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Multifocal Extremity Sarcoma: An Uncommon and Controversial Entity

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Background: The primary site of metastasis from extremity sarcomas is the lung. When patients with extremity sarcoma present with the disease in more than one site but not in the lung, the question of whether the disease is multifocal or metastatic is difficult to resolve.

Methods: We reviewed 1423 patients admitted with extremity sarcoma from 1982 through 1996. Patient demographics, primary site, other sites, local recurrence, distant metastasis, and survival were analyzed. Statistics were by Fischer exact test, χ^2, Kaplan-Meier method, and log-rank test where appropriate.

Results: Sixteen (1%) patients were identified with multifocal disease out of 1423 patients with extremity sarcoma. There was no difference in sex, age, size, grade, depth, and margins between multifocal and unifocal disease. In a mean follow-up time of 57 months, 50% had local recurrence of primary tumor, 80% had distant metastasis, and only 30% were alive at the time of the analysis. Whereas 21% of all patients with solitary disease develop lung metastasis, 63% of patients with apparent multifocal disease develop lung metastasis. The 5-year disease-specific survival of patients with multifocal disease was not different from that of all patients presenting with metastatic disease to lung.

Conclusion: Whether multifocal disease exists or is merely a form of metastasis is unproven by this analysis, but the outcome is the same. Management algorithms should suggest treating patients with multifocal disease as if it is metastatic disease.

Key words: Multifocal disease—Soft tissue sarcoma.

Multifocal sarcoma is a rare and controversial entity. It was first described in the literature in 1934 when Siegmund published a report of multiple fatty tumors he labeled as "Lipoblastische Sarkomatose." He concluded this was a systematic malignant disease of the soft tissue (1). Sixty-two years later, only 32 cases have been reported in the world literature (1–9). Debate still exists as to whether this entity represents a rare variant of an already rare disease or whether it is simply a more unusual metastatic pattern. Because most of the published reports are descriptions of single cases, no one has examined the natural history of this entity. The purpose of this study is to examine the clinical and pathological factors that affect survival to determine the biology of this disease and whether it represents a true entity or an unusual pattern of metastasis.

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PATIENTS AND METHODS

From July 1982 to June 1996, 2956 patients with soft tissue sarcoma (STS) were admitted to and treated at Memorial Sloan-Kettering Cancer Center (New York, NY). All patients were prospectively followed and data prospectively collected. Of these, 1389 patients presented with primary extremity sarcoma; data from these cases were used for the analysis.

Patients with multifocal desmoid tumors (low-grade fibrosarcoma) were excluded, as were all patients with non-extremity lesions. The patient demographics age (< 50 years or ≥50 years) and sex were used for analysis. Tumor variables—location of primary (upper or lower

extremity), other sites, size (≤5 cm, ≥5–10 cm, ≥10 cm), grade (high or low), depth of invasion (superficial or deep), and gross and microscopic margins also were analyzed. Finally, outcome was analyzed in terms of local recurrence, metastasis, and disease-specific survival. We defined multifocality as the presence of more than one site of sarcoma before the manifestation of disease in sites where extremity sarcoma is known to metastasize (i.e., lung, liver, and brain). First, we compared patients with multifocal disease (n = 16) to all patients with unifocal disease (n = 1389). However, to distinguish multifocal sarcoma from metastatic sarcoma, we directly compared the same parameters to those of all patients with known metastasis. Fisher exact test and χ^2 were used to compare proportions. Disease-specific survival, metastasis, and local recurrence rates were analyzed by the Kaplan-Meier method and log-rank test. A P value ≤ .05 was considered significant.

RESULTS

Sixteen (1%) patients were identified with multifocal disease out of 1389 patients with extremity sarcoma. Nine patients were women, and seven were men. Eleven patients were younger than 50 years, and six patients were 50 years of age or older at the time of presentation. Histologic subtypes of the primary tumors included nine patients with liposarcoma (56%), three with MFH (19%), one with angiosarcoma (6%), one with lymphangiosarcoma, one with leiomyosarcoma, and one with extraosseous chondrosarcoma. Inspection of the first specimens removed from the extremity of these patients revealed that there were 12 high- and four low-grade tumors. Fourteen of the original tumors were considered deep, and two were superficial. Three patients had positive gross margins, and two had additional positive microscopic margins at the time of their original operation for extremity sarcoma.

Fourteen patients had lower extremity tumors, and two had upper extremity primary tumors. Mean follow-up time was 57 months. Patients with multifocal tumors had disease that could not be explained simply by direct extension of locally advanced disease; their disease does not appear to follow known pathways of metastasis for extremity STS. For example, other sites of tumor included 12 patients with other areas of soft tissue tumors, seven with intraperitoneal tumors, six with retroperitoneal tumors, three with mediastinal tumors, and one with a tumor of the external genitalia. Similarly, of the nine patients with multifocal liposarcoma, three patients later presented with retroperitoneal disease, two had mediastinal disease, five patients had disease in the mesentery or the omentum, and one patient even had disease in the axilla (Table 1). Eight (50%) patients had a local recurrence at the site of their primary tumor. Ten patients had lung metastasis (63%), and an additional three patients had liver or brain metastasis. Thirteen (80%) patients had distant metastasis overall. Only six (30%) patients were alive at the time of the analysis, with a 5-year survival of 36%.

We found that there was no significant difference in sex or age between patients with multifocal and and those with solitary disease. Likewise, there was no difference in size, grade, depth, and margins of the primary extremity tumors removed between patients with multifocal disease and patients with unifocal disease. This indicates that primary extremity sarcoma in patients with multifocal disease does not appear to be a more aggressive locally invasive tumor. Analyzing the 1389 patients with solitary disease, 294 (21%) had lung metastasis in some part of the course of their disease compared to 10 out of 16 (63%) patients with multifocal disease (Fig. 1; $P < .01$). Similarly, 354 (25%) of patients with solitary disease died, compared to 10 of 16 (63%) patients with multifocal disease (Fig. 2; $P < .01$). The data were the same for the nine patients with multifocal liposarcoma: six of the nine patients (67%) had lung metastasis, and

TABLE 1. *Characteristics of patients with multifocal disease*

Patient No.	Sex	Histology	Primary site	Multiple sites	Metastasis	Follow-up (mo)	Outcome
3	F	Liposarcoma	Groin	Retroperitoneum, liver	Lung	48	AWD
5	F	Liposarcoma	Thigh	Groin, pelvis	Lung	12	AWD
7	M	Liposarcoma	Thigh	Intraperitoneum	Lung	12	DOD
8	M	Liposarcoma	Thigh	Retroperitoneum, supraclavicular lymph node	Lung	12	AWD
9	M	Liposarcoma	Thigh	Mesentery, liver, retroperitoneum	None	36	DOD
10	F	Liposarcoma	Arm	Thigh, axilla, mesentery, small bowel	None	36	AWD
11	M	Liposarcoma	Thigh	Abdominal wall	Lung	56	DOD
12	M	Liposarcoma	Thigh	Spine, pelvis, omentum, mediastinum	Lung	96	DOD
16	F	Liposarcoma	Groin	Mediastinum, small bowel, liver, supraclavicular	Aorta	60	DOD

AWD, alive with disease; DOD, dead of disease.

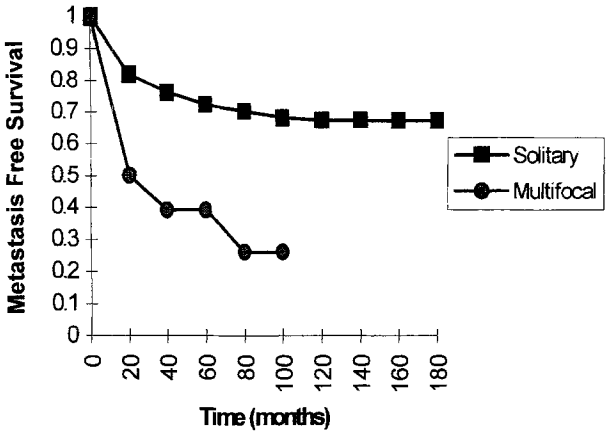

FIG. 1. Time to metastasis. Percentage of patients with metastatic multifocal (n = 16) vs. solitary (n = 1373) disease. $P < .05$.

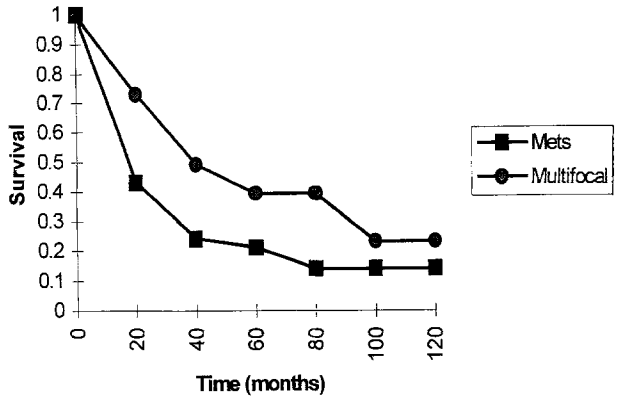

FIG. 3. Disease-specific survival. Proportion of patients surviving from sarcoma, multifocal (n = 16) vs. metastatic (n = 294) disease. P = NS.

only five of them (56%) were alive at the time of the analysis.

Two hundred ninety-four patients developed metastasis after receiving treatment at Memorial Sloan-Kettering Cancer Center; of these patients, 220 died of disease (75%), compared to 10 of 16 (63%) patients with multifocal disease (Fig. 3; P = NS). Therefore, patients with multifocal disease had similar disease-specific survival when compared to patients with known metastatic disease.

DISCUSSION

Multifocal STS has been described intermittently in the literature dating back to the earlier years of this century. The first reports in the literature were based on autopsy data and add little to our knowledge of the natural history of this entity (Table 2) (1–3,6,7). The largest series in the literature is a study of 20 cases published by

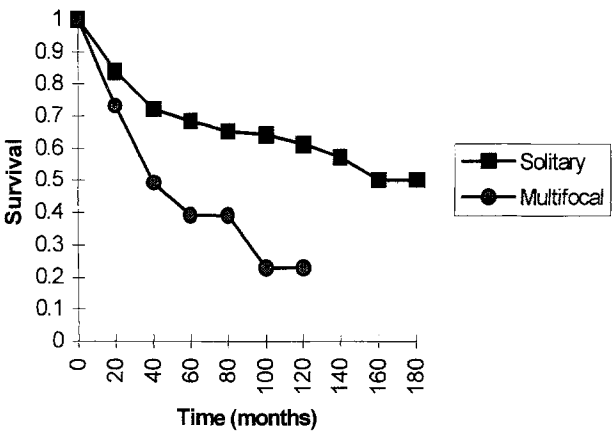

FIG. 2. Disease-specific survival. Proportion of patients surviving sarcoma, multifocal (n = 16) vs. solitary (n = 1373) disease. $P < .05$.

Enzinger and Winslow in 1962 based on the Armed Forces Institute of Pathology data with no clinical follow-up (3). Later, more recent publications are only case reports and add little new information to our understanding of this disease (4–9). The other previous reports have variable lengths of follow-up. Based on the data in the literature, it is difficult to predict the ultimate outcome for patients with this type of extremity sarcoma.

Our series has the second largest number of patients reported in the literature to date and is the first study that prospectively followed patients who were considered to have multifocal disease. This analysis attempts to study more accurately the true biology of this disease and the prognosis of patients who present with this type of disease. The true power of our study is that, although there are only a small number of patients with multifocal disease, there is a high incidence of events among these patients, and furthermore, we are comparing their course to a large number of control patients. These factors allow us to more confidently compare time to metastasis and disease-free survival as a way to understand the biologic behavior of this entity. We have found that solitary extremity sarcoma has a 21% rate of pulmonary metastasis and a 75% 5-year survival, results that agree with previously reported series (8–13). In contrast, patients with multifocal sarcoma have a 63% rate of pulmonary metastasis and only a 36% 5-year survival. Patients with multifocal disease undoubtedly have worse outcomes than do patients with solitary disease. However, our analysis failed to show that the disease behaves differently in patients with multifocal disease compared to patients with known pulmonary metastasis; both groups had similar disease-specific survivals.

Based on the data from this study, we can more accurately counsel patients with suspected multifocal extremity sarcoma on the prognosis of their disease and their

TABLE 2. *Summary of previously reported cases of multifocal liposarcoma*

Author	No. patients	Pathology	Outcome
Siegmund, 1934 (1)	1	Liposarcoma	DOD < 5 y
Ackerman et al., 1944 (2)	1	Liposarcoma	AWD 4 y
Enterline et al., 1960 (6)	2	Liposarcoma	1 DOD < 1 y 1 DOD at 6 y
Enzinger and Winslow, 1962 (3)	20	Liposarcoma	Autopsy specimens; unknown clinical follow-up
Reszel et al., 1966 (4)	5	Liposarcoma	3/5 alive at 5 y
Georgiades et al., 1969	1	Liposarcoma	AWD at 3 y
Shibata et al., 1986 (8)	1	Liposarcoma	Alive at 1 y
Altho and Larsen, 1992 (9)	1	Liposarcoma	DOD at 3 y

treatment options. The only way to separate multifocal disease from metastatic disease accurately is at a molecular and genetic level. The next step in this project is to analyze whether these multiple tumors represent the same clone of malignancy and are metastatic or are different clones and are truly multifocal disease. However, regardless of whether this disease consists of multiple clones or a single clone, we can conclude that the prognosis is poor. Current management algorithms should suggest treating patients with multifocal disease as if they have metastatic disease.

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