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Managem
Soft Tissue

Management of Soft Tissue Sarcoma

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Springer

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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.

In addition, there are few data collected in one place regarding systemic therapy for different diagnoses. While 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 have endeavored to collect at least some of those data herein, and to speculate based on anecdote and case reports possible treatments for rarer subtypes.

We stand on the cusp of a revolution in the diagnosis of cancer, with the emergence of genetic and other sophisticated tests of specific cancers now leading rapidly to the development and use of new agents to treat those cancers. One need not look beyond the success of imatinib in Gastrointestinal Stromal Tumors (GIST) or chronic myeloid leukemia (CML), vemurafenib in melanoma, or crizotinib in anaplastic lymphoma kinase (ALK)+lung cancer (and ALK+inflammatory myofibroblastic tumor) to realize that we will not diagnose or treat sarcomas the same way 10 years from now as we do today. We hope this contribution will serve as a cairn on a long and otherwise largely unmarked journey to best identify, characterize, treat, and hopefully eliminate these forms of cancer.

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 Memorial Sloan-Kettering Cancer Center 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. Most recently, Nicole Moraco has been responsible for the oversight and maintenance of the quality of the databases and production of the majority of the figures in this text.

As we review a database of more than 9,000 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.

Contents

Chapter 1
General Description

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 CE), it was suggested they were a cancerous tumor and caution was 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 them 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 University Medical College 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

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Fig. 1.1 Fred W. Stewart, M.D., Ph.D., 1894–1991, Pathologist, Memorial Sloan-Kettering Cancer Center (Used with permission from Brennan and Lewis [7])

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].

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 from 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 postmastectomy patients with chronic lymphedema [8].

Fig. 1.2 Norman Treves, MD, 1894–1964, Breast Surgeon, Memorial Sloan-Kettering Cancer Center (Used with permission from Brennan and Lewis [7])

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.

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 8,000 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 seen 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 in Fig. 1.6. The distribution of dominant histology type by site is in Fig. 1.7.

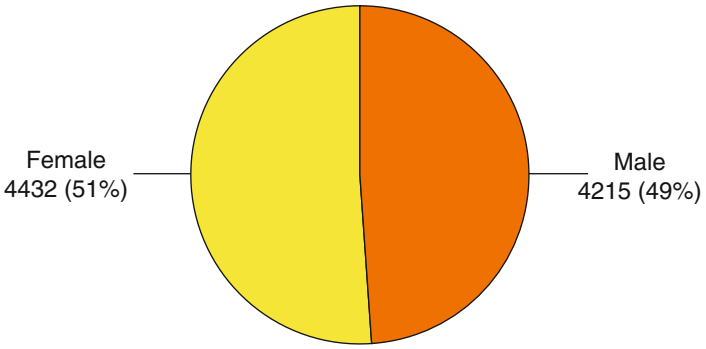
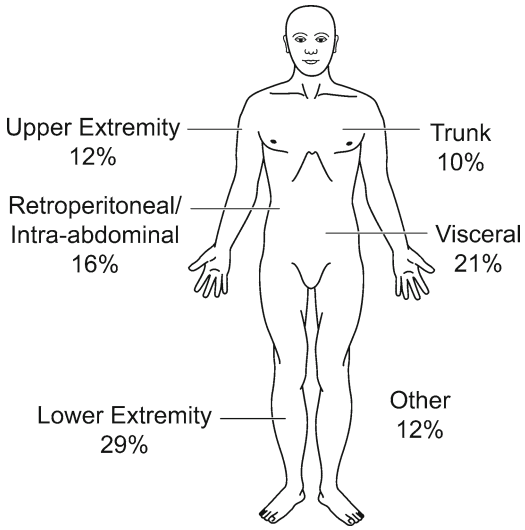


Fig. 1.3 Distribution by gender for adult patients with soft tissue sarcoma, all sites. MSKCC 7/1/1982-6/30/2010 n = 8,647

Fig. 1.4 Distribution by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982-6/30/2010 n = 8,647



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

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

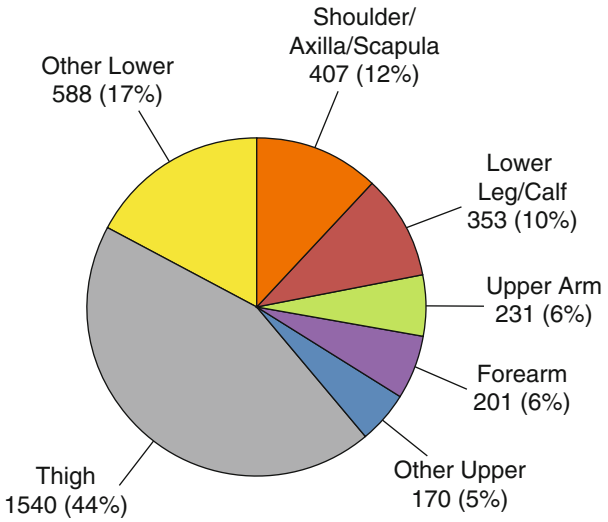


Fig. 1.5 Distribution by site within the extremities for adult patients with soft tissue sarcoma. MSKCC 7/1/1982-6/30/2010 n = 3,490

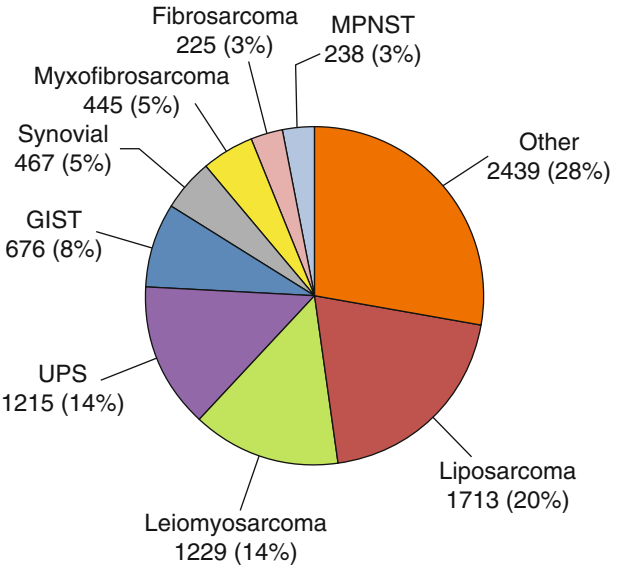


Fig. 1.6 Distribution by histology for adult patients with soft tissue sarcoma, all sites. MSKCC 7/1/1982-6/30/2010 n = 8,647. *GIST* gastrointestinal stromal tumor, *UPS* undifferentiated pleomorphic sarcoma, *MPNST* malignant peripheral nerve sheath tumor

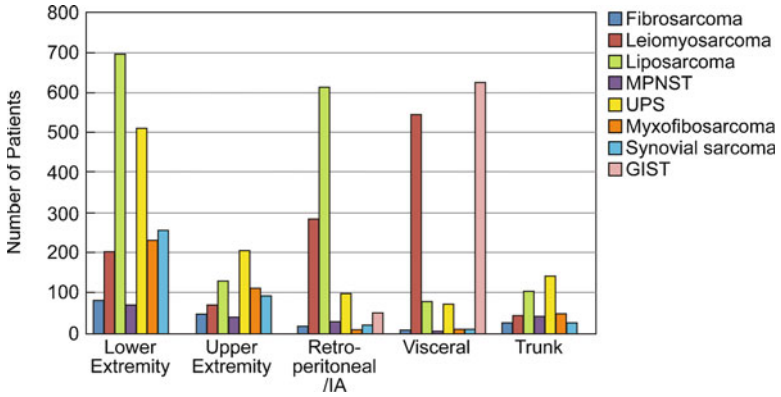


Fig. 1.7 Predominant histopathology by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982-6/30/2010 n = 5,653. *MPNST* malignant peripheral nerve sheath tumor, *GIST* gastrointestinal stromal tumor, *UPS* undifferentiated pleomorphic sarcoma, *IA* intra-abdominal

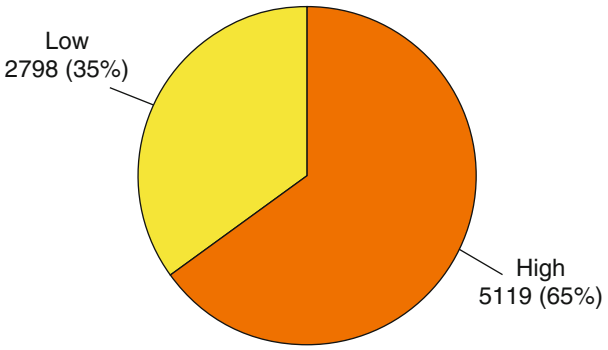
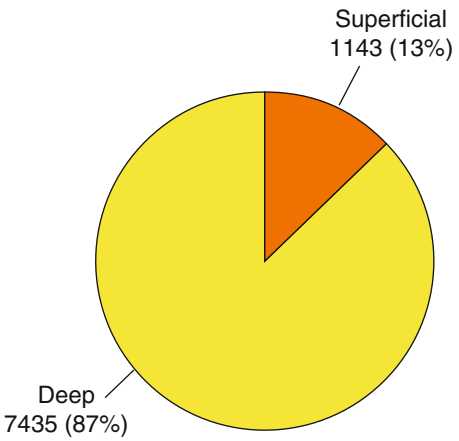


Fig. 1.8 Distribution by grade for adult patients with soft tissue sarcoma (excludes GIST), all sites. MSKCC 7/1/1982-6/30/2010 n = 7,917

Fig. 1.9 Distribution of primary lesion by depth for adult patients with soft tissue sarcoma. MSKCC 7/1/1982-6/30/2010 n = 8,578



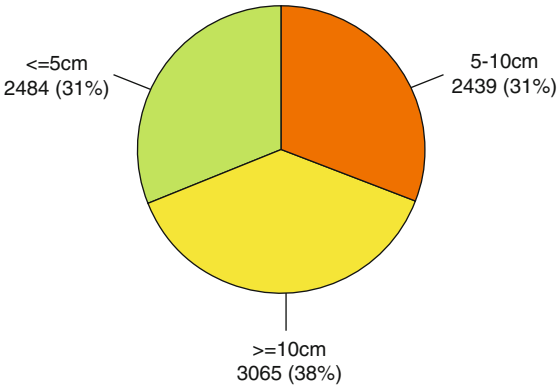


Fig. 1.10 Distribution by size for adult patients with soft tissue sarcoma, all primary sites. MSKCC 7/1/1982-6/30/2010 n = 7,988

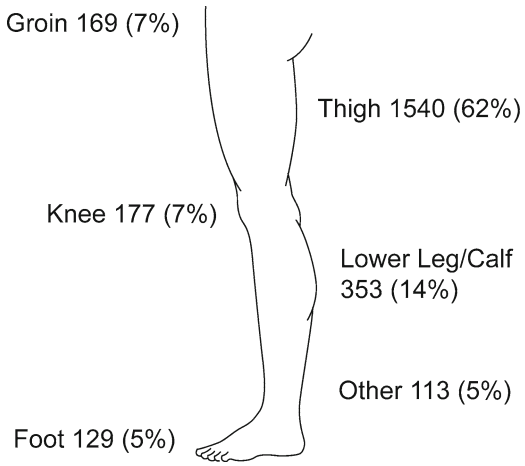


Fig. 1.11 Distribution within the lower extremity by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982-6/30/2010 n = 2,481

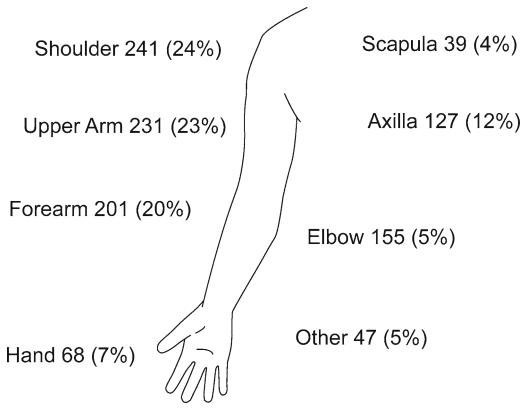


Fig. 1.12 Distribution within the upper extremity by site for adult patients with soft tissue sarcoma. MSKCC 7/1/1982-6/30/2010 n = 1,109

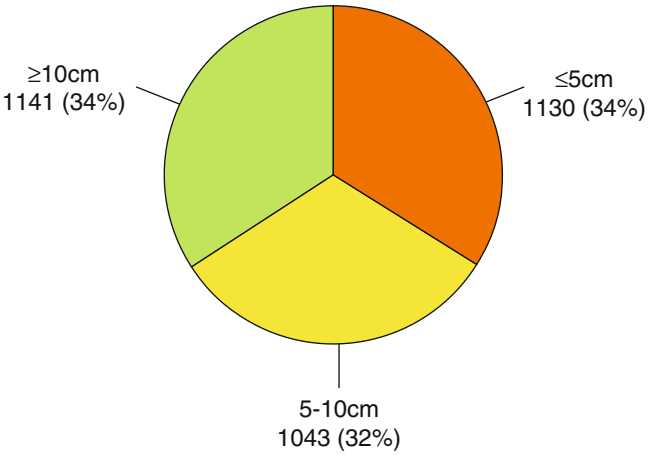


Fig. 1.13 Distribution within extremities by size for adult patients with soft tissue sarcoma. MSKCC 7/1/1982-6/30/2010 n = 3,314

Predisposing and Genetic Factors

Predisposing and genetic factors have been identified and include the genetic predisposition in the patient with neurofibromatosis (Fig. 1.14), familial adenomatous polyposis (FAP) coli, Li-Fraumeni syndrome, and retinoblastoma, although the majority of soft tissue sarcomas have no clear identified cause. There are two separate types: one that contains specific genetic alterations (Table 1.1), including variable gene rearrangements, fusion genes, reciprocal translocations, and specific mutations, such as those seen for *KIT* or *PDGFRA* in gastrointestinal stromal tumors 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 and multiple and represent variable chromosomal gains or losses. This latter group often has a high prevalence of *TP53* and *RB1* mutations or deletion. *TP53* mutations have been associated with the Li-Fraumeni syndrome [83]. 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 to the genetic predisposition to soft tissue sarcoma as has been seen in neurofibromatosis [84] and familial adenomatous polyposis [85]. 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 [86]. Patients who

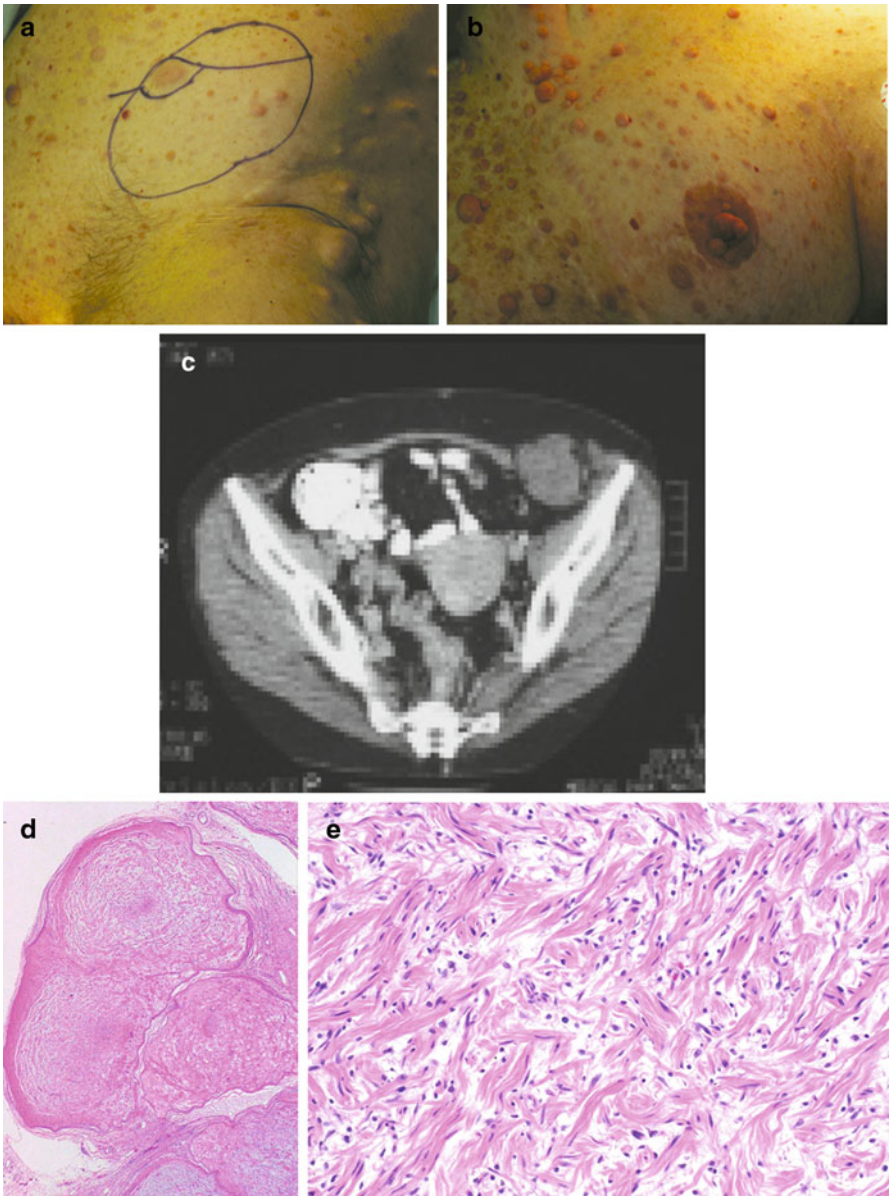


Fig. 1.14 Neurofibromatosis – neurofibroma left abdominal wall: (**a**, **b**) gross appearance of multiple neurofibromas and café au lait spots; (**c**) contrast-enhanced CT scan of the pelvis showing a soft tissue neurofibroma; (**d**) whole mount low-power microscopic appearance (H&E) and (**e**) high-power (200×)

Table 1.1 Cytogenetic table

Sarcoma subtype	Genetic alteration	Affected gene(s)	Frequency	References
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FOXO1A*	70%	[9–11]
	t(1;13)(p36;q14)	*PAX7-FOXO1A*	15%	
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	*ASPSCR1-TFE3*	>95%	[12]
Angiomatoid fibrous histiocytoma	t(2;22)(q34;q12)	*EWSR1-CREB1*	>90%	[13, 14]
	t(12;22)(q13;q12)	*EWSR1-ATF1*	<5%	
Clear-cell sarcoma (melanoma of soft parts)	t(12;22)(q13;q12)	*EWSR1-ATF1*	>90%	[15–19]
	t(2;22)(q34;q12)	*EWSR1-CREB1*	<5%	
Atypical Ewing sarcoma	t(4;19)(q35;q13.1)	*CIC-DUX4*	unk	[20–24]
	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%	[25, 26]
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	*COL1A1-PDGFB*	>60%	[27–29]
Desmoplastic round cell tumor	t(11;22)(p13;q12)	*WT1-EWSR1*	>90%	[30–33]
Endometrial stromal sarcoma	t(7;17)(p15;q11)	*JAZF1-SUZ12*	>65%	[34–36]
	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	[37]
Epithelioid hemangioendothelioma	t(1;3)(p36.3;q25)	*WWTR1-CAMTA1*	>90%	[38]
Epithelioid sarcoma	*INI1* inactivation [22(q11.2)]	*hSNF5/INI1*	>80%	[39–43]
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*EWSR1-NR4A3*	>80%	[44–46]
	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%	[47, 48]
	t(21;22)(q22;q12)	*EWSR1-ERG*	5–10%	
Fibromyxoid sarcoma (Evans' tumor)	t(7;16)(q33;p11)	*FUS-CREB3L2*	>70%	[49–51]
	t(11;16)(p11;p11)	*FUS-CREB3L1*	<20%	
Gastrointestinal stromal tumor	4q	*KIT* exon 11 mut	65%	[52–57]

	4q	*KIT* exon 9 mut	15%	
	4q	*PDGFRA mut*	<5%	
Giant cell tumor of tendon sheath	t(1;2)(p13;q37)	*COL6A3-CSF1*	>75%	[58]
Inflammatory myofibroblastic tumor[a]	t(2;19)(p23;p13.1)	*TPM4-ALK*	unk	[59–61]
	t(1;2)(q22-23;p23)	*TPM3-ALK*	unk	
Myoepithelial tumors	t(6;22)(p21;q12)	*EWSR1-POU5F1*	10%	[62]
	t(1;22)(q23;q12)	*EWSR1-PBX1*	10%	[61]
		Other fusion partners		
Myxoid-round cell liposarcoma	t(12;16)(q13;p11)	*FUS-DDIT3*	>90%	[63–65]
	t(12;22)(q13;q12)	*EWSR1-DDIT3*	<5%	
Pericytoma with t(7;12)	t(7;12)(p22;q13)	*ACTB-GLI*	unk	[66, 67]
(Extrarenal) rhabdoid tumor	del 22(q11.2)	*hSNF5/INI1*	~50%	[68–70]
Synovial sarcoma	t(X;18)(p11;q11)	*SS18-SSX1/SSX2*	>95%	[71–76]
		SS18-SSX4	<5%	
Well-differentiated/dedifferentiated liposarcoma	12q amplification	*CDK4, MDM2*, others	>80%	[77–82]

[a]Other fusion partners or alterations are known
mut mutation, *unk* unknown

have had retinoblastoma have an increased risk of development of non-ocular tumors [87]. A review of the data suggests that 211 of 1,506 patients with retinoblastoma developed a second tumor, 142 died before any malignancy developed, and 28 developed 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 dose-dependent and has spurred the rise of intra-arterial chemotherapy as primary treatment for retinoblastoma [88].

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 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 alone 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 [89] 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 osteogenic sarcoma, angiosarcoma, and what used to be termed "malignant fibrous histiocytoma," now seen more commonly as undifferentiated pleomorphic sarcoma (UPS) or myxofibrosarcoma (see below). It is rare for these patients to have low-grade tumors or 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 1,000 at 15 years [90]. This risk appears to continue to increase with time. Studies performed from the Scandinavian datasets 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 recently been reported [91]. Radiation-associated sarcomas are described more fully under Chap. 16.

We have had a long-standing interest in the association of lymphedema with the development of soft tissue sarcoma since the earliest report by Stewart and Treves from our institution [8]. While often the lymphedema is associated with extent of operation and radiation therapy, it is not a radiation-induced sarcoma per 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 [92].

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 are suggestive of chemical association. 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.

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.

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