How Long Should We Follow Patients With Soft Tissue Sarcomas?

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Abstract

Background Guidelines suggest that followup for low-grade soft tissue sarcomas should be every 3 to 6 months for 2 to 3 years and then annually, and for high-grade sarcomas every 3 to 6 months for 2 to 5 years, then every 6 months for the next 2 years, and then annually. However, there is only very limited evidence to support these strategies.

Questions/purposes In a population of patients treated surgically for soft tissue sarcomas, we evaluated the (1) timing of diagnosis of local recurrences after sarcoma excision; (2) timing of diagnosis of distant metastases; and (3) the difference in those parameters based on tumor size and grade.

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Methods Patients diagnosed with soft tissue sarcomas and who underwent surgical excision between 1978 and 2008 were retrospectively reviewed. Age, histologic diagnosis, Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade, tumor location, and size were reviewed at a mean of 6 years (range, 1 month to 30 years). We met with patients every 3 months for 5 years, every 6 months for 10 years, and then annually until 15 years after surgery. Eight hundred sixty-seven patients with a median age at diagnosis of 52 years were eligible for analysis. The incidence of local recurrence and metastases was calculated for every 2-year period and presented per 1000 person-years. **Results** Ninety-eight patients (11%) developed local recurrence at a median time of 19 months; 90% of patients who had local recurrences had them within 7.1 years, and 95% occurred by 8.6 years. One hundred ninety-eight patients (23%) developed distant metastases at a median time of 12 months; 90% of patients who developed metastases developed them by 4.2 years and 95% did so by 7.3 years. High-grade tumors had a higher incidence of local recurrence and metastases in first 2 years, whereas low-grade tumors recurred at a constant rate throughout the followup period.

Conclusions Followup beyond 10 years does not yield a sufficient number of local recurrences or metastases to warrant further monitoring.

Level of Evidence Level II, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

After treatment of primary soft tissue sarcomas, 11% to 14% of patients develop local recurrence and 18% to 50%

of patients develop metastases [3, 8, 12, 15, 16, 19, 23]. Local recurrence may require additional surgery, radiotherapy, or even amputation. Local recurrence may predict decreased overall survival [3, 9, 12, 14]. However, the ultimate determinant of survival in patients with soft tissue sarcoma is the development of metastases, most of which occur in the lungs [1, 17]. Even with systemic treatment, overall survival with those who had metastases is approximately 50% at 5 years with a median survival or approximately 12 months from diagnosis of metastases in large, high-grade sarcomas [8].

The guidelines published by the National Comprehensive Cancer Network [13] and the European Society of Medical Oncology [4] have been used to monitor patients with soft tissue sarcomas. Both guidelines are similar; they suggest following patients with high-grade sarcomas every 3 to 6 months for 2 to 3 years, then twice a year for up to 5 years, and once a year thereafter. Recommendations for patients with low-grade sarcomas are to follow for local relapse every 3 to 6 months in the first 2 to 5 years, and then annually, although there are few data in the medical literature on the effectiveness of these recommendations [4, 13].

Any attempt to define effective strategies requires an understanding of patterns of local recurrence and metastases of these tumors. Tumor size and grade have been identified as prognostic factors that help define the risk of metastases [5, 16, 21]. Histologic grade also may predict the development of metastases [2, 10]. Tumor size may affect the rate of metastases and fewer than 1% of patients with T1 (size equal to or small than 5 cm) primary extremity soft tissue sarcomas were found to have pulmonary metastases [5]. Most local recurrences and metastases arise in the first 5 years after diagnosis [7]. That same study found 72% of pulmonary metastases occur within the first 2 years after treatment of the primary tumor in high-grade lesions and an additional 20% between 2 and 5 years. Low-grade tumors may locally relapse late; thus, longer followup is recommended for these [8]. However, the exact timing of recurrences and metastases and the effect of tumor size and grade on the timing of recurrences and metastases, both remain incompletely characterized.

Accordingly, we sought to determine the (1) timing of diagnosis of local recurrences after sarcoma excision; (2) timing of diagnosis of distant metastases; and (3) the difference in those parameters based on tumor size and grade.

Patients and Methods

We retrospectively reviewed the charts of all 867 patients with soft tissue sarcomas and who underwent surgical excision of a sarcoma at the Cancer Institute Hospital in Tokyo from 1978 to 2008. Because treatment strategies,

including adjuvant therapies, have changed over the years, we excluded patients diagnosed before 1978. Patients who presented with metastases at diagnosis were excluded. Age, size, tumor location, grade, histologic diagnosis, and duration of followup were reviewed for each patient.

The median age of the study population was 52 years (range, 6 months to 99 years). There were 477 males (55%) and 390 females (45%). Data on local recurrence and metastases were collected. Primary tumor characteristics were tabulated with tumor size (equal to or less than 5 cm, greater than 5 cm), the site of the primary tumor (trunk, extremity), depth (superficial, deep), grade, and histologic subtype. Tumor size was determined by the imaging studies at diagnosis using maximal diameter measured on CT or MRI. We used pathologic specimens to measure the size before 1980, because CT scans were not available then. Five hundred forty-eight patients (63%) presented with tumors larger than 5 cm, whereas 37% had tumors equal to or less than 5 cm (Table 1). A tumor was considered to be in the extremity if it was at or beyond the shoulder or at or below the hip. Other tumors were considered to be in the trunk. Most patients had tumors located in the extremity (717 patients [83%]) and 10 patients had tumors of the retroperitoneum. Tumors located superficial to the fascia were considered to be superficial and tumors on or deep to the fascia were considered as deep soft tissue sarcomas. Grade 1 in the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system [22] was categorized as low grade. Grade 2 and Grade 3 were considered as high grade in this study. Histologic diagnosis was confirmed by our pathologists (RM, NH) experienced in musculoskeletal pathology. The most frequent histologic subtype was malignant fibrous histiocytoma followed by liposarcoma (Table 2).

Surgical procedures for primary tumor (limb-sparing, amputation), chemotherapy, and radiotherapy for primary tumor were recorded. Forty-eight patients were treated with amputation proximal to the wrist or ankle (Table 1). One hundred forty-three patients underwent radiotherapy and 304 patients were treated with chemotherapy. Before 1980, local recurrences were detected by xerography, and we evaluated patients for possible metastases with chest radiography because CT was not available. Local recurrences and metastases were evaluated with CT between 1980 and 1985. After 1985, all patients underwent chest CT and physical examination with ultrasound every 3 months, and we obtained MRI for deep tumors or tumors with unclear borders. We obtained MRI when ultrasound was not sufficient to evaluate local recurrence or if we suspected local recurrence. All local recurrences were confirmed with MRI. We met with patients every 3 months for 5 years, every 6 months for 10 years, and then annually until 15 years after surgery. Radiation exposure from chest CT is

Table 1. Patient and tumor characteristics of 867 patients

Patient characteristics	Number	Percent
Tumor size		
≤ 5 cm	319	37
> 5 cm	548	63
Primary tumor site		
Extremity	717	83
Trunk wall	140	16
Retroperitoneum	10	1
Depth		
Superficial	276	32
Deep	591	68
Grade		
Low (FNCLCC 1)	278	32
High (FNCLCC 2–3)	589	68
Surgical procedure		
Limb salvage	819	94
Amputation	48	6
Radiation		
Yes	143	16
No	724	84
Chemotherapy		
Yes	304	35
No	563	65

FNCLCC = Fédération Nationale des Centres de Lutte Contre le Cancer.

Table 2. Histologic tumor subtypes

Subtype	Number of patients	Percent
Malignant fibrous histiocytoma	279	32
Liposarcoma	133	15
Well-differentiated liposarcoma	101	12
Synovial sarcoma	70	8
Dermatofibrosarcoma protuberans	43	5
Leiomyosarcoma	32	4
Malignant peripheral nerve sheath tumor	25	3
Solitary fibrous tumor	21	2
Myxoid chondrosarcoma	20	2
Ewing's sarcoma	17	2
Fibrosarcoma	17	2
Others	109	13

6.9 mSv; thus, annual radiation exposure for four visits is 28 mSv, which is less than the maximum allowable radiation exposure for radiation workers (50 mSv) in Japan. We evaluated patients by physical examination and did not obtain chest CT after 15 years. In addition, abdominal and pelvic CTs were obtained for patients with liposarcoma,

retroperitoneal tumors, and histologic subtypes, which are known for a higher rate of lymph node metastases such as rhabdomyosarcoma, epithelioid sarcoma, and clear cell sarcoma [18]. Because PET-CT was not covered by the health insurance system in Japan before 2010, none of these patients was evaluated with PET-CT. No patients were recalled specifically for this study; all data were obtained from the medical records. Ninety-eight patients (11%) were lost to followup before the minimum 2-year period.

We recorded local recurrence of tumor with the time of failure and defined local control as the time between surgical resection or amputation and the detection of local recurrence of disease. We defined metastasis-free survival as the time interval between the initial visit to the detection of a metastasis. Incidence of local recurrence and metastases was calculated for every 2-year period and presented per 1000 person-years. The effect of tumor size and grade on local recurrence-free survival and metastases-free survival was assessed with a log rank test. All data were analyzed using statistical software Stata 10 (StataCorp, College Station, TX, USA).

Results

Ninety-eight patients (11%) developed local recurrence at a median time of 19 months and 90% of patients who had local recurrence had them by within 7.1 years and 95% by 8.6 years. Three patients (3% of all local recurrences) developed local recurrence after 10 years. One hundred ninety-eight patients (23%) developed distant metastases at a median time of 12 months and 90% of patients who had metastases developed them by 4.2 years and 95% by 7.3 years. Six patients (3% of all metastases) developed metastases after 10 years.

Patients with high-grade tumors had a higher rate of local recurrence ($p = 0.009$) than patients with low-grade tumors. The rate of local recurrence of high-grade tumors during the first 2 years was 51 per 1000 person-years (confidence interval [CI], 39–66/1000 person-years) and decreased to 21 per 1000 person-years (CI, 12–35/1000 person-years) in the next 2 years (Fig. 1A). Low-grade tumors recurred at a constant rate throughout the followup period (Fig. 1B) and the rate of local recurrence in first 2 years was 14 per 1000 person-years (CI, 7–30/1000 person-years). Patients with high-grade tumors ($p < 0.001$) or large tumors ($p = 0.003$) had a higher rate of metastases. The rate of metastases of high-grade tumors was 153 per 1000 person-years (CI, 130–180/1000 person-years) during the first 2 years and decreased to 33 per 1000 person-years (CI, 22–51/1000 person-years) in next 2 years (Fig. 2A). Low-grade tumors rarely metastasized (Fig. 2B) and the rate of metastases during the first 2 years was 16 per

1000 person-years (CI, 8–32/1000 person-years). Both large and small tumors showed a higher rate of metastases during the first 2 years posttreatment compared with the period after 2 years (Fig. 3). Two cases of local recurrence and two cases of metastasis were observed for low-grade tumors after 10 years.

Discussion

The generally accepted guidelines for monitoring patients after sarcoma treatment outline a prudent followup schedule that avoids excessive testing, although there are few data to support these recommendations. We believed an evidence-based rationale for followup of soft tissue sarcomas was warranted. We therefore determined the

incidence of local recurrence and metastasis with respect to grade and size for different time periods to see when local recurrence and metastases were most likely to occur. We anticipated that (1) high-grade tumors would have a different trend of local recurrence and metastases compared with low-grade tumors; (2) that the incidence of local recurrence and metastases would be higher in the first 2 years and more than 90% of events would occur in 10 years; and (3) that large tumors would have a higher incidence of metastases.

We acknowledge several limitations in this study. First, our study is limited by the fact that it is nonrandomized. In our country, probably fewer patients were treated with radiotherapy than in the United States or Europe; thus, it is possible that our patients developed local recurrence earlier

Fig. 1A–B Incidence rate of local recurrence of high-grade tumors (A) and low-grade tumors (B) is shown. High-grade tumors had a higher rate of local recurrence in the first 2 years but low-grade tumors recurred constantly throughout the followup period.

Fig. 2A–B Incidence rate of metastases of high-grade tumors (A) and low-grade tumors (B) is shown. Most metastases were seen in patients with high-grade tumor within the first 2 years of followup.

Fig. 3A–B Incidence rate of metastases of large tumors (> 5 cm, **A**) and small tumors (≤ 5 cm, **B**) is shown. Both large and small tumors showed similar trends and they had a higher rate of local recurrence in the first 2 years of followup.

than in centers where patients are treated with radiotherapy. Different adjuvant chemotherapy protocols used in these years may affect the result of the study. Second, our study population lacks generalizability to all populations because all of our patients are Japanese and the tumors may behave differently in other populations. Third, MFH was the term used during our study period, although this has been changed to undifferentiated pleomorphic sarcoma according to the WHO classification of soft tissue tumors in 2002 and essentially represents a diagnosis of exclusion [6]. Tumor subtypes could have been categorized differently, although this should not have an influence on the results because we used the FNCLCC grading system. Fourth, this study has all the limitations of a retrospective study and 98 patients were lost to followup before 2 years. Local recurrences and metastases could have been underestimated for this reason. Fifth, advanced imaging modalities such as CT and MRI were not available in the early stage of our study period; thus, local recurrences and metastases could have been overlooked. We only had 13 patients before 1980 when CT came into use and nine of them were followed without local or distant metastases after 1980. One patient was diagnosed with metastases and one patient with local recurrences before 1980. Two of them were lost to followup; thus, we believe that the impact of differences in imaging modalities on our results is small. Sixth, all local recurrences were biopsy-proven, although we did not perform biopsy for all metastatic disease, in particular when they were large enough or increasing in size. Metastases could have been underestimated, but we believe it is unlikely and we performed biopsies for suspicious lesions.

In our study, 95% of local recurrences were detected by 8.6 years. The rate of local recurrence of high-grade tumors in the first 2 years was high and decreased after 2 years; thus, frequent followup may be necessary for high-grade

tumors for the first 2 years. The value of surveillance for detection of local recurrences and metastases in patients with soft tissue sarcomas after definitive surgical resection of the primary tumor is based on the premise that early recognition and treatment of local or distant recurrence can prolong survival. Local recurrence should ideally be detected as early as possible to avoid extensive surgery or amputation, which could adversely affect functional outcomes. Aggressive resection may provide a cure for patients with recurrent disease. Singer et al. [20] reported a 67% salvage rate after reexcision of recurrent tumors with or without radiotherapy. The association of local recurrence with overall survival is controversial, although some reports identified local recurrence as a predictor of decreased overall survival [3, 9, 12, 14].

Ninety-five percent of metastases developed by 7.3 years and the rate of metastases was extremely high for high-grade tumors during the first 2 years. Because the rate of local recurrence and metastases was higher in the first 2 years, frequent followup may be reasonable for high-grade tumors, especially for metastases during this period as the current guidelines suggest. Kim et al. have shown prolonged survival in patients with single pulmonary metastases that have been completely resected [11], although hematogenous metastases to the lung may lead to incurable systemic spread of the disease. Systemic treatments for patients with metastatic soft tissue sarcoma are not curative with median survival times less than 12 months from diagnosis of metastases [8]. Published response rates for chemotherapy vary enormously from 10% to 50% depending on the drugs used, patient selection, and histologic subtype [8]. Because we do not have definitive treatment for advanced disease, it is likely but controversial that early detection of metastases could extend survival of patients.

High-grade tumors have a different trend of local recurrence and metastases than low-grade tumors in our study; high-grade tumors showed a higher rate of local recurrence and metastases. This result is consistent with a previous study reporting histologic grade was an independent predictor of metastasis development [2, 10]. Our results support guidelines recommending more intensive followup for high-grade tumors and less frequent followup for low-grade tumors. Large tumors had a higher rate of metastases than small tumors in our study, although both large and small tumors had similar trends for metastases because both had higher rates of metastases in the first 2 years (Fig. 3). This suggests that we should focus more on grade than size of the tumor when making decisions on a followup standard.

High-grade tumors had a higher rate of local recurrence and metastasis compared with low-grade tumors, especially in the first 2 years. Low-grade tumors recurred constantly throughout the followup period and rarely metastasized. Based on this, we recommend followup for patients with high-grade soft tissue sarcomas every 3 months for the first 2 years, then every 6 months until 5 years, and then annually until 10 years. For low-grade sarcomas, we recommend followup every 6 months for 5 years and then annually until 10 years. According to our study, 95% of local recurrence and metastases will be identified if we follow patients for 9 years. Followup beyond 10 years does not yield a sufficient number of local recurrences or metastases to warrant further monitoring.

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