PROGNOSTIC FACTORS IN SOFT TISSUE SARCOMAS

Fatores prognósticos em sarcomas de partes moles

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Os sarcomas de partes moles são relativamente raros, com incidência anual entre 5.000 a 6.000 novos casos, nos Estados Unidos.

Os sistemas de estadiamento e prognóstico valorizam, principalmente, o grau de malignidade histológica, o tamanho do tumor primário e a presença ou ausência de metástases. O grau de malignidade histológica é o principal fator determinante do prognóstico e sua determinação se baseia no número de mitoses, celularidade, presença de necrose, diferenciação e conteúdo estromal. Existem vários sistemas de graduação, todos eles devem ser considerados como categorias do espectro histológico. Para finalidade terapêutica, a divisão em baixo grau e alto grau é suficiente. Seguramente, estas decisões arbitrárias talvez sejam difíceis, mas elas facilitam a abordagem prática do paciente. O risco de metástases nos tumores de baixo e alto grau é de 15% e 50%, respectivamente.

O tamanho tem sido considerado o fator de menor importância no comportamento biológico, mas, progressivamente, observa-se o fato de que as lesões maiores podem estar associadas com recorrências tardias. Lesões muito pequenas, com diâmetro máximo, menor de 5 cm, quando tratadas corretamente, pela primeira vez, têm baixo risco para metastatizar. Fatores prognósticos adicionais incluem a localização do tumor, sua profundidade, apresentação com recidiva e margens macro ou microscopicamente contaminadas. Atualmente, reavaliações dos sistemas de estadiamento estão sendo feitas, com grande ênfase nas combinações do tamanho e grau, ao invés de fazer do grau fator absolutamente arbitrário, especialmente em lesões muito pequenas.

Palavras-chave: *Sarcoma, fatores prognósticos, estadiamento.*
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Introduction

Soft tissue sarcomas are rare and unusual neoplasms. They comprise a group of anatomically and histologically diverse tumors that share a common embryologic origin. Despite this diversity, they tend to behave in a similar manner and the prognostic factors and treatment are therefore similar for these tumors. Although mesodermal components (the connective tissues) comprise 75% of the body composition, the annual incidence in the United States is approximately 5,000-6,000 and this number has remained relatively constant. Approximately 50% of these patients will go on to die from their disease. This chapter describes the prognostic factors in soft tissue sarcomas in the adult (> 16 years old) age group.

Pathology and histological subtypes

Soft tissue sarcomas are grouped according to their presumed cell of origin, although several of them have unknown

cells of origin. Classification of histogenesis is often aided by electron microscopy and immunohistochemistry. Electron microscopic visualization of ultrastructural microfilaments, actin-myosin complexes, dense bodies and neurofibrils may help to define the histogenesis (1). In addition, immunohistochemistry for proteins such as vimentin, S-100, desmin, factor VIII, keratin, myoglobin, and actin may facilitate histotyping (2). Histologic subtype definition is reliable for well differentiated tumors, however as the degree of differentiation declines it becomes increasingly difficult to determine cellular origin. While this may lead to disparity amongst different pathologists, a specific histologic diagnosis is of secondary importance because histogenesis is not directly related to biologic behavior and prognosis (3).

The histological subtypes most commonly found are liposarcoma, malignant fibrous histiocytoma (MFH) and leiomyosarcoma. In general, a specific histological diagnosis appears currently to be of secondary importance in determining biology and management. However, this may in part be due to our inability to have large enough numbers of histological subtypes. Biologic behavior is currently best predicted based on histologic grade as determined by the mitotic index, cellularity, necrosis and degree of nuclear anaplasia (4). The difficulty in grading leiomyosarcoma and the impression that the majority of these tumors appear to be high grade may account for the suggested poorer prognosis of this histological subtype. Increasing use of molecular and tissue specific immunohistochemistry may better define this issue.

Presentation and diagnosis

Any soft tissue mass in an adult which is symptomatic or enlarging, is greater than 5 cm in size, or any new mass that persists beyond four weeks should be considered for biopsy (5). Biopsy technique is very important so as to not compromise future treatment. For any mass that is (≥5 cm, an incisional biopsy is usually preferred with a longitudinal incision (extremity lesions) to facilitate subsequent wide local excision. The incision should be centered over the mass in its most superficial location. No tissue flap should be raised, and meticulous hemostasis should be assured to prevent cellular dissemination by hematoma. At the time of definitive resection, the previous scar should be excised en bloc together with the tumor. If the mass is small (< 5 cm) and superficial, and easily removable with clear margins an excisional biopsy should be performed. Again, attention to the same details as with incisional biopsy are applicable.

Tru-Cut® core biopsies have a defined role in diagnosing soft tissue masses. Tru-Cut® core biopsies have been found to have an accuracy of 98% for diagnosing malignancy, and 94% for diagnosing sarcoma (6). We have recently reviewed the Memorial Sloan-Kettering Cancer Center experience and found the accuracy of Tru-Cut® biopsy to be 95% in 56 patients (7). Tumor type and grade are correctly identified in almost all patients. The advantages of ease of performance, low cost, and low complication rate, make this technique attractive.

Patients with intra-abdominal or retroperitoneal sarcomas often experience non-specific abdominal discomfort and gastrointestinal symptoms prior to diagnosis (8). The diagnosis is usually suspected on finding a soft tissue mass on abdominal CT or MRI scan. Fine needle aspiration biopsy has no role in the routine diagnostic evaluation of these patients. Needle biopsy is indicated if abdominal lymphoma is strongly suspected as part of the differential diagnosis. In the majority of patients, exploratory laparoscopy or laparotomy should be performed and the diagnosis made at operation, unless the patient is clearly unresectable or will be undergoing preoperative investigational treatment (8).

Imaging techniques

Non-invasive radiologic examination defines the radiologic size, depth and dimensions of the mass and the anatomic relationship to surrounding structures. CT scanning has been extensively and reliably used (9,10) MRI examination is also reliable for imaging soft tissue masses in the extremity (11). MRI may enhance the contrast between tumor and adjacent structures and provides excellent three dimensional definition of fascial planes. In addition, MRI is of significant value in defining vascular anatomy. Invasive angiography is virtually never required. The relative value of MRI over CT is currently the subject of a Nationwide study in the USA, preliminary results suggest that the two modalities are similar.

Extent of disease evaluation and staging

Current staging systems (table 1) focus on histological grade of the tumor, the size of the primary tumor and the presence or absence of metastasis (12,13). A retrospective review of 1,215 patients from 13 institutions found histologic grade to be a critical determinant of outcome (14). Histological grade is based on degree of mitosis, cellularity, presence of necrosis, differentiation, and stromal content. Various grading systems exist, all of which should be considered as categories of a histological spectrum. For therapeutic planning the broad categories of low - (Grades I or II) or high - (Grades III or IV) grade suffice. Clearly such arbitrary and subjective decisions may be difficult, but they facilitate practical management of the patient. Low grade lesions are assumed to have a low (<15%) risk of subsequent metastasis

Table 1 - Current staging system for soft tissue sarcomas

1.1 AJCC Staging System

G Histologic grade

- *GX Grade cannot be assessed*
- *G1 Low grade*
- *G2 Moderate grade*
- *G3 High grade*
- *G4 Undifferentiated*

T Primary tumor site

- *TX Primary size cannot be assessed*
- *T0 No evidence of tumor*
- *T1 Tumor less than 5 cm*
- *T2 Tumor 5 cm or greater*

N Regional nodes

- *NX Regional nodes cannot be assessed*
- *N0 No regional lymph node metastasis*
- *N1 Regional lymph node metastasis*

M Distant metastasis

- *MX Presence of distant metastasis cannot be assessed*
- *M0 No distant metastasis*
- *M1 Distant metastasis present*

Stage Grouping

Stage IA	*G1*	*T1*	*N0*	*M0*
Stage IB	*G1*	*T2*	*N0*	*M0*
Stage IIA	*G2*	*T1*	*N0*	*M0*
Stage IIB	*G2*	*T2*	*N0*	*M0*
Stage IIIA	*G3,G4*	*T1*	*N0*	*M0*
Stage IIIB	*G3,G4*	*T2*	*N0*	*M0*
Stage IVA	*Any G*	*Any T*	*N1*	*M0*
Stage IVB	*Any G*	*Any T*	*N1*	*M1*

1.2 MSKCC Staging System

Prognostic Factors

	Favorable Factors	*Adverse Factors*
Size	*< 5cm*	*≥ 5cm*
Site	*Superficial*	*Deep*
Histologic Grade	*Low*	*High*

MSKCC Staging

Number of Adverse Factors	*Stage*
0	*0*
1	*I*
2	*II*
3	*III*
Metastasis	*IV*

and the high grade lesions a high (>50%) risk of subsequent metastasis. The disease-specific survivals by histologic grade, for extremity and retroperitoneal sarcomas, are plotted in figures 1 and 2 respectively.

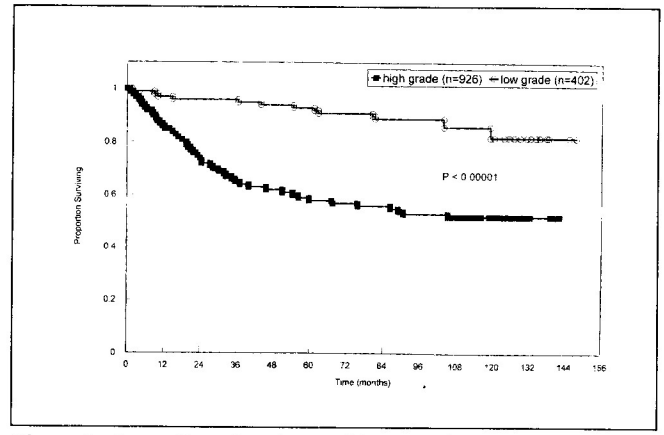

Figure 1 - Proportion of patients with extremity sarcoma surviving from the date of first operation at Memorial Sloan-Kettering Cancer Center for patients with high grade (n=926) and low grade (n=402) extremity sarcomas.
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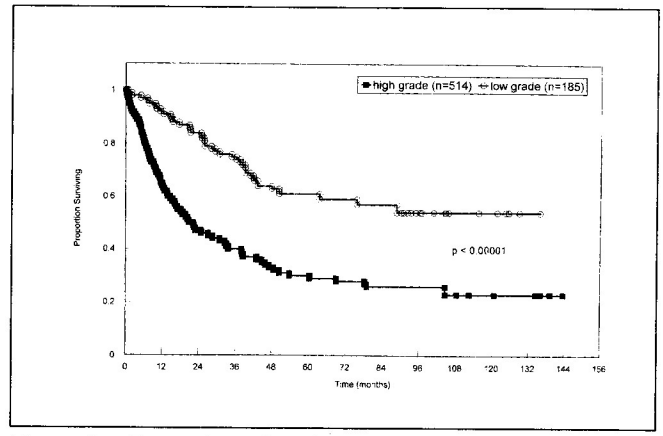

Figure 2 - Proportion of patients with retroperitoneal/visceral sarcoma surviving from the date of first operation at Memorial Sloan-Kettering Cancer Center for patients with high grade (n=514) and low grade (n=185) sarcomas.
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Size has historically been considered a less important determinant of biologic behavior, but we have progressively become more familiar with the fact that large lesions can be associated with late recurrence. Approximately 33% of patients will present with tumors < 5 cm and 66% with tumors (5 cm. Unequivocal characterization of grade is difficult in large lesions, especially in tumors that can reach 2 or 3 kgs! Conversely, very small, high grade lesions less than 5 cm in maximum diameter have limited risk for metastatic disease, if treated appropriately at the first encounter. Current reevaluations of staging systems are being performed, with greater emphasis on combinations of grade and size, rather than making grade an absolutely arbitrary factor, particularly in the very small lesions (15). It is important to recognize that prognostic factors for outcome, such as grade and size, may have

Table 2 - Prognostic Factors for Extremity Soft Tissue Sarcoma(13,31)

Outcome Variable	Factors Prognostic by Multivariate Analysis
Local Recurrence	*presentation with recurrent disease gross or microscopically positive surgical margin*
Distant Metastasis	*high histologic grade* *deep location* *size ≥ 5 cm*
Post Metastasis Survival	*age ≤ 60* *time from presentation to metastasis* *metastasis to sites other than single lung*
Disease Specific Mortality	*high histologic grade* *deep location* *size ≥ 5 cm*

a variable importance with time. For example in early metastases (< 2 years) grade is the dominant predictive variable. In contrast, for late metastases (> 5 years) size and initial microscopic margins are important variables (16).

Once the diagnosis and grade are known, evaluation for sites of potential metastasis can be performed. Lymph node metastases occur in less than 3% of adult soft tissue sarcoma (17). For extremity lesions the lung is the principal site for metastasis of high grade lesions (18), for visceral lesions the liver is the principal site (19). Thus, patients with low grade extremity lesions require a chest X-ray and those with high grade lesions a chest CT scan. Patients with visceral lesions should have their liver imaged as part of the initial abdominal CT or MRI scan. We do not generally perform angiography, as this adds little data that will change the management strategy.

Prognostic factors for outcome

Several multivariate analyses of prognostic factors for patients with soft tissue sarcoma have been reported (13,20-31). The two largest single-institution analyses of extremity lesions (13,31) are from Memorial Sloan-Kettering Cancer Center, and analyze 423 and 1,041 patients respectively. Both analyses emphasize the importance of careful selection of outcome variables for analysis of the impact of prognostic factors. The most recent analysis (31), prospectively collected data from a population of 1,041 adult patients with localized, extremity soft tissue sarcoma. The patients were treated between 1982 and 1994. Patient, tumor, and pathologic factors were analyzed by univariate and multivariate techniques to identify prognostic factors for the endpoints of local recurrence, metastatic recurrence, disease-specific survival, and post-metastasis survival (see tables 1 and 2). The five year survival rate for this cohort of patients was 76%, with a median follow-up of 3.95 years.

Significant adverse prognostic factors for local recurrence were: age greater than 50 years, recurrent disease at presentation, microscopically positive surgical margins, and the histologic subtypes fibrosarcoma and malignant peripheral nerve tumor. For metastatic recurrence: large tumor size, high grade, deep location, recurrent disease at presentation, leiomyosarcoma, and non-liposarcoma histology were adverse prognostic factors. For disease-specific survival: large (≥ 5 cm) tumor size, high grade, deep location, recurrent disease at presentation, the histologic subtypes leiomyosarcoma and malignant peripheral nerve tumor, microscopically positive surgical margins, and lower extremity site were adverse factors. For post metastasis survival: only very large tumor size (≥ 10 cm) was an adverse prognostic factor.

It should be enphasized that these prognostic factors have been derive from studies of localized extremity sarcoma patients. Despite the fact that extremity sarcomas make up approximately 50% of sarcoma patients, these results should not be generalized to the greater population of soft tissue sarcoma patients. Indeed, site itself is a determinant of prognosis and survival (figure 3). Separate analyses of prognostic factors for retroperitoneal, gastrointestinal, head and neck, and genitourinary sarcoma have recently been published (32-37). These are discussed below for each specific anatomic site.

Non-extremity sarcomas

Retroperitoneal sarcomas

These tumors arise in the retroperitoneal space. They are

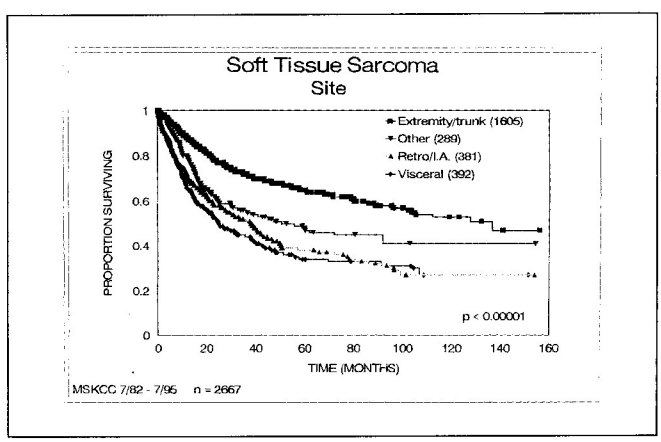

Figure 3 - Survival by site, patients with retroperitoneal and visceral sarcomas do worse than those with extremity tumors. (permission to reproduce from Lewis and Brennan, Soft tissue sarcomas, current problems in surgery 1996, Mosby-Year Book).

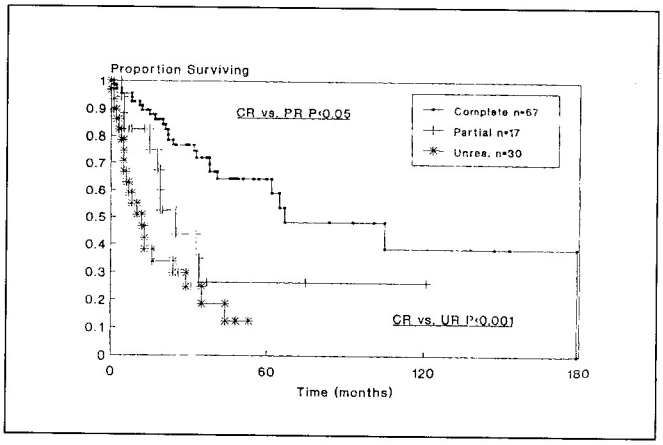

Figure 4 - Complete surgical resection is the primary prognostic factor for survival in retroperitoneal sarcoma. (permission to reproduce from Lewis and Brennan,* Soft tissue sarcomas, current problems in surgery *1996, Mosby-Year).

relatively uncommon and constitute approximately 15% of soft tissue sarcoma. In patients with completely resected tumors, the 5-year actuarial survival ranges between 54% and 64% (38-40). Five year survival for patients who are incompletely resected ranges from 10 to 36%. By far the most important prognostic factor is complete resection. The influence of resection on subsequent survival is depicted in figure 4. Local recurrence occurs in the majority of these patients with rates between 53% and 68% reported (39,41). The median time to recurrence is 16 months. Complete resection of recurrent disease is possible in about 44% of patients and may be associated with prolonged five year survival of up to 50% (38).

Gastrointestinal sarcomas

Gastrointestinal sarcomas are uncommon, comprising approximately 4% of sarcoma patients. The most common histologic subtype is leiomyosarcoma, and this accounts for 92% of these tumors (42). Univariate analysis of survival suggests that tumor size <5 cm, low grade tumors, localized disease, and complete resection are favorable prognostic factors (35). Multivariate analysis suggest that complete resection is the most significant favorable prognostic factors. In this study, the median survival of patients undergoing complete resection was 46 months compared to 21 months for those undergoing incomplete resection. Despite complete resection, recurrence rates are still high, ranging from 42% to 90% with a median time to recurrence of 18 to 24 months (34,43). Most patients who present with recurrent disease recur in the liver (50% to 65%), with about 30% of patients presenting with intraperitoneal recurrence and 8% with distant metastases (43). If the intra abdominal recurrence is completely resected, survival is improved and this should be attempted in patients who are a good operative risk (19,43,44). Extent of disease may limit the application of resection, and certainly when contemplating hepatic resection, anything less than complete resection is not indicated (19).

Head and neck

These lesions are uncommon, accounting for 3% of all sarcomas. The most common histologic subtypes in adults are fibrosarcoma (30%), rhabdomyosarcoma (24%), and malignant peripheral nerve tumor (13%) (40,45). Despite adequate treatment, local recurrence remains a significant problem, with overall rates of local recurrence ranging from 14% to 48% (40,46,47). Metastatic disease develops in 12 to 31 percent of patients, despite complete resection (47). The overall five year survival rate is 45% to 68% (40,46,48,49). Large size, high grade, positive surgical margin, bony invasion and presence of metastasis are unfavorable prognostic factors for survival (40,46,48).

Genitourinary

Soft tissue sarcomas of the urinary tract and genital tract in adults are uncommon. They are more common in the pediatric population, accounting for up to 8% of all malignant disease in children less than 15 years of age (50). The most common histologic subtypes are leiomyosarcoma (44%) and rhabdomyosarcoma (33%), with a spectrum of other subtypes

Table 3 - Prognostic Factors for Disease Specific Mortality in Extremity Sarcoma (31)

Variable		Univariate Cox p-valve	Cox Model p-value	Relative Risk (CI)
Age	*≤ 50 yr >50 yr*	*0.0025*	-	-
Presentation	*Primary Recurrence*	*0.57*	*0.0033*	*1.5 (1.02-2.2)*
Size	*< 5 cm ≥ 5 cm*	*0.0001*	*0.0001*	*2.1 (1.5-3.0)*
Depth	*Superficial Deep*	*0.0001*	*0.0002*	*2.8 (1.6-4.8)*
Grade	*Low High*	*0.0001*	*0.0001*	*4.0 (2.5-6.6)*
Microscopic surgical margins	*Negative Positive*	*0.0014*	*0.0011*	*1.7 (1.2-2.3)*

occurring (51). One of the characteristic features of genitourinary sarcomas is the fact that the vast majority are high grade. In a recent review from Memorial Sloan-Kettering Cancer Center, 86% of these lesions were high grade, and 56% were ≥ 5 cm in size (51). This is similar to the findings at MD Anderson Cancer Center, where the overwhelming majority of kidney sarcomas were large and high grade (52). Consequently, survival for these patients is relatively poor with a five year actuarial survival of 48% for patients with high grade tumors and 30% for those with large tumors. In the series from Memorial Sloan-Kettering Cancer Center, univariate analysis demonstrated tumor size <5 cm, low grade, and para-testicular or bladder site (versus kidney or prostate) to be favorable prognostic features (51). Complete resection was possible in 72% of these patients and the 5-year actuarial survival was 64%. No patient with an incomplete resection survived five years.

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Summary

Soft tissue sarcomas are relatively rare with an annual incidence of 5,000 to 6,000 in the United States. Current staging and prognostic systems focus on histological grade of the tumor, the size of the primary tumor and the presence or absence of metastasis. Histological grade is a major prognostic determinant and is based on degree of mitosis, cellularity, presence of necrosis, differentiation, and stromal content. Various grading systems exist, all of which should be considered as categories of a histological spectrum. For therapeutic planning the broad categories of low - or high-grade suffice. Clearly such arbitrary decisions may be difficult, but they facilitate practical management of the patient. Low grade lesions are assumed to have a low (<15%) risk of subsequent metastasis and the high grade lesions a high (>50%) risk of subsequent metastasis.

Size has historically been considered a less important determinant of biologic behavior, but we have progressively become more familiar with the fact that large lesions can be associated with late recurrence. Very small, high grade lesions less than 5 cm in maximum diameter have limited risk for metastatic disease, if treated appropriately at the first encounter. Additional prognostic factors include the site of the primary tumor, the tumor depth, presentation with recurrent disease and gross or microscopically positive margins. Current reevaluations of staging systems are being performed, with greater emphasis on combinations of grade and size, rather than making grade an absolutely arbitrary factor, particularly in the very small lesions.

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