Soft-Tissue Sarcoma in Adults: An Update on the Current State of Histiotype-Specific Management in an Era of Personalized Medicine

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Abstract: Soft-tissue sarcomas (STS) are rare tumors that account for 1% of all adult malignancies, with over 100 different histologic subtypes occurring predominately in the trunk, extremity, and retroperitoneum. This low incidence is further complicated by their variable presentation, behavior, and long-term outcomes, which emphasize the importance of centralized care in specialized centers with a multidisciplinary team approach. In the last decade, there has been an effort to improve the quality of care for patients with STS based on anatomic site and histology, and multiple ongoing clinical trials are focusing on tailoring therapy to histologic subtype. This report summarizes the latest evidence guiding the histiotype-specific management of extremity/truncal and retroperitoneal STS with regard to surgery, radiation, and chemotherapy. **CA Cancer J Clin 2020;0:1-30. © 2020 American Cancer Society.**

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Introduction

The Need for Centralization: A Call to Action

Soft-tissue sarcomas (STS) represent a cohort of rare and heterogeneous tumors that account for 1% of all adult malignancies. In 2019, an estimated 13,500 people were diagnosed with an STS in the United States.[1] STS are complicated malignancies encompassing at least 100 different histologic and molecular subtypes, with each subtype displaying variable clinical behavior.[2] During the past decade, we have seen the pendulum swing from a *one-size-fits-all* treatment paradigm to a more histology-specific treatment algorithm, one that attempts to tailor not only the type and extent of oncologic resection to be performed but also the use and indication of multimodality therapy. This complex management paradigm, combined with the rarity and heterogeneity of the disease, highlights the importance of a multidisciplinary approach involving a specialized team of radiologists, pathologists, radiation and medical oncologists, and surgical and orthopedic oncologists with expertise in the treatment of patients with STS. As a result, there has been a recent movement to centralize the treatment of STS to institutions with such experienced teams. Indeed, across the oncology literature, several studies of various malignancies have demonstrated a relationship between increased hospital volume and improved short-term and long-term patient outcomes.[3-5] For sarcoma specifically, 2 recent studies using data from the National Cancer Database (NCDB) showed that the centralization of treatment for patients with retroperitoneal sarcomas (RPS) to high-volume centers is associated with improved outcomes.[6,7] In an analysis of 1131 patients with RPS, Keung et al reported that patients treated at high-volume centers had lower 30-day readmission, lower 30-day and 90-day mortality, and longer median and 5-year overall survival (OS).[6] These findings have also been documented in France, where a study of 35,784 patients found that those treated at specialized sarcoma referral

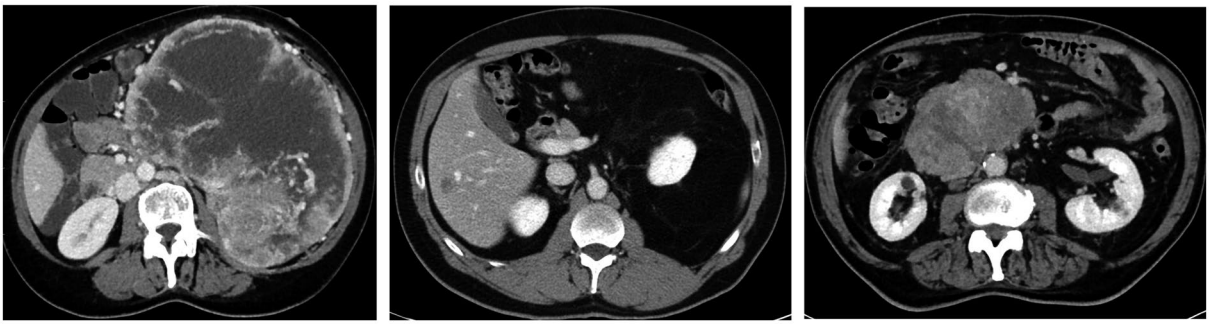

FIGURE 1. Preoperative Computed Tomography Imaging of Soft-Tissue Sarcoma Aids in Establishing a Diagnosis and in Determining the Local Extent of a Lesion and its Relationship to Adjacent Structures. Images show (*Left*) dedifferentiated liposarcoma, (*Middle*) well-differentiated liposarcoma, and (*Right*) leiomyosarcoma.

centers had a reduction in the risk of local relapse, progression, and death (hazard ratio [HR], 0.64, 0.83, and 0.68, respectively; all $P < .001$).[8] The importance of centralization of care is also underscored by the need to develop multiinstitutional clinical trials that will help address an unmet need in the treatment of STS. Because the recruitment of sufficient patients can be challenging for such a rare disease, centralization of care at academic centers is crucial to ensure accrual and feasibility of multiinstitutional trials and ultimately to enable the development of more efficient regimens for the treatment of patients with localized and advanced STS. Given the existing data, referral to a specialized center is recommended for patients who have RPS or a truncal/extremity lesion that is suspicious for sarcoma, such as superficial/subcutaneous lesions >5 cm in size or deep/intramuscular, soft-tissue masses.[9]

This review focuses on STS and highlights the importance of multidisciplinary management by elaborating on the available evidence supporting the use of 3 primary treatment modalities, including surgery, chemotherapy, and radiation. The article begins with a broad overview of STS pathology and subsequently addresses management guidelines in localized STS by primary tumor location (trunk, extremity, and retroperitoneum) as well as advanced or metastatic STS, with an emphasis on histiotype-specific strategies. Finally, the article highlights emerging treatment strategies and summarizes recommendations for posttreatment surveillance.

The Importance of Sarcoma Specialists and Centers

Because STS constitutes a heterogeneous group of rare tumors, management by an experienced multidisciplinary team of specialists should be the standard of care from the time of diagnosis. Referral to a specialized sarcoma center should be initiated for any patient who has a superficial soft-tissue mass with a diameter >5 cm, a deep soft-tissue mass, or a retroperitoneal tumor of any size.[9] A specialized sarcoma team generally includes a radiologist, pathologist, radiation and medical oncologist, and surgical and orthopedic oncologist specialized in the treatment of sarcoma, so that every decision is taken with an understanding of the latest scientific evidence and knowledge of available clinical trials.

Before formal diagnosis, appropriate cross-sectional imaging based on the location of the tumor is crucial to help establish a differential diagnosis and guide further referrals. In addition, understanding and recognizing the spectrum of appearances of different sarcoma histiotypes can aid in final diagnosis (Fig. 1). After imaging, a core needle biopsy should be obtained, and the results should be reviewed by a dedicated and specialized sarcoma pathologist because the complexity of the histopathologic assessment of STS, in combination with the introduction of molecular testing in the assessment of soft-tissue tumors, mandates such expertise. Given the rarity of these tumors, STS represents a subspecialty area of pathology in which the risk for error might be high. In fact, the literature has demonstrated that the reproducibility of an STS diagnosis is relatively poor across pathologists who are not familiar with these lesions.[10]

Because radiation therapy and chemotherapy may play a role in the neoadjuvant or adjuvant setting, it is important that radiation and medical oncologists experienced in treating sarcomas evaluate the patient at the time of diagnosis, thus facilitating a multidisciplinary plan before definitive resection. Their collaboration also enables the expedient enrollment of any eligible patient onto available clinical trials. With regard to the need for surgical expertise, there are recent data describing a higher rate of microscopic negative margins and a trend toward improved outcomes in patients treated at high-volume centers with specialized sarcoma surgeons.[7] Furthermore, a recent study found that patients with extremity STS who underwent surgery at high-volume hospitals had survival rates of 87% at 2 years, 73% at 5 years, and 58% at 10 years, whereas patients treated at low-volume hospitals had survival rates of 84%, 65%, and 53%, respectively, for the same periods.[11] These findings support the axiom that surgical oncologists and orthopedic surgeons with experience in treating

patients with STS are crucial and are more knowledgeable regarding the latest literature on oncologic surgical practices.

In addition to a multidisciplinary management team, patients with sarcoma may benefit from ancillary services that are usually only provided in specialized centers. In patients undergoing surgery for extremity STS, specialized sarcoma centers may be able to provide access to rehabilitation services and physiotherapists with experience in managing patients with sarcoma, which is of particular importance considering the younger age range of these patients. Unfortunately, some patients will develop recurrences, which can lead to debilitating symptoms and challenging quality of life. Specialized sarcoma or cancer centers may also provide supportive oncology specialists, and access to such services may be more seamless if a patient has been treated by sarcoma specialists from the time of initial diagnosis.

Pathology of STS

Background

According to the fourth edition of the World Health Organization (WHO) *Classification of Tumours of Soft Tissue and Bone*, there are more than 100 different histologic subtypes of soft-tissue tumors, the majority of which are STS, each with unique prognostic, clinical, and therapeutic features (Table 1).[2] When considering all adult STS, the most common histiotypes include liposarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma (UPS) (Fig. 2).[8] The usual approach to soft-tissue tumor classification is by presumed cell lineage and is based on morphologic, immunohistochemical, and genetic features.[12] Currently, tumors are categorized as adipocytic, fibroblastic or myofibroblastic, so-called fibrohistiocytic, smooth muscle, pericytic, skeletal muscle, vascular, chondro-osseous, and an "uncertain differentiation" category.[2] Aside from tumor site and grade, the histologic subtype of STS is a major prognostic indicator.[13] Because of the rarity of each histiotype, however, histology-specific analyses have been difficult to perform in both retrospective and prospective studies, and much of the available data regarding optimal therapeutic strategies have used mixed histiotypes.

Histologically, the diagnosis is usually made by immunohistochemical staining and can be further aided with molecular testing, such as fluorescence in situ hybridization or reverse transcriptase–polymerase chain reaction, which can detect the translocations, mutations, and recurrent gene amplifications present in certain sarcoma histologic subtypes. Molecular classification based on genetic alteration divides sarcoma into 3 main categories: 1) sarcomas with specific genetic alterations, such as synovial sarcoma, which are now characterized by the *SYT-SSX* fusion gene; 2) sarcomas with simple oncogenic mutations, such as gastrointestinal stromal tumors, which are characterized by a specific activating mutation in the *c-KIT*

TABLE 1. World Health Organization Classification of Soft-Tissue Tumors[a]

Adipocytic tumors	Chondro-osseous tumors
Atypical lipomatous tumor	Soft-tissue chondroma
Well-differentiated liposarcoma	Extraskeletal osteosarcoma
Liposarcoma, NOS	Gastrointestinal stromal tumors
Dedifferentiated liposarcoma	Gastrointestinal stromal tumor, malignant
Myxoid/round cell liposarcoma	Nerve sheath tumors
Pleomorphic sarcoma	Malignant peripheral nerve sheath tumors
Fibroblastic/myofibroblastic tumors	Epithelioid malignant peripheral nerve sheath tumor
Dermatofibrosarcoma protuberans	Malignant triton tumor
Fibrosarcomatous dermatofibrosarcoma protuberans	Malignant granular cell tumor
Pigmented dermatofibrosarcoma protuberans	Tumors of uncertain differentiation
Solitary fibrous tumor, malignant	Ossifying fibromyxoid tumor, malignant
Inflammatory myofibroblastic tumor	Stromal sarcoma, NOS
Low-grade myofibroblastic sarcoma	Myoepithelial carcinoma
Adult fibrosarcoma	Phosphaturic mesenchymal tumor, malignant
Myxofibrosarcoma	Synovial sarcoma, NOS
Low-grade fibromyxoid sarcoma	Synovial sarcoma, spindle cell
Sclerosing epithelioid fibrosarcoma	Synovial sarcoma, biphasic
Fibrohistiocytic tumors	Epithelioid sarcoma
Giant cell tumor of soft tissues	Alveolar soft-part sarcoma
Smooth muscle tumors	Clear cell sarcoma of soft tissue
Leiomyosarcoma	Extraskeletal myxoid chondrosarcoma
Pericytic (perivascular) tumors	Extraskeletal Ewing sarcoma
Malignant glomus tumor	Desmoplastic small round cell tumor
Skeletal muscle tumors	Intimal sarcoma
Embryonal rhabdomyosarcoma	Undifferentiated/unclassified sarcoma
Alveolar rhabdomyosarcoma	Undifferentiated spindle cell sarcoma
Pleomorphic rhabdomyosarcoma	Undifferentiated pleomorphic sarcoma
Spindle cell/sclerosing rhabdomyosarcoma	Undifferentiated round cell sarcoma
Vascular tumors	Undifferentiated epithelioid sarcoma
Retiform hemangioendothelioma	Undifferentiated sarcoma, NOS
Papillary intralymphatic angioendothelioma	
Composite hemangioendothelioma	
Pseudomyogenic hemangioendothelioma	
Kaposi sarcoma	
Epitheliod hemangioendothelioma	
Angiosarcoma of soft tissue	

Abbreviation: NOS, not otherwise specified.
[a]See Fletcher et al, 2013.[2]

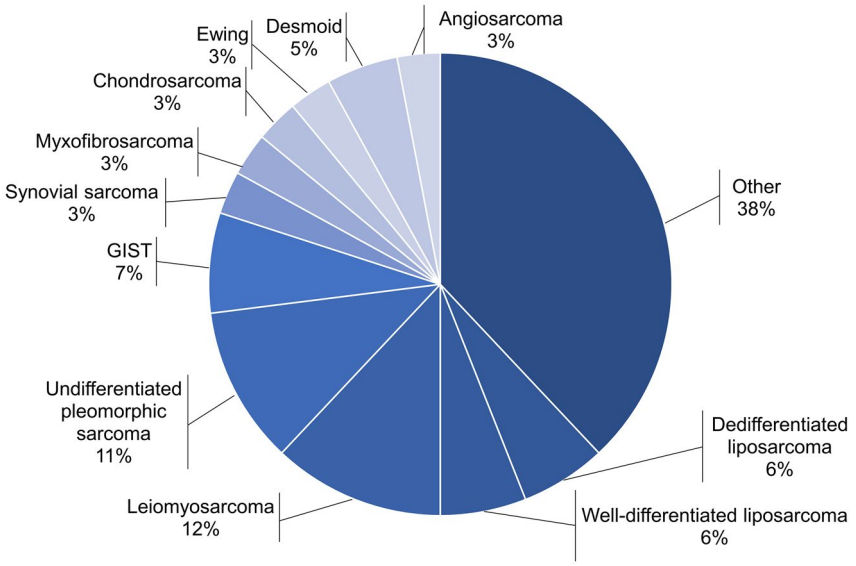

FIGURE 2. Distribution of Histiotypes in Adult Patients With Soft-Tissue Sarcoma.[8] GIST indicates gastrointestinal stromal tumor.

gene; or 3) sarcomas displaying multiple complex karyotypic abnormalities with no specific pattern, such as UPS or leiomyosarcoma.[14,15] As the field progresses, diagnoses and clinical decisions increasingly will be based on a combination of histologic criteria and the molecular identification of genetic abnormalities that are indicative of biologic properties.

Biopsy

A pretreatment biopsy with subsequent histologic examination by a dedicated sarcoma pathologist is essential for STS diagnosis. Accordingly, referral to a specialized center for further workup should be pursued if a clinical diagnosis of sarcoma is suspected. Although data are currently conflicting regarding the long-term outcomes of nononcologic, unplanned excisions (see Truncal and Extremity STS, below), there is certainly added morbidity if reresection is needed to achieve negative margins because this may entail a larger procedure than a de novo resection, thus affecting the patient's functional and cosmetic result.[16-18]

A pretreatment biopsy is performed as a core needle biopsy either in the office or under image guidance, depending on the location and accessibility of the tumor. If an incisional biopsy is needed for a truncal or extremity STS, it should be carefully planned so that the biopsy site can be excised en bloc at the time of the definitive resection. For retroperitoneal tumors, a posterior/lateral image-guided approach is preferred to avoid going through the peritoneal cavity and potentially seeding it, especially if modern coaxial biopsy needles are not used. In addition, the collection and storage of fresh-frozen tissue are encouraged to allow new molecular pathology assessments to be made at a later stage if needed.[9] Tissue diagnosis is particularly important for cases in which neoadjuvant therapy will be given. A review of the specimen should be performed by an experienced sarcoma pathologist with access to ancillary techniques, such as immunohistochemistry, classical cytogenetics, and molecular genetic testing, if needed to make a definitive diagnosis. Molecular testing with fluorescence in situ hybridization-based or reverse transcriptase–polymerase chain reaction-based methods has become more widely used as an ancillary technique in the diagnosis of STS because numerous sarcoma subtypes harbor characteristic genetic aberrations.

Tumor Grade

Tumor grade should be provided on all specimens because of its prognostic value.[19] In accordance with the College of American Pathologists, the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system developed by Trojani et al is preferred over the National Cancer Institute (NCI) grading described by Costa et al because of its ability to better predict the metastatic risk between tumor grades.[20,21] The FNCLCC grade is determined by 3 parameters, including differentiation, necrosis, and mitotic rate (Table 2), and the score within each category is subsequently added to classify tumors into 3 major categories (Table 3).[20] Tumor differentiation is the most subjective aspect of this scoring system, and it may not be available for every histologic subtype. The NCI system is based on tumor histologic type and subtype, location, and the amount of tumor necrosis.[2] The current TNM staging system recommends the FNCLCC system and collapses the 3 categories into either low-grade or high-grade (FNCLCC grade 1 tumors are considered low-grade, and FNCLCC grade 2 or 3 tumors are considered high-grade). Importantly, the assignment of tumor grade may be affected by prior treatments, such as chemotherapy or radiation, and specimens may be assigned a

TABLE 2. Parameters That Determine Tumor Grade

PARAMETER	DEFINITION
Differentiation score	
1	Sarcomas closely resembling normal adult mesenchymal tissue
2	Sarcomas for which histologic typing is certain
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft-tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor of soft tissue
Mitotic count score	
1	0-9 mitoses per 10 HPF
2	10-19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF
Tumor necrosis	
0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

Abbreviation: HPF, high-power field.

lower tumor grade than the initial pretreatment designation. It is currently recognized that histologic grade is the most important prognostic factor for STS and is predictive of distant metastasis and disease-specific survival (DSS). In a retrospective study of 1240 patients with nonmetastatic STS from the FNCLCC by Coindre et al, the 5-year metastasis-free survival rate was 91% for grade 1 tumors, 71% for grade 2 tumors, and 43% for grade 3 tumors.[19] Importantly, that study accounted for other prognostic variables, including tumor size, neurovascular or bone involvement, and tumor depth. Similarly, in a study of 10,000 patients with STS, Brennan et al demonstrated that the systemic recurrence rate was <10% in patients with low-grade lesions at 20 years, whereas among patients with high-grade lesions, the rate of death from disease was approximately 40% at 10 years.[13] The largest limitation of both histologic grading systems is that they are not site-specific or histology-specific; therefore, this pathologic variable alone should be used with caution when prognosticating the natural history of this disease. Indeed, in the study mentioned above of 1240 patients, Coindre et al demonstrated that grading is most useful in so-called malignant fibrous histiocytomas, unclassified sarcomas, synovial sarcomas, leiomyosarcomas, and liposarcomas but has no prognostic value in pediatric-type STS (ie, rhabdomyosarcoma).[19] Another large study with over 1000 patients from Japan noted that the predictive capability of tumor grade for survival was only applicable in 3 tumor subtypes, including malignant fibrous histiocytoma, leiomyosarcoma, and liposarcoma.[22] Furthermore, because the natural history of retroperitoneal STS depends predominantly on achieving microscopic negative margins during resection, tumor grade only becomes a prognostic factor for long-term outcomes once the tumor has been completely resected.[23] Similarly, for extremity STS, local recurrence rates depend mostly on tumor size rather than grade.[24] At this time, given the rarity of each histologic subtype and anatomic site and the difficulty of developing a grading system for every combination of these 2 prognostic factors, the FNCLCC and NCI grading systems represent acceptable grading alternatives but should always be evaluated in the context of the larger disease process.

TABLE 3. French Federation of Cancer Centers Sarcoma Group Histologic Grade

GRADE	DEFINITION
GX	Grade could not be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Given the recent strides forward in molecular genetics and the concept of targeted therapy, grading could eventually be complemented or even replaced by molecular parameters. In 2004, Lee et al reported on one of the first expression profiling studies leading to a prognostic signature in sarcoma. Comparing expression profiles from both metastatic and nonmetastatic leiomyosarcomas, those authors identified 335 genes that were differentially expressed between primary tumors and metastases, which would allow the prediction of future development of metastases of primary tumors ($P = .001$).[25] This type of molecular signaling can help to identify potential targets for future treatments. For example, the treatment of gastrointestinal stromal tumors was transformed after identification of the *c-KIT* mutation, which is targeted by imatinib, a tyrosine kinase inhibitor. Treatment with this agent led to significant improvements in survival, with overall response rates of 80%.[26] New targeted therapies are desperately needed in sarcoma. In the meantime, the main value of tumor grade is to guide the use of (neo)adjuvant therapy, a topic that is further reviewed in the sections below.

Nomograms and Staging Systems

Overall, approximately 25% of patients with STS will develop distant metastatic disease, even after undergoing curative resection of the primary tumor.[13,27] This incidence increases to 50% in high-risk tumors that measure >5 cm, are deep to the fascia, and are intermediate-grade or high-grade.[13,19] In nearly 70% of the metastatic cases, disease occurs in the lungs, with other sites including the skin, bone, liver, and brain.[28-30] The ability to accurately predict

TABLE 4. Nomograms for Patients With Extremity Soft-Tissue Sarcoma

			NOMOGRAM DETAILS			EXTERNAL VALIDATION	
STUDY	SELECTION CRITERIA	TIMEFRAME	PREDICTED OUTCOMES	NO. OF PATIENTS	NOMOGRAM'S COVARIATES	YES/NO	CONCORDANCE INDEX
Mariani 2005[32]	Primary completely resected extremity STS	1980-2000	10-y SSD	642	Grade, histology, age, size, depth, site	No	—
Cahlon 2012[36]	Primary extremity STS treated with limb-sparing surgery without adjuvant therapy	1982-2006	3-y and 5-y LR rate	684	Histology, surgical resection margin, grade, age, size	No	—
Callegaro 2016[37]	Primary extremity STS treated with surgery	1994-2013	5-y and 10-y OS	1452	Size, histology, age, grading	Yes	0.70-0.77

Abbreviations: LR, locoregional recurrence; OS, overall survival; SSD, sarcoma-specific death; STS, soft-tissue sarcoma.

these outcomes based on each patient's clinicopathologic and molecular characteristics is of increasing interest, particularly in the era of precision medicine. Therefore, prognostic nomograms that incorporate factors associated with survival, such as anatomic site, age, and histologic subtype, are useful tools for patient counseling, scheduling of surveillance imaging, and determination of clinical trial eligibility. The first nomogram used for patients with STS was developed in 2002 by Kattan et al from Memorial Sloan Kettering Cancer Center (MSKCC).[31] This nomogram is often referred to as the MSKCC Sarcoma Nomogram and was developed based on patients with primary, resectable, any-site STS. It combines 5 covariates, including age at diagnosis, tumor size, histologic grade, histologic subtype, and anatomic site, to predict the 12-year sarcoma-specific death probability for both patients with low-grade tumors and patients with high-grade tumors. Although multiple external validations have demonstrated its reliability, some limitations include the use of tumor size as a categorical variable and the finding that some histologies adopted in the nomogram either no longer exist or have been reclassified.[32-34] In 2003, the MSKCC group produced a nomogram based on the same covariates to predict the 5-year sarcoma-specific death probability in patients with locally recurrent STS while adjusting for the competing effect of mortality unrelated to STS.[35]

Because anatomic site is a major determinant of outcome and pattern of recurrence, site-specific nomograms have also recently been created. Three site-specific nomograms have been published for extremity STS to predict locoregional recurrence, OS, and DSS (Table 4).[32,36,37] The nomogram used to predict 3-year and 5-year locoregional recurrence is based on 5 independent prognostic factors, including older age, tumor size, tumor grade, and histology, and can be used to guide adjuvant treatment strategies in patients at higher risk for local recurrence.[36] There are 4 available nomograms for RPS that predict OS and disease-specific death (Table 5).[38-41] Of these, only the nomogram by Gronchi et al has been externally validated and is endorsed by the American Joint Committee on Cancer (AJCC) staging system for RPS.[40] This 2013 nomogram predicts OS after surgical resection and includes age, tumor size, tumor grade, histologic subtype (dedifferentiated liposarcoma [DDLS], leiomyosarcoma, malignant peripheral nerve sheath tumor, solitary

TABLE 5. Nomograms for Patients With Retroperitoneal Sarcoma

			NOMOGRAM DETAILS			EXTERNAL VALIDATION	
STUDY	SELECTION CRITERIA	TIMEFRAME	PREDICTED OUTCOMES	NO. OF PATIENTS	NOMOGRAM'S COVARIATES	YES/NO	CONCORDANCE INDEX
Anaya 2010[38]	Primary or recurrent, nonmetastatic, resected	1996-2006	Median OS, 3-y OS, 5-y OS	343	Histology, completeness of resection, age, multifocality, tumor size, presentation	No	—
Ardoino 2010[39]	Primary, localized, resected	1985-2007	5-y OS, 10-y OS	192	Histology, FNCLCC grade, size, surgical resection margins, age	No	—
Gronchi 2013[40]	Primary, localized, resected	1999-2009	7-y OS	523	FNCLCC grade, tumor size, histology, age, multifocality, extent of surgical resection	Yes	0.67-0.73
Tan 2016[41]	Primary, localized, resected	1982-2010	3-y, 5-y, 10-y DSD	632	Histology, extent of surgical resection, no. of organs resected, size, radiation	No	—

Abbreviations: DSD, disease-specific death; FNCLCC, French Federation of Cancer Centers Sarcoma Group; OS, overall survival.

TABLE 6. American Joint Committee on Cancer Staging System for Soft-Tissue Sarcoma of the Trunk and Extremities and the Retroperitoneum (Eighth Edition, 2016)

CATEGORY	DEFINITION
Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤5 cm in greatest dimension
T2	Tumor >5 cm and ≤10 cm in greatest dimension
T3	Tumor >10 cm and ≤15 cm in greatest dimension
T4	Tumor >15 cm in greatest dimension
Regional lymph nodes (N)	
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

fibrous tumor, UPS, and well differentiated liposarcoma [WDLS]), multifocality, and quality of surgery (complete vs incomplete).[40] The 2016 nomogram for disease-free survival (DFS) includes all of the previous variables except for age and quality of surgery. This nomogram is important for informing decisions about the possible role of postresection therapies for RPS and to help more accurately stratify patients who participate in clinical trials based on the risk of RPS recurrence.[41]

One of the main limitations of nomograms is that they rely on clinicopathologic variables that are best assessed postoperatively, and therefore their preoperative applicability can be limited. Nomograms can also quickly become invalid as new treatment strategies evolve, and they must be updated to maintain applicability in the current era.[42] In the future, nomograms could include serum biomarkers, molecular variables, genomic data, and radiomic data to aid prediction.

Similar to prognostic nomograms, the AJCC staging system stratifies the risk of recurrence or death by considering the interplay of several prognostic factors. Until the eighth edition of the AJCC staging system, STS prognosis and treatment were not based on site of origin. It is now widely recognized that anatomic site is one of the most important prognostic factors. Accordingly, in the eighth edition of the *AJCC Cancer Staging Manual*, site-specific staging systems for STS of the trunk and extremities, retroperitoneum, head and neck, and abdomen and thoracic visceral organs have been developed (Tables 6, 7, and 8). In that edition, 4 prognostic factors are incorporated into determining the sarcoma stage, including tumor size, lymph node involvement, metastasis, and histologic grade.[43] Depth is no longer used in the staging system, but it continues to be recorded relative to the investing fascia of the extremity and trunk and has no relevance for retroperitoneal or intraabdominal tumors. The main limitation of staging systems, in general, is the exclusion of specific histiotypes, thus making them less individualized and potentially less accurate compared with nomograms. Nonetheless, staging systems still provide valuable information because they create a common language that is easily translated internationally and across institutions, thus allowing the standardized evaluation of outcomes across various populations.

Truncal and Extremity STS

Background

Approximately 40% to 50% of STS occur in the extremities, and approximately 13% occur in the trunk (Fig. 3).[8,13] Recent series indicate that the most common histiotypes in the trunk or extremity include UPS, leiomyosarcoma, liposarcoma, and synovial sarcoma.[44] However, any of the nearly 100 histiotypes can develop within the trunk or extremity. The prognostic factors for DSS in patients who have truncal and extremity STS include tumor grade, size, and histologic subtype. Some studies have also found that deep location, positive margins, and lower extremity site are significantly associated with long-term outcomes.[24,32,37] Depending on the exact histiotype and its respective malignant potential, there is variation in the natural history of the STS, ranging from an increased risk of locoregional recurrence to a substantial risk of distant failure. However, with high-grade tumors accounting for nearly 75% of truncal and extremity STS, the main pattern of failure is usually distant metastases

TABLE 7. AJCC Anatomic Stage/Prognostic Groups for Extremity Soft-Tissue Sarcoma (Eighth Edition, 2016)

	AJCC CLASSIFICATION			
STAGE	TUMOR	LYMPH NODE	METASTASIS	GRADE
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
Stage IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Abbreviation: AJCC, American Joint Committee on Cancer.

TABLE 8. AJCC Anatomic Stage/Prognostic Groups for Retroperitoneal Soft-Tissue Sarcoma (Eighth Edition, 2016)

	AJCC CLASSIFICATION			
STAGE	TUMOR	LYMPH NODE	METASTASIS	GRADE
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

Abbreviation: AJCC, American Joint Committee on Cancer.

because local recurrences can be managed with limb-sparing reresection or, in rare circumstances, amputation.[45] As mentioned above, prognostic nomograms can improve patient risk stratification and help tailor management to the individual patient. The Sarculator (sarculator.com) includes an extremity-specific STS nomogram that predicts the probability of OS and the incidence of distant metastasis at 5 and 10 years after surgery based on patient age, tumor histology, size, and grade.[37] This section covers our latest understanding of histiotype-specific management of truncal and extremity sarcoma in the context of 3 primary treatment modalities, including surgery, radiation, and chemotherapy.

Limb Preservation Versus Amputation for Localized Disease

The cornerstone of curative treatment for patients with localized STS of the trunk or extremity, regardless of histiotype, is surgical resection with negative microscopic margins (R0 resection).[46] However, there are certain STS histiotypes, such as WDLS, in which simple excision with complete gross removal of the tumor is an acceptable endpoint.[47] For extremity STS, the goal of resection should be a limb-sparing, function-preserving oncologic resection with adequate margins. Microscopically positive margins are known to be associated with a higher rate of local recurrence and a resultant lower rate of DFS. The largest series have shown how biology governs the early outcome, whereas the quality of surgical margins is the stronger predictor of late related death. In other words, patients who survive the biology of the tumor have a higher risk of death if microscopic margins are positive after the initial resection.[24,48-51]

The concept of limb preservation for extremity STS was first described nearly 4 decades ago by the landmark randomized controlled trial at the NCI, which demonstrated that limb-sparing surgery with radiation resulted in nearly equivalent OS and DFS compared with amputation (OS: 83% vs 88%, respectively [$P = .99$]; DFS: 71% vs 78%, respectively [$P = .75$]).[52] As a result, current rates of amputations for patients with STS are approximately <5% for those with primary tumors or from 9% to 14% for recurrent disease, with such procedures reserved for cases in which resection or reresection with adequate margins cannot be performed without sacrificing the functional outcome of the limb.[53,54]

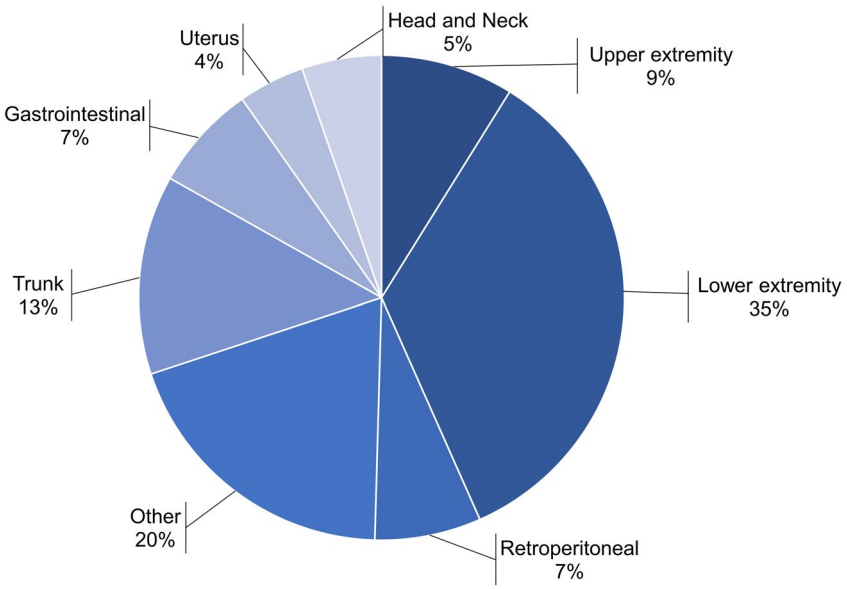

FIGURE 3. Anatomic Distribution of Soft-Tissue Sarcoma in Adult Patients.[8]

Because benign extremity soft-tissue tumors are common compared with sarcomas, approximately 30% of patients with extremity STS undergo unplanned nononcologic excisions, which frequently result in residual disease.[55,56] Although the current standard of care mandates that these patients undergo systematic re-excision to achieve appropriate margins and reduce locoregional recurrence rates, the impact of these unplanned excisions on long-term outcomes remains controversial in the literature, likely because of the heterogeneity in prognostic factors between patients who undergo unplanned and planned excisions.[17,57] A recent 2019 study of 500 patients with stage III extremity STS demonstrated that unplanned excisions were not associated with worse OS, metastasis-free survival, or local recurrence-free survival (RFS). However, patients who required re-excision had higher rates of plastic reconstruction and amputations, thus highlighting that unplanned excisions result in increased morbidity.[58] Similarly, a propensity-matched study by Zaidi et al showed that unplanned excisions were associated with worse locoregional RFS only in patients with high-grade tumors. This earlier locoregional recurrence, however, did not translate into earlier distant metastases or worse DSS but could still be associated with added morbidity because of the increased need for re-excision of local recurrences.[18] The impact of a "watch-and-wait" approach after unplanned excisions was evaluated in a 2019 French study, which determined that, although systematic re-excision offers the best chance at local control (HR, 0.44; $P = .01$), this does not translate into an improvement in OS, thus observation after unplanned excisions may be a reasonable approach for select patients without macroscopic residual disease or for those who undergo piecemeal excisions during the index operation.[59] In addition, the impact of unplanned excision may be different among the various histologic subtypes. The fact that the literature demonstrates that unplanned excisions could result in inferior outcomes not only reflects the complexity of the management of STS but also provides compelling evidence that all patients with soft-tissue tumors should be referred to specialized centers and should be managed by expert teams.

The Role of Radiation for Localized Disease

Two early randomized trials established the role of radiation in enhancing local control for extremity and truncal STS. The first trial of adjuvant radiation was conducted in 1996 and included 164 patients who were randomized intraoperatively to receive either adjuvant brachytherapy or no further therapy after undergoing complete resection of an extremity or superficial trunk STS. With a median follow-up of 76 months, the 5-year local control rates were 82% in the brachytherapy group compared with 69% in the surgery alone group ($P = .04$).[60] A subsequent 1998 trial at the NCI demonstrated that patients who underwent surgery alone had significantly increased rates of local recurrence compared with those who underwent surgery plus adjuvant radiation (24.3% vs 1.4%). Although long-term follow-up studies showed that radiation resulted in significantly worse limb strength, edema, and range of motion, these deficits were often transient and had few measurable effects on quality of life.[61] Given these data, the National Comprehensive Cancer Network (NCCN) guidelines recommend either preoperative or postoperative radiation for stage II, IIIA, and IIIB extremity STS, but surgery alone can be considered for stage IA or IB tumors that are resected with wide margins.[46]

Although the role of radiation is well established in extremity STS, the optimal radiation-surgery sequence in terms of oncologic outcomes has not yet been defined. Various studies have examined the role of preoperative or postoperative radiation for extremity or truncal STS, and the results have failed to demonstrate the superiority of one approach over another.[61-67] A seminal 2002 phase 3 randomized control trial by the Canadian Sarcoma Group included 190 patients and demonstrated that preoperative radiation was associated with a greater incidence of acute wound complications compared with postoperative radiation (35% vs 17%), but it also was associated with decreased fibrosis (32% vs 48%), less frequent extremity edema (15.5% vs 23.2%), and joint stiffness (17.8% vs 23.2%) at longer follow-up secondary to the smaller field and dose of radiation required in the preoperative setting.[64,68] Notably, equivalence of postoperative and preoperative radiation in terms of local RFS (HR, 1.2; 95% CI, 0.4-3.5 [$P = .76$]) and DSS (HR, 1.1; 95% CI, 0.7-2.0 [$P = .64$]) was demonstrated, but the study was not powered to test the superiority of one modality over the other. More recently, a retrospective study from the NCDB included 27,969 patients with extremity STS and compared the rate of R0 resection among preoperative, postoperative, and no radiation cohorts. The rates of R0 resection were 90% in the preoperative radiation cohort compared with 75% in the postoperative radiation cohort and 80% in the no radiation cohort ($P < .001$).[67] These data form the basis for counseling patients on the risks and benefits of preoperative and postoperative radiation. In general, younger patients may be able to better tolerate a wound complication rather than a long-term compromise of limb functionality. Conversely, an older patient with more comorbidities may be more susceptible to the effects of a wound complication, whereas the long-term effects of radiation may not be as relevant. This further emphasizes the importance of a multidisciplinary discussion of each of these cases in a center with expertise in the management of patients with STS.

The studies presented here have all used conventional external-beam radiation. More recently, advances in imaging techniques have led to the development of more sophisticated radiation modalities, including intensity-modulated

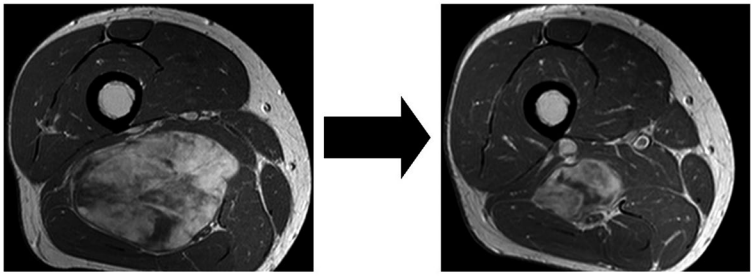

FIGURE 4. Axial Views of Contrast-Enhanced Computed Tomography Scans of a High-Grade Myxoid Liposarcoma of the Thigh Abutting the Sciatic Nerve. Studies were obtained (*Left*) before and (*Right*) after concurrent preoperative chemotherapy (doxorubicin and ifosfamide) and radiation (total dose, 50 grays).

radiation therapy. These newer radiation techniques, along with the possible use of particle therapy, will enhance the cost/benefit ratio of radiation and allow its broader use in the preoperative setting, where its effect is expected to be greater.[69-72] Indeed, although it is generally believed that the use of radiation in the preoperative setting is equally effective to its use in the postoperative setting, in borderline resectable disease or when preservation of function is at risk, the use of preoperative radiotherapy can counteract the negative prognostic impact of a microscopic positive margin. The same effect is not obtained when radiation is delivered in the postoperative setting, even if at higher doses.[73,74]

The routine dose of preoperative radiation is 50 grays (Gy) in 1.8-Gy to 2.0-Gy fractions and is delivered to a smaller field with the tumor in place. Postoperative radiation can be considered in the setting of microscopic positive margins if reresection is not feasible. For patients treated with preoperative radiation followed by surgery, the NCCN guidelines recommend observation alone because the addition of a postoperative boost has not been shown to improve local control outcomes.[46] Adherence to these guidelines cannot be overemphasized, as a recent study by Voss et al demonstrated an association between adherent treatment and improved survival for patients with extremity STS.[75] Because of the established role of radiation in extremity STS, it is critical that a radiation oncologist specialized in treating sarcomas evaluates the patient at the time of diagnosis.

The Role of Neoadjuvant and Adjuvant Chemotherapy in Localized Disease

The rarity and heterogeneity of the biologic behavior among STS subtypes pose the largest obstacles in designing a study to demonstrate the efficacy of neoadjuvant therapy in truncal or extremity STS. In 2001, a phase 2 neoadjuvant chemotherapy trial from the European Organization for Research and Treatment of Cancer (EORTC) randomized a total of 134 patients with high-risk STS to either definitive surgery alone or 3 cycles of preoperative chemotherapy with doxorubicin and ifosfamide followed by definitive surgery. Most of the patients (92%) included in that trial had a primary extremity STS. At a median follow-up of 7.3 years, the results demonstrated a nearly equivalent 5-year OS rate between the surgery only and neoadjuvant chemotherapy groups (64% vs 65%; $P = .22$).[76] Unfortunately, the trial was closed after completion of the phase 2 portion because accrual was too slow to justify expanding it into the scheduled phase 3 study. More recently, Gronchi et al completed a phase 3 randomized controlled trial in which high-risk patients with high-grade, deep, >5-cm truncal or extremity tumors were randomized to receive standard neoadjuvant chemotherapy (anthracycline and ifosfamide) or histology-tailored neoadjuvant chemotherapy for 5 specific sarcoma histiotypes, including UPS, myxoid liposarcoma (MLS), synovial sarcoma, malignant peripheral nerve sheath tumor, and leiomyosarcoma. With a median follow-up duration of 12.3 months, the projected DFS rate at 46 months was 62% in the standard chemotherapy group and 38% in the histiotype-tailored chemotherapy group ($P = .004$).[77] After a longer follow-up, the histiotype-tailored chemotherapy group had better DFS than initially detected, suggesting some effect of the histiotype-tailored chemotherapy. That trial confirms the value of neoadjuvant chemotherapy in patients with high-risk truncal or extremity STS and further highlights the possibility of histology-specific recruitment strategies in future randomized trials. There have also been other small retrospective series that have attempted to identify a cohort of patients with extremity STS who might benefit from neoadjuvant chemotherapy.[78,79] These studies suggest that there may be a high-risk group of patients, such as those with high-grade tumors measuring >10 cm, for whom neoadjuvant chemotherapy can be considered. Finally, the local impact of preoperative treatments should not be overlooked. In other words, although the primary aim of neoadjuvant chemotherapy in operable patients is systemic, a local benefit is likely to occur at least in a proportion of patients (Fig. 4). The preoperative combination of chemotherapy with radiation was shown to be feasible and to offset the adverse impact of positive surgical margins.[80,81] Function preservation may also be part of this benefit.

The role of adjuvant chemotherapy in STS has been explored in 20 randomized trials and 2 meta-analyses. Despite these efforts, results have been conflicting, and the benefit of adjuvant chemotherapy remains uncertain.

Results from early trials were summarized by the 1997 Sarcoma Meta-Analysis Collaboration, which included 14 studies and 1568 patients with the aim of evaluating the efficacy of adjuvant doxorubicin-based chemotherapy in patients with localized, resectable STS. The results demonstrated a significant improvement in RFS (HR, 0.75; 95% CI, 0.64-0.87 [$P = .0001$]) but only a 4% difference in OS at 10 years with adjuvant chemotherapy. Within the subgroup of patients with extremity STS, there was a 7% absolute difference in 10-year OS with adjuvant chemotherapy ($P = .029$), suggesting that adjuvant chemotherapy may be beneficial in this population.[82] The current applicability of results from this meta-analysis for extremity STS is very limited because of the inclusion of patients with tumors at all anatomic sites, the lack of stratification on histologic subtype, and the use of anthracycline-only regimens. Since then, 4 additional randomized trials have explored the benefit of anthracycline and ifosfamide-based therapy with the addition of hematopoietic growth factors, which allowed more dose-intense regimens.[83-87] A subsequent updated meta-analysis in 2008 pooled the studies included in the 1997 Sarcoma Meta-Analysis Collaboration and the more recent 4 randomized trials, for a total of 18 trials representing 1953 patients. That meta-analysis demonstrated a marginal OS benefit with adjuvant chemotherapy compared with surgery alone (HR, 0.77; $P = .01$). Subset analysis demonstrated that studies reporting the use of adjuvant doxorubicin alone did not result in a statistically significant reduction in mortality, whereas studies that used a combined doxorubicin and ifosfamide regimen did demonstrate a survival benefit (HR, 0.56; $P = .01$).[88] Finally, the EORTC performed the largest adjuvant chemotherapy trial to date from 1995 to 2003. Patients with extremity, limb-girdle, or head and neck STS were randomized within 4 weeks of complete resection to receive either adjuvant therapy with doxorubicin, ifosfamide, and lenograstim for 5 cycles at 3-week intervals or no chemotherapy. OS did not differ significantly between groups when considering all anatomic sites (HR, 0.94; 95% CI, 0.68-1.31 [$P = .72$]). On subgroup analysis of patients with limb STS only, adjuvant chemotherapy also did not benefit survival (HR, 0.84; 95% CI, 0.56-1.26). However, there was a trend toward improved RFS and OS in the subgroup with extremity, large, grade III sarcomas.[87] As with many other sarcoma trials, this study was limited by the inclusion of a heterogeneous group of patients in terms of tumor size, grade, and anatomic location. Notably, the authors also discuss that the addition of this trial to the 2008 meta-analysis did not change its results. It is also interesting to note that the results of this EORTC study were recently revisited. Patients were stratified by the predicted OS using a validated nomogram.[37] The analysis showed how the study population was marked by a median predicted OS >70%. When a cutoff of 60% was used, patients with a predicted OS <60% had a significant benefit in DFS and OS from the administration of adjuvant chemotherapy.[89] Interestingly, the proportional (not only the absolute) risk reduction from the administration of chemotherapy appears to be lower when the baseline risk is lower.[90] One may hypothesize that adjuvant or neoadjuvant chemotherapy should be reserved for patients with STS who have a high baseline risk. Clearly, a higher risk corresponds on average to a higher malignancy grade and thus potentially to higher efficacy of chemotherapy. Given these inconclusive findings, adjuvant chemotherapy is not considered a standard treatment for patients with localized extremity STS, although it can be proposed for a shared decision in a multidisciplinary setting for patients with chemosensitive histiotypes, such as MLS and synovial sarcomas, and for patients with sarcomas at high risk of recurrence.

Every chemotherapy study and trial in adult STS has been conducted on a relatively small cohort of patients with various histologies and molecular subtypes, thus making the identification of chemotherapy regimens challenging. Future studies will have to use validated nomograms to focus on more homogeneous groups of patients with carefully defined prognostic and predictive factors and tumors with specific histologic and molecular subtypes.

The Role of Limb Perfusion

For patients with unresectable intermediate-grade or high-grade extremity STS, regional limb therapies such as isolated limb perfusion (ILP) or isolated limb infusion (ILI) have been evaluated as limb-sparing treatment options. First described in 1958 by Creech et al, ILP entails obtaining surgical vascular access to either axillary or femoral vessels and administering tumor necrosis factor α along with chemotherapy, such as melphalan or doxorubicin.[91] ILI is a less invasive alternative that requires percutaneous access only and thus may be considered for patients who have a compromised performance status. Certain European centers have shown that ILP can induce tumor shrinkage, thus enabling a complete resection of the recurrent tumor in up to 70% of cases.[92,93] In the largest systematic review to date, which included 19 studies and 1288 patients, ILP and ILI yielded favorable outcomes. The aggregated overall response rate postprocedure was 73.3%, the complete response rate was 25.8%, and the overall limb salvage rate was 73.8%.[94] As with many of the other studies in sarcoma, there was substantial variation in the histiotypes, the types of tumors included, and the outcomes reported. Therefore, it is difficult to establish optimal patient selection or treatment regimens from these data. In addition, it is important to note that because tumor necrosis factor α is not available in the United States, this treatment modality has not been widely implemented across US centers. Nonetheless, further prospective trials are needed to better define the role of ILP and ILI in the management of patients with unresectable extremity STS.

In the meantime, the use of these techniques is limited to centers with the expertise to perform these procedures and manage the associated potential complications.

Histiotype-Specific Outcomes

As mentioned above, the most common STS subtypes in the trunk and extremities include UPS, liposarcoma, leiomyosarcoma, and synovial sarcoma. UPS lacks immunohistochemical markers for a specific lineage of differentiation, thus always representing a diagnosis of exclusion.[19] It commonly arises in the deep tissue of the lower extremities and has an aggressive tumor biology, with local recurrence and distant metastatic rates approaching 30% to 35% often developing within 12 to 24 months after initial diagnosis.[95] The use of (neo)adjuvant chemotherapy in this histology remains controversial for all the reasons discussed above and should be discussed on a case-by-case basis. Interestingly, a recent retrospective, multiinstitutional analysis by Zaidi et al demonstrated that patients with truncal or extremity UPS who were treated with neoadjuvant chemotherapy had a trend toward improved 5-year OS (66% vs 52%; $P = .103$).[96] In addition, UPS was identified as the most responsive histologic subtype and was associated with the best outcome in a randomized trial comparing the use of 3 versus 5 neoadjuvant chemotherapy cycles of anthracycline plus ifosfamide.[97] Indeed, more prospective data are necessary before recommendations can be made regarding the standard use of systemic therapy in a neoadjuvant approach; however, given the data described above, there are reasons to consider it when the risks of recurrence and death are expected to be high. There are no histiotype-specific data to specifically support the use of radiation therapy for this histiotype, although the use of radiation for extremity STS is common based on data from randomized and retrospective studies, as summarized above (see The Role of Radiation for Localized Disease).

Liposarcomas arise from precursors of adipocytes and represent 25% of extremity STS.[98,99] The 3 main morphologic subgroups with their corresponding high-grade counterparts are WDLS/DDLS, MLS/round cell liposarcoma (RCLS), and pleomorphic liposarcoma (PLS), with clear differences in recurrence and survival patterns between the different liposarcoma subtypes.[100] WDLS/DDLS are associated with amplification of chromosome segment 12q13-15, which carries the oncogenes *MDM2*, *CDK4*, and *HMGA2*.[99] In the extremity, WDLS are considered to have a generally favorable prognosis after resection, with a 5-year local RFS rate of up to 86% and an OS rate of 81%, whereas DDLS have a similar local RFS rate of 83% but a lower 5-year OS rate of 45%.[100] The mainstay of treatment for this histology is complete resection of all disease to obtain long-term local control.[101] More specifically, because of its low recurrence rate, truncal/extremity WDLS can be simply excised, and wide margins are not necessary; this differs from DDLS, in which the surgical approach would be to achieve microscopic negative resection. Although a range of systemic options is available for patients with advanced DDLS, (neo)adjuvant systemic therapy is currently not the standard of care. However, there are data to suggest a role in select high-risk patients with DDLS, such as those with tumors that are high-grade, deep, or >5 cm, and its use should be discussed on an individual basis in a multidisciplinary tumor board and/or under an institutional protocol or clinical trial.[102] Radiation is not routinely used in WDLS cases and should not be considered even in the case of a positive microscopic margin because of the indolent and favorable outcome of this liposarcoma subtype in the trunk and extremity. However, it is commonly used in cases of DDLS of the extremity that are deep and >5 cm in diameter or in the case of an R1 resection (microscopically positive margins) that cannot be improved without resulting in major morbidity.[101]

MLS/RCLS most commonly develop within the deep musculature of the thigh.[2] The treatment approach to MLS/RCLS is nearly identical to that for WDLS/DDLS, with limb-sparing resection as the standard of care. The 5-year local recurrence rate for this histology is similarly low, approaching only 11% for MLS and 14% for RCLS.[36,103-105] It is important to note that this subtype is quite radiosensitive, thus radiation can be considered in large tumors for which tumor reduction would allow for a less morbid operation. The Hypofractionated Radiotherapy in Locally Advanced Myxoid Liposarcomas of Extremities or Trunk Wall (LIPOMYX) trial is an ongoing trial estimated to be completed in 2024 that seeks to evaluate the use of preoperative hypofractionated radiation in patients with locally advanced MLS of the extremities or trunk wall with a primary outcome of wound complication rates (ClinicalTrials.gov identifier NCT03816475). Notably, MLS/RCLS has a peculiar tendency to metastasize to extrapulmonary sites, with a predilection to the spine and abdominal cavity, and this should be considered when planning surveillance imaging for these patients.[106] The use of systemic chemotherapy for primary MLS/RCLS with either epirubicin plus ifosfamide or histiotype-tailored trabectedin can be considered in high-risk lesions, such as those >5 cm in diameter, based on results of the recent neoadjuvant trial by Gronchi et al, which demonstrated similar DFS with either regimen.[77] Doxorubicin is also commonly used as an alternative to epirubicin because neither agent has been demonstrated to be superior.[107] Similarly, a small retrospective study of 61 patients with extremity STS demonstrated that those with MLS who underwent resection and received adjuvant or neoadjuvant, ifosfamide-based chemotherapy had a 22% improvement in DSS compared with those who received no systemic therapy.[108] The last morphologic subtype of liposarcomas, PLS, occurs mostly in the deep tissues of the extremities and is a

highly aggressive tumor with early distant metastasis, usually to the lungs.[109,110] PLS also exhibits high rates of local recurrence, approaching 25%, with 5-year OS rates of 40% to 60%.[100,111] Again, treatment is with wide, local, limb-sparing resection plus radiation.[101]

Extremity leiomyosarcomas comprise 10% to 15% of extremity sarcomas, with a preference for the lower limb. Similar to leiomyosarcoma in the retroperitoneum or intraabdominal sites, leiomyosarcoma in the extremities tends to have a decent prognosis, with a 6% rate of local recurrence, a 46% rate of distant recurrence, and a 5-year DSS rate of 75%.[112,113] Resection remains the cornerstone of treatment, and radiation can be considered for lesions >5 cm in size.[114] There are no data to support the use of chemotherapy in extremity leiomyosarcoma.

As evidenced here, there is increasing recognition of the importance for subtype-guided management in sarcoma given the heterogeneity in tumor biology. However, the rarity of each histiotype is a major barrier to recruiting patients to randomized controlled trials. In a 2016 study evaluating endpoints and the quality of trials currently available in the field of sarcoma, only 13% of all selected trials included patients based on specific histology.[115] As the field of oncology continues to move in the direction of precision therapy, histiotype-specific management will become more relevant. Continued collaboration among sarcoma centers globally will be paramount to optimize management for this challenging disease based on histology.

Retroperitoneal STS

Background

RPS accounts for approximately 10% of all STS (Fig. 3) and frequently presents at an advanced stage with nonspecific symptoms, including abdominal pain, increasing abdominal girth, and a change in bowel habits.[116,117] In the retroperitoneum, WDLS/DDLS, leiomyosarcoma, and solitary fibrous tumor are the most common histologic subtypes encountered, each with its own distinct biologic behavior in terms of risks of local or distant recurrence and OS (see Histiotype-Specific Outcomes, below). In fact, over the past decade, there has been increased recognition that RPS is not a single disease, and this has triggered the establishment of collaborative groups to standardize practice patterns and clinical guidelines. One such group is the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), a collaboration between European, North American, and Asian sarcoma clinicians established in 2013 that has contributed to the update of the European Society of Medical Oncology Clinical Practice Guidelines for Sarcoma and Gastrointestinal Stromal Tumors and has produced consensus guidelines on the management of primary RPS.[9] Retrospective data from this collaborative has also been critical in advancing our understanding of the natural history of this disease. In 2016, Gronchi et al reported data from 8 TARPSWG institutions from 1007 patients with RPS highlighting the value of histologic subtype as an important predictor for pattern of recurrence.[118] Recognition of this biologic variability has subsequently led to the current, more "personalized," histology-based management of RPS, including select integration of nonsurgical treatments such as radiation and systemic therapy. In addition, this group also led to the establishment of a prospective registry as of January 2017 (Retroperitoneal Sarcoma Registry: An International Prospective Initiative [RESAR]; ClinicalTrials.gov identifier NCT03838718), which aims to collect standardized variables from patients with primary RPS who undergo resection at reference centers. Data from this registry are expected to fuel additional randomized controlled trials in this field. The sections below highlight landmark studies for this disease site and the current roles of surgery, radiation, and chemotherapy.

Optimal Surgical Approach

Surgical resection remains the cornerstone of treatment for primary, localized RPS and provides the only opportunity for cure. The importance of complete resection with macroscopic tumor clearance in long-term DFS for RPS has been firmly established in the literature.[119-121] Thus preoperative cross-sectional imaging with computed tomography of the chest, abdomen, and pelvis is paramount to evaluate surgical candidacy by assessing the extent of disease and technical resectability. However, because of the lack of fascial planes in the retroperitoneum and the proximity of retroperitoneal lesions to critical structures, obtaining negative margins can be challenging and, compared with other anatomic locations, microscopic positive margins are more common for RPS. In an MSKCC analysis of 2084 patients with STS, 45% of those with RPS had positive microscopic margins compared with only 19% of those with extremity STS ($P < .005$).[48] Although grossly positive margins (R2 resection) have demonstrated only marginally improved patient outcomes compared with outcomes in patients who have unresectable disease, the long-term oncologic effects of microscopically positive margins (R1 resection), compared with microscopically negative margins (R0 resection), in RPS is unclear because results have been conflicting in several retrospective series.[23,122,123] In a series of 500 patients reported by Lewis et al, local RFS and DSS were similar between patients who underwent complete resection with microscopically negative margins versus microscopically positive margins ($P = .2$).[23] Conversely, in a retrospective study of 382 patients by Bonvalot et al, patients who underwent resection with microscopic negative margins had decreased abdominal recurrence ($P = .008$) and improved OS ($P = .03$).[122] Similarly, the largest retrospective series to date included 4015 patients

from the NCDB and demonstrated a 10.4% absolute 5-year improvement in OS when an R0 resection was achieved.[123] The discordance in the available literature can be largely attributed to the retrospective design of these studies, the difficulty of accurately assessing the status of all margins on large tumors, and the inclusion of multiple histiotypes, each with its own distinct tumor biology. As such, the results of these studies should be interpreted with caution until a standardized way of assessing margins on retroperitoneal tumors is developed.

The approach to RPS has been fine-tuned by the concept of extended or compartmental resections, which was first introduced in 2009 by 2 retrospective studies from centers in Italy and France. In this approach, adjacent, uninvolved organs and structures are systematically resected en bloc to maximize the chance of a microscopic negative margin, analogous to the approach undertaken for truncal/extremity STS.[122,124] This is frequently achieved by multivisceral resection, which often includes the kidney, colon, pancreas/spleen, psoas, and/or diaphragm muscles, as well as the removal of all ipsilateral retroperitoneal fat from the diaphragm to the iliac vessels on the side of the tumor. In the first study in 2009 by Gronchi et al, extended resection in 152 patients resulted in a 5-year local recurrence rate of 29% compared with 48% in 136 patients who underwent standard resection, defined as resection of only involved organs in which direct tumor invasion was appreciated at the time of surgery.[124] Subsequent follow-up at 5 years demonstrated improved OS for low-grade and intermediate-grade tumors only.[125] Bonvalot et al reported that extended resection in 120 patients resulted in a 3.3-fold lower rate of local recurrence compared with 65 patients who underwent standard resection.[122] In that study, the improved recurrence rate did not translate into an improved survival outcome, thus generating significant controversy. Furthermore, a recent 2019 retrospective study by Judge et al used data from the American College of Surgeons National Surgical Quality Improvement Program and sought to address 30-day morbidity and mortality rates associated with multivisceral resection for RPS. In their study of 564 patients, when comparing multivisceral resections with nonmultivisceral resections, there was no significant difference noted in overall morbidity (22% vs 17%; $P = .13$), severe morbidity (11% vs 8%; $P = .18$), or mortality (<1% vs 2%; $P = .25$).[126] Therefore, extended operations with multiorgan en bloc resections and/or vascular reconstructions should be considered for all RPS with the goal of achieving a macroscopically complete resection, with a single specimen encompassing the tumor and involved contiguous organs, while minimizing microscopically positive margins. This is best achieved by resecting the tumor en bloc with adherent structures, even if they are not overtly infiltrated, while taking care to avoid intraoperative tumor rupture and piecemeal excision because these are associated with an increased risk of local recurrence and worse survival.[118] Notably, the best chance of resection with curative intent is at the time of primary presentation. Given the lack of consensus guidelines, management regarding extended or compartmental resection is variable among high-volume specialty centers.

As our understanding of the natural history and biology of the various STS histiotypes encountered in the retroperitoneum has improved, we have also learned to tailor the extent of surgical resection to the histologic subtype. As a matter of fact, wider resections are needed for liposarcomas because their well differentiated component is virtually undistinguishable from retroperitoneal normal fat, and their prognosis is dominated by the risk of locoregional recurrence. Instead, less extended procedures can be planned for leiomyosarcomas or solitary fibrous tumors because of their limited locoregional recurrence risk.[127,128] Because incomplete resection does not improve survival, resections in which gross negative margins cannot be achieved are not indicated.[129]

Despite curative resection, locoregional recurrence is common, occurring in up to 30% of patients, and accounts for 75% of RPS-related deaths.[130,131] Curative resection should be considered for isolated locoregional recurrences, particularly in the setting of favorable histiotypes such as WDLS, although a period of observation may be prudent to space out the interval between operations.[132] The extent of resection should be dictated by the ability to achieve macroscopic complete removal of the tumor, with a goal of avoiding complications of progression and preserving function.[133-135] A 2011 study demonstrated that patients with recurrent disease who were able to undergo reresection had a median survival of 53 months compared with 30 months in those who did not undergo surgery ($P = .01$).[135] Although reresection is often feasible, the potential improvement in survival should be balanced with the chance of mortality and serious morbidity, especially if the patient is asymptomatic. Because multifocal intraabdominal disease is difficult to completely resect and the oncologic benefit, in this case, is likely minimal, these cases should only be undertaken with a palliative intent.[132] The approach to local recurrences is discussed in more detail below (see Histiotype-Specific Outcomes).

The Role of Radiation in Localized Disease

Locoregional recurrence is the main pattern of treatment failure in retroperitoneal liposarcoma, with rates ranging from 30% to 50%, and constitutes the primary cause of disease-related mortality.[136] This local failure rate has led clinicians to search for effective multimodal treatment regimens, and radiation therapy offers a potential benefit. The first randomized controlled trial comparing neoadjuvant radiotherapy with surgery alone (Surgery With or

Without Radiation Therapy in Treating Patients With Primary Soft Tissue Sarcoma of the Retroperitoneum or Pelvis [ACOSOG Z9031]; ClinicalTrials.gov identifier NCT00091351) closed prematurely in 2004 because of low accrual rates. More recently, the Surgery With or Without Radiation Therapy in Untreated Nonmetastatic Retroperitoneal Sarcoma (STRASS-1) trial (ClinicalTrials.gov identifier NCT01344018), an international, phase 3, randomized controlled trial, assessed oncologic outcomes in patients with RPS undergoing neoadjuvant radiation followed by surgery compared with patients undergoing upfront surgery alone. Results were released at the 2019 American Society of Clinical Oncology Annual Meeting and demonstrated a lack of benefit with preoperative radiation for RPS. Specifically, the 3-year abdominal RFS rate was 60.4% in the radiation group versus 58.7% in the surgery-only group ($P = .954$). Although the trial was not powered for subset analyses, results showed that patients with specific histiotypes, such as WDLS and low-grade DDLS, may benefit from neoadjuvant radiation (3-year abdominal RFS, 71.6% vs 60.4%, respectively).[137] Conversely, no benefit at all was shown for leiomyosarcoma. Limitations of this trial include the lack of stratification based on histology and limited long-term follow-up. The rest of the evidence for the use of radiotherapy for RPS has been extrapolated from small, single-institution, retrospective studies, which historically have reported inconsistent and equivocal results, likely because of the inclusion of patients with both primary and recurrent tumors and the use of various types of radiation (external-beam radiation, intraoperative radiation, and brachytherapy).[122,124,138-140] In the largest retrospective study to date evaluating the effect of radiotherapy on OS in patients with RPS, radiotherapy was associated with improved OS compared with surgery alone in either the neoadjuvant or adjuvant setting (neoadjuvant radiation: HR, 0.70 [95% CI, 0.59-0.82; $P < .0001$]; and adjuvant radiation: HR, 0.78 [95% CI, 0.71-0.85; $P < .0001$]).[141] Conversely, a recent 2019 study from the TARPSWG compared surgery alone versus surgery with perioperative radiation in patients with WDLS and DDLS and found no significant differences with regard to OS or the rate of distant metastases, thus highlighting that the appropriate selection of radiotherapy in this disease remains challenging.[142]

The benefit of using radiotherapy in the neoadjuvant setting is the ability to safely administer higher radiation doses to the tumor with limited exposure to the surrounding radiosensitive structures, such as the stomach and bowel, which are often displaced by the tumor itself. A 2016 systematic review of the literature by Cheng et al on the use of neoadjuvant radiotherapy for RPS included 15 studies and 464 patients. Results were again inconclusive compared with historical controls and demonstrated median 5-year OS, progression-free survival (PFS), and locoregional recurrence rates of 58%, 71.5%, and 25%, respectively.[143] Despite the lack of a definitive survival benefit, preoperative radiotherapy may render certain tumors more amenable to resection and increase the rate of R0/R1 resections. As such, NCCN guidelines recommend 50-Gy preoperative radiotherapy at 1.8 to 2.0 Gy per fraction, and some centers use this approach in patients with marginally resectable tumors.[46]

The data for postoperative radiotherapy are similarly conflicting, and there are no randomized trials of surgery with and without adjuvant radiation therapy. In retrospective uncontrolled series, the addition of postoperative radiation therapy reduced the risk of local recurrence and increased RFS.[139,144-146] These results, however, have not translated into OS improvements. Because of the high risk of radiotherapy-related bowel and abdominal viscera toxicity, most experts discourage the use of adjuvant radiation and recommend that radiation, if indicated, be given in the neoadjuvant setting after discussion in a multidisciplinary setting.

The Role of Neoadjuvant and Adjuvant Chemotherapy in Localized Disease

The role of chemotherapy in the treatment of RPS is not well defined. Evidence regarding chemotherapy regimens used for RPS is mostly based on retrospective series or extrapolated from clinical trials on extremity STS that have included a small number of patients with RPS. From an oncologic standpoint, the use of chemotherapy for RPS is of particular importance given that common histiotypes in the retroperitoneum, such as high-grade leiomyosarcoma and DDLS, tend to metastasize hematologically to distant sites, such as the lungs.[147] Thus the use of preoperative chemotherapy in particular may offer the theoretical advantage of addressing micrometastatic disease as well as downsizing the tumor to allow a higher rate of negative-margin resections.[148]

To date, 7 studies have reported outcomes in patients with RPS after neoadjuvant chemotherapy and surgery, of which 5 also included radiotherapy preoperatively.[120,149-153] Among these, a 2014 retrospective series by Bremjit et al investigated the difference in OS among patients who were treated with neoadjuvant chemotherapy and those who underwent surgery alone. Among 132 patients with primary RPS, 28 received neoadjuvant chemotherapy and 57 were treated with surgery alone. At the time of surgery, 8 patients had progressed (29%), 14 had stable disease (50%), and 2 had responsive disease (7%). No survival improvement was observed in patients who received neoadjuvant chemotherapy; rather, there was a trend toward worse OS in this cohort (HR, 1.6; 95% CI, 0.8-3.2).[120] A 2015 propensity-match NCDB study of over 8600 patients with localized RPS evaluated survival

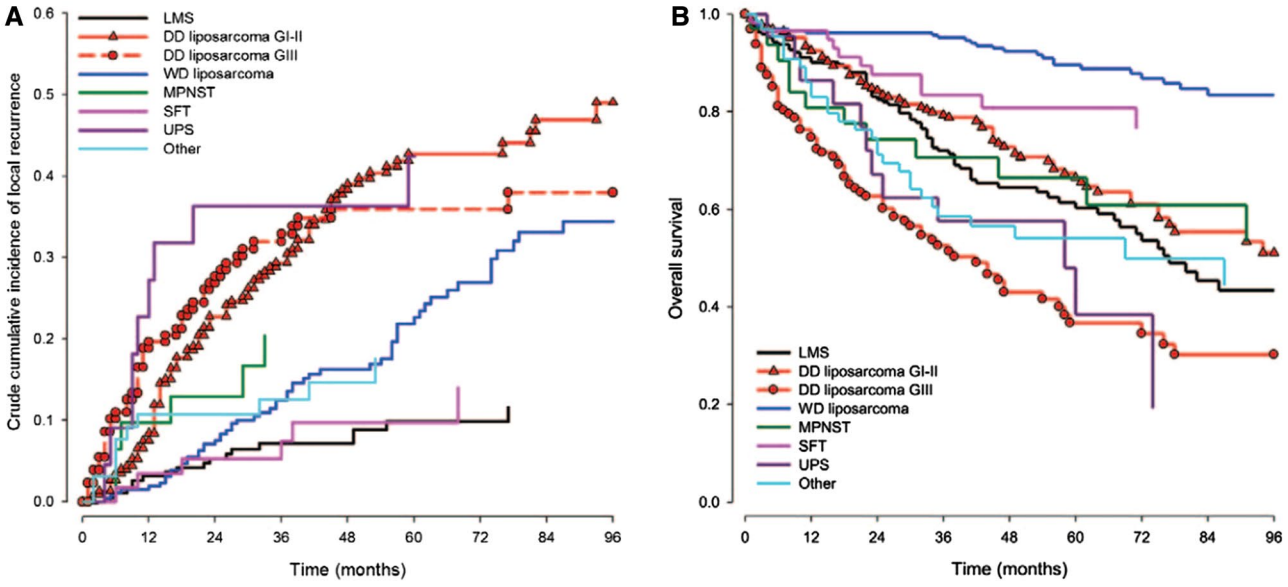

FIGURE 5. (A) Crude Cumulative Incidence of Local Relapse According to Retroperitoneal Sarcoma Histologic Subtype and (B) Overall Survival Curves According to Retroperitoneal Sarcoma Histologic Subtype. DD indicates dedifferentiated; GI-II, grade 1 and 2; GIII, grade 3; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibrous tumor; UPS, undifferentiated pleomorphic sarcoma; WD, well differentiated. Reprinted from Gronchi A, Strauss DC, Miceli R, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the Multi-institutional Collaborative RPS Working Group. *Ann Surg*. 2016;263:1002-1009, with permission from Wolters Kluwer Health, Inc (insights.ovid.com/pubmed?pmid=26727100).[118]

after receipt of adjuvant or neoadjuvant chemotherapy. That study actually demonstrated significantly worse median OS for patients who received perioperative chemotherapy compared with surgery alone (40 vs 52.4 months; $P < .01$), with an increased hazard of death (HR, 1.17; 95% CI, 1.04-1.31).[152] With no prospective data available, there are no guidelines to support the use of neoadjuvant chemotherapy for RPS, and its use must be carefully discussed in a multidisciplinary setting on a case-by-case basis or within the context of a clinical trial. We currently await results of a new randomized trial, STRASS2 (Surgery With or Without Neoadjuvant Chemotherapy in High Risk Retroperitoneal Sarcoma), which will analyze the role of neoadjuvant chemotherapy for grade 3 DDLS and high-grade leiomyosarcoma of the retroperitoneum (ClinicalTrials.gov identifier NCT04031677).

The majority of the data regarding the use of adjuvant chemotherapy for RPS are generalized from the data presented above regarding adjuvant chemotherapy for extremity or truncal STS.[82,84] For this reason, the use of adjuvant chemotherapy is not advocated for resectable RPS. To date, no randomized controlled trial has evaluated the role of preoperative versus postoperative chemotherapy.

Histiotype-Specific Outcomes

Liposarcoma, and particularly WDLS and DDLS, is the most common histiotype in the retroperitoneum, encompassing 45% of all cases.[154] Primary MLS/RCLS are relatively uncommon, accounting for only 7% of patients with primary retroperitoneal liposarcoma, and, when present, typically represent metastatic foci from a primary truncal/extremity MLS/RCLS.[130] Radical surgical resection remains the cornerstone of treatment for localized liposarcoma in the retroperitoneum. In the 2016 study by Gronchi et al mentioned above, results demonstrated a 5-year cumulative incidence of local recurrence of 20% for WDLS, 40% for grade I and II DDLS, and 35% for grade III DDLS (Fig. 5A) and a 5-year cumulative incidence of distant recurrence of 10% for grade I and II DDLS and 30% for grade III DDLS. Notably, WDLS rarely metastasizes distantly.[118] Unfortunately, local recurrences of retroperitoneal liposarcoma are a major cause of disease-related mortality, which underscores the importance of an initial appropriate resection of the primary tumor by a surgeon with expertise in the treatment of these tumors.[155] The rates of local and distant recurrence are related to the reported 5-year OS rates of 90% for WDLS, 70% for grade I and II DDLS, and 40% for grade III DDLS (Fig. 5B).[118,130] Because of the relative resistance of WDLS and DDLS to systemic therapy, recurrences are often managed with reresection, and the extent should be as required to achieve complete gross resection.[9] According to consensus guidelines from the TARPSWG, reresection of recurrent WDLS can be delayed to space out the interval between operations, particularly among patients who are asymptomatic.[132] Success of salvage operation for this histology relies predominantly on appropriate patient selection, including those with no history of tumor rupture,

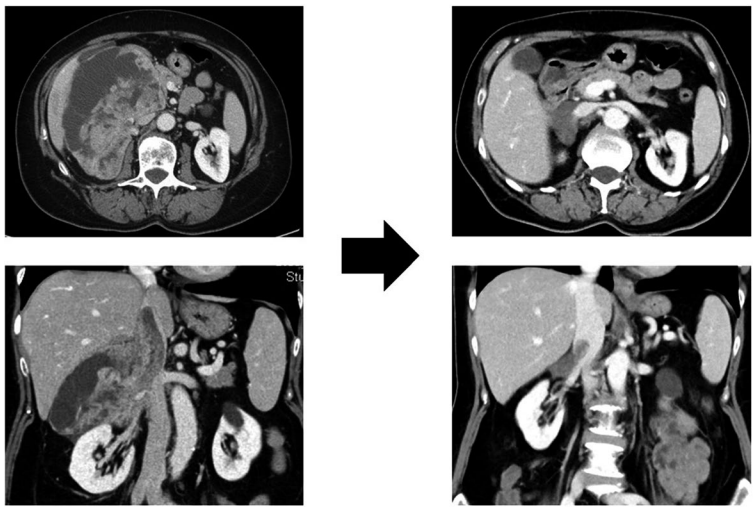

FIGURE 6. Leiomyosarcoma of the Right Retroperitoneum Originating From the Inferior Vena Cava. Left: (*Top*) Axial and (*Bottom*) coronal contrast-enhanced computed tomography images before preoperative chemotherapy are shown. Right: (*Top*) Axial and (*Bottom*) coronal contrast-enhanced computed tomography images after 3 cycles of doxorubicin and dacarbazine are shown.

long recurrence-free intervals (>12 months), tumor growth rates <0.9 cm per month, unifocal disease, and the ability to achieve complete resection at the recurrent operation.[156,157] In a single-institution study at The University of Texas MD Anderson Cancer Center, salvage surgery for patients with recurrent WDLS achieved macroscopically negative margins in 87% of cases and resulted in a median OS of 7.4 years after resection. That study also demonstrated that a recurrence-to-salvage interval ≥6 months was associated with longer DFS because of improved patient selection and planning for salvage surgery.[156] In the largest study to date of patients with recurrent RPS by the TARPSWG, which reported the outcomes after resection of recurrent liposarcoma, patients with WDLS had a 3-year DFS rate of 60%, compared with 40% for grade II DDLS and 20% for grade III DDLS.[158] Because of these biologic differences in outcomes, reresection for DDLS should be undertaken in carefully selected cases in which macroscopic resection can be achieved. There are currently no data to support the use of radiation or systemic therapy in the setting of recurrent disease, and the option of multimodality therapy should be discussed on a case-by-case basis in a multidisciplinary evaluation.

Leiomyosarcoma is the second most common sarcoma histiotype in the retroperitoneum, representing 10% to 20% of all cases, and most often originates from large vessels, such as the inferior vena cava, renal vein, gonadal vein, or iliac vein.[159] Although the uterus is the most common location for this sarcoma histiotype, a discussion of uterine leiomyosarcomas is beyond the scope of this review article. Independent of the site of origin, surgery remains the cornerstone of treatment.[160] The rates of local recurrence range from 6% to 10% for retroperitoneal leiomyosarcoma, whereas the risk of distant recurrence is >50%.[41,113,118] Major vascular resections with or without reconstruction are often required. In addition, because of the low incidence of local recurrences, currently, neoadjuvant radiation is not routinely recommended for retroperitoneal leiomyosarcomas, a recommendation that is further supported by the recently presented, randomized controlled trial assessing the role of neoadjuvant radiation in patients with resectable RPS—STRASS-1.[137] There have been no specific trials exploring the role of (neo)adjuvant chemotherapy in retroperitoneal leiomyosarcoma alone, although it has been used on a case-by-case basis with success (Fig. 6). Similar to the management of liposarcoma, recurrent leiomyosarcoma should be managed with reresection. A 2018 retrospective study out of The University of Texas MD Anderson Cancer Center demonstrated that patients who underwent salvage surgery had a longer median OS after recurrence of 5.6 years compared with 3.3 years in those who did not undergo salvage surgery.[161]

Solitary fibrous tumors are the third most common histiotype in the retroperitoneum, although they remain an extremely rare histiotype, accounting for <2% of all soft-tissue tumors.[162] This specific sarcoma histiotype more commonly has a low malignant potential, with a 5-year local recurrence rate of 7% and a distant recurrence rate of 20%, resulting in a favorable survival outcome, with a 5-year cumulative incidence of 19% for disease-specific death.[163] Because of this favorable tumor biology, simple surgical resection without the need for multivisceral or extended resection can often be performed. Given the low recurrence rates compared with other RPS histiotypes, combined with its rarity and the resultant limited existing literature, additional treatment strategies are currently not recommended. Because of its radiosensitive nature, however, neoadjuvant radiation can be considered for instances in which tumor downsizing would allow for a less morbid operation.[1,164]

These variations in outcome are critical to our understanding that STS is not a single entity, and as such, deliberate efforts should be made to design studies and trials that are histiotype-specific. The information presented here is also crucial for counseling patients about their specific outcomes.

Update on Therapy in the Advanced Stage

Advanced STS, or stage IV disease, is defined as tumors that have spread to lymph nodes or that more commonly have metastasized to distant parts of the body, such as the lungs.[165] Select patients with advanced tumors may be amenable to individually tailored, multidisciplinary care, such as curative resection or local therapy options with radiation. The section below outlines the current standard treatment for patients with advanced or metastatic disease. Given the varied chemosensitivity of STS subtypes, the histiotype and patient characteristics must be considered when defining the optimal treatment. Finally, new insights into the molecular characterization of STS are changing the approach to systemic therapy, and molecularly targeted therapies are now under clinical investigation.

Metastasectomy and Radiation for Lung Metastases

The lungs represent the most common location of distant metastasis after curative resection of STS, and the rate of metastases depends predominantly on tumor grade, with the majority occurring within the first 2 years after resection.[19,28,29,166] Surgical metastasectomy remains the primary treatment modality for isolated lung metastases, and several retrospective series have demonstrated 3-year survival rates of 40% to 50% after complete metastasectomy compared with <10% in historical controls.[166-179] Patient selection for metastasectomy is crucial, and a thorough preoperative evaluation must demonstrate no other organ involvement. Although several groups use the Bethesda criteria to evaluate patients for surgical candidacy, including a tumor doubling time ≥20 days, ≤4 metastatic nodules, and a disease-free interval of 12 months, others recommend surgical intervention in all patients with technically resectable pulmonary metastases.[166] Even when resection is not feasible, other lung-directed strategies, such as radiofrequency ablation or stereotactic body radiotherapy, have demonstrated acceptable local control rates with minimal toxicity and 1-year and 3-year survival rates of 58% and 29%, respectively.[180-182]

Chemotherapy

For the majority of patients with unresectable and metastatic disease, the standard treatment is administered with palliative intent and consists of single-agent doxorubicin, dacarbazine, epirubicin, or ifosfamide or anthracycline-based combination regimens with doxorubicin/epirubicin plus ifosfamide and/or dacarbazine. Doxorubicin-based systemic therapy has been shown to produce response rates of 12% to 24% in patients with locally advanced or metastatic STS.[183,184] Combination therapy with doxorubicin and ifosfamide was explored in the randomized phase 3 EORTC 62012 trial, which compared single-agent doxorubicin with ifosfamide and doxorubicin alone. A total of 455 patients who had locally advanced, unresectable or metastatic, grade 2 or 3 STS were randomized to receive either single-agent doxorubicin (75 mg/m^2) or doxorubicin (75 mg/m^2) plus ifosfamide (10 g/m^2 over 4 days) with growth factor support. Patients were treated every 3 weeks for a maximum of 6 cycles or until disease progression. At a median follow-up of 56 months, the median OS was 14.3 months with the combination therapy and 12.8 months with doxorubicin alone (HR, 0.83; $P = .076$). However, the median PFS was 7.4 months with the combination and 4.6 months with doxorubicin alone, accounting for a 26% reduction in risk (HR, 0.74; $P = .003$).[185] Given the lack of survival benefit, ifosfamide is reserved for patients in whom tumor shrinkage is specifically desired, such as in attempts to come to surgery or when a critical structure is threatened.[183] The use of anthracycline-based therapy is further reserved for patients with good performance status because of concerns regarding its cardiac toxicity.[183]

The evidence for systemic therapy beyond the first-line setting is less robust (Table 9).[185-196] Gemcitabine in combination with docetaxel, vinorelbine, or dacarbazine

TABLE 9. Systemic Therapies for Advanced or Metastatic Soft-Tissue Sarcoma

DRUG (STUDY)	ORR, %	MEDIAN PFS, MONTHS	MEDIAN OS, MONTHS
Doxorubicin (Bramwell 2003[188])	16.0-27.0	4.6	7.7-12.8
Doxorubicin + ifosfamide (Judson 2014[187])	14.0-34.0	7.4	7.3-14.3
Gemcitabine + docetaxel (Hensley 2008[189])	5.0-52.0	6.0-6.2	16.0-26.9
Taxanes (Casper 1998[190])	7.0-89.0	—	7.0-9.5
Cyclophosphamide + prednisone (Mir 2011[191])	26.9	6.8	—
Ifosfamide (Sharma 2013[192])	20.0-25.0	—	12.0
Gemcitabine (Maki 2007[193] and Svancarova 2002[194])	3.2-27.0	1.5-6.3	7.2-20
Dacarbazine (Garcia-Del-Muro 2011[195] and Buesa 1991[196])	4.0-18.0	2.0	8.2-11.5
Eribulin (Schoffski 2016[197])	4.0	2.6	13.6
Pazopanib (van der Graff 2012[198])	6.0	4.6	12.5

Abbreviations: ORR, overall response rates; OS, overall survival; PFS, progression-free survival.

has activity in patients with advanced-stage or metastatic STS.[191,193,197,198] The combination of gemcitabine and docetaxel has been shown to be superior to single-agent gemcitabine but at the cost of increased toxicity.[191] The combination of gemcitabine and dacarbazine is better tolerated and has been shown to improve PFS and OS compared with single-agent gemcitabine, particularly in patients with uterine leiomyosarcoma.[199] Trabectedin is a novel DNA-binding agent that has also shown overall response rates of up to 8% in phase 2 and 3 studies in patients with advanced STS, specifically in those with liposarcoma or leiomyosarcoma.[200,201] One of the major advantages is the lack of cumulative toxicity, so patients can remain on this agent for months if response rates are achieved. The sensitivity of these chemotherapeutic agents varies widely according to the histologic subtype, as evidenced in the section below.

Histiotype-Specific Chemotherapy

Liposarcoma

For advanced-stage or metastatic liposarcoma, anthracycline-based chemotherapy remains the first line of treatment. This practice is based on the subgroup analysis of the phase 3 EORTC 62012 randomized trial, which compared doxorubicin alone versus doxorubicin plus ifosfamide as first-line treatment in advanced-stage or metastatic STS. The results demonstrated that liposarcoma had a better tumor response to chemotherapy compared with other histiotypes.[202] Several other studies have further supported the use of doxorubicin-based therapy, particularly in patients with MLS/RCLS.[108,203]

There are also systemic therapies available as second-line agents for each liposarcoma histiotype. Translational studies have shown that the expression of the FUS-DDIT3 oncoprotein, which is classically associated with MLS, might correlate with sensitivity to trabectedin.[206] A single-arm, phase 2 trial by Demetri et al compared 2 trabectedin regimens in 270 adult patients with pretreated, unresectable, metastatic MLS or leiomyosarcoma. One group received a 24-hour infusion every 3 weeks, and the second group received a 3-hour infusion weekly. The median time to disease progression was 1.4 months (HR, 0.755; $P = .042$), with a trend toward improved OS favoring the 24-hour infusion.[200] These data are further supported in some retrospective studies that demonstrated improved outcomes in patients who had liposarcoma that was treated with trabectedin.[205] The trial by Demetri et al led to the approval of trabectedin in Europe in 2007. Trabectedin was subsequently approved in the United States in 2015 for use in pretreated liposarcoma and leiomyosarcoma after a randomized, phase 3 trial showed improved PFS in patients who received trabectedin compared with those who received dacarbazine.[201] On the basis of the results from a randomized, phase 2 trial by the French Sarcoma Group, trabectedin should be continued in patients with advanced STS until disease progression.[206] An additional drug with activity in liposarcoma is eribulin, a fully synthetic, microtubule-destabilizing anticancer agent that was approved for use in liposarcoma in 2016 after a randomized, phase 3 trial demonstrated a 2-month survival benefit compared with dacarbazine in patients with liposarcoma and leiomyosarcoma.[195] The roles of other second-line agents, such as gemcitabine plus docetaxel and tyrosine kinase inhibitors, remain to be defined for the treatment of advanced liposarcoma.[193,209]

Leiomyosarcoma

Leiomyosarcomas show moderate sensitivity to chemotherapy, although uterine leiomyosarcoma has been shown to be more chemosensitive than leiomyosarcoma of other locations.[208] Doxorubicin and ifosfamide have both demonstrated response rates between 10% and 25% as single agents.[196] Because of its worse toxicity profile, however, ifosfamide is generally regarded as a second-line agent. Dacarbazine has also demonstrated an overall response rate of 15.5% in a phase 2 clinical trial, and some retrospective data have shown overall response rates of almost 37% when used in combination with doxorubicin.[209,210] Although not yet proven in a clinical trial, the combination of doxorubicin with dacarbazine is currently favored in clinical practice.

In the second-line setting, studies have shown that other agents are also beneficial. Trabectedin has demonstrated an overall response rate of 7.5% in leiomyosarcoma, which was higher than that demonstrated among other STS subtypes.[211] Other agents have demonstrated activity in uterine leiomyosarcoma, including gemcitabine, temozolomide, liposomal doxorubicin, and etoposide.[212-214]

Undifferentiated pleomorphic sarcoma

Despite being one of the most common histiotypes, few data are available regarding systemic therapy for this particular subtype of STS.[215] Anthracyclines, ifosfamide, and gemcitabine plus docetaxel are the current therapies considered for advanced UPS based on the above-mentioned randomized study of gemcitabine plus docetaxel versus gemcitabine alone for patients with recurrent or metastatic STS, which demonstrated that UPS is sensitive to both regimens.[191]

Synovial sarcoma

Synovial sarcoma is recognized as one of the most chemosensitive subtypes of STS and is particularly sensitive to alkylating agents, such as ifosfamide, and anthracyclines, such as doxorubicin.[216] These can be used as monotherapy or in combination, depending on prior exposure. Trabectedin can also be used when available because it has demonstrated some minor activity in a single-arm phase 2 study, which demonstrated that 21% of patients with synovial

TABLE 10. Chromosomal Translocations in Soft-Tissue Sarcoma

TUMOR (STUDY)	TRANSLOCATION	GENE INVOLVEMENT
Myxoid liposarcoma (Turc-Carel 1986[221])	t(12;16)(q13;p11) or t(12; 22)(q13,q12)	*EWS*, *CHOP*
Synovial sarcoma (Clark 2005[222])	t(X;18)(p11.2;q11.2)	*SSX1* or *SSX2*, *SYT*
Myxoid/round cell liposarcoma (Clark 2005[222])	t(12;16)(q13;p11)	*CHOP*, *TLS*
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q21	*CTNNB1* or *APC* mutations

sarcoma were free of progression at 12 weeks.[217] Pazopanib is a multitargeted tyrosine kinase inhibitor that is currently available for clinical use in patients with advanced-stage or metastatic synovial STS. In a 2012 phase 3 randomized controlled trial, pazopanib was compared with placebo in patients with metastatic STS who had received at least one anthracycline-based regimen. The patients randomized to pazopanib achieved a PFS of 4.6 months compared with 1.6 months in the placebo group ($P < .0001$). This significance was retained in a subgroup analysis of patients with synovial sarcoma.[196] Pazopanib was approved in the United States in 2012 as second-line therapy for patients with advanced STS and for those with progressive disease within 1 year after neoadjuvant therapy.

Immunotherapy

Although systemic chemotherapy remains the cornerstone of treatment for patients with advanced-stage or metastatic disease, outcomes are still poor, and treatment strategies remain limited. More recently, advancements in the molecular characterization of STS have led to the development of new therapeutic strategies that show promising results in patients with certain histologic types of advanced or metastatic STS. There are currently various strategies under investigation including: 1) vaccination with autologous tumor cells or with peptides derived from tumor-associated antigens; 2) adoptive cell transfer using engineered T cells expressing T-cell receptor directed at NY-ESO-1; and 3) immune checkpoint inhibitors targeting cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and programmed death 1/programmed death–ligand 1 (PD1/PDL1).

Takahashi et al reported a cocktail peptide vaccination phase 2 study of 20 patients with bone sarcomas and STS and demonstrated stable disease in 6 patients, with regression of pulmonary metastasis and long-term survival in patients who had malignant fibrous histiocytoma and synovial sarcoma, respectively.[218] Some sarcomas have specific chromosomal translocations that may serve as unique targets for immunotherapy (Table 10).[219,220] Synovial sarcoma and MLS/RCLS often express high levels of self-antigen, notably NY-ESO-1. In 2014, Robbins et al reported a clinical trial using autologous T-cell receptor-transduced T cells directed against NY-ESO-1 after a lymphodepleting chemotherapy. The study showed objective clinical responses in 11 of 17 patients with synovial sarcoma.[221] Although preliminary, these findings provide support for the development of additional trials targeting NY-ESO-1 and other antigens expressed in STS.

Ipilimumab, a monoclonal antibody against CTLA-4, and pembrolizumab and nivolumab, both antibodies that target PD-1, have been successfully used as immunotherapy drugs, particularly for melanoma, and there is optimism that this success can be translated to sarcoma. In a phase 2 study, 6 patients with synovial sarcoma were treated with ipilimumab every 3 weeks. PFS ranged from 0.5 to 2.1 months, and neither a clinical nor an immunologic response was observed.[222] Despite the negative results from this trial, the sample size was small, and further assessments are needed to further guide the use of ipilimumab in STS. Nowicki et al reported that PD-1 and PD-L1 expression was significantly higher in metastatic tumors than in primary tumors and that PD-1 positivity was significantly associated with PFS in patients with synovial sarcoma.[223] To date, however, there are very few studies investigating the use of PD-1 inhibitors, and results have been conflicting. In a phase 2 trial of PD-1 inhibition with nivolumab in patients with advanced uterine leiomyosarcoma, 12 patients were enrolled, and none achieved an objective response.[224] Similarly, in the Alliance A091401 trial, nivolumab achieved only a 5% response rate, whereas the combination of nivolumab and ipilimumab achieved a 16% response rate in patients with locally advanced, unresectable, or metastatic sarcoma.[225] Conversely, according to interim results from the phase 2 SARC028 trial (A Phase II Study of the Anti-PD1 Antibody Pembrolizumab [MK-3475] in Patients With Advanced Sarcomas; clinicaltrials.gov identifier NCT02301039), pembrolizumab reduced tumor size for 40% of patients with UPS and 33% of patients with DDLS. Enrollment to expanded cohorts of both of these subtypes is currently ongoing.[226] There is also substantial interest in combining checkpoint blockade agents with other approaches, including chemotherapy, radiation therapy, and other immunotherapy agents.[227] Most recently, a group at MSKCC completed accrual on a trial evaluating the combination of ipilimumab and talimogene laherparepvec (TVEC), a genetically engineered virus that secretes granulocyte-macrophage–colony-stimulating factor selectively inside the tumor cells, thus initiating a tumor-directed immune response (ClinicalTrials.gov identifier NCT03069378). We currently await the results of this promising trial.

In conclusion, vaccination with autologous tumor cells can induce a clinical and immunologic response, adoptive

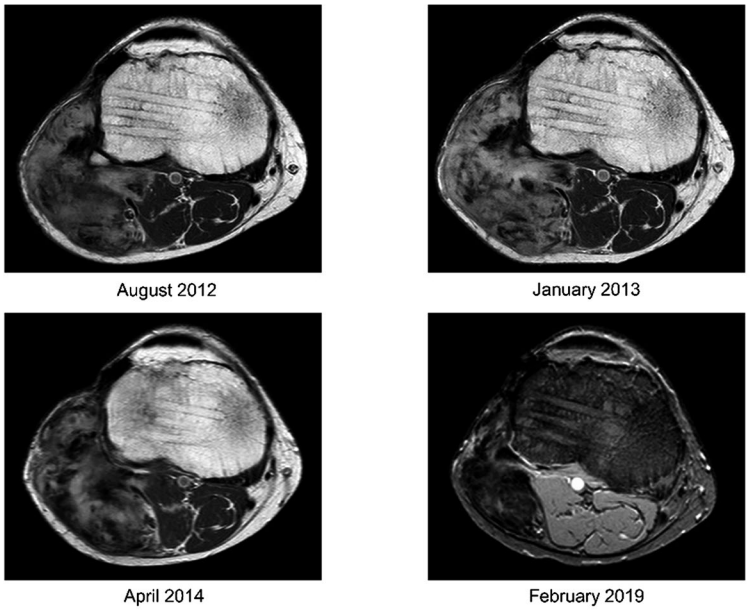

FIGURE 7. Axial View of a Contrast-Enhanced T1-Weighted Magnetic Resonance Image of a Desmoid-Type Fibromatosis of the Right Knee in a Man Aged 56 Years Demonstrating Evolution Over Time With an Initial Slight Increase in Size, Followed by Stabilization and then Reduction With Symptom Resolution Without Any Treatment.

therapies using T cells directed against germline antigens may be effective at mediating tumor regression in patients with synovial STS, and finally, favorable results are anticipated for clinical trials of immune checkpoint inhibitors in patients with sarcoma.

Select Topics

Desmoid-Type Fibromatosis

Desmoid-type fibromatosis is a rare, benign fibroblastic proliferation that can occur in any anatomic location.[228] These tumors do not have the ability to metastasize but can cause considerable morbidity because of their local infiltrative behavior.[101] Approximately 85% of sporadic desmoids contain β-catenin (*CTNNB1*) mutations, which can be used as a diagnostic tool.[229] Desmoid tumors have been reported to occur in 7.5% to 16% of patients who have familial adenomatous polyposis (FAP) and Gardner syndrome, and all patients diagnosed with desmoid tumors should undergo molecular testing or evaluation for a family history of FAP.[230,231] The mesentery is the preferred site for FAP-associated desmoid tumors, whereas sporadic desmoid tumors most commonly occur either in the abdominal wall in patients with a recent history of pregnancy or spontaneously in the extremity or trunk.[228] Desmoid tumors generally present as a painless mass in the extremity, abdominal wall, or trunk or as abdominal fullness in the case of intra-abdominal location. The initial workup for desmoid tumors includes cross-sectional imaging of the anatomic site with computed tomography or magnetic resonance imaging and subsequent tissue diagnosis with either a core needle or incisional biopsy, depending on tumor location.

Although resection was previously recommended as the primary treatment for patients with desmoid tumors, more recent evidence has demonstrated a rate of spontaneous regression in 20% to 30% of patients and disease stabilization in approximately 50% of patients.[232-235] As a result, nonoperative management with careful observation for progression can be safely offered to most patients, particularly those with indolent lesions that are small and asymptomatic (Fig. 7).[236] The challenge remains to identify those patients who are going to progress versus those who will continue to have an indolent course. Experts recommend that patients who have tumor growth on 3 consecutive imaging studies over a period of 1 to 2 years should be considered for either medical therapy or surgical resection, depending on the individual case.[228] For symptomatic patients with large tumors causing pain and functional limitations, complete surgical resection should be offered in the setting of minimal morbidity. Because of the infiltrative nature of these tumors, negative margins can be difficult to achieve. As some recent data suggest no difference in outcomes between patients treated with R0 or R1 resections, R1 margins are acceptable, particularly if achieving microscopic negative margins would result in significant morbidity.[237,238] Indeed, only 30% of patients with positive margins will recur at any time.[239] If surgical morbidity is unacceptable, then a period of medical therapy is warranted. Treatment for these recurrences should follow the same guiding principles followed for primary resectable or unresectable tumors. A treatment algorithm is provided in Figure 8.[240]

Historically, a variety of pharmacologic treatments, including nonsteroidal anti-inflammatory drugs, antiestrogen

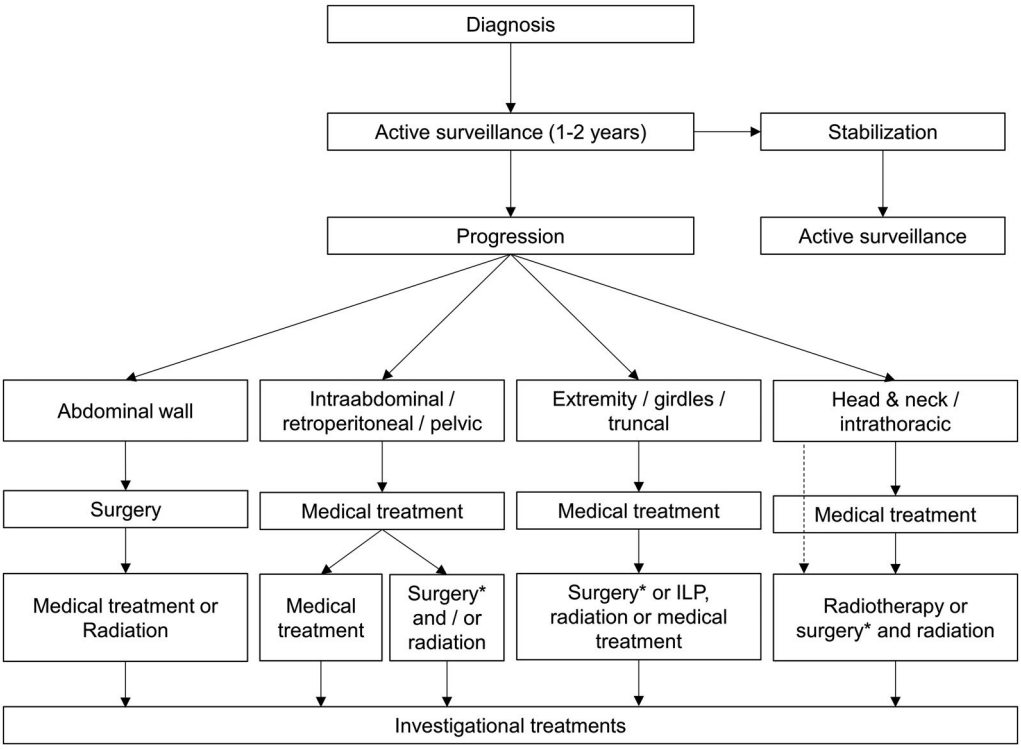

FIGURE 8. Treatment Algorithm for Desmoid Tumors. ILP indicates isolated limb perfusion. Adapted from The Desmoid Tumor Working Group, 2020.[240]
*Surgery if morbidity is limited.

agents, and cytotoxic chemotherapy agents, were used in the treatment of this disease. However, with our current understanding of its natural history with regard to spontaneous regression and stability, the true efficacy of many of these drugs is unknown.[241-245] To date, however, no randomized controlled studies have compared one treatment strategy over another. Systemic therapy should be considered in patients with symptomatic, locally advanced disease in whom the morbidity of resection would be significant. Accepted chemotherapy options include a low-dose regimen with methotrexate and/or vinblastine/vinorelbine, anthracycline-based regimens if a more rapid response is desired, or pegylated liposomal doxorubicin.[246] Sorafenib, an oral, multitargeted receptor tyrosine kinase inhibitor, can also be considered in the setting of progressive or symptomatic desmoid tumors according to a recent randomized phase 3 trial, which demonstrated an objective response rate of 81% compared with 36% in the placebo group ($P < .001$).[247] Another novel option for patients with progressive disease is cryoablation, an interventional radiology technique that uses several series of freeze/thaw cycles that lead to cell death. A recent prospective, nonrandomized study from France (CRYODESMO01; Evaluation of the Cryodestruction of Non Abdominopelvic Desmoid Tumors in Patients Progressing Despite Medical Treatment; ClinicalTrials.gov identifier NCT02476305) using cryoablation in 50 patients reported an 86% rate of nonprogressive disease at 12 months.[248] Additional study results are pending, but this technique poses a potential option in the future for patients with desmoid tumors that are refractory to medical therapy. Radiotherapy is not generally recommended for desmoid tumors that are located in the abdominal cavity and is only recommended for desmoid tumors in the extremities, superficial trunk, or head and neck after multiple failed lines of treatment or when surgery would involve functional impairment.[249] In fact, a recent phase 2 trial demonstrated 3-year local control rates of 81.5% with radiotherapy in patients with extremity or truncal inoperable desmoid tumors.[250] However, the potential toxicity of radiation therapy must be carefully considered in the setting of a benign disease process. Patients with desmoid fibromatosis should be followed by a sarcoma specialist with cross-sectional imaging every 3 to 6 months for 2 or 3 years and every 6 to 12 months thereafter.[46]

Surveillance

Approximately one-third of all patients with STS will develop a local or distant recurrence.[48,251] The risk of recurrence is greatest in the first few years, with 60% to 70% of recurrences occurring by 2 years and >90% occurring by 5 years.[13,24] The aim of an effective surveillance program is to detect cancer recurrence at an early stage so that a curative intervention can be implemented. In patients with isolated locoregional recurrence of extremity STS, local treatment, such as reoperation with or without radiation therapy, can be effective for disease control.[252-254] For patients with RPS, early detection of a locoregional recurrence may improve

resectability and also prevent potential complications, such as bowel obstruction. Distant recurrences most frequently occur in the lungs and, for isolated lung metastases, several studies have demonstrated that surgical metastasectomy offers improved survival.[166-179] Even when resection is not feasible, other lung-directed strategies, such as radiofrequency ablation or stereotactic body radiotherapy, have demonstrated acceptable local control rates.[180-182] Given the availability of salvage therapy, experts agree that surveillance for STS is paramount. However, there is a lack of clinical trials evaluating the optimal surveillance frequency and modality that will result in improved survival, minimize morbidity, and optimize resource utilization. A recent retrospective study by Gamboa et al sought to evaluate the optimal modality of surveillance of lung metastases in patients with resected, high-grade STS. The results demonstrated that a chest x-ray, compared with a computed tomography scan, did not result in worse OS. Findings from that study are being further evaluated in a randomized trial, which is currently in development.[255] Ultimately, the fundamental question is whether more intense surveillance protocols and more sophisticated imaging modalities are not only better at detecting recurrences but also whether this earlier detection has clinical relevance. Given the lack of prospective data to help address these questions, current guidelines are informed predominantly by expert consensus and a few retrospective studies.[256]

Because the natural history of STS is determined largely by the anatomic site of origin, surveillance strategies are generally based on the primary site of disease. For example, the NCCN (version 2.2018) has separate recommendations for extremity or superficial trunk STS and RPS.[46] For patients with resected, stage IA/IB extremity or superficial trunk STS, postoperative surveillance includes a history and physical examination every 3 to 6 months for 2 or 3 years and then annually afterward, with a consideration for chest imaging with either chest x-ray or computed tomography as well as baseline postoperative and periodic imaging of the primary site of disease based on the estimated risk of locoregional recurrence. For patients with resected stage II or IIIA disease, surveillance includes history and physical examination every 3 to 6 months for 2 or 3 years, then every 6 months for the next 2 years, and then annually, as well as chest imaging and baseline postoperative and periodic imaging of the primary tumor site. NCCN guidelines for the surveillance of patients with resected RPS include a physical examination with cross-sectional imaging every 3 to 6 months for 2 or 3 years, then every 6 months for the next 2 years, and annually afterward. The European Society of Medical Oncology has also published practice guidelines for STS that include recommendations for postoperative follow-up. In the future, postoperative surveillance strategies should be tailored to the specific histiotype given the differences in tumor biology and patterns of recurrence. The value of molecular surveillance with circulating tumor cells is also being investigated.[257,258]

Conclusions

STS accounts for only 1% of all adult malignancies. As such, generating high-quality evidence for the management of STS is challenging. The heterogeneity of these tumors has hindered the development of robust, evidence-based treatment strategies, and our therapeutic approach is neither histology-specific nor widely standardized. The strength of sarcoma research in the current academic climate is collaboration. Continued collaborative efforts will allow studies to be both sufficiently large and sufficiently focused to generate evidence that is clinically meaningful in specific STS patient populations. ■

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