ABSTRACT  Soft tissue sarcoma (STS) is an extremely heterogeneous group of rare tumors that share a putative mesenchymal cell origin. STS can occur in any soft tissue in the body, yet all share a common feature of primarily disseminating hematogenously, particularly to the lungs. Staging for STS is particularly useful in prognosis, design of effective multimodality treatment programs, and comparing treatment outcomes from different centers and different eras. The current iteration of AJCC STS staging includes Tumor, Grade, Node, and Metastasis with “a” indicating superficial and “b” indicating deep designations. Further opportunities to improve this process exist, particularly as molecular considerations become more apparent, and future evolution into an even more useful STS staging system can be anticipated. (CA Cancer J Clin 2006;56:282–291.) © American Cancer Society, Inc., 2006.

INTRODUCTION

Soft tissue sarcoma is an extremely rare form of malignancy that constitutes less than 1% of adult solid malignancy. There are approximately 9,530 new cases per year in the United States.1 The STS disease entity includes more than 50 separate histologic subtypes, many of which have distinctive natural biological behavior. Unlike the vastly more common carcinomas, which are of epithelial origin, soft tissue sarcomas are of putative mesenchymal derivation and can involve connective tissue structures as well as viscera and integument anywhere in the human body. Approximately two-thirds of all soft tissue sarcomas occur in an extremity, whereas one-third are located in the trunk, retroperitoneum, abdomen, or other locations. Overall survival is approximately 50% at 5 years; the key determinant of survival is control of both local recurrence as well as distant dissemination.

Depending on stage, effective treatment usually requires surgical extirpation with the addition of radiotherapy and/or chemotherapy. STS disseminates primarily via the hematogenous route, particularly to the lungs. Although distant metastasis is an ominous finding, the role of metastasectomy in combination with other treatments continues to expand, and patients with STS who are so treated can anticipate a 30% overall survival rate at 5 years after dissemination has been successfully addressed in this manner. Unlike many other types of malignancy, local recurrence is not necessarily a harbinger of soon-to-emerge systemic failure. Indeed, the majority of patients with local-only STS failures can be salvaged, and many will subsequently enjoy long-term disease-free survivorship.

Most soft tissue sarcomas have no clearly defined etiology, although multiple associated or predisposing factors have been identified. As with any other cancer, genetic factors play a crucial role in the initiation and progress of the sarcomas. Genetic mutations in pluripotent mesenchymal stem cells are believed to give rise to malignant clones, which lead to the formation of these disease types. Several inherited cancer syndromes have STS as a component. These include neurofibromatosis Type 1 (von Recklinghausen disease), retinoblastoma, Li-Fraumeni syndrome, Gardner syndrome, Werner syndrome, Gorlin syndrome (basal cell nevus syndrome), Carney triad, and tuberous sclerosis.

Mutations in tumor suppressor genes and oncogenes have been associated with predisposition to STS and may also play a role in the prognosis of this disease. The best-known tumor suppressor genes that have been so implicated include RB-1 and P53. Extensive cytogenetic abnormalities may also occur in STS. These are usually associated with high-grade tumors, and in these situations such abnormalities may be useful as diagnostic tools. STS such as Ewing sarcoma/
primitive neuroectodermal tumors (PNET), myxoid/round cell liposarcoma, alveolar rhabdomyosarcoma, malignant melanoma of soft tissues/clear cell sarcomas, desmoplasic small round cell tumor, and synovial sarcoma all can have distinctive cytogenetic alterations whose presence may have treatment and prognosis implications.

The development of soft tissue sarcoma as a result of dose-dependent exposure to radiation has long been well established. The most common histologic subtypes of radiation-associated sarcoma are extraskeletal osteogenic (21%), malignant fibrous histiocytoma (16%), and angiosarcoma/lymphangiosarcoma (15%); most (87%) of these radiation-induced tumors are high-grade lesions.2

Lymphedema is a known risk factor for the development of lymphangiosarcoma, as initially described by Stewart and Treves in the early 1940s. Exposure to phenoxyherbicides and chlorophenols has been implicated in STS etiology as well.3 There is an association between certain viral infections (notably human herpesvirus-8 and human immunodeficiency virus-1) and some STS subtypes such as Kaposi sarcoma, a neoplasm also occasionally seen in iatrogenically immunocompromised patients such as organ transplant recipients.

## ROLE OF STAGING SYSTEMS

Developing robust and reproducible criteria for staging is critical if progress is to be made in tumor management. Such staging systems enable accurate inference about prognosis that in turn helps clinicians select appropriate therapies. Staging systems also allow the comparison of clinical experiences among centers, among treatments, and over the continuum of time. As developments in our knowledge increase regarding the genes and cognate proteins that drive tumor proliferation and dissemination, it will be increasingly important to use this information as part of our heretofore primarily anatomic- and pathologic-based staging systems. To successfully introduce these new perspectives, collaborative efforts among front-line clinicians, pathologists, and biostatisticians will be imperative.

Staging is also important in establishing uniform criteria for clinical trial eligibility and entry. This latter factor is particularly relevant in STS; because of the rarity of this type of malignancy, satisfactory clinical trials patient accruals usually require multicenter participation, frequently on the international level. The need for robust and reproducible trials entry criteria is apparent. Indeed, because of the rarity of STS, centers of excellence with large-scale experience in managing STS are not nearly as prevalent as facilities distinguished in the management of the more common epithelial tumors. Treatment algorithms can vary markedly from center to center, and so the importance of reliable STS staging systems looms even larger when comparing STS outcomes as a potential driver of patient referral patterns.

The varied sites in which soft tissue sarcoma can occur, the various STS histologic subtypes, and the existence of competing STS staging systems speak simultaneously to the need, as well as the difficulties, in comparing clinical results when different treatment algorithms have been used. In addition to the American Joint Committee on Cancer (AJCC) Staging System, there are other systems available such as that proposed by the Musculoskeletal Tumor Society, which is used primarily by orthopedic oncologists (see Table 1 and further discussion below). The

### Table 1: Surgical Staging System by Musculoskeletal Tumor Society22

| Stage | Grade | Local Extent       | Metastasis |
|-------|-------|--------------------|------------|
| I-A   | Low   | Intracompartmental | None       |
| I-B   | Low   | Extracompartmental | None       |
| II-A  | High  | Intracompartmental | None       |
| II-B  | High  | Extracompartmental | None       |
| III   | Any   | Any                | Present    |

Note: Intracompartmental tumors are those confined within the boundaries of well-defined anatomic structures such as a functional muscle group, joint, and subcutis; extracompartmental neoplasms are those that arise within or involve secondarily extrafascial spaces or planes that have no natural anatomical barriers to extension.

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existence of two STS staging systems further hampers interinstitutional comparisons and points to the unequivocal need for a universal staging approach in this disease.

The general history of cancer staging dates back to 1929, when the concept of describing malignant disease by extent was first introduced by the World Health Organization of the League of Nations. Predecessor articles in this series thoroughly describe the ensuing history of cancer staging, and the interested reader is referred to these reports for more information. AJCC STS staging dates back to the fourth edition of the AJCC Cancer Staging Manual, published in 1992. Table 2 demonstrates the changes with subsequent revisions of AJCC STS staging as they have appeared in the fifth and sixth editions of the AJCC Manual. Stages I to III describe localized STS, whereas Stage IV disease includes STS that has metastasized to lymph nodes and/or other distant sites. As can be discerned by inspection of Table 2, the data-justified departure from the fourth edition AJCC Manual concept that Stage I is Grade 1, Stage II is Grade 2, and Stage III is Grade 3 disease embodied a later realization (fifth edition AJCC Manual) that the interplay between size and grade, and superficial versus deep location more precisely defined clinical stage in localized STS. These alterations have only been possible because of the development of large, prospective, relational clinical databases such as the National Cancer Database of the Commission on Cancer that is sponsored by the American College of Surgeons (ACoS) with American Cancer Society (ACS) support, or the Memorial Sloan-Kettering Cancer Center Sarcoma database, initiated by Dr. Murray Brennan in the mid-1980s. As discussed below, several additional prognostic factors merit consideration for subsequent inclusion in the AJCC STS staging system, which could perhaps be further modified in the future as a nomogram incorporating appropriately weighted prognostic factors in addition to the T, N, M, G, and “a” versus “b” criteria currently included in the AJCC STS staging system. Such a nomogram has already been developed at Memorial Sloan-Kettering Cancer Center and this approach merits further careful consideration.

**TABLE 2 Changes in AJCC Staging**

|                   | Grade | Tumor   | Node | Metastasis |
|-------------------|-------|---------|------|------------|
| **AJCC (4th edition)** |       |         |      |            |
| I A               | G1    | T1      | N0   | M0         |
| I B               | G1    | T2      | N0   | M0         |
| IIA               | G2    | T1      | N0   | M0         |
| IIB               | G2    | T2      | N0   | M0         |
| IIIA              | G3-4  | T1      | N0   | M0         |
| III B             | G3-4  | T2      | N0   | M0         |
| IVA               | Any G | Any T   | N1   | M0         |
| IV B              | Any G | Any T   | Any N| M1         |
| **AJCC (5th edition)** |       |         |      |            |
| I A               | G1-2  | T1a-b   | N0   | M0         |
| I B               | G1-2  | T2a     | N0   | M0         |
| IIA               | G1-2  | T2a-b   | N0   | M0         |
| IIB               | G3-4  | T1a-b   | N0   | M0         |
| III C             | G3-4  | T2a     | N0   | M0         |
| III               | G3    | T2b     | N0   | M0         |
| IV                | Any G | Any T   | N1   | M0         |
|                  | Any G | Any T   | Any N| M1         |
| **AJCC (6th edition)** |       |         |      |            |
| I                 | G1-2  | T1a-b, T2a-b | N0 | M0         |
| II                | G3-4  | T1a-b, T2a | N0 | M0         |
| III               | G3-4  | T2b     | N0   | M0         |
| IV                | Any G | Any T   | N1   | M0         |
|                  | Any G | Any T   | N0   | M1         |

**APPLYING THE AJCC STS STAGING SYSTEM**

The clinical symptoms accompanying the diagnosis of soft tissue sarcoma are nonspecific.
The most common finding at presentation is a painless and gradually enlarging mass. It is interesting to note that a trivial trauma to the primary STS site may frequently call initial attention to the presence of a tumor. However, trauma per se has not been implicated as a causative factor in this disease. The size of the tumor at diagnosis varies according to the site; tumors of the distal limbs and head or neck are usually smaller because they are more likely to be noticed earlier, whereas tumors of the thigh and retroperitoneum may become very large before they are detected. If unimpeded by anatomic constraints, soft tissue sarcomas can expand circumferentially and create a tumor pseudocapsule that consists of a zone of compression of surrounding normal tissue. As the tumor expands, patients with these tumors may present with site-dependent symptoms of increased pressure, such as paresthesia, distal edema, or hollow viscus compromise or even frank obstruction. The growth rate of STS varies as a function of the biological aggressiveness of the tumor. Some STS histologies, such as liposarcoma, tend to be “pushing” rather than infiltrative tumors. In contrast, other histologic subtypes (eg, synovial sarcoma) tend to be markedly infiltrative lesions. Low-grade tumors may evolve over a long period and may be mistaken for benign neoplasms, resulting in delay of diagnosis.

Diagnostic imaging should be performed only after a thorough clinical examination has been completed and before any biopsy or treatment procedures. The physical examination may help specify the most appropriate imaging modality to be used. A biopsy performed before imaging may create radiologic artifact, rendering subsequent imaging studies less useful or even suboptimal. Imaging helps in assessing the local and regional extent of the lesion and may occasion ally aid in definitive diagnosis by suggesting the most likely histologic STS subtype.

Plain radiographs may be useful in ruling out primary bone neoplasms or detecting calcifications that can be characteristic of synovial sarcoma. A chest radiograph is useful as a screening tool, although preoperative computed tomography (CT) of the thorax is more sensitive for detecting pulmonary metastases. CT is usually performed to delineate intraabdominal, pelvic, or chest STS. Ultrasound may be helpful in demonstrating the possible cystic nature of an intraabdominal, intrapelvic, or intrahepatic STS. It may also help rule out certain pseudotumors, such as popliteal cyst, synovial cyst, abscess, or vascular malformations. The multiplanar images and superior anatomic resolution possible with magnetic resonance imaging (MRI) is a key advantage; this nonirradiating procedure is preferred for the diagnosis of STS in body compartments devoid of structures capable of causing motion artifact, and continues to play a central role in diagnosis and management planning for tumors within these sites.

Recent technological advances in diagnostic imaging have improved the capabilities of radiological and nuclear modalities to assist in the diagnosis, delineation of tumor extent, and accurate staging of STS. Several imaging approaches offer particularly noteworthy future promise. Dynamic gadolinium-enhanced MRI can be used to demonstrate early enhancement of viable tumor tissue in contrast to surrounding reactive tissues. Combining functional imaging with anatomic detail may aid in the diagnostic effectiveness of both types of imaging techniques. For example, positron emission tomography (PET) scanning combined with MRI can increase the utility of these techniques in certain specific situations. At present, it appears that the usefulness of PET in STS is primarily to help identify unsuspected sites of metastasis in patients with recurrent high-grade tumors. MRI angiography allows delineation of vascular structures in proximity or even traversing through STS and also allows three-dimensional reconstruction, which may be particularly useful in certain situations such as vena caval leiomyosarcoma. Magnetic resonance spectroscopy may be useful in some circumstances, such as assessing patient responses to neoadjuvant chemotherapy when resection has not yet been performed. The diagnostic use of proton spectroscopy has recently been evaluated in preliminary studies, but has yet to reach clinical applicability.

Histologic examination of a tumor specimen is required before treatment is initiated, particularly if nonsurgical neoadjuvant approaches are being considered. Although fine-needle aspiration for definitive diagnosis is not commonly
Staging Soft Tissue Sarcoma

used outside of several major sarcoma centers, percutaneous core needle biopsy is safe and can be performed with the patient under local anesthesia for palpable masses or in conjunction with CT, ultrasound, or MRI for deep-seated tumors. If an incisional biopsy is performed in an extremity lesion suspected of being STS, the biopsy trajectory and scar should lie within the area of a subsequent en bloc tumor resection and should be oriented parallel to the long axis of the extremity to minimize normal tissue contamination that will require subsequent excision. The histologic subtype and grade of the STS can be determined for the vast majority of core needle biopsies, and pathologists experienced in examining STS have a reproducible diagnostic accuracy approaching 95% to 99% when comparing core needle with incisional biopsy diagnostic approaches. Incisional biopsy is the diagnostic procedure of choice if needle biopsy is not feasible; it provides sufficient tissues for histologic diagnosis as well as other laboratory studies that may be occasionally useful, such as immunohistochemical or chromosomal analyses.

Physical examination, diagnostic radiology, and biopsy provide the AJCC criteria input data needed to stage STS. This is extremely important because accurate staging drives treatment: most Stage I STSs are treated by surgery alone; Stage II STSs are generally treated with surgery and radiotherapy; Stage III STSs are frequently treated by surgery, radiotherapy, and chemotherapy; and Stage IV STS is treated primarily by chemotherapy with surgery and radiotherapy reserved for palliative control of symptoms. Over the years several staging systems have been developed based on clinicopathologic classification and prognostic factors; however, the AJCC/International Union Against Cancer (UICC) staging system is the most widely accepted STS classification system worldwide. The Enneking staging system of the Musculoskeletal Tumor Society is based on tumor grade and compartmental status (Table 1). Although useful as an indicator of extent of resection needed to achieve local control, this system does not provide as accurate prognostic information as that of the AJCC.

In using the AJCC STS staging system (Tables 2 and 3), it is important to note that Kaposi sarcoma, dermatofibrosarcoma protuberans, desmoid tumor, and sarcoma arising from the dura mater, brain, parenchymatous organs, or hollow viscera are not included. This is because STSs of these histologic subtypes/anatomic locations frequently behave in a manner very atypical relative to other STSs. The emergence of gastrointestinal stromal tumor (GIST) as a distinct clinical entity will need to be addressed in subsequent revisions of the AJCC STS staging system, particularly regarding the issue of hollow visceral origin; at this time such GISTs would not be amenable to grading as per these criteria. As an additional consideration, restaging should be performed for recurrent tumors.

The AJCC STS staging system is a mixed clinical-pathologic algorithm. Assignment of grade usually requires initial determination of histologic subtype in that some subtypes (ie, Ewing sarcoma) are by definition high grade. Pathologic grading is performed on either a pre-resection biopsy or a surgical specimen; cyto logic preparations are usually not adequate for this purpose. Considerable latitude is allowed in selecting criteria for pathologic grading, and to date there is no universally accepted roster of standard inclusive pathologic criteria used to

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TABLE 3 AJCC TNM Classification for STS19

| Primary Tumor (T) |   |
|-------------------|---|
| TX                | Primary tumor cannot be assessed |
| T0                | No evidence of primary tumor |
| T1                | Tumor ≤5 cm in greatest dimension |
| T1a               | Superficial tumor |
| T1b               | Deep tumor |
| T2                | Tumor >5 cm in greatest dimension |
| T2a               | Superficial tumor |
| T2b               | Deep tumor |

| Regional lymph nodes (N) |   |
|--------------------------|---|
| NX                       | Regional lymph nodes cannot be assessed |
| N0                       | No regional lymph node metastasis |
| N1                       | Regional lymph node metastasis |

| Distant metastasis (M) |   |
|------------------------|---|
| MX                     | Distant metastasis cannot be assessed |
| M0                     | No distant metastasis |
| M1                     | Distant metastasis |

| Histologic grade (G)   |   |
|------------------------|---|
| GX                     | Grade cannot be assessed |
| G1                     | Well-differentiated |
| G2                     | Moderately differentiated |
| G3                     | Poorly differentiated |
| G4                     | Poorly differentiated or undifferentiated |
assign grade. A variety of pathologic findings may be useful, and these commonly include degree of differentiation, mitotic activity, degree of necrosis, nuclear atypia, and so on. Histologic subtype should also be specified and may occasionally require immunohistochemical analysis, cytogenetics, or even electron microscopy. However, there is a high degree of discordance (2% to 40%)\textsuperscript{23} even among expert sarcoma pathologists regarding STS histologic subtyping and grade assignment, emphasizing the usefulness of histologic peer (and even expert) review, as well as the importance of developing objective and standardized methods for sarcoma histopathologic typing and grading.

The AJCC Staging System uses a four-grade scheme ranging from G1 (well-differentiated) to G4 (poorly differentiated or undifferentiated). A three-step grading system devised by the French Federation of Cancer Centers Sarcoma Group\textsuperscript{24} is widely used by some centers and takes into account the degree of differentiation, the mitotic count, and the extent of necrosis. In practice, most clinicians use a three-tiered or even two-tiered grading system. In most three-tiered systems, Grade 1 is considered as low grade, whereas Grades 2 and 3 are considered high grade. In four-tiered systems, Grades 1 and 2 are considered low grade, while Grades 3 and 4 are considered high grade. The bona fide need for STS pathology grade standardization is clear.

It is noteworthy, however, that standardization in sarcoma grading does not imply that criteria for evaluating histologic features such as mitotic activity and necrosis be applied uniformly to all soft tissue lesions. Rather, grading should be done in the context of a lesion’s histologic type and subtype. For example, alveolar rhabdomyosarcoma and extraskeletal Ewing sarcoma/primitive neuroectodermal tumor are always considered high-grade lesions, whereas well-differentiated liposarcoma and dermatofibrosarcoma protubersans are classified as low-grade. Many sarcoma subtypes can be considered to have a limited range of grades, and features such as the degree of mitotic activity and necrosis can be used to assign a grade from within that range.

Size of the tumor is an additional staging component and can markedly influence distant metastatic-free and overall survival rates. The impact of primary tumor size on risk of subsequent local recurrence is debatable, although the suggestion has been made that primary tumor size greater than 10.0 cm is a positive and significant risk factor for subsequent local recurrence. The tumor size (T) is subdivided into T1 tumors, which are those less than or equal to 5.0 cm, or T2 tumors, which are those greater than 5.0 cm; the tumor size may be determined either by radiologic or physical examination. Depth is also considered as part of the sarcoma staging system and is evaluated relative to the investing fascia of either the extremity or the trunk, depending on the primary tumor location. Superficial STSs are those lacking involvement of the superficial investing muscular fascia and are noted as “a” lesions. Deep sarcomas are defined as either deep to or involving the superficial fascia and are designated as “b” tumors. The a or b designation follows immediately after the T status (eg, T2a). For staging purposes, all retroperitoneal STSs are considered to be deep lesions, as are all intraabdominal visceral sarcomas, intrathoracic tumors, and most head and neck STSs.

The presence (N1) or absence (N0) of regional lymph node involvement is a prognostic factor in the overall survival for patients with STSs. Nodal disease may be suspected on the basis of radiographic study or physical examination and confirmed with tissue analysis. Although the presence of regional lymph node involvement is considered Stage IV disease, recent studies\textsuperscript{25,26} suggest that nodal status may not confer as ominous a prognostic impact as distant metastatic disease. These contemporary analyses suggest that isolated lymph node metastases may more closely resemble an AJCC Stage III rather than Stage IV survival pattern. This possibility raises the question about appropriate management of lymphatic metastasis-prone STS histologic subtypes, such as epithelioid sarcoma or synovial sarcoma, including the specific issue of whether such individuals should be offered sentinel node evaluation as part of their treatment program, perhaps under the aegis of a prospective clinical trial.\textsuperscript{27} The presence of distant metastasis (M1) necessitates a Stage IV group assignment and is the single strongest predictive factor of survival if M1 disease is detected at the time of initial presentation.
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Several changes in the AJCC STS staging system have been introduced in the current sixth edition of the *AJCC Cancer Staging Manual* compared with the fifth edition. Because of a distinctly different biological behavior, angiosarcoma is no longer included in the list of STS stageable histologic subtypes. In contrast, gastrointestinal stromal tumor (GIST) and Ewing sarcoma/primitive neuroectodermal tumor are now recognized as distinct STS histologic subtypes and have been added to the AJCC STS staging system. Fibrosarcoma Grade I has been replaced by fibromatosis (desmoid tumor) in recognition of the change in histopathologic nomenclature; because desmoids tumors lack metastatic potential, they are not included in the list of histologic subtypes for which AJCC STS staging system is applicable. The last AJCC STS staging system change of the sixth edition is that G1–2 T2b N0 M0 tumors have been moved from Stage II to Stage I because of their recently recognized more favorable biological behavior.

**OTHER PROGNOSTIC FACTORS**

There are additional prognostic factors that the current AJCC STS staging system does not specifically incorporate. These include site of primary tumor, the margin status of the resected tumor, possible molecular staging/prognosis markers, size of STSs beyond 5.0 cm, and whether the tumor is a de novo or recurrent lesion. While these factors may be included at some time point in the future, they are not currently part of the AJCC STS staging system. Nonetheless, for a given tumor their specification is of potential prognostic value. STS site-specific 5-year survival rates vary among primary tumor anatomic loci as a complex interplay between anatomic constraints to resection, margin status, underlying tumor biology, and initial definitive treatment at an STS referral center versus elsewhere. Crude 5-year survival rates in most series from major STS centers range from 25% to 55% in retroperitoneum and head and neck sites versus 60% to 75% or better for Stage III extremity STSs. To eliminate the confounding impact of several of these variables, an arguably more informative analysis of 402 patients with relapsed STS treated at MD Anderson Cancer Center demonstrates that the site of primary tumor/site of local recurrence has ongoing STS-specific survival implications (see Table 4).28

An additional prognostic factor is the margin status achieved after primary STS resection. Perhaps the most compelling analysis of the importance of margin status as a prognostic factor has been provided by the Memorial Sloan-Kettering Cancer Center group in 2002.29 Five-year actuarial and crude rates of disease-specific survival according to relevant prognostic factors were extracted from this report and are presented in Table 5.

Margin status was also identified as being of prognostic importance in an additional series from MD Anderson Cancer Center.30 In this study of 1,225 patients with Stage III disease treated at our institution, margin status was scored as either negative, uncertain (patient referred from another institution for radiotherapy at MD Anderson Cancer Center without margin status indicated or retrievable), or positive (Table 6). De novo primary tumor status versus locally recurrent STS status is an additional important prognostic factor. Most analyses identify previous local recurrence as a major (if not the major) risk factor for subsequent local recurrence. A 2003 report examined the University of California–Los Angeles experience with 753 patients with intermediate- and high-grade extremity STSs who received all treatment at that institution,31 demonstrating that the single greatest risk factor for developing subsequent recurrence was a

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**TABLE 4.** Site-specific STS Survival

| Tumor Site (LR)                        | 5-year STS-specific Survival Rate (%) | 10-year STS-specific Survival Rate (%) | P Value |
|---------------------------------------|---------------------------------------|----------------------------------------|---------|
| Head and neck + deep trunk            | 16                                    | 8                                      | <0.001  |
| Extremity + superficial trunk         | 55                                    | 54                                     |         |

LR = local recurrence.
Development of local recurrence was the most significant factor associated with decreased STS-specific survival; with local recurrence, an individual patient was three times more likely to die from disease than a recurrence-free patient. The MD Anderson Cancer Center experience with 1,225 patients with localized STSs identified a similar prognostic impact of local recurrence (Table 7).

Primary STS size greater than 5.0 cm is currently considered to be a T2 designation; however, STS size greater than 10.0 cm and greater than 15.0 cm may have additional prognostic implications. The Royal Marsden group examined this issue in 1999 in a report in which an alternative to the AJCC STS staging system was proposed based on their analysis of 316 previously untreated patients who received therapy at their institution.20 In addition to identifying margin status as an independent prognostic factor, their multivariate regression analysis also demonstrated that further stratification by tumor size was additionally informative of prognosis (Table 8).

Reliable predictive factors are essential for the stratification of patients with cancer into useful clinical/prognostic staging categories. In an era of major new insights into the molecular biology of cancer, more specific molecular prognostic markers for staging are on the horizon. The development of high-throughput screening technologies such as genomic and proteomic analysis and tissue microarray analysis have resulted in powerful evaluative tools capable of simultaneously processing large numbers of tumor specimens to detect expression levels for multiple panels of relevant genes and cognate proteins. These approaches can facilitate rapid analysis of hundreds of molecular markers in the same (potentially large) set of specimens, which can then be integrated with data describing disease progression, treatment response, and survival,

### Table 5: Prognostic Factors Relevant to STS Survival Not Included in AJCC STS Staging System

| Variable      | 5-year Survival Rate (%) | P Value |
|---------------|--------------------------|---------|
| Extremity     | 81                       | <0.001  |
| Retroperitoneum | 70                      |         |
| Size ≤ 5 cm   | 89                       | <0.001  |
| Size > 5 – ≤ 10 cm | 79                  |         |
| Size > 10 cm  | 69                       |         |
| Margin (−)    | 80                       | <0.001  |
| Margin (+)    | 70                       |         |

### Table 6: Margin Status Impact on STS Recurrence

| Resection Margin | 5-year Control (%) | 15-year Control (%) | P Value |
|------------------|--------------------|---------------------|---------|
| Negative         | 88                 | 86                  |         |
| Uncertain        | 76                 | 72                  | <0.001  |
| Positive         | 64                 | 56                  | <0.001  |
| Positive + uncertain | 71             | 66                  | <0.001  |

### Table 7: Impact of Local Recurrence on Subsequent Recurrence

| Prior Local Recurrence | 5-year Control (%) | 15-year Control (%) | P Value |
|------------------------|--------------------|---------------------|---------|
| No                     | 85                 | 82                  |         |
| Yes                    | 70                 | 64                  |         |
| 1                      | 74                 | 66                  |         |
| >1                     | 62                 | 58                  |         |

LR = local recurrence.
ultimately resulting in possible inclusion in revised staging systems. Numerous candidate molecular markers of STS progression can be readily identified (Table 9). In the future, the linkage of high-throughput technologies with STS tumor samples derived from patients of known clinical outcome will provide exciting opportunities to determine whether any of these (other) molecular markers may ultimately be included in future editions of the AJCC STS staging schema, hopefully to the benefit of patients burdened by this debilitating disease.

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### TABLE 9 Molecular Markers of Potential Importance in Prognosis of Soft Tissue Sarcomas

| Molecular Markers | References | Molecular Markers | References |
|-------------------|------------|-------------------|------------|
| p53               | 33         | CD44              | 34         |
| pRB               | 35         | Ki-67             | 36         |
| PDGFR alpha       | 37         | Beta-catenin      | 38         |
| c-KIT             | 37         | Mdm2              | 39         |
| Fem1a gene product| 40         | p16               | 41         |
| Osteopontin       | 42         | p8ARF             | 41         |
| Ezrin             | 43         | Cyclin D1         | 44         |
| Wt1               | 45         | p53               | 46         |
| Insulin-like growth factor type 1 receptor | 47 | PON1            | 48         |
| Vascular endothelial growth factor (VEGF) | 49 | |

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