Management of Soft Tissue Sarcoma

Murray F. Brennan
Cristina R. Antonescu
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Murray F. Brennan, MD
International Center
Department of Surgery
Memorial Sloan Kettering Cancer Center
New York, NY, USA

Kaled M. Alektiar, MD
Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center
New York, NY, USA

Cristina R. Antonescu, MD
Department of Pathology
Memorial Sloan Kettering Cancer Center
New York, NY, USA

Robert G. Maki, MD, PhD
Monter Cancer Center
Hofstra Northwell School of Medicine
and Cold Spring Harbor Laboratory
Lake Success, NY, USA

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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.

New York, NY — Murray F. Brennan
New York, NY — Cristina R. Antonescu
New York, NY — Kaled M. Alektiar
Lake Success, NY — Robert G. Maki

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.

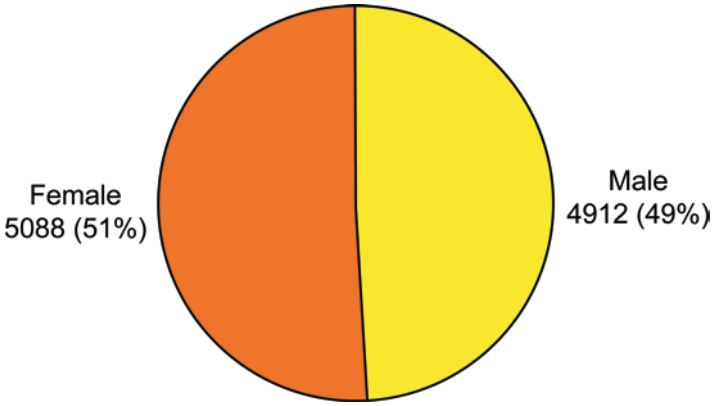

Fig. 1.3 Distribution by gender for adult patients with soft tissue sarcoma, all sites. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$

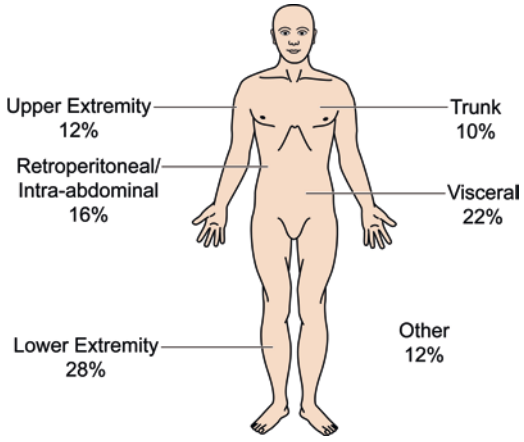

Fig. 1.4 Distribution by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$

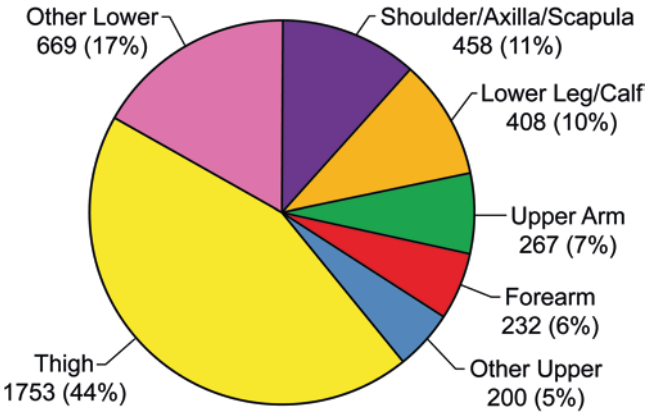

Fig. 1.5 Distribution by site within the extremities for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 3987$. With permission from: Brennan MF, et al. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. Ann Surg 260(3):416–422, 2014

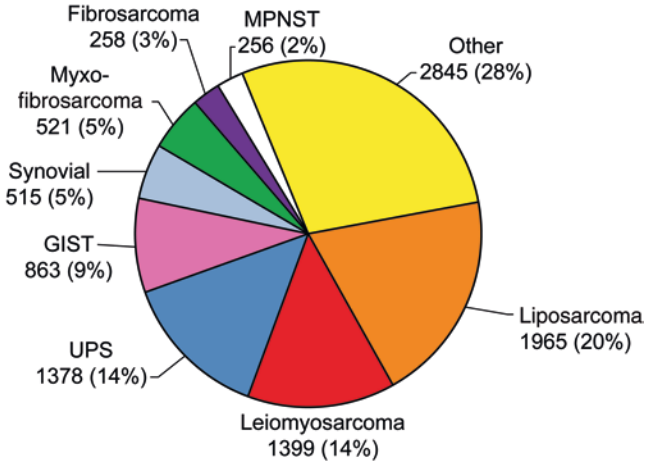

Fig. 1.6 Distribution by histology for adult patients with soft tissue sarcoma, all sites. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$. *MPNST* malignant peripheral nerve sheath tumor, *GIST* gastrointestinal stromal tumor, *UPS* undifferentiated pleomorphic sarcoma

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.

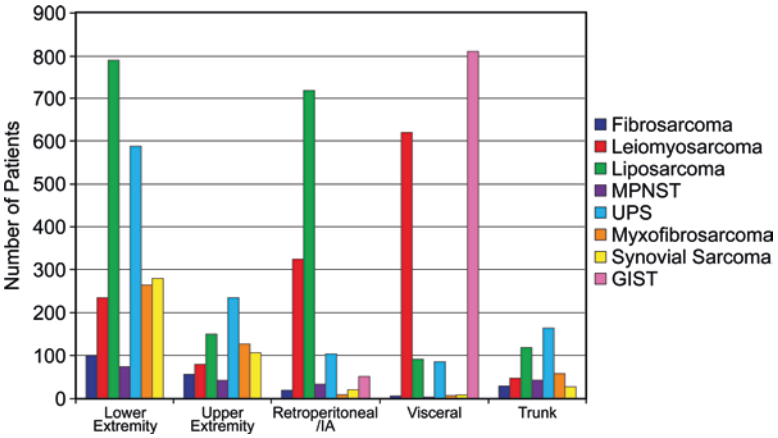

Fig. 1.7 Predominant histopathology by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 6536$. *MPNST* malignant peripheral nerve sheath tumor; *GIST* gastrointestinal stromal tumor; *UPS* undifferentiated pleomorphic sarcoma; *IA* intra-abdominal. With permission from: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

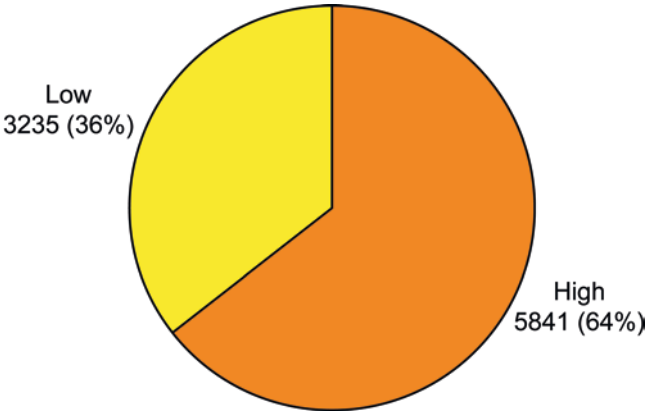

Fig. 1.8 Distribution by grade for adult patients with soft tissue sarcoma (excludes GIST), all sites. MSKCC 7/1/1982–5/31/2013 $n = 9076$

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

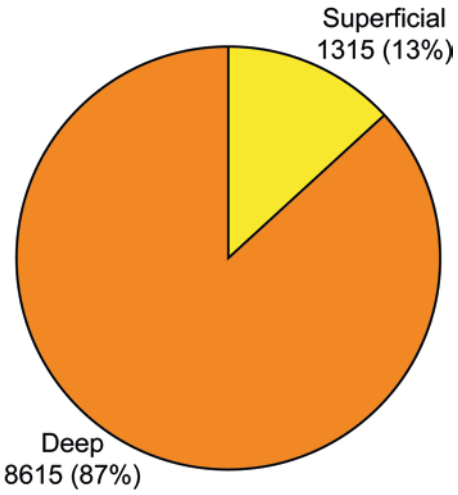

Fig. 1.9 Distribution of primary lesion by depth for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 9930$

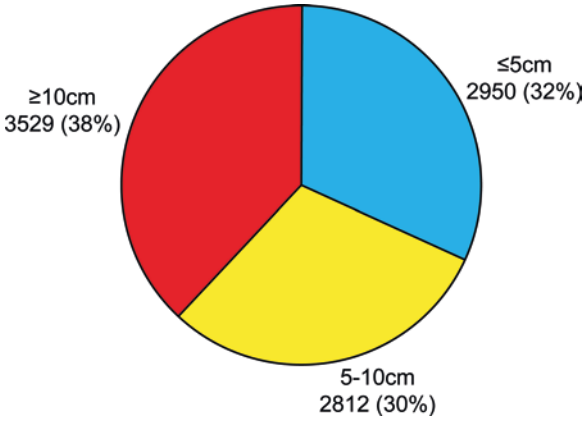

Fig. 1.10 Distribution by size for adult patients with soft tissue sarcoma, all primary sites. MSKCC 7/1/1982–5/31/2013 $n = 9291$

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

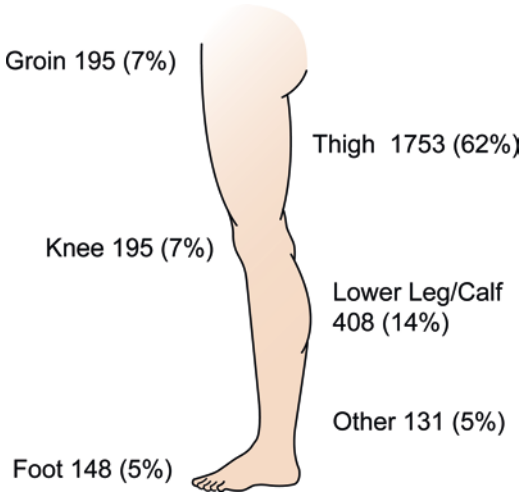

Fig. 1.11 Distribution within the lower extremity by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 2830$

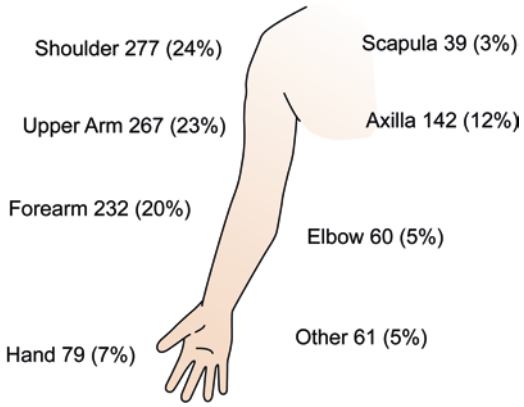

Fig. 1.12 Distribution within the upper extremity by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 1157$

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-

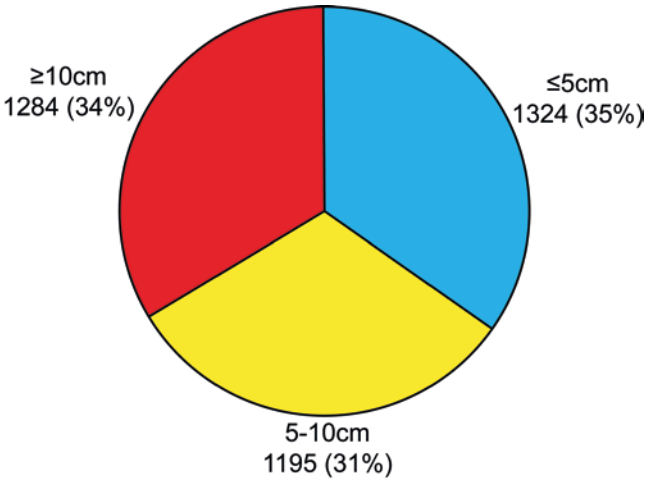

Fig. 1.13 Distribution within extremities by size for adult patients with soft tissue sarcoma. MSKCC 7/1/1982–5/31/2013 $n = 3803$

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

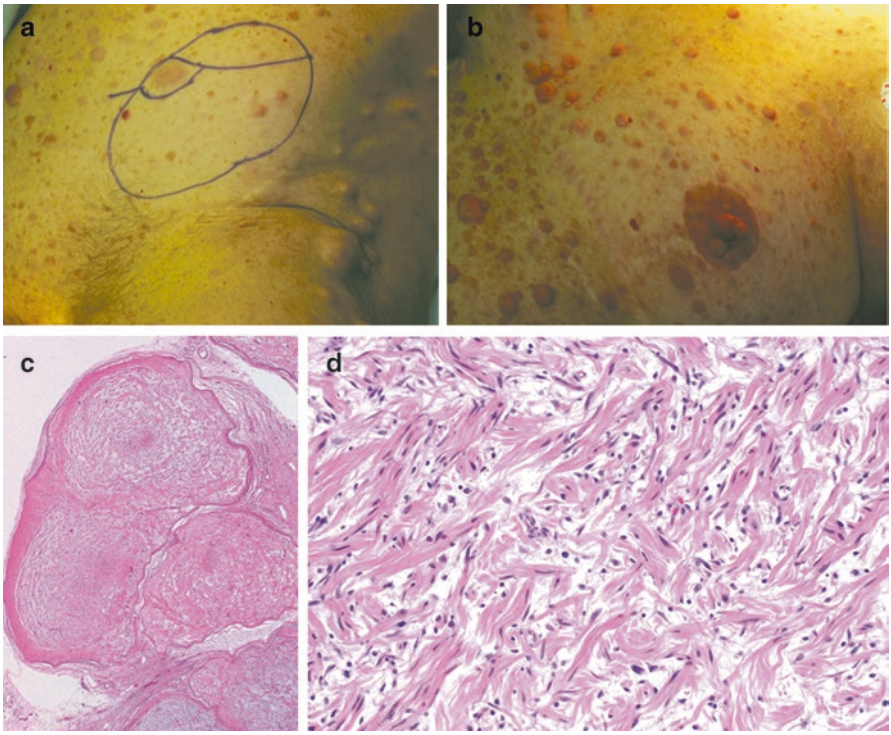

Fig. 1.14 Neurofibromatosis—neurofibroma left abdominal wall: (**a** and **b**) Gross appearance of multiple neurofibromas and café au lait spots; (**c**) whole mount low power microscopic appearance (H&E) and (**d**) high power

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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