Chapter 27
Soft Tissue Sarcomas

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Introduction

Soft tissue sarcomas are a group of tumors that arise from any extraskeletal nonepithelial tissue, including adipose and fibrous tissues, as well as muscle, tendon, nerve, lymphatic, and vascular tissues. Hence, these neoplasms are heterogeneous in nature, and although they are generally classified histopathogically according to the tissue they most resemble, such classification is difficult (and in some cases impossible) because of the tendency of tumors to lose histologic differentiation [1]. The World Health Organization classification of tumors currently lists more than 50 different histopathologic subtypes of soft tissue sarcomas [2]. Soft tissue sarcomas are also rare. Of the more than 1.5 million cancers expected to be diagnosed in the USA in 2010, The American Cancer Society expects only 10,520 of them to be soft tissue sarcomas. Of the more than 500,000 expected cancer deaths, about 3,920 will be from this cancer [3]. The heterogeneity of these tumors poses both a diagnostic and therapeutic challenge, especially in the setting of a rare disease.

Because the tissues from which these tumors arise are distributed throughout the body, the tumors can arise in any anatomic location. Most (60%) are seen in the extremities, and 10% occur in the head and neck. Another 30% of these neoplasms are found in the torso, including retroperitoneal and intra-abdominal tumors, where they can grow extensively before causing symptoms and are therefore often associated with delayed diagnosis [4].

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Historical Perspective

Management of Nonmetastatic Disease

In the absence of metastasis, surgical resection has been and remains the standard of care in the management of soft tissue sarcomas. From a historical standpoint, large soft tissue sarcomas arising in the extremities managed by local surgical excision resulted in high recurrence rates (30–60%). For this reason, radical compartmental excisions or amputations were performed in an attempt to achieve better local control, which successfully brought down recurrence rates to 5–20%, albeit at the expense of functional outcomes [1].

Subsequently, these radical procedures for tumor management were replaced by limb-sparing procedures that incorporated radiotherapy and chemotherapy. The first randomized clinical trial that incorporated multidisciplinary care in the treatment of patients with extremity sarcoma was a phase 3 trial that enrolled patients with high-grade soft tissue sarcoma to receive amputation or limb-sparing resection plus adjuvant radiotherapy, with both groups receiving adjuvant chemotherapy. Disease-free survival rates at 5 years were equivalent in both groups; therefore, clinical practice changed from amputation to multidisciplinary care that incorporated limb-sparing surgery, with comparable outcomes [2]. Over time, with the use of multimodality treatment strategies, amputation rates have decreased to less than 10%, with limb-sparing treatment predominating in the majority of patients [3]. Surgery is also integral to the management of localized soft tissue sarcomas occurring in other parts of the body. Historically, dissection along the tumor pseudocapsule (enucleation or "shelling out") has been associated with local recurrence in one-third to two-thirds of patients. On the other hand, wide local excision with a margin of normal tissue around the lesion has resulted in local recurrence rates of 10–31%.

The role of radiotherapy in the treatment of patients with resectable disease was well illustrated by Yang et al. [4] when they randomized 91 patients with high-grade extremity lesions following limb-sparing surgery to receive adjuvant chemotherapy alone or concurrent chemotherapy and radiotherapy. In the same trial, 50 patients with low-grade sarcomas were also randomized to receive adjuvant radiotherapy or no further treatment after limb-sparing surgery. The local control rate for those who received radiotherapy was 99% compared with 70% in the non-radiotherapy group, with similar results in the low-grade and high-grade tumors. Pisters et al. evaluated the role of adjuvant brachytherapy in a randomized trial of 126 cases who were randomized to receive surgery alone or surgery followed by brachytherapy. Local control rates were 70% in the surgery-alone group but were 91% in the brachytherapy group. Both of these clinical trials showed the significant role of radiotherapy along with surgery in the treatment of nonmetastatic soft tissue sarcoma.

The role of adjuvant chemotherapy in the treatment of resectable soft tissue sarcomas has been investigated by several individual clinical trials, and in 1997, a meta-analysis of 14 individual trials was conducted to further investigate outcomes in a larger sample of patients. Results of the meta-analysis showed improved local

and distant recurrence-free survival but failed to show a difference in overall survival except in the subset of extremity sarcomas. Modern-day adjuvant chemotherapy for soft tissue sarcomas of the extremity incorporates a combination of an anthracycline with ifosfamide. The utility of this approach was best demonstrated in a randomized clinical trial by an Italian Sarcoma Study Group who showed that the combination of ifosfamide and epirubicin with growth factor support resulted in a median disease-free survival duration of 48 months in patients who received chemotherapy as opposed to 16 months in the control group. Median overall survival was 75 months for patients who received chemotherapy but was 46 months for those who received no chemotherapy [5]. With longer follow-up (median, 7.5 years), the distant metastases-free survival curves have shown convergence, suggesting some loss of chemotherapy benefit over time and the need for better agents with a curative potential [6].

Unresectable Soft Tissue Sarcoma

MD Anderson Cancer Center has played a pivotal role in the development of chemotherapeutic options for soft tissue sarcoma. Doxorubicin, the single most effective and widely used drug in the treatment of soft tissue sarcomas, was first used to treat soft tissue sarcomas [7] at this institution in 1971. Subsequently, results from clinical trials at MD Anderson in 1972 showed that the combination of doxorubicin and dacarbazine was effective in the treatment of sarcomas [8]. This combination continues to be used in the treatment of leiomyosarcomas and other unresectable/metastatic soft tissue sarcomas. The addition of cyclophosphamide to the doxorubicin/dacarbazine combination was investigated in a phase III Southwestern Oncology Group (SWOG) trial that failed to demonstrate any significant differences in response rates [9]. Superiority of ifosfamide over cyclophosphamide was suggested by a phase 2 randomized study of the two agents that showed a higher response rate for patients treated with ifosfamide [10]. This subsequently led to the deletion of dacarbazine, a weak agent with overlapping myelosuppression, and the adoption of combined dose-intense doxorubicin and ifosfamide as the standard for treatment of adult soft tissue sarcomas [11].

The MD Anderson Cancer Center Experience

The data set used for this discussion was derived from a total of 6,907 patients who presented at MD Anderson with soft tissue sarcomas between 1944 and 2004. Excluding those with other primary cancers and those who were treated elsewhere prior to presentation here, our data set included 1,382 patients who received their initial definitive treatment at this institution. Survival data were calculated from initial presentation.

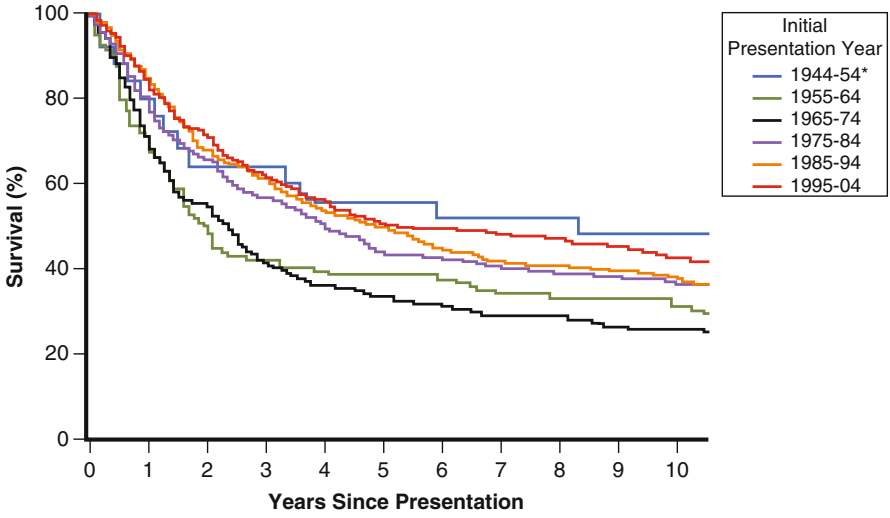

Fig. 27.1 Overall survival rates for patients with soft tissue sarcoma (1944–2004) ($P<0.0001$, log-rank test for trend). *Note: 88% of 1944–1954 patients had local-stage disease.

Table 27.1 Kaplan–Meier overall survival

Decade	Percent survival	
Year	5 years	10 years
1944–1954[a]	56.5	48.0
1955–1964	38.5	31.3
1965–1974	33.6	25.7
1975–1984	43.7	36.5
1985–1994	49.8	38.1
1995–2004	50.4	42.7

[a]88% of 1944–1954 patients had local-stage disease.

The overall survival trends reflected in Fig. 27.1 and Table 27.1 indicate improvements in both 5- and 10-year survival rates over the 60-year time span. During the 1944–1954 timeframe, overall survival was higher than in any of the following decades, most likely a function of the small sample size and a larger proportion of localized disease (88%) during that period. From 1965 to 1974, we see a lower (rather than higher) overall survival rate than that of the preceding decade. This difference in trend may be explained by a higher proportion of patients with metastatic disease during that time period. Interestingly, among patients with metastatic disease, there is a marked increase in the percentage of patients surviving 5 years: from 6.7% in

Table 27.2 Kaplan–Meier survival by SEER stage

	Percent survival by SEER stage					
	Local (years)		Regional (years)		Distant (years)	
Year	5	10	5	10	5	10
1944–1954	59.1	50.0	NA	NA	NA	NA
1955–1964	56.5	47.7	38.6	28.3	4.8	0.0
1965–1974	50.5	38.9	29.6	18.5	6.7	6.7
1975–1984	61.8	52.6	39.2	33.5	11.5	8.2
1985–1994	69.7	54.2	45.0	35.1	13.7	6.8
1995–2004	68.3	57.6	51.0	44.5	14.4	10.9

SEER Surveillance, Epidemiology, and End Results program

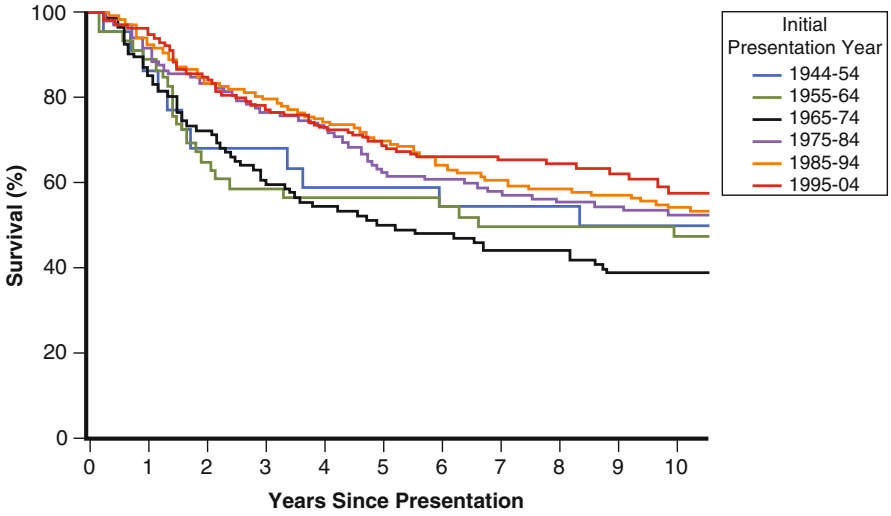

Fig. 27.2 Survival rates for patients with local (SEER stage) soft tissue sarcoma (1944–2004) ($P = 0.049$, log-rank test for trend).

1965–1974 to 11.5% in 1975–1984. The latter period saw a sharp increase in the use of systemic treatment options for the management of metastatic disease such as doxorubicin, whereas effective chemotherapy options were virtually absent before 1975 (Table 27.2) (Figs. 27.2, 27.3, and 27.4).

Finally, there are other treatment advances that should not go unmentioned: even though they did not increase survival, they significantly affected its quality. These include limb-sparing surgical techniques, palliative radiation, and surgery to relieve symptoms, and better management of adverse effects from chemotherapy and radiotherapy.

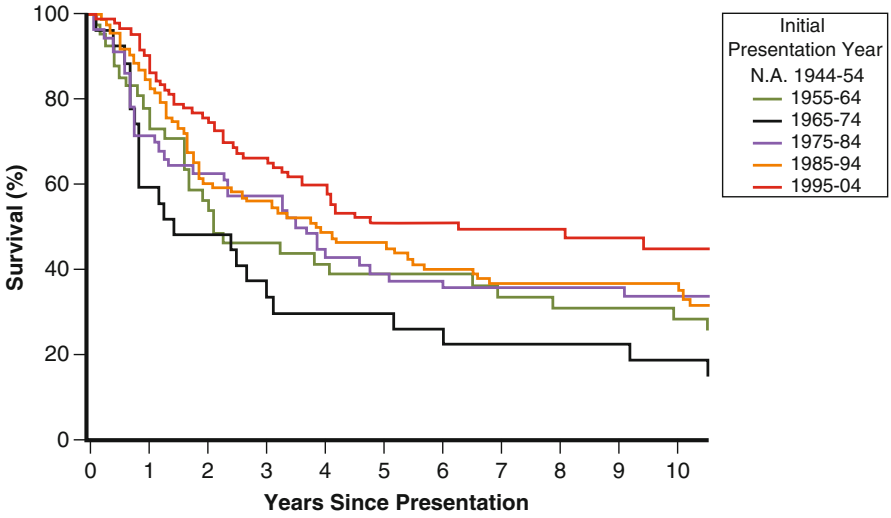

Fig. 27.3 Survival rates for patients with regional (SEER stage) soft tissue sarcoma (1944–2004) ($P=0.025$, log-rank test for trend). Because no individuals with regional soft tissue sarcoma were seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

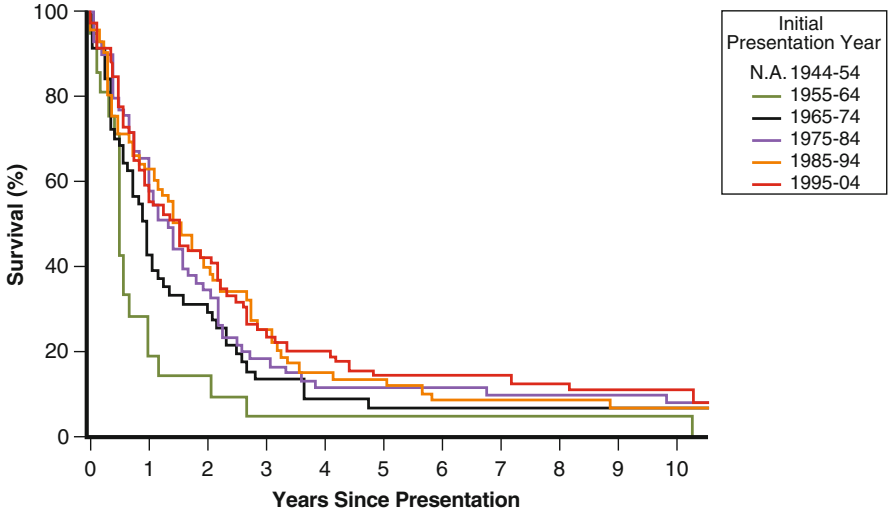

Fig. 27.4 Survival rates for patients with distant (SEER stage) soft tissue sarcoma (1944–2004) ($P=0.014$, log-rank test for trend). Because of the very small number of individuals with distant soft tissue sarcoma seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

Current Management Approach

The National Comprehensive Cancer Network (NCCN) currently publishes standard treatment guidelines for four broad categories of soft tissue sarcoma: tumors of the extremity or trunk, retroperitoneal or intra-abdominal tumors, gastrointestinal stromal tumors, and desmoid tumors. This is a disease for which there are many histologic variants, a myriad of anatomic manifestations, and pathologic tumor grades that pose greater risks than others in terms of advancement or metastasis.

Given this complexity, it is possible to state generally that for most patients, the definitive treatment is surgery (when the tumors are resectable), and chemotherapy and radiotherapy may be used singly or in combination as adjuncts either preoperatively or postoperatively. In general, our approach to all of these tumors relies on multidisciplinary assessment of the risk posed by both the tumor and treatment.

For low-grade sarcomas, the risk of metastatic disease is considered to be low and they are primarily managed by surgery with or without radiotherapy. High-grade sarcomas larger than 5 cm have a higher likelihood of micrometastases; therefore, a multidisciplinary approach incorporating chemotherapy and preoperative radiotherapy followed by surgery is often necessary. Since there is considerable variability in the response to chemotherapy within various histologic subtypes, preoperative chemotherapy is preferred because it enables assessment of the patient's disease response to treatment. On the other hand, the effectiveness of postoperative adjuvant chemotherapy is almost impossible to determine in real time because of the absence of any visible disease to follow. Sarcomas that fall into the intermediate-grade category tend to metastasize later in their course and often merit systemic therapy if larger than 8–10 cm. In this category, risk of recurrence and risk of chemotherapy have to be weighed carefully before finalizing the plan of care.

For patients with advanced or metastatic disease, systemic therapy becomes the primary modality for treatment. These patients may qualify for surgical procedures with curative intent, depending on the response to chemotherapy, extent of disease, and durability of the response to systemic therapy. For the most part, surgery and radiotherapy in a patient with uncontrolled metastatic disease have only a palliation role in treating tumor-related symptoms.

We expect these approaches to bring continued improvement in survival and quality of life for patients with soft tissue sarcomas. More significant improvements in survival will depend on continued research in the following areas:

- Identification of genomic and proteomic aberrations in soft tissue sarcomas that would help us understand the key pathogenic pathways that drive these rare tumors.
- Identification of targeted drugs and drug combinations that specifically inhibit the key pathogenic pathways.

The use of imatinib in patients with gastrointestinal stromal tumors (GISTs) is an excellent example of how application of the above-mentioned principles results in improved survival. Gastrointestinal stromal tumors are generally resistant to

conventional chemotherapy, and before the advent of imatinib had an extremely poor clinical course. Identification of the key molecular aberration in GISTs, i.e., activating a mutation in the *KIT* or *PDGFRA* gene, was a critical step in developing effective therapies for this tumor. We hope that application of similar principles in other sarcoma subtypes will result in treatments that are specific and highly effective while limiting adverse effects to a minimum.

References

1. Shiu M, Castro E, Hajdu S, et al. Surgical treatment of 297 soft tissue sarcomas of the lower extremity. Ann Surg. 1975;182:597–602.
2. Rosenberg S, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg. 1982;196: 305–15.
3. Milliard W, Hajdu S, Casper E, et al. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. Ann Surg. 1992;215:269–75.
4. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol. 1998;16:197–203.
5. Frustaci S, Gherlinzoni F, De Paoli A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol. 2001;19:1238–47.
6. Frustaci S, De Paoli A, Bidoli E, et al. Ifosfamide in the adjuvant therapy of soft tissue sarcomas. Oncol. 2003;65 Suppl 2:80–4.
7. Middleman E, Luce J, Frei III E. Clinical trials with adriamycin. Cancer. 1971;28:844–50.
8. Gottlieb JA, Baker LH, Quagliana JM, et al. Chemotherapy of sarcomas with a combination of adriamycin and dimethyl triazeno imidazole carboxamide. Cancer. 1972;30:1632–8.
9. Baker LH, Frank J, Fine G, et al. Combination chemotherapy using adriamycin, DTIC, cyclophosphamide, and actinomycin D for advanced soft tissue sarcomas: a randomized comparative trial. A phase III, Southwest Oncology Group Study (7613). J Clin Oncol. 1987;5: 851–61.
10. Bramwell VH, Mouridsen HT, Santoro A, et al. Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. Eur J Cancer Clin Oncol. 1987;23:311–21.
11. Patel SR, Vadhan-Raj S, Burgess MA, et al. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. Am J Clin Oncol. 1998;21:317–21.