, presenting as small dermal nodules and classified as low grade regardless of histological appearance.

Leiomyosarcomas are easier to recognize microscopically due to its relatively consistent expression of markers such as desmin and smooth muscle actin using standard immunohistochemistry (Fig. 6.6). In contrast, leiomyosarcomas with epithelioid or myxoid features often pose diagnostic challenges and have a less consistent smooth muscle immunohistochemistry profile although the clinical relevance of these rare subtypes remains undefined.

6.1 Imaging

In the extremity, MRI is usually preferred although CT provides similar information. In the retroperitoneum, CT and MRI provide differing information but the MRI, on occasion, showing better vascular delineation. Unfortunately, in incompletely resected lesions, local–regional progression is common (Fig. 6.7). Metastases are readily identified on CT, with the liver as a common site for visceral primaries (Fig. 6.8) and lung the most common metastatic sites for uterine and extremity primaries.

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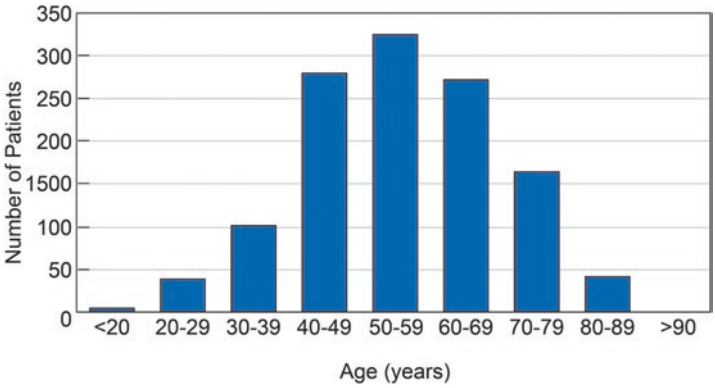

Fig. 6.1 Distribution by age of adult patients with leiomyosarcoma, all sites. MSKCC 7/1/1982–6/30/2010 $n = 1229$

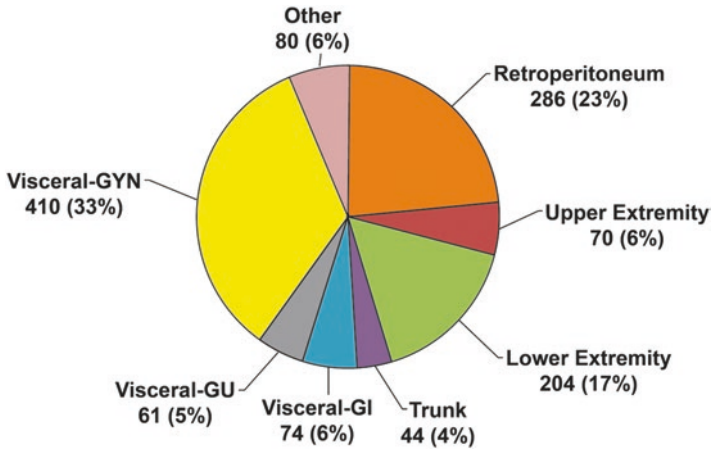

Fig. 6.2 Distribution by site of adult patients with leiomyosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 1229$ *GYN* gynecologic, *GU* genitourinary, *GI* gastrointestinal

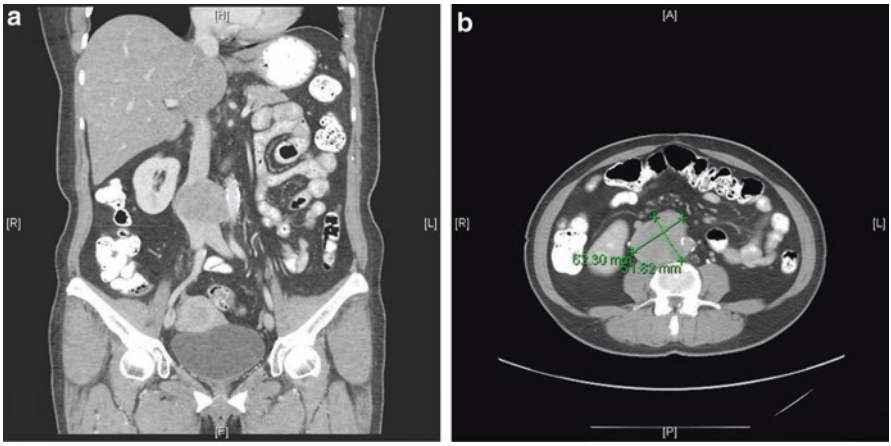

Fig. 6.3 CT scan (**a**, **b**) of high-grade leiomyosarcoma of inferior vena cava

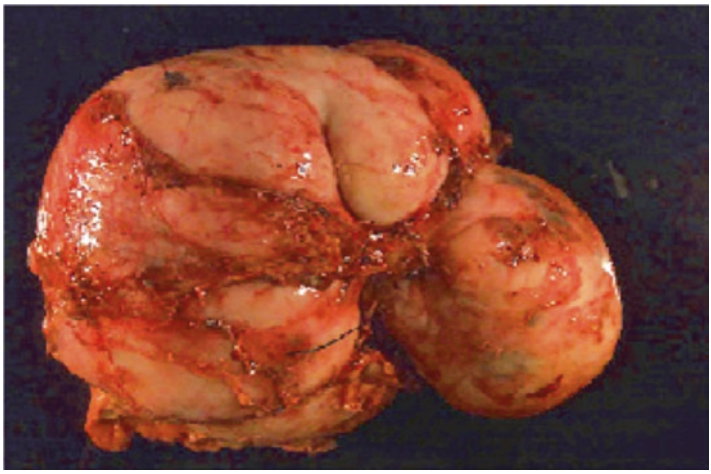

Fig. 6.4 Gross specimen of leiomyosarcoma of inferior vena cava

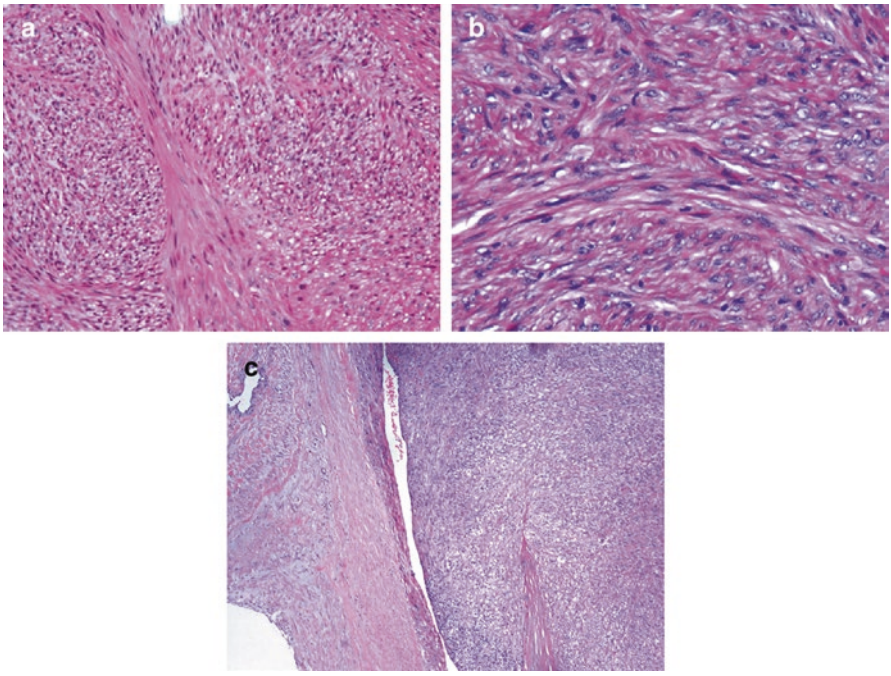

Fig. 6.5 Microscopic features (**a**–**c**) of leiomyosarcoma, with IVC wall invasion

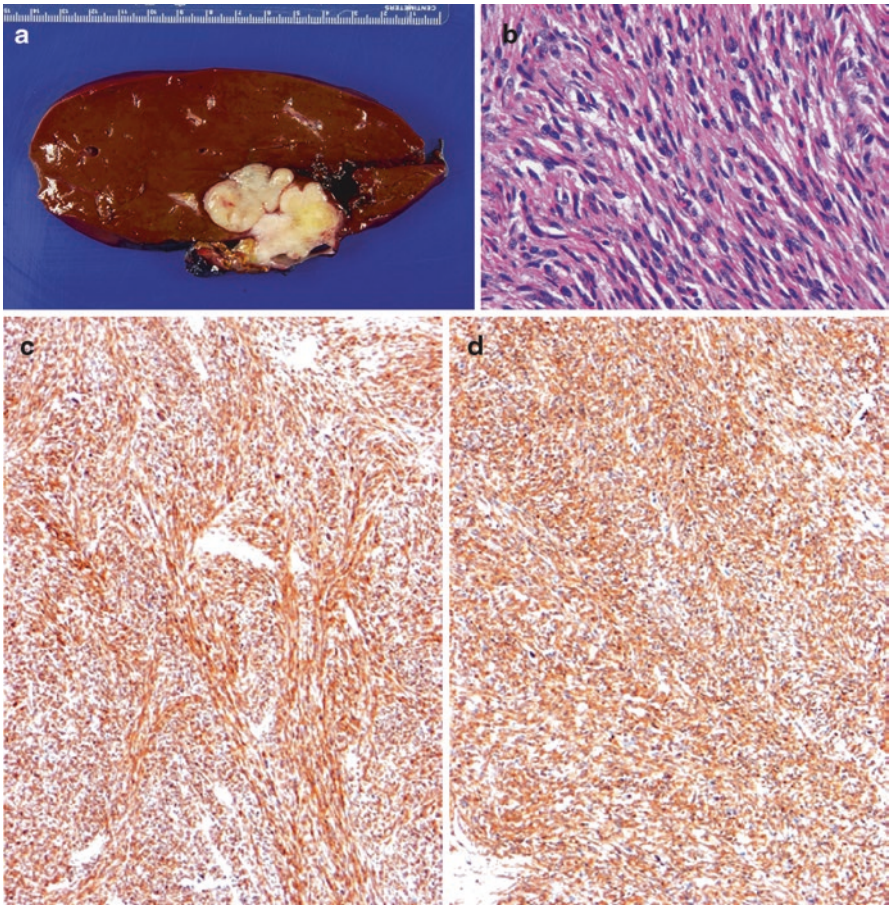

Fig. 6.6 Leiomyosarcoma of inferior vena cava with hepatic invasion, (**a**) gross specimen, (**b**) microscopic features, immunohistochemistry for (**c**) desmin, and (**d**) smooth muscle actin (SMA)

6.2 Diagnosis, Molecular Pathology

Leiomyosarcomas (LMS) are typically composed of eosinophilic spindle cells arranged in intersecting fascicles at 90° angles and associated with variable amounts of necrosis, mitotic activity, and atypia, depending on the grade of the lesion (Fig. 6.9).

By immunohistochemistry, leiomyosarcomas are positive for desmin, smooth muscle actin, muscle specific actin, and caldesmon, and rarely other markers such as cytokeratins or EMA in the epithelioid subtype. Leiomyosarcomas have an aneuploid karyotype [1–3]. More than half of leiomyosarcomas examined show karyotypes with profound structural aberrations, e.g., numerical changes and deletions of chromosomes 1, 13, 14, 16, 18, and 22, but the frequency of any specific aberration

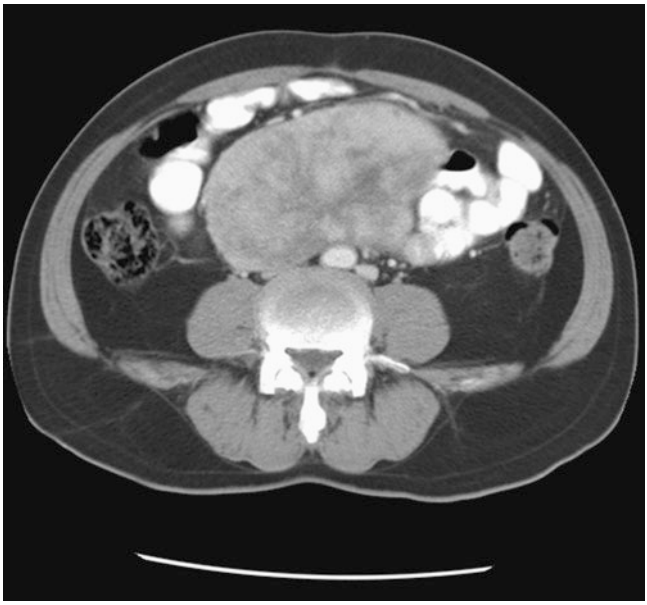

Fig. 6.7 CT of incompletely resected leiomyosarcoma of retroperitoneum

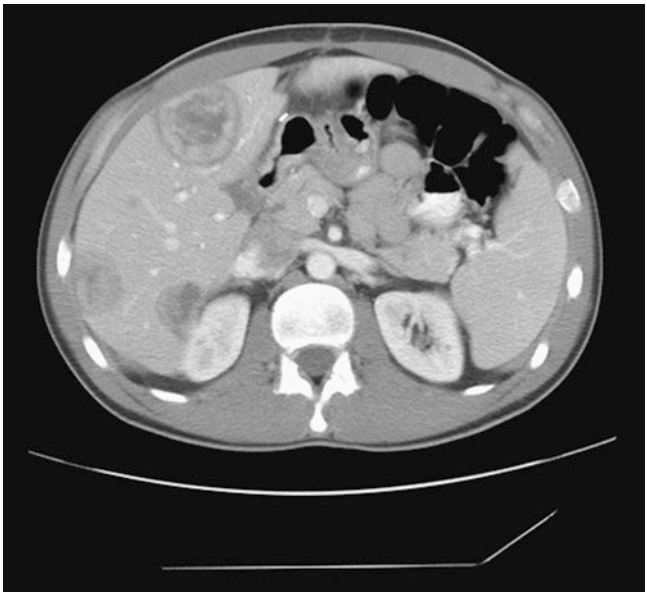

Fig. 6.8 CT of metastatic leiomyosarcoma to liver

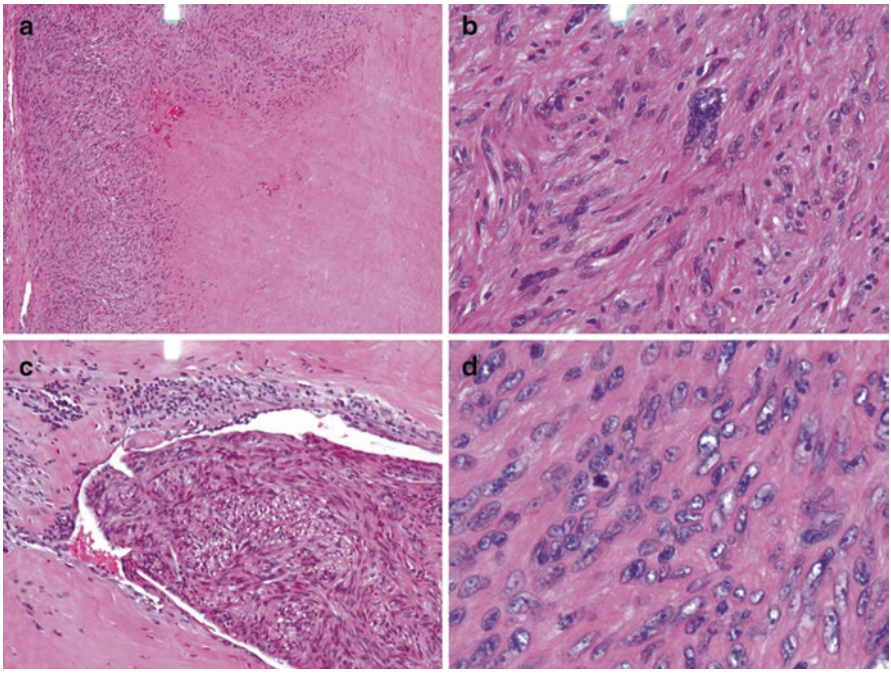

Fig. 6.9 Histologic features of high-grade leiomyosarcoma (**a**–**d**)

is <20 %. Few recurrent mutations are observed in leiomyosarcomas, other than already well-recognized *TP53* and *CDKN2A* mutations. In next-generation sequencing, some clues have been observed in a fraction of LMS that may predict for more aggressive behavior. A marker of alternative lengthening of telomeres (ALT), i.e., loss of ATRX expression, is associated with poor outcome in LMS patients and may help distinguish more aggressive lesions among lower grade tumors [4, 5].

Low-grade leiomyosarcomas must be first differentiated from benign mesenchymal lesions, such as leiomyomas, cellular schwannomas, as well as other sarcomas such as GIST, depending on the anatomic location. The differentiation between leiomyoma and leiomyosarcoma is particularly difficult in the uterus, where even benign lesions may have an atypical (symplastic) features or a high mitotic rate. As a result, for borderline uterine lesions the term smooth muscle tumor of uncertain mitotic potential (STUMP) is used [6]. It has been suggested that high levels of CA125 can help to distinguish the uterine leiomyosarcoma from uterine leiomyoma, but this remains to be confirmed [7]. Historically, many of the gastrointestinal leiomyosarcomas have proven to be GIST based on immunoreactivity to *KIT*. High-grade leiomyosarcoma with prominent pleomorphism need to be distinguished from UPS or pleomorphic rhabdomyosarcoma based on a more detailed immunohistochemical profile.

One needs to distinguish true leiomyosarcomas from a rare low-grade lesion termed Epstein–Barr virus-associated smooth muscle tumor (EBV-SMT), found in patients on chronic immunosuppressive therapy or with HIV disease. EBV-SMT usually presents in unusual anatomical locations and can be multifocal, which mimics

metastases and is characterized by very slow but persistent growth. Similarly, perivascular epithelioid cell tumors (PEComas) must be differentiated from leiomyosarcomas, the former expressing both smooth muscle and melanocytic markers [8].

6.3 Primary Treatment

As with other sarcomas, the primary treatment is surgical with complete resection necessary for prolonged survival. Lesions of unusual sites such as the inferior vena cava can require some technically challenging resections and reconstruction [9]. It has long been suggested that the replacement of the vena cava is required but we have found that it is not necessary and the majority of patients, as long as they have adequate venous drainage from at least one kidney, can safely have the vena cava tied distal to the inflow of the hepatic veins without major long-term sequelae. As the inferior vena cava is commonly occluded at the time of presentation, collaterals have developed such that caval replacement is not necessary. However, the extensive collaterals can complicate the procedure, as all such vessels not involved by tumor should be preserved. Diligent attention in the immediate postoperative period to the prevention of peripheral edema is such that significant edema is prevented and resolved, usually followed by clinical improvement and resolution of swelling of the lower extremities within 6–8 weeks of the procedure. Exercise tolerance appears limited in some patients following IVC ligation, perhaps owing to the vasodilation and venous pooling that occurs with exercise. Situations where the vena cava can be simply patched are preferable to its ligation if possible. A simple alternative using peritoneum to patch the vena cava [10] has been supplanted by other alternatives such as bovine pericardium.

6.4 Radiation Therapy

The relatively small number of leiomyosarcomas, compared to other histologies, makes it difficult to determine the impact of radiation therapy in this histology. In the BRT randomized trial of extremity and superficial trunk from MSK, there were 12/164 patients with leiomyosarcoma; local recurrence developed in 3/8 patients who didn't receive BRT as opposed to none in the four patients who received BRT. Therefore as with other soft tissue sarcomas, adjuvant radiation is generally employed for tumors over 5 cm in size or those with difficult anatomic constraints such as those of the head and neck and retroperitoneum. There remains controversy regarding the use of radiation therapy in the adjuvant setting for uterine leiomyosarcomas, though published data indicate no clear benefit in terms of progression free or overall survival, though local recurrences were reduced [11, 12]. In the EORTC randomized trial in stage I–II uterine sarcomas, there 99 patients with LMS. The rate of isolated local recurrence was 14% in those treated with surgery alone vs. 2% for those treated with postoperative pelvic radiation therapy [13]. These risks of distant

metastasis in these patients surpass the potential benefit of adjuvant radiation, making its role less appealing. In our practice, adjuvant radiation is employed for uterine leiomyosarcomas only for overt involvement of pelvic wall structures.

6.5 Systemic Therapy

6.5.1 Adjuvant Chemotherapy for Leiomyosarcoma

Adjuvant chemotherapy with doxorubicin or with gemcitabine–docetaxel has been examined prospectively in patients with uterine leiomyosarcomas. The Gynecologic Oncology Group conducted the first prospective randomized trial comparing adjuvant chemotherapy to no further therapy in patients with stage I or II uterine sarcoma, the majority of which were leiomyosarcomas. No significant improvement was noted in progression-free interval or overall survival with chemotherapy [14].

In a pilot study of patients with any stage primary uterine leiomyosarcoma rendered free of disease, promising results were seen in terms of progression free and overall survival with four cycles of gemcitabine–docetaxel chemotherapy [15]. The relative success of this study, at least in comparison to historical controls, led to a further phase II evaluation of the sequential use of four cycles of gemcitabine–docetaxel then four cycles of doxorubicin therapy in the adjuvant setting after resection of primary, nonmetastatic uterine leiomyosarcoma [16]. A total of 47 women with disease limited to the uterus were enrolled. With median follow-up of 27.4 months, 78 % of women were progression free at 2 years, and median progression-free survival was 39.3 months [16].

These data may lead to randomized studies examining this question further in leiomyosarcomas of the uterus and other sites alike. The authors have learned that a number of oncologists use adjuvant doxorubicin–gemcitabine–docetaxel, despite lack of proof of any survival benefit. The 2016 standard of care pending a phase III trial from the GOG/NRG, as noted by the first author of the study, is surgery alone without adjuvant chemotherapy [17]. Data regarding epirubicin-ifosfamide for extremity sarcoma in the neo-adjuvant setting do not directly answer the use of these agents in abdominal or visceral primary leiomyosarcoma.

6.6 Outcomes After Primary Therapy

For extremity, leiomyosarcoma actuarial disease-specific survival is approximately 70 %. Survival based on size for primary extremity lesions, i.e., ≤5 cm, 5–10 cm, and >10 cm, is shown in Fig. 6.10. Considering all primary sizes for retroperitoneal leiomyosarcomas together, the outcomes are poor and consistent with their typically large size at presentation (Fig. 6.11) [18] (Table 6.1).

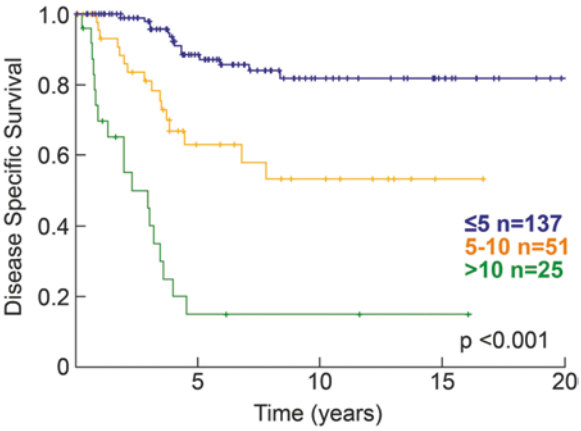

Fig. 6.10 Disease-specific survival for adult patients with primary extremity leiomyosarcoma, by size. MSKCC 7/1/1982–6/30/2010 $n=213$

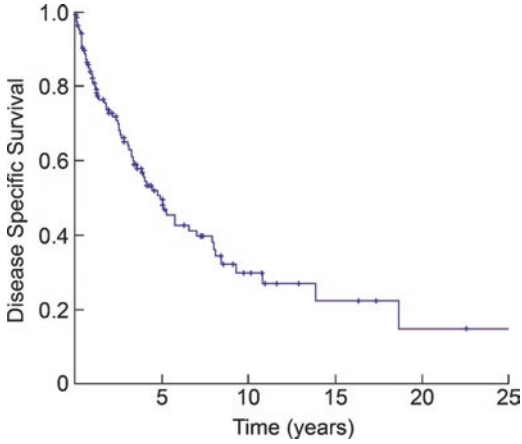

Fig. 6.11 Disease-specific survival for adult patients with retroperitoneal leiomyosarcoma. MSKCC 7/1/1982–6/30/2010 $n=146$

6.7 Patterns of Recurrence

The anatomic site of primary disease for a leiomyosarcoma also dictates if and how these sarcoma will recur. In an analysis of the MSKCC database, Gladdy et al. [18] examined 353 patients, of which 170 (48 %) presented with extremity 144 (41 %) with abdominal/retroperitoneal, and 39 (11 %) with truncal tumors. Median follow-up was 50 months. Most tumors were high grade (75 %), deep (73 %), and completely resected (97 %); median size was 6.0 cm.

Abdominal/retroperitoneal location was associated with worse long-term DSS compared to extremity or trunk ($P=0.005$). However, by multivariate analysis, only high grade and size were significant independent predictors of DSS. Overall, 139 patients (39 %) had recurrence: 51 % of those with abdominal/retroperitoneal, 33 % of extremity, and 26 % of truncal disease. Significant independent predictors for local recurrence were size and margin, whereas predictors for distant recurrence were size

Table 6.1 Cumulative incidence rates of DSS and factors predictive of DSS in primary leiomyosarcoma patients

Prognostic factor	*n*	5-Years DSS (%)	Univariate *P* value	Multivariate *P* value	Hazard ratio	95 % CI
Age (years)						
≤60	203	77	0.104	–		
>60	150	66				
Sex						
Female	157	72	0.605	–		
Male	196	72				
Grade						
High	265	65	<0.001	0.001	3.7	1.7–8.2
Low	88	98.5				
Size[a]						
≤5 cm	155	91	<0.001			
>5 to ≤10 cm	95	71		0.049	1.8	1.0–3.3
>10 cm	99	47		<0.001	3.4	1.9–6.3
Depth						
Deep	257	66	<0.001	0.076	2.0	0.9–4.5
Superficial	96	90				
Site						
Extremity	170	75	0.005			
Abdominal/ retroperitoneal	144	67		0.696	0.9	0.6–1.4
Trunk	39	81				
Margin						
Negative	289	74	0.226	–		
Microscopically positive	52	70				
Grossly positive	12	42				

With permission from: Gladdy RA, et al. Ann Surg Oncol 20:1851–1857, 2013
DSS disease-specific survival, *CI* confidence interval
[a]Size not available for four patients

Table 6.2 Competing risk analysis for local and distant recurrence in primary leiomyosarcoma

	Local recurrence			Distant recurrence		
Clinicopathologic variable	*P* value	Hazard ratio	95 % CI	*P* value	Hazard ratio	95 % CI
Margin R1 vs. R0[a]	0.024	2.1	1.1–3.9	–	–	–
Site abdominal/retroperitoneal vs. extremity/trunk	0.744	1.1	0.6–2.2	0.258	0.8	0.5–1.2
Size >10 cm vs. ≤10 cm	0.013	2.9	1.2–6.7	0.001	2.6	1.5–4.6
High vs. low grade	0.266	1.7	0.7–4.4	<0.001	3.9	1.9–7.8
Deep vs. superficial	0.125	2.7	0.8–9.2	0.059	1.9	1.0–3.6

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CI confidence interval
[a]R2 margins were excluded

and grade (Table 6.2). Site was not an independent predictor of recurrence; however, late recurrence (>5 years) occurred in 9 % of abdominal/retroperitoneal and 4 % of extremity lesions (Figs. 6.12 and 6.13).

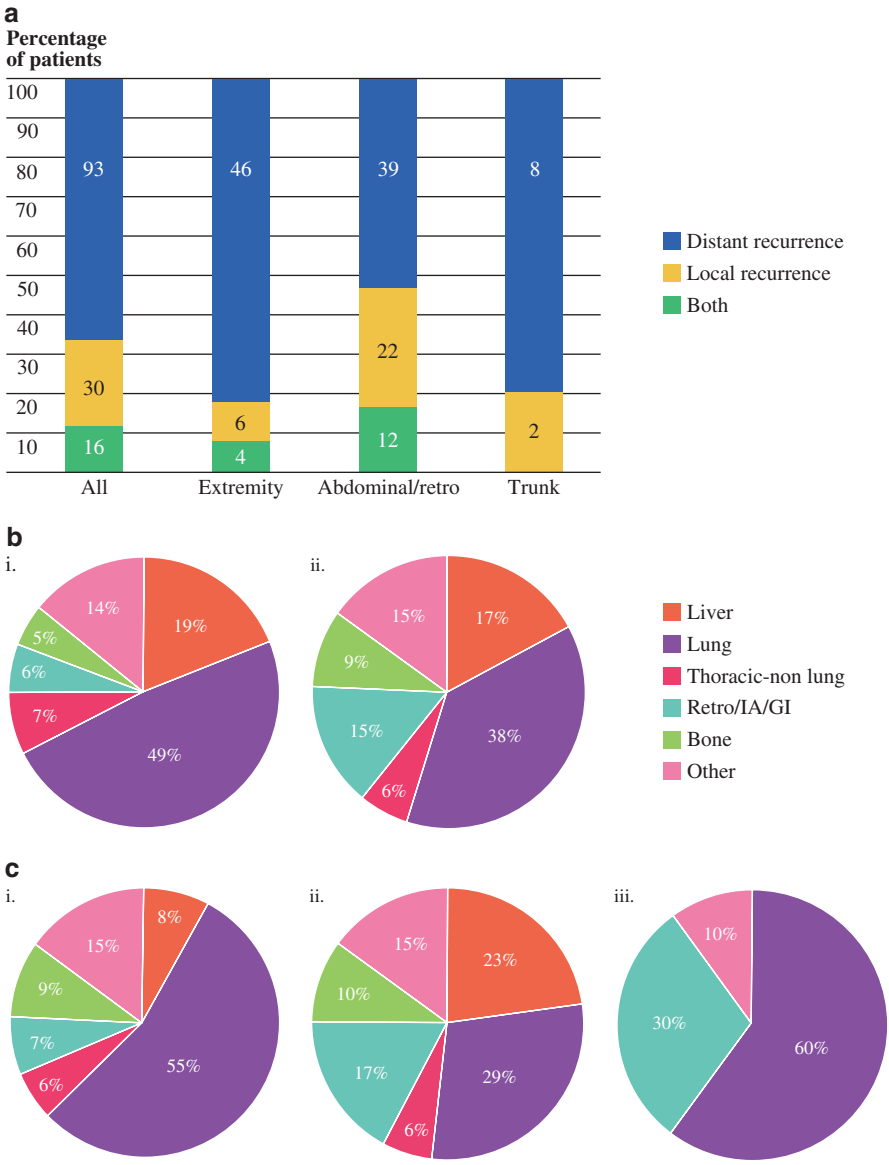

Fig. 6.12 Patterns of recurrence and sites of metastasis in primary leiomyosarcoma. (**a**) Percentage of initial recurrence location in primary leiomyosarcoma patients. (**b**) Sites of metastasis in all patients; site of first DR (*i*) and all DR (*ii*). (**c**) All DR by site; extremity (*i*), abdominal/retroperitoneal (*ii*), and trunk (*iii*). Thoracic—non-lung chest wall, soft tissue, and/or mediastinum, retro/IA/GI retroperitoneal/intra-abdominal; other brain or lymph node. With permission from: Gladdy RA, et al. Ann Surg Oncol 20:1851–1857, 2013

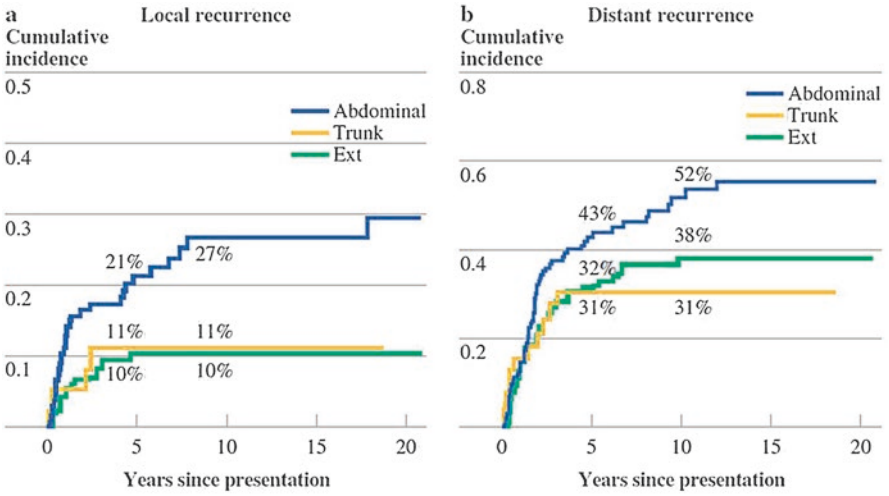

Fig. 6.13 Local (**a**) and distant recurrence (**b**) rates by site in primary leiomyosarcoma. Five-year and 10-year recurrence rates are displayed. *Ext* extremity. With permission from: Gladdy RA, et al. Ann Surg Oncol 20:1851–1857, 2013

6.7.1 Treatment of Recurrence

With single site recurrence, surgical resection can be anticipated and is potentially curative. As leiomyosarcomas are the commonest histology resected in the lung, pulmonary resections should be considered where possible. Some practitioners advocate for radiofrequency ablation, cryotherapy, or radiosurgery for such lesions; there are no comparative data regarding one technique vs. the other. Barring other options, systemic therapy may be employed with palliative intent.

6.8 Metastatic Disease

Analysis of a variety of randomized studies allows one to delineate the differential response of leiomyosarcoma vs. others such as liposarcoma, synovial sarcoma, or undifferentiated pleomorphic sarcoma (formerly MFH, malignant fibrous histiocytoma) [19]. It should be noted that subset analyses cannot substitute for primary trials of chemotherapy, but still can be useful in generating hypotheses.

In considering leiomyosarcomas as a whole, doxorubicin is clearly active, but ifosfamide appears to add relatively little to the response rate, based on both primary data and retrospective analysis clinical trials [20, 21]. Some of the data are difficult to parse since there is obvious contamination of the leiomyosarcoma group with what would today be termed GIST, which represents the majority of the sarcomas of the gastrointestinal tract. Dacarbazine (DTIC) and the related oral compound temozolomide have at least minor activity against leiomyosarcoma, but little

to no activity against other sarcoma subtypes except perhaps solitary fibrous tumor [22, 23]. Doxorubicin–DTIC combinations are also active against leiomyosarcoma [19, 24], but there is not obvious synergy of the combination in comparison to the single agents. The overall survival advantage afforded by anthracycline and olaratumab makes it a rational 1st line therapy for metastatic leiomyosarcoma.

In studies of uterine sarcomas specifically (largely leiomyosarcomas), the Gynecologic Oncology Group compared doxorubicin alone to doxorubicin and dacarbazine in a randomized trial. Response rates and overall survival did not differ between the two arms; the response rate to doxorubicin of 28 women with leiomyosarcoma was 25 % [25]. There is at least a weak association of estrogen or tamoxifen exposure to uterine leiomyosarcoma development [26–29]. However, estrogen receptor- or progesterone receptor-positive leiomyosarcomas only rarely respond to hormonal therapy such as aromatase inhibitors [30]. For an asymptomatic patient with low volume metastatic disease, it may provide a less toxic option for care than standard cytotoxic chemotherapy.

The above studies raise the idea that leiomyosarcomas from different anatomical primary sites could respond differently to chemotherapy, just as their risk of recurrence differs based on anatomic site. The difference in response rates for different sites of leiomyosarcoma is highlighted in the trials from cooperative groups [20, 21, 31]. Although only 20–25 % of uterine leiomyosarcomas responded to chemotherapy, uterine leiomyosarcoma was approximately twice as responsive to chemotherapy compared to leiomyosarcomas arising from the GI tract (mostly GISTs). These data are at odds with the cumulative EORTC meta-analysis of therapy for metastatic sarcomas [32]; however, in this EORTC analysis, leiomyosarcomas were not stratified with respect to site; poorly responding GIST were likely grouped together with better responding leiomyosarcomas of other sites.

The distinction of histology, anatomic site, and chemotherapy responsiveness extends to the gemcitabine–docetaxel combination, at least as later line therapy for metastatic disease. While there is activity of gemcitabine–docetaxel in leiomyosarcoma from a variety of anatomic sites, phase II data support the contention that uterine primaries respond better than those from other sites [33–38]. Randomized and non-randomized data also support the idea that combination therapy is superior to single agent gemcitabine [34, 35, 38–41], and that activity of gemcitabine–docetaxel is similar in first or second line for metastatic disease [34, 35]. Conversely, there is at least one randomized study exclusively of patients with leiomyosarcoma that indicates the equivalence of gemcitabine and gemcitabine–docetaxel [42]. It is also notable that the gemcitabine–docetaxel combination may have even greater activity against other sarcoma histologies, including UPS, pleomorphic liposarcoma, and pleomorphic rhabdomyosarcoma than leiomyosarcoma (all of which are sarcomas with aneuploid karyotypes) [38]. Other options for gemcitabine combinations for soft tissue sarcoma include those using vinorelbine [43] or dacarbazine [44]. The data regarding dacarbazine are notable for the observation of an overall survival advantage for the combination [44], as was seen for the gemcitabine–docetaxel combination [38].

Data also support the activity of the DNA minor groove binding agent trabectedin (ET-743) in patients with recurrent or metastatic leiomyosarcoma

although the response rate for leiomyosarcoma appears significantly below that of patients with myxoid/round cell liposarcoma [45–48]. With data from one randomized phase II study and other clinical trials, trabectedin was approved in Europe for use against metastatic sarcomas, while it was only approved in the United States after a positive phase III trial vs. dacarbazine [49]. As a reminder, trabectedin vs. dacarbazine was studied in both liposarcoma and leiomyosarcoma, showing a superior PFS for trabectedin (approximately 4 mo vs. 2 months), but no overall survival advantage [49]. Interestingly, with nearly the same trial design as the trabectedin study, eribulin was superior to dacarbazine, but not in leiomyosarcoma, and thus was approved in the United States only for liposarcomas [50].

As noted in a previous chapter, pazopanib has approval for use in several countries for leiomyosarcoma as one of several histologies studies as part of a large phase III placebo controlled trial (PALETTE) [51]. A study of liposarcoma and leiomyosarcoma patients with trabectedin vs. dacarbazine demonstrated a 2-month progression-free survival advantage for trabectedin, but no OS advantage [49]. Interestingly, with nearly the same trial design as the trabectedin study, eribulin was superior to dacarbazine, demonstrating a 2-month overall survival advantage [50].

While there has been little activity of kinase-directed agents in clinical trials involving sarcoma patients, the addition of bevacizumab appears to have been answered. Bevacizumab was first tested with doxorubicin and with gemcitabine–docetaxel in phase II studies. In the former study, only 2/17 patients with leiomyosarcoma had a response to doxorubicin with bevacizumab, lower than expected given the single agent activity of doxorubicin in leiomyosarcoma. Of equal or greater concern was the finding of six patients with grade 2–4 cardiac toxicity (usually reversible) on study [52]. It would appear difficult to move forward with doxorubicin–bevacizumab given these data. A recent randomized study of gemcitabine–docetaxel ± bevacizumab fared no better; the proposed 130 patient study was closed after 107 patients were accrued for futility, with numerically inferior PFS for the bevacizumab containing arm [53].

Clearly, we collectively must determine which molecular features of leiomyosarcoma are related to chemotherapy responsiveness. Whether subsets of leiomyosarcoma defined by immunohistochemistry [46] or by more sophisticated molecular techniques can predict for chemotherapy responsiveness or overall outcome remains a topic of research today. For example, there are few data to indicate why leiomyosarcomas are relatively sensitive to pazopanib compared to other sarcoma subtypes. Similarly, PD1-directed immune checkpoint inhibitors appear to have little activity as single agents in leiomyosarcoma, but may be more active in combination with other immunotherapeutics. Results from clinical trials of immune checkpoint inhibitors should become available in 2017.

In summary, leiomyosarcomas, although relatively uniform at first glance histologically, vary in their biological profile, as we are beginning to see with a fraction of the tumors with *ATRX* mutation and loss of expression, as well as variability in responsiveness to chemotherapy based on anatomic site. Doxorubicin with olaratumab,

Table 6.3 Recommendations for systemic therapy for patients with leiomyosarcoma[a]

Clinical scenario		Comments
Neoadjuvant / Adjuvant chemotherapy		Adjuvant chemotherapy is of limited benefit in extremity leiomyosarcomas and without clear benefit for abdominal or visceral leiomyosarcoma. Data from the 1998 Pervaiz meta-analysis provide some support for the use adjuvant systemic therapy in leiomyosarcoma patients as of 2016
Metastatic disease	First line	Anthracycline wtih olaratumab[b]
	Second line	Gemcitabine, alone or in combination[c], trabectedin, dacarbazine, temozolomide, or pazopanib
	Third line	Agent not used in second line; eribulin is available in some countries
	Fourth line	Ifosfamide (in fit patient); clinical trial; supportive care; PD1-directed immune checkpoint inhibitors appear to have little activity as single agents but may be more active in combination with other immunotherapeutics

[a]Clinical trials are always appropriate if available. Hormonal therapy, e.g., an aromatase inhibitor, is an option in uterine and retroperitoneal leiomyosarcomas, which are more commonly ER+ or PR+
[b]PEGylated liposomal doxorubicin (Doxil®/Caelyx®) if poor KPS or elderly
[c]Weekly gemcitabine–docetaxel has activity as well. There are no data comparing weekly low-dose therapy to a gemcitabine d1/d8, docetaxel d8 schedule. Gemcitabine and vinorelbine or dacarbazine may also have some degree of synergy

DTIC, gemcitabine–docetaxel, pazopanib, eribulin, and trabectedin all have activity in metastatic disease although there is no proven role of any chemotherapy in the adjuvant setting as of 2016. Further progress in defining subsets responsive to therapy, and determination of the mechanism by which leiomyosarcoma aneuploidy is maintained should help lead to new ideas for therapy, such as immunotherapeutic agents or drugs that affect metabolism or the epigenetic state of the cell (Table 6.3).

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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.

M.F. Brennan et al., *Management of Soft Tissue Sarcoma*,
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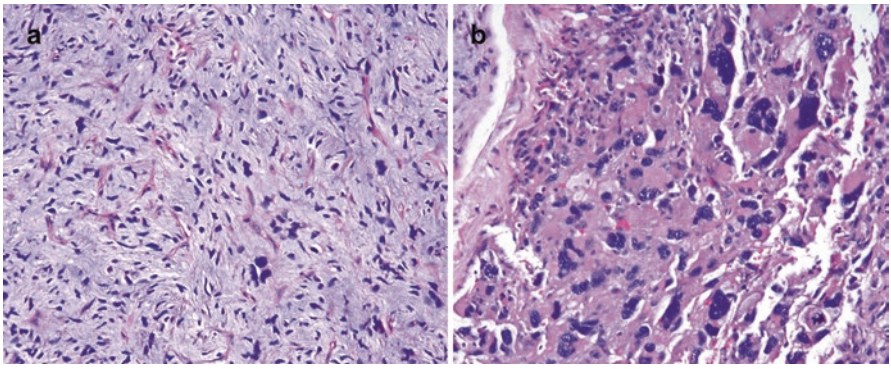

Fig. 7.1 (**a**) Myxofibrosarcoma: spindle and pleomorphic cells embedded in a predominantly myxoid stroma and associated with a rich vascular network. (**b**) High-grade pleomorphic type UPS (undifferentiated pleomorphic sarcoma) bizarre, multinucleated cells, with hyperchromasia and anaplasia

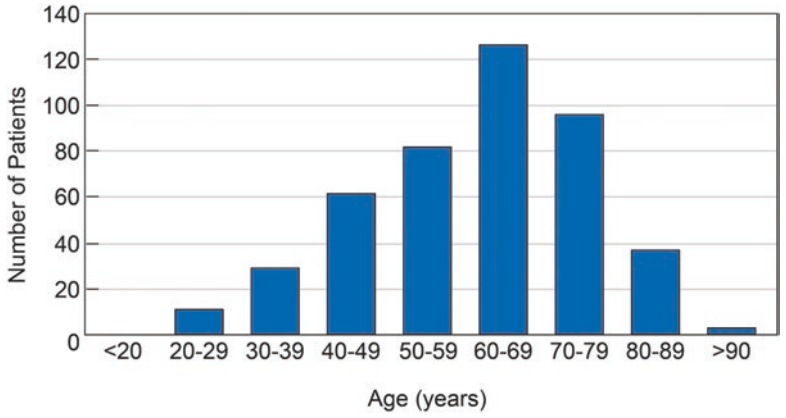

Fig. 7.2 Distribution by age for adult patients with myxofibrosarcoma, all sites. MSKCC 7/1/1982 – 6/30/2010, $n = 445$

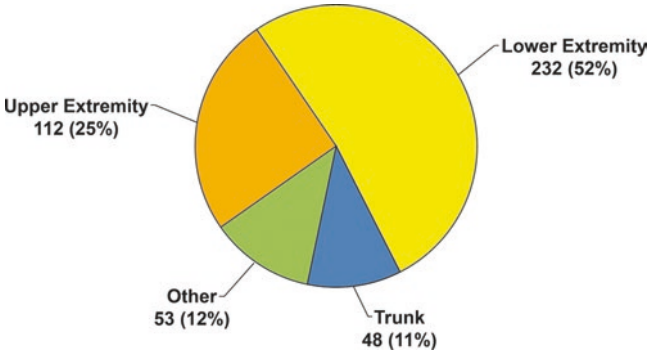

Fig. 7.3 Distribution by site for adult patients with myxofibrosarcoma. MSKCC 7/1/1982 – 6/30/2010, $n = 445$

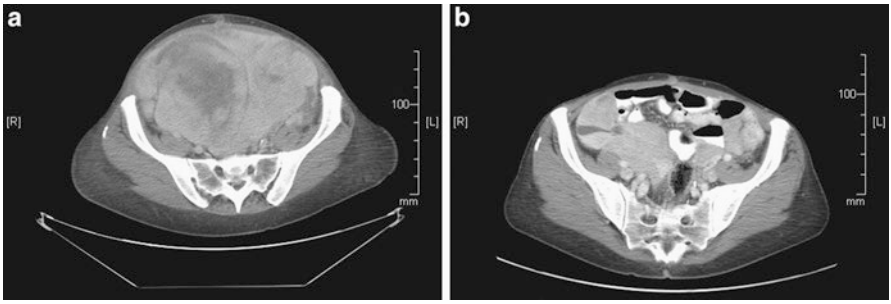

Fig. 7.4 CT of malignant fibrous histiocytoma /undifferentiated pleomorphic sarcoma of abdomen (**a**), and response to treatment at 4 months (**b**)

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)

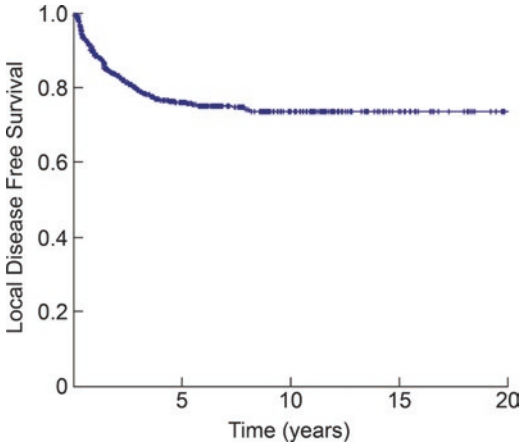

Fig. 7.5 Local disease-free survival for adult patients with primary malignant fibrous histiocytoma/ undifferentiated pleomorphic sarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 772$

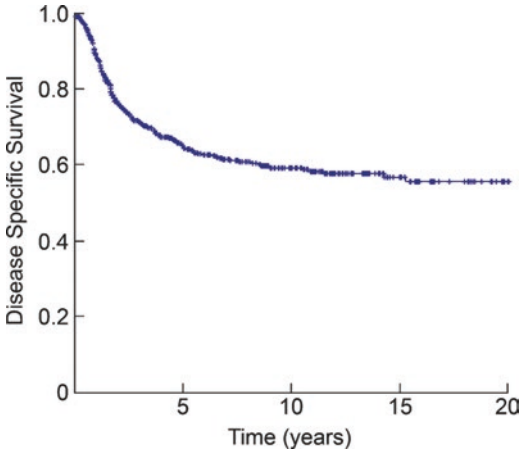

Fig. 7.6 Disease-specific survival for adult patients with primary malignant fibrous histiocytoma/ undifferentiated pleomorphic sarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 772$

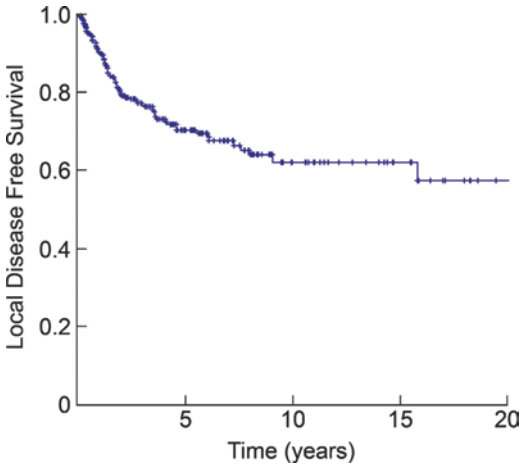

Fig. 7.7 Local recurrence-free survival for adult patients with primary myxofibrosarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 361$

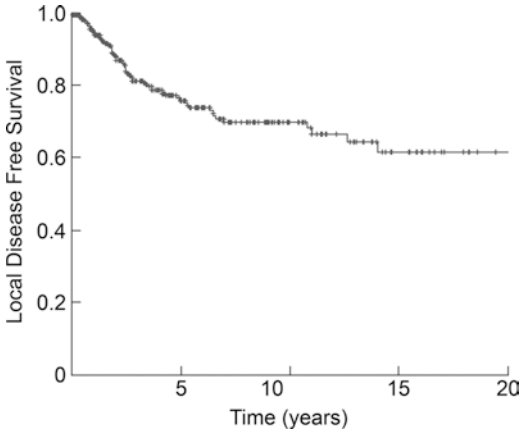

Fig. 7.8 Disease-specific survival for adult patients with primary myxofibrosarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 361$

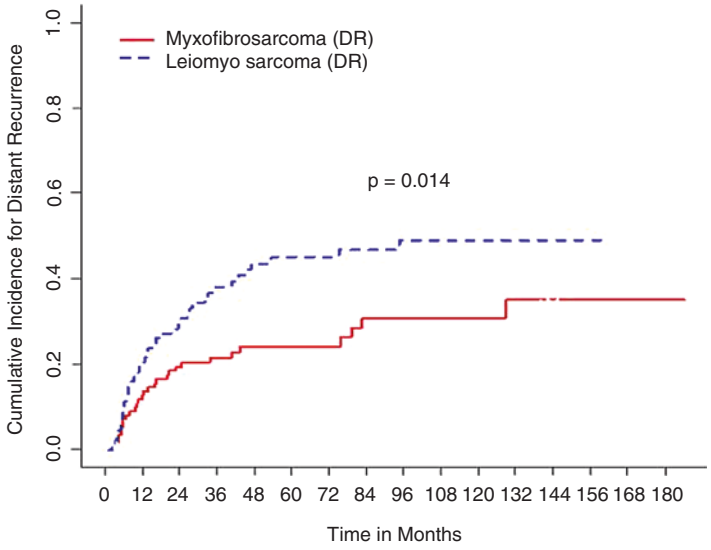

Fig. 7.9 The cumulative incidence of distant recurrence (DR) is illustrated according to histologic subtype. With permission from : *Mutter RW, et al. Cancer 118(2):518-527, 2012*

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Chapter 8
Synovial Sarcoma

Synovial sarcomas present typically as a mass lesion in the extremities. In the authors' experience, it is a soft tissue sarcoma that presents as a painful mass more commonly than other sarcomas. Historically thought to be associated with peripheral joints, it is clear that there is no association of this sarcoma with synovium per se. Clinical presentation is that of younger age groups than other sarcomas, predominantly a disease of adolescent and young adulthood. As our data set includes patients over age 16, we underemphasize the presence in adolescents (Fig. 8.1). Site distribution for this adult cohort is shown in Fig. 8.2. This histology stands to become an excellent proof of principle diagnosis for immunotherapy and epigenetic therapy in the coming few years.

8.1 Imaging

As with other sarcomas, CT and MRI are the basis of imaging (Fig. 8.3). Synovial sarcomas may occur in the mediastinum, pleura, or lung as a primary site, but do not have particular radiological features to discern them from other sarcomas, other than occasional calcifications. Imaging more frequently demonstrates bone invasion in comparison to other sarcoma subtypes.

8.2 Diagnosis, Molecular Pathology

While being of uncertain histogenesis, mouse models indicate the satellite cells of skeletal muscle as a possible cell of origin for synovial sarcoma [1]. Monophasic and biphasic variants of synovial sarcoma are well recognized; 2/3 of synovial sarcomas are monophasic (Figs. 8.4 and 8.5). Monophasic synovial sarcoma cells are arranged in intersecting fascicles and show a monotonous cytomorphology. They

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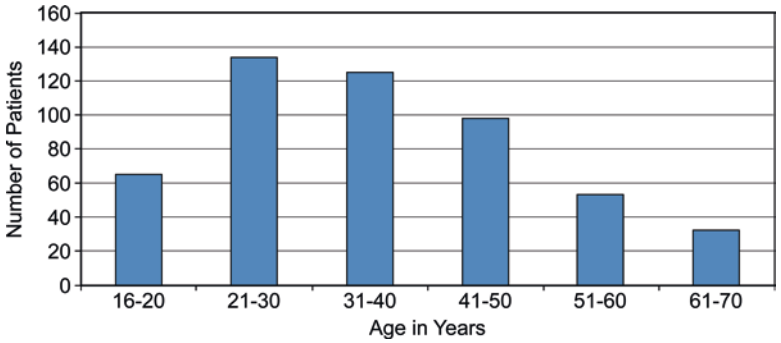


Fig. 8.1 Distribution by age of adult patients with synovial sarcoma, all sites. MSKCC 7/1/1982 - 5/31/2013, $n = 515$

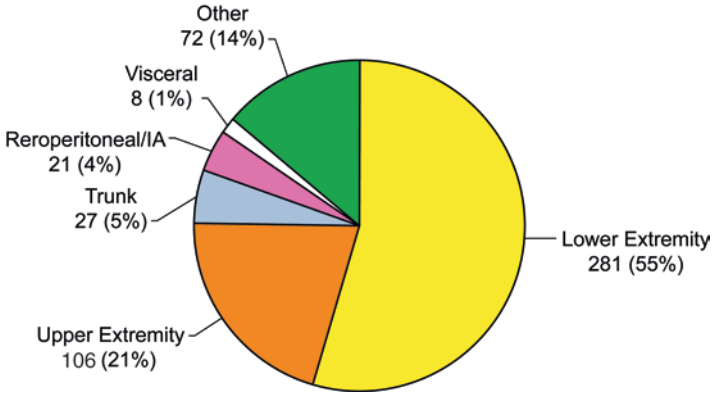
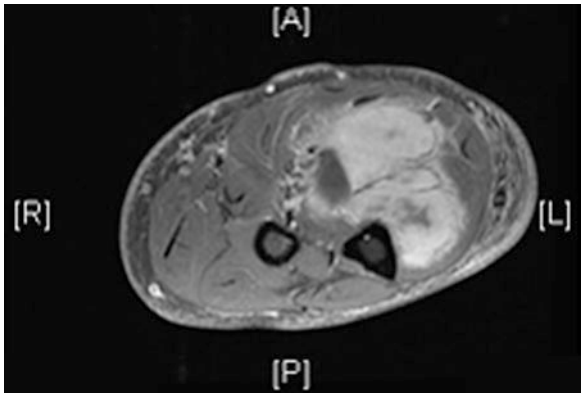


Fig. 8.2 Distribution by site of adult patients with synovial sarcoma. MSKCC 7/1/1982 - 5/31/2013, $n = 515$, *Retro/IA* retroperitoneal/intra-abdominal

Fig. 8.3 MRI of extensive thigh synovial sarcoma



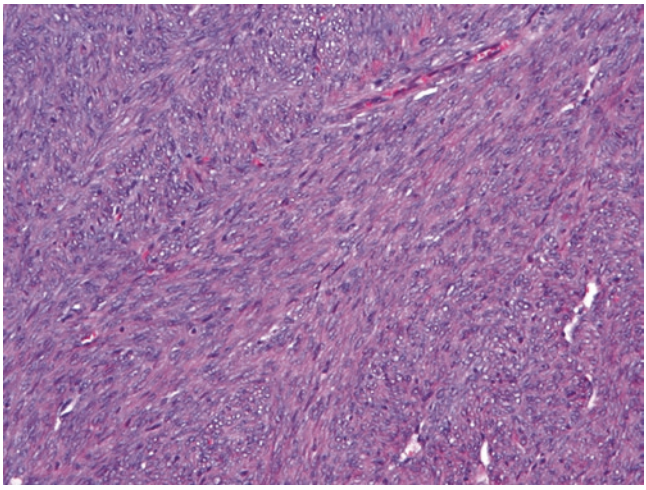


Fig. 8.4 Monophasic synovial sarcoma showing a cellular but monotonous proliferation of spindle cells arranged in long, intersecting fascicles. Typically, no nuclear pleomorphism or necrosis is noted (HE, ×200)

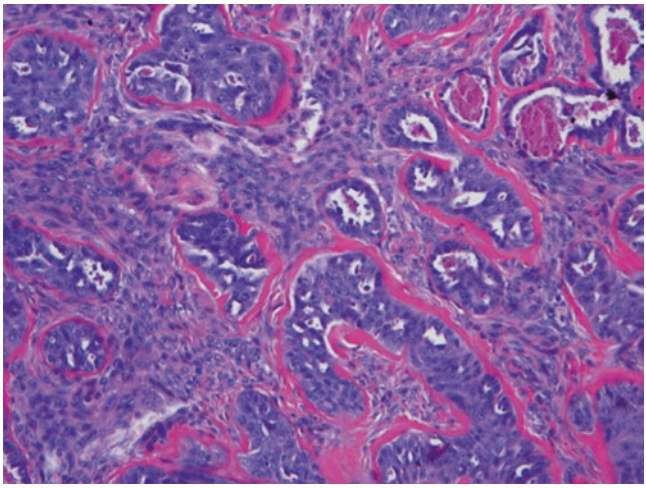


Fig. 8.5 Biphasic synovial sarcoma showing well-defined glandular spaces, in the background of a spindle cell component and thick, refractile collagenous stroma (HE, 200×)

often have a hemangiopericytoma-like vascular pattern, and not infrequently contain intralesional calcification. The biphasic variant looks similar in its spindled areas, interrupted by evidence of glandular differentiation, lined with low cuboidal to columnar epithelioid cells. There is a rarer poorly differentiated variant that has evidence of a more aggressive small round cell component and could be mistaken for Ewing sarcoma or rhabdomyosarcoma [2]. EMA and cytokeratins can stain both the glandular and spindle components of tumors.

The characteristic translocation of synovial sarcoma is t(X;18)(p11.2;q11.2) [3], with *SS18* on chromosome 18 (formerly termed *SYT*) fused to *SSX1*, *SSX2*, or rarely *SSX4* [4, 5]. A tumor with such a translocation by FISH, RT-PCR, or cytogenetics confirms the diagnosis of synovial sarcoma, helping with the differential diagnosis [6]. Most biphasic tumors contain *SS18-SSX1*, while monophasic tumors have a roughly equal chance of containing *SS18-SSX1* or *SS18-SSX2*. *SS18-SSX2* synovial sarcomas are nearly all monophasic [7]. The variation between *SSX1* or *SSX2* expression in synovial sarcoma impacts differentiation seen in synovial sarcomas through expression of genes *Snail* or *Slug*, both of which can suppress E-cadherin expression [8, 9]. E-cadherin mutations are also a common finding in synovial sarcoma [10].

As a consequence of the *SS18-SSX* fusion gene, the diagnosis of synovial sarcoma has now been seen in what historically would be considered unusual sites such as the prostate, retroperitoneum, and diaphragm. They are an excellent example for the use of molecular diagnosis to characterize tumors that were thought to occur in a particular age group or in a particular site and realize that they can occur at any age and in any site.

In a biochemical tour de force, Kadoch et al. demonstrated that the translocation product displaces native SS18 and BAF47 from BAF (SWI/SNF) chromatin remodeling complexes, altering the pattern of H3K27me3 histone marks on chromatin, impacting synovial sarcoma proliferation. The clear demonstration of the role of epigenetic histone modifiers gives the hope that it will be possible to develop novel agents that target this critical epigenetic regulator in synovial sarcoma and perhaps in other translocation-associated sarcomas as well [11]. Synovial sarcomas also frequently express the cancer-germ line antigen NY-ESO-1, making it a target for T cell-directed therapy directed against NY-ESO-1, already successful in initial studies [12].

8.3 Treatment

Treatment is primarily surgical, with the use of radiation in selected patients (usually primary size >5 cm) as an adjuvant to minimize the risk of local recurrence. Adjuvant chemotherapy (see below) has been suggested as valuable, and more valuable than in other sarcoma subtypes, particularly in regimens including ifosfamide [13].

That said, there was no clear benefit of adjuvant ifosfamide-based chemotherapy in the combined EORTC database of two trials and 819 patients, which enrolled a total of 108 synovial sarcoma patients [14].

8.4 Radiation Therapy

While we typically employ radiation for synovial sarcoma >5 cm in greatest dimension, for areas where local control is difficult, such as the head and neck, radiation can be considered for smaller lesions, bearing in mind the risks of short- and long-term

toxicities vs. the risk of local failure. In a report from MD Anderson Cancer Center, 150 patients with non-metastatic synovial sarcomas were treated with conservative surgery and radiation therapy. With a median follow-up of 13.2 years, the 10-year local control was 82%. The 10-year rate was 86% for upper extremity and 80% for lower extremity sites [15]. The rate of local control was 96% in 30 primary synovial sarcomas of the extremity treated with adjuvant radiation therapy at MSKCC [16].

8.5 Chemotherapy

There remains debate as to the benefit of chemotherapy in the adjuvant setting for patients with soft tissue sarcoma. While a new meta-analysis of prior adjuvant chemotherapy clinical trials demonstrated an overall survival advantage with the use of adjuvant chemotherapy [13], this study did not examine individual data of patients in performing the meta-analysis, unlike a similar effort published in 1997 [17]. These data are in conflict with the largest single study of adjuvant therapy from the EORTC, which showed no benefit in overall survival in patients who received chemotherapy [18]. An analysis of patients from UCLA and MSKCC indicated that those patients who received chemotherapy fared better than the MSKCC nomogram would have predicted, a nomogram including patients who most had not received chemotherapy in the adjuvant setting [19] (Figs. 8.6 and 8.7).

Given the relative chemotherapy sensitivity of synovial sarcoma, this is one scenario (along with myxoid-round cell liposarcoma and sarcomas more common in a pediatric population) in which we generally consider chemotherapy in the adjuvant

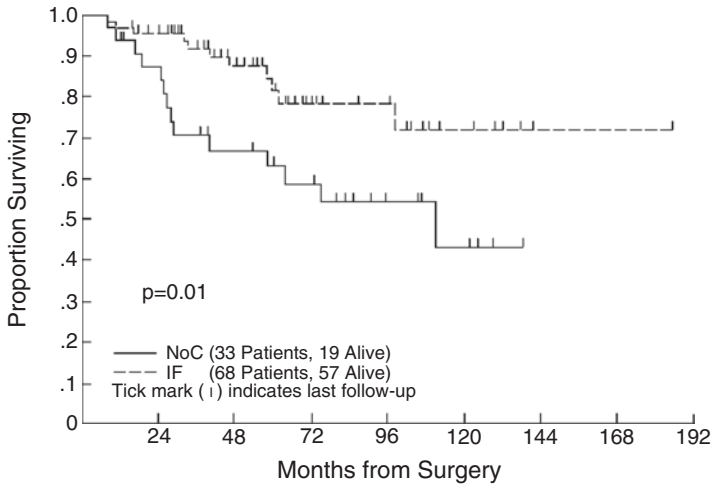
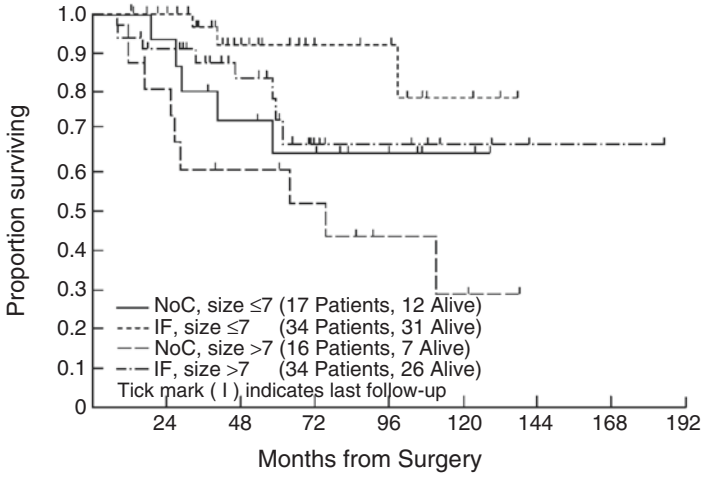


Fig. 8.6 Primary extremity synovial sarcoma—disease-specific survival by ifosphamide (IF) treatment. From: Eilber FC, Brennan MF, Eilber FR, et al. *Ann Surg* 2007; 246(1):105-113



	Total	# Events	2-Year	4-Year
IF, ≤7	34	3	1.00	0.92 (0.81-1.00)
NoC, ≤7	17	5	0.93 (0.81-1.00)	0.73 (0.50-0.96)
IF, >7	34	8	0.91 (0.81-1.00)	0.83 (0.70-0.97)
noC, >7	16	9	0.81 (0.61-1.00)	0.61 (0.36-0.85)

Fig. 8.7 Primary extremity synovial sarcoma—disease-specific survival by size and iphosphamide (IF) treatment. From: Eilber FC, Brennan MF, Eilber FR, et al. *Ann Surg* 2007; 246(1):105-113

setting for higher risk tumors, i.e., those over 5 cm in greatest dimension. Adjuvant chemotherapy remains a contentious question given the lack of benefit in the combined EORTC trial database noted above [14]. For those patients accepting the toxicity of therapy, we generally employ 5–6 cycles of AIM, i.e., doxorubicin 75 mg/m^2 and ifosfamide 9 g/m^2 in split doses over 3 days (doxorubicin IV push, ifosfamide over 3 h, with mesna). A schedule used at MD Anderson Cancer Center employs doxorubicin 75 mg/m^2 and ifosfamide 10 g/m^2 per cycle. Neutrophil growth factors (i.e., filgrastim or pegfilgrastim) are necessary to aid recovery from the neutropenia and mucositis common with this regimen.

8.6 Treatment of Recurrence

8.6.1 Local Recurrence

An attempt at surgical resection of locally recurrent disease is appropriate for patients. Local recurrence may be the result of either technical issues (close/positive margins in the primary) or aggressive biology of the tumor. In many cases, this will mean greater morbidity or sacrifice of critical structures such as nerves, veins,

arteries, or bone, some of which cannot be spared without loss of the extremity. In synovial sarcomas of the hand, a ray amputation may still be limb preserving, but in synovial sarcomas recurrent in the foot a transmetatarsal or below the knee amputation may be the only options for tumor control. Re-irradiation is typically not feasible in someone who has already received a lifetime dose to a particular anatomic site. However, we have shown that in some patients having received prior irradiation, additional irradiation by the brachytherapy technique is possible with minimal morbidity [20, 21].

As with other high-grade sarcomas, local recurrence is a poor prognostic sign, often premonitory for overt metastatic disease. In patients with local recurrence, it is wise to reimage the patient to confirm lack of metastatic disease before proceeding with surgery. If metastatic disease is found, the degree of metastatic involvement and local control issues are weighed, to develop the best treatment plan for a patient.

8.7 Systemic Treatment

Limb perfusion with tumor necrosis factor (TNF) and chemotherapy has been successfully employed in patients with locally recurrent sarcomas when amputation is the only local control option [22–24]. Limb perfusion is EMA-approved in Europe and available at specialized centers, but the lack of the availability of TNF in the United States has limited limb perfusion in the United States to chemotherapy only. The use of TNF with chemotherapy adds both tumor anti-vascular effects and also apparently allows for greater intratumoral uptake of chemotherapy [22]. Systemic therapy for a purely local recurrence of tumor is typically ineffective save for the occasional patient in whom there will be stabilization of disease. Synovial sarcoma may represent one of the few histologies in which there can be frank shrinking of tumor with chemotherapy in the locally recurrent setting.

For metastatic disease, ifosfamide and anthracyclines are the most active agents, and can be used singly or in combination depending on prior exposure and need to palliate symptoms. The approval of doxorubicin + olaratumab makes it a good standard of care in 1st line metastatic disease as well. In contrast to UPS and leiomyosarcoma, gemcitabine-docetaxel has nearly no activity against synovial sarcoma, at least in adults. Trabectedin (ET743) [25] is active in at least a minority of patients and can be employed when available; eribulin may also have minor activity; as noted in other sections, these two agents have activity in other sarcoma histologies, but synovial sarcoma was not included in these studies [26]. We have had modest success with the occasional patient with cisplatin-etoposide (Figs. 8.8), or even oral etoposide alone, 50 mg oral daily, 7 days on, 7 days off, for patients with poor performance status. Also noted previously, phase II and III studies indicate activity of pazopanib in synovial sarcoma, which was not often observed with sorafenib or sunitinib in phase II studies, thus making it perhaps the most viable option for an oral multitargeted tyrosine kinase inhibitor for systemic therapy outside a clinical trial [27]. In our experience, it is one of the histologies that responds best to pazopanib, for unclear mechanistic reasons.

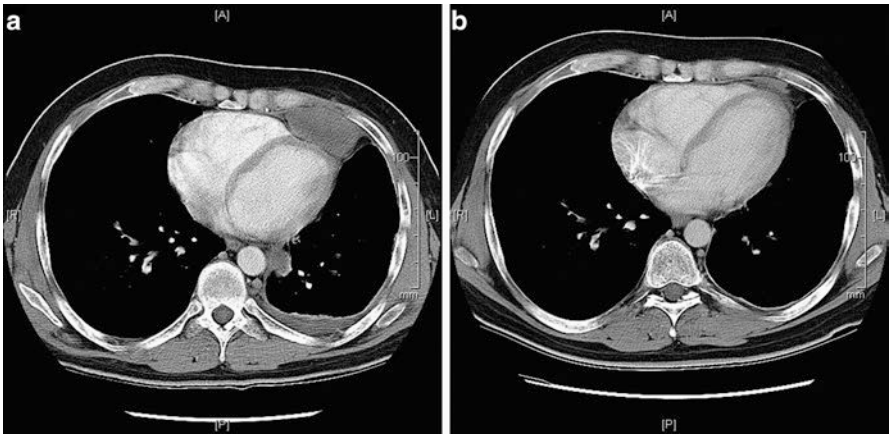


Fig. 8.8 Response of metastatic synovial sarcoma to ifosfamide chemotherapy

Table 8.1 Recommendations for systemic therapy for patients with synovial sarcoma[a]

Clinical scenario		Comments[b]
Neoadjuvant/ Adjuvant chemotherapy		Anthracycline/ifosfamide × 5–6 cycles for high-risk tumors for those patients will accept toxicity of such therapy
Metastatic disease	1st line	Ifosfamide ± anthracycline (if not employed before). Some investigators use a higher dose of ifosfamide than previously employed. Doxorubicin + olaratumab is a good option in 1st line given survival advantage over doxorubicin alone
	2nd line	Anthracycline, if not employed previously; Trabectedin (in countries where available).
	3rd line +	Pazopanib; etoposide as a single agent or possibly in combinations; gemcitabine-docetaxel appears largely inactive in adults. PD1 and CTLA4 immune checkpoint inhibitors appear inactive in initial trials; it is not clear if combinations will prove more active. Engineered T cell therapy against NY-ESO-1 appears active in patients who are HLA-A2+

[a]Clinical trials are always appropriate if available, in particular those examining NY-ESO-1 immune responses or epigenetic approaches. HLA-A testing is necessary for NY-ESO-1 T cell trials. Gemcitabine and combinations appear inactive

[b]PEGylated liposomal doxorubicin (Doxil®/Caelyx®) if poor KPS or elderly

Patients who are HLA-A*0201+ are eligible for T cell therapy, either autologous T cells matured extracorporeally, or engineered T cell studies. Patients have demonstrated signs of radiological and clinical benefit from this approach [12]. Other immunotherapeutic studies focused on the NY-ESO-1 may be worth considering as well, given the near universal expression of NY-ESO-1 in synovial sarcomas (Table 8.1). That said, the study of immune checkpoint inhibitors is off to an inaus-

picious start; a small study of relatively late-stage patients treated with CTLA-4 inhibitor ipilimumab yielded no radiological responses [28].

Newer approaches for systemic therapy are needed, and one approach that will require systematic examination is that of epigenetic agents or drugs targeted metabolic dependencies of this sarcoma subtype, given the strong preclinical rationale developed in the laboratories of Nielsen et al. and Kadoch et al. [11, 29–31].

8.8 Outcome

SS18-SSX gene fusion type has been suggested to have some significance in predicting outcome. In a description of the experience from our institution [32], it was found that patients with *SSX2* gene fusions fare worse than those with *SSX1* fusion, but these data were contradicted by other data showing no significant difference in outcome based on fusion type [33]. Our earlier analyses [34] looking at 126 patients suggested that the majority presented with a relatively small lesion involving the lower extremity. Less than 10 % of those patients have had a local recurrence, but up to 30 % have developed metastatic disease. As this was an analysis of extremity-only patients, the lung was the commonest site. In that paper, we first identified the importance of bone invasion in these lesions, with bone invasion being relatively uncommon in other types of sarcoma.

Disease-specific survival and local recurrence for adults with synovial sarcoma are shown in Figs. 8.9 and 8.10.

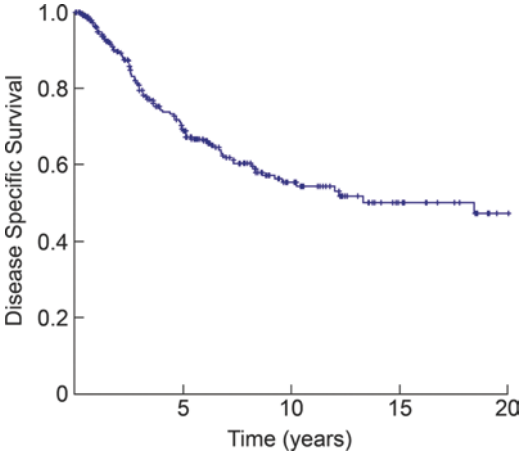


Fig. 8.9 Disease-specific survival of adult patients with synovial sarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 297$

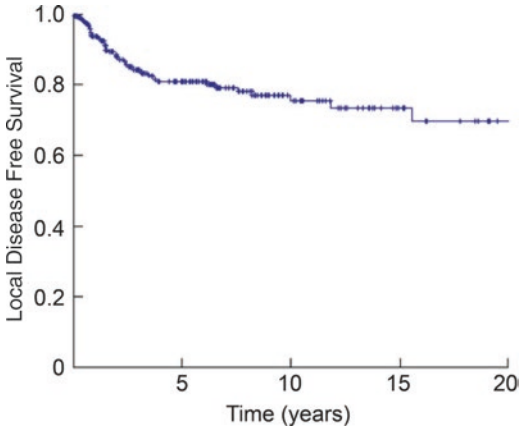


Fig. 8.10 Local recurrence free survival of adult patients with synovial sarcoma, all sites. MSKCC 7/1/1982–6/30/2010, $n = 297$

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Chapter 9
Malignant Peripheral Nerve Sheath Tumor (MPNST) and Triton Tumor

Malignant peripheral nerve sheath tumors (MPNST) are tumors that arise from cellular components of a normal nerve, i.e., Schwann and perineurial cells, or from preexistent benign peripheral nerve sheath tumors (PNST). They are relatively uncommon and highly aggressive soft tissue tumors seen in three settings, sporadic, status postradiation, and associated with neurofibromatosis type 1 (NF1). Despite these different clinical scenarios, the biological background, loss of neurofibromin (*NF1*) expression by deletion or mutation, is believed to be similar. Beautifully conducted studies show common recurrent chromatin remodeling complex PRC2 inactivation through *EED* and *SUZ12* mutations in a high proportion of all these MPNST clinical subsets, as a justification for examining epigenetic agents in MPNST [1, 2]. Older, abandoned terms for MPNST include neurofibrosarcoma, malignant schwannoma, and neurogenic sarcoma. It is recognized that epithelioid MPNST is not associated with NF1 and harbors different genetic signature than conventional MPNST, with often loss of tumor suppressor INI1, which may impact therapeutic options for this sarcoma subtype.

9.1 Presentation

MPNST arises as a mass lesion that is often painful. Approximately one-third will be associated with NF1. Age distribution (Fig. 9.1) and site distribution (Fig. 9.2) for adult patients at MSKCC are shown. A different series described had a median age of 33 with a male predominance and a median size of 9.5 cm [3].

In NF1 patients, MPNST commonly arise in plexiform neurofibromas that undergo malignant transformation, typically in large nerves, such as the sciatic nerve, lumbosacral, or brachial plexus (Fig. 9.3). Remarkably, 10 % or fewer of patients with NF1 (also termed von Recklinghausen disease) will develop an MPNST. Conversely, other tumors are more common in NF1 patients, including

M.F. Brennan et al., *Management of Soft Tissue Sarcoma*,
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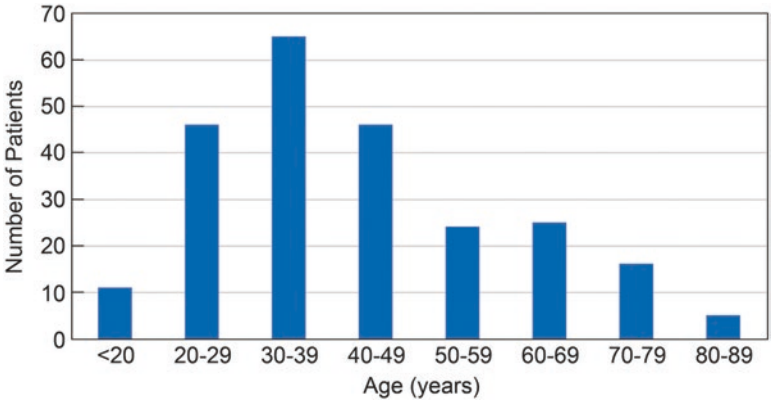

Fig. 9.1 Age distribution of adult patients with malignant peripheral nerve sheath tumor. MSKCC 7/1/82–6/30/2010 $n = 238$

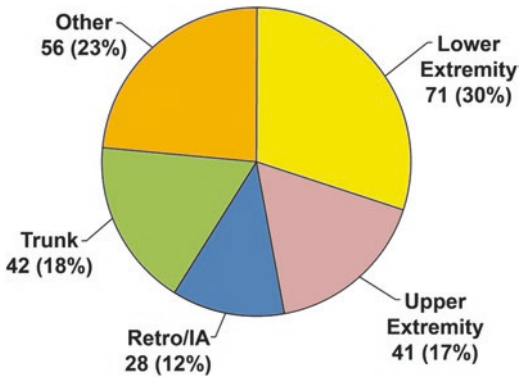

Fig. 9.2 Anatomic primary site distribution of adult patients with malignant peripheral nerve sheath tumor. MSKCC 7/1/82–6/30/2010 $n = 238$

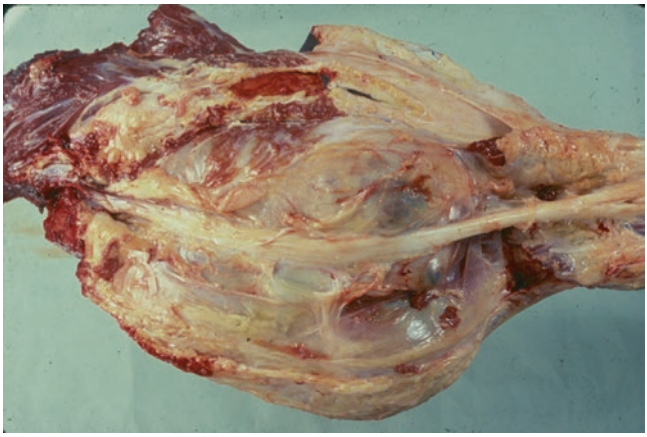

Fig. 9.3 Gross pathology image of a sciatic nerve malignant peripheral nerve sheath tumor, highlighting the nerve entering and exiting the tumor

benign dermal neurofibromas which are nearly universal, and plexiform neurofibromas, which occur in as many as half of NF1 patients, and optic gliomas (as many as 10–15 %) [4].

9.2 Imaging

Imaging as for other primary high-grade sarcomas is predominantly MRI & CT, with one not preferred over the other (Figs. 9.4 and 9.5). That said, for tumors involving the brachial or lumbosacral plexus, MRI may have an advantage in outlining extent of tumor. The use of ^{18}F-FDG PET scan to discern plexiform neurofibroma from MPNST is investigational [5], and only infrequently helpful in the presence of neurofibromas, in our experience. Unfortunately, metastatic disease is all too common (Fig. 9.6) and appears to be more common than with many other forms of soft tissue sarcoma.

9.3 Diagnosis, Pathology

MPNST is characterized by monomorphic spindle cells arranged in intersecting fascicles and often associated with geographic areas of necrosis (Figs. 9.7 and 9.8). It can be difficult to discern MPNST from monophasic synovial sarcoma or melanoma, especially in the head and neck area [6, 7]. A significant number of reported MPNST may represent spindle cell melanoma; this distinction is becoming easier to make with the advent of better molecular tumor testing.

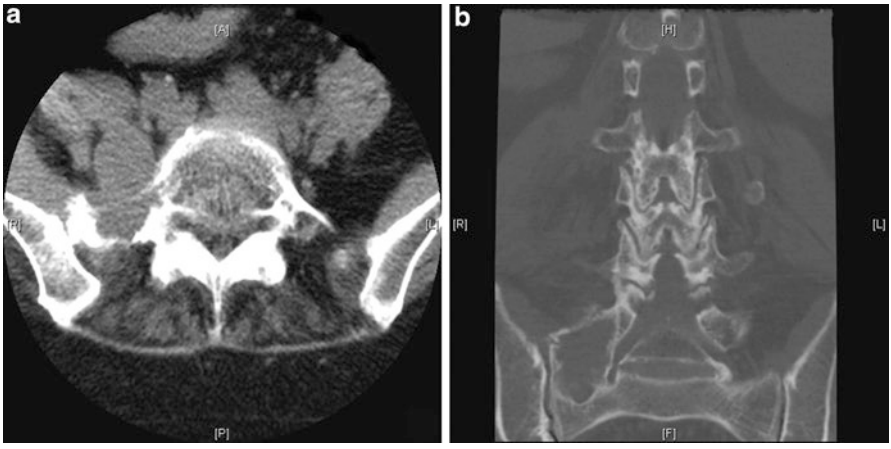

Fig. 9.4 Noncontrast axial (**a**) and coronal (**b**) CT images of a malignant peripheral nerve sheath tumor of a right-sided lumbar nerve root developing after sacral irradiation

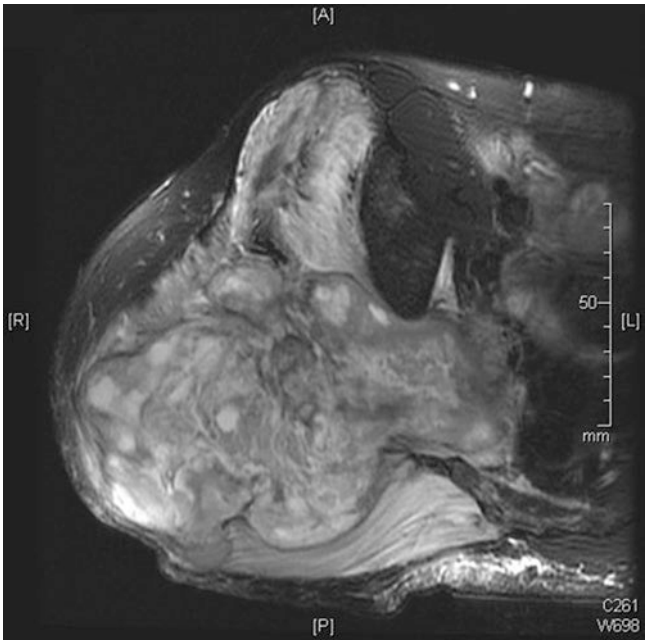

Fig. 9.5 T2-weighted MRI image of a large sciatic nerve malignant peripheral nerve sheath tumor

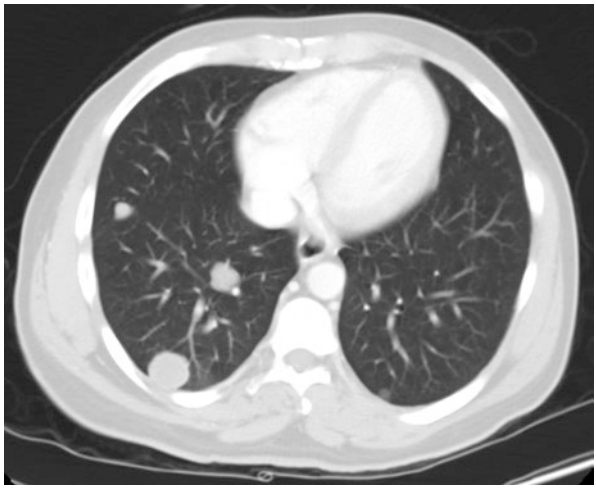

Fig. 9.6 Contrast enhanced CT scan of a metastatic malignant peripheral nerve sheath tumor to lung

Triton tumor is a name given to MPNST with rhabdomyosarcomatous divergent differentiation [8]. Masson gave this tumor its name in 1932 after observing that it appeared microscopically similar to the supernumerary limbs in Tritons (salamanders of the genus *Triturus*) grown by implantation of the cut end of the sciatic nerve into the soft tissues of the back. Triton tumors are also highly aggressive [8] and are managed similarly with other MPNST types.

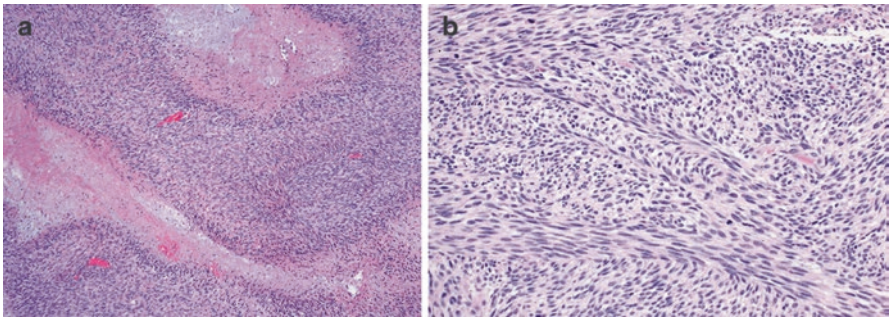

Fig. 9.7 Microscopic anatomy of malignant peripheral nerve sheath tumor (H&E). (**a**) Low power showing typical large areas of geographic necrosis, ×100. (**b**) Higher power showing intersecting fascicles composed of monotonous spindle cells with hyperchromatic nuclei and high mitotic activity, ×200

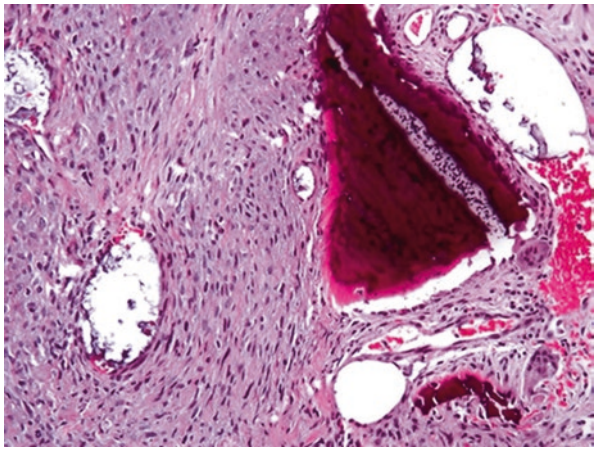

Fig. 9.8 Radiation-induced malignant peripheral nerve sheath tumor with bone invasion, H&E, ×100

A variety of gene expression profiling and other molecular and genetic analyses have been performed, comparing MPNSTs to other sarcomas [9, 10], to Schwann cells [11], and to plexiform neurofibromas [12–15]. Recent genetic studies using comprehensive genomic approaches have identified frequent somatic alterations in *CDKN2A* (81 % of all MPNSTs) and *NF1* (72 % of non-NF1-associated MPNST), both of which co-occurring with PRC2 alterations [1]. The loss of function mutations of the Polycomb repressive complex 2 (PRC2) components, *EED* and *SUZ12*, occurred in 92 % of sporadic, 90 % of radiotherapy-associated MPNST, and 70 % of NF1-related MPNST. MPNST with PRC2 loss showed complete loss of the histone methylation mark H3K27me3, which may be used as a powerful ancillary marker.

9.4 Neurofibromatosis Type 1 and Outcome

In neurofibromatosis type 1, the underlying gene abnormality is deletion or loss of *NF1* on chromosome 17, causing loss of a functional protein (neurofibromin) that is normally a suppressor of p21-ras. The *NF2* gene, on chromosome 22, is more commonly associated with benign central nervous system tumors, such as schwannomas and meningiomas.

The preponderance of data from several review studies indicates that MPNST arise earlier in patients with NF1 and fare worse than people who have an MPNST arise spontaneously [16–23]. However, when MPNST from NF1 patients and those arising sporadically were compared in a large surgical series corrected for other known prognostic factors such as size and site, these differences disappeared (Fig. 9.9) [24].

An analysis of 120 cases from the Mayo clinic [19] suggests that the prevalence of MPNST in neurofibromatosis was ~5 % and the tumors occurred at an earlier age (Fig. 9.10) and outcome was worse (Fig. 9.11); however, most MPNST associated with neurofibromatosis are large and high grade, known poor prognostic factors.

In 105 patients treated at MSKCC, there was no clear survival difference between sporadic and NF1-associated MPNSTs; however, there was a trend to an inferior outcome for radiation-associated MPNST [25].

9.5 Treatment

The primary treatment is surgical, and as they typically arise from major nerve plexuses, potential morbidity is very high. Primary disease presents multiple problems in terms of local control. For tumors arising from large nerves the loss of function is obvious. With MPNST arising from plexiform neurofibromas, it is often difficult to discern which portion of the large nerve plexus is affected by tumor and which area is not. As benign neurofibromata can be PET avid, ^{18}F-FDG-PET has not been helpful to discern benign from malignant lesions. There is obviously greater morbidity associated with loss of multiple nerve roots, which must be balanced with the understanding of the poor prognosis of such patients even with optimal surgery. It is not unusual to see tumor recurrences that skip portions of normal nerve, frustrating attempts at local control. On occasions the lesions are so large and involve such major nerves that amputation is necessary. In our earlier series almost one-third came to amputation either primarily or because of otherwise unresectable recurrence.

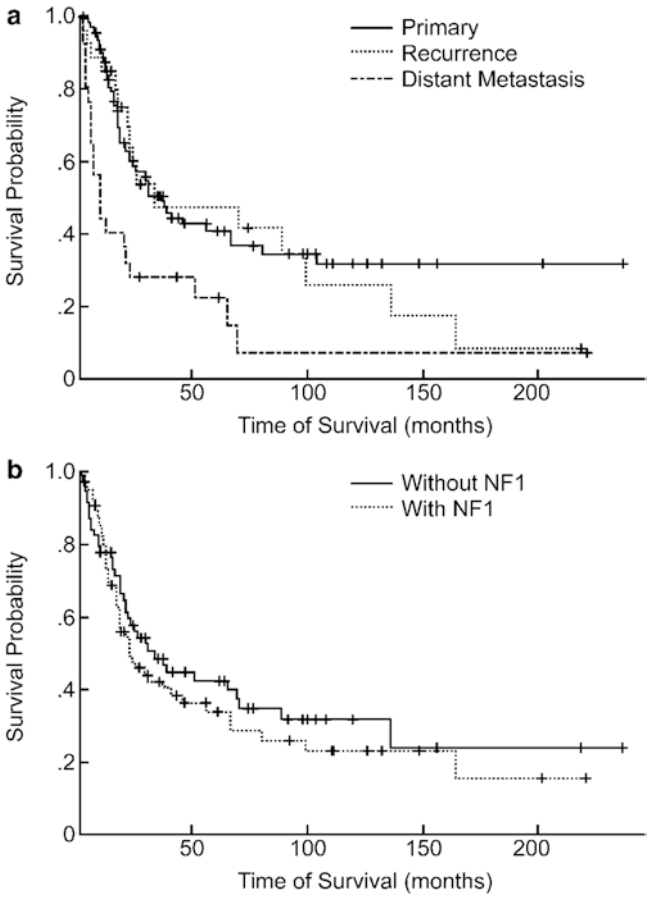

Fig. 9.9 Kaplan–Meier curves of overall survival for different cohorts of patients with MPNST. (**a**) Patients with metastatic disease (*dotted line*) fare worse than those with localized primary disease (*dark solid line*, $p=0.0025$). There was no difference in disease-specific survival for patients with primary versus recurrent disease (*light solid line*, $p=0.92$). (**b**) There is no statistical difference in overall survival comparing patients with NF1-associated MPNST (*light solid line*) versus those with sporadic MPNST (*dark solid line*). From: Zou C, Smith KD, Liu J, et al. *Ann Surg* 2009; 249(6):1014–1022

9.6 Radiation Therapy

The clinical situation is made more difficult by either early development of metastatic disease for most patients with larger (>5 cm) tumors or the development of multiple primary tumors simultaneously in some patients. As with other large primary sarcomas, radiation therapy is standard of care in the adjuvant setting [26]. In a report by Bishop et al, 71 patients with localized MPNST were treated with surgery and radiation. With a median follow-up of 118 months, the 5-year local control was 84%, and the 5-year distant relapse free survival was 62 % [26].

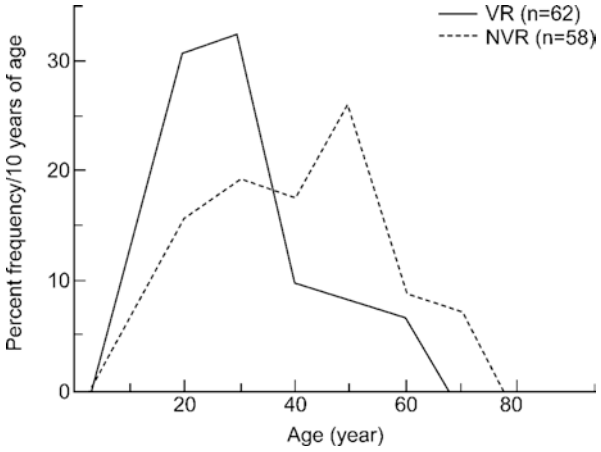

Fig. 9.10 MPNST in patients with NF1 (*solid line*) develops earlier than those with sporadic MPNST (*dotted line*). From: Ducatman BS, Scheithauer BW, Piepgras DG, et al. *Cancer* 1986; 57(10):2006–2021

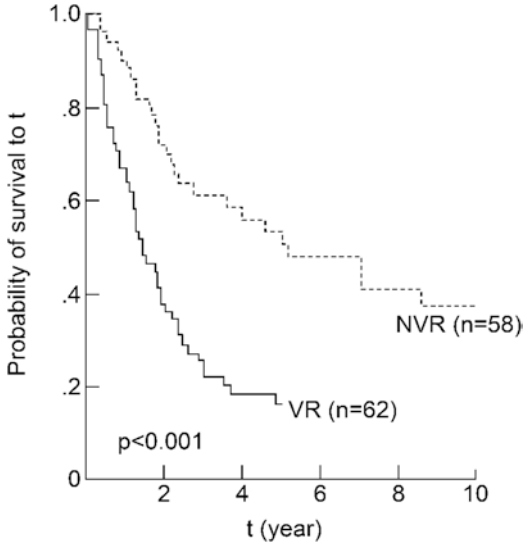

Fig. 9.11 Data from an independent series from Fig. 9.10 indicating inferior overall survival for patients with NF1-associated MPNST (*solid line*) compared to patients with sporadic MPNST (*dotted line*). From: Ducatman BS, Scheithauer BW, Piepgras DG, et al. *Cancer* 1986; 57(10):2006–2021

9.7 Chemotherapy for MPNST

Our general practice is to not offer adjuvant chemotherapy for patients with primary MPNST, given the relative lack of activity of chemotherapy in the metastatic setting. Adjuvant chemotherapy is administered by some physicians in consideration of the high risk of metastatic disease. In our experience, the RECIST response rate for doxorubicin–ifosfamide is under 10 % using doxorubicin at 75 mg/m^2 per cycle and ifosfamide at 9 g/m^2/cycle.

Table 9.1 Recommendations for systemic therapy for patients with malignant peripheral nerve sheath tumor

Clinical scenario		Comments
Neoadjuvant/ Adjuvant chemotherapy		Difficult to recommend given lack of sensitivity with metastatic disease; however, anthracycline-ifosfamide may be associated with improved survival in one randomized trial
Metastatic disease	First line	doxorubicin + olaratumab, solely based on less than dramatic results with ifosfamide-based therapy
	Second line and later	Ifosfamide ± etoposide Pazopanib; erlotinib is inactive in one phase II study. We have not observed dramatic results with gemcitabine-based therapy in a small number of patients treated. Immune checkpoint inhibitors are unexplored as of 2016

For metastatic disease similar poor options exist for therapy. There is a low response rate in our experience with both doxorubicin–ifosfamide and gemcitabine combinations for patients with MPNST, with perhaps the greatest response rate for a single agent from ifosfamide. Doxorubicin + olaratumab is an approved combination in this setting. Cisplatin may have minor activity, and given the overexpression of *TOP2A* in MPNST [27], one might expect etoposide or doxorubicin to have greater activity in MPNST than other sarcomas, but it is not clear if such relative overexpression represents a marker for sensitivity or resistance to topoisomerase II inhibitors.

Among targeted agents, although the epidermal growth factor rector (EGFR) is expressed in MPNST, erlotinib was inactive in one multicenter phase II [28]. Similarly, by virtue of elimination of NF1 expression in MPNST and activation of ras-raf pathways, sorafenib was of interest for metastatic disease, but only minor responses (and no RECIST responses) were observed in a phase II study of sorafenib in MPNST patients [29]. The minor responses in the latter study indicate that a better raf inhibitor could be associated with greater activity, and also calls for examination of combinations of other agents, e.g., those agents that block mTOR or MEK, in addition to RAF inhibitors [30]. Identification of other treatment strategies seems paramount [31, 32]. Since <10 % of patients with neurofibromatosis type 1 develop MPNST, it stands to reason that mutation or deletion of *NF1* is associated with the preneoplastic lesion, i.e., a neurofibroma, but that other genetic changes (e.g., alterations in *Rb* or *TP53*) are necessary to yield an MPNST, making targeting such tumors potentially much more difficult (Table 9.1).

9.8 Outcome

As with other high-grade sarcomas, margin positivity predicts an unfavorable local recurrence rate but does not appear to be causative for death from disease as amputation is not associated with improved survival [3]. Local recurrence-free survival and disease-specific survival curves for patients with MPNST are shown in Figs. 9.12 and 9.13. A recent review from the Mayo Clinic of 175 patients found a local recurrence rate of 22 % and 5- and 10-year disease-specific survival of 60 % and 45 %, respectively, with known poor prognostic factors of grade and large size [33].

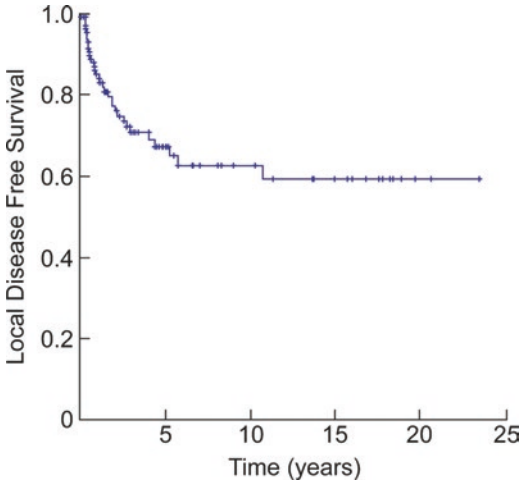

Fig. 9.12 Local recurrence-free survival for adult patients with primary MPNST. MSKCC 7/1/82–6/30/2010 $n = 141$

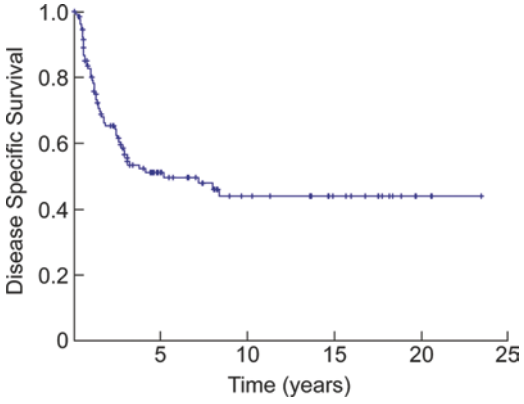

Fig. 9.13 Disease-specific survival for adult patients with primary MPNST. MSKCC 7/1/82–6/30/2010 $n = 141$

It is not clear if there is a biological different between sporadic and NF1-associated MPNST. A study from MSKCC examined outcome of sporadic neurofibromatosis and radiation-associated MPNST [25]. A total of 105 patients were examined, 42 with NF1-associated, 49 sporadic, and 14 RT-associated MPNST. Median age was 38 years, with mean tumor diameter of 5.5 cm for RT associated and 9.7 cm for NF1 associated. Factors influencing poor disease-specific survival were large size, positive margin (Fig. 9.14).

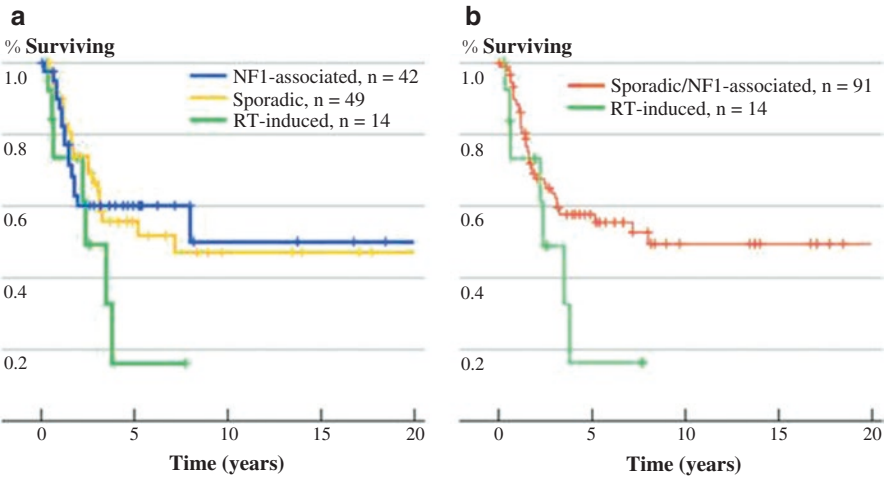

Fig. 9.14 DSS for primary, high-grade MPNST (**a**) according to etiologic subtype (**b**) comparing combined sporadic/NF1-associated versus RT-induced. With permission from: LaFemina J, Qin LX, Moraco NH, et al. *Ann Surg Oncol* 2013; 20(1):77–72

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Chapter 10
Desmoid Tumor/Deep-Seated Fibromatosis (Desmoid-Type Fibromatosis)

Desmoids are enigmatic clonal malignancies of myofibroblastic cells that do not have the ability to metastasize, but cause morbidity and occasionally mortality by locally aggressive growth. They are sometimes termed deep fibromatoses, to distinguish them from superficial fibromatoses such as Dupuytren contracture, trigger finger, or Peyronie disease.

Desmoids can occur at any anatomic site (Fig. 10.1) and the age at presentation is variable (Fig. 10.2). A clinical classification of desmoids distinguishes three scenarios. In the first, a desmoid arises in the abdominal wall in the setting of pregnancy. This form of desmoid tumor may be hormonally driven and can dissipate postpartum. The second common clinical scenario is that of spontaneous development of a desmoid in the extremity or trunk (Fig. 10.3). The vast majority of desmoid tumors contain a single mutation in the beta-catenin gene (*CTNNB1*). The different degree of the admixture of desmoid tumor cells with fibroblasts appears to account for the finding of "wild-type" desmoids.

Mesenteric desmoids frequently feature as a complication of familial adenomatous polyposis (FAP), with its characteristic loss of expression of the adenomatous polyposis coli (*APC*) gene. FAP-associated desmoids are more commonly diffuse than a discrete mass and can be associated with bowel perforation or bowel obstruction. The very small proportion of desmoids that have no *CTNNB1* mutation may have loss of *APC* as an apparent mechanism of development.

At least 10 % of all patients with familial adenomatous polyposis (FAP) develop mesenteric desmoids [1], although desmoids in such patients occasionally arise at other sites such as trunk or extremity. The lesions that develop in the vicinity of the proximal mesenteric arterial and venous drainage increase the risk of severe morbidity from either overaggressive treatment or from progression of disease, creating a fundamentally difficult situation with respect to management.

In the patient with FAP, the desmoid tumor is assuming a more prominent role in the death of the patient following the prevention of metastatic colon cancer by prophylactic colectomy, and with peripancreatic carcinoma is a common cause of death for patients with FAP who have colectomy [1].

M.F. Brennan et al., *Management of Soft Tissue Sarcoma*,
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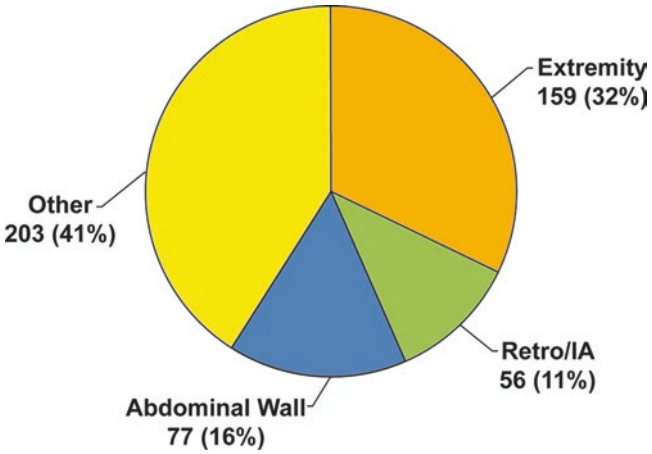

Fig. 10.1 Primary site distribution of adult patients with desmoid tumor/deep fibromatosis. MSKCC 7/1/1982–6/30/2010. $n = 238$. *Retro/IA* retroperitoneal/intra-abdominal

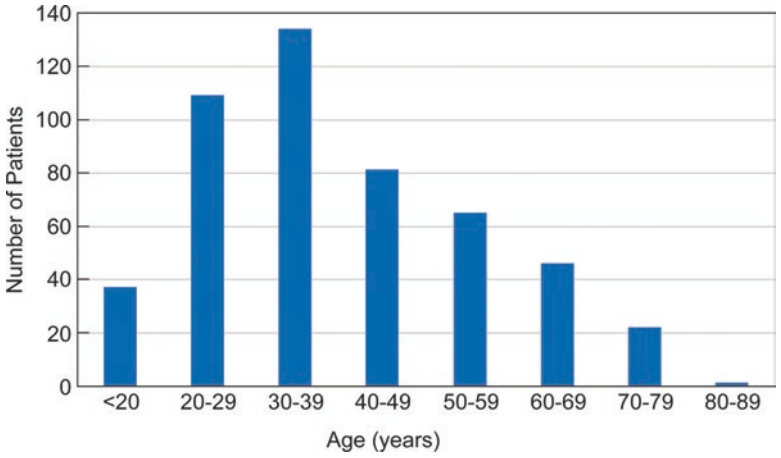

Fig. 10.2 Age distribution of adult patients with desmoid tumor/deep fibromatosis. MSKCC 7/1/1982–6/30/2010 $n = 495$

FAP may not be the only sarcoma diagnosis associated with development of desmoid tumors. There appears to be a nonrandom association between development of GIST (gastrointestinal stromal tumor) and desmoid tumors; GISTs do not contain *CTNNB1* mutations, so the mechanistic rationale for observing both tumors in a patient remains unknown [2]. The degree of this association will probably best be determined by examination of large national databases such as that of SEER or other national registries. FAP is also associated with jaw osteomas, epidermoid cysts, congenital retinal pigmented epithelium hypertrophy, and less commonly other malignancies such as gastric and thyroid cancers, ampullary and other small

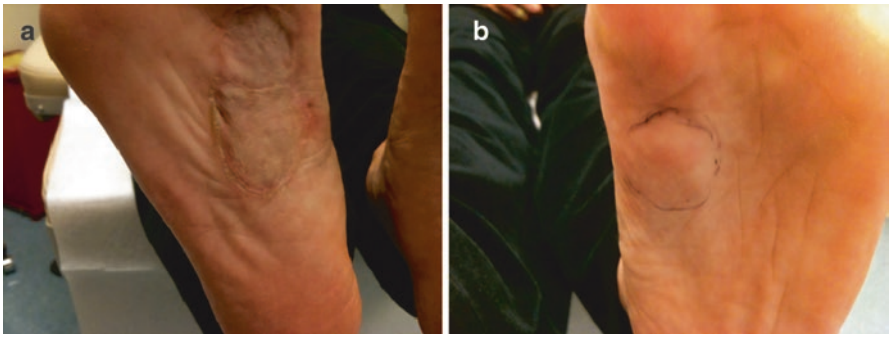

Fig. 10.3 Images of a patient with bilateral plantar desmoid tumor (**a** right, **b** left) who also had Dupuytren contracture of both hands

bowel cancers, bile duct carcinomas, pancreatic cancer, adrenal cancer, and pediatric hepatoblastoma, all of which must be kept in mind in follow-up of such patients and their affected family members.

10.1 Clinical Presentation

The clinical presentation is of a localized, firm to hard mass often in the proximal extremity or in the abdominal wall. The diagnosis is suspected when a lesion is in a classic position, e.g., the abdominal wall of a parturient female or in the retroperitoneum of a patient with a familial polyposis [3, 4].

10.2 Imaging

Both CT and MRI are utilized in diagnostic imaging (Fig. 10.4). The T2 signal on MRI imaging may serve as a surrogate for the relative cellularity of the lesion, with T2 bright lesions being more cellular, and T2 dark lesions representing more collagenous and acellular areas of a tumor [5, 6]. We have observed two radiographic patterns of desmoids, which we term nodular, with rounded surfaces, or diffuse, with tentacles of tumor extending into surrounding tissues. The latter pattern is most commonly encountered in the mesenteric variety of desmoids.

10.3 Diagnosis, Molecular Pathology

Desmoids are myofibroblastic proliferations that can be sometimes difficult to discern from scar tissue, nodular fasciitis, and other diagnoses (Fig. 10.5). As expected, desmoids associated with FAP demonstrate inactivation of adenomatous polyposis

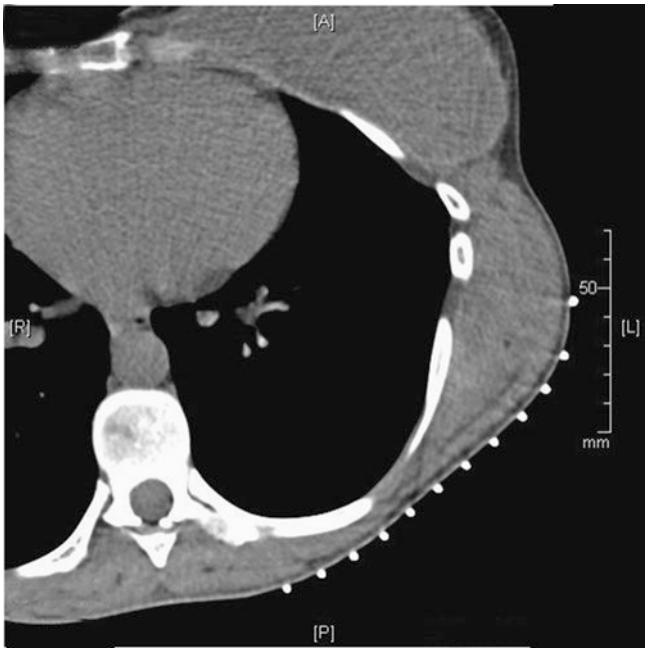

Fig. 10.4 Noncontrast CT image (with CT markers) of a patient with a left subscapular desmoid tumor

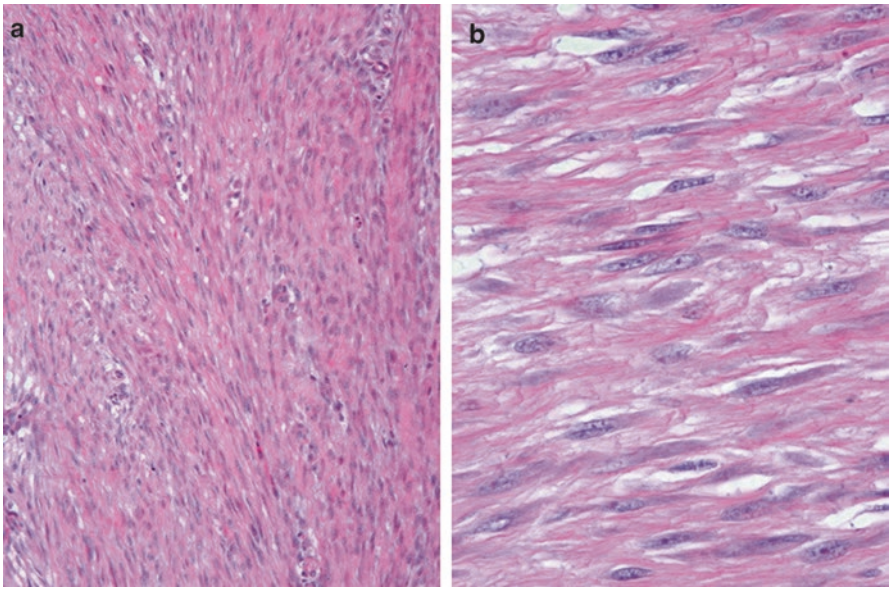

Fig. 10.5 Light microscopy of desmoid tumor (deep fibromatosis), H&E staining. (**a**) Low power image demonstrating uniform spindle cells arranged in long intersecting fascicles (×100); (**b**) higher power demonstrating bland spindle cells with open chromatin and small nucleoli, separated by abundant collagenous stroma. The cells typically lack hyperchromasia or cytologic pleomorphism that would suggest a spindle cell soft tissue sarcoma

coli (*APC*) gene by mutation or deletion. Sporadic desmoids frequently contain beta-catenin (*CTNNB1*) mutations, typically in codons 41 or 45 of exon 3 [7]. Both APC and beta-catenin are elements of the Wnt signaling pathway. Alterations in APC and CTNNB1 lead to stabilization of nuclear beta-catenin, and subsequent binding to members of the T cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors. The specific site of *APC* mutation in patients with FAP dictates the risk of developing desmoid tumors versus polyps and associated colon cancers [8, 9].

Domont et al. [10] reported that 85 % of desmoid tumors contain a *CTNNB1* mutation, predominantly in codons 41 or 45 of exon 3, which can be used as a diagnostic tool. In addition, there may be prognostic information based on the type of mutation in *CTNNB1* observed. In particular, the exon 3 S45F mutation appears to be associated with increased recurrence rate, while wild-type *CTNNB1* or mutations in codon 41 may indicate a desmoid less likely to recur [7, 11]. In studying a given tumor sample more carefully, it is clear that *CTNNB1* mutations are nearly universal in sporadic desmoid tumors and represents differences in allele frequency (normal tissue vs. tumor tissue) in resected tumor specimens [12].

Nuclear beta-catenin positivity by immunohistochemistry appears to be a useful ancillary tool, where it is difficult to differentiate between recurrent desmoid and simple scar tissue (Fig. 10.6) [13, 14]. Other lesions in the differential diagnosis

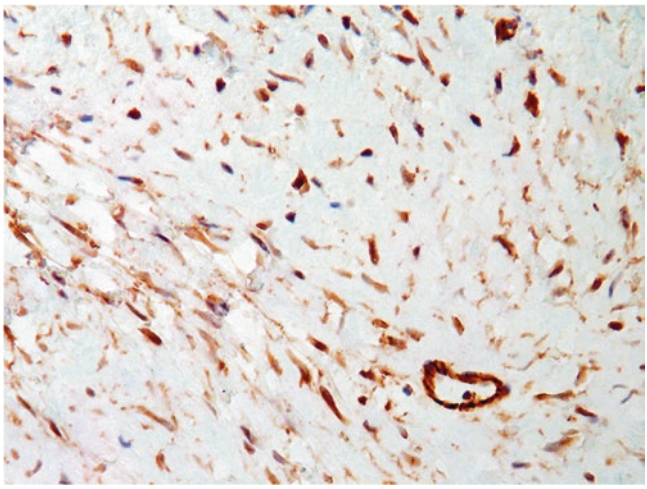

Fig. 10.6 Immunohistochemical staining demonstrating nuclear beta-catenin in a desmoid tumor of the abdomen (×200)

include nodular fasciitis, fibrosarcomas, GIST (gastrointestinal stromal tumor), leiomyosarcoma, and other sarcomas, depending on the anatomic location. Other tumors that can contain *CTNNB1* mutations include pilomatrix carcinomas of skin, hepatoblastoma, and solid pseudopapillary tumor of pancreas, among others, so it is unlikely to make errors in diagnosis on this basis. Desmoids express ER (estrogen receptor)-beta, which is distinct from the form found in breast cancer (ER-alpha), but perhaps the reason some desmoids are sensitive to estrogen blockade or deprivation [15].

10.4 Natural History

The enigmatic behavior of the desmoid tumor has been well recognized and is part of the reason that management varies from one institution to another [4, 16, 17]. It is increasingly recognized that conservative management yields the best outcome for many patients; spontaneous regression of desmoids may be observed in more than 25 % of such tumors presenting for initial care to surgical oncologists, with a median follow-up of more than 2.5 years [18]. The natural behavior is of an infiltrative and persistent lesion without metastatic potential. Some lesions show only sluggish change and few symptoms, while others can grow with a relentless course. Some are easily removed by wide excision, while others appear in difficult areas such as the axilla or near the root of mesentery, where anatomic limitations make primary management difficult [3, 4, 19, 20]. Only limited numbers of desmoids are ultimately unresectable or unresectable without amputation, and desmoids may respond to either radiation therapy or systemic therapy, be it hormonal agents, cytotoxic chemotherapy, or kinase-specific agents such as sorafenib [21–23]. Any claimed response to treatment must be weighed against the finding of those patients with spontaneous improvement; however, in most of the studies to date patients have recurrent, persistent, or worsening disease despite prior therapy. The differences in anatomic location, association with FAP, growth rate, and potential utility of multiple modalities for this diagnosis make comparison of different series of patients complicated.

10.5 Treatment

The primary treatment of the desmoid tumor is surgical resection. However, this treatment decision must be finely balanced between the aggressiveness of the lesion and the aggressiveness of the surgical process [3, 20, 24–26]. It is clear that observation alone initially is a good standard of care for many patients [18, 27, 28]. On the other end of spectrum of aggressiveness, it has been suggested that small bowel autograft or allograft are options for the patient with desmoids or as a consequence of aggressive resection that has resulted in loss of small intestine and dependence

upon intravenous nutrition [29]. Emphasis, however, remains on complete gross resection in the setting of minimal morbidity; both the quoted series and our own experience with people who have sought out bowel transplantation for desmoids of the mesentery have suggested a high short-term mortality rate and longer term morbidity rate from the procedure and development of extra-abdominal desmoids.

Given the variable nature of progression in these tumors, for many patients a suggestion for initial management has been to follow a wait-and-see policy [18, 27, 28, 30]. For more indolent lesions, serial observation by exam and imaging may be useful, but this finding should be predicated on information from the patient examination and imaging studies [25]. It is important to emphasize that a conservative approach to surgery in patients with desmoids is always an option and should certainly be considered when the side effects of the treatment are significant.

10.6 Treatment of Recurrence

Treatment of recurrence of desmoid tumors has become increasingly conservative. We have moved from extraordinary aggression to trying to select only those patients with recurrence who are symptomatic or who have high probability of becoming symptomatic. After all, desmoid tumors do not metastasize. The real challenge, however, is the person who has marked progression with small bowel loss with potential demise. The challenge remains to identify those patients who are going to progress versus those patients who have an indolent course. Desmoids with wild-type *CTNNB1* or exon 3 codon 41 mutations may fare better than those with the S45F mutation, but this favorable group represents only a minority of desmoids [7, 31, 32].

While radiation is not routinely recommended for patients with resectable disease, it may play an important part for patient with unresectable symptomatic recurrence. In a report by Guadagnolo et al, 41 patients with gross disease were treated with definitive radiation. Local control was achieved in 68 % of patients. The recommended dose is typically 56 Gy using shrinking field technique [33].

10.7 Systemic Therapy

Despite many case reports of the use of nonsteroidal anti-inflammatory agents in desmoids tumors, we have not observed significant activity of such agents in patients with desmoid tumors; some of these responses may have been related to spontaneous improvement seen in as many as 10–15 % of patients in some case series. The utility of antiestrogen therapy is well recognized and often a good first line of therapy in relatively asymptomatic patients with growing tumors [34, 35]. The first series reporting the activity of systemic chemotherapy came from MD Anderson in 1993, in which the activity of doxorubicin with dacarbazine was readily demonstrated [22].

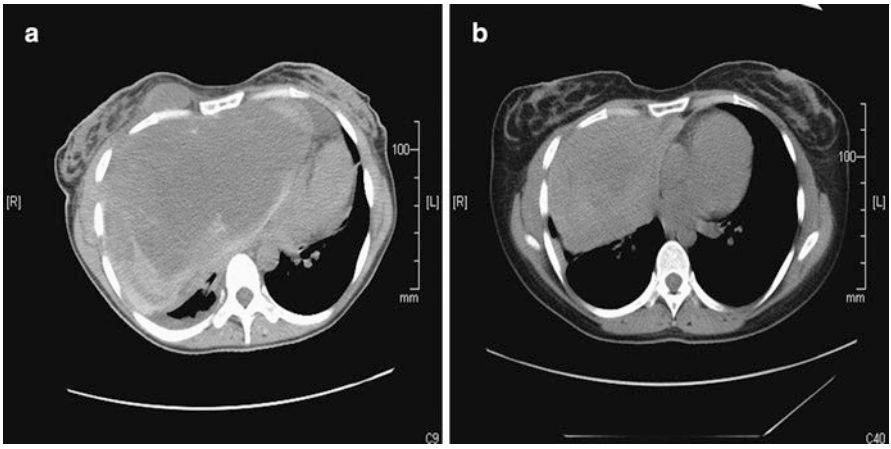

Fig. 10.7 Noncontrast CT images of a 35-year-old female patient with aggressive chest wall desmoid with cardiovascular collapse who responded to sorafenib. (**a**) Pretreatment. (**b**) 28 months after starting sorafenib

We have employed this manuscript and others as templates for potentially active agents, deconstructing combinations into individual agents, given the increased toxicity of combination therapy, and the lack of recognized synergy of any particular combination. Other series have reported on the activity of vinblastine and methotrexate, vinorelbine and methotrexate, or hydroxyurea [36–39].

We reported our experience with systemic therapy for desmoids (68 patients, 157 lines of therapy) in 2009 [21]. The most active agents in our analysis included anthracyclines and antiestrogens. The activity of anthracyclines was further confirmed in a retrospective analysis in France [40]. Progression-free survival rates of ~70 % at 3–5 years were commonly observed, and there were few relapses in patients after a patient had a response. In another review [41] the group at MD Anderson examined the use of systemic therapy for nonresectable lesions. Of the 29 patients who received systemic therapy, there was one complete response, 11 partial responses, and two with stable disease. Like our own and other series, these data are difficult to evaluate with the variable nature of the disease, as seen in other series only one patient died due to uncontrolled progression of the desmoid, again emphasizing the importance of balancing the morbidity of any treatment against the subsequent morbidity of the disease and the risk for demise. Responses to any one of a number of interventions are possible (Fig. 10.7).

Several series report on the activity of imatinib in desmoid tumors. While responses are durable in some patients, the Radiological Evaluation Criteria in Solid Tumor (RECIST) response rate is only 6–15 % [42–45]. In our own patients, imatinib was inferior to both anthracycline-based and antiestrogens [21]. One of the few prospective trials [42] described to date involved a series of patients who were not curable by surgical resection or in whom surgery would lead to an inappropriate functional impairment were treated with imatinib 300 mg twice daily with response outcome at 2 and 4 months being measured. Fifty-one patients were

studied and 4-month progression-free survival of 94 % and 88 % were identified. One-year progression-free survival was 66 %. It would appear that proven benefit of imatinib in this often slow growing and spontaneously stable tumor is of little value. An objective RECIST response rate of 6 % (3 of 51) was identified.

The activity of second-generation small molecule tyrosine kinase inhibitors was first suggested by Skubitz et al. [46], who noted a patient who failed imatinib but responded to sunitinib [46]. We observed clinical improvement in an index patient on sorafenib and used it in an off-label setting. In a retrospective analysis of treated patients, the RECIST (Response Evaluation Criteria In Solid Tumors) response rate appears to be significantly greater than imatinib (~30 %), but this is a retrospective analysis of patients in an off-trial setting; there are some patients with disease progression after stopping treatment after 8–12 months of therapy, but many people continue to enjoy tumor control without regrowth [47]. Patients with extremity tumor appear to fare better than those with desmoids in other sites, and those with FAP appear to benefit least from such an approach. The relationship of *CTNNB1 or APC* mutations to response to sorafenib or anthracycline therapy remains unknown. Also interesting are phase I and II trials of desmoid patients with responses to gamma-secretase inhibitors (inhibitors of the Notch signaling pathway), which is at least somewhat logical given that gamma secretase expression is at least in part controlled by beta-catenin signaling. Substantial activity was observed in a phase I trial of the gamma secretase inhibitor PF03084014 [48], which was also observed in a follow-up phase II study [49], However, as of 2016 there are no studies available for this or other gamma secretase inhibitors for desmoid tumor patients. Pazopanib and other tyrosine kinase inhibitors may also demonstrate benefit against desmoids but this hypothesis requires prospective evaluation (Table 10.1).

10.8 Treatment by Observation

There is an increasing tendency to follow some patients with observation only. In a series of 142 patients who were treated with observation ($n=83$) or assorted medical therapy ($n=59$) 47 % treated with vinblastine/methotrexate chemotherapy, 34 %, hormonal treatment, and 19 % the observation group were younger, more likely female, and asymptomatic [25]. There was no difference in progression-free survival (Fig. 10.8). Figure 10.9 is an example of a patient with 15-year follow-up of a desmoid of the pelvis and hip initially recommended to have a hemipelvectomy, having been followed with observation alone.

10.9 Radiation Therapy

Historically, radiation therapy is widely used in the management of desmoids for any persistent disease and in particular for any patient with positive margins. However, it is now clear that at least two-thirds of patients who have positive

Table 10.1 Recommendations for therapy for patients with desmoid tumor/deep fibromatosis[a]

Primary disease	Observation in selected patients; surgical extirpation when not unduly morbid. Systemic therapy as noted later can be considered in patients with locally advanced disease in whom morbidity would be significant
Adjuvant therapy after primary disease resection	Radiation to be considered in patients with overt positive margins, bearing in mind both that desmoids do not metastasize, and that patients must live with the risk of long-term side effects from radiation
Recurrence	Observation, surgery, or systemic therapy
Multifocal, recurrent, or unresectable disease (or unresectable without amputation): first line	Antiestrogens (e.g., tamoxifen, toremifene, anastrozole, letrozole, GnRH agonist)
Recurrent intra-abdominal desmoids refractory to other therapy	Pegylated liposomal doxorubicin (Doxil/Caelyx), doxorubicin, doxorubicin–dacarbazine first line; other active agents include methotrexate/vinorelbine. The authors are unimpressed with the activity of hydroxyurea. There are no data regarding olaratumab
Extremity desmoids refractory to other therapy	Sorafenib or other tyrosine kinase inhibitors; systemic agents as above

[a]Note: Clinical trials of novel agents, in particular inhibitors of the Notch pathway, are recommended when available

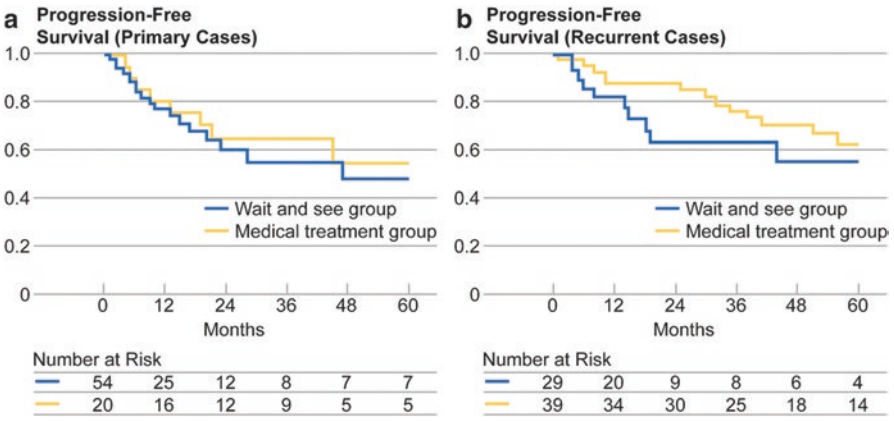

Fig. 10.8 Progression-free survival for patients with (**a**) primary and (**b**) recurrent desmoid tumors who underwent observation only (*dark lines*) or medical therapy (*light colored lines*). Patients may undergo a period of surveillance and only a proportion of them will show tumor growth over 2–3 year median follow-up. From: Fiore M, Rimareix F, Mariani L, et al. *Ann Surg Oncol* 2009; 16(9):2587–2593

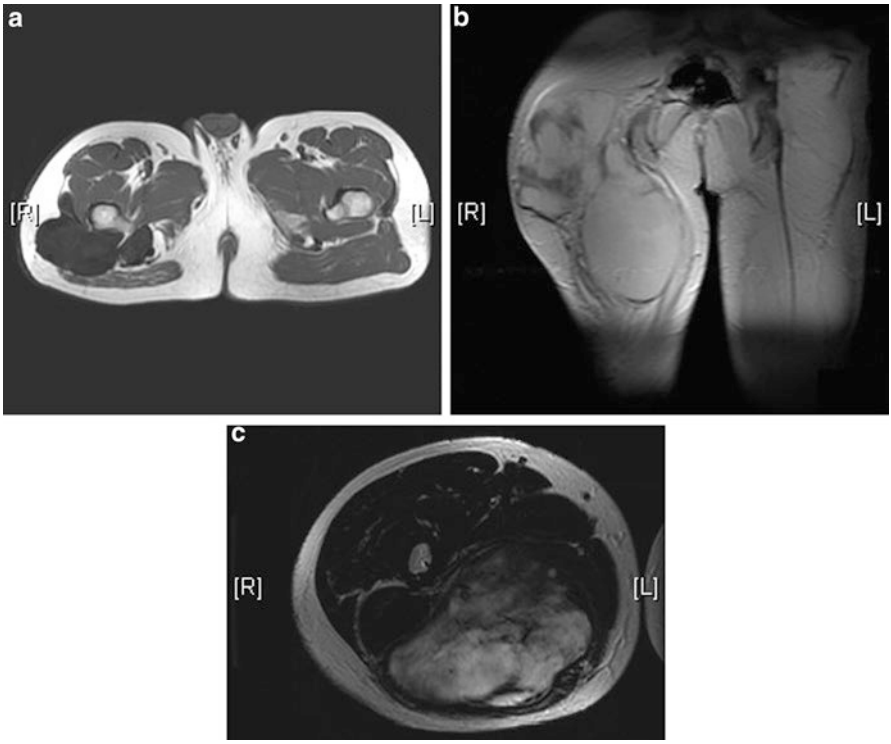

Fig. 10.9 MRI images of a desmoid tumor of the pelvis and thigh in a patient who had received a recommendation for hemipelvectomy at presentation. No change in the tumor was observed in 15 years of follow up

margins do not recur, the uniform utilization of radiation therapy is not indicated, paying particular attention to younger patients [4, 50, 51]. Radiation therapy can be utilized for control in the symptomatic patient with an unresectable lesion.

10.10 Patterns of Failure

As described earlier, the desmoid is a locally infiltrative lesion. The pattern of failure is highly dependent on the presence of the initial lesion. Multifocal lesions have been described [24] and are difficult to understand on a biological basis outside of a field effect on a precursor cell that duplicates and becomes part of each affected area of the limb. Multifocal desmoids are most commonly seen in young women, in the distal extremity both proximal and distal, and multifocal recurrence is common. With age, these appear to progress much more in an indolent fashion suggesting a hormonal association, although this supposition is unproved. Antiestrogens do not appear any more active against multifocal desmoids, also questioning the relationship of multifocal desmoids to estrogen signaling.

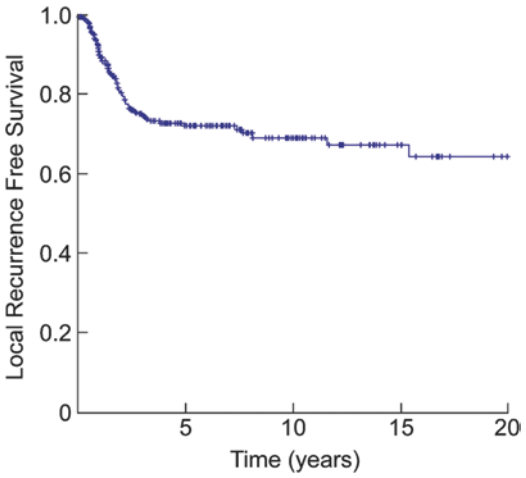

Fig. 10.10 Local disease-free survival for adult patients with primary desmoid tumor/deep fibromatosis. MSKCC 7/1/1982–6/30/2010 $n = 361$

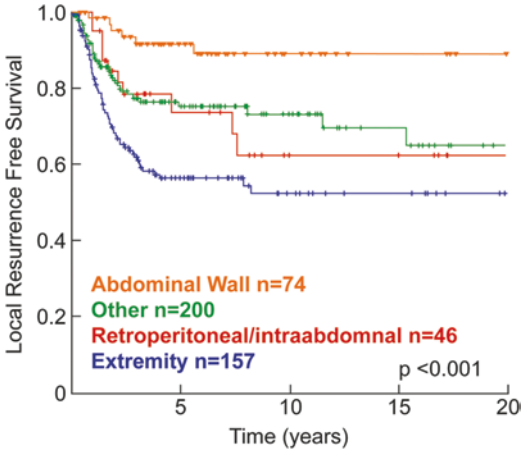

Fig. 10.11 Local disease-free survival by primary site for adult patients with desmoid tumor/deep fibromatosis, including patients with primary disease and local recurrence. MSKCC 7/1/1982–6/30/2010 $n = 477$

10.11 Outcome

The local disease-free survival of patients presenting with a primary lesion to MSKCC is shown in Fig. 10.10, with 40 % recurrence. Site-dependent local recurrence-free survival is in Fig. 10.11 and disease-specific survival in Fig. 10.12.

The relationship of recurrence by microscopic margin is a subject of debate (Table 10.2) and it is difficult to evaluate series where reoperation is performed. It is also hard to evaluate those patients receiving radiation therapy. Both modalities have been used selectively making outcome analysis difficult. Once a patient has a recurrence, however, further recurrences can be anticipated. Perhaps the greater question is why patients with positive margins do not recur, rather than why those

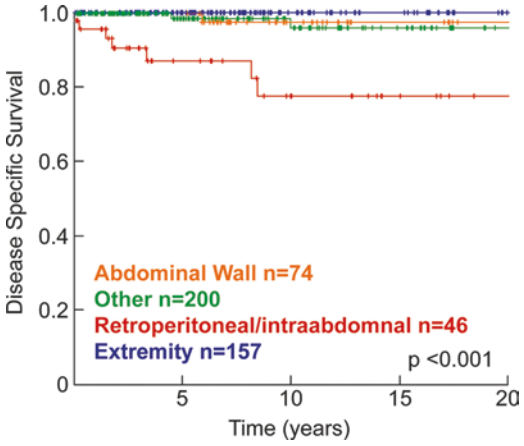

Fig. 10.12 Disease-specific survival by primary site for adult patients with desmoid tumor/deep fibromatosis, including patients with primary disease and local recurrence. MSKCC 7/1/1982–6/30/2010 $n=477$

Table 10.2 Larger series ($n>100$) examining local recurrence of extremity and trunk desmoids

Author	Year	Number of patients	Primary desmoid (*n*)	Recurrent desmoid (*n*)	Median follow up (months)	5 Year PFS (%) with R0 margins	5 Year PFS (%) with R1 margins	*p*-Value
Posner et al. [17]	1989	128	78	53	88	85	50	0.002
Merchant et al. [4]	1998	105	105	–	49	70	78	0.51
Ballo et al. [54]	1999	189	85	104	112	75	50	0.003
Gronchi et al. [55]	2003	203	128	–	130	82	79	0.5
			–	75	153	65	47	0.16
Stoeckle et al. [56]	2008	106	69	37	123	n.d.	n.d.	–
Fiore et al. [25]	2009	142	74	68	33	n.d.	n.d.	–
Salas et al. [52]	2011	426	426	–	52	64	62	n.s.

n Number of patients, *n.d.* not done, *n.s.* not significant, *PFS* progression-free survival

with positive margins do recur. Local recurrence occurs in approximately 25 %, and it is important to understand that the natural history is very long. The results of local recurrence by site and by margin status are included in Figs. 10.13 and 10.14.

One analysis [41] examined two groups of 189 patients treated in two time intervals, 1995–2005 and 1965–1994. The progressive trend to use more systemic therapy was identified and suggested an improved local recurrence rate in the later group. These data are difficult to validate in the absence of a randomized trial. The manuscript authors' recommendation was that patients resected with positive margins receive radiation therapy and that those patients who have lesions with

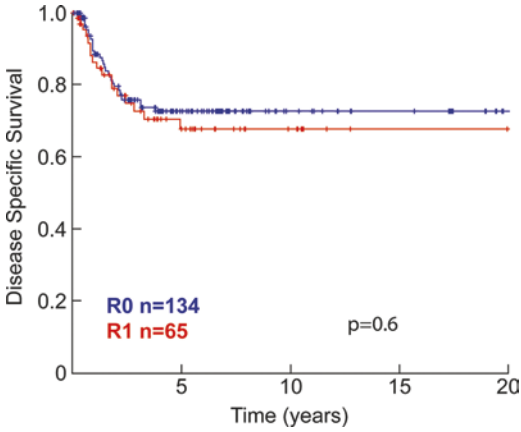

Fig. 10.13 Local disease-free survival by primary site for adult patients with desmoid tumor/deep fibromatosis of the extremity and trunk, classified by margin status, R0 vs. R1. MSKCC 7/1/1982–6/30/2010 $n=199$

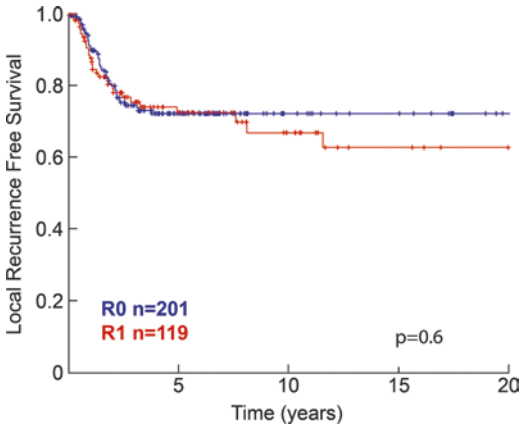

Fig. 10.14 Local disease-free survival by primary site for adult patients with desmoid tumor/deep fibromatosis of all sites, classified by margin status, R0 vs. R1. MSKCC 7/1/1982–6/30/2010 $n=319$

significant operative risk of morbidity should receive preoperative radiation therapy. This is not an approach that we have taken, given that in patients with positive margins only 30 % recur at any time in their course [4]. We argue that it is hard to justify the uniform use of radiation therapy which at best limits local recurrence from 30 to 15 % (Fig. 10.15a, b).

A more recent analysis of outcomes after initial resection of primary desmoids derived from European series provides insight into clinical risk stratification [52]. In a multivariate analysis, age, tumor size, and tumor site were independent risk factors. Scoring each of the unfavorable prognostic factors (age over 37 at time of presentation [crude hazard ratio 1.97], size>7 cm [crude HR 1.64], and extra-abdominal primary [vs. abdominal wall as lowest risk group, HR 2.55] yielded three groups with distinguishable risk of local recurrence (0 and 1 risk factors, 2 risk factors, and 3). In the multivariate analysis, intra-abdominal location was worse than abdominal wall, but there was only a trend to inferiority for this anatomic site in multivariate analysis (HR 1.95, $p=0.084$). These findings will become of even greater value once molecular data regarding beta-catenin mutations are linked to the clinical data.

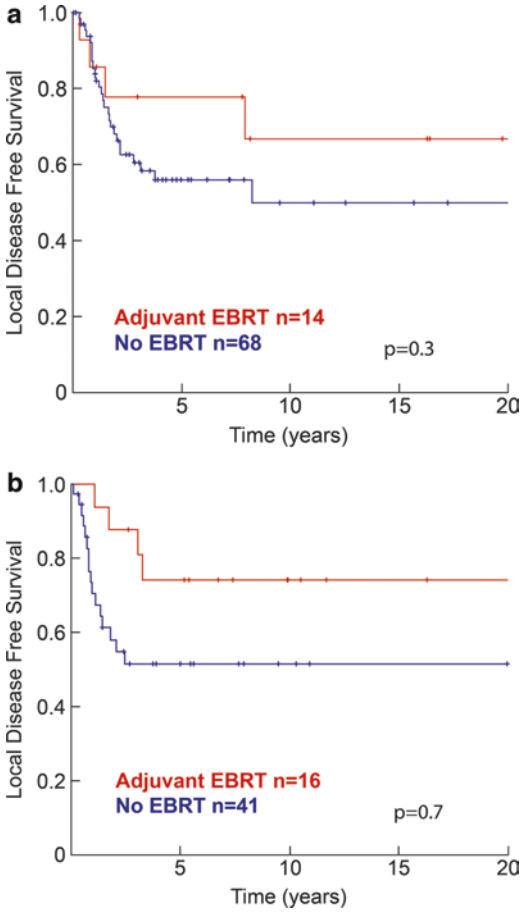

Fig. 10.15 Local disease-free survival by primary site for adult patients with desmoid tumor/deep fibromatosis of the extremity with (**a**) R0 $n=82$ or (**b**) R1 resection $n=57$, classified by use of external beam radiation. MSKCC 7/1/1982–6/30/2010

Our most recent analysis [53], where we analyzed 495 patients (382 primary, 113 recurrent) all treated in a single institution, suggested an overall local recurrence rate of 30 % at 10 years. Greater than 90 % of those who recurred did so within 5 years. Less than 2 % died, all after R2 resection.

The important factors predicting recurrence were location, where extremity was more likely to recur than chest wall, more likely than intra-abdominal, more likely than other, more likely than abdominal wall. Patients with age under 25 and over 65 were more likely to recur. Size >10 cm was an important factor in increased recurrence. Positive microscopic margin (R1) was not a predictor of increased recurrence, and we could not show a benefit to radiation treatment. In fact, with a diminishing use of radiation (7 % after 1996, 30 % before 1997) there was no impact on local recurrence. This has allowed the generation of a predictive nomogram [53]. In 439 patients with complete gross resection 100 (23 %) had local recurrence. Five-year local recurrence-free survival was 69 %. Eight patients died all after R2 resection. In multivariable analysis, factors associated with local recurrence were

extremity location, young age, and large tumor size, but not margin status or use of radiation. Future versions of this nomogram will incorporate the molecular findings regarding recurrence from other studies. More challenging will be the better understanding of the biological reason for different degrees of aggressiveness of desmoid tumors affecting specific patients [49].

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Chapter 11
Solitary Fibrous Tumor/Hemangiopericytoma

Solitary fibrous tumor (SFT) can occur at any age (Fig. 11.1) and any site (Fig. 11.2). Solitary fibrous tumor/hemangiopericytoma (SFT/HPC) represents a spectrum of tumors ranging from benign tumors with bland spindle shaped cells to histologically malignant tumors with a high mitotic rate and significant risk of metastatic disease. SFT/HPC arises in the pleura, soft tissue, and in the dura.

In the pleura, an old name for SFT was fibrous mesothelioma, but it has no relationship to mesothelial cells (or to asbestos exposure). The cell of origin or line of differentiation is most likely fibroblastic, since SFT/HPC lack actin reactivity, typically found in the perivascular pericytic cells [1, 2]. SFT/HPC are CD34 immunoreactive, and often stain positive for Bcl2 and CD99, and more recently shown to express STAT6 (see later). The common origin of SFT and HPC appeared likely, given the related pattern of gene expression observed regardless of the primary site of the tumor (Fig. 11.3) [3]. This hypothesis was subsequently confirmed by the use of RNA sequencing, which identified a recurrent *NAB2-STAT6* fusion in the majority of SFT/HPC cases, regardless of degree of malignancy or anatomic location, in keeping with a common pathogenesis [4]. Based on this genetic signature, STAT6 nuclear immunoreactivity is now used as a main ancillary test for confirming the diagnosis [5]. The type of *NAB2-STAT6* fusion may also account for some of the biological differences seen in the behavior of this family of tumors [6].

SFT/HPC is typically a tumor that grows slowly over many years, and raises few suspicions until it is large in size [7]. Those SFT/HPCs with a greater degree of aggressiveness microscopically ("malignant" SFT/HPC), defined as having >4 mitotic figures/10 high powered fields have a higher risk of metastatic disease [8], while that risk is very low for tumors lacking overt malignant changes (Figs. 11.4 and 11.5).

M.F. Brennan et al., *Management of Soft Tissue Sarcoma*,
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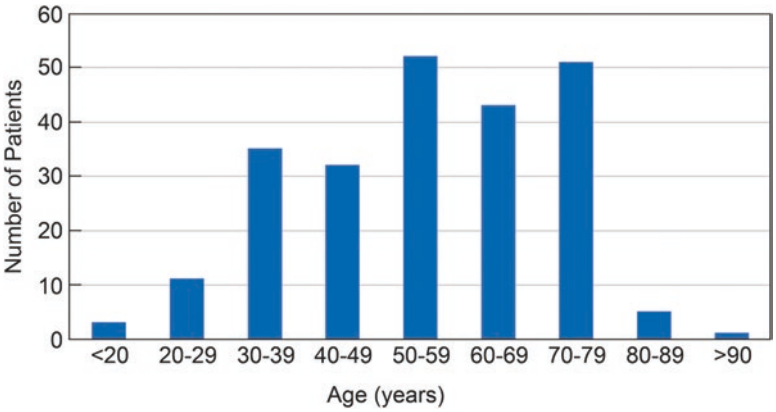

Fig. 11.1 Age distribution of adult patients with solitary fibrous tumor/hemangiopericytoma. MSKCC 7/1/1982–6/30/2010 $n = 233$

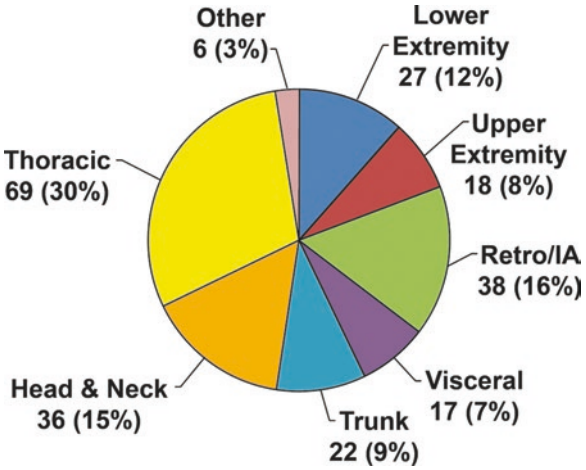

Fig. 11.2 Primary site distribution of adult patients with solitary fibrous tumor/hemangiopericytoma. MSKCC 7/1/1982–6/30/2010 $n = 233$. *Retro/IA* retroperitoneal/intra abdominal

11.1 Doege–Potter Syndrome

This is a paraneoplastic syndrome where patients become hypoglycemic. Most commonly associated with the presence of a solitary fibrous tumor previously considered as hemangiopericytoma. This hypoglycemia is the result of the tumor producing an insulin-like growth factor. Doege first described it in 1930 [9]. It was similarly described at the same time by Potter [10, 11]. The syndrome is very rare and occurs in both benign and malignant forms of solitary fibrous tumor. However, less than 5 % of solitary fibrous tumors actually have the associated hypoglycemia. These are tumors that are large with high rate of mitosis and the symptoms do resolve with removal of the tumor.

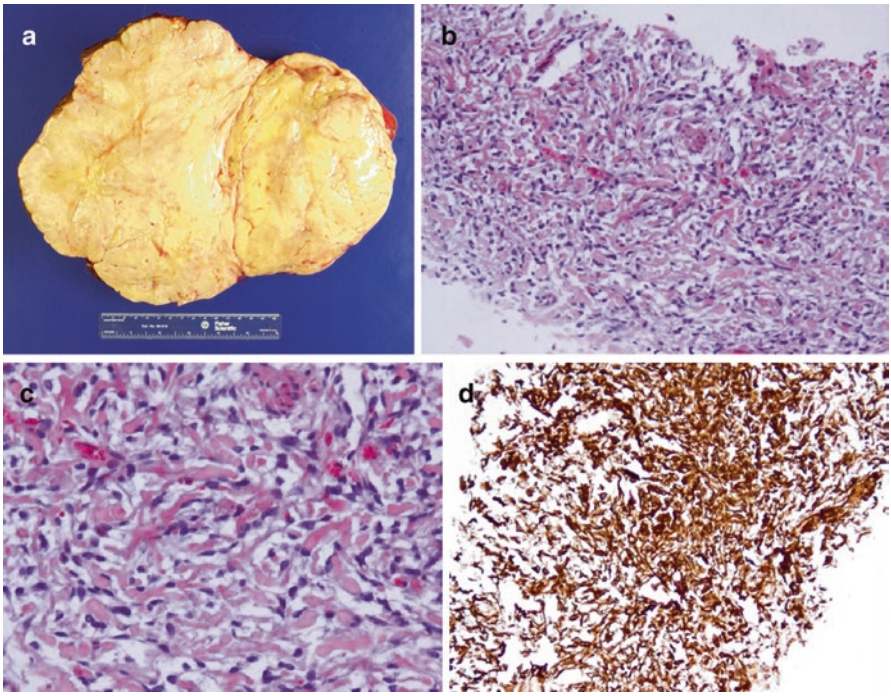

Fig. 11.3 Malignant solitary fibrous tumor—(**a**) Gross pathology, (**b**) high power (H&E, ×400), and (**c**) immunohistochemical staining for CD34 in a solitary fibrous tumor

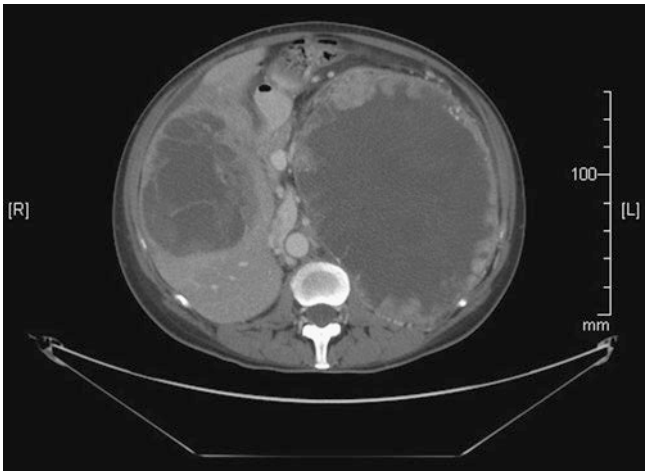

Fig. 11.4 Contrast enhanced CT image of a large metastatic solitary fibrous tumor with liver metastasis. A substantial degree of central necrosis is observed in both large lesions

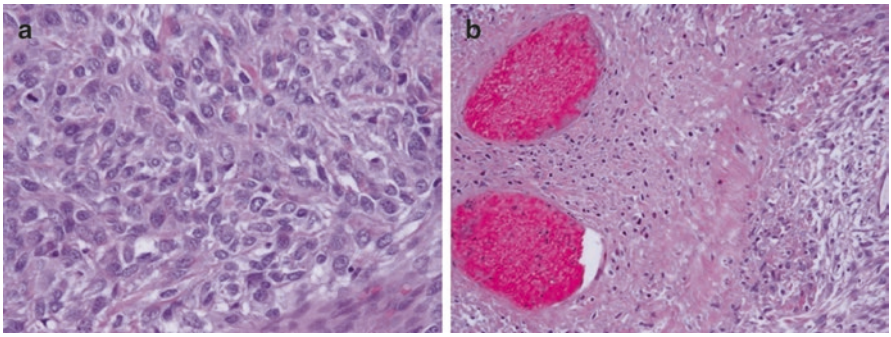

Fig. 11.5 Features differentiating malignant solitary fibrous tumor from a less aggressive lesion: (**a**) increased mitotic activity (5 mitoses/10 high power fields); (**b**) focal necrosis

11.2 Primary Therapy

Primary therapy remains surgical, and those tumors in the pleura arise on a stalk and thus prove easier to remove than expected for a tumor of large size at presentation. Radiation is not generally employed as part of primary therapy due to the relatively low risk of local-regional recurrence for tumors removed with an R0 resection especially for benign tumors. For malignant variants, some advocate for adjuvant RT with excellent local control results [12]. Adjuvant chemotherapy is not used for these tumors, many of which will not recur, and those that do recur often do so after only an extended period of time.

11.3 Systemic Therapy for Metastatic Disease

Metastatic disease is often only appreciated 10–20 years after initial diagnosis, and bone, lung, and liver appear to be common sites of metastatic disease. Radiation therapy can be employed for particular painful sites of what are typically bony metastases.

As for systemic therapy, in our experience anthracyclines are inactive, but ifosfamide with or without cisplatin appears to have at least modest activity. Data from Stacchiotti and colleagues in Milan and from MD Anderson have better defined the spectrum of treatment of these sarcomas [13].

Dacarbazine alone can have activity in this class of tumors [14]. Data have been generated regarding antitumor activity with antiangiogenic compounds such as sunitinib [7, 15, 16], pazopanib [17], sorafenib [18], and with bevacizumab (the latter with temozolomide) [19], which causes tumor devascularization detectable on scans, without dramatic size change in tumor masses in most patients. This phenomenon ("Choi response") has also been observed with gastrointestinal stromal tumors (GIST) exposed to imatinib and other tyrosine kinase inhibitors [20], and progression of disease, like in GIST, is demonstrated by reactivation of the vasculature of the tumor. An angle on therapy recently brought to the fore is highlighted by Doege–Potter syndrome [11, 20, 21], in which SFT/HPC causes hypoglycemia on the

Table 11.1 Systemic therapy recommendations for patients with solitary fibrous tumor/hemangiopericytoma

Clinical scenario		Comments[a]
Neoadjuvant/adjuvant chemotherapy		Not administered due to low risk of relapse and poor response to traditional chemotherapy in the metastatic setting
Metastatic disease	First line	Pazopanib or similar multi-targeted tyrosine kinase inhibitor; bevacizumab and temozolomide; doxorubicin + olaratumab are approved but largely untested in this specific diagnosis, noting that doxorubicin has minor activity at best as a single agent
	Second line	Ifosfamide-based therapy. Gemcitabine–docetaxel appears to have little activity. Immune checkpoint inhibitors are untested in SFT as of 2016

[a]Clinical trials are always appropriate if available, in particular agents that are directed at IGF1R signaling or epigenetic targets

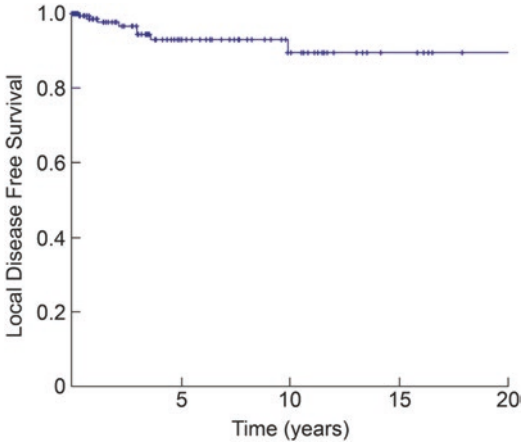

Fig. 11.6 Local disease-free survival for adult patients with adult primary solitary fibrous tumor of all sites. MSKCC 7/1/1982–6/30/2010 $n = 169$

basis of excessive production of an abnormal version of IGF-2. Since IGF-2 binds IGF1R, one hypothesizes that IGF1R inhibitors could be active in SFT/HPC, and this appears to be the case for at least a minority of patients with metastatic disease from this diagnosis (Table 11.1) [22]. It is unclear if there is any relationship between IGF2 expression and markers of chromatin remodeling, such as histone 3 lysine 4 (H3K4) methylation status, a topic that requires further study [15]. Another future link to biology that will be worth pursuing in the future is the interruption of STAT6 signaling that appears critical to the development and maintenance of this family of sarcomas.

11.4 Outcome

Local recurrence in 169 primary SFT is shown in Fig. 11.6 with disease-specific survival for primary presentation in Fig. 11.7. Risk of recurrence/metastases is largely limited to those SFT/HPC with malignant changes. The risk of recurrence of SFT/HPC without these changes is very low.

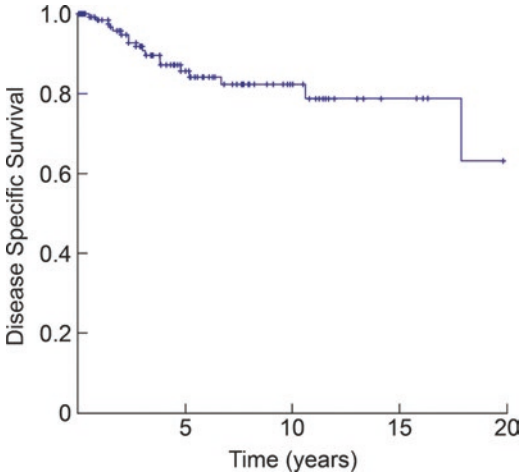

Fig. 11.7 Disease-specific survival for adult patients with adult primary solitary fibrous tumor of all sites. MSKCC 7/1/1982–6/30/2010 $n = 169$

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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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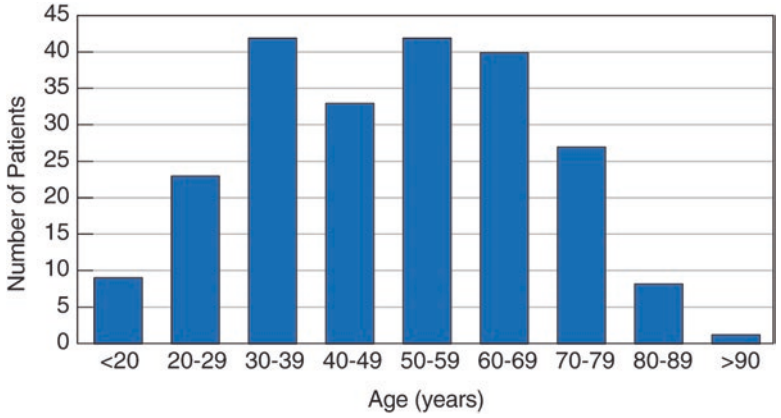

Fig. 12.1 Age distribution of adult patients with fibrosarcoma (all types except DFSP). MSKCC 7/1/1982–6/30/2010 $n = 225$

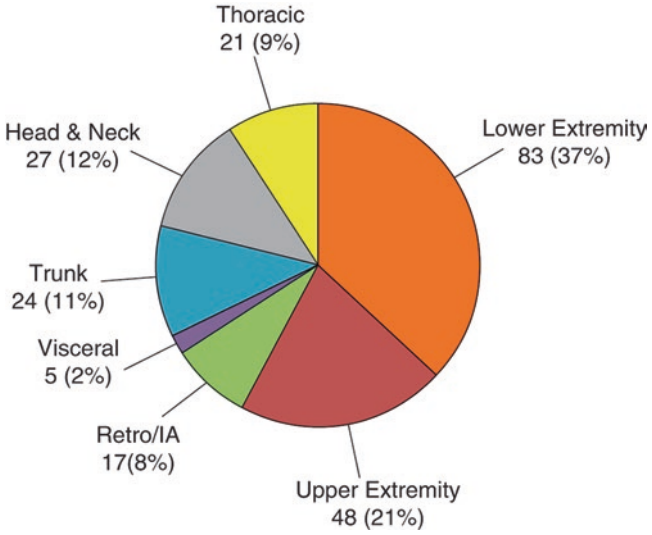

Fig. 12.2 Anatomic primary site distribution of adult patients with fibrosarcoma (all types except DFSP). MSKCC 7/1/1982–6/30/2010 $n = 225$. *Retro/IA* retroperitoneal/intra abdominal

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,

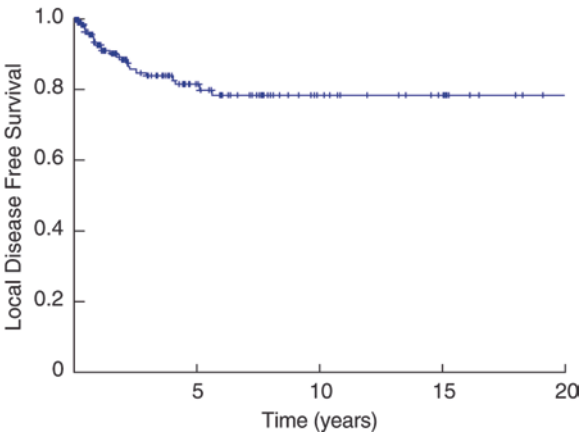

Fig. 12.3 Local disease-free survival for adult patients with primary fibrosarcomas (all types except DFSP). MSKCC 7/1/1982–6/30/2010 $n = 164$

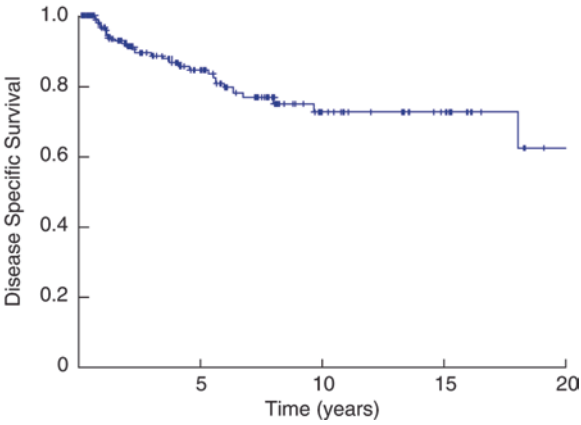

Fig. 12.4 Disease-specific survival for adult patients with primary fibrosarcomas (all types except DFSP). MSKCC 7/1/1982–6/30/2010 $n = 164$

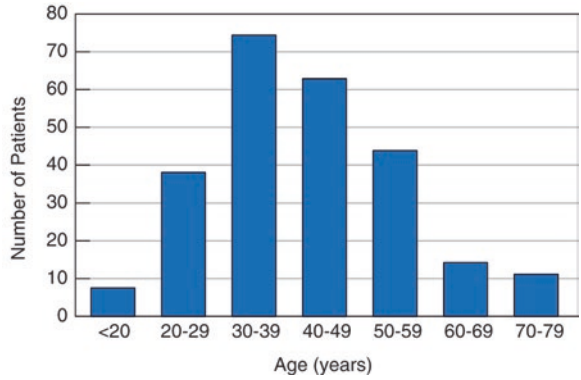

Fig. 12.5 Age distribution of adult patients with dermatofibrosarcoma protuberans. MSKCC 7/1/1982–6/30/2010 $n = 252$

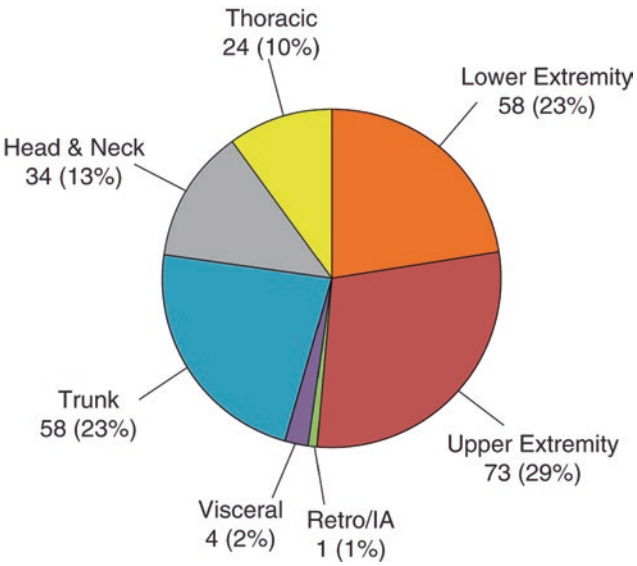

Fig. 12.6 Anatomic primary site distribution of adult patients with dermatofibrosarcoma protuberans. MSKCC 7/1/1982–6/30/2010 $n = 252$. *Retro/IA* retroperitoneal/intra abdominal

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

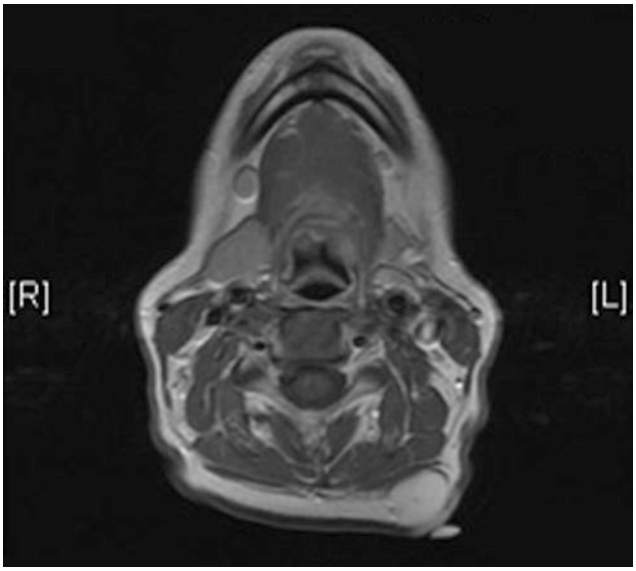

Fig. 12.7 T1-weighted contrast enhanced MRI image of a 2 cm dermatofibrosarcoma protuberans of the superficial posterior left neck

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

	Primary ($n=196$)		Local recurrence ($n=44$)		
Characteristic	No.	%	No.	%	*P* value[a]
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

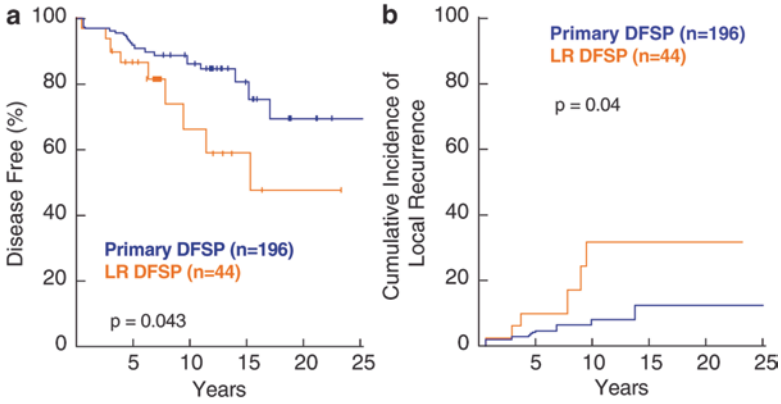

Fig. 12.8 (**a**) Disease-free survival and (**b**) cumulative incidence of local recurrence of DFSP in patients presenting with primary disease (*dark line*) or locally recurrent disease (*light line*). From: Fields RC, et al. Ann Surg Oncol 2011;18:328–336

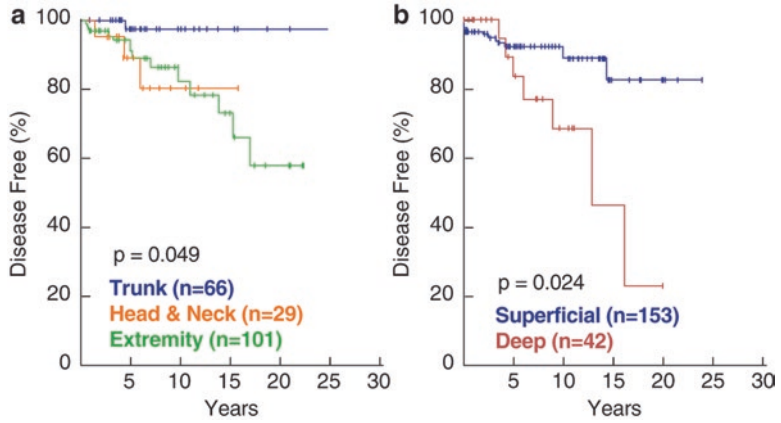

Fig. 12.9 Disease-free survival as a function of (**a**) anatomic primary site and (**b**) tumor depth at presentation. From: Fields RC, et al. Ann Surg Oncol 2011;18:328–336

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

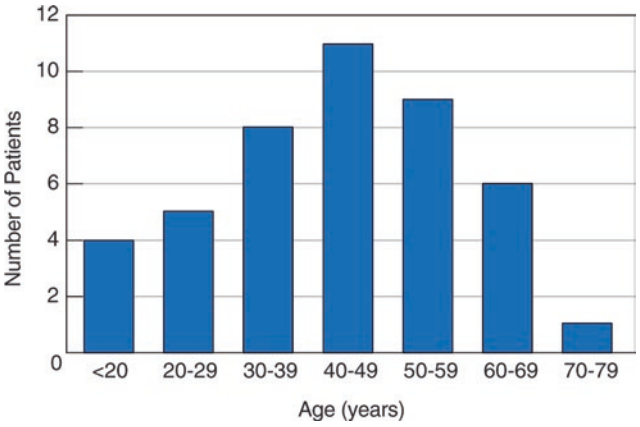

Fig. 12.10 Age distribution of adult patients with fibromyxoid sarcoma. MSKCC 7/1/1982–6/30/2010 $n=45$

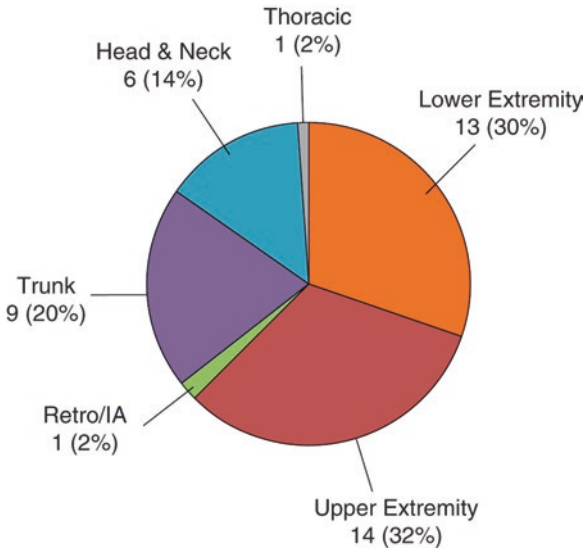

Fig. 12.11 Anatomic primary site distribution of adult patients with fibromyxoid sarcoma. MSKCC 7/1/1982–6/30/2010 $n=45$. *Retro/IA* retroperitoneal/intra abdominal

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.

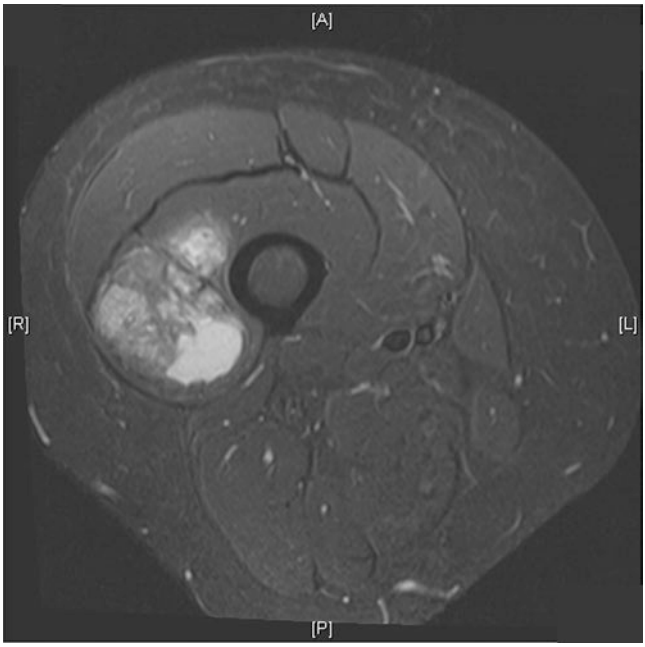

Fig. 12.12 T2-weighted MRI image of a 7 cm right thigh fibromyxoid sarcoma

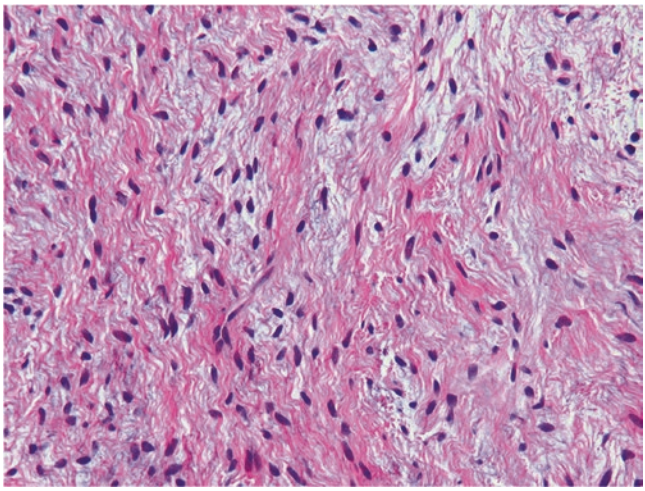

Fig. 12.13 Microscopic appearance of fibromyxoid sarcoma showing deceptively bland spindle cells embedded in a loose fibrous and myxoid stroma (H&E, ×200)

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

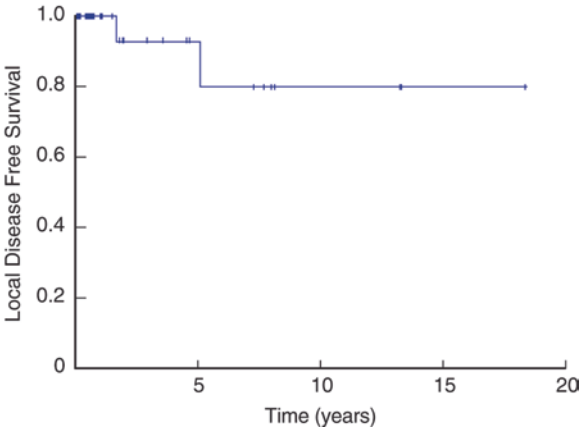

Fig. 12.14 Local disease-free survival for adult patients with primary fibromyxoid sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 36$

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

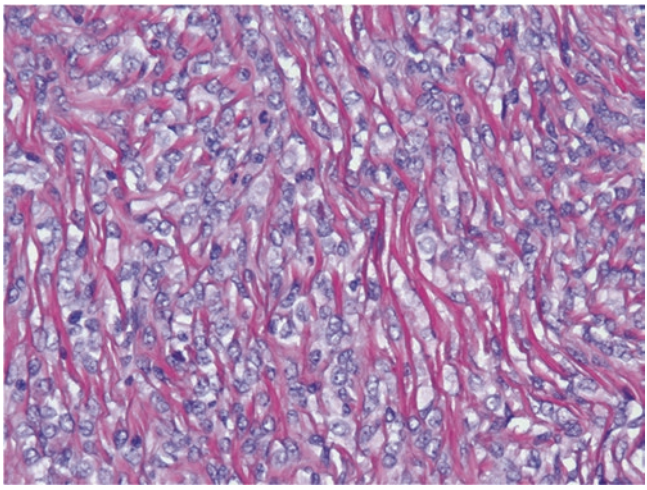

Fig. 12.15 Microscopic appearance of sclerosing epithelioid fibrosarcoma showing monotonous epithelioid cells with scant amphophilic cytoplasm arranged in cords, separated by refractile collagenous columns (H&E, ×400)

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

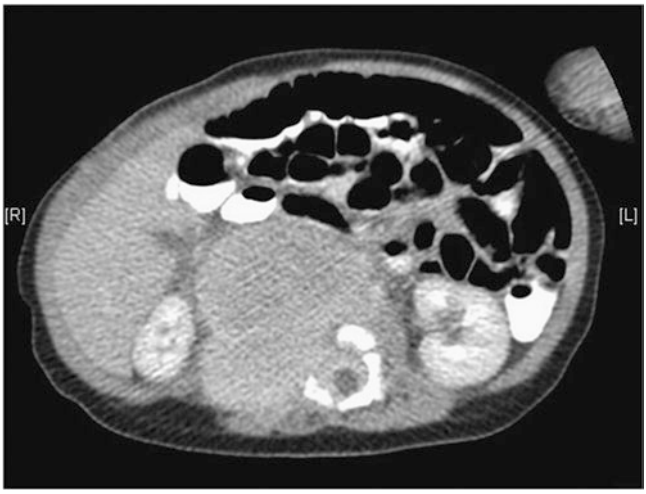

Fig. 12.16 Contrast-enhanced CT image of a patient with infantile fibrosarcoma of the right psoas musculature causing destruction of the spine and involvement of the spinal canal

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).

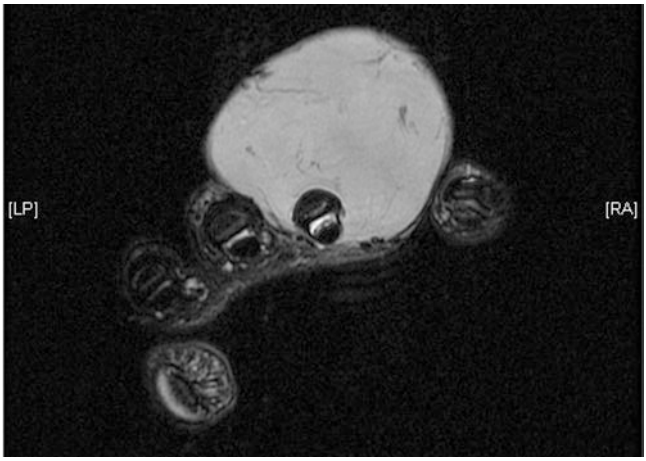

Fig. 12.17 T2-weighted MRI image of a 5 cm true fibrosarcoma of the fourth metatarsal soft tissues and extensor tendons of the right third, fourth, and fifth digits

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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Chapter 13
Vascular Sarcomas

Vascular tumors run the gamut from benign hemangiomas to low-grade epithelioid hemangioendotheliomas, to highly aggressive angiosarcomas. We refrain in this section in discerning vascular sarcomas from similar tumors arising from lymphatics (lymphangiosarcomas) as there have not been good markers to definitively separate the two forms of tumors.

13.1 Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is a rare vascular neoplasm with distinctive morphologic appearance, presenting as a deep painful soft tissue mass, although can be found primarily in lung, bone, and liver [1]. Multicentric presentation is often seen, particularly with visceral lesions (Fig. 13.1). The average age of presentation is 50 years, with no gender difference (Fig. 13.2).

The tumors are composed of epithelioid cells with densely eosinophilic cytoplasm, arranged in cords, strands, or nests and often with intracytoplasmic vacuoles (Fig. 13.3). Often there is a myxochondroid background and generally low mitotic rate. Mature vascular lumen formation is typically absent; this feature distinguishes EHE from other epithelioid vascular lesions, including epithelioid hemangioma and epithelioid angiosarcoma. Immunohistochemistry shows CD31, CD34, and ERG positivity [2]. The novel translocation t(1;3), resulting in *WWTR1-CAMTA1* fusion, has been identified in the majority of EHE samples examined [3, 4] and can be used as a very useful molecular test in challenging diagnosis. Additionally a small subset of EHE, with somewhat different morphologic appearance shows oncogenic activation of TFE3, as a result of *YAP1–TFE3* fusions [5]. This finding links EHE to other tumors with TFE3 oncogenic activation, such as alveolar soft part sarcoma and pediatric Xp11-renal cell carcinoma.

M.F. Brennan et al., *Management of Soft Tissue Sarcoma*,
DOI 10.1007/978-3-319-41906-0_13

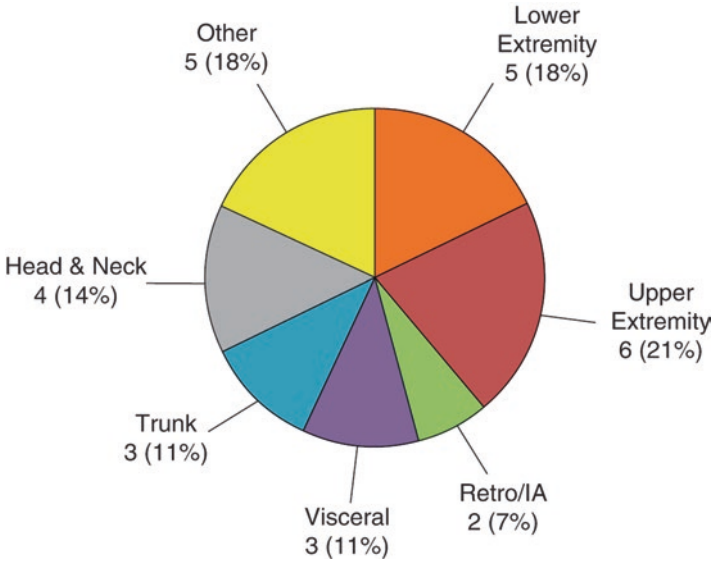

Fig. 13.1 Primary site distribution of adult patients with hemangioendothelioma. MSKCC 7/1/1982–6/30/2010 $n=28$. *Retro/IA* retroperitoneal/intra abdominal

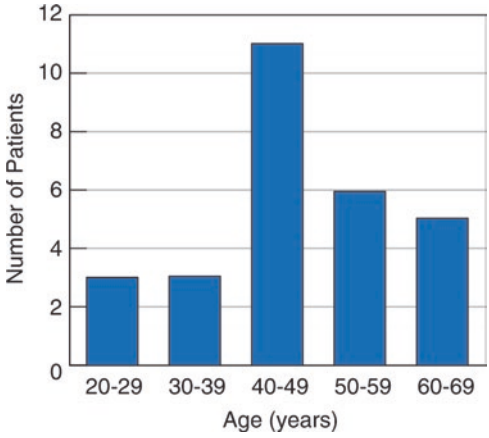

Fig. 13.2 Age distribution of adult patients with hemangioendothelioma. MSKCC 7/1/1982–6/30/2010 $n=28$

The tumor is most commonly seen as multifocal disease affecting liver, lung, pleura, or several of these sites simultaneously (Fig. 13.4). Various studies report 15 % local recurrence rates, 30 % with distal metastasis, and 50 % involvement with regional lymph nodes. Only a minority of these tumors progress over the course of 1–3 years with many appearing largely dominant for a decade or more suggesting observation as a viable option for management of such patients with unresectable multifocal disease. Approximately 20 % of EHE are more aggressive and thus may require immediate intervention.

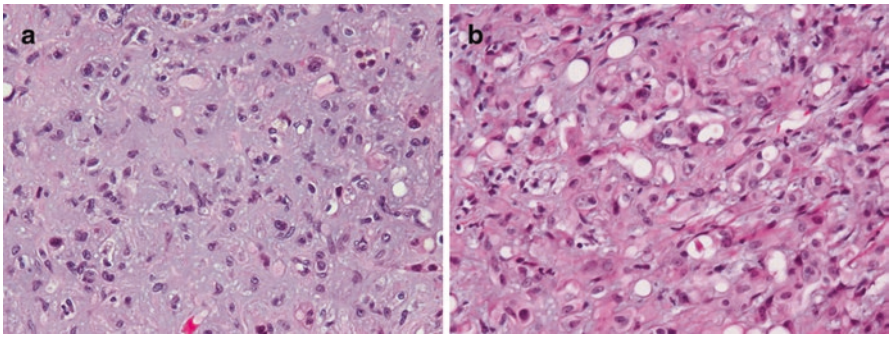

Fig. 13.3 (**a**) Microscopic appearance (H&E, ×200) of epithelioid hemangioendothelioma demonstrating bland, single epithelioid cells embedded in a distinctive myxochondroid stroma. (**b**) A second example demonstrating intracytoplasmic vacuoles with digested erythrocytes. In comparison to angiosarcoma, epithelioid hemangioendothelioma typically lacks the well-formed vascular channel formation and high degree of anaplasia

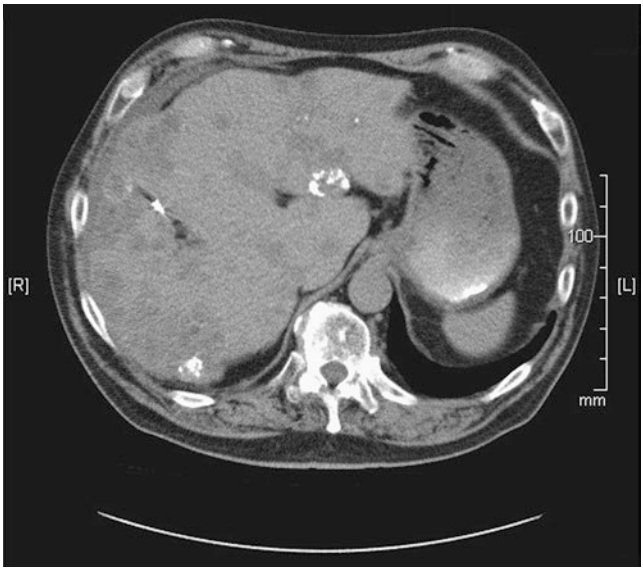

Fig. 13.4 Noncontrast CT image of multicentric epithelioid hemangioendothelioma affecting the liver. Heterotopic calcifications are demonstrated. The radiological abnormalities were essential unchanged over 5 years of monitoring

When feasible, primary treatment is surgical excision with an uncertain role for radiation and chemotherapy.

Liver-only disease has been treated with chemotherapy, bland embolization, chemo-embolization, or even liver transplant in those rare patients who develop liver failure from disease.

Table 13.1 Systemic therapy recommendations for epithelioid hemangioendothelioma

Clinical scenario		Comments
Neoadjuvant/ adjuvant chemotherapy		Not used, given the low response rate of systemic therapy in metastatic disease
Metastatic disease	First line	A variety of agents have minor activity, but no consistent response pattern has been observed by the authors. Consideration can be given to liposomal doxorubicin/Doxil®/ Caelyx®, gemcitabine-based therapy, vinorelbine, and other agents. Hepatic embolization and other local therapies can be considered for liver-predominant disease. Doxorubicin + olaratumab is also approved in this situation but prospective data are lacking
	Second line	Pazopanib, or other oral VEGFR-blocking kinase inhibitor; clinical trials remain very relevant. Immune checkpoint inhibitors are not tested as of 2016 in epithelioid hemangioendothelioma

There has been only erratic responsiveness of EHE to chemotherapy; the authors have observed occasional responses to a number of chemotherapy agents but no reliable alternative as a definitive first-line agent or agents. There have been only hints of benefit in metastatic EHE patients from oral kinase inhibitors. In the largest prospective study including this diagnosis, 2/15 patients had a RECIST partial response to sorafenib; this study serves as a good baseline for evaluation of future therapeutics (Table 13.1) [6]. A high mitotic rate and marked nuclear atypia are independent predictors of survival [7]. The WHO classification suggests the use of 'malignant EHE' terminology for this group of lesions, to distinguish from the more bland appearing examples.

EHE should be distinguished from another fusion-positive vascular tumor, the so-called pseudomyogenic hemangioendothelioma (a.k.a. epithelioid sarcoma-like hemangioendothelioma). Most of these cases follow an indolent course, but occasionally behave aggressively and show distant spread; such as in this unusual example of a 30-year-old male (Fig. 13.5a–g) with metastatic disease to bone and soft tissue confined to the unilateral lower extremity—note the staining for vascular markers. Pseudomyogenic hemangioendotheliomas have characteristic t(7;19)(q22;q13) *SERPINE1-FOSB* translocations [8], different from the *ZFP36-FOSB* t(19;19) balanced translocations (or chromosomal 19 interstitial deletions) found in epithelioid hemangiomas [9].

13.2 Angiosarcoma/Lymphangiosarcoma

Angiosarcomas constitute a difficult family of tumors to manage, both given their local-regional failure as well as high risk of mortality from metastatic disease (Figs. 13.6 and 13.7). Angiosarcoma does present a unique profile of sensitivity to chemotherapy [10], and similar to leiomyosarcomas of different sites there appears to be differential sensitivity to systemic therapeutic agents based on the anatomic origin of the tumor (see earlier).

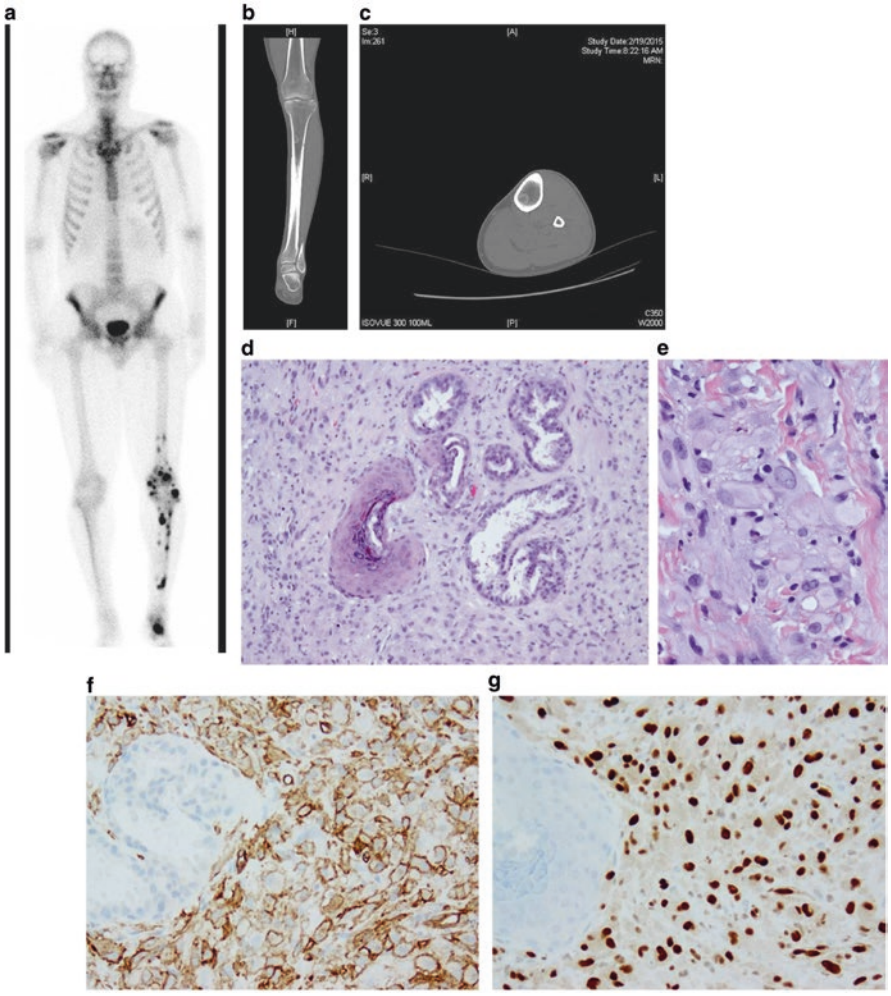

Fig. 13.5 (**a**–**c**) Case of pseudomyogenic hemangioendothelioma of the left lower leg—Has a positive bone scan, and good CT/MRI as variant of epithelial hemangioendothelioma. Bone scan and CT show multiple lesions within the distal femur and tibia. (**d**–**g**) Microscopic appearance showing tumor encasing skin adnexal structures, which at higher power have a distinctive epithelioid morphology with abundant, glassy eosinophilic cytoplasm. Tumor cells are diffusely positive for CD31 and ERG endothelial markers

Angiosarcomas tend to occur after age 50; the head and neck is a common primary site (Figs. 13.8, 13.9, and 13.10) [11–15]. Angiosarcomas have been observed in every conceivable location, and challenge surgeons and medical oncologists by their local regional recurrence risk and convincing but brief responses to a variety of systemic agents. Forms of angiosarcoma are associated with therapeutic radiation (Fig. 13.11) or lymphedema (Stewart–Treves syndrome) (Fig. 13.12), or lymphedema from other causes such as, filariasis [16] (Fig. 13.13) and are particularly

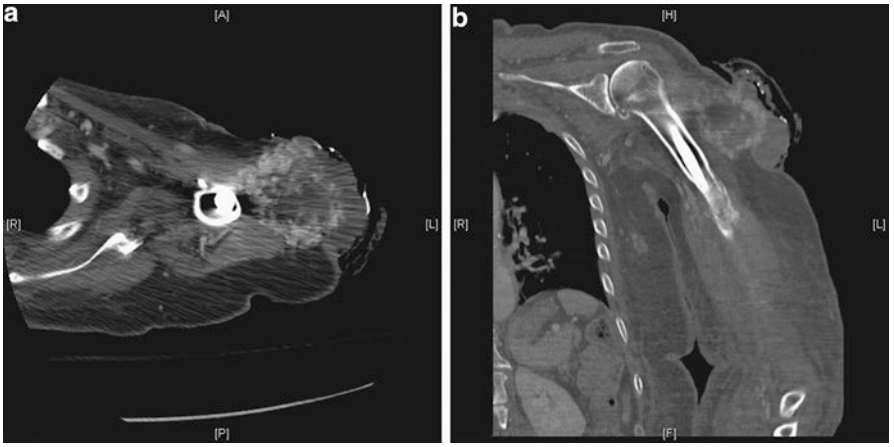

Fig. 13.6 CT images (**a**, **b**) of angiosarcoma of the humerus causing pathological fracture (s/p fixation) with demonstration of soft tissue metastases affecting the left upper extremity soft tissues

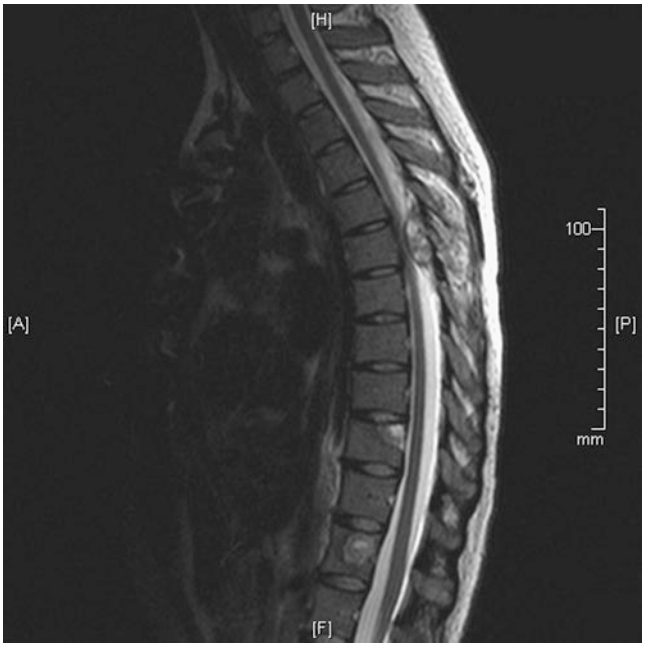

Fig. 13.7 T1 weighted MRI images of metastatic cardiac angiosarcoma with spinal metastases and invasion into the spinal canal

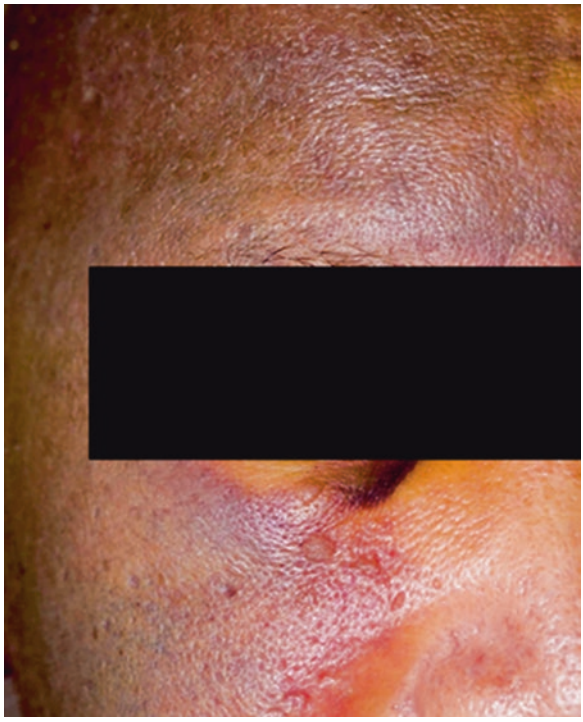

Fig. 13.8 Photograph of the upper right quadrant of the face in a 66-year-old Asian male demonstrating unresectable angiosarcoma involving the face, scalp, and neck

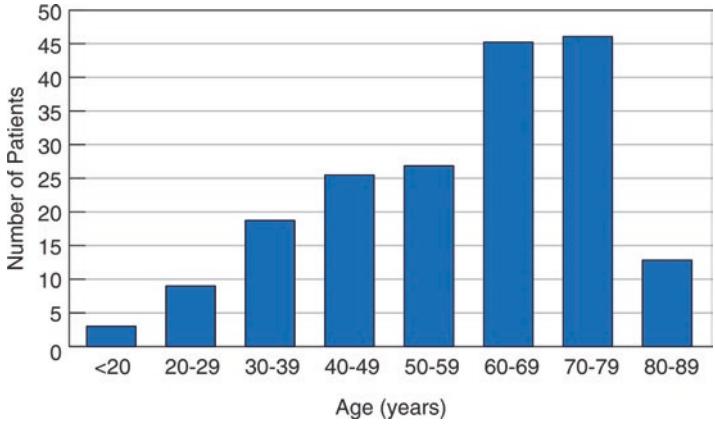

Fig. 13.9 Age distribution of adult patients with angiosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 188$

deadly in those settings, as are those that arise in bone as a primary site. Primary therapy, as for other sarcomas, includes excision with negative margins, and consideration of irradiation for those tumors that did not arise after prior radiation. In particular, in the head and neck area requires both wide margins and even larger radiation port if local-regional control is to be achieved.

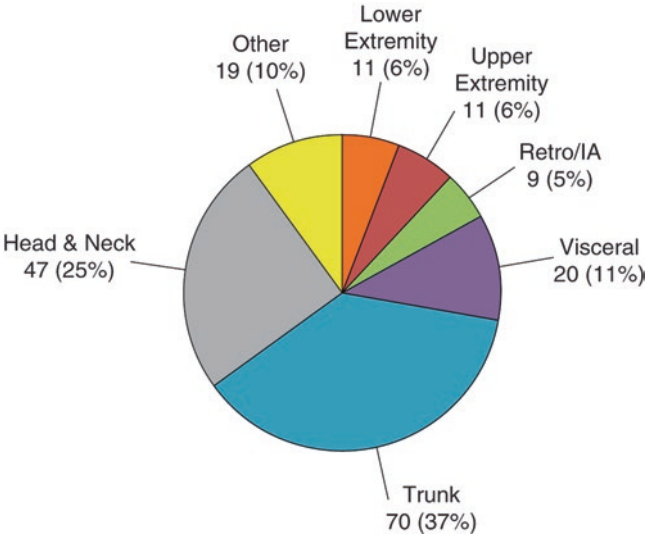

Fig. 13.10 Anatomic primary site distribution of adult patients with angiosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 187$. *Retro/IA* retroperitoneal/intra abdominal

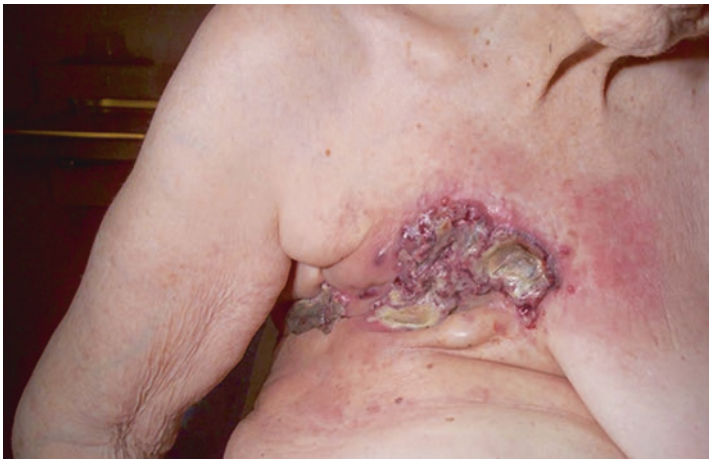

Fig. 13.11 Angiosarcoma of the right chest wall in a 77-year-old Caucasian woman 8 years after surgery and radiation therapy for infiltrating ductal adenocarcinoma of the breast

Tumors are typically CD31 and ERG positive, as expected for a cell of endothelial origin, and about half are positive for CD34. Microscopic imaging of a radiation-induced angiosarcoma is shown in Fig. 13.14. VEGFR3/FLT4 is positive by immunohistochemistry in a majority of cases, and positivity for KIT or cytokeratins are occasionally found in angiosarcomas as well. There is no characteristic genetic change in angiosarcomas known to date, although ~10 % of angiosarcomas (breast

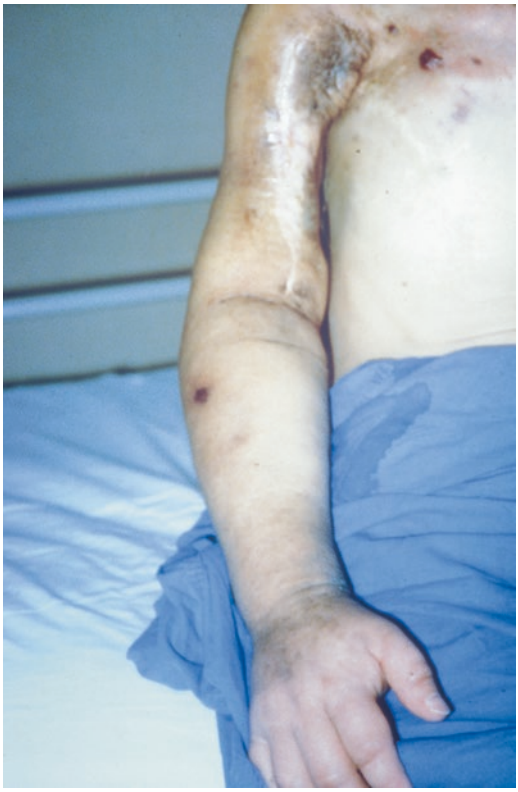

Fig. 13.12 Postmastectomy, postradiation lymphedema with multifocal lymphangiosarcoma (Stewart-Treves Syndrome) With permission from: Brennan MF, Lewis JJ. *Diagnosis and Management of Soft Tissue Sarcoma*. London: Martin Dunitz Ltd., 1998

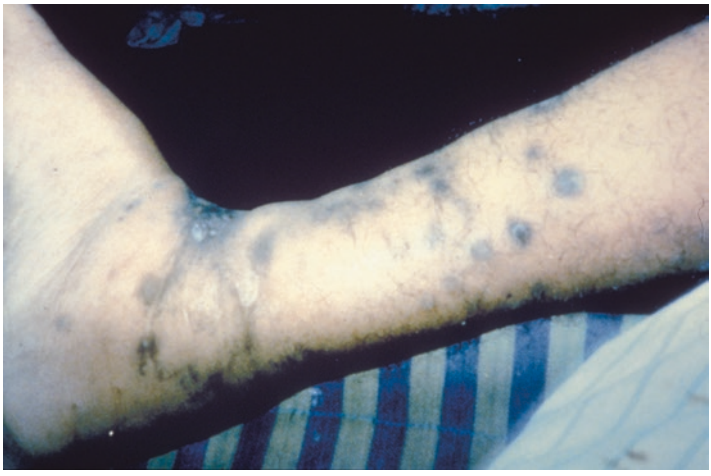

Fig. 13.13 Postfiliarial lymphedema with multifocal angiosarcoma. With permission from: Brennan MF, Lewis JJ. *Diagnosis and Management of Soft Tissue Sarcoma.* London: Martin Dunitz Ltd., 1998

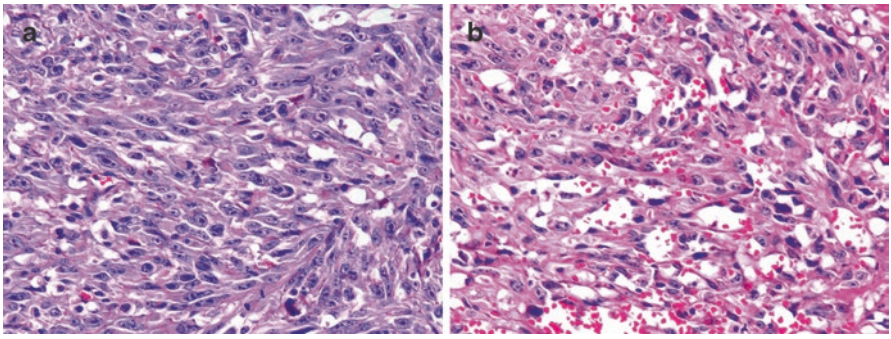

Fig. 13.14 Microscopic appearance (H&E, ×200) of postradiation angiosarcoma of the breast, demonstrating (**a**) a solid undifferentiated component with high mitotic activity and (**b**) a vasoformative component with inter-anastomosing, slit-like channels. The images are from the same primary tumor specimen

primaries or secondary to radiation for breast cancer) harbor mutations in *VEGFR2/KDR* [17]. It is not clear in that setting if the mutation is a driver or passenger mutation, but the overexpressed gene can be inhibited with VEGFR inhibitors such as sunitinib or sorafenib. Using multiple sequencing technologies on 39 angiosarcomas, mutations in *PTPRB* and *PLCG1* were found in 26 % and 9 % of samples [18]. PTPRB will prove hard to target, since it is a phosphatase, and replacing its activity after truncating mutations is tantamount to replacing a tumor suppressor gene. Another sequencing study underscored that mutation of elements of the MAPK pathway are mutated in over half of angiosarcomas, including mutations or amplifications in over half of the angiosarcomas ($n = 18$, 53 %) harbored genetic alterations affecting the MAPK pathway, involving mutations in *KRAS, HRAS, NRAS, BRAF, MAPK1*, and *NF1*, or amplifications in *MAPK1/CRKL, CRAF,* or *BRAF* [19].

Given a tumor that is chemotherapy sensitive but frequently progressing after a relatively short interval, adjuvant chemotherapy can be considered with active agents such as anthracyclines and taxanes [10, 20, 21]. However, it is not clear if adjuvant chemotherapy impacts survival in this disease. Ifosfamide has somewhat less active in angiosarcoma than in other sarcoma subtypes, in our experience.

Angiosarcomas appear to respond as well as other sarcomas to first-line chemotherapy. In a pooled analysis of 108 locally advanced and metastatic angiosarcoma patients separated from 2557 patients with other STS histologies, 25 % of angiosarcoma patients had a measured CR or PR to therapy. The median PFS was 4.9 months and OS 9.9 months [22].

Agents such as bevacizumab, sorafenib, and sunitinib directed against VEGF receptors have some activity against angiosarcomas. We have observed the best responses in women with breast angiosarcomas, while for other sites such as head and neck we have observed (at best) stable disease to blanching of extensive tumor lesions, but few if any overt partial responses (Table 13.2) [23]. However, a study from France demonstrated little activity of sorafenib in angiosarcoma patients [24]. While the RECIST response rate was 15 % in the patients with superficial tumors,

Table 13.2 Systemic therapy recommendations for angiosarcoma

Clinical scenario		Comments
Adjuvant chemotherapy		To consider any or all of anthracycline, taxane, or ifosfamide; may at least delay recurrence; some investigators use paclitaxel and radiation followed by surgery for resectable or marginally resectable primary tumors
Metastatic disease	First line	Anthracycline + olaratumab or taxane if not given; gemcitabine or combination. Paclitaxel is as effective as paclitaxel and bevacizumab, thus combination therapy with the two is not indicated
	Second line	Pazopanib, single agent bevacizumab, or other oral VEGFR-blocking kinase inhibitor; ifosfamide; clinical trials remain very relevant. There are anecdotal data as of 2016 that angiosarcomas can be sensitive to PD1 inhibitors or combinations with other immune checkpoint inhibitors

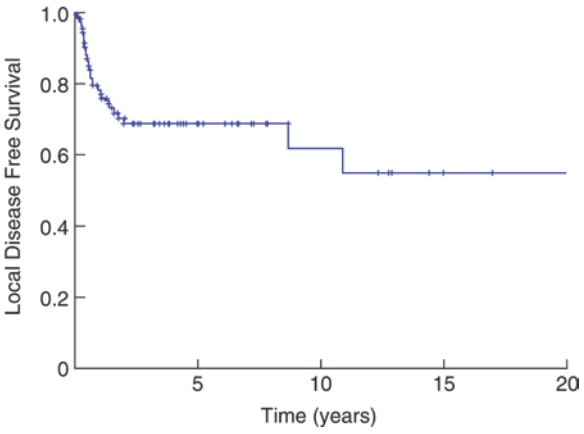

Fig. 13.15 Local disease-free survival for adult patients with primary angiosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 108$

the median PFS was under 2 months in this cohort. Furthermore, there is no synergy between paclitaxel and bevacizumab; patients receiving the combination fared no better than those receiving single agent paclitaxel [25].

The Dabska tumor is a low-grade angiosarcoma often appearing in the skin particularly that of children. It has a characteristic histological appearance with vascular channels and papillary pouching. The lesion is very rare and was originally described by Maria Dabska in 1969 [26].

13.3 Outcome

Local disease-free survival is shown in Fig. 13.15, for those with primary presentation and disease-specific survival in Fig. 13.16, emphasizing the high risk of metastatic disease even in those with only a primary tumor at presentation.

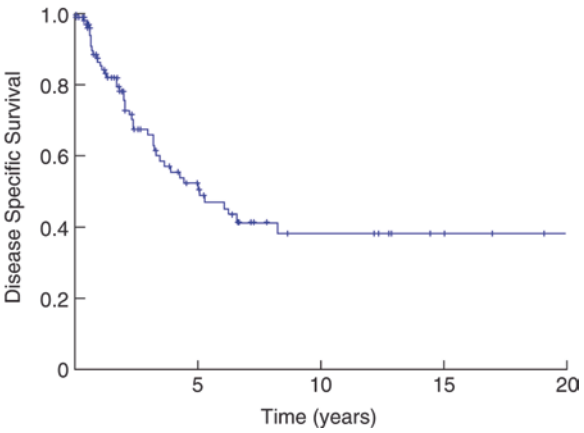

Fig. 13.16 Disease-specific survival for adult patients with primary angiosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 108$

13.4 Kaposi Sarcoma

Kaposi sarcoma (KS) has "historically" been a complicating factor of HIV (human immunodeficiency virus) disease, although Kaposi first described it in 1872 [27, 28]. It is less well appreciated that it also arises endemically in a population with low CD4+ T cell counts in the Mediterranean basin and in Africa, where it is most commonly observed. A version of KS has been recognized more recently in people who are therapeutically immunosuppressed to prevent rejection of organ transplants. In each situation, human herpesvirus-8 (HHV8, also called Kaposi sarcoma herpesvirus, KSHV) is the etiological agent. What was once a devastating disease in the HIV population has been largely suppressed with the use of ART (antiretroviral therapy), such that cases of KS are now relatively uncommon in the HIV population. It is not clear if there are direct effects of HIV-directed therapy against HHV8, or if improvement in CD4+ T cell counts is most responsible for the improvement in such patients. In endemic cases and in HIV-related cases alike, local therapy can be active for skin lesions and systemic therapy can be used for visceral disease or when local therapies fail.

KS affects skin most commonly, but also involves lymph nodes and visceral organs, in particular the gastrointestinal tract. Since KS typically affects multiple sites of skin, surgery is usually not indicated. Local control of individual skin lesions can be achieved by a number of means, be it alitretinoin gel, which was proved effective in controlling the plaque form of the disease [29] compared with a placebo gel alone, and other agents with anti-KS activity include intralesional vinca alkaloids [30], intralesional sodium tetradecyl sulfate (a soap) [30], and other topical agents.

The viral pathogenesis of KSHV/HHV8 is revealing important aspects of angiogenesis. The viral G protein coupled receptor vGPCR/ORF74 is a critical component of the virus in pathogenesis [31]. Proinflammatory pathways such as EphrinA2

Table 13.3 Systemic therapy recommendations for Kaposi sarcoma

Clinical scenario		Comments
Primary therapy	First line	Depends on anatomic distribution; can involve topical or intralesional therapy for skin-only disease; taxanes or PLD is a good option for systemic therapy for disseminated disease. Doxorubicin + olaratumab is technically approved in this situation, but prospective data are lacking
Persistent/metastatic disease	First line	Agent not used earlier; lenalidomide has activity, as may oral etoposide; TOR inhibitors such as sirolimus in patients not on antiretroviral therapy (pharmacodynamic interaction)
	Second line	Clinical trials, including those involving immune checkpoint inhibitors; VEGFR targeted tyrosine kinase inhibitors—caution should be taken regarding interaction with anti-HIV medications (thus coordinated care with HIV physician is a must)

*PLD: pegylated liposomal doxorubicin; VEGFR: vascular endothelial growth factor receptor

serve as a receptor for the virus, usurping a guidance mechanisms used by neurons and blood vessels for propagation by triggering endocytosis of the virus [32]. Interestingly, EphrinB2, another angiogenesis related gene, is upregulated by epigenetic modifier EZH2, suggesting another pathway that is usurped by KSHV for survival [33]. Finally, paradoxically, the mTOR pathway is involved in KSHV signaling and the immunosuppressive TOR inhibitors such as sirolimus could inhibit critical viral functions [34]. As a result, a number of options exist for new therapies for treatment of Kaposi sarcoma that were not considered even a few years ago.

In terms of randomized studies involving actively used agents, pegylated liposomal doxorubicin (PLD, Caelyx®/Doxil®) has been shown superior to combination chemotherapy in at least two randomized studies and is a good standard of care for local disease refractory to other therapy, or for disseminated disease [35, 36], though paclitaxel appeared to have superior progression-free survival in one randomized study [37]. PLD is less toxic than liposomal daunorubicin, which was also shown useful in KS [38]. Taxanes are active against KS [37, 39], as are a variety of agents tested in phase II studies such as interferon-alfa [40], interleukin-12 [41], or etoposide [42]. Since the first publication of disappearance of KS lesions in solid tumor organ transplant patients after switching immunosuppression from cyclosporine to sirolimus [43], other case reports have supported the utility of mTOR inhibitors in Kaposi sarcoma. The use of sirolimus in the HIV+ KS population has been limited by pharmacodynamic interaction between protease inhibitors and sirolimus [44]. (Table 13.3) There are case reports that lenalidomide is active in patients with Kaposi sarcoma, the subject of an ongoing clinical trial [45]. In principle, oral VEGFR kinase inhibitors could inhibit KSHV signaling, but again, pharmacodynamic interactions often interfere with use of these agents for people on commonly used antiretroviral agents, which affect cytochrome P450 3A4 metabolized compounds. Bevacizumab has at least some activity and does not interfere with the cytochrome P450 system [46].

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Chapter 14
Epithelioid Sarcoma

Epithelioid sarcomas tend to occur in young adults (Fig. 14.1) either in distal locations (classic form) or in the perineum/groin area (so-called the proximal type). The classic form typically arises in the feet, lower extremity, digits, or forearms of younger men, and can be sometimes difficult to distinguish from reactive processes, such a granuloma annulare or an ulcer base. In contrast, the proximal-type epithelioid sarcoma exhibits a high degree of cytologic atypia, sometimes displaying rhabdoid morphology microscopically (Fig. 14.2) [1]. The classic form of epithelioid sarcoma is usually a slowly growing lesion, that metastasizes relatively early to lymph nodes, which will be positive in 1/3 to 1/2 of cases (Fig. 14.3) [2, 3]. The proximal type is often associated with a more aggressive clinical behavior, with local, regional, and metastatic disease developing over several years.

In the case of proximal-type epithelioid sarcoma, the differential diagnosis typically includes other high-grade malignancies, such as metastatic carcinoma and melanoma. Epithelioid sarcomas are EMA+ and generally positive for keratins. CA125 may be a serum tumor marker for this malignancy [4].

Nuclear hSNF5/INI1 expression is distinctly lost in these tumors, which may help excluding other diagnostic considerations (Fig. 14.4) [5, 6]. FISH analysis demonstrates the presence of large, homozygous *SMARCB1* deletions in >90 % of both classic and proximal types of epithelioid sarcoma and can be used to distinguish from other tumors that show INI1 loss at protein level [7]. Primary therapy is resection, and given the frequency of nodal disease, sentinel node mapping seems advisable, with more complete node dissection in appropriate cases. Adjuvant radiation is generally not given except in tumors with positive or close margins as may be found proximally, and it is not clear if it is helpful in this histology in preventing recurrence, since local-regional relapse despite radiation and surgery is common.

Chemotherapy is not given in the adjuvant situation for this tumor given its relatively slow evolution and at-best modest response to chemotherapy in the metastatic setting. The slow moving nature of the tumor means that long exposures to chemotherapy (months) may be necessary to achieve evidence of tumor shrinking. We have observed at least minor responses to a variety of drugs used for epithelial

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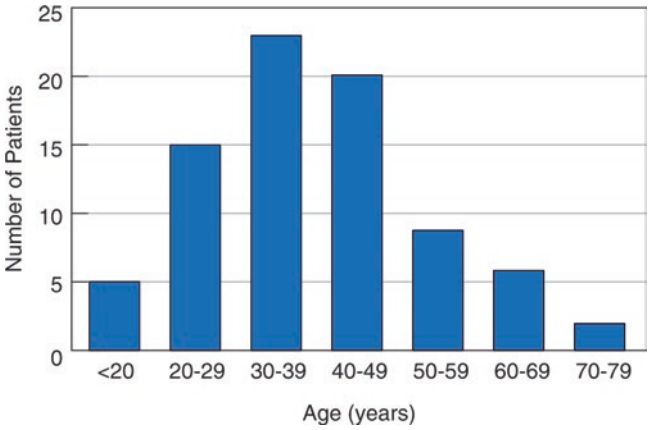

Fig. 14.1 Age distribution of adult patients with epithelioid sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 80$

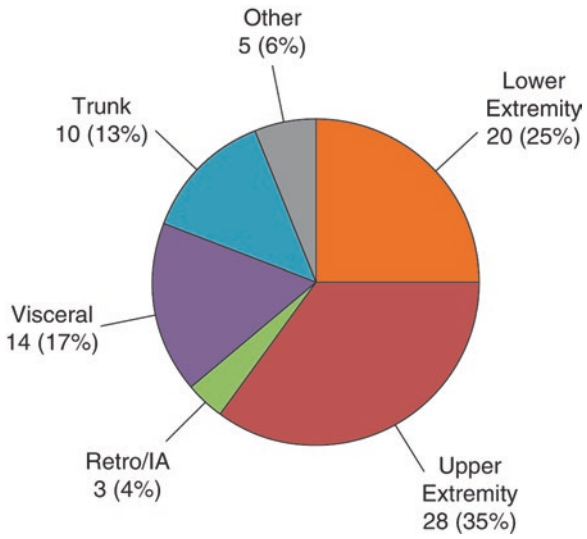

Fig. 14.2 Primary site distribution of adult patients with epithelioid sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 80$

tumors and sarcomas as well, such as doxorubicin, ifosfamide, vinorelbine, cisplatin, and others, but since people may need to be treated for many years for recurrence, parsimony is appropriate in patients with minimal symptoms (Table 14.1). A new concept arising is that of epigenetic therapy, which uses either HDAC inhibition or EZH2 inhibition to take advantage of the INI1 loss [8]. This has not been formally tested to date, however. Immune checkpoint inhibitors have not been formally tested in this diagnosis as of 2016, though there is an anecdote of activity in a case series [9].

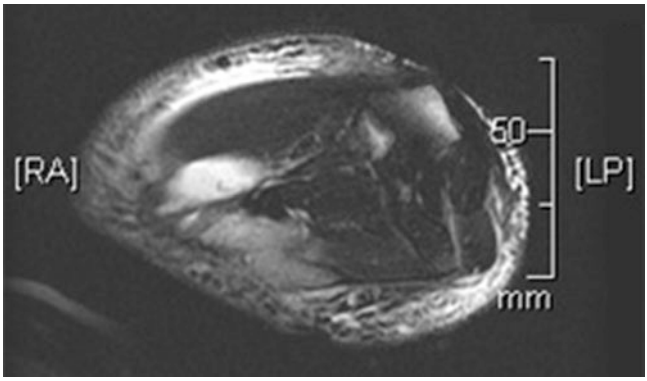

Fig. 14.3 T1-weighted MRI image of metastatic epithelioid sarcoma of the left upper extremity causing edema and multiple cutaneous and soft tissue implants

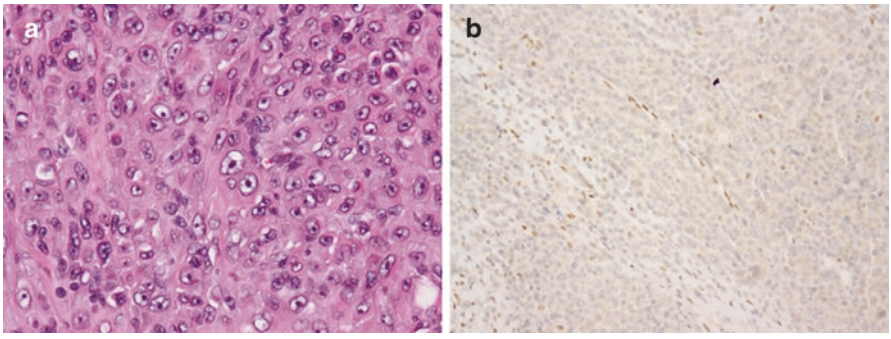

Fig. 14.4 Microscopic appearance of proximal-type epithelioid sarcoma. (**a**) Solid sheets of epithelioid cells are seen, having ill-defined cell borders, eosinophilic cytoplasm, and macronuclei (H&E, ×400). (**b**) BAF47 immunohistochemistry demonstrating complete loss of INI1 staining expression in the tumor cells; an internal positive control is positive staining in blood vessels, not shown

Table 14.1 Systemic therapeutic recommendations for patients with epithelioid sarcoma

Clinical scenario		Comments
Neoadjuvant/ adjuvant chemotherapy		Not generally administered; can be considered for marginally resectable primary disease
Metastatic disease	First line	Doxorubicin + olaratumab; doxorubicin + ifosfamide also a viable 1st line option in a symptomatic patient
	Second line and greater	Platinum-based therapy or combinations; vinorelbine; taxanes; clinical trials; in particular, epigenetic therapy is a rational approach for therapy. Studies are underway as of 2016 with EZH2 inhibitors
		Immune checkpoint inhibitors are formally untested in epithelioid sarcoma as of 2016, though anecdotes of activity have been noted

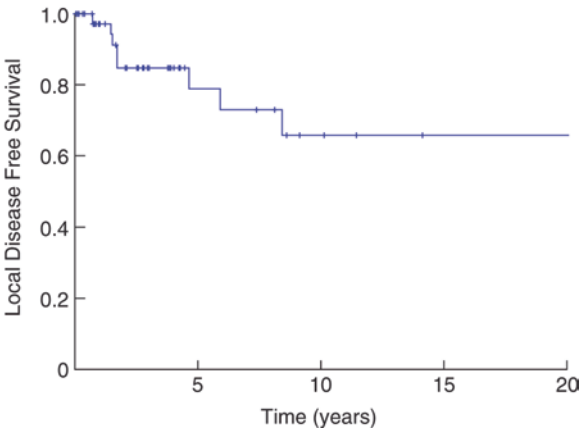

Fig. 14.5 Local disease-free survival for adult patients with primary epithelioid sarcoma (all types). MSKCC 7/1/1982–6/30/2010 $n=48$

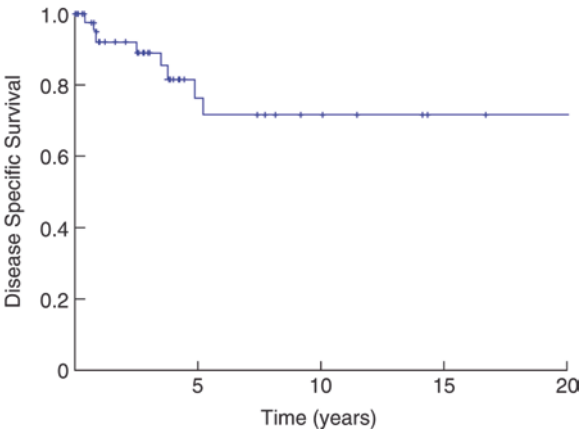

Fig. 14.6 Disease-specific survival for adult patients with primary epithelioid sarcoma (all types). MSKCC 7/1/1982–6/30/2010 $n=48$

14.1 Outcome

Local disease-free survival is shown in Fig. 14.5 and disease-specific survival in Fig. 14.6.

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Chapter 15
Sarcomas More Common in Children

15.1 Soft Tissue Sarcomas More Commonly Observed in Pediatric Patients

Several types of sarcomas are more common in children, the most common of which include osteogenic sarcoma, Ewing sarcoma, rhabdomyosarcoma, and mesenchymal chondrosarcoma. While osteogenic sarcoma presents similarly in children and adults under age 40, there are a variety of differences in the presentation of Ewing sarcoma in adults versus pediatric patients. Ewing sarcoma is predominantly a bone tumor in children, while in adults it occurs much more commonly in soft tissue. As is also noted below, there is a new class of sarcomas that are similar in appearance to Ewing sarcoma, but contain genetic alterations other than the classic t(11;22) translocation (resulting in *EWSR1-FLI1* fusion). Pleomorphic rhabdomyosarcoma is much more common in adults than in children, while alveolar rhabdomyosarcoma are rare in adults. The clinical presentation of mesenchymal chondrosarcoma appears similar in pediatric and adult age groups.

Regardless, pediatric randomized studies showing efficacy of chemotherapy for the sarcomas more common in children provide the standard by which adults receiving therapy for these rare sarcomas are treated. While it is not typically possible to treat adults with chemotherapy at the same intensity as children (using, for example, the weekly administration of vincristine for rhabdomyosarcoma), these regimens provide a good basis by which adults with these diagnoses can be treated. Discussed below are the treatment of two sarcomas more common in children than adults, i.e., the Ewing sarcoma family of tumors (EFT) and rhabdomyosarcoma.

M.F. Brennan et al., *Management of Soft Tissue Sarcoma*,
DOI 10.1007/978-3-319-41906-0_15

15.2 Ewing Sarcoma Family of Tumors

The Ewing sarcoma family of tumors (EFT) includes Ewing sarcoma, primitive neuroectodermal tumor (PNET), and Askin tumor of the chest wall. In 1921, James Ewing described the tumor that now bears his name in a 14-year-old girl, calling it "diffuse endothelioma of bone" [1]. With the advent of karyotyping, it became clear that all EFT members contain the defining chromosomal translocation t(11;22) resulting in *EWSR1-FLI1* or related translocations, and that they should be treated in the same manner. Conversely, not all tumors positive for an *EWSR1-related* translocation should be considered and treated like Ewing sarcoma. For example, clear cell sarcoma and extraskeletal myxoid chondrosarcoma contain *EWSR1* fusions, but involve different gene partners than those involved in Ewing sarcoma, and are essentially impervious to standard chemotherapy agents. Furthermore, *EWSR1* rearrangements have more recently described in benign tumors as well, such as angiomatoid fibrous histiocytoma [2] and myoepithelial tumors [3].

While 80 % or so of EFT in the pediatric population occurs in bone, some 75 % or more of adult EFT occurs in soft tissues, an example of which is shown in Figs. 15.1, 15.2, 15.3, 15.4, 15.5, and 15.6. Surprisingly, extraskeletal Ewing sarcoma (EES) was not described until 1969 [4]. EES most commonly affect trunk and extremity, but unusual sites such as head and neck, or retroperitoneum are also observed. There is no gender predominance of this form of the disease, and as expected from above the median age of presentation is higher than for those patients with bone primaries.

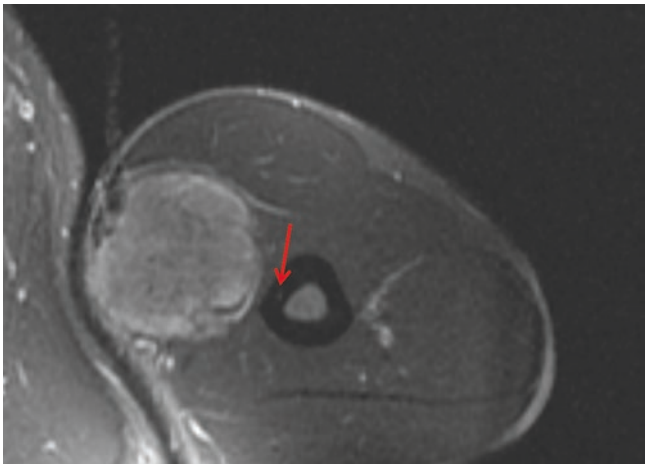


Fig. 15.1 T2 fat-saturated MRI image of a 9 × 4.5 × 4.5 cm bicipital Ewing sarcoma in a 34-year-old woman without other symptoms. *Red arrow*: possible local bony involvement with tumor. The patient had no evidence of viable tumor in the bone after neoadjuvant chemotherapy

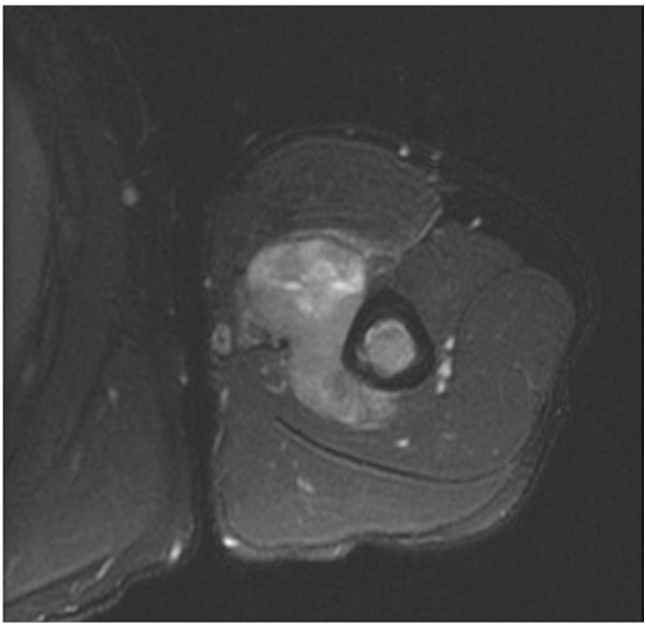


Fig. 15.2 T2 fat-saturated MRI image of a local-regionally soft tissue and bone marrow recurrence Ewing sarcoma of the right upper extremity in a 50-year-old woman despite primary neoadjuvant chemotherapy, surgery, and radiation. The patient is without evidence of disease 6 years after surgery and further chemotherapy

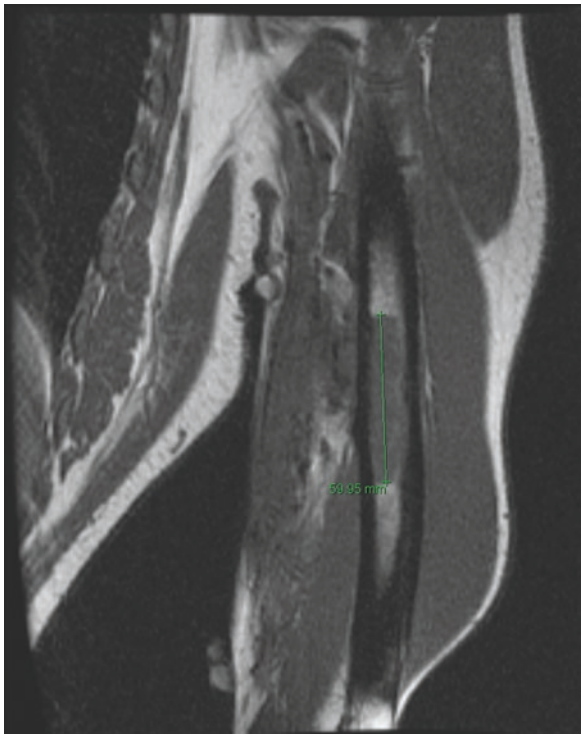


Fig. 15.3 T1 weighted MRI image of the patient of figure 15.2 after neoadjuvant chemotherapy. The soft tissue component has decreased in size, but the bony component has not changed significantly in size

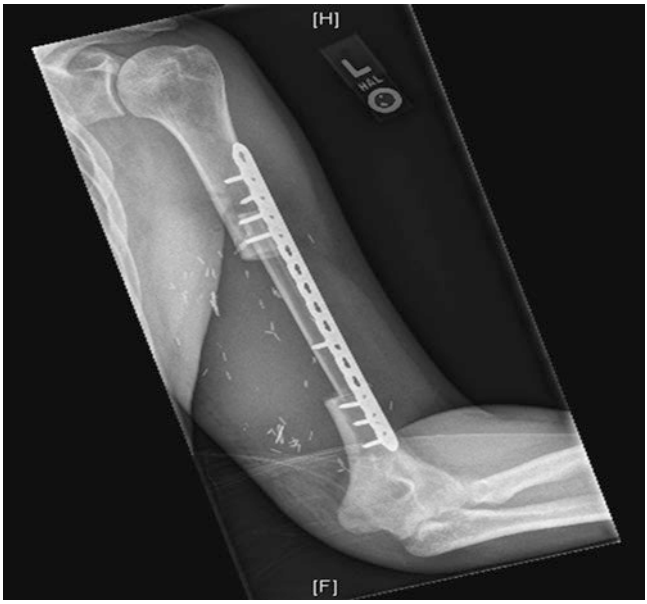
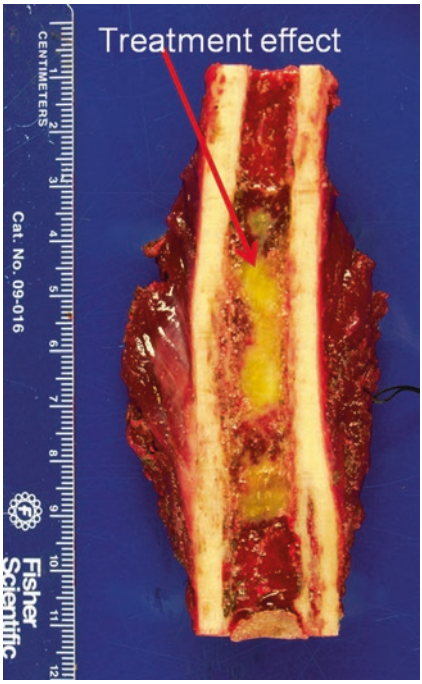


Fig. 15.4 Plain radiograph of the surgical result after limb sparing operation for the locally recurrent disease for the patient of figures 15.2 and 15.3

Fig. 15.5 Gross image of the surgical specimen of the patient in figures 15.2–15.4 after neoadjuvant chemotherapy and surgery



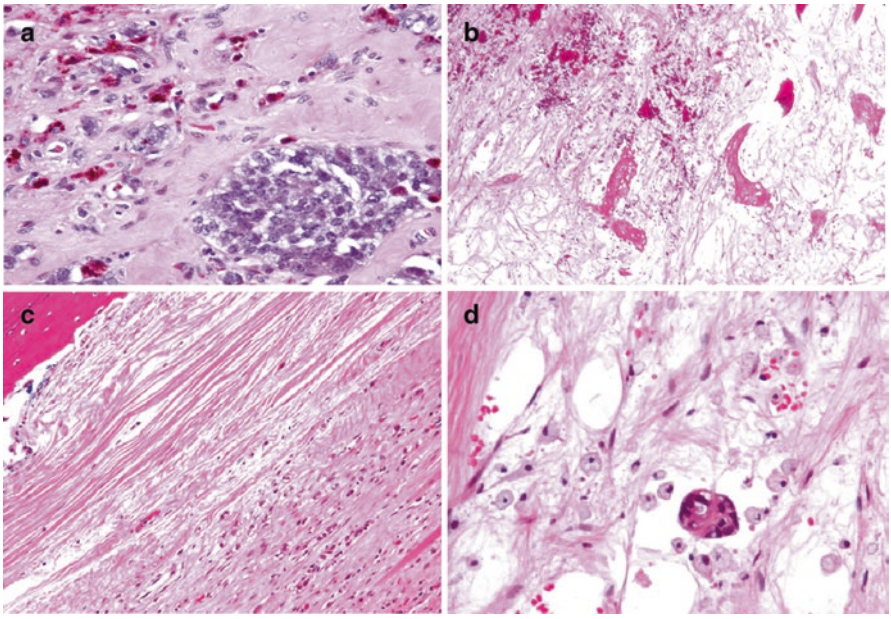


Fig. 15.6 (**a**–**d**) Microscopic images of the surgical specimen of figure 15.5 demonstrating ~80 % treatment effect of tumor (H&E, ×100–400)

Specific genetic events seen in individual patients were suggested to impact patient outcome, e.g., type of *EWSR1-FLI1* fusion [5], though this prognostic benefit could not be confirmed in a large European prospective study [6]. Adults appear to fare poorly compared to pediatric patients [7]. There appears to be a stronger relationship between *TP53* mutation or *INK4A* deletion and poorer prognosis [8]. A subset of *EWSR1*-negative small round blue cell tumors has been identified with novel translocations, e.g., *CIC-DUX4* and *BCOR-CCNB3*, which may account for a portion of the inferior outcomes with chemotherapy in this family of tumors in adults versus children [9–12] (Fig. 15.7). This subtype is discussed in more detail below.

The advent of RNA and genomic sequencing has revealed a relatively low mutational burden in tumors overall, but recurrent mutations in cohesin subunit *STAG2* in approximately 20 % of Ewing sarcoma patient samples, and less frequent homozygous deletion of *CDKN2A* (14 %), and *TP53* mutation (6 %) in one series. In addition, there was an increased frequency of a *BRCA2* K3326X polymorphism (7 %) [13].

These molecular data do not presently impact upon the choice of chemotherapy agents for adjuvant treatment of primary disease. In particular, until we have better data about the Ewing sarcoma variants with translocations that do not have *EWSR1*, it is difficult to recommend other than similar therapy for this similar appearing tumor, as crude as this underestimate of tumor biology may be.

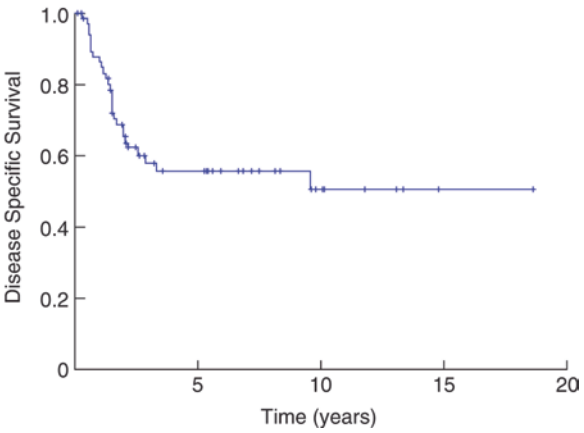


Fig. 15.7 Disease-specific survival for adults with primary soft tissue Ewing sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 70$

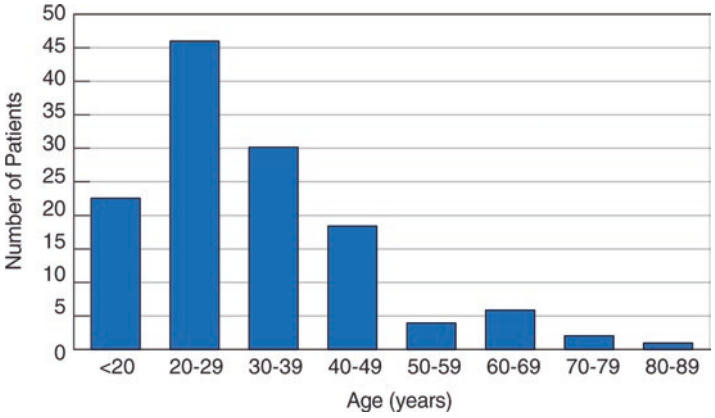


Fig. 15.8 Age distribution of adult patients with Ewing sarcoma of soft tissue. MSKCC 7/1/1982–6/30/2010 $n = 129$

15.3 Demographics

Even as the anatomic primary site changes from bone in children to soft tissue in adults, Ewing sarcoma is most common in younger patients, although we have treated rare patients over age 70 with this diagnosis (Fig. 15.8). The anatomic distribution is wide, with lower extremity the most common in adults (Fig. 15.9). Local disease control is on a par with other soft tissue sarcomas (Fig. 15.10), but survival in adults appears inferior to that of children (Fig. 15.7), although SEER data indicate soft tissue sites for Ewing sarcoma may have a superior prognosis to those arising in bone [14]. Patients with European ancestry have a higher incidence of Ewing sarcomas than patients with Asian or African ancestry, but in US data outcomes are superior for white non-Hispanic patients, implicating access to care as a significant risk factor for outcomes for this type of sarcoma [15].

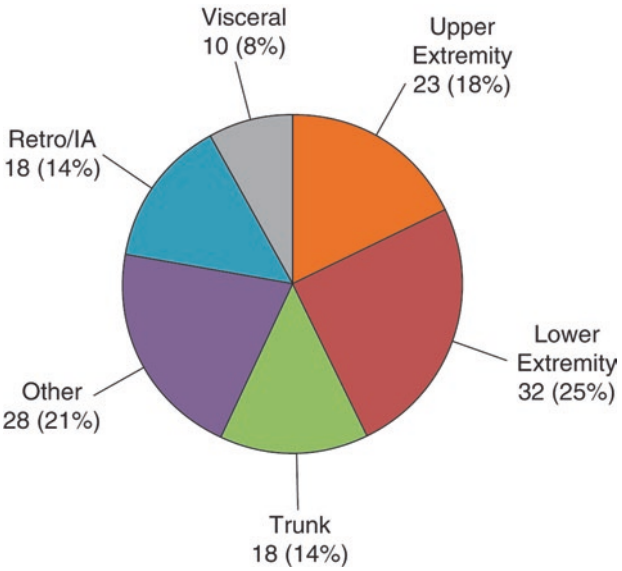


Fig. 15.9 Primary site of adult patients with Ewing sarcoma of soft tissue. MSKCC 7/1/1982–6/30/2010 $n = 129$ Retro/IA = retroperitoneal/intra-abdominal

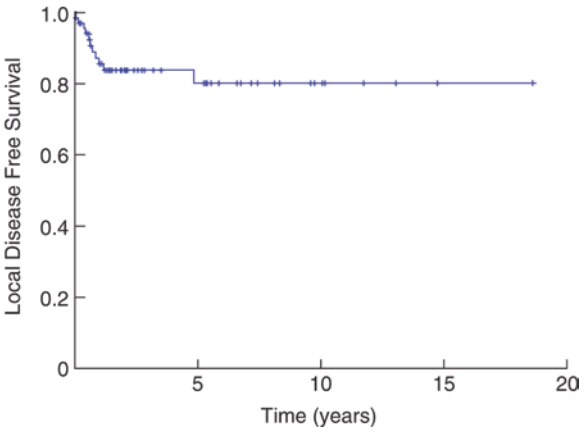


Fig. 15.10 Local disease-free survival for adult patients with primary soft tissue Ewing sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 70$

15.4 Primary Therapy

Presently, the primary management of Ewing sarcoma involves multidisciplinary treatment including chemotherapy, surgery, and often radiation therapy. Historical data demonstrate that survival for patients with primary EFT (Ewing Family of Tumors) treated with local therapy alone is poor, on the range of 15 %. The addition of systemic chemotherapy has increased the cure rate for EFT to ~75 % in children with primary disease, but only ~50 % in adults (Fig. 15.7). The addition of chemotherapy

for the treatment of EFT provides among the most dramatic improvements in overall survival compared to primary treatment alone of any solid tumor.

Surgery remains an integral portion of treatment for pediatric sarcomas such as Ewing sarcoma; however, it is common to use neoadjuvant chemotherapy in pediatric clinical trials before primary surgery, with radiation typically given only after several cycles of chemotherapy have been given. RT can be given safely in the extremities during cycles of ifosfamide–etoposide chemotherapy, or omitting the etoposide for concerns of increased risk of leukemia. The dose of radiation is generally 50.4 Gy for microscopic positive margins and 55.8 Gy for gross disease. In patients who have surgery first, adjuvant chemotherapy can be administered thereafter. In some patients with areas difficult to resect, definitive radiation therapy is the primary treatment of choice. Casey et al. reported on 57 adult patients (≥18 years old) who were treated with radiation either definitively or in the adjuvant setting. The 5-year local control rate was 75%, with 11/57 presenting with metastatic disease [16].

15.5 Adjuvant Chemotherapy

Cyclophosphamide, doxorubicin, and dactinomycin were all found to be active in Ewing sarcoma in single agent studies in the 1960s and 1970s [17, 18]. These studies led to performance of randomized studies that led to present day adjuvant therapy. The randomized Intergroup Ewing's Sarcoma Study IESS-I showed that the inclusion of doxorubicin was associated with improved overall survival [19]; IESS-II showed that higher dose therapy was superior to moderate dose continuous infusion therapy [20].

In Europe, different approaches have been taken for adjuvant chemotherapy that have led to much the same synthesis of agents, albeit using different schedules and doses. The CESS-86 (Cooperative Ewing's Sarcoma Studies) study showed patients with high-risk Ewing sarcoma fared as well as patients with lower risk disease if they received ifosfamide as part of their treatment program [21]. In Italy, the results of the REN-3 study showed that the addition of ifosfamide to standard VACA (vincristine, dactinomycin, cyclophosphamide, doxorubicin) therapy was associated with an improved histological response compared to patients treated on prior studies. Use of ifosfamide (VAIA [vincristine, doxorubicin, ifosfamide, dactinomycin]) was associated with improved disease-free survival compared to VACA therapy for standard risk patients in the European Intergroup Cooperative Ewing's Sarcoma Study EICESS-92, and addition of etoposide gave further benefit for high-risk patients compared to VAIA, although the difference did not reach statistical significance [22]. These studies have supported the utility of ifosfamide and etoposide in the primary therapy of Ewing sarcoma.

For most of the last 20 years, a large randomized clinical trial of the Pediatric Oncology Group/Children's Cancer Group (POG-9354/CCG-7942) defined the standard of care in the United States for primary EFT. In this trial, the standard arm

was vincristine–doxorubicin–cyclophosphamide, and the experimental arm was the same combination alternating with cycles of ifosfamide–etoposide [23]. Although this decreased the dose density of each treatment combination by half, survival was improved for patients with nonmetastatic disease (from 61 to 72 % at 5 years), but not with metastatic disease, presumably since the patients progressing on the standard three drug arm could receive benefit from ifosfamide–etoposide after progression. Of note, 20–25 % of patients with metastatic disease, typically with lung metastases as the only site of metastatic disease, were cured with this multimodality approach.

Two studies varying the intensity of the five-drug Ewing sarcoma regimen are very instructive regarding current approaches for adjuvant treatment of Ewing sarcoma. In the COG study from Granowetter et al. [24], the doses of cycles of therapy were increased to shorten the time of administration of standard CAV (cyclophosphamide, doxorubicin, and vincristine) and ifosfamide/etoposide regimens from 48 weeks to 30 weeks. There was no significant difference in 5-year event-free survival between the two arms (76 % versus 75 %, respectively) [24].

Conversely, the present standard of care is based on a COG study in which shortening the cycle length had an impact on overall survival in patients under 18 years old receiving CAV-IE (ifosfamide, etoposide). Patients who received cycles of therapy every 2 weeks instead of every 3 had improved overall survival (only in patients under 18 years of age) [25]. Median cycle length in the 2-week arm of the study was actually 18 days. This is proof of principle of the idea of dose density, as described by Norton and Simon [26, 27]. Over age 18, the 3-week interval alternating CAV-IE combination remains a standard of care in the United States, since the data showing interval compression did not hold true in the subset of adult patients analyzed, although an attempt to more rapidly cycle chemotherapy in adults (i.e., every 2 weeks) is valid as well, given the overall results of the study. The lack of benefit seen with higher doses per cycle of chemotherapy used in the Granowetter COG study [24] argue against schedules the P6 regimen (involving 4.2 g/m^2 cyclophosphamide per cycle) in the treatment of small round cell sarcomas.

15.6 High-Dose Systemic Therapy for Metastatic Disease

For metastatic EFT, cures remain uncommon, with a cure rate in the 20–25 % range in the study by Grier et al. [23] High-dose therapy with autologous stem cell transplant (ASCT) has been abandoned in most centers in the United States based on poor survival data from retrospective analyses [28].

Conversely, other data support the potential utility of high-dose therapy and ASCT in patients with metastatic Ewing sarcoma. A series of 33 EFT patients with relapsed or progressive disease treated with a variety of conditioning regimens and bone marrow or peripheral blood stem cells showed some promise for the modality, with 5-year EFS (event-free survival) of 38 % [29]. In addition, a series of 97 patients with metastatic disease at diagnosis, 75 % of whom received high-dose

therapy and ASCT, had a 5-year EFS of 37 % [30]. The ISG/SSG III study, closed in December 2006, also points to the potential viability of high-dose chemotherapy with ASCT in EFT. With a median follow-up of 37 months, the 5-year overall and event-free survival were 74 % and 66 %, respectively, and importantly the EFS for poor responders who received HDCT (high-dose chemotherapy) (68 %) and for the good responders (71 %) were similar [31].

The combination of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) is associated with significant responses in high-risk patients [32] and was used as the induction regimen before comparing high-dose therapy with autologous stem cell support versus vincristine, dactinomycin, ifosfamide chemotherapy for patients with high-risk Ewing sarcoma (European Ewing Tumour Working Initiative of National Groups, Euro-E.W.I.N.G 99 study) [22]. Two hundred eighty one patients received six cycles of VIDE, one cycle of vincristine–dactinomycin ifosfamide, local treatment, followed by high-dose busulfan–melphalan supported by stem cell transplantation. Event-free survival (EFS) at 3 years was 27 % and overall survival (OS) at 3 years was 34 %. A total of 169 patients (60 %) received stem cell-based therapy. For children under age 14, the 3 years EFS was 45 % ($n=46$). The authors were able to define risk factors that predicted for poor outcome (tumor volume over 200 mL, more than one bony metastatic site, bone marrow metastases, age over 14, and additional lung metastases), graded with a point system. Patients in group 1 (score 3 or lower) had 3 year EFS of 50 %, those in group 2 (score = 4) had 3 year EFS of 25 %, and those in group 3 (score of 5 or more) and 3 year EFS of 10 %. The study is the first to indicate the patients in whom more aggressive therapy may be warranted, but randomized data are lacking. These data are also used as a justification for bone marrow biopsy in all patients. However, since the bone marrow biopsy does not change therapy, it is difficult to justify in the evaluation of patients off study. It is also not clear that more aggressive therapy is better than standard dose chemotherapy alone as the cure rate in metastatic disease in the CCG-POG Ewing sarcoma study was 22 %. Randomized data will be the best way to address this issue. Another investigational approach is use of allogeneic transplant in appropriate high-risk patients.

15.7 Standard Cytotoxic Chemotherapy After Disease Relapse

While they are not useful in other adult sarcomas, topoisomerase I inhibitors demonstrate significant activity in Ewing sarcoma (as well as rhabdomyosarcoma). For metastatic disease temozolomide–irinotecan has activity, but is associated with a relatively brief duration of benefit and diarrhea from the protracted irinotecan schedule typically employed (5 days of treatment 20 mg/m^2, 2 weeks on, 1 off) [33]. The authors question the use of temozolomide since there are no single agent data to indicate that either dacarbazine or temozolomide are active in Ewing sarcoma,

while conversely there are good data to support the use of irinotecan in EFT and rhabdomyosarcoma [34–36]. Notably, adjustments in the dose or schedule are necessary in adult patients treated with the pediatric regimen of 20 mg/m^2 IV daily × 5, 2 weeks on, 1 off; supportive care is of the essence in children receiving this regimen, and diarrhea in adults on this schedule at these doses can be life-threatening. Cyclophosphamide–topotecan is another active combination with greater myelotoxicity and less gastrointestinal toxicity than temozolomide–irinotecan [37–40]. There are no data comparing these two regimens.

A variety of other agents have been examined in Ewing sarcoma in metastatic disease without significant success, as outlined below.

15.8 Investigational Approaches

The finding of patients with responses to insulin-like growth factor 1 receptor (IGF1R) inhibitors led to a flurry of interest in using such agents in patients with refractory Ewing sarcoma. However, only modest but consistent RECIST response rates of 10–15 % have been observed in a series of phase I–II studies of a variety of monoclonal antibodies, all directed against IGF1R [41–46]. The low response rate is still higher than seen in other malignancies and points out the validity of the target in a subset of Ewing sarcoma patients—we simply do not know which subset. We note that very few responses in other sarcoma patients have been seen with IGF1R inhibitors, save for occasional patients with solitary fibrous tumor and desmoplastic small round cell tumor responding. Perhaps part of the reason for this finding is the genuine dependence of the cell on one signaling pathway. In one study, there was an association with high serum IGF1 level and longer survival [44], but it is not known if this is a feature of the therapy, patient, or the tumor itself. The COG are conducting a study with IGF1R inhibitors for primary Ewing sarcoma, which will hopefully provide some of the next data that will ultimately identify a subset of patients that benefit from blockade of this pathway. With respect to other kinases known to be activated, the receptor tyrosine kinase KIT is often overexpressed in Ewing sarcoma, like small cell lung carcinoma, there appears to be no activity of the KIT inhibitor imatinib in Ewing sarcoma, based on data from one prospective phase II study [47].

It is hoped that new approaches, based on the biology of activation of downstream effectors of the EWSR1-FLI1 translocation product, immunological or other approaches, will yield data that will yield new avenues for clinical trials in the near future. One of the most promising recent avenues is the use of poly(ADP-ribose) polymerase (PARP) inhibitors in the treatment of Ewing sarcoma, found in two very different sets of investigations of Ewing sarcoma cell lines [48, 49]. (Suggestions for therapy—Table 15.1) The failure of a PARP inhibitor in a phase II study indicates the need to consider combinations with cytotoxic agents [50]. Phase I–II trials examining a PARP inhibitor with temozolomide are underway as well.

Table 15.1 Systemic therapy recommendations for patients with Ewing sarcoma

Clinical scenario		Comments
Neoadjuvant/ adjuvant chemotherapy		Enrollment of clinical trials: pediatrics studies are often open to adult patients. Off trial, chemotherapy includes agents with a doxorubicin backbone, e.g., VAdrC—Ifosfamide–Etoposide (VACIE) alternating cycles, or VIDE. For VACIE in patients under age 18, every 2 week therapy, when feasible, is superior to every 3 week therapy. In adults, every 3 week therapy remains a standard of care on the basis of one randomized study but an attempt to compress cycle length appears prudent
Metastatic disease	First line	Irinotecan, irinotecan–temozolomide, or cyclophosphamide–topotecan
	Second line	Pazopanib, trabectedin in countries where available, other clinical trials, e.g., IGF1R inhibitors, PARP inhibitors, epigenetic agents. PD1 inhibitors appear to be inactive in Ewing sarcoma; there are no data on olaratumab combinations as of 2016

VActC vincristine + dactinomycin + cyclophosphamide, *VAdrC* vincristine + doxorubicin + cyclophosphamide, *VIDE* vincristine + ifosfamide + doxorubicin + etoposide, *PARP* poly(ADP-ribose) polymerase

New sequencing data coupled with mechanistic analysis have shown that histone demethyases may be a target for Ewing sarcoma [51], one such LSD1 inhibitor has been examined in vitro to underscore the potential relevance of this target, but remains untested in people [52]. Mithromycin, a drug used in decades past for hypercalcemia, was found in a drug retargeting screen to be an agent worth testing in a clinical trial, and such a study is presently underway [53].

15.9 Ewing Sarcoma-Like Small Blue Round Cell Tumors

The finding of small blue round cell tumors that do not contain translocations seen in Ewing sarcoma, synovial sarcoma, round cell liposarcoma, or alveolar rhabdomyosarcoma has caused consternation regarding their management. Are such tumors to be treated like Ewing sarcoma or as another sarcoma, perhaps undifferentiated pleomorphic sarcoma?

Classification of translocation-negative small blue round cell tumors is now made somewhat easier with the finding of a consistent morphology and novel gene fusions found in a significant percentage of these sarcomas [9–11, 54–61]. Initial reports described individual cases of such tumors [9, 10, 54, 56–60], and subsequently two larger series identified groups of patients with consistent *CIC-DUX4* translocations [11, 55]. The assessment of these translocations has been made both difficult and intriguing with the finding of *DUX4* in more than one chromosome, as the result of duplication events over evolution at the ends of chromosome 4 and 10, yielding either t(4;19) (q35; q13) or t(10;19)(q26.3; q13). Notably, defective splicing in *DUX4* is found in fascioscapular muscular dystrophy [62], highlighting as

with other sarcoma oncogenes the need for the proper cellular context for transformation rather than apoptosis in a given cell type.

Microscopically, *CIC-DUX4*-positive sarcomas demonstrate small to medium-sized round to oval cells, packed in solid sheets with minimal or absent intervening collagen [11]. Distinct areas of spindle shaped cells are seen only infrequently. Most tumor cells had an ill-defined cell border, with scant amount of amphophilic or lightly eosinophilic cytoplasm, and contained vesicular nuclei, with distinct, often enlarged nucleoli. Although the presence of larger, pleomorphic cells was not seen, there was a higher degree of heterogeneity in nuclear shape and size compared with the rather consistent appearance seen in Ewing sarcoma. Geographic areas of necrosis are commonly seen, as is individual cell necrosis with "starry sky" appearance. A high mitotic rate of >10 mitotic figures per 10 HPFs was observed in all cases. There does not appear to be a difference in morphology between the tumors that do and do not have *CIC* rearrangements. Approximately two-thirds of *EWSR1* rearrangement-negative small round blue cell tumors in one series appear to contain a *CIC-DUX4* rearrangement [11].

The clinical features of this new sarcoma entity are still somewhat unclear given the small number of cases characterized to date. The series of 15 patients from Italiano et al. [11] combined with 9 other cases reported from other investigators indicate a male predominance (male:female gender ratio 1.4), median age at diagnosis of 24 years (range 6–62), frequent primary tumor location in the limb (50 %), and high rate of metastatic relapse (11 cases out of 22 with available follow-up, 50 %). Therefore, besides similar histological patterns, these tumors share with the Ewing family of tumors an aggressive clinical course.

Shortly thereafter, the publication of the cases containing *CIC-DUX4* translocations, a novel intrachromosomal X-chromosome fusion *BCOR-CCNB3* was described in Ewing-like sarcomas of bone in a screen of 594 sarcomas lacking *EWSR1* or other known sarcoma fusion products [61]. Notably, these tumors could also be identified uniquely with simple CCNB3 immunohistochemistry. BCOR is a gene encoding a ubiquitously expressed transcriptional co-repressor that binds BCL6 and proteins involved in chromatin dynamics, while CCNB3 encodes an otherwise testis-specific meiotic cyclin. Perhaps related to both of these novel sarcoma genomic subtypes are other already and waiting to be found, e.g., *FUS-NFATc2* and *CIC-FOXO4*, found by tumor RNA sequencing and whole exon and whole genome sequencing [13].

These new Ewing-like sarcoma subtypes will inform us on new approaches to manage these tumors, as there may be continued commonalities between these tumors and hematological and other malignancies. There is little doubt that the use of newer generations of sequencing techniques will rapidly give us new data to both characterize and treat these tumors over the next few years.

In terms of clinical outcomes for these patients, there are few data to provide guidance as of 2015. Preliminary data regarding neoadjuvant therapy and response in metastatic disease indicate the *CIC-DUX4* Ewing sarcoma subtype is less sensitive than Ewing sarcoma to standard chemotherapy agents (doxorubicin–ifosfamide, or combination of five drug therapy with vincristine–doxorubicin–cyclophosphamide

Table 15.2 Histological classification of rhabdomyosarcoma

Superior prognosis
Botryoid rhabdomyosarcoma
Spindle cell rhabdomyosarcoma
Intermediate prognosis
Embryonal rhabdomyosarcoma
Poor prognosis
Alveolar rhabdomyosarcoma
Undifferentiated sarcoma
Subtypes whose prognosis is not presently evaluable
Rhabdomyosarcoma with rhabdoid features

with ifosfamide–etoposide) [11], while data are yet to be published on the clinical behavior of *BCOR-CCNB3* Ewing-like sarcomas. Thus, it is presently not clear from these data if this new tumor category should be considered enough like a Ewing sarcoma to mandate systemic chemotherapy, but that is the conservative approach being taken presently.

15.10 Rhabdomyosarcoma

Rhabdomyosarcomas (RMS) are a family of rare tumors with evidence of skeletal muscle differentiation, of which there are perhaps 300–50 cases a year in the United States (incidence ~1 per million). It qualifies as the most common soft tissue sarcoma in the pediatric population and has led pediatric oncologists to coin the term non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) for diagnoses other than rhabdomyosarcoma though this makes little sense to the oncologist caring for adult patients who treats patients with a panoply of soft tissue tumors.

Rhabdomyosarcoma, *sui generis* even among sarcomas, is made complex due to several factors. Multiple classification systems have been developed, but the most recent recognizes subtypes based on prognosis (Table 15.2), including a slight modification of the classically recognized subtypes of alveolar, embryonal, botryoid, and pleomorphic RMS.

15.11 Demographics

As with Ewing sarcoma, rhabdomyosarcoma remains a primary sarcoma of patients under age 21 (Fig. 15.11), with most patients presenting in their first 5 years of life having embryonal rhabdomyosarcoma and a second peak around age 15 of alveolar rhabdomyosarcoma [63]. In adults, the pleomorphic variety is most common with a

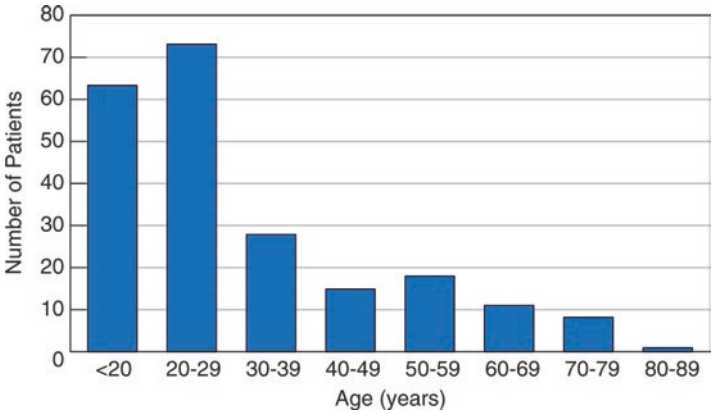


Fig. 15.11 Age distribution of adult patients (>16 years) with rhabdomyosarcoma (all types). MSKCC 7/1/1982–6/30/2010 $n = 217$

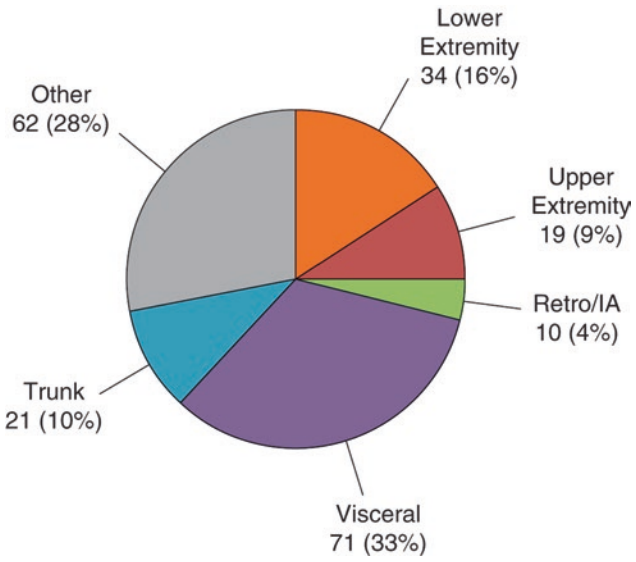


Fig. 15.12 Primary site of adult patients (>16 years) with rhabdomyosarcoma (all types). MSKCC 7/1/1982–6/30/2010 $n = 217$ Retro/IA retroperitoneal/intra-abdominal

peak incidence in the sixth decade. It is notable that RMS is one class of sarcomas (as well as well-differentiated/dedifferentiated liposarcoma and gastrointestinal stromal tumor, for example) in which primary site is an important factor in clinical outcome. There is a wide anatomic distribution (Fig. 15.12). The anatomic site of presentation (not accounting for age) is most commonly head and neck (the orbit and other parameningeal sites are classic primary sites of disease), or trunk (with

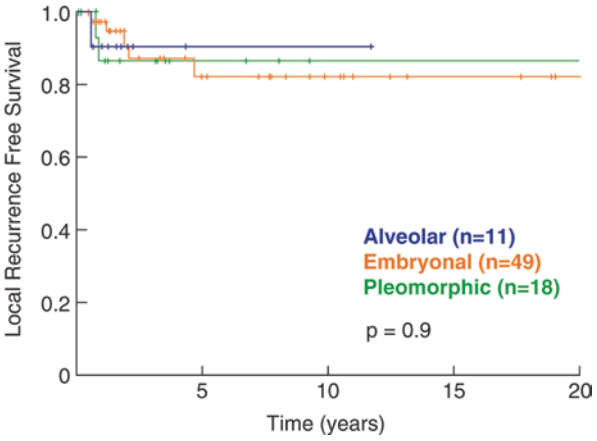


Fig. 15.13 Local disease-free survival for adult patients with primary rhabdomyosarcoma, distinguished by histology. MSKCC 7/1/1982–6/30/2010 $n=78$

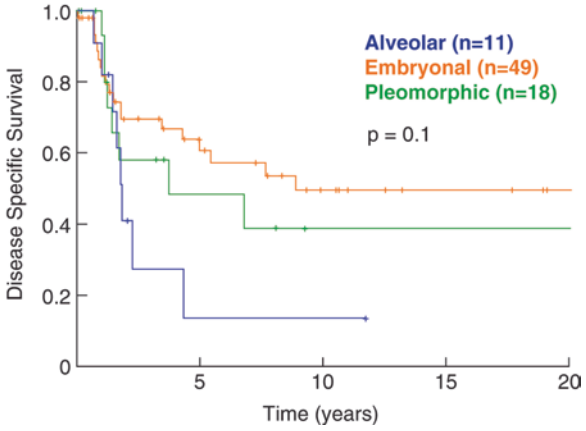


Fig. 15.14 Disease-specific survival for adult patients with primary rhabdomyosarcoma, distinguished by histology. MSKCC 7/1/1982–6/30/2010 $n=78$

paratesticular disease being common), more than extremities or other sites [64]. The histologic subtype also varies by primary site [65], with alveolar RMS most common in the extremities, and embryonal RMS most common in the head and neck, genitourinary, and retroperitoneal sites [65].

Males are more frequently affected than females (approximately 4:3 ratio), and Caucasians appear to be affected somewhat more commonly than people of other ethnicities. As with Ewing sarcoma and other primary soft tissue sarcomas, there is usually very good local control independent of histology (Fig. 15.13), but patients frequently die of metastatic disease. Even patients with embryonal rhabdomyosarcoma, a "favorable" histology, have only a 50% 10-year disease-specific survival rate (Fig. 15.14).

15.12 Molecular Biology

The molecular biology of each form of RMS is distinct, in keeping with their different biological behavior and risk of recurrence (Figs. 15.15 and 15.16).

Alveolar RMS has a characteristic translocation t(2;13), with a minority of cases involving a variant translocation t(1;13) [66–68]. The translocation fuses the *PAX3* gene on chromosome 2 (which regulates a transcriptional program for neuromuscular development) with the *FOXOA1* (a member of the forkhead family of transcription factors). The fusion transcription factor appears to activate both transforming and differentiation gene programs. The variant t(1;13) fuses the *PAX7* gene on chromosome 1 with *FOXOA1*. Fusion-positive alveolar RMS occurs more often in the extremity and in somewhat younger patients compared to translocation-negative tumors.

Embryonal RMS frequently have loss of heterozygosity (LOH) at chromosome 11p15.5; [69, 70] the target of this inactivation is still not well defined, but may involved *GOK* [71–73], a gene that can control growth of RMS cell lines. Trisomy 8 is also common in embryonal RMS.

Pleomorphic RMS most typically has an aneuploid karyotype, most similar to other forms of high-grade undifferentiated pleomorphic sarcoma, formerly termed malignant fibrous histiocytoma.

Rarer subsets of rhabdomyosarcoma have yielded interesting results and new genomic entities that may explain the favorable outcomes in children with these diagnoses. Specifically, Sclerosing rhabdomyosarcoma (ScRMS) and spindle cell rhabdomyosarcoma (SRMS) have been recently reclassified as a unique pathologic entity to be differentiated from embryonal RMS. A subset of ScRMS/SRMS contain

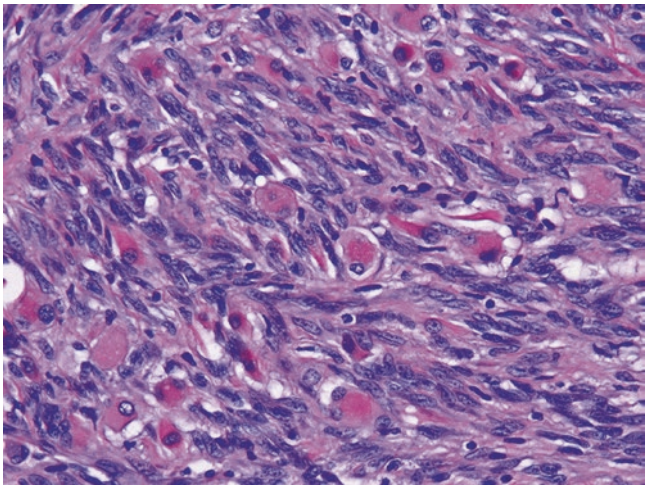


Fig. 15.15 Microscopic appearance of embryonal rhabdomyosarcoma, demonstrating large rhabdomyoblasts with abundant cytoplasm filled with eosinophilic whorls of myosin fibrils (H&E, ×200)

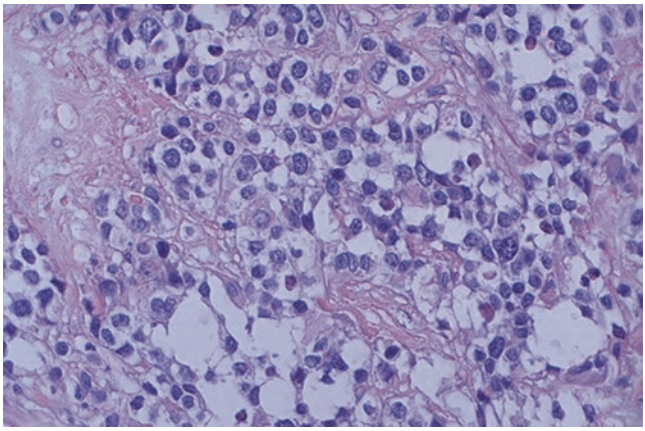


Fig. 15.16 Microscopic appearance of alveolar rhabdomyosarcoma, demonstrating nests of cells typical for the histology (H&E, ×200)

NCOA2 gene rearrangements, while such sarcomas occurring in older children or adults contain *MYOD1* mutations with or without *PIK3CA* mutations. In a 2016 study, 10 of the 11 congenital/infantile SRMS that were studied contained recurrent fusion genes: *VGLL2* rearrangements seen in 7, (*VGLL2-CITED2* fusion in 4, *VGLL2-NCOA2* in 2 cases). Three cases contained *NCOA2* gene fusions as shown previously, including *TEAD1-NCOA2* in 2 and *SRF-NCOA2* in 1. As an important clinical correlation, all fusion-positive congenital/infantile SRMS patients with available long-term follow-up were alive and well, none developing distant metastases. For 15 SRMS patients older than 1 year of age, 10 tumors contained *MYOD1* L122R mutations, with most of them dying of disease despite aggressive multimodality treatment. These data underscore the importance of defining the molecular subtype of rhabdomyosarcomas in defining an optimal treatment plan [74].

It is clear from genomic studies of the pediatric versions of rhabdomyosarcoma that there are few recurrent mutations observed that might impact on the choice of treatment of these tumors. The mutation rate was higher in embryonal than alveolar [75]. Members of the *RAS* gene family are most commonly altered. As was recognized regarding IGF1R signaling in rhabdomyosarcoma, there is activation of the receptor tyrosine kinase—ras—PIK3CA axis in many tumors, suggesting this will still be the best signaling pathway to attack this family of tumors. These data do not at present have an impact on therapeutic choices in these diagnoses, and we continue with clinical–pathological staging to define risk and treatment plans.

Table 15.3 Intergroup Rhabdomyosarcoma Study Group IRS-V tumor classification

Group I	Localized disease, completely resected; regional nodes not involved—lymph node biopsy or sampling is highly advised/required, except for head and neck lesions
	(a) Confined to muscle or organ of origin
	(b) Contiguous involvement—infiltration outside the muscle or organ of origin, as through fascial planes
Group II	Total gross resection with evidence of regional spread
	(a) Grossly resected tumor with microscopic residual disease
	(b) Regional disease with involved nodes, completely resected with microscopic residual
	(c) Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node (from the primary site) in the dissection
Group III	Incomplete resection with gross residual disease
	(a) After biopsy only
	(b) After gross or major resection of the primary (>50 %)
Group IV	Distant metastatic disease present at onset (lung, liver, bones, bone marrow, brain, and distant muscle and "nodes")

15.13 Risk Stratification

An expanded classification system is used for the present randomized study of patients with RMS, based on risk categories of tumors, denoted in Table 15.3. This staging system includes anatomy, histology, and differentiates patients fairly well in terms of outcome, given that stage III patients (Table 15.4 and 15.5) have a ~50 % survival rate, and there are presently no standardized criteria as to how to better risk stratify such patients. With the new classification system, low-risk patients have an estimated 3-year failure-free survival (FFS) rate of 88 %; for intermediate-risk patients 3-year FFS is ~65 %, and for high-risk patients it is under 30 %.

15.14 Staging

In addition to routine staging with physical exam, routine laboratory data, and the like, a few other tests that are useful in the patient workup include assessment lactate dehydrogenase, which can be an indicator of tumor bulk, magnetic resonance imaging (MRI), or computed tomography (CT) of the primary site, and CT of the chest to rule out metastatic disease. For tumors of the head and neck, CT or MRI of the head/brain is indicated. A bone scan will help to rule out bony metastatic disease, and cerebrospinal fluid (CSF) cytology assessment for tumor cells is appropriate for patients with parameningeal tumors. Oncologists treating adult patients at our institutions do not routinely obtain bone marrow biopsies or aspirates given the very low yield of such tests and lack of impact on therapeutic decision-making although it is still performed as part of many clinical trials of therapy for RMS.

Table 15.4 Pretreatment staging of rhabdomyosarcoma

Stage	Sites	T	Size	N	M
1	Orbit, head and neck, (excluding parameningeal), GU—non-bladder/non-prostate, biliary tract/liver	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, etc.) except biliary tract/liver	T1 or T2	a	N0 or Nx	M0
3	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, etc.) except biliary tract/liver	T1 or T2	a	N1	M0
			b	N0 or N1 or Nx	M0
4	All	T1 or T2	a or b	N0 or N1	M1

Tumor
T (site)1 confined to anatomic site of origin
a. ≤5 cm in diameter in size
b. >5 cm in diameter in size
T (site)2 extension and/or fixative to surrounding tissue
a. ≤5 cm in diameter in size
b. >5 cm in diameter in size
Regional nodes
N0 regional nodes not clinically involved
N1 regional nodes *clinically* involved by neoplasm
Nx clinical status of regional nodes unknown (especially sites that preclude lymph node valuation)
Metastasis
M0 no distant metastasis
M1 metastasis present

Table 15.5 Simplified rhabdomyosarcoma risk categories, based on Intergroup Rhabdomyosarcoma and Children's Oncology Group studies

Risk category	Histology	Clinical group	Stage
Low	Embryonal and variants	I–III	1
	Embryonal and variants	I–II	2–3
Intermediate	Embryonal and variants	III	2–3
	Alveolar	I–III	1–3
High	Any	IV	4

15.15 Imaging

Rhabdomyosarcomas are radiologically indistinguishable from other soft tissue sarcoma (Fig. 15.17). They also behave similar to other soft tissue sarcomas other than their sometimes explosive growth, as well as risk of lymph node metastatic disease that occurs more commonly than with other sarcomas.

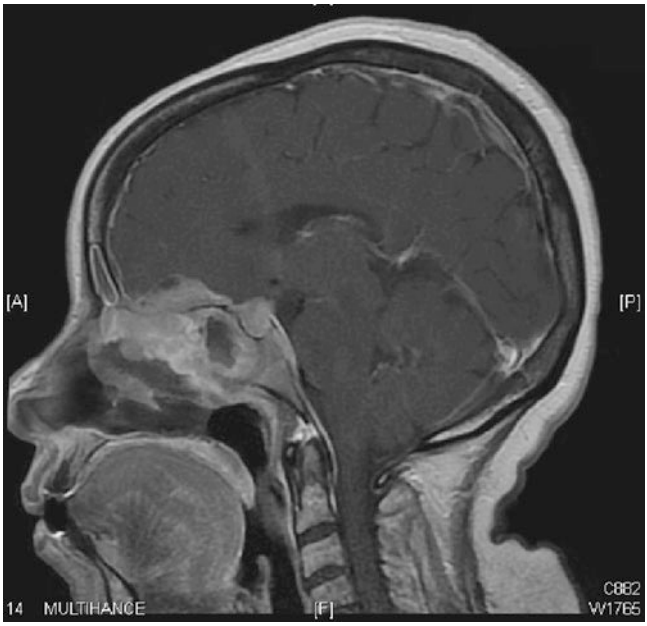


Fig. 15.17 Contrast enhanced T1 weighted sagittal MRI image of a primary sinus alveolar rhabdomyosarcoma in a child

15.16 Primary Therapy

In the era before chemotherapy, the mortality rate from RMS was high, except in patients with favorable subtypes in favorable locations in which the tumor could be controlled with surgery and radiation. The mortality rate in older series varies from 30 to over 90 %, depending on the stage, anatomic site, and treatment [76]. Chemotherapy, which was recognized as active in RMS in the early 1960s [77], quickly became a standard of care, as did radiation therapy to the primary site [76]. Details of adjuvant chemotherapy and treatment of metastatic disease are indicated below.

Multidisciplinary care is the present standard for patients with RMS, as it is for patients with Ewing sarcoma. While surgery, radiation, chemotherapy are all employed for patients with RMS, the effects on growth and long-term effects of radiation make one more circumspect about the use of radiation for younger pediatric patients with RMS. The intensity of the therapy and need for multidisciplinary expertise make this one diagnosis where referral to expert centers is appropriate for most patients [78].

Adults with RMS benefit from a high proportion of pediatric patients being enrolled on clinical trials which have advanced the standard of care over the last 35 years doubling the cure rate over that time [79–83]. The full details of these studies are beyond the scope of this text, but several important findings of these studies helps to direct care for patients with all patients with RMS.

In Intergroup Rhabdomyosarcoma Study IRS-I, three randomized studies were performed within one larger study, based on clinical risk categories (clinical groups 1, 2, or 3–4) [81]. Patients with low-stage disease (clinical group 1, those with local disease and complete resections) did not benefit from radiation added to vincristine, dactinomycin, and cyclophosphamide (VActC). Those with regional disease but gross complete resection (clinical group 2) who received radiation did not benefit from the addition of cyclophosphamide to vincristine and dactinomycin. Those with more extensive disease (clinical groups 3 [gross residual disease after surgery] and 4 [metastatic disease]) did not benefit from the addition of doxorubicin to aggressive VActC plus irradiation. Distant metastatic recurrence was more common than local recurrence, and overall survival was 55 % for all patients involved. Tumors of the orbit and gastrointestinal tract had the best prognosis.

IRS-II also attempted to answer several questions regarding optimal care for patients in different clinical groups, enrolling 999 patients [82, 84]. VActC and VAct gave similar results for patients in clinical group 1. Patients in Group 2, excluding extremity alveolar RMS, received radiation and were randomized to VAct or repetitive-pulse VActC, and DFS and survival were similar. Thus, it became feasible to use less intense therapy for patients with group 1–2 disease. Patients in group 3 and 4 received radiation and were randomized to repetitive-pulse VActC or repetitive-pulse VAdrC alternating with CAV (vincristine, doxorubicin, cyclophosphamide). Complete remission (CR) rates were similar, as were survival rates, indicating that doxorubicin did not add to dactinomycin in the cure rate for such patients. Central nervous system prophylaxis with radiation for group 3 patients with cranial parameningeal sarcoma increased the survival rate to 67 % from 45 % in IRS-I.

Over 1000 patients were enrolled in IRS-III, in which patients were stratified by risk factors in addition to clinical groupings [79]. Like IRS-II, VAct was found as useful as VActC for patients with favorable group 1 patients. The addition of doxorubicin did not significantly alter the outcome for patients with favorable group 2 patients over those who received VAct alone. The addition of cisplatin–etoposide did not improve outcomes over VActC alone for patients with group 3–4 tumors.

IRS-IV examined multiple subgroups in detail and developed a new risk-based staging system integrating the stage and clinical groupings of IRS I–III [80]. Younger patients with group 1 paratesticular embryonal primary tumors, and patients with group 1 or 2 orbit or eyelid tumors had a >90 % cure rate with vincristine and dactinomycin, with the addition of radiation for patients with group 2 disease. For group 3 patients, patients could be randomized to hyperfractionated radiotherapy compared to conventional radiotherapy, but no benefit was noted. Most notably, VActC, VAct + Ifosfamide, or vincristine–ifosfamide–etoposide with surgery (with or without RT) were equally effective for patients with local or regional rhabdomyosarcoma, indicating the standard of care remained VActC, since it was less myelotoxic than other regimens.

A follow-up study to IRS-IV is a study of VActC versus alternating VActC/vincristine–topotecan–cyclophosphamide for intermediate risk rhabdomyosarcomas (group 3) [83]. This study showed no advantage to the more complex regimen in comparison to VActC, which for this intermediate risk group of tumors remains the standard of care.

Attempts have been made to decrease chemotherapy intensity in the lowest risk patients. In Children's Oncology Group study D9602, radiotherapy doses were reduced and cyclophosphamide was eliminated for the lowest risk patients, with survival rates similar for the lower radiation therapy dose patients but the suggestion of slightly inferior outcome for the patients not receiving cyclophosphamide. The follow-up study for patients with low-risk ERMS (ARST0331) uses data from IRS-IV and D9602. The ideas for the new study being tested include decreasing the duration of vincristine–dactinomycin chemotherapy to 22 weeks for subset 1 patients (stages 1 and 2 groups I/II, stage 1 group III orbit) and adding a total cumulative dose of 4.8 g/m^2 of cyclophosphamide. For patients with orbital and group IIA tumors, decreased RT doses will be used, and they will receive vincristine–dactinomycin and 4.8 g/m^2 of cyclophosphamide. Finally, cyclophosphamide cumulative dose will be reduced to 4.8 g/m^2 for subset 2 patients, i.e., those with stage 1 group III nonorbital primaries, and stage 3 groups I/II primaries [85].

While the trend in IRS trials has been to lessen the intensity of chemotherapy and reducing the dose of radiation, it is important to note that these trials have demonstrated the importance of radiation therapy in the multimodality management of these patients. The dose of radiation varies depending on the extent of disease; gross disease 45–50 Gy, nodal disease 41 Gy, and margin positive 36 Gy. The timing of radiation in relationship to chemotherapy depends on risk stratification. For low/intermediate risk, radiation therapy generally start around week 12 of chemotherapy, whereas, for high risk especially parameningeal sites, radiation therapy should start early in the course. Gerber et al. reported on 148 adult (≥16 years old) patients with RMS. Radiation to the primary site was given in 65 % of patients. In the subgroup of patients with nonmetastatic disease at time of presentation, the 5-year local control was 66 % and 5-year overall survival was 45 % [86]. The dose of radiation for adult patients with pleomorphic rhabdomyosarcomas should follow the same guidelines as other soft tissue sarcoma histologies.

15.17 Chemotherapy for Metastatic Disease

For metastatic RMS, a variety of agents show at least modest activity, depending on the subtype. For alveolar and embryonal RMS, as with Ewing sarcoma, single agent topoisomerase inhibitors using topotecan [38, 87–90], irinotecan [34–36, 91, 92], or combinations involving them [38, 92] have activity. Best studied of these agents or combinations include irinotecan, irinotecan–temozolomide, and cyclophosphamide–topotecan.

In a few patients treated in a randomized study as well as anecdotally, gemcitabine and combinations (e.g., with docetaxel) have significant activity for patients with pleomorphic rhabdomyosarcoma [93]. The activity of gemcitabine and combinations in other forms of rhabdomyosarcoma is unknown though apparently single agent activity of gemcitabine against RMS in general is relatively low [94].

Table 15.6 Systemic therapy recommendations for patients with rhabdomyosarcoma

Clinical scenario		Comments
Primary treatment		Clinical trial enrollment is preferred since pediatric studies often now accrue adult patients. In an off-study setting, primary treatment usually involves surgery and often radiation as well. Adults have a very high risk of relapse and we recommend polychemotherapy (VDactinoC, VAdrC—Ifosfamide–Etoposide regimen as for Ewing sarcoma or VIDE are all reasonable treatment options in the absence of adult-specific data)
Metastatic disease	First line	Irinotecan, irinotecan–temozolomide or cyclophosphamide–topotecan
	Second line	Gemcitabine combinations (in particular for pleomorphic rhabdomyosarcoma); clinical trials, in particular for combinations of IGF1R targeted agents in alveolar rhabdomyosarcoma, epigenetic agents in embryonal rhabdomyosarcoma. Immune checkpoint inhibitors are not tested as of 2016

VActC vincristine + dactinomycin + cyclophosphamide, *VAdrC* vincristine + doxorubicin + cyclophosphamide, *VIDE* vincristine + ifosfamide + doxorubicin + etoposide

IGF1 receptor (IGF1R) inhibitors, mostly monoclonal antibodies, block IGF1R signaling thought to be critical in permitting the *PAX3* or *PAX7-FOXO1* translocation of alveolar RMS to transform cells and cause RMS [95–100]. However, responses to IGF1R inhibitors or combinations are very infrequent based on trials in adults and children alike [101, 102]. Given the biological distinctiveness of each of the primary forms of rhabdomyosarcoma, it is clear that one treatment is not appropriate for all RMS subtypes. Resistance to IGF1R inhibitors in rhabdomyosarcomas appears to be through continued signaling through AKT [99, 103] apparently by switching kinases from IGF1R to other(s) [104]. This finding appears consistent with the transient benefit seen in genetically engineered mouse models of rhabdomyosarcoma treated with IGF1R inhibitors [105] as well as in humans with recurrent rhabdomyosarcoma treated with anti-IGF1R monoclonal antibodies. As a result, blocking multiple receptor tyrosine kinases may provide a way forward in some patients.

Future directions are examining IGF1R inhibitors and temozolomide in high-risk RMS, while for embryonal RMS, given the number of interesting oncogenes involved in an area of loss of heterozygosity in these tumors, perhaps epigenetic therapy will prove useful in this tumor with clear alterations in DNA methylation; that being said, embryonal RMS is more sensitive to standard therapy than alveolar or pleomorphic RMS. For pleomorphic RMS, hopefully future therapeutics can be built from the few anecdotes of patients responding well to known gemcitabine-based combinations, suggesting another sarcoma that will benefit from more careful analysis of cell cycle-specific compounds. Hints of activity of trabectedin in alveolar rhabdomyosarcoma in a small randomized trial of the drug in translocation-associated sarcomas gives hope that there will be a way forward in therapeutics using already approved agents [106] (Table 15.6. Treatment Recommendations).

15.18 Mesenchymal Chondrosarcoma

This rare and unusual lesion can present as a primary abdominal lesion (Fig. 15.18a) and can be highly malignant with pulmonary metastasis (Fig. 15.18b, c) the current lesion shows calcification, pulmonary metastasis, and extra soft tissue extent in the mediastinum.

Pathology is of great interest with definitive markers (Fig. 15.18d). This lesion was originally described by Dahlin in 1962 [107]. The tumor consists of benign appearing chondroid islets with anaplastic tissue suggesting primitive mesenchyme. The lesion can occur in both bone and extraskeletal subtypes it is thought that women are more commonly affected than men. Unusual soft tissue metastases, as in this patient, are often seen. It is said to be more common arising in the facial bones and hard palate but can occur in the ribs and other extraskeletal sites. A series was reported by Huvos from our institution, 30 years ago [108]. Recent identification of the classical marker for this lesion has confirmed the diagnosis.

Many centers will use adjuvant or neoadjuvant chemotherapy (typically Ewing sarcoma type regimens) for this diagnosis, but it is not clear what the activity is of such therapy, given low response rates of the diagnosis when metastatic disease is apparent. Hints of activity have been seen with trabectedin in a randomized trial of translocation-associated sarcomas in Japan [106].

15.19 Embryonal Sarcoma

Embryonal sarcoma is a rare sarcoma unique to the liver, typically occurring in children around the age of 10, akin to other small blue round cell tumors. It can be difficult to distinguish histologically from rhabdomyosarcoma or Wilms tumor, in particular the former, since rhabdomyosarcoma can affect the biliary tree [109]. However, in comparison to rhabdomyosarcoma, embryonal sarcoma does not express the classic rhabdomyosarcoma MyoD or myogenin. Embryonal sarcoma does not bear the chromosomal translocation involving *PAX3* or *PAX7* and the *FOXO1* (*FKHR*) gene. Given its rarity, it is not entirely clear that chemotherapy is necessary in primary treatment of such tumors. Nonetheless, given (1) poor outcomes with surgery alone from older studies [110], (2) the outcomes such patients experienced on chemotherapy when included in International Rhabdomyosarcoma Study (IRS) groups, as well as (3) the response of patients with unresectable disease to chemotherapy [111], we advocate the use of neoadjuvant or adjuvant chemotherapy using a Ewing sarcoma regimen such as VAdrC-IE 5-drug therapy as used in the United States or VIDE, more commonly employed in Europe. Given the data from IRS studies, a dactinomycin regimen could be considered as well (Suggestions for Therapy—Table 15.7).

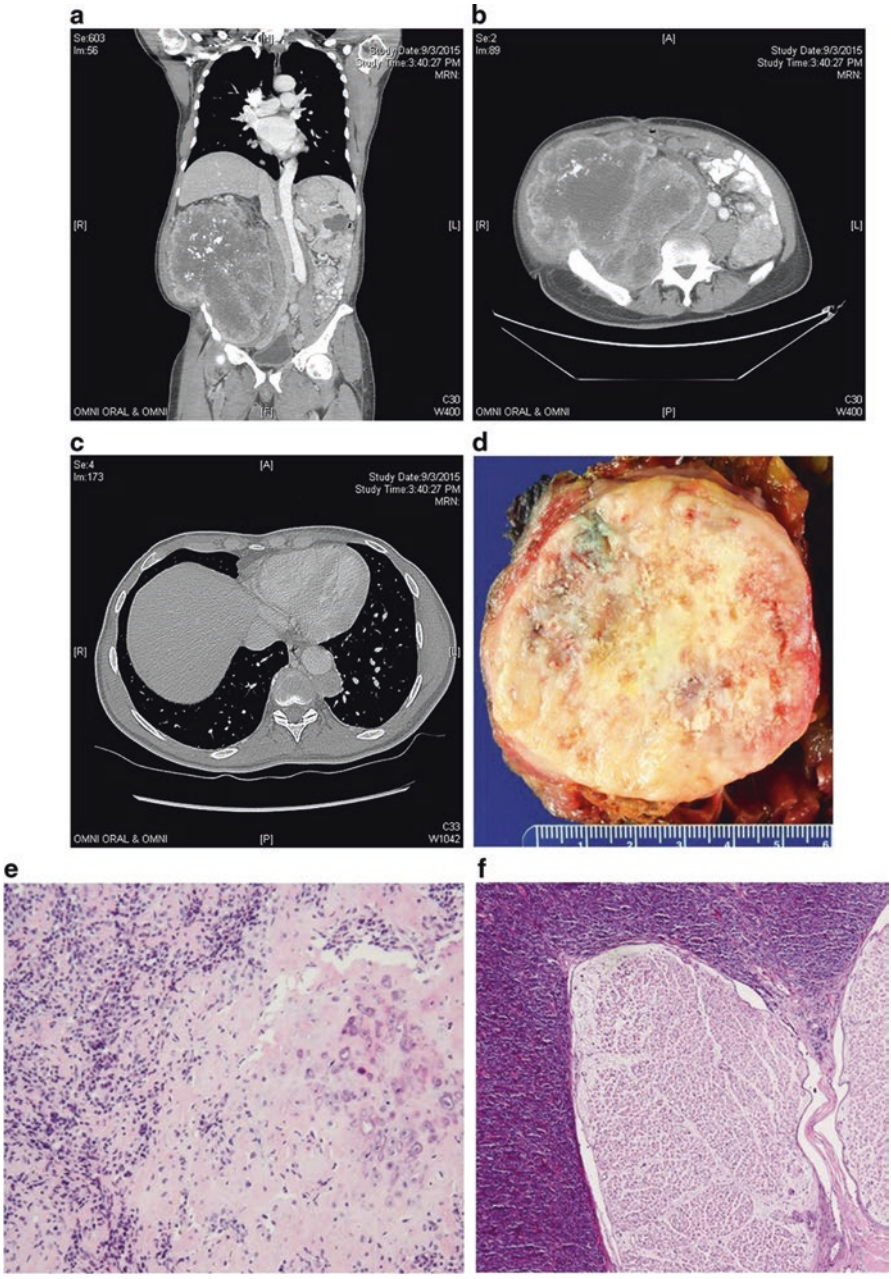


Fig. 15.18 Mesenchymal chondrosarcoma. (**a**) Primary abdominal lesion. (**b**, **c**) Pulmonary metastasis and soft tissue extent in the mediastinum. (**d**) Well-circumscribed large retroperitoneal mass showing a variegated cut surface; (**e**) microscopically, it has a biphasic appearance with alternating primitive round cells and chondrosarcoma areas. (**f**) Other areas were composed mainly of the round cell, here encasing femoral nerve. FISH confirmed the NCOA2-HEY1 fusion

Table 15.7 Systemic therapy recommendations for patients with embryonal sarcoma

Primary therapy	Surgery and neoadjuvant or adjuvant chemotherapy. Regimens used for Ewing sarcoma or rhabdomyosarcoma. We have opted to use the five drug VAdrC-IE regimen; VIDE would be used more commonly in Europe
Recurrent disease	Surgery and or chemotherapy as directed toward small round blue cell sarcoma. Clinical trials are appropriate as well. Immune checkpoint inhibitors are not yet studied in this diagnosis

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Chapter 16
Radiation-Induced Sarcoma

One of the few known causes of sarcomas is therapeutic irradiation. Therapeutic radiation has also been associated with development of breast cancer, lung cancer, and accelerated coronary artery disease in patients receiving thoracic radiation [1–3]. With the increased recognition of second cancers as a long-term side effect of radiation therapy, attempts have been made to use radiation more sparingly. For example, there is a question as to whether surgery for ductal carcinoma in situ is necessary, whereas at least one present standard of care is lumpectomy and radiation therapy, despite the ability to obtain negative margins in at least 95 % of patients with surgery alone, and no difference in long-term breast cancer mortality with the addition of radiation therapy [4, 5]. The incidence of a sarcoma after radiation is not precisely known, and may vary from one part of the body to the next. In a series of patients treated for cancer of all sites in Finland, for example, the crude risk was of the order of 0.05 % [6].

In the prospectively collected series from MSKCC, consistent patterns have arisen regarding the types of diseases treated with radiation and the forms of sarcoma that arise after radiation. The most recent MSKCC update comes from Gladdy et al. from 2010 [7]. A total of 130 radiation-induced sarcomas (RIS) were examined in over 7600 patients treated surgically for sarcoma at MSKCC. A total of 34 % of patients with RIS were treated for breast cancer, 18 % for leukemia or lymphoma, and 17 % for genitourinary tumors. In this update, the median latency for development of the RIS was 10 years; however, the median latency varied based on the type of sarcoma involved, with the shortest median latency for liposarcomas (median 4.3 years) and longest for leiomyosarcoma (23 years).

Common RIS histologies included high grade undifferentiated pleomorphic sarcoma (26 %), angiosarcoma (21 %), leiomyosarcoma (12 %), and fibrosarcoma not otherwise specified (12 %). These data are somewhat different from other series, in which osteosarcomas were seen more frequently than in this series. Median age at presentation was 58.5 years (range 18–86). The trunk was the most common primary site (61 %) highlighting secondary sarcomas of the breast. Five-year

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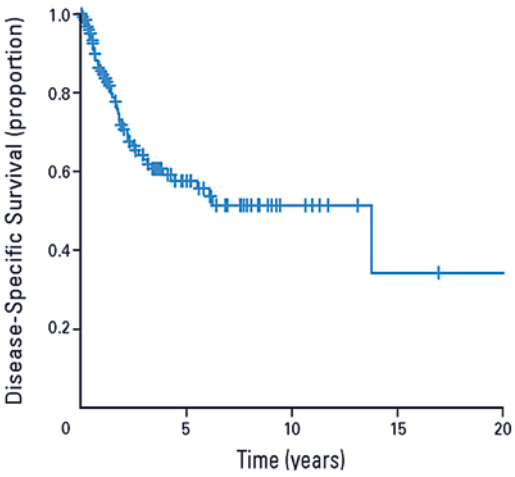

Fig. 16.1 Disease-specific survival (DSS) for resected primary radiation-associated sarcomas (RASs). *LMS* leiomyosarcoma, *AS* angiosarcoma, *MFH* malignant fibrous histiocytoma, *MPNST* malignant peripheral nerve sheath tumor, *FS/MYXF* fibrosarcoma or myxofibrosarcoma. With permission from: Gladdy RA, et al. J Clin Oncol 28:2064–2069, 2010

disease-specific survival was 58 % (Fig. 16.1), and independent predictors of poor outcome were large size >5 cm, margin status, and RIS histology.

Primary management of RIS remains surgical. Given the difficulty in administering radiation to control these tumors, and given the nature of the field to be operated upon, it is not surprising that there is a significant local–regional recurrence risk postoperatively, and survival appears inferior to patient with similar sarcomas that are not radiation induced (Fig. 16.2) [3, 7–10]. Radiation therapy, in particular the use of brachytherapy for resectable tumors and/or IMRT preoperatively to deliver highly localized radiation therapy, can be entertained in some patients, despite prior use of radiation as a treatment for the initial clinical problem, especially for patients who had a longtime interval from their initial radiation.

The development of RIS begs the question of whether less radiation therapy can be employed to decrease the risk of such malignancies developed. For example, can surgery without radiation therapy be employed for primary treatment of sarcomas? Given the low local recurrence risk of tumors under 5 cm in size in the MSKCC series, surgery alone is a good standard of care for sarcomas removed with negative margins, if there is a follow-up operation that can still be limb sparing. However, if there is a question of a margin, in particular in regions of the body such as the head and neck, where a second operation is less likely to achieve a good margin, then adjuvant or neoadjuvant radiation therapy should be considered.

An example of a radiation-induced sarcoma is shown in Figs. 16.3, 16.4, 16.5, 16.6, 16.7, and 16.8, a 48-year-old woman treated with radiation therapy following excision of ductal carcinoma in situ of the breast. Two years later she presented with a high grade undifferentiated pleomorphic sarcoma. She was treated by local resection and she then presented 2 years later (Fig. 16.3) with a fungating mass (Fig. 16.4) involving the chest wall with multiple foci. This was resected with the chest wall (Fig. 16.5) with reconstruction using methylmethacrylate for the rib cage (Fig. 16.6) and a rotational flap to cover the defect (Fig. 16.7). All margins were negative at the time. Within 2 years, she had further recurrence of a left anterior chest wall nodule

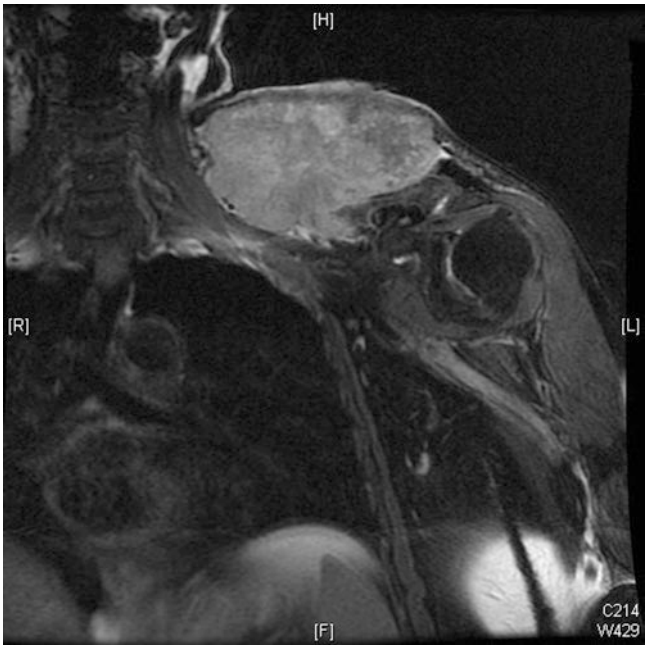

Fig. 16.2 Sagittal T2-weighted fat-saturated MRI image of a radiation-induced high grade myofibroblastic sarcoma of the left trapezius/supraspinatus

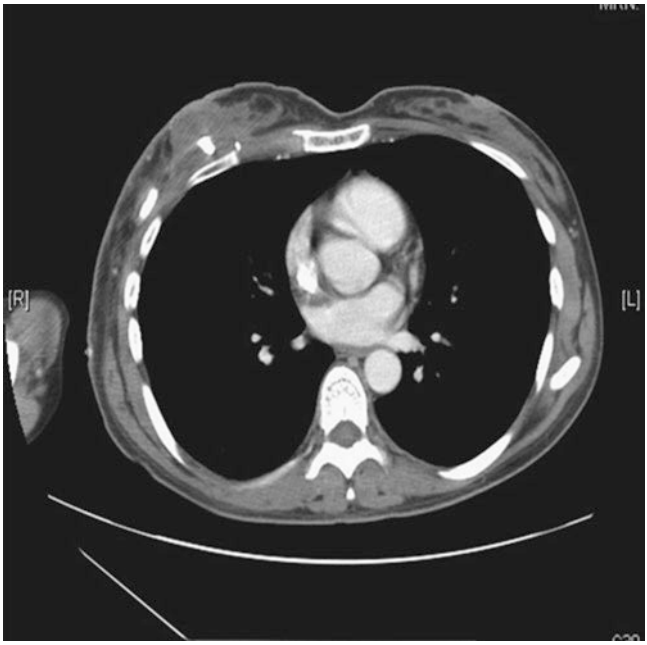

Fig. 16.3 Contrast-enhanced CT image of a radiation-induced sarcoma of the right chest wall after surgery and radiation therapy for ductal carcinoma in situ

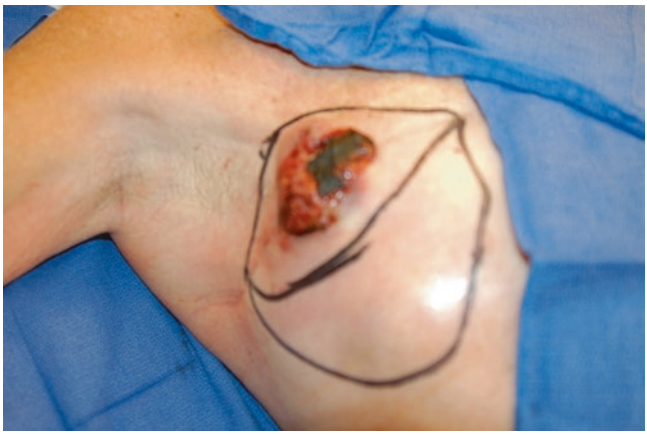

Fig. 16.4 Preoperative CT image of the right chest wall radiation-induced sarcoma from Fig. 16.3

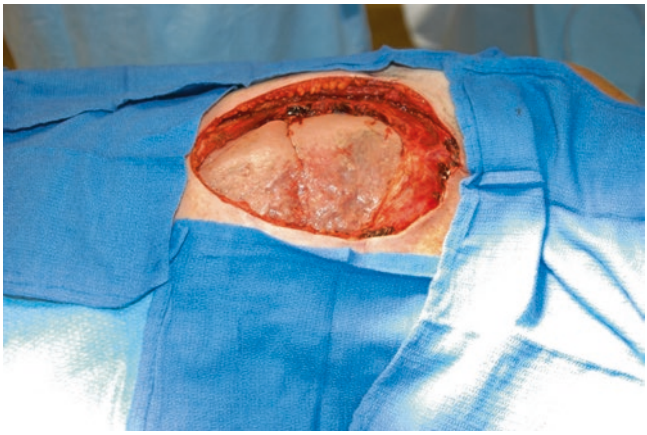

Fig. 16.5 Post-resection CT image of the chest wall resection of the patient in Figs. 16.3 and 16.4

and received chemotherapy. She progressed to demise within 1 year with extensive intrathoracic and chest wall recurrence (Fig. 16.8). A similar lesion in the right groin of a radiation-induced extraskeletal osteogenic sarcoma is demonstrated (Fig. 16.9), requiring a tissue flap for reconstruction of the defect.

Treatment for these lesions follows the principles used for the specific histological subtypes discussed elsewhere in this volume. There are few histology-specific data. In a large series of what was termed UPS at MD Anderson, those UPS associated with radiation had inferior outcomes both in terms of local recurrences and disease-specific survival [3]. As for chemotherapy for RIS, there are no specific guidelines, other than to use agents appropriate for the histology at hand. For exam-

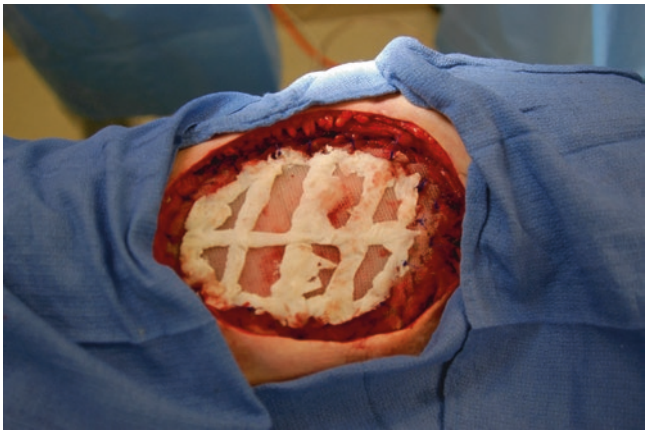

Fig. 16.6 Reconstruction of the chest wall after resection of the tumor from Figs. 16.3, 16.4, and 16.5

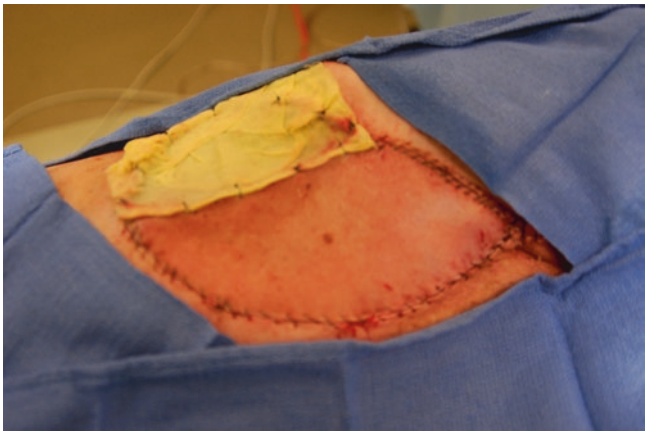

Fig. 16.7 Final surgical result for the patient from Figs. 16.3, 16.4, 16.5, and 16.6.

ple, angiosarcomas are responsive to anthracyclines and taxanes, and recent clinical data suggest that agents targeting VEGF (vascular endothelial growth factor) receptors can be active in radiation-induced angiosarcoma of the breast [11], although at present it is unclear if this is due to presence of KDR/VEGFR2 mutations in some breast angiosarcomas [12] or not. It should be noted that limb perfusion with tumor necrosis factor and chemotherapy such as melphalan is a possible option for patients with recurrent disease despite attempts at local control, if the tumor site can be isolated for such therapy [13]. It is also notable that RIS such as UPS are among the most highly mutated sarcomas. Given the responses noted in early studies of PD1 inhibitors of UPS and some osteosarcomas these may be good targets for immune checkpoint or related immunological approaches [14].

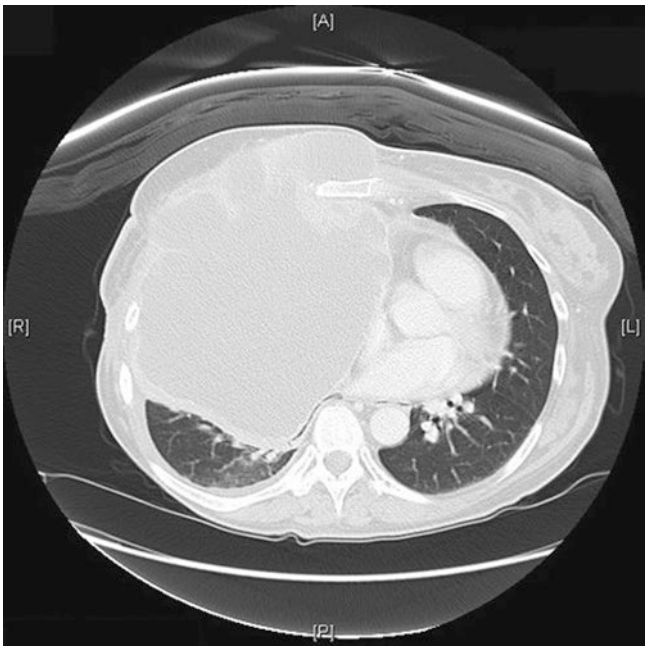

Fig. 16.8 Radiation-induced sarcoma after surgery and radiation for infiltrating ductal breast adenocarcinoma

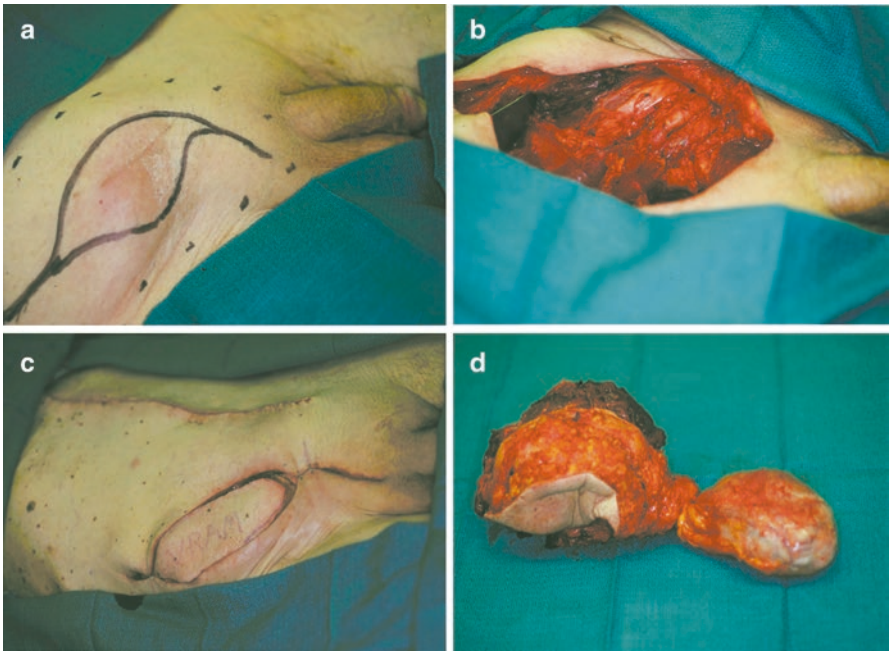

Fig. 16.9 Resection of a radiation-induced extraskeletal osteosarcoma of the right groin: (**a**) preoperative, (**b**) intraoperative, and (**c**) postoperative, and (**d**) an image of the resection specimen

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Chapter 17
Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) is a rare sarcoma that typically arises in the lower extremity in adolescents and young adults between 15 and 40 years of age. Distributions by age and site in adults are shown in Figs. 17.1 and 17.2 for all adult ASPS. In children, a number of cases arise from the tongue and orbit, where it can be confused to some degree with embryonal rhabdomyosarcoma. ASPS is extremely rare, even at referral centers, which have been hard pressed to identify more than one to two patients a year per center in published series [1–3]. It frequently presents with innumerable small, round metastatic lesions in the lungs and shows a very slow rate of progression, one reason for the late presentation of what is often a primary >10 cm in greatest dimension. Progression is typically slow, but ultimately taking the patient's life after 10–15 years of metastatic disease. Compared to most other sarcomas, brain metastases are a more common complication of ASPS, with an incidence at least thrice of that of other sarcomas in one series and documentation in other series [4–6].

17.1 Imaging

ASPS characteristically presents with a slow growing primary, mass (over years) as well as innumerable, round lung metastases. Bony metastases are more common than other sarcomas (Figs. 17.3 and 17.4).

17.2 Diagnosis, Molecular Pathology

ASPS has a highly characteristic microscopic appearance by H&E (hematoxylin and eosin) staining, with epithelioid cells with abundant eosinophilic cytoplasm and round nuclei arranged in nests and alveolar structures, separated by thin fibrous

M.F. Brennan et al., *Management of Soft Tissue Sarcoma*,
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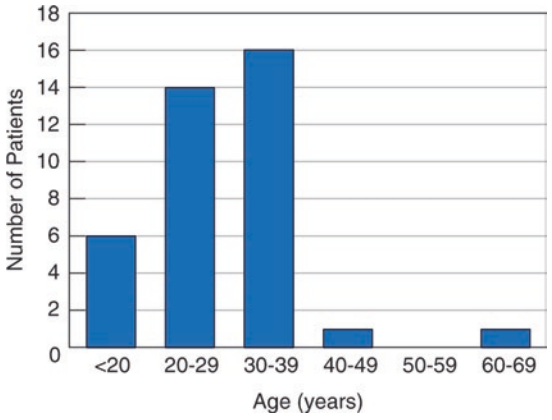

Fig. 17.1 Age distribution of adult patients (>16 years) with alveolar soft part sarcoma. MSKCC 7/1/1982–6/30/2010, $n = 37$

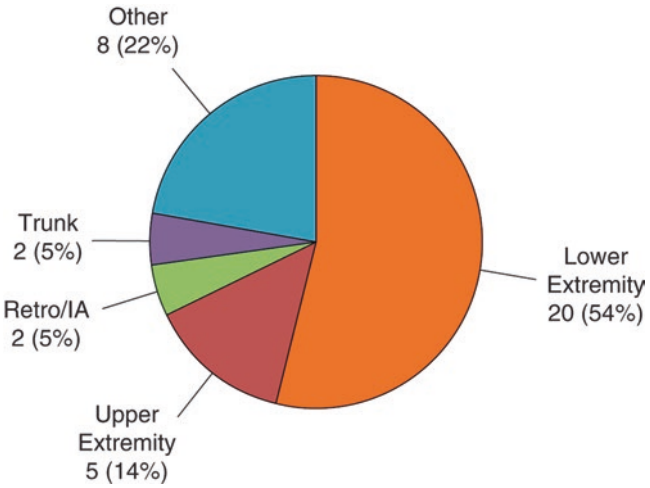

Fig. 17.2 Primary site of adult patients (>16 years) with alveolar soft part sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 37$

septae (Fig. 17.5). It contains an equally characteristic unbalanced chromosomal translocation, t(X;17), involving *ASPL-TFE3* [3, 7]. The same, but balanced t(X;17),translocation is found in a proportion of mostly pediatric papillary renal cell cancers [8], indicating the context dependence of the oncogene in the development of the tumor in question. By electron microscopy, cytoplasmic granules of specific proteins, monocarboxylate transporter 1 (MCT1) and CD147, correlate with the eosinophilic deposits seen in the endoplasmic reticulum of ASPS cells by H&E staining (Fig. 17.5) [9]. An interesting mouse model of ASPS highlighted the fact that there is a mechanistic reason for so much MCT being present in ASPS—lactate, which is imported by MCT1, is fuel for the ASPS cell, causing tumor cell proliferation and angiogenesis [10]. This finding suggests that metabolic therapy or epigenetic therapies may be effective in ASPS.

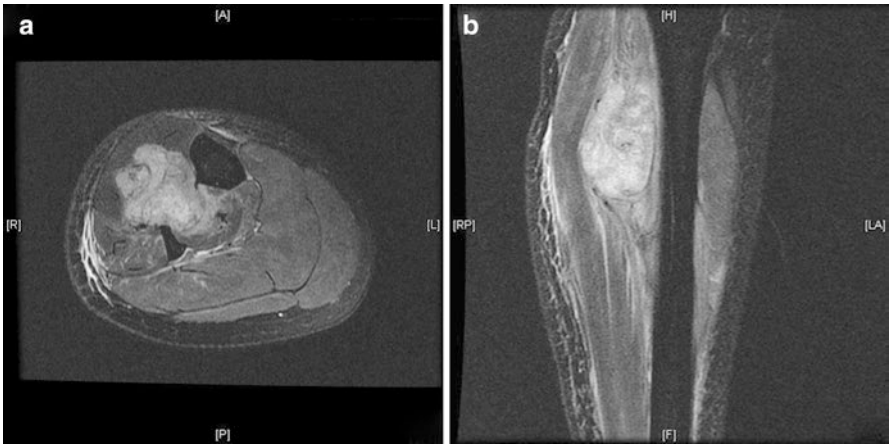

Fig. 17.3 T2 contrast-enhanced fat-saturated MRI images of a primary alveolar soft part sarcoma of the calf. Tumor extends through the interosseous membrane

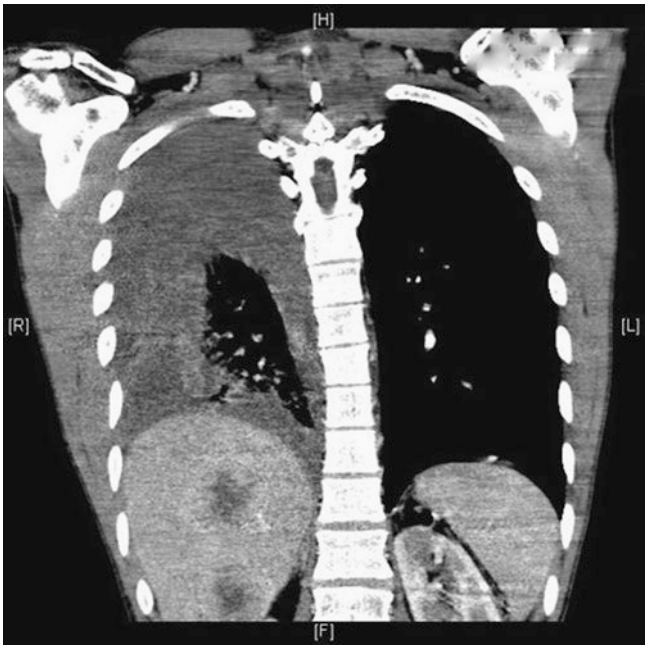

Fig. 17.4 Reconstructed contrast-enhanced coronal CT images of metastatic alveolar soft part sarcoma with substantial pleural-based and liver metastatic disease. A more typical pattern involves bilateral innumerable round lung metastases

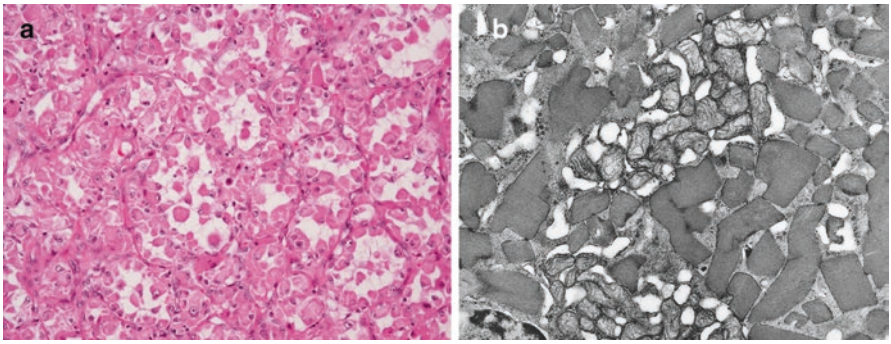

Fig. 17.5 Microscopic and ultrastructural detail of alveolar soft part sarcoma. (**a**) Microscopic appearance demonstrating well-defined alveolar structures lined by large epithelioid cells with abundant eosinophilic cytoplasm and eccentric nuclei with small nucleoli (H&E, ×100). (**b**) An electron micrograph demonstrates characteristic large rhomboid crystals as well as abundant mitochondria

Table 17.1 Systemic therapy recommendations for patients with alveolar soft part sarcoma

Clinical scenario	Suggested therapy
Primary disease	Surgery; radiation; Since cytotoxic chemotherapy is inactive, it is not used in the neoadjuvant or adjuvant settings
First line for metastatic disease	Pazopanib, other VEGFR-targeted tyrosine kinase inhibitor; cediranib, tested in a phase II trial, is not available as of 2016
Second line and later for metastatic disease	Clinical trial; trabectedin, other VEGF-directed therapy where available. Immune checkpoint inhibitors have anecdotal activity but are formally not tested as of 2016. Metabolic and epigenetic agents also appear of interest

17.3 Primary Treatment

Primary surgery is appropriate for patients with both primary only disease, and in our opinion also for patients with metastatic disease, since most symptoms can at least initially be related to the large primary, although metastatic lung disease typically dictates the late course of the tumor. Usually so many nodules are observed as metastatic disease in the lungs that surgery cannot be contemplated rationally (Table 17.1). The indolent course of this sarcoma makes the use of radiation appealing. In a review of SEER data, 118 patients with localized disease were identified. The use of adjuvant RT was an independent predictor of improved local control, despite the fact that those receiving RT were larger in size than those treated with surgery alone [11].

17.4 Treatment of Metastatic Disease

Systemic therapy for sarcomas continues to evolve and has affected the treatment of ASPS, although not to the degree of tyrosine kinase inhibitors for GIST. Systemic cytotoxic chemotherapy is essentially useless against ASPS in our experience, although there are isolated reports of responses in patients with metastatic disease [6]. There are also case reports of interferon-alfa2a being active in metastatic ASPS [12, 13], suggesting an antiangiogenic approach for treatment of ASPS. This idea has been developed further with newer antiangiogenic agents. The striking activity of cediranib against ASPS in two prospective clinical trials reinvigorated interest in systemic therapy for ASPS [14–16]. Sunitinib, commercially available unlike cediranib as of the time of publication, has activity against metastatic ASPS as well [17]. How the ASPS translocation leads to signaling or dependence on VEGF (vascular endothelial growth factor) related pathways remains unknown. In the setting of resistance to a VEGFR (VEGF receptor) tyrosine kinase inhibitor, other agents that target VEGF signaling, be it bevacizumab or other agents affecting downstream signaling steps from the VEGFRs, would appear to make most sense to investigate. The data from the Jones laboratory indicating the importance of lactate in tumor growth and survival may provide another means to attack ASPS with less toxicity than other modalities [10]. Interestingly, anecdotes of responses of ASPS to immune checkpoint inhibitors are described, contradicting the idea that cancers must be highly mutated to respond to these agents. One can hypothesize that like renal cancer that tumors with HIF1α overexpression/VEGF dependence may be targets of immune checkpoint inhibitors because of this unique biology instead.

17.5 Outcome

Because these tumors are rare and prolonged survival occurs despite metastatic disease, long follow-up (10 years or more) is necessary. Overall survival for all patients is shown in Fig. 17.6 and the influence of metastatic disease highlighted in Fig. 17.7. A recent single institution study of 49 patients confirmed the high metastatic rate (72 %), predominantly to lung, but with relatively long overall survival compared to other soft tissue sarcoma [18].

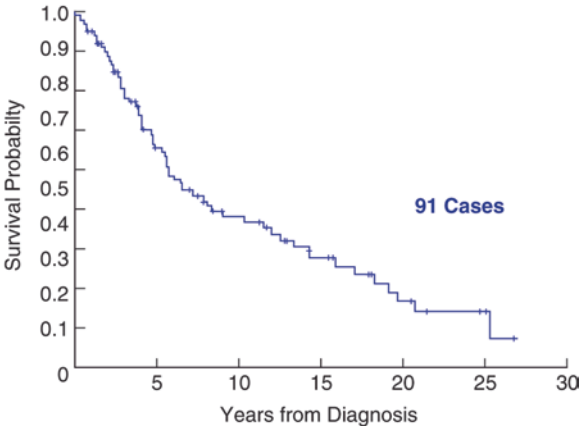

Fig. 17.6 Overall survival of 91 patients with alveolar soft part sarcoma. Lieberman PH, Brennan MF, Kimmel M, et al. Alveolar soft-part sarcoma. A clinico-pathologic study of half a century. From: Lieberman PH, Brennan MF, Kimmel M, et al. *Cancer* 1989; 63(1):1–13

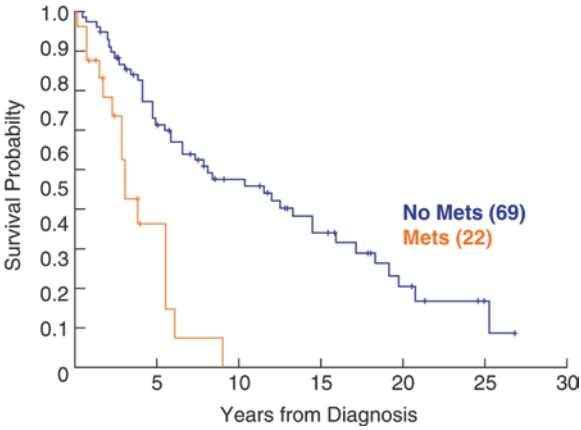

Fig. 17.7 Overall survival of 91 patients with alveolar soft part sarcoma, distinguishing primary from metastatic disease. Mets = metastases From: Lieberman PH, Brennan MF, Kimmel M, et al. *Cancer* 1989; 63(1):1–13

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Chapter 18
Clear Cell Sarcoma/Melanoma of Soft Parts

Is it a sarcoma? Is it a melanoma? Clear cell sarcoma (CCS), also called clear cell sarcoma of tendons and aponeuroses [1, 2], has features of both. CCS represents <1 % of all sarcomas. Since it starts in soft tissue and usually does not affect skin [3], CCS is anatomically distinct from melanoma. Patients are typically younger, between 15 and 45 years of age, and women are more commonly affected than men, though some series indicate equal incidence. The foot and ankle are common primary locations for this rare sarcoma. Age and site distribution for adult patients are shown in Figs. 18.1 and 18.2.

18.1 Imaging

The appearance of clear cell sarcoma of the ankle, knee, and gastrointestinal tract is not distinguishable from other sarcomas, except for the higher risk of lymph node metastases compared to other sarcomas (Figs. 18.3 and 18.4).

18.2 Diagnosis, Molecular Pathology

Soft tissue CCS contains a characteristic translocation [4], typically t(12;22), *EWSR1-ATF1*, and much less commonly t(2;22), *EWSR1-CREB1* [5]. The reversed pattern is seen in the gastrointestinal tract CCS, where *EWSR1-CREB1* fusion is the most common abnormality. Both translocations also can be found in angiomatoid fibrous histiocytoma (AFH) [6, 7] suggesting the same translocation creates a tumor that is context-dependent upon the affected precursor cell, as with the *ASPL-TFE3* translocation of papillary renal cell cancer and alveolar soft part sarcoma. CCS does not contain mutation in *BRAF,* such as the V600E mutation commonly detected in melanoma.

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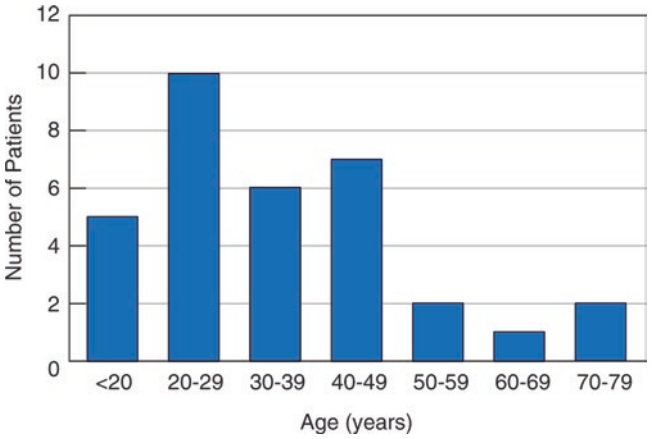

Fig. 18.1 Age distribution for adult patients with clear cell sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 33$

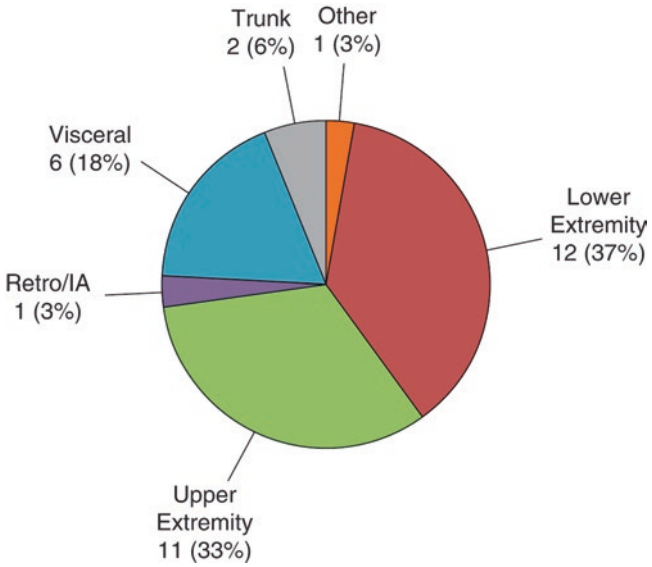

Fig. 18.2 Primary site distribution of adult patients with clear cell sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 33$ Retro/IA = retroperitoneal/intra-abdominal

Unlike most sarcomas, CCS can metastasize to locoregional lymph nodes, and it is typically positive for markers commonly observed in melanoma, such as S100, MiTF, HMB45, melan-A, and tyrosinase, making diagnosis without the clinical history difficult (Fig. 18.5). The tumor frequently invades dense connective tissue of tendons, where nests of tumor cells are separated by fibrous septa. The differential diagnosis includes MPNST and epithelioid sarcoma, while in the GI location also includes GIST and carcinoid tumor. It is worth noting that melanocytic markers are

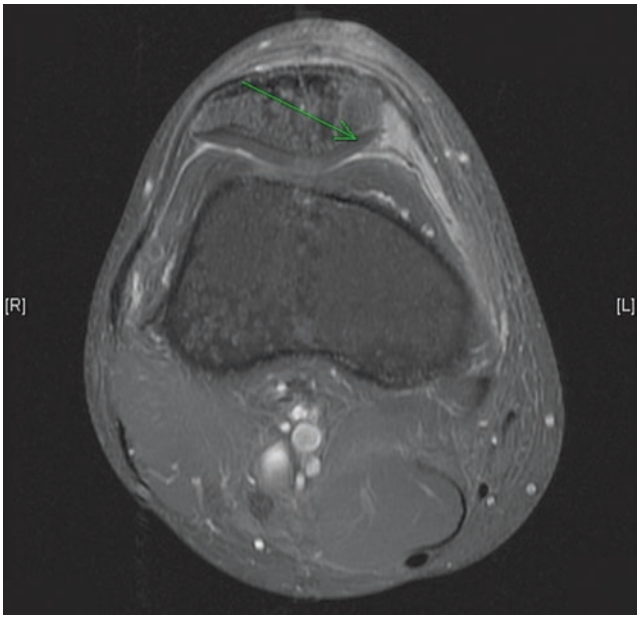

Fig. 18.3 Contrast-enhanced T2-weighted fat-saturated MRI image of a clear cell sarcoma of the knee with patellar invasion. The tumor was confirmed to have an *EWSR1* rearrangement

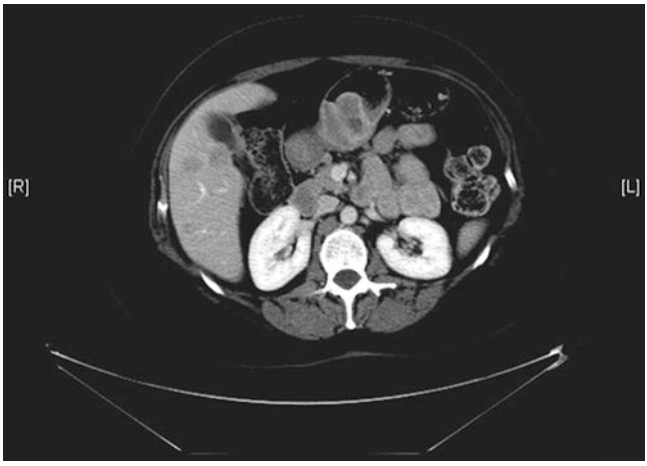

Fig. 18.4 Contrast-enhanced CT image of a gastric clear cell sarcoma with evidence of liver metastatic disease

often negative in the gastrointestinal CCS [5]. Gastrointestinal CCS typically follows a much more aggressive clinical course with early lymph nodes and liver metastases [5]. Finally, the anatomic diversity of this genomic family of sarcomas is evident by the identification of *EWSR1-CREB1* translocation in a new histological entity, termed pulmonary myxoid sarcoma, which typically arises from airways rather from the lung parenchyma itself [8].

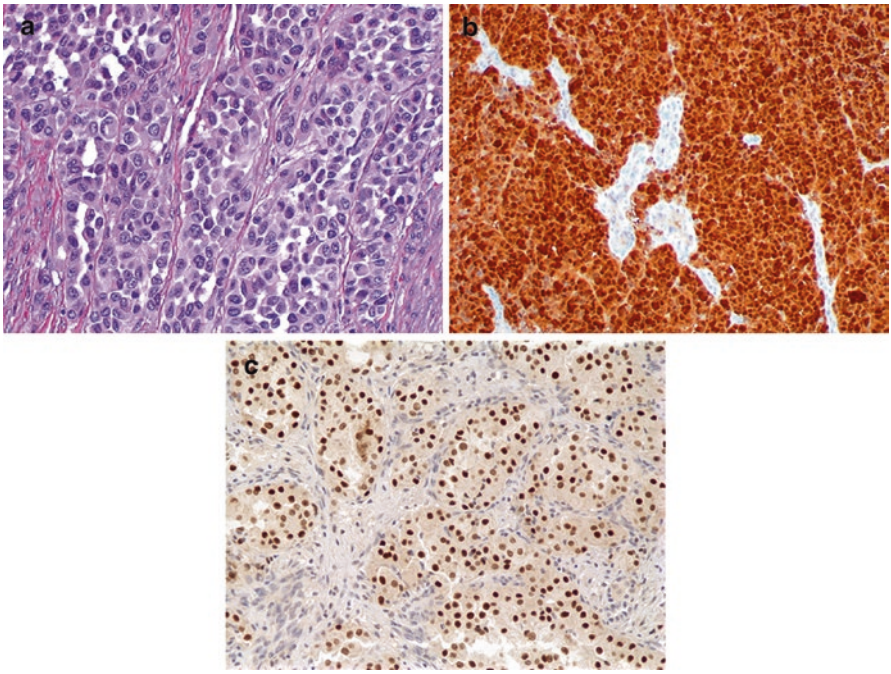

Fig. 18.5 Microscopic images of clear cell sarcoma demonstrating characteristic features. (**a**) High power image of clear cell sarcoma demonstrating cords of loosely arranged small cells with eosinophilic cytoplasm separated by refractile collagen bundles, H&E, ×200. (**b**) Immunohistochemical staining showing strong S100 staining, ×100. (**c**) Strong nuclear staining for MiTF by immunohistochemistry, ×100

18.3 Treatment

Surgery remains the mainstay of primary treatment for this diagnosis. Given the ability of at least some CCS to metastasize to lymph nodes, we argue that sentinel lymph node biopsy is a reasonable standard of care as part of staging, similar to melanoma, with completion lymphadenectomy if positive. Primary surgery is often made difficult given the anatomy of the ankle and foot. As lymph node metastasis is relatively common compared to other soft tissue sarcomas (hence the name melanoma of soft parts), therapeutic lymph node dissection, should be performed when lymph node metastasis are present [9, 10].

For recurrent disease, the chemotherapy sensitivity pattern of CCS is perhaps more consistent with melanoma in the era prior to kinase inhibitors, with occasional responses to platinum-based chemotherapy [11]. Ifosfamide is active in the occasional patient [12]. Overall, there is a very low response rate to classical cytotoxic chemotherapy [12]. Like other sarcomas involving *ATF1/CREB1* rearrangements, CCS can express MET, suggesting an antiangiogenic approach to treat these tumors. However, a study of a MET inhibitor (ARQ179) showed but one RECIST (Response

Table 18.1 Suggestions for therapy for clear cell sarcoma[a]

Clinical scenario	Treatment
Primary disease	Surgical excision; radiation when anatomically feasible without functional loss. Sentinel lymph node sampling may aid in staging, as may PET scans. Chemotherapy is not recommended as adjuvant therapy given low response rates in metastatic disease
Recurrent/metastatic disease	Clinical trial; ifosfamide; trabectedin; platinum-based chemotherapy; doxorubicin has little activity, but it is not clear if doxorubicin + olaratumab could provide benefit
Chemotherapy-refractory disease	Multitargeted tyrosine kinase inhibitor, such as pazopanib; clinical trial. Immune checkpoint inhibitors are intriguing for more than one reason, but are formally untested as of 2016

[a]A clinical trial is appropriate when available

Evaluation Criteria In Solid Tumors) partial response, implying that MET signaling, implying either an overall ineffective degree of MET inhibitions or alternative bypass survival pathways for CCS [13]. A patient with CCS has responded to sunitinib, giving hope that receptor tyrosine kinase specific agents could have activity in CCS [14]. Future studies will focus on signaling pathways activated or interacting in this tumor by the translocation product, similar to Ewing sarcoma and the EWSR1-FLI1 translocation product, and IGF1R signaling [15]. It is also feasible that immunotherapy agents useful in melanoma could be useful in clear cell sarcoma, since melanin and related proteins are expressed by this tumor. However, clear cell sarcoma has overall a much lower mutational burden than melanoma at least by virtue of the few samples examined to date by whole genome or whole exome sequencing.

We note that chemotherapy for Ewing sarcoma is inactive against clear cell sarcoma; the presence of an *EWSR1* translocation positive tumor does not predict sensitivity to cytotoxic chemotherapy, in and of itself. However, there are at least hints of activity of trabectedin in clear cell sarcoma based on a small number of patients treated in a trial conducted in Japan [16] (Table 18.1).

18.4 Outcome

Local recurrence is uncommon but numbers in the various series are small. Our local recurrence in 13 patients is shown in Fig. 18.6, but systemic recurrence and death from disease are likely (Fig. 18.7) [17]. Unfortunately, even in large institutions, the experience is limited, and metastasis frequent, with demise within 2 years of appearance of metastatic disease. Only initial tumor size over 5 cm appears to be a predictor of poor outcome [18]. In the largest published series to date (31 patients), 5- and 10-year disease-specific survival rates for primary localized patients were 72 and 53 %. Male gender, age under 30, truncal tumor location, and size greater than 5 cm were poor prognostic factors by univariate analysis [19].

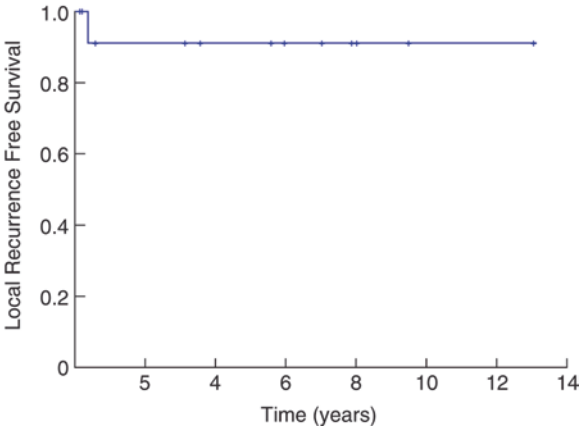

Fig. 18.6 Local disease-free survival for adult patients with primary clear cell sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 13$

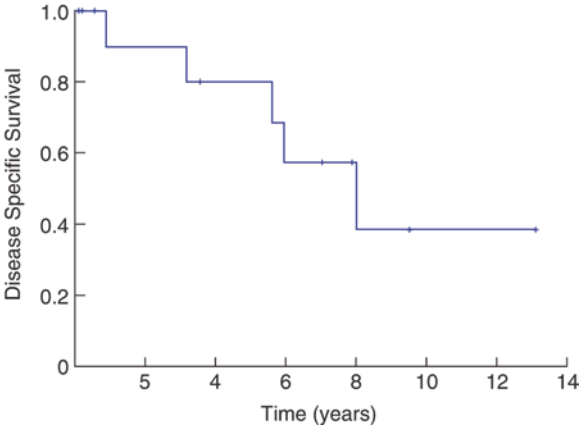

Fig. 18.7 Disease-specific survival for adult patients with primary clear cell sarcoma. MSKCC 7/1/1982–6/30/2010 $n = 13$

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Chapter 19
Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a somewhat chemotherapy sensitive, but highly lethal sarcoma diagnosis. Distribution by age for adults is shown in Fig. 19.1 emphasizing that it is an uncommon tumor, seen mainly in adolescents and young adults (age 15–30). There is a strong male predominance (~5:1), and nearly always affects the peritoneum as multifocal/metastatic disease (Fig. 19.2). The best outcomes from therapy are those who have both a good response to chemotherapy (using agents typically employed for Ewing sarcoma) and successful surgical debulking [1]. Rare patients will present with disease elsewhere; if disease is localized, the cure rate is expected to be higher than the 5–15 % typically encountered for those patients with primary abdominal disease [1, 2].

19.1 Imaging

The CT or MR scans of patients with DSRCT reflect tumor biology, typically with multiple large, dense masses in the abdomen, sometimes with central necrosis (Fig. 19.3). Those patients who develop lung metastases show signs of similar fibrotic patterns consistent with desmoplastic changes in the lung.

19.2 Diagnosis

DSRCT characteristically presents as multiple firm fibrous masses with significant vascularity that contain nests of small round blue cells surrounded by dense fibrous (desmoplastic) stroma on microscopic examination (Fig. 19.4). Mesothelial markers are negative, distinguishing DSRCT from mesothelioma. The tumor shows a polyphenotypic expression by IHC, showing both cytokeratin and desmin reactivity. While NSE (neuron-specific enolase) can be positive in many tumors, other

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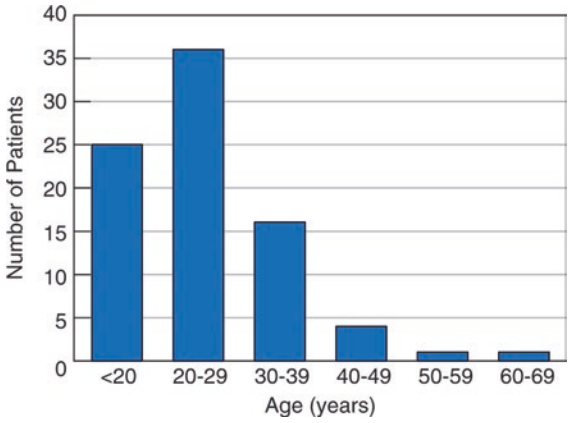

Fig. 19.1 Age distribution of adult patients with desmoplastic small round cell tumor. MSKCC 7/1/1982–6/30/2010 $n = 83$

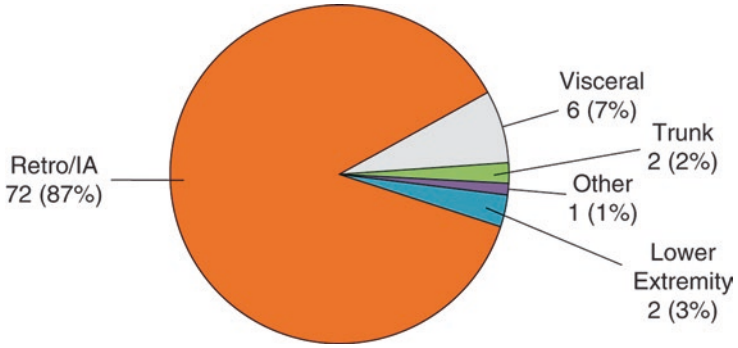

Fig. 19.2 Primary site distribution of adult patients with desmoplastic small round cell tumor. MSKCC 7/1/1982–6/30/2010 $n = 83$ Retro/IA = retroperitoneal/intra-abdominal

neuroendocrine markers are typically negative [3, 4]. C-terminal WT1 (Wilms tumor gene) staining is positive, on the basis of its characteristic t(11;22) translocation [5–8]. The *EWSR1-WT1* fusion product appears to upregulate PDGF, apparently accounting at least in part for the densely fibrotic nature of the tumor [9, 10].

19.3 Treatment

Combined modality therapy with chemotherapy and surgery is standard of care, but is clearly inadequate based on the poor overall survival rate. Combinations of drugs used for Ewing sarcoma are typically employed, i.e., vincristine-doxorubicin-cyclophosphamide, ifosfamide-etoposide, or the AIM (doxorubicin, ifosfamide, and mesna) or VIDE (vincristine, ifosfamide, doxorubicin, etoposide) regimens [11–13]. In the pediatric setting, the P6 regimen of very high dose VAC/IE (cyclophosphamide, doxorubicin, vincristine/etoposide, ifosfamide) therapy has been

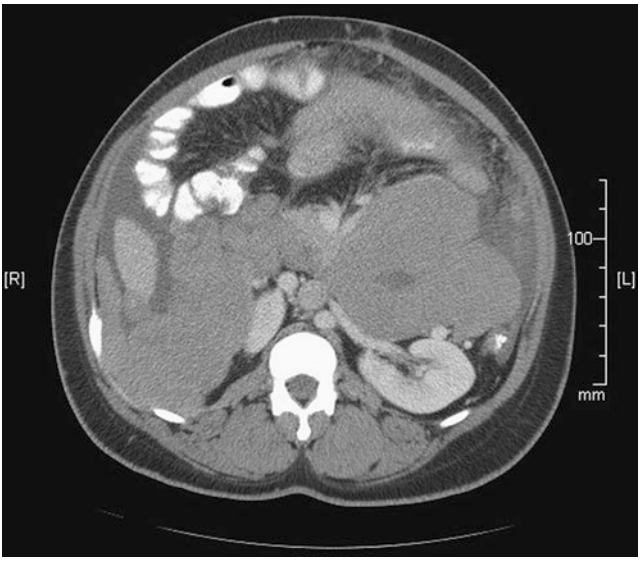

Fig. 19.3 Evidence of multiple abdominal implants from desmoplastic small round cell tumor on contrast-enhanced CT imaging of the abdomen

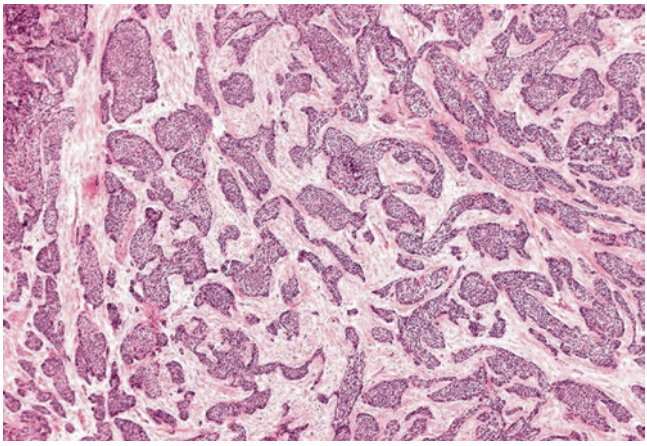

Fig. 19.4 Microscopic appearance of desmoplastic small round cell tumor. Nests of small round blue cells are seen, separated by a bland, desmoplastic fibrous stroma. The diagnosis is confirmed by expression of cytokeratins, desmin, and WT1, or at the molecular level by demonstration of the *EWSR1-WT1* fusion transcript

employed [14], but is next to impossible to successfully administer to adults beyond 1–2 cycles of therapy, owing to the cyclophosphamide dose of 4.2 g/m^2/cycle. There are no published data that these high doses are superior to standard dose VAC/IE as given to patients with Ewing sarcoma. In fact, higher doses of chemotherapy

administered to patients with Ewing sarcoma as part of a randomized clinical trial were associated with no better outcome than standard doses, in this more chemotherapy sensitive disease (at least compared to desmoplastic small round cell tumor) [15]. It therefore stands to argue that standard Ewing sarcoma dosing should be employed as part of management of this diagnosis outside of the setting of a study. Whole abdominal radiation therapy has also been used in some of these patients. In a study from MSK, 31 patients received multi-agent chemotherapy, tumor debulking, followed by whole abdomen radiation to 30 Gy. With a median follow-up of 19 months, the 3-year progression-free and overall survival rates were 24 and 50 %, respectively [16].

Out of desperation from treating this diagnosis with poor outcomes, some clinicians employ intraperitoneal chemotherapy after optimal debulking surgery as treatment. One obvious difficulty with this diagnosis is that it does not spread in a superficial manner as ovarian or appendiceal carcinoma, but rather forms (even subclinical) masses or aggregates that intraperitoneal chemotherapy would not be expected to penetrate. In the authors' opinion, the use of intraperitoneal chemotherapy for DSRCT remains highly investigational [17], given the selection bias inherent in treatment series and lack of randomized data, as are high dose therapy with stem cell support [18, 19] and therapy with WT1-directed immunotherapy [20–23], another avenue in which one hopes for eradication of metastatic disease by virtue of successes with other cancers.

As an example of the potential benefit of very aggressive therapy, a group of 32 patients treated consistently with chemotherapy, debulking surgery followed by hyperthermic intraperitoneal chemoperfusion (HIPEC), then whole abdominal radiation with intensity-modulated radiation or volumetric-modulated arc therapy. With a median 18 months of follow-up, 20 patients had recurrence, with a median recurrence-free survival of 10 months. Grade 3 or higher toxicities occurred in 84 % of patients. Median overall survival was a surprising 60 months, perhaps indicating some effect of the debulking and radiation despite median recurrences within a year of the completion of therapy [24].

VEGFR inhibitors may have some activity; of eight patients receiving sunitinib for DSRCT in a retrospective series, two had a RECIST PR and three had SD as best result of therapy; an anecdotal response was seen in a phase II trial of sunitinib as well [25, 26]. Similar findings from another pooled analysis of nine treated patients from trials involving pazopanib were observed [27]. Thus, VEGFR-targeted agents appear to have at least minor degrees of activity.

Combinations of PDGFR-directed agents with cytotoxic chemotherapy, if technically feasible, may be one way forward for primary therapy for such patients. For example, 3G3/olaratumab, a PDGRFB-specific monoclonal antibody, may be worth testing in this diagnosis. Regimens used for relapse of Ewing sarcoma, e.g., cyclophosphamide-topotecan [28], are often used for disease progression refractory to anthracycline-ifosfamide-based therapy (Table 19.1).

Table 19.1 Suggestions for therapy for desmoplastic small round cell tumor

Clinical scenario	Suggested treatment
Initial presentation	Chemotherapy as used for Ewing sarcoma; surgery when feasible (debulking). Treatment with high dose chemotherapy and stem cell rescue, abdominal radiation and intraperitoneal chemotherapy remain investigational; there are no prospective data as of 2016 with olaratumab
Disease progression	Temozolomide-irinotecan; cyclophosphamide-topotecan; VEGFR inhibitors such as pazopanib or sunitinib; trabectedin in countries where it is approved; clinical trials are very much appropriate. The possible use of olaratumab as an anti-fibrotic agent is appealing. There are no data as of 2016 regarding immune checkpoint inhibitors

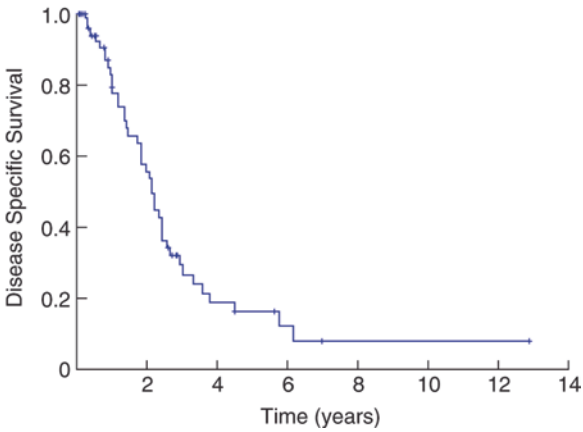

Fig. 19.5 Disease-specific survival for adult patients with a primary diagnosis of desmoplastic small round cell tumor. Most patients present with metastatic disease. MSKCC 7/1/1982–6/30/2010 $n = 69$

19.4 Outcome

Outcome of adult patients primarily treated by us is shown in Fig. 19.5, with few long-term survivors in our experience. Given improved supportive care and imaging, a randomized study may be necessary to confirm the benefit of any new therapy that shows promise.

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Chapter 20
Extraskeletal Myxoid Chondrosarcoma

Extraskeletal myxoid chondrosarcoma (EMC) is a relatively slow growing soft tissue sarcoma that often presents with metastatic disease, typically innumerable round lung nodules of varying sizes that also grow slowly but relentlessly [1, 2]. It is different in all genetic and histopathological aspects from skeletal chondrosarcoma [3]. EMC typically affects people between ages 30 and 60 [1, 4] (Fig. 20.1), and occurs most commonly in the lower extremity (Fig. 20.2). Men are affected more commonly than women, but there does not appear to be a difference in incidence based on race [5]. Tumors present as painless, slow growing multi-lobulated masses, and are soft, gelatinous in consistency, and often hemorrhagic.

20.1 Imaging

Radiology easily demonstrates the primary mass lesion (Fig. 20.3), which is indistinguishable from other sarcomas. However, metastases are usually noted early in the lungs (Fig. 20.4) as innumerable round marble-like lesions, which can develop central necrosis as they increase in size (Fig. 20.5).

20.2 Diagnosis

EMC demonstrates a broad group of morphological patterns, with bland epithelioid to ovale cells arranged in a reticular pattern within a rich myxoid background consistent with expression of chondroitin sulfates (perhaps the only true link to skeletal chondrosarcoma) and relatively infrequent mitoses (Fig. 20.6). Histologic grading remains controversial, some authors suggesting that regardless of morphologic features it should be regarded as a low grade sarcoma. We and others have shown that histologic grade (based on nuclear pleomorphism mitoses, necrosis) correlates with

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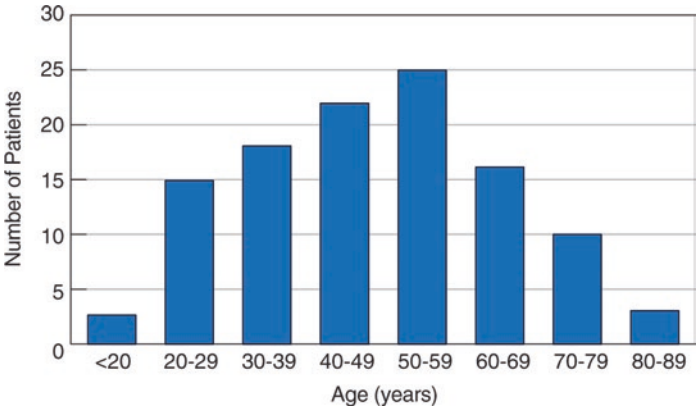

Fig. 20.1 Age distribution for adult patients with extraskeletal myxoid chondrosarcoma. MSKCC 7/1/82–6/30/10 $n = 111$

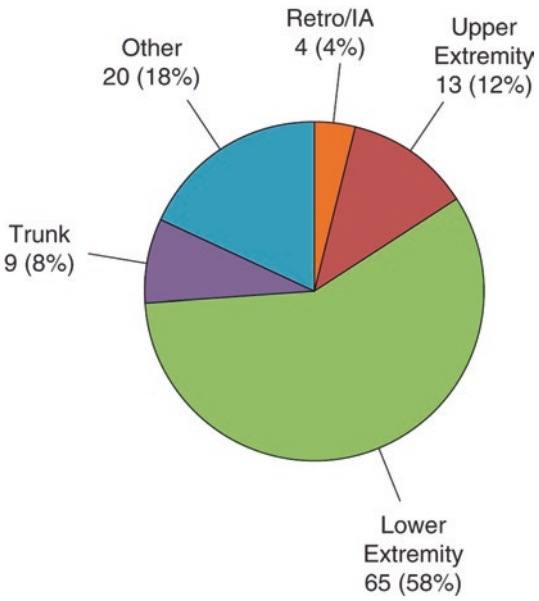

Fig. 20.2 Primary anatomic site for adult patients with extraskeletal myxoid chondrosarcoma. MSKCC 7/1/82–6/30/10 $n = 111$ Retro/IA = retroperitoneal/ intra-abdominal

outcome [3]. In the high grade lesions a predominantly solid, non-myxoid pattern with rhabdoid morphology may occur.

Most EMC contain the characteristic chromosomal translocation t(9;22), resulting in *EWSR1-NR4A3* fusion [6–9]. However other variant fusions have been described especially associated with the high grade non-myxoid and rhabdoid phenotype of EMC [10]. Thus *TAF15-NR4A3* is detected in up to 27 % of cases, while rare cases of other translocation partners with *NR4A3* are also observed. Thus, FISH assay for *NR4A3* gene rearrangements, along with *EWSR1*, should be applied to confirm the EMC diagnosis in challenging cases.

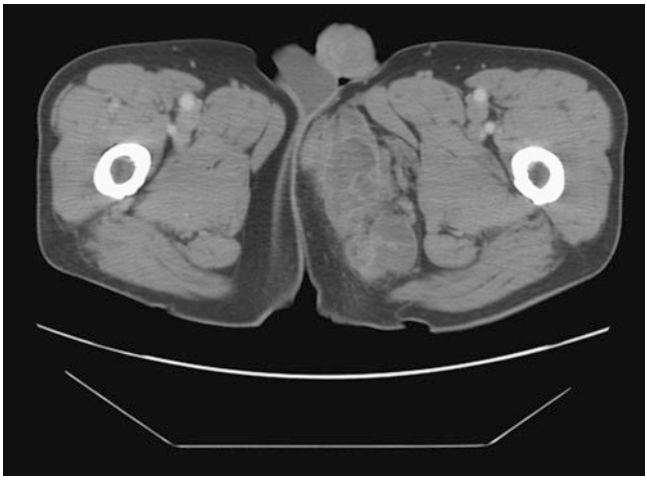

Fig. 20.3 Contrast-enhanced CT image of a peroneal/upper thigh extraskeletal myxoid chondrosarcoma

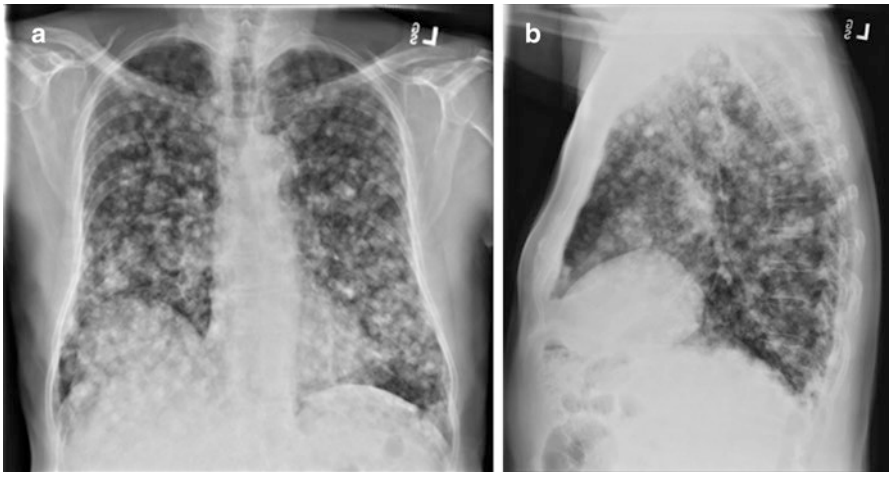

Fig. 20.4 (**a** - AP, **b** - lateral) Chest radiographs of the patient in figure 20.3; there is widespread lung metastasis in the setting of a relatively small primary tumor

20.3 Treatment

Primary therapy is surgery; given the local recurrence risk over many years in the primary site it is not clear that radiation therapy adds to surgery for this particular diagnosis [4] Even with metastatic disease, the primary site is relatively large, and symptom relief could be anticipated for resection of the primary site in that setting

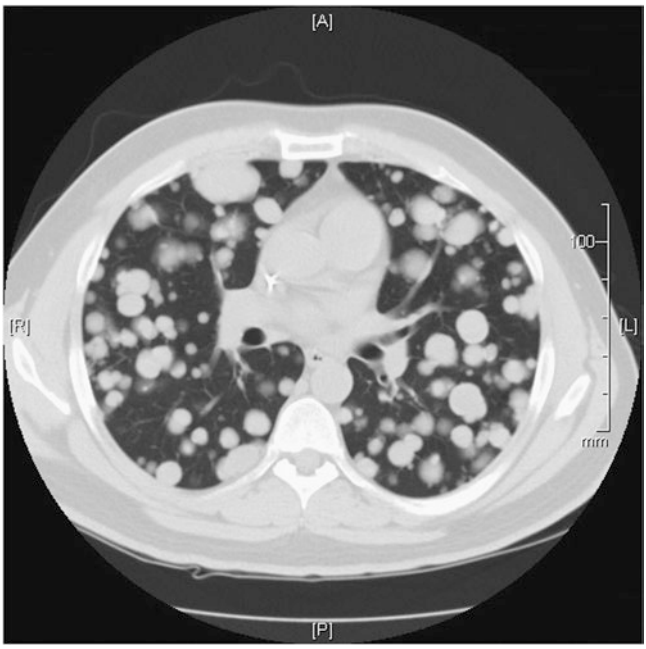

Fig. 20.5 Contrast-enhanced CT image from a patient with metastatic extraskeletal myxoid chondrosarcoma, alive over 5 years after diagnosis of metastatic disease

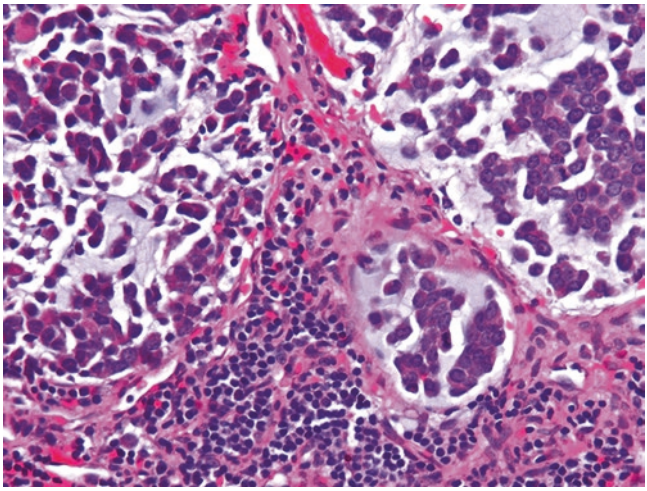

Fig. 20.6 Microscopic appearance of extraskeletal myxoid chondrosarcoma, in this demonstrating tumor metastatic to lymph node, with uniform epithelioid cells with scant eosinophilic cytoplasm, embedded in a myxoid stroma (H&E, ×200)

Table 20.1 Therapeutic recommendations for patients with extraskeletal myxoid chondrosarcoma

Primary disease	Surgical resection; radiation therapy controversial. Resection can be contemplated for larger tumors even in setting of metastatic disease, given the long survival for many patients with metastatic disease; neoadjuvant or adjuvant chemotherapy are not generally used given low response rates in metastatic disease
Recurrent/metastatic disease, first line	Doxorubicin + olaratumab is approved but there are few prospective data
Recurrent/metastatic disease, second line	Pazopanib, sunitinib, or other VEGFR inhibitors. Trabectedin or ifosfamide are considerations. Clinical trials are always appropriate. There are no data regarding immune checkpoint inhibitors in this diagnosis as of 2016

since patients can often live for years despite metastatic disease. For recurrent disease responses have been few [2], making this a diagnosis looking for a targeted agent that is responsible for the survival of EMC cells based on the tumor's specific translocation.

There is no well-defined standard of care for chemotherapy, since standard agents have been largely inactive in our experience [2]. Thus, the presence of an *EWSR1*-containing translocation does not predict for sensitivity to chemotherapy used for Ewing sarcoma. However, the metastases are typically slow growing, and as a result periods of observation are frequently observed. It is conjecture if one form of kinase-directed or DNA modifying agent would be any more effective than chemotherapy. In a different clinical series that is a glass half-full instead of half-empty, Stacchiotti et al. in Milan reported activity of standard doxorubicin-based therapy in EMC, with 4/10 patients with RECIST PR to first-line doxorubicin [11]. She also reported activity of sunitinib in this diagnosis with 6/10 patients with a RECIST PR, similar to anecdotes of multitargeted oral kinase inhibitors in this diagnosis. As a result, VEGFR inhibitors are a very reasonable second-line therapy for this diagnosis [12]. Importantly, the Milanese group also examined kinases found activated in EMC, and found a predominance of RET activation in this tumor. Although the NR4A3-related pathway biological function is largely unknown, it is a potential target for future therapy [13], given its relationship to steroid binding nuclear receptors. Given the understanding that the translocation product may suppress rather than promote gene expression in a general fashion, thus decreasing expression of pro-apoptotic proteins, DNA modifying agents may merit further investigation as well (Table 20.1). Another sarcoma responding in a similar pattern as EMC is alveolar soft part sarcoma; it will be interesting to see if kinases common to both tumors may be targetable.

20.4 Outcome

Local recurrence-free survival for patients with primary adult EMC is shown in Fig. 20.7, and for disease-specific survival in Fig. 20.8. Relatively long-term survival following the development of metastatic disease is not unusual (Fig. 20.5).

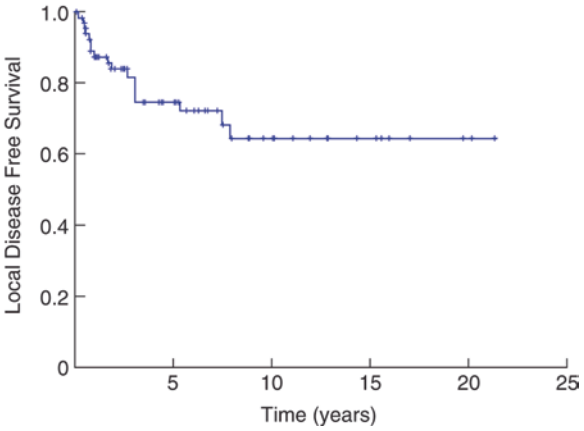

Fig. 20.7 Local recurrence-free survival for adult patients with primary extraskeletal myxoid chondrosarcoma. MSKCC 7/1/82–6/30/2010 $n=71$

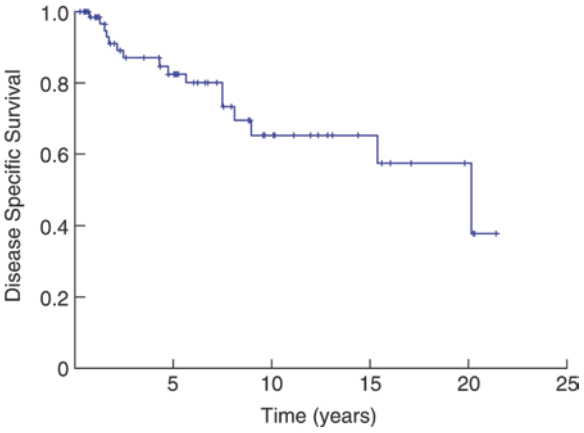

Fig. 20.8 Disease-specific survival for adult patients with primary extraskeletal myxoid chondrosarcoma. MSKCC 7/1/82–6/30/2010 $n=71$

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Chapter 21
Other Uterine Sarcomas

Beyond leiomyosarcoma, uterine sarcomas and tumors that contain "sarcoma" in the name (i.e., carcinosarcoma) are well-recognized biological entities. The non-leiomyosarcoma tumors, (low grade) endometrial stromal sarcoma, high grade endometrial stromal sarcoma, undifferentiated uterine sarcoma, and mixed Müllerian tumors (including carcinosarcoma) are all very different from one another biologically. A new classification of these tumors was undertaken in the 2014 WHO fascicle on gynecological tumors [1, 2]. They are often omitted in discussions of soft tissue pathology as different groups of pathologists generally review such cases in expert centers than those who review soft tissue or bone tumors. Age distribution for adult uterine endometrial stromal tumors is shown in Fig. 21.1.

21.1 Low Grade Endometrial Stromal Sarcoma

Low grade endometrial stromal sarcoma (LGESS) resembles proliferating endometrial stroma, but a distinct malignancy compared to its benign relative, endometrial stromal nodule (ESN). LGESS is relatively indolent, but can be associated with locoregional (Fig. 21.2) as well as lung metastatic disease (Fig. 21.3) over the course of many years (not uncommonly a decade or more) in as many as a third of patients [3, 4]. It is the one sarcoma in which hormonal therapy reproducibly controls disease in a manner not dissimilar from estrogen receptor positive (ER+) breast adenocarcinoma. LGESS is usually both ER+ and progesterone receptor positive (PR+).

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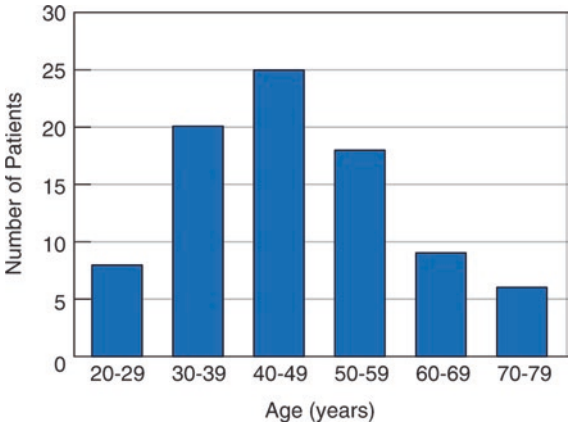

Fig. 21.1 Age distribution of adult patients with uterine endometrial sarcomas, all grades. MSKCC 7/1/1982–6/30/2010 $n = 86$

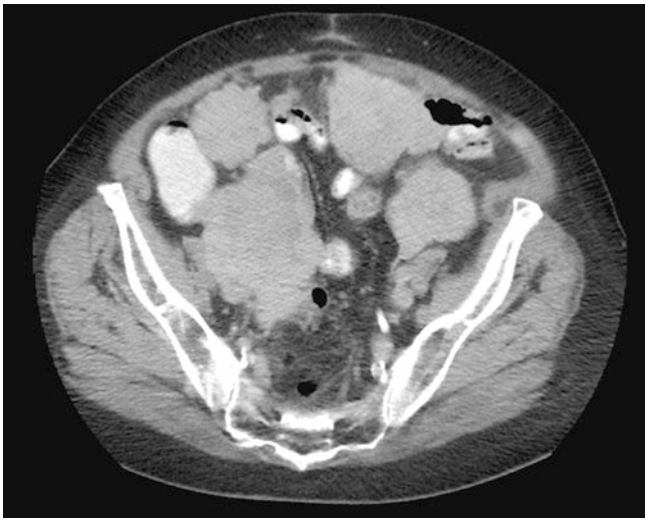

Fig. 21.2 Intravenous and oral contrast-enhanced CT image of a 71-year-old woman with metastatic endometrial stromal sarcoma

21.1.1 Diagnosis

Like many endometrial stromal nodules, LGESS usually contains a translocation t(7;17)(p15;q21) involving *JAZF1* at 7p15 and *SUZI2* at 17q21 as the most common change, although t(6;7) and t(6;10) and others have been described, more since the era of tumor RNA sequencing arrived [5–9]. What has been called in the past high grade endometrial stromal sarcoma may represent a separate entity, and distinct from what is now termed undifferentiated endometrial sarcoma, and thus is a diagnosis in transition, based on the genomics of these tumors (see below). These findings were incorporated into the WHO tumor fascicle on gynecological tumors from 2014 [10].

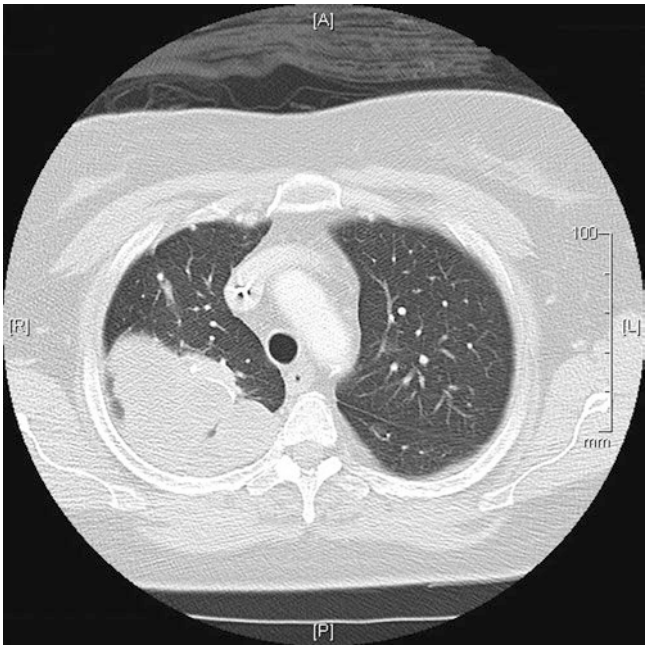

Fig. 21.3 Intravenous contrast-enhanced CT image of metastatic disease in a patient with undifferentiated endometrial sarcoma

21.1.2 Treatment

Primary treatment is hysterectomy. Small studies and analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database have examined if lymphadenectomy improved survival, since nodes are positive in 5–10 % of patients with ESS. No survival advantage was noted, so it is difficult to routinely recommend the more extensive operation [11–14]. Radiation did not appear to affect clinical outcome and is generally not administered for patients with adequate primary surgery [11].

There are no randomized data to suggest the utility of hormonal therapy in the adjuvant setting for ESS [15–17], oophorectomy or GnRH agonists have activity as other means to affect estrogen levels in ESS, and patients who undergo total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) as primary therapy may contaminate any benefit seen from adjuvant therapy.

For metastatic disease, progestins and antiestrogens are effective and usually relatively less toxic systemic therapy than chemotherapy, which also has activity [18–20]. It is also worth noting that given the slow evolution of disease in most patients it is worthwhile considering surgery in the metastatic disease in selected patients (Table 21.1).

Table 21.1 Treatment recommendations for low grade endometrial stromal sarcoma

Clinical scenario		Comments
Adjuvant systemic therapy		None; no clear benefit of adjuvant systemic therapy given long evolution of disease and effects of oophorectomy or other surgical procedures; for large bulky tumors, neoadjuvant hormonal therapy can be contemplated
Metastatic disease	First line	Progestins, e.g., medroxyprogesterone, megestrol; oophorectomy or GnRH agonists in selected patients
	Second line	Antiestrogens, e.g., aromatase inhibitors
	Third line	Anthracyclines + olaratumab; ifosfamide; clinical trial. In particular, given hormone sensitivity, CDK4 inhibitors may be useful, in analogy to hormone receptor positive breast cancer. Immune checkpoint inhibitors are untested as of 2016

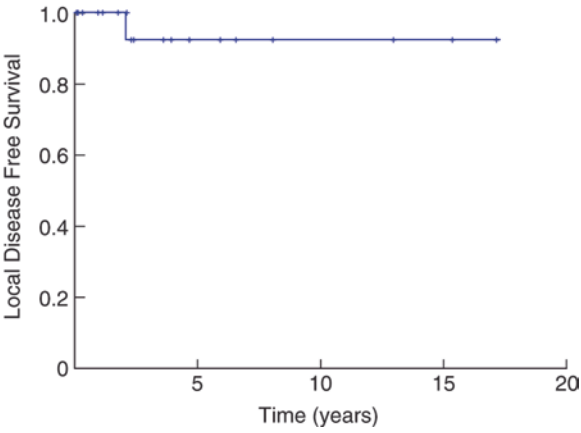

Fig. 21.4 Local disease-free survival for adult patients with primary uterine endometrial stromal sarcoma, all grades. MSKCC 7/1/1982–6/30/2010 $n = 29$

21.1.3 Outcome

Outcome for local recurrence and disease-specific survival for primary endometrial stromal tumors are shown in Figs. 21.4 and 21.5.

21.2 High Grade Endometrial Stromal Sarcoma

High grade endometrial stromal sarcoma (HGESS) is now accepted as a separate entity from low grade endometrial stromal sarcoma, and is further differentiated from undifferentiated uterine sarcoma (UUS), largely based on mitotic rate (greater than LGESS) and cytomorphology, but now also by their genomic profile. HGESS is usually estrogen receptor negative (ER−) and progesterone receptor negative (PR−), which differentiates HGESS from LGESS (Fig. 21.6). Furthermore, HGESS

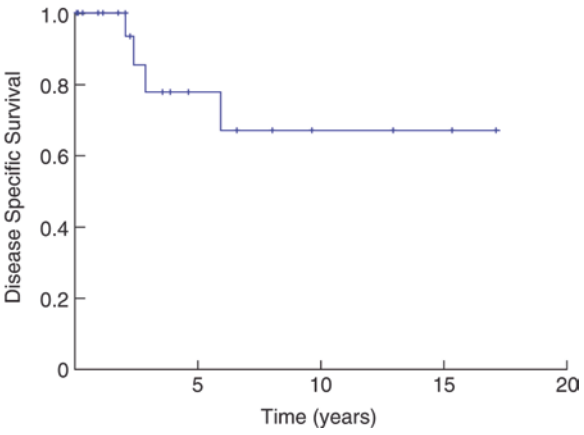

Fig. 21.5 Disease-specific survival for adult patients with primary uterine endometrial stromal sarcoma, all grades. MSKCC 7/1/1982–6/30/2010 $n = 29$

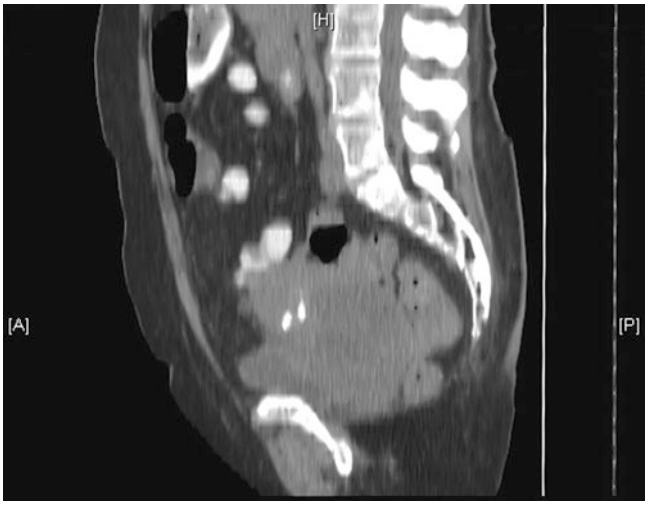

Fig. 21.6 CT image of a patient with a primary undifferentiated endometrial sarcoma, with extensive local extension

does not appear to contain the translocations typically observed in LGESS [21]. A collaborative effort has identified group of translocations involving *YWHAE*, which hopefully will impact therapy for this aggressive sarcoma [22]. The t(10;17)(q22;p13) translocation, resulting in *YWHAE-NUTM2A/B* fusions, was associated with a high grade round cell morphology and aggressive clinical behavior compared to JAZF1-positive LGESS [23]. However, in a subset of these high grade lesions in addition to the undifferentiated round cell areas, there was a cytologically bland and mitotically weakly active spindle cell component, which was diffusely positive for ER, PR, and CD10, in contrast to the round cell areas, which were negative. This latter finding suggests the possibility of a histologic progression from an HGESS to

Table 21.2 Treatment suggestions for high grade endometrial stromal sarcoma

Clinical scenario		Comments
Adjuvant chemotherapy		Not recommended, since the response rate in the metastatic setting is low despite the tumor's aggressive nature
Metastatic disease	First line	Minor responses have been observed with ifosfamide-based therapy; doxorubicin + olaratumab is untested as of 2016, though doxorubicin has little activity as a single agent
	Second line	Clinical trials are most appropriate; IGF1R inhibitors could have minor activity, as may drugs impacting epigenetics of the tumor subtype. There are not enough data with any specific chemotherapy to be sanguine about any specific systemic therapeutic. Immune checkpoint inhibitors are untested as of 2016

a UUS, which is borne out by the idea that UUS have highly aneuploid karyotypes. Of note, the same *YWHAE-NUTM2A/B* translocation was reported in the clear cell sarcoma of kidney [24].

In our experience, ifosfamide has at best modest activity in this disease, but the response rate is low, making it difficult to recommend adjuvant chemotherapy for women with this diagnosis [20] (Table 21.2). We observed relatively long-lasting stable disease in one patient treated with an IGF1 receptor inhibitor, a finding we hope will be explored further, since YWHAE, a 14-3-3 protein, can interact with IGF1R-associated protein IRS1.

21.2.1 Outcome

An analysis utilizing the prior 2003 WHO classification of three endometrial stromal sarcoma (ESS) subtypes, including noninvasive, invasive low grade, and invasive undifferentiated [25], indicated 5- and 10-year recurrence-free survival for 91 invasive ESS was 82 and 75 %. Necrosis was an important prognostic predictor for overall survival, with 10-year survival of 89 % in the absence of necrosis and 49 % in those with prominent necrosis. By defining ESS low grade as mild atypia with no necrosis, and undifferentiated as moderate/severe atypia present or necrosis present, disease-specific survivals were 98 vs. 48 %. Updated data for the new stratification of uterine sarcomas are being collected.

21.3 Undifferentiated Uterine Sarcoma (UUS)

Undifferentiated uterine sarcoma (UUS) is a diagnosis evolving from the increasing genomic analysis of uterine sarcomas. It is clear that UUS have a distinct cytomorphology, and are the most aneuploid of these tumors, with copy number changes found on all chromosomes, with the greatest number of changes found on

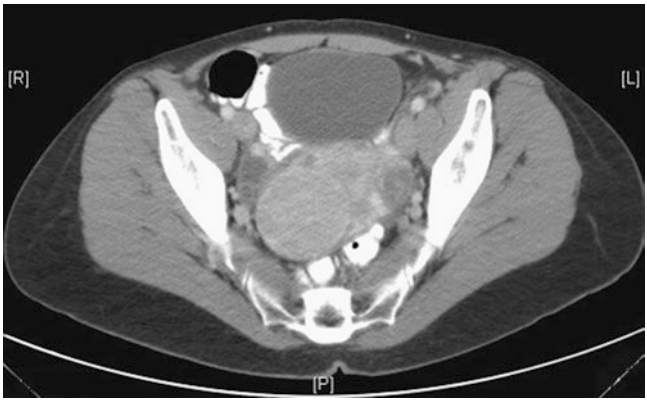

Fig. 21.7 Intravenous contrast-enhanced CT scan of a patient with a 6 cm PEComa of the uterus

chromosomes 1q, 2q, 13 and gains of 1q and 17p [26]. Primary treatment is the same for other uterine sarcomas, but the risk of metastatic disease is higher than other uterine sarcomas. However, this subset of a rare tumor can respond to systemic therapy, with responses documented to both doxorubicin-based therapy and gemcitabine-docetaxel [27]. The existence of these entities confirms that sarcomas are different from carcinomas of the gynecological tract and that agents other than carboplatin and paclitaxel have to be employed for these unusual tumors.

21.4 PEComas

Perivascular epithelioid cell tumors (PEComas) are a relatively newly coined diagnostic category of tumors having hybrid smooth muscle and melanocytic differentiation. The uterus is among the most common sites of origin of this rare tumor (Fig. 21.7). Uterine PEComas, similar to other anatomic sites, have either mutations in *TSC2* or translocations involving *TFE3* [28]. In contrast with other sites, a small subset of uterine PEComas harbor *RAD51B* fusions, which may occur in association with *TSC2* mutations [28].

21.5 Uterine Carcinosarcomas and Other Malignant Mixed Müllerian Tumors

Though carcinosarcomas appear to represent divergent differentiation of what is at heart a uterine carcinoma, they are encountered frequently enough in a sarcoma practice to be mentioned here. The age distribution for adult carcinosarcoma is shown in Fig. 21.8. Mixed Müllerian tumors have elements of both stroma and

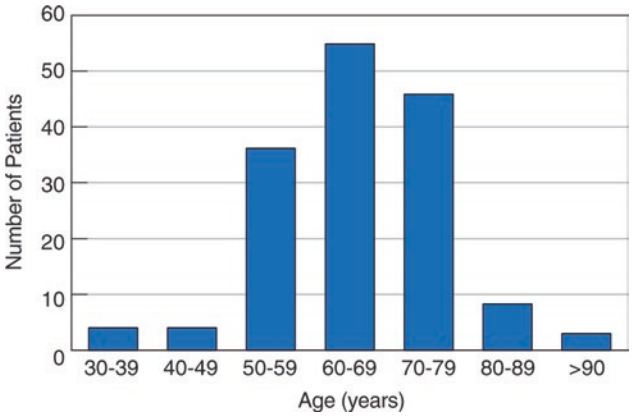

Fig. 21.8 Age distribution of adult patients with uterine carcinosarcoma (malignant mixed Müllerian tumors). MSKCC 7/1/1982–6/30/2010 $n = 156$

epithelium, and include adenofibroma, adenosarcoma, carcinofibroma, and carcinosarcoma. While adenofibroma is benign, the other tumors are malignancies. Carcinosarcoma, which presents in postmenopausal women as uterine bleeding, may represent a uterine carcinoma with divergent differentiation towards a sarcoma lineage. CA125 is often elevated in patients with carcinosarcoma and may serve as a tumor marker. Carcinosarcoma is more aggressive overall compared to uterine carcinomas, with frequent metastasis to both peritoneum and lung, and thus appears to be clinically distinct from uterine carcinoma.

No recurrent genetic event has been observed in carcinosarcoma, and the tumors are generally aneuploid. Gene expression analysis of uterine carcinomas showed greater kinship with uterine sarcomas than uterine carcinoma, despite the higher potential for metastasis as the carcinomatous part of the carcinosarcoma over time. In one study of carcinosarcomas vs. uterine sarcoma vs. endometrial carcinomas, chromosome 19q13.1 appeared amplified in carcinosarcomas, which include the *TGFB1* locus, a gene involved in so-called "epithelial mesenchymal transition" (EMT) observed in some carcinomas. Essentially by definition, carcinosarcoma is a cancer demonstrating EMT, or at least a dual phenotype not observed in most carcinomas [29].

Primary therapy for carcinosarcoma is TAH-BSO, and proper gynecological staging with lymphadenectomy, omentectomy, and testing of peritoneal cytology. Both local–regional relapse and metastatic spread of carcinosarcoma are common, which has raised the question of the utility of abdominal radiation and systemic chemotherapy in the adjuvant setting. A randomized study of adjuvant radiation for early stage uterine sarcomas and carcinosarcomas showed better local control but no improvement in overall survival. Conversely, a retrospective analysis of a large number of patients treated with radiation suggested possible clinical benefit from adjuvant irradiation [30, 31].

Table 21.3 Treatment suggestions for undifferentiated uterine sarcoma

Clinical scenario		Comments
Adjuvant chemotherapy		Not recommended, since the response rate in the metastatic setting is low. Given the activity of systemic therapy in metastatic disease and high risk of high mortality rate from this sarcoma subtype, adjuvant therapy as used for metastatic disease cannot be faulted
Metastatic disease	First line	Doxorubicin + olaratumab, given futility of other chemotherapy options in the past; ifosfamide can also be contemlated
	Second line	Gemcitabine + docetaxel, ifosfamide or trabectedin where available. Clinical trials; immune checkpoint inhibitors are untested as of 2016

A phase III GOG study showed that adjusting for stage and age, the recurrence rate was 21 % lower for patients who received ifosfamide-cisplatin adjuvant therapy over whole abdominal radiation for stage I–IV carcinosarcoma, although the crude data showed no significant difference in the recurrence rate [32]. While thus a reasonable standard of care in the adjuvant setting, cisplatin-ifosfamide is obviously a toxic regimen, and careful patient selection for such treatment is necessary.

Other agents active in carcinosarcoma include carboplatin and taxanes. For example, carboplatin and paclitaxel were tested in stage III and IV disease (in 46 evaluable patients), with a RECIST CR rate of 13 % and PR rate 41 %, for an overall response rate of 54 %. The GOG conducted a randomized trial comparing paclitaxel plus carboplatin to paclitaxel plus ifosfamide. The results from this trial will help answer the question of whether ifosfamide is needed in carcinosarcoma. For patients with stage I–II disease, a combination of multiagent chemotherapy and intravaginal brachytherapy has been shown to be feasible [33].

For metastatic disease, agents not used in the adjuvant setting can be considered. Cisplatin, ifosfamide, carboplatin, and paclitaxel all appear to have some activity. Topotecan has modest activity in metastatic disease [34], as may doxorubicin or gemcitabine as a single agent. The combination of gemcitabine and docetaxel [35] has minor activity. Imatinib, sorafenib, pazopanib, and thalidomide are all largely inactive against carcinosarcoma from phase II studies. Immune checkpoint inhibitors are untested in this diagnosis as of 2016; the National Cancer Institute is including carcinosarcomas in the list of rare cancers they will treat with nivolumab and ipilimumab in a coming study (Table 21.3).

21.6 Outcome

Outcome for primary adult carcinosarcoma by local and disease-specific survival are shown in Figs. 21.9 and 21.10. Outcome, as with other uterine malignancy, is highly stage dependent, with curative surgery with or without adjuvant therapy, and

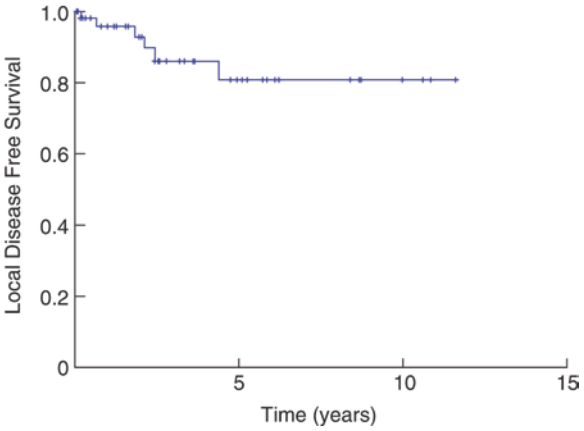

Fig. 21.9 Local disease-free survival for adult patients with primary uterine carcinosarcoma (mixed malignant Müllerian tumor). MSKCC 7/1/1982–6/30/2010 $n=56$

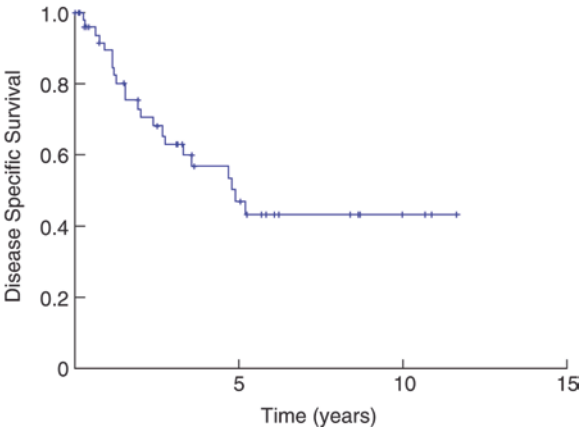

Fig. 21.10 Disease-specific survival for adult patients with primary uterine carcinosarcoma (mixed malignant Müllerian tumor). MSKCC 7/1/1982–6/30/2010 $n=56$

poor long-term prognosis in advanced or metastatic disease. For the uncommon patient with uterine carcinosarcoma arising in the setting of hereditary nonpolyposis colorectal cancer, in which DNA mismatch repair defects occur, immunotherapy is a consideration given impressive responses of colorectal cancer to immune checkpoint inhibitors in this setting (Table 21.4).

Table 21.4 Treatment recommendations for uterine carcinosarcomas and other malignant mixed Müllerian tumors

Clinical scenario		Comments
Primary therapy		For completely resected disease, cisplatin-ifosfamide is superior to whole abdominal radiation therapy, but risk is still high for relapse; carboplatin-paclitaxel is used by many clinicians instead of the more toxic doublet
Metastatic disease	First line	Topotecan, platinum agents, taxanes, combinations
	Second line	Clinical trials, gemcitabine or combinations. Pazopanib has negligible activity. Immune checkpoint inhibitors are untested as of 2016, but are appealing given mismatch repair defects seen in some uterine carcinomas

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Chapter 22
Extraskeletal Osteogenic Sarcoma

Osteogenic sarcoma can arise in soft tissue although it is much more commonly observed as a primary bone tumor. There is debate as to whether extraskeletal osteogenic sarcoma (ESOS) should be managed as a soft tissue or a bone tumor. Biologically, the tumor is typically the osteoblastic subtype, and can arise spontaneously or after irradiation.

Age distribution for adult patients over age 16 is shown in Fig. 22.1 and site distribution in Fig. 22.2. The lower extremity is the dominant site.

22.1 Imaging

Primary ESOS is often multilobulated in appearance and has evidence of calcification, as the tumor name implies (Figs. 22.3, 22.4, and 22.5). Bone invasion occurs (Fig. 22.6). Satellite lesions and soft tissue metastatic spread may be more common than with other soft tissue sarcoma subtypes.

22.2 Diagnosis

Microscopic pathology of ESOS lesions shows highly pleomorphic cells in a background of lace-like osteoid matrix, which is the basis for the calcification seen in masses radiographically (Fig. 22.7). As with other osteosarcomas, ESOS is aneuploid without defining molecular changes save for mutations in DNA repair genes such as *TP53*.

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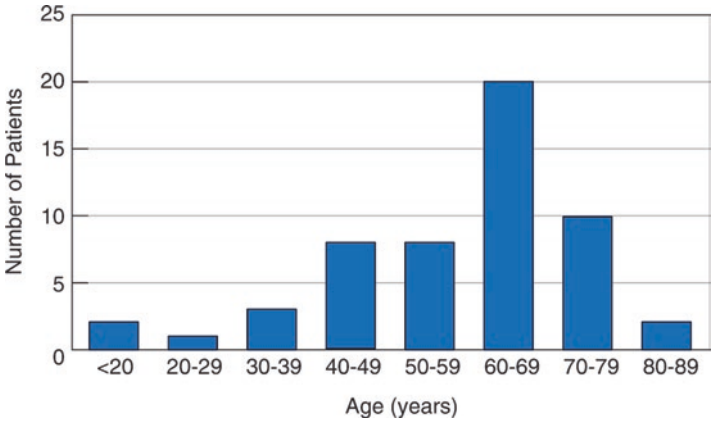

Fig. 22.1 Age distribution of adult patients with primary extraskeletal osteosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 54$

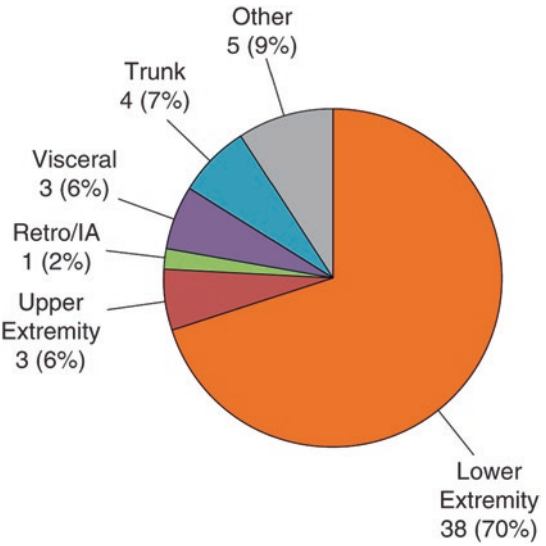

Fig. 22.2 Site distribution of adult patients with primary extraskeletal osteosarcoma. MSKCC 7/1/1982–6/30/2010 $n = 54$ Retro/IA = retroperitoneal/ intra-abdominal

22.3 Treatment

As with osteogenic sarcoma of bone, primary resection of ESOS is paramount. It is not clear if adjuvant irradiation or chemotherapy is helpful to improve the poor cure rate in adults. A number of patients in one of the few series published in adults received chemotherapy for metastatic disease with a low response rate, suggesting that adjuvant chemotherapy is not helpful for people with this diagnosis [1]. However, a summary of patients treated with ESOS on a pediatric clinical trial of

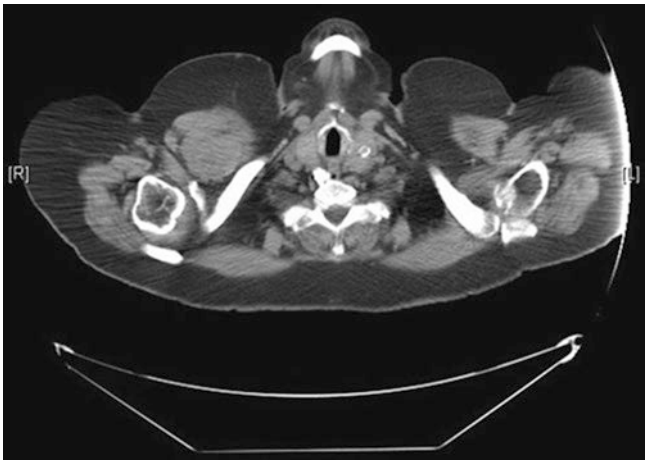

Fig. 22.3 Non-contrast CT image of a right subpectoral extraskeletal osteosarcoma

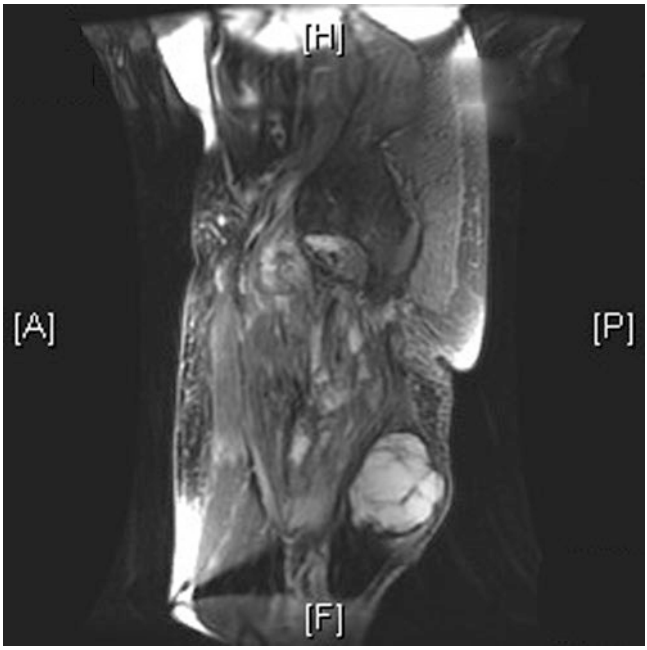

Fig. 22.4 T1-weighted MRI image of a left thigh extraskeletal osteosarcoma

osteogenic sarcoma of bone fared better than historical controls [2]. The topic remains unsettled as the event-free survival for the patients in these two studies was 56 % in the German study (who received adjuvant chemotherapy) and 47 % in the MD Anderson series (who did not receive adjuvant chemotherapy).

In the metastatic setting, agents active in osteosarcoma or soft tissue sarcoma can be utilized but the response rate is low (Table 22.1).

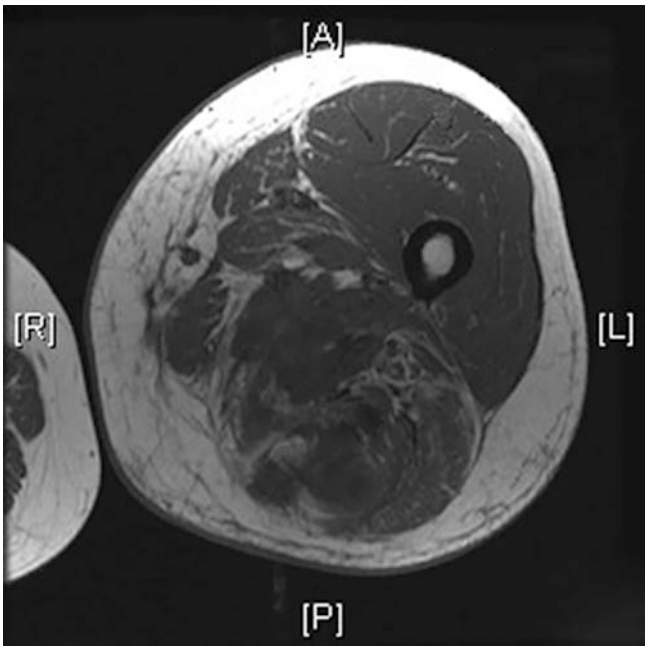

Fig. 22.5 T1-weighted MRI image of a left thigh extraskeletal osteosarcoma

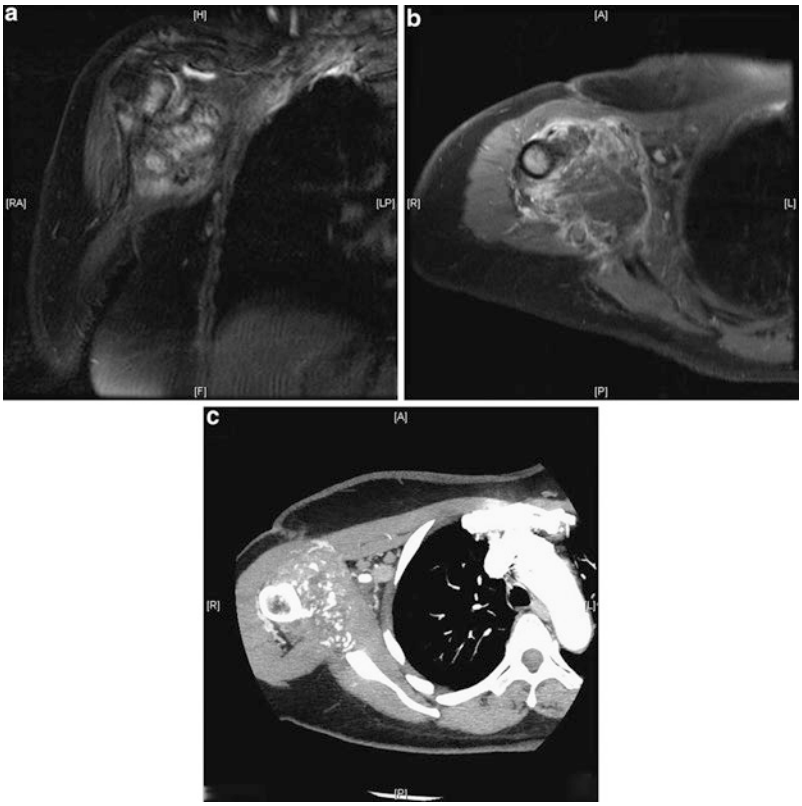

Fig. 22.6 (**a**–**c**) Extraskeletal osteogenic sarcoma bone invasion

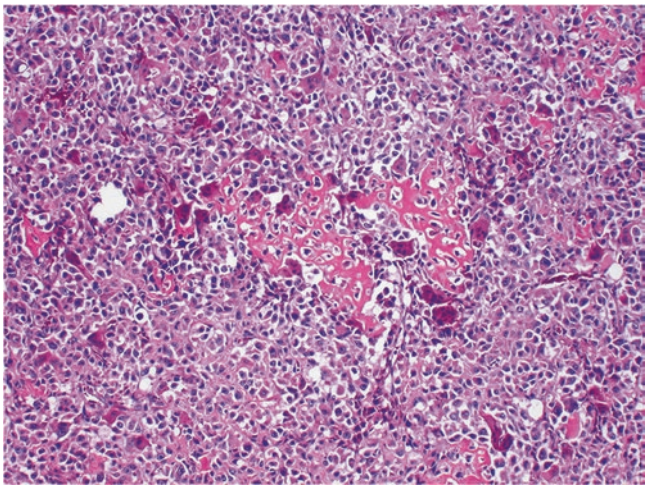

Fig. 22.7 Microscopic H&E image of high grade extraskeletal osteosarcoma showing lace-like osteoid matrix deposition by highly pleomorphic sarcoma cells

Table 22.1 Systemic therapy recommendations for patients with extraskeletal osteogenic sarcoma

Clinical scenario		Comments
Neoadjuvant/ adjuvant chemotherapy		Controversial; one study indicated patients fare better compared to historical controls with use of regimens used for osteosarcoma of bone
Metastatic disease	First line	Doxorubicin + olaratumab or ifosfamide-based therapy, if not used previously
	Second line	Gemcitabine or combinations; pazopanib; clinical trials are always appropriate. There are no data on immune checkpoint inhibitors in extraskeletal osteosarcoma as of 2016

22.4 Outcome

Local recurrence for adult patients treated primarily at MSKCC is shown in Fig. 22.8, and for those patients disease-specific survival in Fig. 22.9. Patient and tumor characteristics are summarized in Table 22.2. The 32 patients who underwent primary surgery at MSKCC had a 3-year disease-specific survival of 59% and 3-year event-free survival of 56%. Patients with superficial tumors had a significantly lower incidence of death due to disease at 3 years (Table 22.3) (Fig. 22.10) [3].

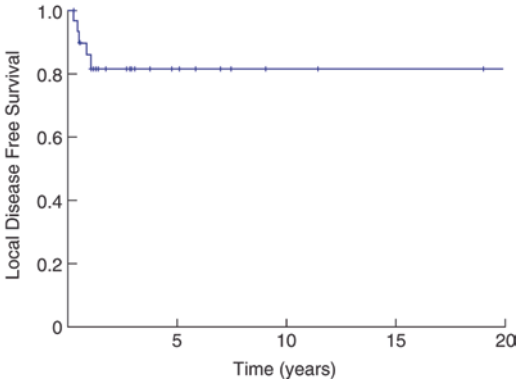

Fig. 22.8 Local disease-free survival of adult patients with primary extraskeletal osteosarcoma. MSKCC 7/1/1982–6/30/2010 $n=33$

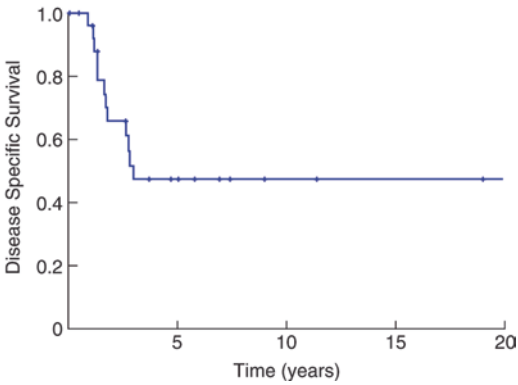

Fig. 22.9 Disease-specific survival of adult patients with primary extraskeletal osteosarcoma. MSKCC 7/1/1982–6/30/2010 $n=33$

Table 22.2 Summary of patient demographics and tumor characteristics

Demographics and characteristics	All patients ($n=53$)	Patients with localized disease ($n=42$)
Patient age[a] (year)	64	64.5
Patient sex[b]		
Male	23 (43)	19 (45)
Female	30 (57)	23 (55)
Site of primary tumor[b]		
Upper extremity	6 (11.3)	6 (14.3)
Lower extremity	41 (77.4)	31 (73.8)
Axial	6 (11.3)	5 (11.9)
Tumor grade[b]		
Low	2 (3.8)	2 (4.8)
High	51 (96.2)	40 (95.2)
Tumor size[b]		
≤5 cm	13 (24.5)	11 (26.2)
>5 to ≤10 cm	20 (37.7)	14 (33.3)
>10 cm	20 (37.7)	17 (40.5)
Tumor depth[b]		
Superficial	11 (21)	10 (24)
Deep	42 (79)	32 (76)

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[a]The value is given as the median

[b]The values are given as the number of patients, with the percentage in parentheses

Table 22.3 Log-rank test comparing event-free survival rates in patients with localized extraskeletal osteosarcoma

Variable	No. of patients	No. of events	Three-year event-free survival rate[a]	*P* value
All patients	42	18	0.50 (0.36–0.70)	–
Patient age				0.09
Fifty years or less	11	2	0.75 (0.50–1.00)	
More than 50 years	31	16	0.42 (0.27–0.67)	
Patient sex				0.73
Female	23	10	0.49 (0.30–0.78)	
Male	19	8	0.53 (0.34–0.83)	
Site of primary tumor				0.12
Axial	5	3	NA[b]	
Extremity	37	15	0.54 (0.39–0.75)	
Tumor grade				0.93
Low	2	1	0.50 (0.13–1.00)	
High	40	17	0.50 (0.36–0.71)	
Tumor size				0.26
≤5 cm	11	3	0.70 (0.47–1.00)	
>5 cm	31	15	0.43 (0.27–0.68)	
Tumor depth				0.03
Superficial	10	1	0.89 (0.71–1.00)	
Deep	32	17	0.38 (0.23–0.63)	
Resection margin status				
R0	35	13	0.57 (0.41–0.78)	0.03
R1	7	5	0.17 (0.03–1.00)	
Patient history of radiation therapy				0.08
No	39	16	0.53 (0.38–0.73)	
Yes	3	2	NA[b]	
Treatment type				0.83
Surgery alone	19	7	0.55 (0.34–0.88)	
Surgery and chemotherapy	5	1	0.80 (0.52–1.00)	
Surgery, radiation therapy, and chemotherapy	8	4	0.50 (0.25–1.00)	
Surgery and radiation therapy	10	6	0.36 (0.15–0.87)	

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[a]The values are given as the 3-year event-free survival rate, with the 95% confidence interval in parentheses

[b]*NA* not available. These values are not estimable for axial sites and those with prior radiation therapy because the last event occurred before year 3

All recurrences and deaths from disease occurred before 5 years of follow-up. These data are consistent with the findings from the MD Anderson and European series, and involved a group of patients who largely did not receive adjuvant chemotherapy. These data continue to call into question any benefit of adjuvant chemotherapy for this aggressive sarcoma subtype.

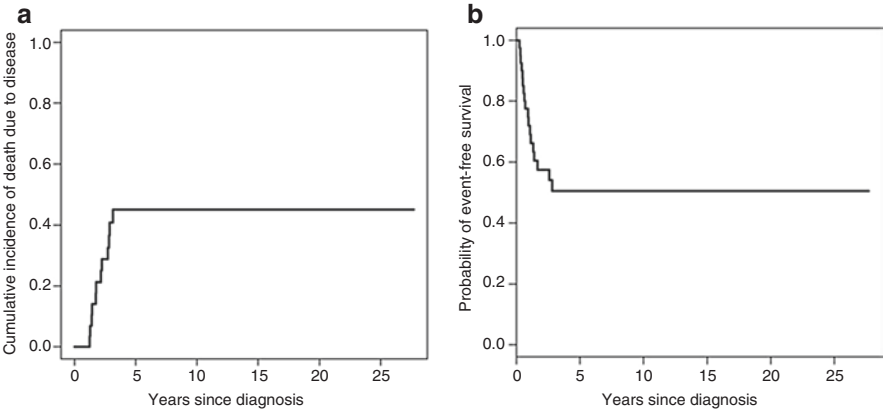

Fig. 22.10 Kaplan–Meier curves showing cumulative incidence of death due to disease (**a**) and event-free survival (**b**) for 42 patients with localized extraskeletal osteosarcoma. The 3-year cumulative incidence of death due to disease was 39 %, and the median event-free survival was 45.8 months. With permission from: Choi LE, Healey JH, Kuk D, et al. *J Bone Joint Surg Am* 2014; 96(1):1–8

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Chapter 23
Sustentacular Tumors of Lymph Tissue

As proof that cancers can occur in essentially any cell type, antigen-presenting cells (e.g., dendritic cells or Langerhans cells) can form cancers. Since these tumors can arise from lymph nodes, but do not arise from lymphocytes themselves, they are sometimes termed sarcomas. Other pathologists use the more noncommittal term "tumor" instead of "sarcoma" in this context. If anything, sustentacular tumors of lymphatic tissue represent the correct use of the term "histiocytic sarcoma," as opposed to malignant fibrous histiocytoma (MFH, now termed undifferentiated pleomorphic sarcoma [UPS]), which are not composed of histiocytes, as are these tumors.

Dendritic cell tumors, also termed reticulum cell tumors, can arise in either lymph nodes or extranodal lymphatic tissue. Follicular dendritic cell tumors (FDCT) are tumors that affect the follicular dendritic cells that present antigens to B cells, and as a result arise in germinal centers of lymph nodes. Conversely, interdigitating reticulum cell tumors (IDRCT) are conventional dendritic cells derived from Langerhans cells that migrate to lymph nodes, where they present antigen to T cells, and thus arise in the cortex of the lymph node. Langerhans cell histiocytoses (LCH) can arise in skin, lung, and bone, and represent a separate class of tumors associated with a variety of pathologies, such as lung infiltrates and pituitary dysfunction.

Characteristic markers of these rare tumors are indicated below for reference purposes (Table 23.1). Age and site distribution for these rare tumors presenting as primary lesions in adults are shown in Figs. 23.1 and 23.2.

23.1 Follicular Dendritic Cell Tumor and Interdigitating Reticulum Cell Tumor

Reviews of series of these patients are helpful guides to FDCT and IDRCT [1–3]. Of the two diagnoses, IDRCT is the more aggressive, with inferior outcomes [1–5]. FDCT arise in neck lymph nodes more than in other sites such as abdomen; if

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Table 23.1 Immunohistochemical characteristics of sustentacular tumors of lymph tissue

Tumor type	CD21	CD35	S100	CD1a	Clusterin	CD11c	CD68	Desmin
FDCT	(+)	(+)	Occasionally (+)	(−)	(+)	(−)	(−)	(−)
IDRCT	(−)	(−)	(+)	Variable, usually (−)	(−)	(+)	(−)	(−)
LCH	(−)	(−)	Varies	(+)	(−)	(+)	(−)	(−)
True histiocytic sarcoma	(−)	(−)	Varies	(−)	(−)	(+)	(+)	(−)

FDCT follicular dendritic cell tumor, *IDRCT* interdigitating reticulum cell tumors, *LCH* Langerhans cell histiocytoses

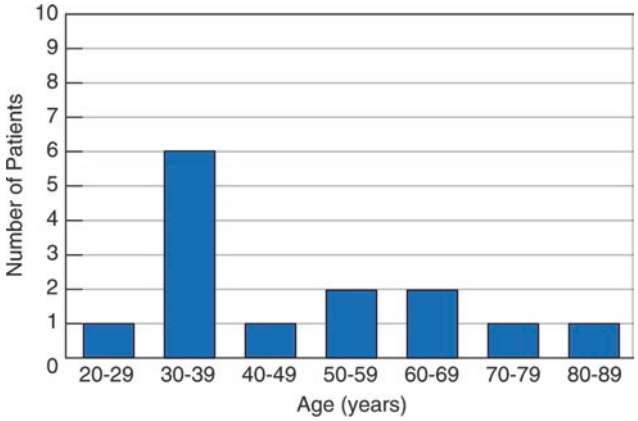

Fig. 23.1 Age distribution of adult patients with primary sustentacular malignancies of lymph nodes. MSKCC 7/1/1982–6/30/2010 $n = 14$

limited in size, surgery can render patients disease free. In the series from MSKCC, the abdominal cavity was the most common site of FDCT ($n = 31$ cases), while head and neck was more common for IDRCT and extremities for true histiocytic sarcoma [5]. Underscoring the relationship between FDCT and Langerhans cell histiocytosis (LCH) [3], FDCT may contain the canonical V600E mutation in *BRAF* in a fraction of cases (5/27 examined in one series), suggesting BRAF and MEK inhibitors in their therapy [6]. There is presently no characteristic genetic change known in IDRCT. Clusterin, gamma-synuclein, CXCL13, and podoplanin appear to be markers for FDCT; EGFR may be activated in these tumors as well, with potential therapeutic implications [3, 7–9].

PET scan can be helpful in delineating other sites of tumor as these tumors demonstrate some features of Hodgkin lymphoma and some features of sarcomas, with spread to other local regional lymph nodes as well as to lung and other sites.

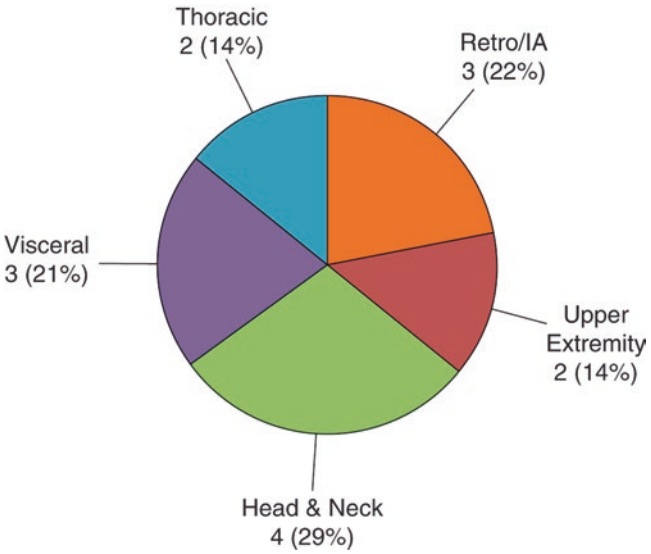

Fig. 23.2 Site distribution of adult patients with sustentacular malignancies of lymph nodes. MSKCC 7/1/1982–6/30/2010 $n = 14$ Retro/IA = retroperitoneal/intra-abdominal

Since they are confused with non-Hodgkin lymphomas (NHL), it is not surprising that anthracycline-based regimens such as CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone) have been used for both FDCT and IDRCT, with only hints of success. In our experience, responses have been modest and much less pronounced than that seen for NHL or Hodgkin lymphoma. In the MSKCC series, adjuvant chemotherapy was not associated with improved survival [5]. For recurrent disease therapy all bets are off as to active agents; anthracycline-containing regimens have yielded little in terms of durable responses. The role of high dose therapy with stem cell support for patients with these diagnoses is unknown. We have also observed anecdotes of patients with responses to sorafenib and other multi-targeted tyrosine kinase inhibitors. The target in other FDCT and IDRCT is unknown but could be CSF1, FLT3, or others (Table 23.2).

23.2 True Histiocytic Sarcoma

Like FDCT and IDRCT, true histiocytic sarcoma is a tumor of antigen-presenting cells, in this case a monocyte-derived cell. It tends to occur in the skin and bowel, where in the former case Langerhans cell tumor is in the differential diagnosis, while in the latter case FDCT and IDRCT are both in the differential diagnosis [10–12]. In this respect, we are concerned that M5 monocytic leukemia has to be considered in the differential diagnosis as well, and more complete evaluation for leukemia is warranted (e.g., bone marrow analysis). For these rare diagnoses with

Table 23.2 Systemic therapy recommendations for patients with follicular dendritic cell tumor (dendritic reticulum cell tumor [FDCT]) and interdigitating reticulum cell tumor (IDRCT)

Clinical scenario		Comments
Adjuvant therapy		There is no recognized active adjuvant program after surgery for limited primary disease
Metastatic disease	First line	FDCT: BRAF and/or MEK inhibitors in those tumors with *BRAF* or *ARAF* mutations
		IDRCT: anthracycline + olaratumab is technically approved but there are no prospective data; alkylating agents; responses are uncommon
	Second line	Clinical trial; pazopanib; anthracyclines, alkylating agents may have activity among cytotoxic agents. At present, these seem to be tumor types in which genomic profiling is useful. In analogy to B cell lymphomas, immune checkpoint inhibitors are an appealing option, but are untested as of 2016

Table 23.3 Systemic therapy recommendations for patients with true histiocytic sarcoma

Clinical scenario		Comments
Adjuvant chemotherapy		No recognized adjuvant regimen has definite activity
Metastatic disease	First line	*BRAF* mutations are common—BRAF and/or MEK inhibitors if *BRAF* mutation present; at present, this seems to be a tumor type in which genomic profiling is useful
	Second line	Pazopanib may be useful. Clinical trials are always appropriate. In analogy to B cell lymphomas, immune checkpoint inhibitors are an appealing option, but are untested as of 2016

uncertain outcome (certainly some patients with recurrence and death from tumor), chemotherapy can be considered in the adjuvant or recurrent setting (Table 23.3). Again, in the MSKCC series there was no evidence for the benefit of adjuvant chemotherapy [5], but among these tumors V600E BRAF mutations were common suggesting the use of BRAF or MEK inhibitors or both as in melanomas with the same molecular alteration [6]. In addition, the importance of MEK in these tumors was highlighted in a case report of a patient with a true histiocytic sarcoma containing a *MAP2K1* mutation, who had a marked response to MEK inhibitor [5].

23.3 Langerhans Cell Tumors

A large medical literature exists around conditions involving excessive Langerhans cells, including description of histiocytosis X (now termed Langerhans cell histiocytosis [LCH]), Erdheim–Chester syndrome, Letterer–Siwe syndrome (disseminated histiocytosis of children), and Hand–Schüller–Christian disease (osseous children with LCH). Local disease can be treated with surgery alone (or definitive radiation in some situations), but systemic disease is still associated with significant mortality.

Table 23.4 Systemic therapy recommendations for patients with Langerhans cell tumors and related lesions (e.g., Erdheim–Chester disease)

Clinical scenario		Comments
Systemic chemotherapy		Depends on degree of organ involvement, with traditional agents including vinblastine and/or methotrexate; treatment in the future will be a function of presence or absence of V600E *BRAF*, *ARAF*, or *MAP2K1* mutations and related translocations
Recurrent disease	First line	Salvage protocols
		See website: www.histiocytesociety.org
		In analogy to B cell lymphomas, immune checkpoint inhibitors are an appealing option, but are untested as of 2016

The treatment of LCH and related histiocytoses was upended by the era of tumor DNA and RNA sequencing, with the finding of about half of LCH tumors having *V600E* BRAF mutations [13]. Interestingly, *ARAF* is also mutated in LCH in some cases, and vemurafenib and presumably other ARAF/BRAF inhibitors are active as well [14]. These data were extended better explained with the finding of kinase gene fusions in *BRAF*, *ALK*, and *NTRK1*, as well as recurrent, activating *MAP2K1* and *ARAF* mutations in patients with LCH family of tumors (usually Erdheim–Chester disease) that lack *BRAF* V600E mutations. Treatment of patients with *MAP2K1*- and *ARAF*-mutant histiocytoses yielded clinical responses to MEK inhibition and sorafenib, respectively. These finding should dramatically change how these tumors are diagnosed (e.g., a histiocytosis-specific gene panel) and how they are treated [15].

Stepping back to assessing tumor aggressiveness before considering systemic therapy, treatment for LCH is a function of organ involvement. Good references regarding treatment with active traditional cytotoxic agents in this diagnosis are available [7, 16]. That said, given emerging data on ARAF/BRAF or MEK inhibitors in this diagnosis, with impressive responses that appear to be sustained over a period of months [15, 17, 18], one might expect to employ kinase inhibitors and then chemotherapy, to take advantage of both modalities of treatment. Given the inherent resistance seen in a minority of cells in GIST and in melanoma that give rise to clones that evolve out of the primary tumor, kinase inhibitors could be used to decrease the tumor bulk before the initiation of what would be presumably more definitive chemotherapy. Comments regarding adult versus pediatric patients [19] and web sites help keep the community updated on expert centers and available treatment protocols [20] (Table 23.4).

23.4 Outcome

It is presently impossible to meaningfully predict outcomes from these rare lesions; however, for the primary presentation to our institution, local recurrence- and disease-free survivals in the era before BRAF inhibitors are shown in Figs. 23.3

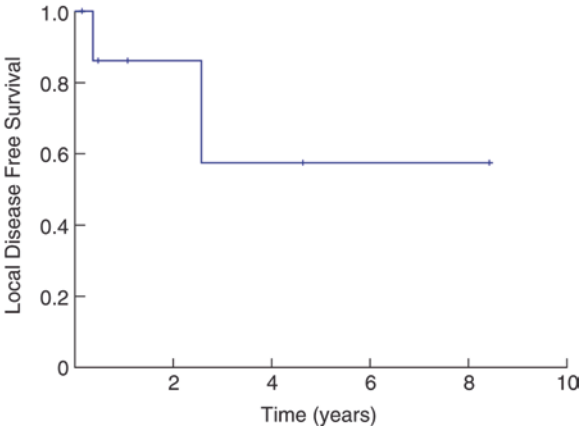

Fig. 23.3 Local recurrence-free survival of adult patients with primary sustentacular malignancies of lymph nodes. MSKCC 7/1/1982–6/30/2010 $n=8$

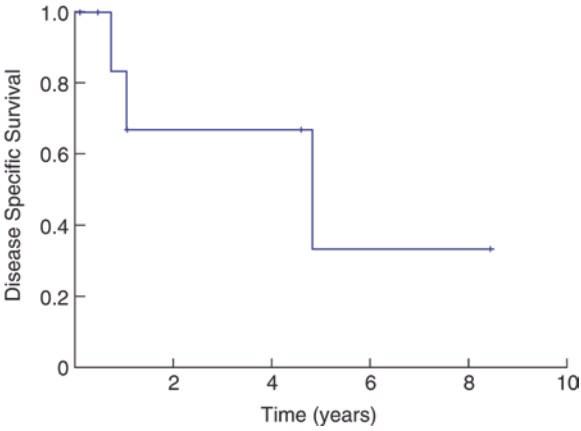

Fig. 23.4 Disease-specific survival of adult patients with primary sustentacular malignancies of lymph nodes. MSKCC 7/1/1982–6/30/2010 $n=8$

and 23.4 [5]. Rare events such as spontaneous regression [21] have been reported. In the era before BRAF inhibitors, a Chinese series of 50 patients, much more favorable results were suggested, with as many as 80 % alive and disease free [22], however that has not been our experience. Any number of reasons, such as variances in pathology interpretation or stage at presentation, makes it difficult to compare across studies. The finding of *BRAF* V600E, *ARAF*, and *MAP2K1* mutations and related translocations in LCH and related histiocytoses, followed by rapid demonstration of activity of kinase inhibitors in this diagnosis is a seminal event for this rare group of cancers, recapitulating the excitement of imatinib in CML and GIST.

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Chapter 24
Uncommon/Unique Sites

24.1 Heart and Great Vessels

The heart and great vessels are rare sites of primary sarcoma but are more commonly observed as the site of metastatic disease [1]. While the clinical presentation is varied from an incidental finding to peripheral emboli to congestive cardiac failure, cardiac sarcomas should be suspected in patients who have undergone prior mediastinal radiation. As a metastatic site, various histologies can be seen whereas primary lesions tend to be either angiosarcoma, leiomyosarcoma, or undifferentiated. A diagnosis unique to this site is intimal sarcoma. Other histologies may rarely include synovial sarcoma (Fig. 24.1) and epithelioid hemangioendothelioma (Fig. 24.2). Histologies of sarcomas of the mediastinum are indicated in Fig. 24.3, and represent a subset of sarcomas of heart and great vessels. The second most common histology is our experience has been high-grade undifferentiated pleomorphic sarcoma (UPS). A recent update [2] suggests that primary cardiac sarcomas represent 20 % of all primary cardiac tumors and diagnosis is predominantly made by transthoracic echocardiography and subsequent sampling.

The largest series of cardiac sarcomas is a publication of 100 tumors indicating an experience in France over 25 years [3]. In this study, intimal sarcoma was the most common diagnosis (42 %) and was supported by the presence of MDM2 gene amplification by FISH. However, this was subsequently challenged by Maleszewski et al., who argued that MDM2 gene amplifications can be seen in a number of sarcoma types, and its presence should not define this tumor type [4]. Our experience supports Neuville and colleagues viewpoint, that intimal sarcomas are distinct from UPS and the presence of MDM2 gene amplification confirms the diagnosis in this specific clinical presentation. Angiosarcoma was the next most common diagnosis (26 %) followed by UPS (22 %). Interestingly all but one angiosarcoma arose in the right heart, while 83 % of what were termed intimal sarcomas and 72 % of UPS arose in the left heart.

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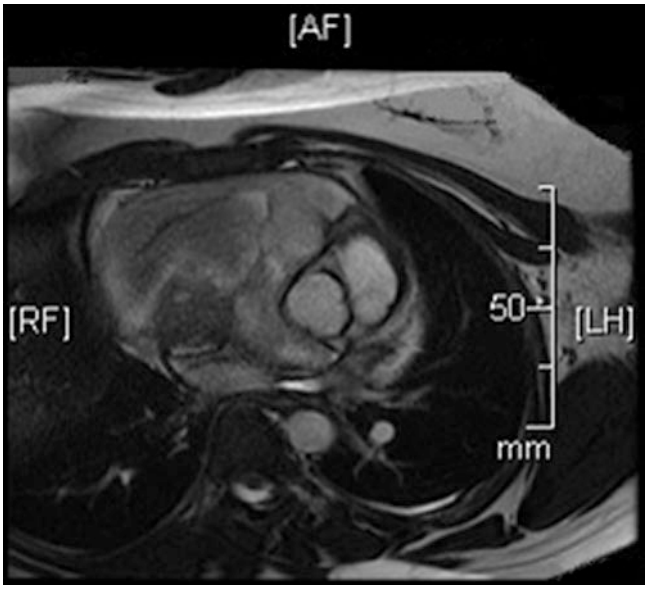

Fig. 24.1 Cardiac gated T1 weighted MRI image of a synovial sarcoma arising in the great vessels

Primary treatment is surgical and increasingly with the opportunities for cardiopulmonary bypass and arrest, this is possible. In selective situations, cardiac transplantation can be utilized [5]. There is consideration that cardiac transplantation should be reserved for patients with low-grade tumors as the risk for metastatic disease in high-grade tumors is so high, and the consequences of transplantation and immunosuppression significantly detrimental to question the value of such an approach. Chemotherapy can be utilized but it is only of palliative value.

The therapeutic options are suggested to be those containing anthracyclines, ifosfamide, or taxanes. Median survival is approximately 9–16 months with patients with left atrial lesions apparently having an improved prognosis but this would appear to be predominantly due to the fact that they are more commonly of lower histological grade and often are technically resectable. Myxomas are common in comparison to primary cardiac sarcoma and only rarely present with metastatic lesions. Systemic therapy for metastatic myxoma is undefined. The presence of chromosome 12q gene amplification provides a mechanistic rationale to use MDM2 or CDK4 inhibitors in patients with recurrent or metastatic intimal sarcoma.

24.2 Primary Sarcomas of the Breast

Primary sarcomas of the breast constitute <5 % of all soft tissue sarcomas and <1 % of all breast tumors. At Memorial Sloan Kettering Cancer Center between July 1982 and June 2010, the types of tumors seen in the breast are shown in Fig. 24.4. One of

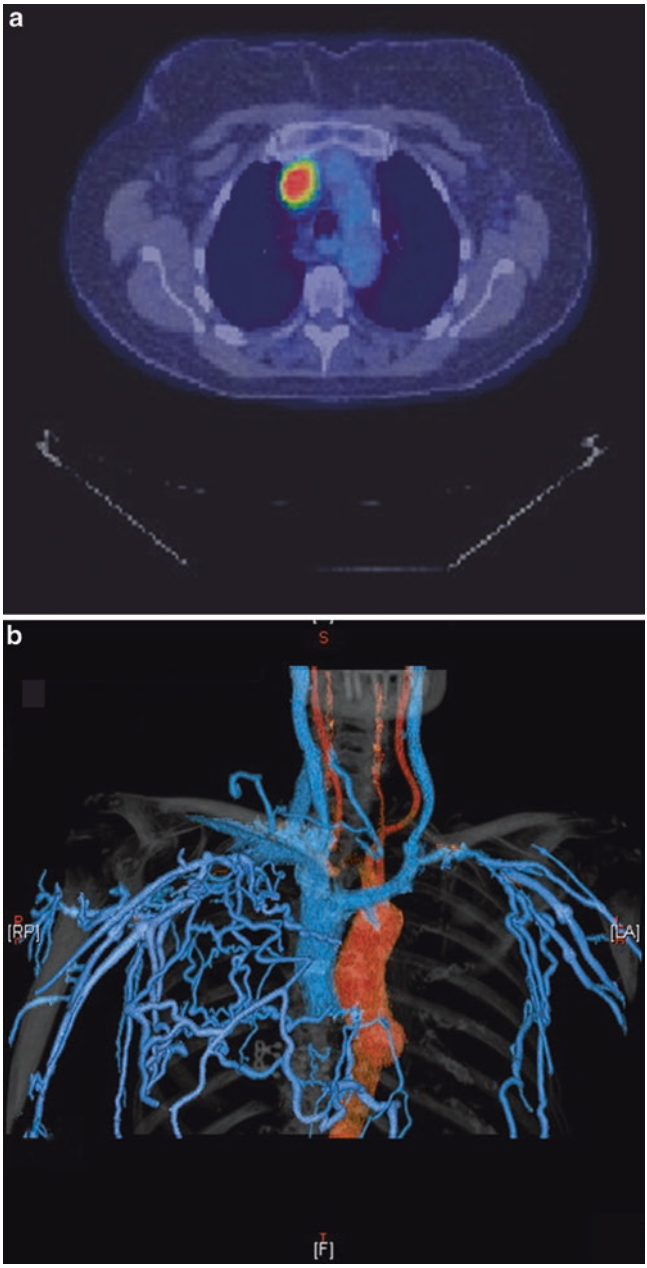

Fig. 24.2 (**a**) Color enhanced axial 18FDE-PET scan of a superior vena cava hemangioendothelioma. (**b**) Color enhanced 3-dimensional reconstructed computed tomography of the same superior vena cava hemangioendothelioma

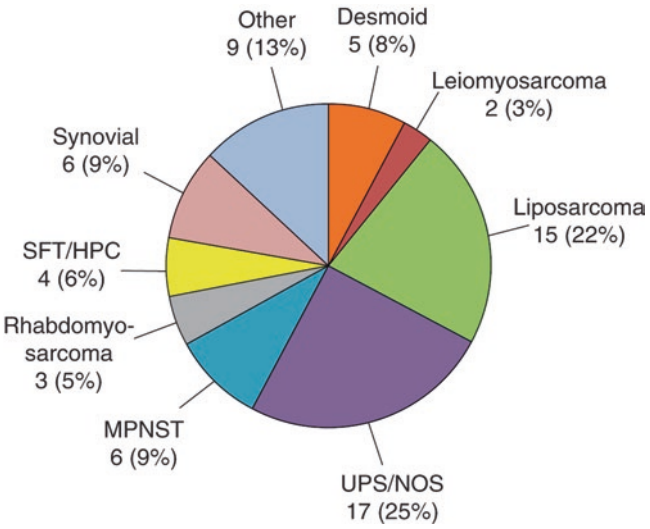

Fig. 24.3 Distribution of histologies of adult primary soft tissue malignancies of the mediastinum. MSKCC 7/1/1982–6/30/2010 $n=67$ SFT = solitary fibrous tumor, HPC = hemangiopericytoma, MPNST = malignant peripheral nerve sheath tumor, UPS = undifferentiated pleomorphic sarcoma, NOS = not otherwise specified

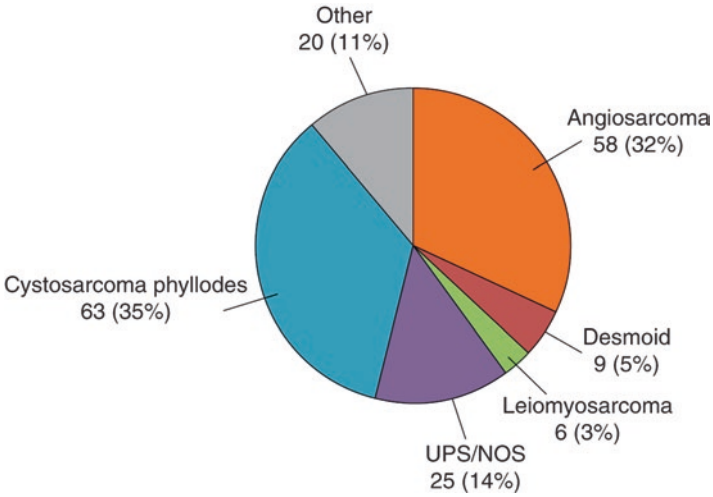

Fig. 24.4 Distribution of histologies of adult primary soft tissue malignancies of the breast. MSKCC 7/1/1982–6/30/2010 $n=181$ UPS = undifferentiated pleomorphic sarcoma, NOS = not otherwise specified

the more common lesions is **cystosarcoma phyllodes**, also termed **phyllodes tumor** (see below). Angiosarcoma is commonly seen in the breast usually post-radiation with or without chemotherapy, but other sarcomatous types can be seen with as radiation-associated tumors (see Predisposing and Genetic Factors in Chap. 1). Primary angiosarcoma of breast is less common and occurs in younger patients, typically in their third decade of life and shows an infiltrative growth pattern within

breast parenchyma. In contrast, secondary, post-radiation breast/chest wall angiosarcomas involve the skin, as multifocal lesions, in elderly patients (See angiosarcoma, Chap. 13.) Treatment is similar to that of other sarcoma, i.e., complete operative excision with or without radiation and subsequent chemotherapy. As with other sarcomas, ancillary nodal dissection is rarely indicated as these tumors rarely spread to lymph nodes [6].

24.2.1 Phyllodes Tumor

Phyllodes tumor is a rare entity thought to arise from predisposing fibroadenoma in many cases. This lesion, often considered benign, does have a malignant subtype. The majority of patients are premenopausal and a retrospective study of 84 patients [7] suggests the median age as 34 years for benign lesions compared to 52 years for those with malignant change. In another review of 124 patients, tumors were benign in 49 %, borderline in 35 %, and malignant in 16 %. It was suggested that malignancy may be more common in patients of Hispanic origin, but referral bias is likely [8].

Patients present with a large painless breast mass which can reach a very large size. The tumor is variegated in color often with cystic areas. Myxoid degeneration is common (Fig. 24.5).

24.2.1.1 Diagnosis

The challenge to define benign from malignant is difficult [9]. The malignant type is described as being similar to adult-type fibrosarcoma. Imaging studies are similar, although on occasion MRI or CT evidence of neoplastic dystrophic tissue containing cartilage or bone can be identified.

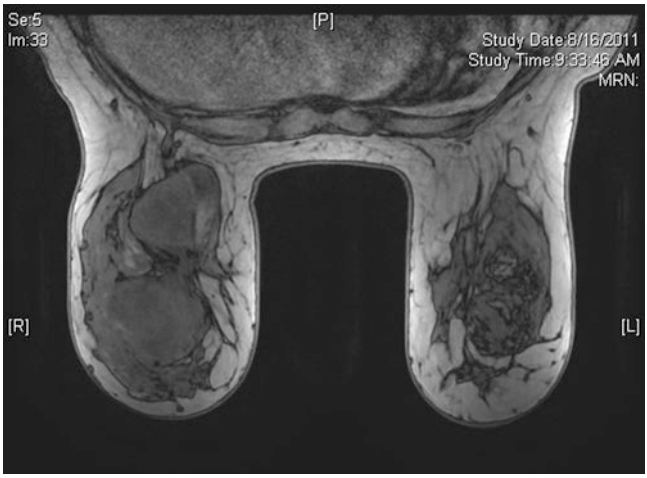

Fig. 24.5 T1 weighted MRI image of a patient with a right breast phyllodes tumor (cystosarcoma phyllodes)

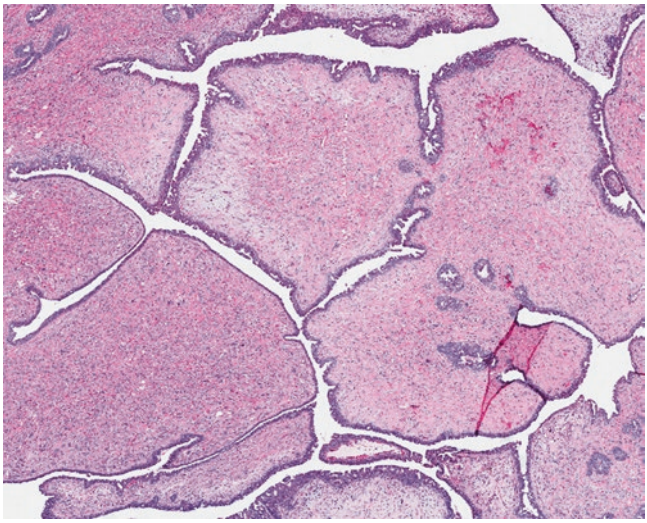

Fig. 24.6 Low power H&E image of a phyllodes tumor of the breast, demonstrating the clefts seen in the gross tumor specimen

Grossly, these tumors are firm and lobulated and on cut surface have a leaf-like architecture (*phyllos* means leaf in Greek). They are well circumscribed grossly, and the cut surface shows a whirling pattern with visible clefts. Larger tumors will present with cystic spaces, and areas of necrosis and/or hemorrhage. Microscopically, these tumors have two elements, like fibroadenomas, having clefts with epithelial cell lining as well as a cellular stromal component (Fig. 24.6). The appearance of the stromal element can vary from relatively benign appearing to frank sarcomatous change with stromal overgrowth, nuclear atypia, higher mitotic rate, and stromal overgrowth of the glandular component. There are now criteria to help predict the risk of recurrence based on clinical and pathologic factors [10]. These tumors are aneuploid, and research is underway to identify specific molecular defects.

Simple mastectomy or wide resection is usually the primary treatment of choice as lymph node metastasis is uncommon. [11] Breast conserving surgery could be considered in an appropriate patient, but given the local recurrence risk, immediate reconstruction seems inadvisable.

Phyllodes tumors are nearly always unresponsive to systemic therapy, be it chemotherapy or hormonal therapy. Adjuvant chemotherapy is not administered to patients, and patients should be considered for clinical trials even in first line for metastatic disease. Ifosfamide-based therapy is a reasonable option for patients without clinical trial options.

24.2.1.2 Outcome

In one series with limited follow-up, local recurrence of 6 % was associated with tumor size grade, mitotic rate, and margin status, similar to other sarcomas [8].

24.3 Head and Neck

Head and neck sarcomas are rare. They usually present as a mass lesion and the histology is diverse (Fig. 24.7). Because of utilization of radiation therapy for lymphoma and other head and neck diseases, sarcoma that is radiation associated is a particularly difficult problem.

As with other sites, imaging predominantly utilizes CT and MRI to determine the extent of the lesion, particularly the involvement of vital structures. Diagnosis is consistent with other sites based on molecular histopathology. Often, given the rarity of sarcomas, they are confused with primary epithelial neoplasms of the head and neck and oropharynx. Identification can often focus on the presence or absence of lymph node metastasis, which, while common in epithelial lesions, is very uncommon in soft tissue sarcoma. Diagnosis is usually made by core needle biopsy, and it is important to establish that a sarcoma is suspected when there is a mass lesion without a primary site identified.

24.3.1 Treatment

Treatment is absolutely constrained because of the close juxtaposition of tumors to major arterial, venous, and neurological structures. The consequence is that, while complete surgical resection remains the primary form of therapy, radiation is more commonly used given the limitations of resection and margin. Preoperative

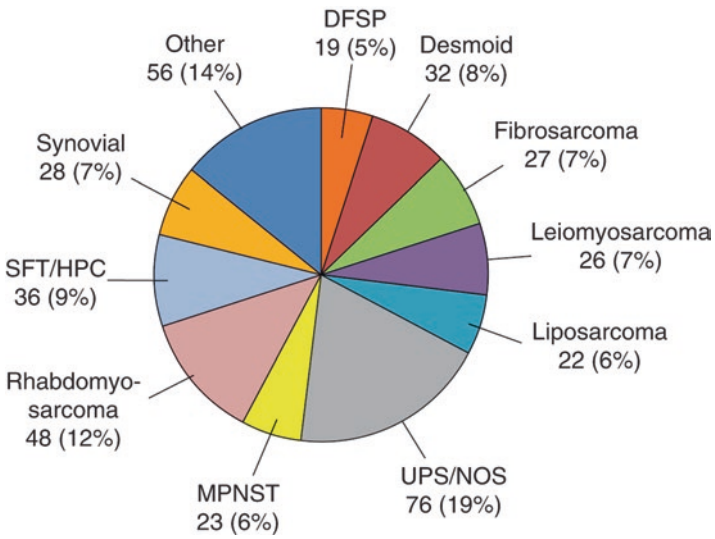

Fig. 24.7 Distribution of histologies of adult primary soft tissue malignancies of the head and neck. MSKCC 7/1/1982–6/30/2010 $n = 393$ DFSP = dermatofibrosarcoma protuberans, MPNST = malignant peripheral nerve sheath tumor, UPS = undifferentiated pleomorphic sarcoma, NOS = not otherwise specified, SFT = solitary fibrous tumor, HPC = hemangiopericytoma

treatment, particularly chemotherapy or radiation in high-grade lesions, can be considered even when the lesions are <5 cm; future versions of AJCC staging criteria will likely include this concept. In similar fashion, adjuvant radiation therapy is perhaps more commonly used than in other sites owing to the morbidity of procedures in the head and neck. Very few valuable studies exist. However, Glenn et al. [12] showed chemotherapy was utilized in 31 patients in a randomized trial. Patients in this group who had complete resection received between 60 and 63 Gy over 8 weeks and adjuvant chemotherapy with doxorubicin, cyclophosphamide, and methotrexate. That study, which has not been reproduced, was at a time when the amount of doxorubicin given was considerably in excess of what would be considered appropriate now. Three-year actuarial survival in the chemotherapy arm was 77 % compared to 49 % in the no-chemotherapy arm ($p=0.075$). Actuarial overall survival was not different, being 68 % in both arms. The high probability is that despite the small numbers, no proven benefit of adjuvant chemoradiation therapy is established.

A review of our experience has been published [13]. In that study, 60 patients over a 7-year period were identified. The most common site was on the face, and the majority of patients presented having had previous treatment. Again, as with other sites of disease, control was improved in low-grade tumors compared to high-grade tumors. Despite close or positive margins, 50 % of those patients did not recur locally. Overall survival was 70 % and disease-free survival was 60 %. Further information is best provided by referring to the relevant histopathology section.

24.4 Primary Sarcomas of the Mediastinum

The wide variation in histopathology for this anatomic site is demonstrated in Fig. 24.3. We have previously reported our limited experience with this particularly rare entity [14]. Forty-seven patients with a median age of 39 years were treated, and all varieties of sarcoma were identified. As with other sites, primary treatment is operation, but only 22 of 47 of those patients were able to undergo complete resection. As a consequence, local recurrence is very high, over 60 % in the reported study by Burt. Because of poor local control, overall survival is poor, approximately 30 %, and as with other sites, high-grade lesions fair worse than low-grade lesions. Sarcomas arising from mediastinal (and other) germ cell tumors present a unique problem in management. Like non-seminomas, both surgery and chemotherapy are typically employed, as may be radiation on a case-by-case basis. A standard of using chemotherapy directed both against the germ cell tumor and the specific sarcoma subtype is generally employed, be it rhabdomyosarcoma, angiosarcoma, or other specific diagnoses. Sarcomas in this setting will be i12p positive, confirming their germ cell origin. Their outcome is poor in comparison to patients with primary germ cell tumors (of both testis and mediastinum) alone [15–17]. Further information is available under the relevant section based on histopathology.

24.5 Liver

Certain histopathologies are relatively common or specific to the liver. Epithelioid hemangioendothelioma is a vascular sarcoma that frequently presents with multifocal disease in the liver, lungs, and pleura, described further in Chap. 13, Fig. 13.4. Unique to the liver is embryonal sarcoma, a primitive small round blue cell tumor treated much like Ewing sarcoma. More information on this rare diagnosis is found in Chap. 15 on sarcomas more common in children. Rhabdomyosarcoma is occasionally found in the biliary tree in children, and must be distinguished from embryonal sarcoma in children. GIST abutting the liver or metastatic to liver is more common in older adults.

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Part III
Benign and Less Aggressive Lesions

Chapter 25
Mostly Benign/Rarely Metastasizing

25.1 Ossifying Fibromyxoid Tumor

Ossifying fibromyxoid tumor (OFMT) is a very uncommon soft tissue lesion that can occur anywhere in the body, but most commonly in the lower extremity. While most tumors are benign, malignant examples may metastasize in more than half of cases [1]. The largest series to date included only typical cases, excluding tumors with other morphologies, and in that series there were no patients who developed metastatic disease. In the few patients that we have observed recurrences, metastases are observed, typically to lung, and local–regional recurrence can be observed in a multifocal "shotgun" pattern around the area of the tumor, as has been observed in patients with epithelioid sarcoma.

The cell of origin of these tumors is unknown, but after the finding of an unbalanced translocation in one tumor by cytogenetics in 2001 [2], perhaps it is not surprising that these sarcomas were found to have recurrent gene fusions, mostly involving *PHF1* gene [3]. The most common translocation in a series of 39 OFMTs is *EP400-PHF1*, while other fusion variants such as *ZC3H7B-BCOR* and *MEAF6-PHF1* were more common in the S100 negative proportion of tumors, or in the malignant subset of OFMT [4]. These findings suggested a genetic overlap between OFMT and low grade endometrial stromal sarcomas (LGESS), since *EPC1-PHF1* translocations are found in both OFMT and LGESS [4].

Radiographically, scattered calcifications can be found throughout the lesion. Primary treatment of these tumors mirrors that of other soft tissue tumors, surgery and radiation for larger tumors, but adjuvant chemotherapy is difficult to recommend as the response rate to standard agents is very low. Given the relatively slow growth rate of the tumor, sustained exposure with lower doses of an agent continuously would appear a better means to treat these tumors than high dose therapy over the short term. The few patients we have treated have not responded durably to standard doxorubicin or ifosfamide, so new options for care are needed (Fig. 25.1)

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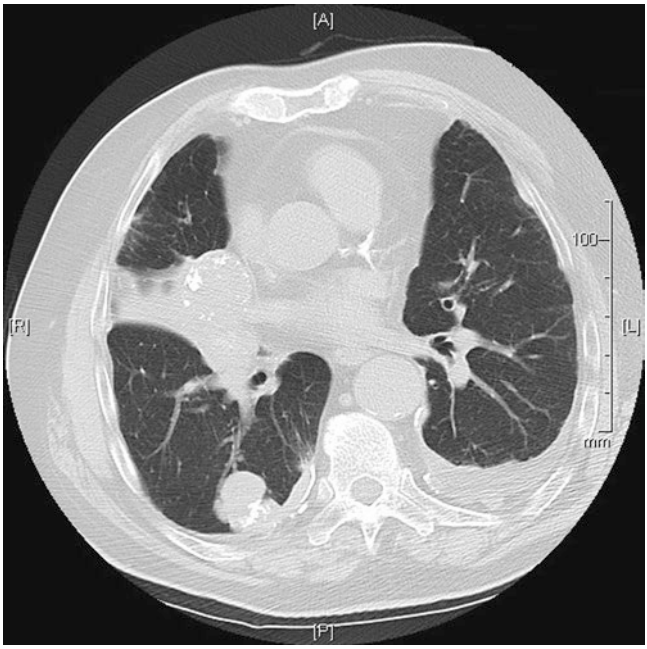

Fig. 25.1 Non-contrast CT image of metastatic ossifying fibromyxoid tumor featuring pleural effusions, lung- and pleural-based metastases, and speckled calcification of the metastatic deposits

Table 25.1 Systemic therapeutic recommendations for ossifying fibromyxoid tumor

Clinical scenario		Comments
Adjuvant chemotherapy		Not administered outside the setting of a clinical trial, given the poor response rate in the metastatic setting
Metastatic disease	First line	Clinical trial; topoisomerase I inhibitor-based therapy, e.g., temozolomide-irinotecan or cyclophosphamide-topotecan, has activity in anecdotal experience. Immune checkpoint inhibitors are untested as of 2016. Doxorubicin + olaratumab is approved in this situation but there are no prospective data as of 2016

(Table 25.1). At least two patients we have treated had durable responses from irinotecan-based therapy, e.g., temozolomide-irinotecan, suggesting a biological relationship to small round blue cell tumors more common in children.

25.2 Perivascular Epithelioid Cell Tumor (PEComa) and Related Entities, Lymphangioleiomyomatosis, Angiomyolipoma, Sugar Cell Tumor

The PEComa family of tumors includes a variety of tumors that express markers of both smooth muscle and melanocytes [5]. Thus, they are positive for SMA (smooth muscle actin), as well as for melanocytes markers such as HMB45 and Melan-A.

A variety of names for these tumors has been developed before the concept of PEComa was recognized as a distinct biological entity, on the basis of all lesions containing perivascular epithelioid cells, an unusual cell with no recognized normal counterpart. As a result, the PEComa family of tumors encompasses a variety of diagnoses such as angiomyolipoma, clear cell "sugar" tumors of the lung and other sites, lymphangioleiomyomatosis, and tumors with a similar morphology at a variety of other sites, such as Xp11 translocation renal cancers [6]. At least a subset of PEComas show inactivating mutations or deletion of *TSC2* (tuberin), causing its loss of expression. Coexistent *TP53* mutations were identified in 63 % of *TSC2*-mutated PEComas [7]. *TSC2*-deleted mouse muscle cells can develop into PEComas, showing a possible lineage for these unusual tumors [8]. Tuberin is one of the genes associated with tuberous sclerosis, as is *TSC1*, also called hamartin [9, 10]. Another subset of PEComas (23 %) harbor *TFE3*-related fusions, which are mutually exclusive to *TSC2* gene abnormalities [7, 11]. The most common fusion was *PSF-TFE3* with one case of *DVL2-TFE3* [7]. In addition, novel RAD51B gene rearrangements were identified in 8 % of uterine PEComas [7]. *TSC2*-deficient PEComas show activation of the mammalian target of rapamycin (mTOR) and activate a program of transcription and translation with the cell as a result [12, 13]. mTOR exists with other proteins in two complexes, mTORC1 and mTORC2. First-generation TOR inhibitors such as sirolimus only block mTORC1 but do not affect mTORC2 signaling, providing a bypass pathway for signaling when mTORC1 is blocked. As *TFE3* translocation PEComas lack *TSC2* mutations [11], it provides a mechanistic rationale that some PEComas would not respond to mTOR inhibitors.

An example is shown in Fig. 25.2 with a well-demarcated lesion in the vastus lateralis with edema in the soft tissue and central necrosis. These lesions, when metastatic, sometimes arise from the uterus, which is one of the more common sites for PEComas. Key pathological identification is the HMP45 which occurs but in patchy distribution. A recent review [14] of 234 cases reported from the literature suggests that size greater than 5 cm and high (1/50 HPF) mitotic rate were the only factors associated with recurrence following resection. Chemotherapy and radiation therapy seem to have little benefit..

25.3 Therapy

Primary treatment is surgical, when feasible; radiation plays little role in the primary treatment of these tumors since they tend to be visceral (Fig. 25.3). For patients with unresectable or recurrent disease, mTORC1 inhibitors, such as sirolimus, have been proved clinically useful in patients with recurrent angiomyolipoma [15], lymphangioleiomyomatosis [15], and recently in recurrent/metastatic PEComas [16–18]. Responses to mTORC1 inhibitors are not as robust as that of imatinib in GIST, with median duration of response on the order of 6–12 months [18]. It is not clear if mTOR inhibitors beyond sirolimus are useful for this diagnosis, but it is the opinion of the authors that the near equivalence of most of the first-generation

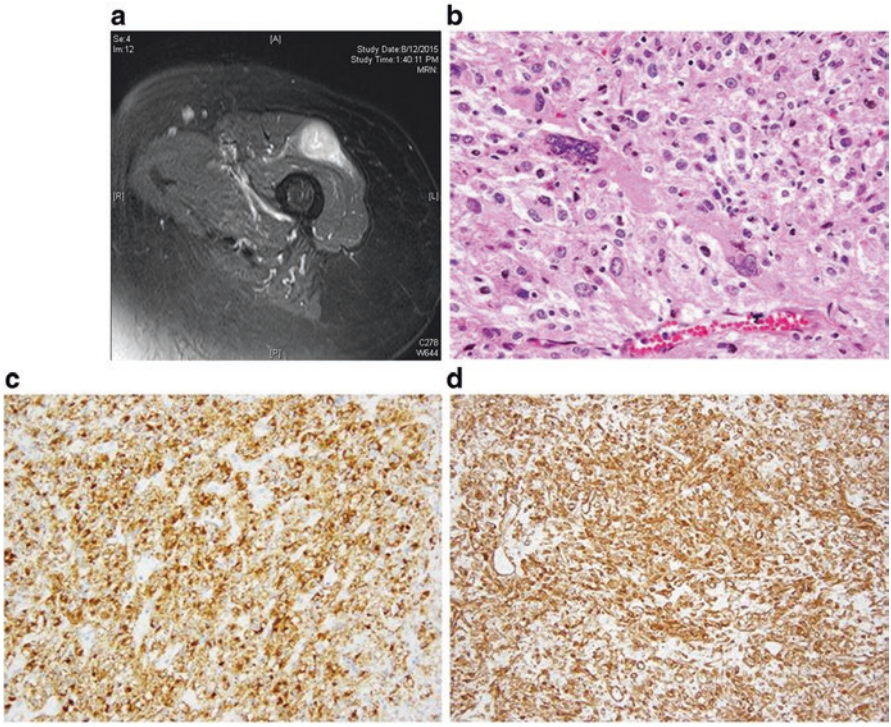

Fig. 25.2 (**a**) PEComa with a well-demarcated lesion in the vastus lateralis with edema in the soft tissue and central necrosis. (**b**) PEComa morphology is characterized by spindle and pleomorphic cells with abundant clear or granular cytoplasm; (**c**, **d**) immunoprofile typically includes reactivity for both melanocytic (HMB45, **b**) and smooth muscle (SMA, **b**) markers

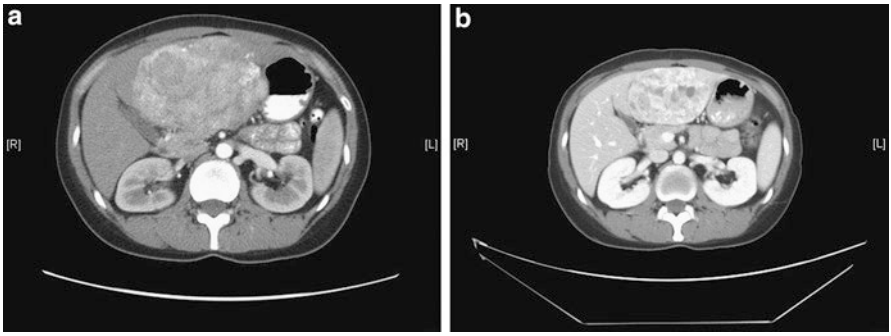

Fig. 25.3 CT response of a recurrent angiomyolipoma (PEComa family of tumors) to sirolimus 4 mg oral daily. (**a**) Pretreatment, 12.6 × 7.6 cm mass; (**b**) after 3 months, mass size 9.1 × 5.6 cm

mTOR inhibitors speaks to their interchangeability and lack of activity of the others if one of them fails. We have not observed activity of anthracyclines or of ifosfamide in the small number of patients we have treated with standard agents, arguing that such patients are appropriate for clinical trials. Less investigated are other

Table 25.2 Systemic therapeutic recommendations for perivascular epithelial cell tumor (PEComa) and related entities, lymphangioleiomyomatosis, angiomyolipoma, sugar cell tumor of the pancreas

Clinical scenario		Comments
Adjuvant chemotherapy		Not administered due to low risk of relapse and lack of long-term efficacy of systemic agents in the recurrent setting; this tumor subtype appears to be one in which genomic analysis would be worth pursuing
Metastatic disease	First line	Sirolimus or other mTOR inhibitor for *TSC2* mutant PEComas
	Second line	It is unclear if other kinase inhibitors, e.g., pazopanib, have any activity, for example in *TFE3*-related sarcomas such as alveolar soft part sarcomas. Clinical trials of agents blocking downstream targets of mTOR and VEGFR, e.g., S6 kinase, or metabolic-directed therapy, may be worth examination as well. Immune checkpoint inhibitors are untested as of 2016

small molecule inhibitors yielding greater "area under the curve," which may be worth examining as well (Table 25.2); in particular, since VEGFR inhibitors have some activity in alveolar soft part sarcomas, it stands to reason that renal PEComas with *TFE3* translocations could be targeted with VEGFR inhibitors such as pazopanib or sunitinib.

25.4 Giant Cell Tumor of Tendon Sheath/Pigmented Villonodular Synovitis

Giant cell tumor of tendon sheath (TGCT), also termed pigmented villonodular synovitis (PVNS), is an uncommon neoplasm of the synovium of joints that can occur in any joint. Unlike synovial sarcoma, which does not appear to be related nor resemble synovium microscopically, TGCT/PVNS is a true tumor of the synovium. The tumor comes in several forms: a localized variety most common in small joints, a diffuse type more common in large joints like the knee, and an extra-articular variety.

The key finding that has changed treatment for TGCT/PVNS is the consistent translocation t(1;2)(p11;q36-37) (*COL6A3-CSF1*) found in a minority of the cells of the lesion, which leads to the production of CSF-1 and presumed activation of FMS (the M-CSF receptor), and local cytokine production that leads to the characteristic inflammatory changes in the lesion [19].

The tumor presents as an inflammatory mass and/or effusion. Primary therapy consists of primary resection, but recurrence is common within several years of primary diagnosis, typically with the diffuse variety of the tumor (Fig. 25.4). Rare cases of metastatic disease to lung are reported. In the past postoperative intra-articular radioactive phosphate (labeled with ^{32}P) or ^{90}Y (yttrium) has been used as

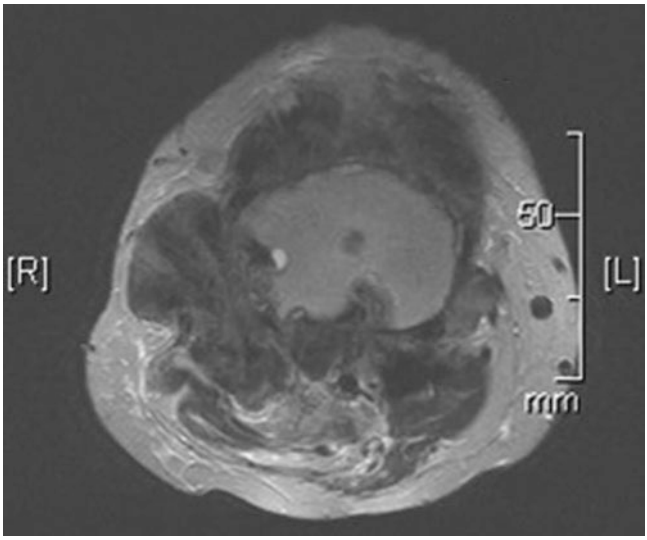

Fig. 25.4 T1-weighted axial MRI image of a multiply recurrent tenosynovial giant cell tumor of the knee

Table 25.3 Systemic therapeutic recommendations for giant cell tumor of tendon sheath/pigmented villonodular synovitis

Clinical scenario		Comments
Adjuvant chemotherapy		Not administered due to low risk of relapse
Recurrent/metastatic disease	First line	Reoperation; imatinib or improved CSF1 inhibitor, e.g., pexidartinib, if available
	Second line	Alternative tyrosine kinase inhibitor; surgery and external beam radiation; clinical trial. Immune checkpoint inhibitors are untested as of 2016

an antiproliferative measure for recurrence of disease, though there is significant toxicity in treating at least certain anatomic sites with intra-articular radionuclides. Postoperative external beam radiation (~35 Gy) has been used successfully in some patients with recurrence of disease [20, 21]. The long-term effects of moderate dose radiation in terms of joint function and secondary cancers are unknown.

As a coincidence, imatinib blocks FMS (as well as BCR-ABL, KIT, PDGFRs, and other targets) owing to their structural similarity, and there are anecdotes of patient responses to imatinib. In the index case study, a responding patient stopped therapy, and the lesion recurred rapidly, but then responded again to another course of imatinib [22]. A group of anecdotes from several centers demonstrated that there was significant activity of imatinib in TGCT/PVNS, but given the concern of recall bias, these data may represent an upper estimate of activity [23] (Table 25.3).

Strikingly, a more specific attack against CSF1R has yielded more potent activity against the tumor. Both monoclonal antibodies and small molecule inhibitors with greater specificity against the CSF1R compared to imatinib have been significantly more effective in TGCT than has been imatinib in its anecdotal experience [24, 25].

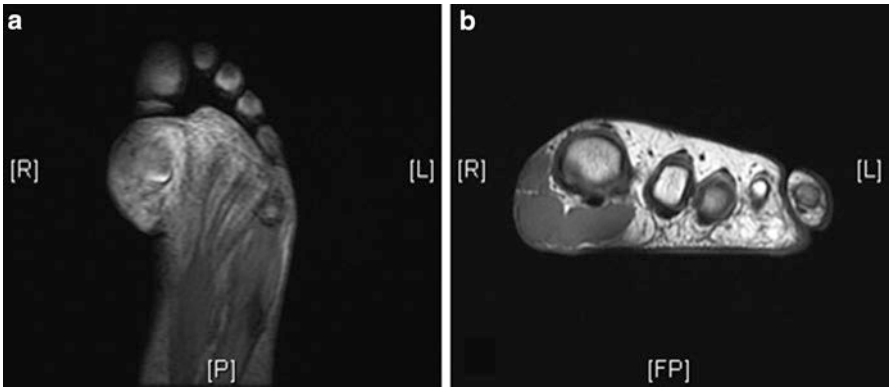

Fig. 25.5 Coronal (**a**) and axial (**b**) T1-weighted MRI images of a left foot low grade myoepithelioma involving flexor hallucis longus and subcutaneous tissue

A randomized trial of the small molecule inhibitor pexidartinib (PLX3397) is underway and may lead to approval of the agent in the near future.

Giant cell tumors of soft tissue can rarely be seen in other sites. They usually occur subcutaneously but can be seen in deep muscle tissue. The cytological characteristics are often clear and can be identified by aspiration cytology. The majority behave in a benign fashion although rare malignant counterparts occur. Surgical excision is usually curative.

25.5 Myoepithelial Tumors of Soft Tissue

Soft tissue myoepithelial tumor is a distinct entity from the pleomorphic adenoma arising in salivary glands, from which a myoepithelial carcinoma ex-pleomorphic adenoma can develop. Myoepithelial tumor of soft tissue is an extremely rare neoplasm which typically occurs in the superficial or deep soft tissue of the limbs or head and neck of both children and adults (Fig. 25.5). Both benign and malignant forms exist, separated by increased mitotic activity, nuclear pleomorphism, and necrosis. Half of myoepithelial tumors (including benign and malignant) have EWSR1 gene rearrangements; the most common fusions being *EWSR1-POU5F1* and *EWSR1-PBX1* [26]. Other less common fusion variants have been reported including *EWSR1-ZNF444* [26, 27], *EWSR1-PBX3*, and *FUS-KLF17* [28, 29]. Soft tissue myoepithelial tumors are defined by the co-expression of cytokeratin +/− EMA and S100 protein +/− smooth muscle actin. In a recent review [30], treatment is standard surgical resection and the majority of the lesions behave in a benign or indolent fashion such that surgery is curative. Malignant examples can occur, often with a virulent course. A good example is illustrated in Fig. 25.6, with a large lesion of the foot with a discontiguous bone lesion and pulmonary metastases in a 25-year-old male.

Chemotherapy is not well defined for patients with such recurrences. It is difficult to more than speculate on treatment given the few cases of this family of tumors treated in the literature; in our own hands no radiological responses have been observed with any specific agent, making clinical trial enrollment paramount for the rare patient with metastatic disease [31].

25.6 Glomus Tumor

Glomus tumors must not be confused with paragangliomas (e.g., glomus faciale, glomus jugulare, glomus tympanicum, glomus vagale, or carotid body tumors) as pertains to anatomy and terminology [32]. While paragangliomas can occur associated with the carotid body, for example, glomus tumors are tumors of the cells that give rise to glomus bodies, the specialized smooth muscle that controls blood flow to the periphery/skin. Glomus tumors have histology that can be classified by their predominant components, e.g., glomangioma, glomangiomyoma, and rare malignant counterparts called malignant glomus tumor or glomangiosarcoma, amongst other varieties.

Benign glomus tumors, which have a broad age distribution among adults, classically present as painful lesions in a subungual location on the fingers or on the skin of the distal extremities. Treatment is surgical for what are typically small tumors [33–35]. They are also occasionally found in the wall of the stomach, and less commonly in other visceral locations, and again surgery is typically curative (Fig. 25.7). These lesions are positive for smooth muscle actin, like leiomyomas and leiomyosarcomas.

Glomus tumors are found in the spectrum of neurofibromatosis type I-related neoplasms. Furthermore, remarkably, there is a familial condition involving familial glomus tumors, which are called glomangiomas or glomangiovenous malformations, mimicking arteriovenous malformations [36–40]. Multiple discolored lesions are found in the skin in this condition, in which there germ line mutations are found in the glomulin gene on chromosome 1p.

More recently recurrent *NOTCH* gene rearrangements have been reported in about half of glomus tumors, including most malignant variants [41]. The most common NOTCH family member involved was *NOTCH2* which was fused to *MIR143*, resulting in significant NOTCH2 upregulation. Less commonly fusions involving NOTCH1 and NOTCH3 were present fused to MIR143 [41].

For the rare person with a malignant glomus tumor (in which there is evidence of mitotic activity or atypical mitotic figures), metastatic spread to lungs is common (similar to leiomyosarcomas) or to peritoneum or bowel (Fig 25.8). Chemotherapy

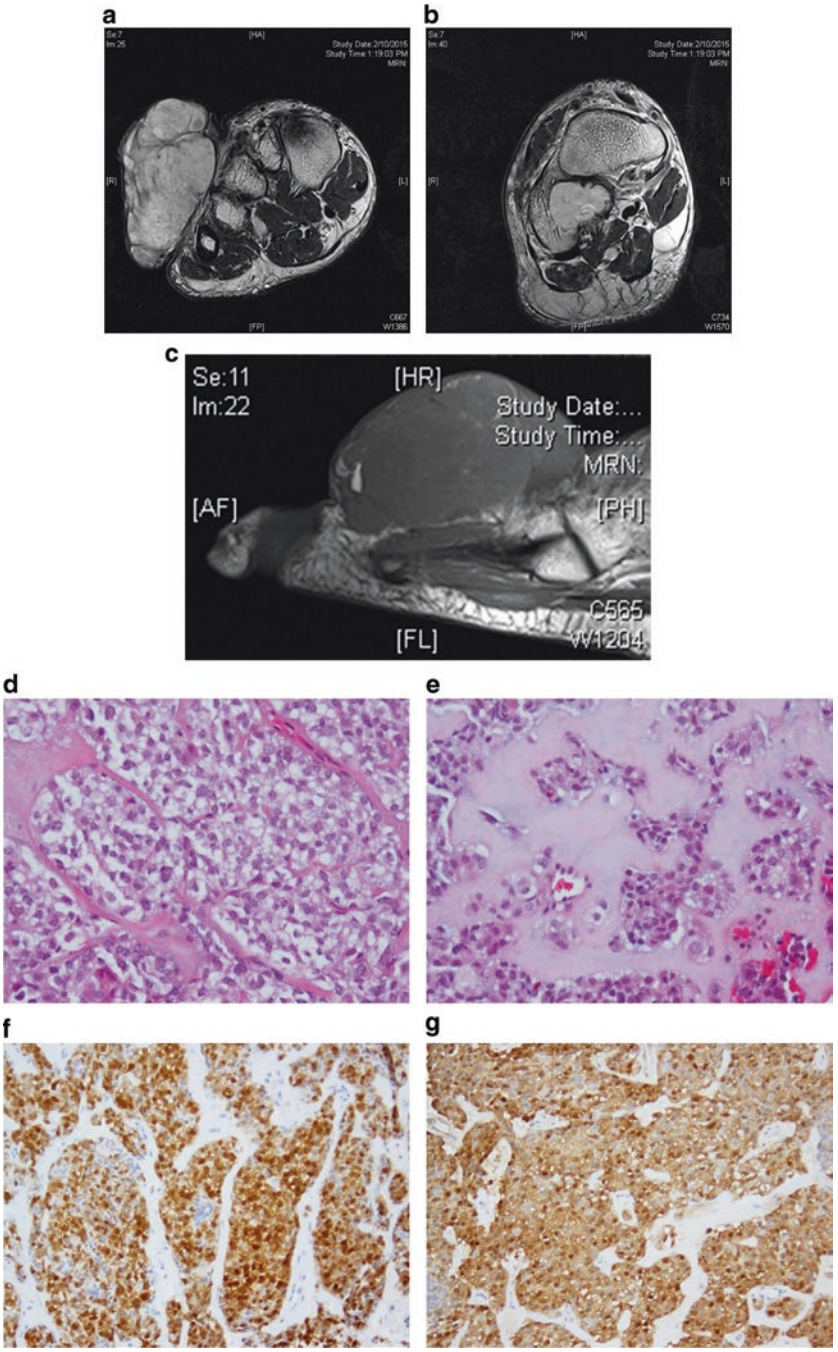

Fig. 25.6 (**a**–**c**) Myoepithelial right foot—large lesion of the foot with a discontiguous bone lesion and pulmonary metastases in a 25-year-old male. (**d**) EWSR1-POU5F1 fusion positive soft tissue myoepithelial tumor showing a nested growth with epithelioid cells with clear cell cytoplasm or (**e**) reticular pattern in a dense chondromyxoid stroma. (**f**) Immunostaining shows strong reactivity for both cytokeratin and (**g**) S100 protein

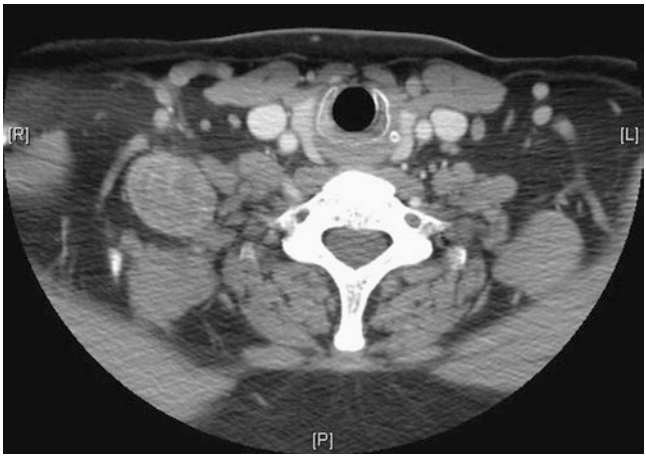

Fig. 25.7 Axial contrast-enhanced CT image of a malignant glomus tumor of the right neck

Table 25.4 Treatment recommendations for malignant glomus tumor

Primary disease	Surgical resection; no adjuvant chemotherapy or radiation is employed
Recurrent/metastatic disease	Clinical trials; we speculate that doxorubicin, dacarbazine, or gemcitabine-based therapy is reasonable if there are no clinical trial options. Notch inhibition is a theoretically interesting approach to consider given the biology of these tumors. Immune checkpoint inhibitors are untested as of 2016. Doxorubicin and olaratumab are approved for this situation but there are no prospective data as of 2016

is undefined for such rare lesions, but agents typically used for leiomyosarcoma for the rare patient requiring chemotherapy can be suggested based on histology alone (Table 25.4), although there are no reports of therapy in the literature (Table 6.1). The new genetic information emerging with recurrent NOTCH-related fusions that result in oncogenic activation of the protein, especially seen in most malignant glomus tumors (glomangiosarcomas), suggests treatment with NOTCH inhibitors might be effective.

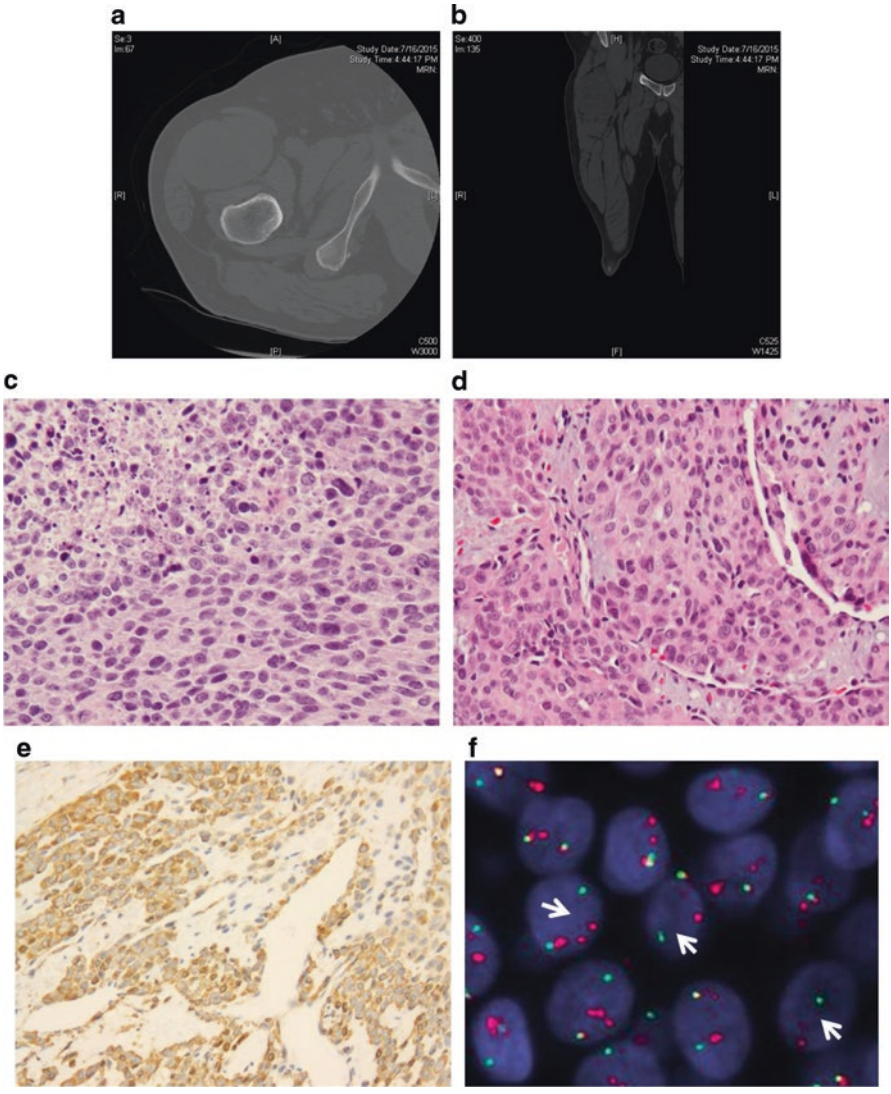

Fig. 25.8 (**a**, **b**) CTs of malignant glomus (**c**) malignant glomus tumor (glomangiosarcoma) shows a high grade morphology with necrosis, indistinguishable from other spindle cell sarcomas; (**d**) areas of classic glomus tumor can be found by extensive sampling, that can lead to the correct diagnosis, (**e**) with reactivity for SMA; and (**f**) NCOA2 gene rearrangement by FISH (*arrows* show break-apart signal, *red*, *green*)

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Chapter 26
Selected Benign Tumors

26.1 Lipoma

Lipomas are the most common benign neoplasm and usually arise in subcutaneous tissue. The trunk and proximal limbs are the most frequent sites. Although deep-seated benign lipomas do occur in the mediastinum or retroperitoneum, seemingly mature fatty neoplasms in the retroperitoneum should be considered well-differentiated (WD) liposarcoma. Most lipomas are solitary, soft, and painless, and grow slowly; 2–3 % of patients have multiple lesions that are occasionally seen in a familial pattern.

Solitary lipomas are well-circumscribed, lobulated lesions composed of fat cells, demarcated from surrounding fat by a thin fibrous capsule. Most subcutaneous, solitary lipomas show reproducible cytogenetic aberrations: translocations involving 12q13-15, rearrangements of 13q, or rearrangements involving 6p21-33 [1].

In spindle cell lipoma, mature fat is replaced by collagen-forming spindle cells; this lesion typically arises in the posterior neck and shoulder in men between the ages of 45 and 65. Spindle cell lipomas show consistent chromosomal aberrations of 13q and 16q [2].

Pleomorphic lipoma is closely related to spindle cell lipoma and is classified as a single family of lesions in the WHO of soft tissue tumors. Local excision of lipoma and these variants is generally curative, with a local recurrence after simple excision in no more than 1–2 % of cases.

Intramuscular lipomas differ by usually being poorly circumscribed and infiltrative (Fig. 26.1). These typically present in mid-adult life as slow-growing, deep-seated mass most often are located in the thigh or trunk. Approximately 10 % of intramuscular lipomas are noninfiltrative and well circumscribed. In a patient with a deep-seated fatty tumor, it is important to exclude an atypical lipomatous tumor, the lowest grade version of well-differentiated liposarcoma (ALT; see Liposarcoma), which tends to be more common than an intramuscular lipoma. As a form of well-differentiated liposarcoma, ALT has a known risk of local recurrence.

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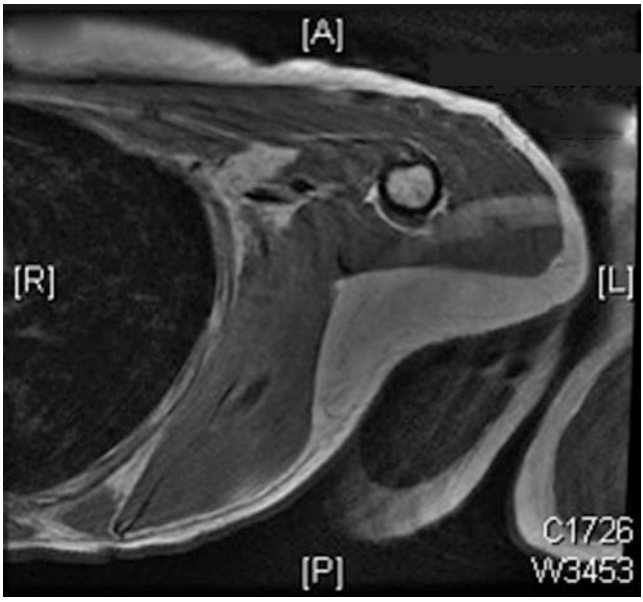

Fig. 26.1 T1 weighted axial MRI image of an intramuscular lipoma of the trunk

Surgical resection of symptomatic lesions or lesions ≥5 cm is usually recommended and often curative.

26.2 Lipomatosis

Lipomatosis is a term applied to poorly circumscribed overgrowth of mature adipose tissue growing in a somewhat infiltrative pattern. It can occur in the intraperitoneal area, in the retroperitoneum, and in multiple other sites. A relationship to mutations in *HMGA2* is suggested [3]. Molecular genomic testing of patients has yielded evidence of mutations causing symmetric lipomatosis, e.g., MERRF or MFN2, which can also be associated with peripheral neuropathy and central nervous system complications [4, 5].

Rarely, lipomatosis has been considered an unusual side effect of cytotoxic chemotherapy. Lipodystrophy is a form of redistribution of body fat more commonly seen than lipomatosis as a complication of antiretroviral agents, among other medications.

An entity considered benign symmetric lipomatosis is described usually in the subcutaneous tissues around the neck. A usual association with alcoholism and the presence of glucose intolerance has been described. This lesion should be considered a lipodystrophy when associated with alcoholism or administration of HIV protease inhibitors. Other unusual sites have resulted in spinal cord compression. There is a variant of congenital type which involves infiltration of the fascial subcutaneous tissue.

26.3 Lipoblastoma/Lipoblastomatosis

Lipoblastoma has been reported to occur in the head and neck in children as a rare, benign encapsulated tumor usually arising from embryonic white fat. It is rare to see such tumors over the age of 20. They usually present as a growing mass in children under the age of five with many occurring before age one. Clinically, the lesions are commonly mistaken for a benign lipoma or hemangioma.

More commonly seen in the extremities and trunk, there is no sex preselection, but tumor can grow quite rapidly. Very rarely do they obtain a size to become symptomatic.

Histological appearance usually contains primitive mesenchymal cells, myxoid and fibrous bands, and variably differentiated adipocytes. They differ from lipoma by their cellular immaturity and their close resemblance to the myxoid liposarcoma.

Confirmation by cytogenetics involves identification of a break point involving chromosome 8q11.2. The gene partners in these translocations are *PLAG1* (pleomorphic adenoma gene 1) with a variety of other genes, e.g., *HAS2*, *COL1A2*, *RADA51L1*, or *RAB2A* [6–8].

Lipoblastoma have an excellent prognosis and surgical excision is the treatment of choice. Inadequate surgical resection is accompanied by recurrence. In surgical treatment, it is important to preserve neurovascular bundles even in the presence of large tumors, since these tumors typically do not recur.

Lipoblastomatosis is a multifocal variant of lipoblastoma.

26.4 Angiolipomas

Angiolipomas present as subcutaneous nodules, usually in young adults, and in more than 50 % of cases are multiple. The most common site is the upper extremity. Angiolipomas rarely reach more than 2 cm in size, but they often are painful, especially during their initial growth period. Microscopically, these tumors consist of adipocytes with interspersed vascular structures. Myxoid and fibroblastic angiolipomas are recognized. Treatment is surgical excision (Fig. 26.2).

26.5 Angiomyolipoma

The term *angiomyolipoma* is used for a non-metastasizing renal or hepatic tumor that is composed of fat, smooth muscle, and blood vessels. Angiomyolipoma is more common in women than in men and renal angiomyolipoma is seen in association with tuberous sclerosis (see more on the section on PEComa, Chap. 25). Although angiomyolipoma is usually well demarcated from normal kidney, it may extend into the surrounding retroperitoneum (Fig. 26.3). Angiomyolipomas may be solitary or multicentric, and may produce abdominal pain, hematuria, or intraperitoneal hemorrhage. Wide excision is usually curative.

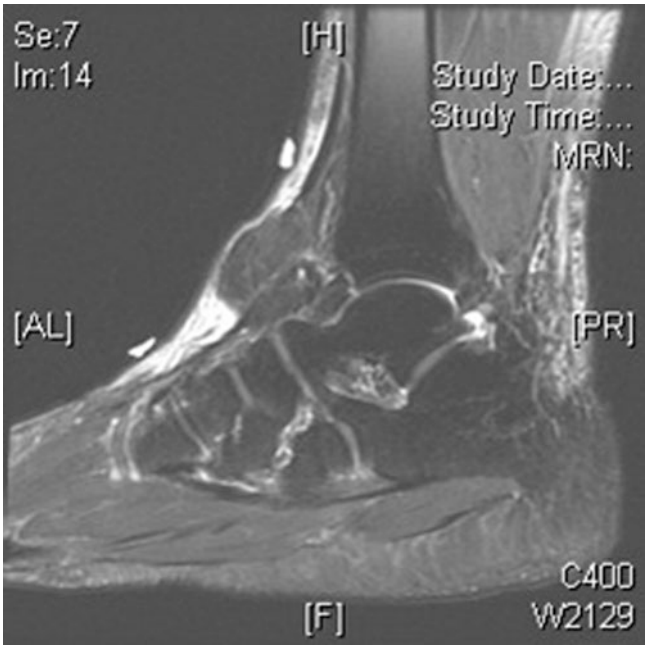

Fig. 26.2 T2 weighted sagittal MRI image of an angiolipoma of the distal ankle and forefoot

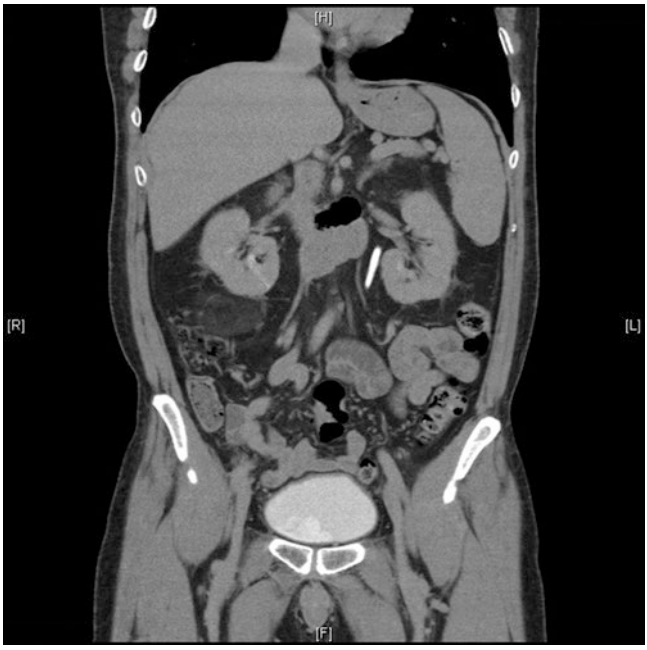

Fig. 26.3 Coronal reconstruction of late contrast enhanced CT images of right kidney angiomyolipoma

In the presence of tubular sclerosis, tumors are often multiple. These are associated with loss of *TSC2* encoding tuberin. Rare cutaneous angiomyolipomas have been reported.

Angiomyolipomas of the liver have been described and may be difficult to differentiate from hepatocellular carcinoma. In a publication of 74 hepatic angiomyolipomas [9], there was a strong female predominance and mean age was 42. As opposed to in the kidney, tuberous sclerosis is only rarely seen. The majority were asymptomatic, as in the kidney. Only one patient developed metastatic disease.

Imaging is classical and can often make the diagnosis with vascular and fatty components readily identified on CT or MRI.

Rare extrarenal angiomyolipomas are observed although in addition to liver, they have been reported in bone, colon, and other structures. They are rare in the adrenal where the lesion is usually angiomyelolipoma (see below).

The usual treatment of angiomyolipoma is surgical resection although many patients have been treated with selective arterial embolization. In many patients, especially those with large hepatic tumors, expectant observation is an acceptable approach.

Tumor rupture with hemorrhage is a severe complication of renal angiomyolipoma and is an indication for selective embolization. The goal in treatment is to perform as much nephron sparing procedure as is possible. Rarely, extensive angiomyolipoma can include inferior vena caval thrombosis. Radiofrequency ablation has been reported for angiomyolipoma, with uncertain results. For systemic therapy of recurrent angiomyolipomas, see Chap. 25, Table 25.2.

26.6 Angiomyelolipoma

Angiomyelolipomas are lesions that commonly occur in the adrenal gland and can be confused with adrenal tumors. They have been reported in association with Carney's Complex (pigmented nodular cortical hyperplasia, intra- and extra-cardiac myxoma, blue nevi, peripheral nerve tumors). A patient may be followed if a diagnosis can be made although in large size lesions excision is usually recommended. Spontaneous rupture has rarely been seen, especially in patients on long-term anticoagulation (Figs. 26.4 and 26.5).

26.7 Hibernoma

Hibernomas are rare tumors that are slow growing and benign. They resemble the glandular fat found in hibernating animals. The tumor is usually well vascularized with some poorly differentiated cells resembling brown adipocyte precursors. Brown adipocytes express the marker protein UCP1 as well as other genes related to lipogenesis, e.g., *PPARA*, *PPARG*, and *PPARGC1A*, and are thought to arise in close association with vessel walls. These tumors commonly occur in young adult

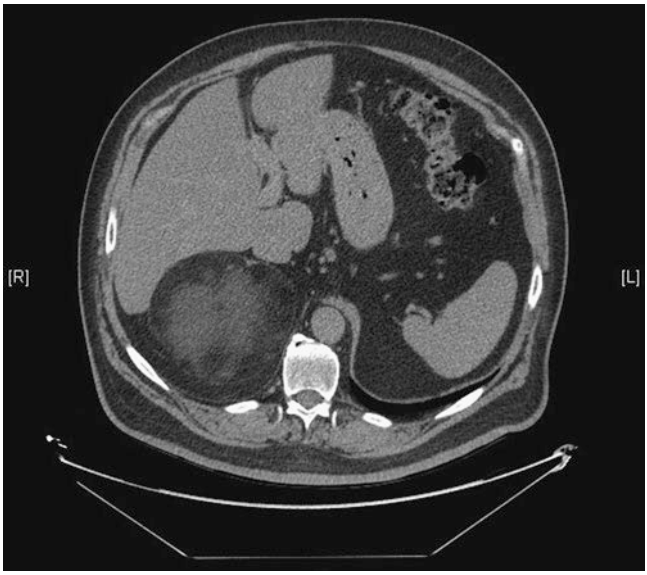

Fig. 26.4 Non-contrast axial CT image of a myelolipoma of the right adrenal gland

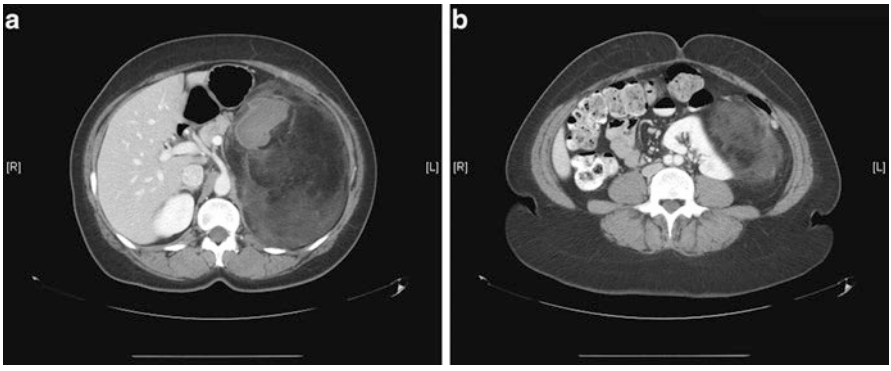

Fig. 26.5 Contrast enhanced axial CT images (**a**, **b**) of a left adrenal myelolipoma

males and usually in the posterior thorax. They are well defined by imaging with intermediate T1 and T2 signaling, and are PET avid, as is normal brown fat [10]. 11q13 chromosomal translocations and rearrangements are common in hibernomas; it was found that the likely genetic cause of these tumors is the loss of tumor suppressors AIP and MEN1, found in hereditary pituitary adenoma syndrome and multiple endocrine neoplasia type I, respectively [11].

Surgical resection is usually curative and rarely the lesions have been identified within the thorax and even within the pericardium (Figs. 26.6 and 26.7). Lesions have been described in the buttock and thigh and may show intense FDG-PET uptake.

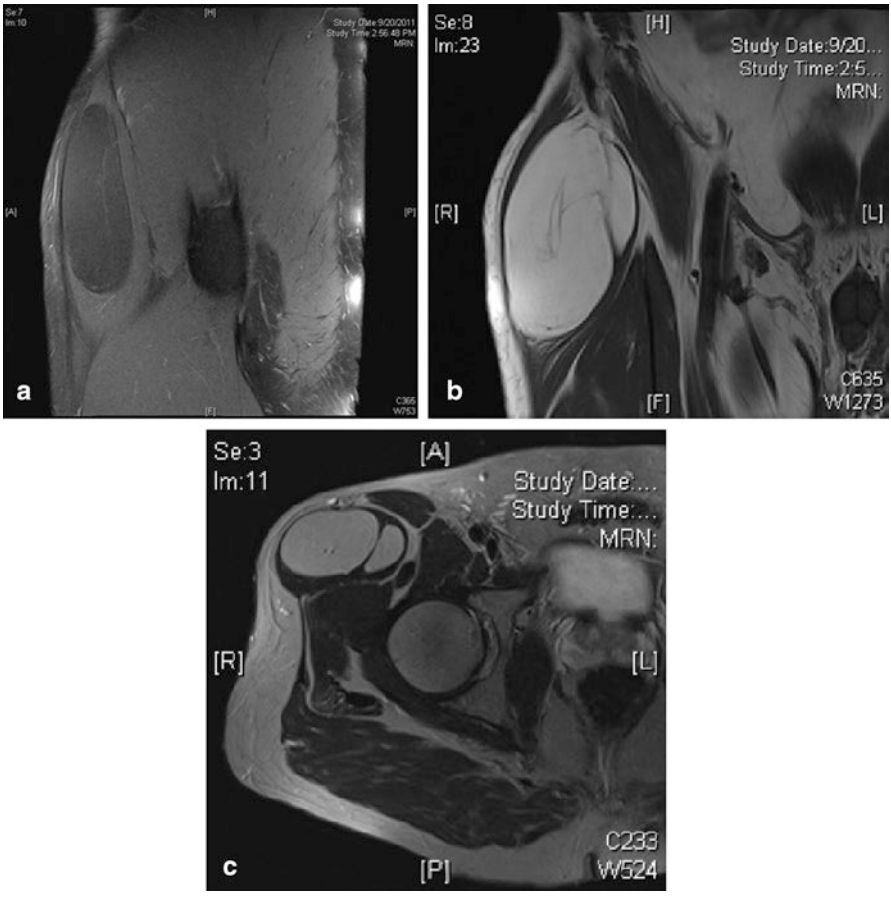

Fig. 26.6 T2 coronal (**a**) and T1 (**b**, **c**) weighted coronal (**b**) and axial (**c**) MRI images of a right thigh hibernoma

26.8 Elastofibroma

Elastofibroma is an uncommon, benign, very slow-growing soft tissue tumor. The cause is unknown and it usually presents at the inferior pole of the scapula (Figs. 26.8 and 26.9). They can be bilateral, often familial and will often have limited symptoms. MRI and CT are excellent imaging modalities and treatment is primarily surgical although there is no real indication for operation in the absence of symptoms. This is particularly true if the lesions are extensive beneath the scapula where resection would have some significant morbidity.

Chromosome analyses have been performed showing variable losses of 1p, 13q, 19p, and 22q and gains in *APC* (5q21) and *PAH* (12q23). The significance of these findings is uncertain. The increased preponderance of lesions on the right side suggests that they may be associated with a response to shoulder motion.

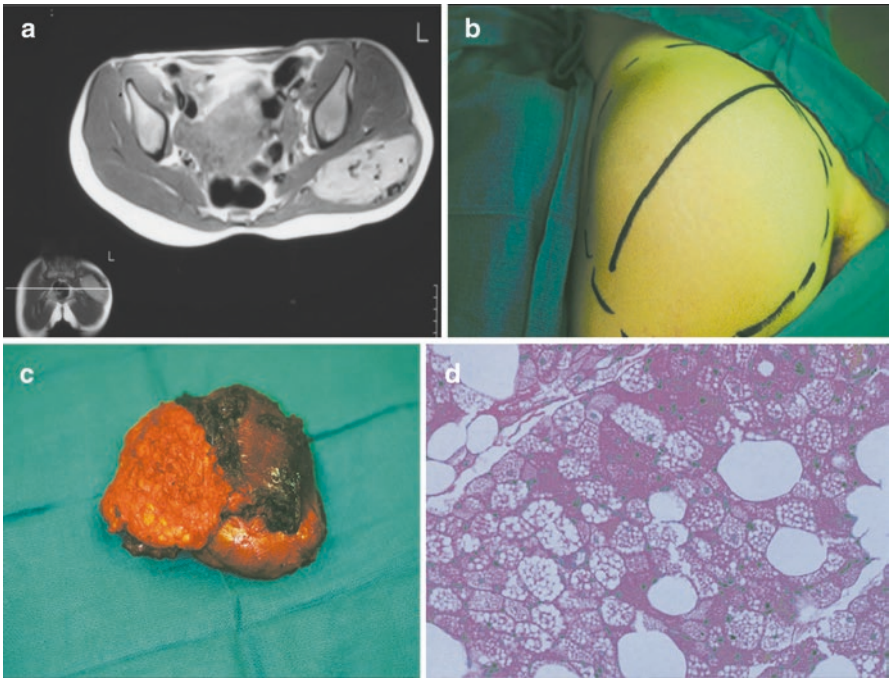

Fig. 26.7 (**a**) Axial T1 weighted image MRI of a left buttock hibernoma. (**b**) Preoperative and (**c**) specimen images of hibernoma. (**d**) High power microscopic image of a hibernoma (H&E, ×40**0**)

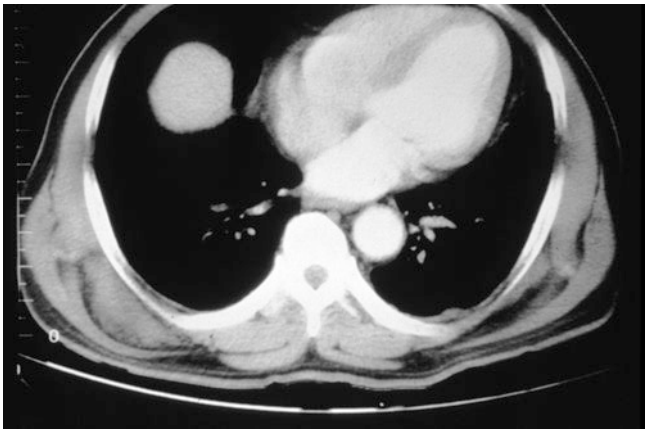

Fig. 26.8 Contrast enhanced axial CT image of an elastofibroma of inferior right peri-scapular soft tissue. From: Brennan MF, Lewis JJ. *Diagnosis and Management of Soft Tissue Sarcoma.* London: Martin Dunitz Ltd., 1998

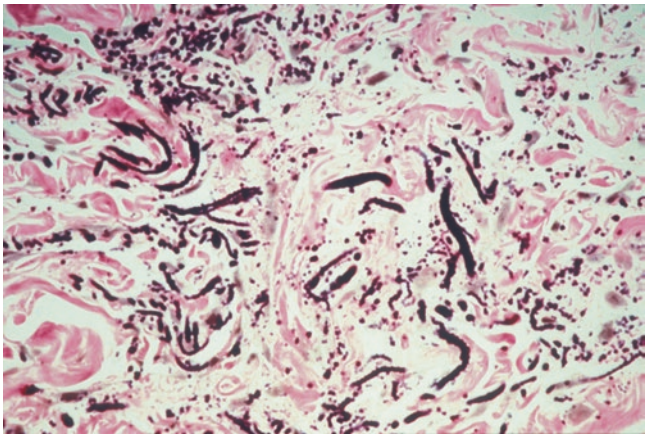

Fig. 26.9 Elastin stained microscopic image of an elastofibroma (×400 magnification). From: Brennan MF, Lewis JJ. *Diagnosis and Management of Soft Tissue Sarcoma.* London: Martin Dunitz Ltd., 1998

26.9 Granular Cell Tumors

Granular cell tumors are neural tumors of Schwann cell derivation with abundant lysosomal content and diffuse S-100 protein reactivity. Many behave in benign fashion but malignant forms have certainly been described.

Granular cell tumors can occur in the most unusual locations. Because of their origin from Schwann cells, they have been seen in the skin, soft tissue, and brain and can occur in synchronous sites. They have also been reported in the tongue and in the brain, but they are seen in any site where Schwann cells can be expected. A malignant version of granular cell tumor is described and behaves much like malignant peripheral nerve sheath tumor (Chap. 9). Case reports indicate activity of pazopanib in the unusual patient with recurrent or metastatic granular cell tumor.

26.10 Hemangioma

Hemangiomas are benign proliferations of blood vessels. They represent one end of a spectrum of tumors of endothelium that extends to borderline tumors with intermediate prognosis such as epithelioid hemangioendothelioma to the frankly malignant and often fatal angiosarcoma, as well as many relatively rare diagnoses along this spectrum. Other benign lesions of vasculature include vascular malformations, reactive proliferations, telangiectasias, and lymphangiomas.

Hemangiomas, which are among the most common soft tissue tumors, are broken down by a number of descriptors. Hemangiomas are typically described as cutaneous, subcutaneous, synovial, osseous, or intramuscular, by type of blood vessel (capillary, venous, cavernous), and/or cell type (e.g., epithelioid, spindle cell). Hemangiomas are

distinguished from vascular malformations as hemangiomas grow over time in excess to the growth of the normal structure, can regress spontaneously, and have a proliferative endothelial component. They also need to be distinguished from reactive lesions such as the lesions of bacillary angiomatosis (*Bartonella* sp. infection) or similar lesions found in Oroya fever (*B. bacilliformis* infection) [12].

Hemangiomas can be managed surgically, but have a wide variety of patterns of change over time, from indolent and slow growing to aggressive and destructive (Figs. 26.10, 26.11, and 26.12). Interestingly, pediatric hemangiomas go through phases of growth and involution and often can be observed. Pediatric hemangiomas are the diagnosis in which Judah Folkman's angiogenesis theories of cancer [13] were first tested, in the form of interferon [14]. It is rather remarkable that involution of hemangiomas can be triggered with the use of beta blockers such as propranolol [15], which may have effects on β2 adrenergic receptors which then have effect on vasoconstriction, angiogenesis, and apoptosis [16]. Glucocorticoids have also been employed and can be used for a brief (2–3 week) course before tapering if there are no beneficial effects observed.

For superficial pediatric hemangiomas in the proliferative stage, pulsed dye lasers (585–590 nm) can treat lesions less than 2–3 mm in thickness [17]. For thicker lesions, laser treatments are not nearly as effective. Radiofrequency ablation can be considered for deep, smaller lesions. There are other situations where more traditional surgical techniques can be employed for the treatment of hemangiomas, for example, partial hepatectomy for giant hemangiomas of the liver causing abdominal pain [18]. The concern for some lesions is the anatomical restrictions of an anatomical site to resect such a lesion completely, for example, in the mediastinum, which not surprisingly is associated with recurrence. In other cases, attempts must be

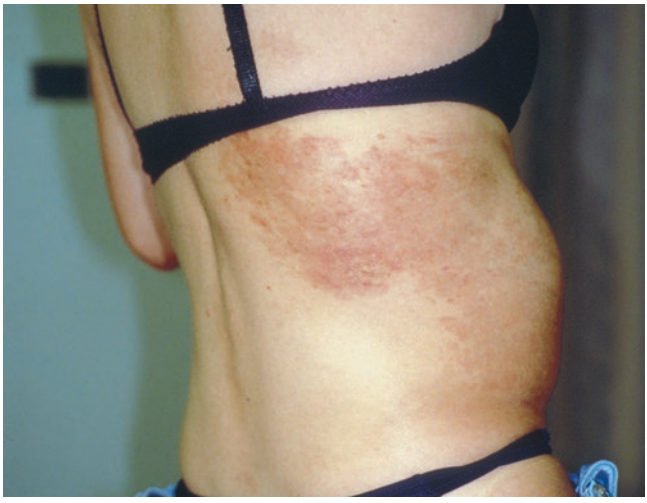

Fig. 26.10 Hemangioma of the entire right lateral chest and abdominal wall. From: Brennan MF, Lewis JJ. *Diagnosis and Management of Soft Tissue Sarcoma.* London: Martin Dunitz Ltd., 1998

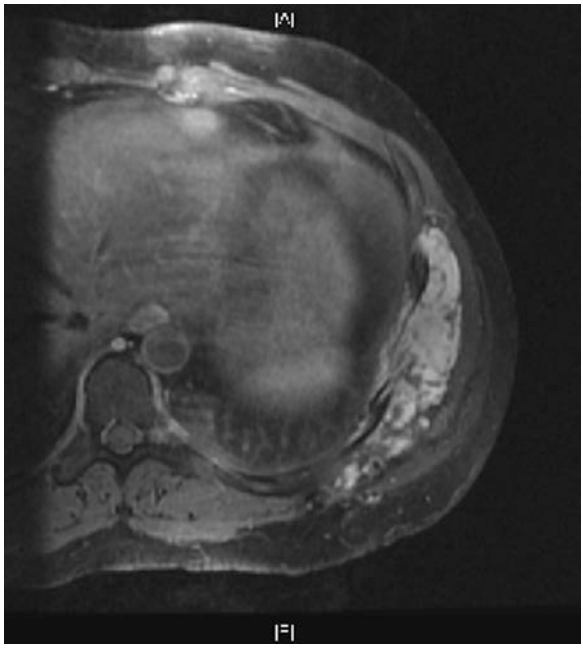

Fig. 26.11 T1 weighted axial MRI image of a chest wall hemangioma

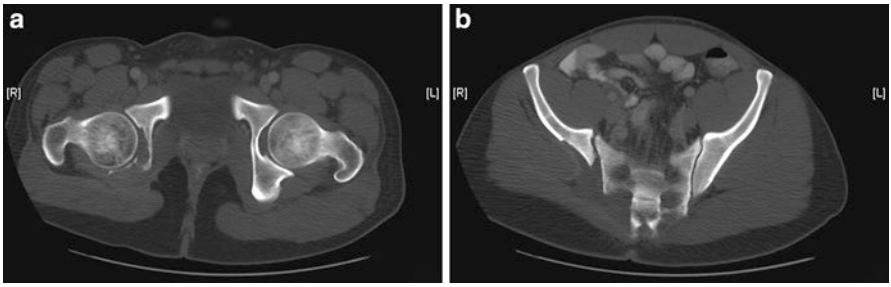

Fig. 26.12 Non-contrast CT images (**a**, **b**) using bone windows demonstrating a soft tissue hemangioma causing bony destruction of the acetabulum, ilium and sacrum

made to resect or at least embolize the primary tumor, given the consumptive coagulopathy observed with some benign vascular lesions, termed Kasabach–Merritt syndrome [19].

Other systemic agents such as vincristine can be employed in symptomatic lesions. Antiangiogenic therapy with bevacizumab has been shown effective in case reports of bevacizumab in choroidal hemangiomas (sometimes in combination with photodynamic therapy), while the use of oral VEGF receptor inhibitors has yielded little benefit in the few patients we have treated with stable disease to minor response in selected patients. The treatment of hemangiomas remains an area open to research and innovation both on local and systemic therapy fronts.

26.11 Leiomyoma

Benign tumors of smooth muscle are much more common in the uterus, but they can occur in the gastrointestinal tract and among some mucosal sites but rarely deep in the extremity or retroperitoneum. In the uterus, leiomyomas are far more common than leiomyosarcomas. Uterine leiomyomas may have an increased mitotic rate, which makes such tumors difficult to distinguish from a very low-grade leiomyosarcoma. Those tumors in the grey zone regarding malignancy are termed smooth muscle tumors of uncertain malignant potential, or STUMP [20]. PEComas, which can also mark positive for smooth muscle markers (and melanoma markers), are part of the differential diagnosis.

26.12 Schwannoma

Schwannomas are benign lesions most commonly identified in the 20–50-year-old age group. Common sites include the retroperitoneum and neck and neck. These lesions are slow growing and when the diagnosis can be made, symptomatic patients can be followed. Given the characteristics and histological picture the diagnosis is readily made even on a core needle biopsy. Retroperitoneal paravertebral schwannomas are more likely to contain a cellular schwannoma, more cellular variant of the classical schwannoma (Fig. 26.13). On occasions, the schwannoma can mimic a malignant tumor with extensive bone invasion.

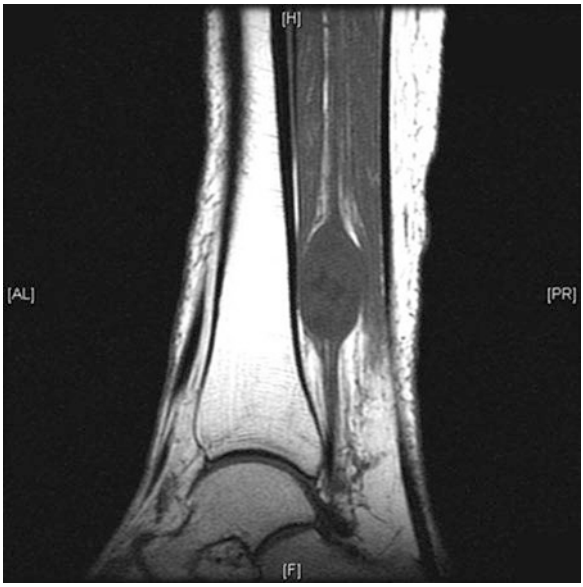

Fig. 26.13 T1 weighted sagittal MRI image of a posterior tibial nerve schwannoma

Rarely, malignant transformation has been described ex-schwannoma, typically presenting as epithelioid malignant peripheral nerve sheath tumors, in the absence of familial syndromes (neurofibromatosis type I or type II) [21]. If the diagnosis is firm and the patient is symptomatic, schwannomas may be removed with minimally invasive surgery to limit morbidity.

26.13 Neurofibroma

Neurofibromas are common and can occur either in the presence or absence of neurofibromatosis. Those occurring as solitary lesions are usually small, slow-growing cutaneous or subcutaneous nodules (Fig. 26.14). Those occurring in neurofibromatosis type I have an autosomal dominant mutation at the 17q11.2 locus, and are associated with other finds such as café au lait spots, multiple cutaneous neurofibromas, and hamartomas of the iris. Patients with neurofibromatosis are at risk of malignant transformation (i.e., malignant peripheral nerve sheath tumors) in their preexistent plexiform or intraneural neurofibromas as well as other malignant lesions in the brain or adrenal gland.

26.14 Myxoma

Intramuscular myxoma is a rare tumor that occurs in adults, usually in the extremities within the larger muscles. Diagnosis is made by histological examination of a lesion characterized with abundant mucoid material, but very few cells. The lesions are often less than 10 cm and behave in a clinically benign fashion [22].

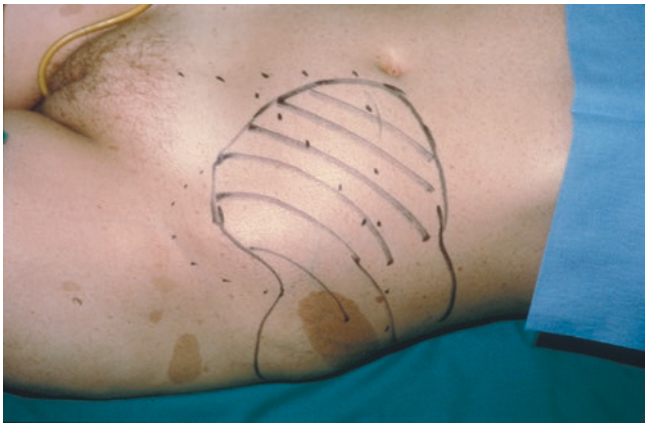

Fig. 26.14 Café au lait spot and large left hip malignant peripheral nerve tumor. From: Brennan MF, Lewis JJ. *Diagnosis and Management of Soft Tissue Sarcoma.* London: Martin Dunitz Ltd., 1998

Myxomas can essentially occur in any muscular area of the body and are a common primary cardiac tumor, most commonly arising in the left atrium [23]. They present slow-growing, deep-seated lesions, which show on CT as an area with thin septation and mild to zero PET image uptake. They have been characterized by content of glycosamine glycans, and the challenge is to separate them from other low-grade myxoid sarcomas, specifically myxoid liposarcoma and less frequently myxofibrosarcomas. Albumin content has also been used for further characterization [24]. A recurrent *GNAS1* activating mutation has been shown to be present in most intramuscular myxomas, which can serve as a very useful molecular test in excluding the look-alike myxoid lesions (i.e., low-grade myxoid sarcomas) [25]. Furthermore, myxomas lack the characteristic chromosomal translocations, as seen in myxoid liposarcoma, low-grade fibromyxoid sarcomas and extraskeletal myxoid chondrosarcomas.

Cardiac myxomas are known to carry mutations in the gene encoding protein kinase A type I-alpha regulatory subunit *PRKAR1A* in patients with Carney complex (distinguished from Carney triad or Carney–Stratakis syndrome) [26, 27]. Carney complex is a multiple neoplasia syndrome characterized by spotty skin pigmentation, cardiac and other myxomas, endocrine tumors, and psammomatous melanotic schwannomas. The findings from the genetic syndrome are carried over to a moderate proportion of sporadic cardiac myxomas, which have mutations in *PRKAR1A* as well [28].

26.15 Angiomyxoma

Angiomyxomas, particularly of the genital, pelvic, or perineal areas, have been confused with scrotal masses, hydroceles, and inguinal hernia, and are thought to be more common in females but also be seen in males (Fig. 26.15). They are usually immunoreactive for estrogen and progesterone receptors. Histologically, they are characterized by oval to spindle cell tumor cells in a myxoid stroma along with hyalinized vessels and a characteristic immunophenotype. Local recurrence can result in very significant morbidity but distant metastases do not occur [29]. The primary management remains surgical resection although gonadotropin releasing hormone agonists and antiestrogens has been utilized for recurrent disease [30] (Fig. 26.16).

26.16 Angiofibroma

There are two pathologic entities being discussed under this section: cellular angiofibroma and angiofibroma of soft tissue, both benign fibroblastic neoplasms which are richly vascularized.

Cellular angiofibroma, a.k.a. male angiomyofibroblastoma-like tumor, is a rare neoplasm with equal gender distribution that occurs in the superficial soft tissues of the vulva and inguinoscrotal regions. This tumor is closely related to spindle cell lipoma and mammary-type myofibroblastoma, sharing deletions at the 13q14 locus, which results in loss of retinoblastoma protein expression by immunohistochemistry [31]. The commonly observed expression for estrogen and progesterone receptors in both genders

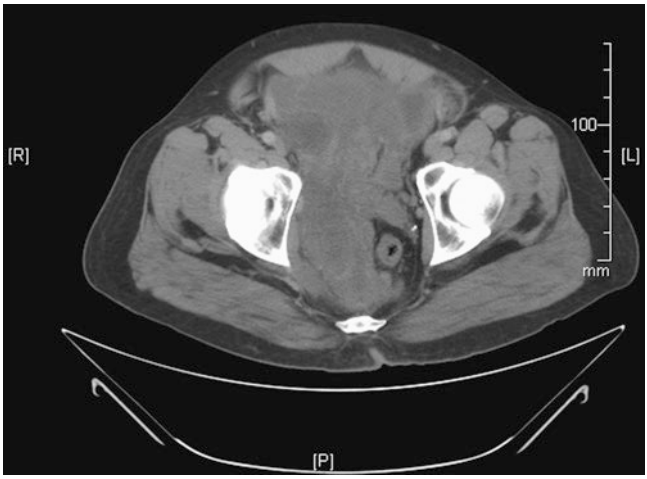

Fig. 26.15 Axial contrast enhanced CT image of a recurrent pelvic angiomyxoma

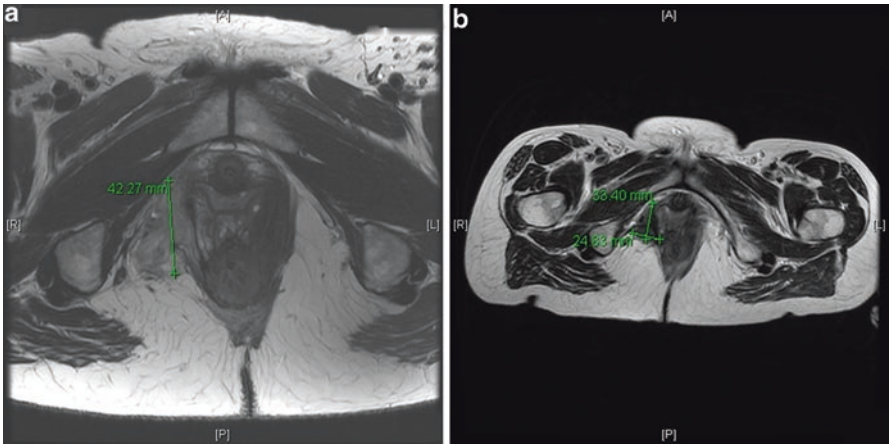

Fig. 26.16 Axial T1 weighted MRI images of a paravaginal angiomyxoma before (**a**) and after (**b**) leuprolide therapy

suggests that these hormones may play a role in the pathogenesis of this tumor. This tumor is also often positive for CD34, and desmin is identified in a small subset of cases.

Angiofibroma of soft tissue is a recently described benign fibrovascular soft tissue tumor, which is associated with a recurrent *AHRR-NCOA2* gene [32, 33]. Microscopically, the tumors are composed of uniform bland spindle cells embedded in a myxoid stroma and a prominent vascular network. The tumors are often EMA positive and less commonly immunoreactive for CD34, SMA, or desmin. The presence of NCOA2 gene rearrangement as demonstrated by FISH can distinguish this lesion from other low-grade myxoid sarcomas with prominent vasculature (Fig. 26.17). Surgery is the primary modality of treatment.

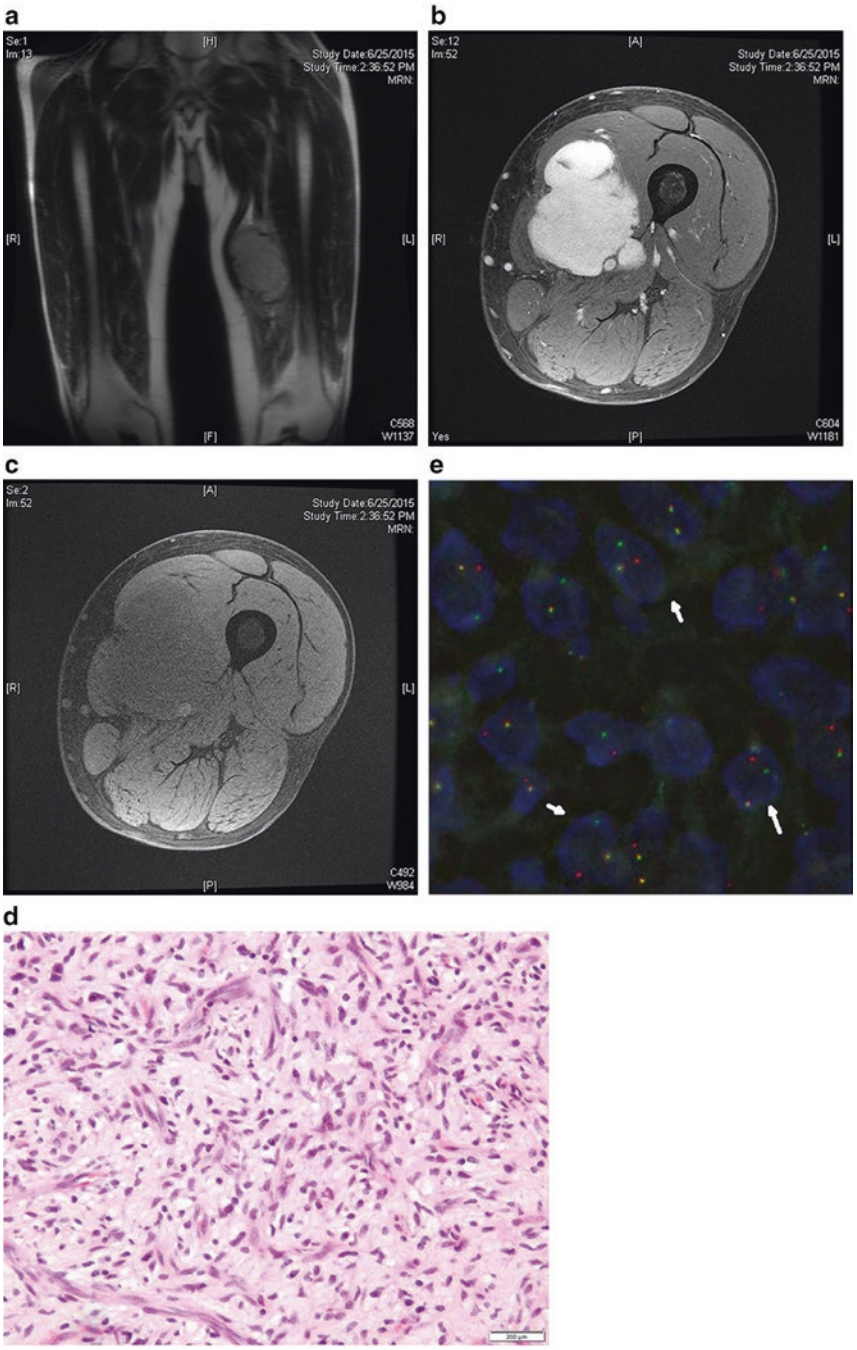

Fig. 26.17 (**a**–**c**) A 51-year-old man with a 8×7×9 cm vascular lesion which partially encases and narrows the femoral artery. (**d**) Proliferation of bland spindle cells associated with a brisk capillary network in a loosely myxoid stroma. (**e**) FISH showing NCOA2 gene rearrangements, white arrow with break-apart signals (*red*, centromeric, green telomeric)

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Chapter 27
Reactive Lesions

27.1 Myositis Ossificans

Myositis ossificans usually occurs in the extremity following an episode of trauma. This diagnosis can usually be excluded in late presentation by a plain film showing soft tissue calcification or an MRI showing the classic infiltration of soft tissues rather than discrete tumor masses (Fig. 27.1). Calcifications are not specific and may occur in synovial sarcoma or osteogenic sarcoma, and should always be considered. Resolution of the lesion is to be expected in myositis ossificans, in particular when the diagnosis is made early. The diagnosis can be difficult and lesions are often hemorrhagic on biopsy, given that other entities including dedifferentiated liposarcoma can calcify, caution should be made before casually giving a diagnosis.

27.2 Nodular Fasciitis

Nodular fasciitis, also termed pseudosarcomatous fasciitis, is a benign lesion usually seen in middle-aged adults but has been reported in older and young patients. The lesion often grows rapidly but is usually self-limited and pain and tenderness are common features of presentation. Most commonly seen in the upper extremity around the elbow joint, the lesion arises in subcutaneous fascia. Diagnosis can be difficult as the lesions are often nodular and nonencapsulated, consisting predominantly of myofibroblasts arranged in irregular bundles or fascicles. Remarkably, a recurrent *MYH9-USP6* gene fusion was described in nodular fasciitis, suggesting a novel model of aborted neoplasia [1]. Simple excision is usually curative.

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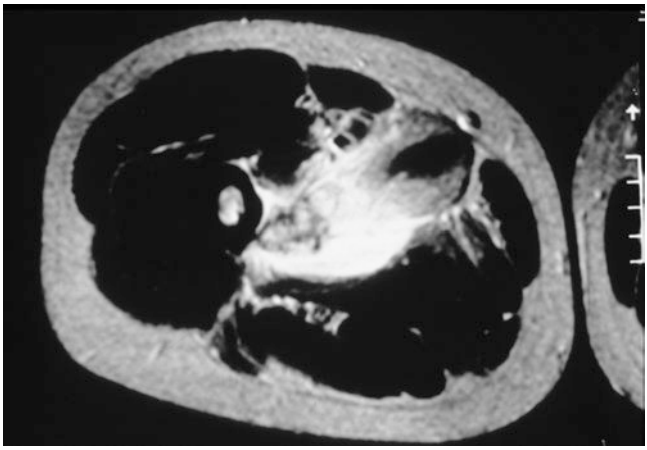

Fig. 27.1 Myositis ossificans: T1 weighted MRI showing the absence of discrete mass and intermuscular extension. From: Brennan MF, Lewis JJ. *Diagnosis and Management of Soft Tissue Sarcoma.* London: Martin Dunitz Ltd., 1998

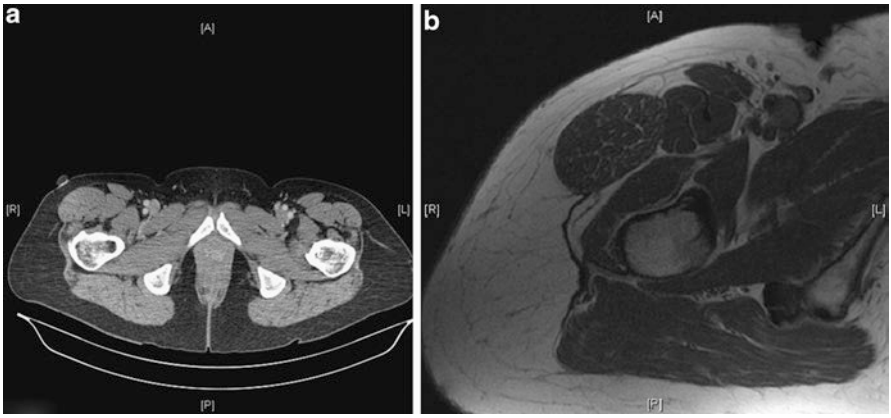

Fig. 27.2 (**a**) CT image and (**b**) T1 weighted MRI image of a patient with unilateral tensor fascia lata hypertrophy

27.3 Sarcoma Masquerade

Unilateral hypertrophy of the tensor fascia lata can be confused with a soft tissue tumor [2]. The patient presents with a palpable mass but it is not discrete. However, it is clearly different from the contralateral side. Although cases are limited it appears to be more common in females but can be readily distinguished on CT or MRI (Fig. 27.2).

A further masquerade is the Morel-Lavallée lesion. This lesion commonly occurs in the proximal thigh and it has characteristic features on MRI. Morel-Lavallée

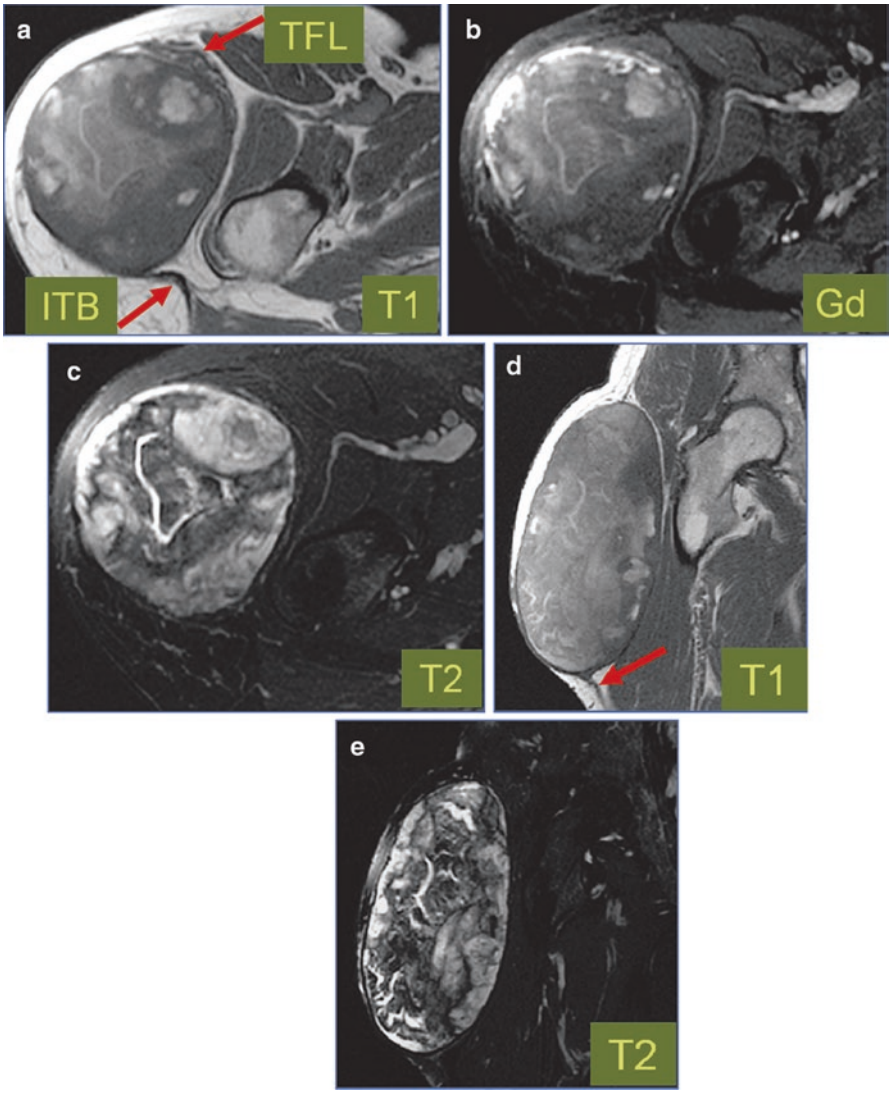

Fig. 27.3 (**a**–**e**) MRI images (T1 or T2 weighted) of a Morel-Lavallée lesion of the proximal right thigh. *TFL* tensor fascia lata, *ITB* iliotibial band, *Gd* gadolinium enhancement

lesions are unusual effusions, usually the result of skin and subcutaneous fatty tissue separating from the underlying fascia. They are common in the trochanteric region because of the rich vascular plexus that pierces the fascia lata. The disrupted capillaries continuously drain into the perifascial plane filling the cavity with blood, lymph, and debris. Because the inflammatory reaction occurs, they can appear encapsulated and be suggestive of sarcoma [3]. An example is shown in Fig. 27.3, where following a resection of a synovial sarcoma recurrence was expected, but instead the sarcoma masquerade demonstrated (see MRI).

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