Length of Symptoms Before Referral

Prognostic Variable for High-grade Soft Tissue Sarcoma?

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Abstract

Background It is commonly assumed patients with high-grade soft tissue sarcomas who are diagnosed and treated quickly after the first onset of symptoms fare better than those with longer symptoms before treatment. The literature contains no substantive data to support this assumption for soft tissue sarcomas, particularly for high-grade lesions. **Questions/purposes** We examined selected potential prognostic factors for high-grade soft tissue sarcoma and determined whether the time from first symptom to diagnosis has an impact on survival or disease-free survival and whether subcutaneous sarcomas are diagnosed more quickly than deep sarcomas.

Methods We retrospectively reviewed 381 consecutive patients treated for high-grade soft tissue sarcoma between 1992 and 2007. Each patient's time from first symptom (pain and/or palpable mass) was prospectively entered into a surgical oncology database. The patients were followed for disease recurrence and survival. We compared length of symptoms with disease-free survival, overall survival, metastases at diagnosis, tumor size, and patient age. Minimum followup was 1 month (mean, 57 months; range, 1–201 months).

Results The overall 5-year survival was 64.7% and disease-free survival was 54.5%. Tumor size and metastatic disease correlated with overall survival and disease-free survival but not length of symptoms. Length of symptoms did not correlate with overall survival or disease-free survival.

Conclusions Our data do not support the assumption that longer length of symptoms before diagnosis predicts worse overall survival, disease-free survival, or metastatic disease at diagnosis.

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

Introduction

Soft tissue sarcomas are rare tumors that tend to present as insidious onset of mass, swelling, and/or pain [9]. The diagnosis of sarcoma can be delayed because of patient- or physician-related issues [7, 8]. Sarcomas of the retroperitoneum, pelvis, thigh, and shoulder girdle can be quite large before they are recognized by the patient or found by the initial treating physician [27]. They frequently mimic deep venous thrombosis by causing venous obstruction and lymphedema of the lower extremity [9, 27]. Patients may ignore painless masses that either do not appear to be increasing in size or do so very slowly. Because lipomas are so common and usually do not require intervention, many soft tissue masses are assumed to be lipomas and ignored by the patient and the physician [9].

When patients with cancer have a diagnosis delayed for any reason, they frequently question whether this time interval before treatment has affected their chance for cure. This can become a source of patient frustration and

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medical-legal challenge [1, 15, 17]. Screening programs for other cancer types have gained popularity in recent decades and have instilled a wave of public awareness to identify all cancers at the first possible sign. The widely believed assumption is earlier diagnosis of any cancer is associated with increased survival [7, 8, 12, 15, 16, 18, 21, 22]. However compelling this argument may be, there is no research to support this assumption. In fact, three studies have addressed this issue in patients with sarcoma [23, 24, 27] and found no adverse effect on survival of those patients with a delay in diagnosis. These three studies included patients with bone sarcomas and low- and high-grade sarcomas and did not separate the two. Therefore, the recent English-language literature does not appear to support the contention that in patients with sarcoma longer length of symptoms before diagnosis affects outcome.

We determined (1) what prognostic factors exist for high-grade soft tissue sarcoma, (2) whether the time from first symptom to diagnosis has an impact on survival or disease-free survival, and (3) whether subcutaneous sarcomas are diagnosed more quickly than deep sarcomas.

Patients and Methods

Between 1992 and 2007, 381 consecutive patients were treated by the lead author (BTR) for high-grade soft tissue sarcoma of the extremity or flank. Histologic grade was based on a three-tiered grading system [10]. Criteria that contributed to the histologic grading included cellularity, differentiation, pleomorphism, mitotic rate, and necrosis. The most important features were mitotic rate and necrosis. All synovial sarcomas were considered high grade. For this study, we included only patients with Grade 3 (high-grade) tumors. There were 158 pleomorphic sarcomas, 43 liposarcomas, 40 synovial sarcomas, 37 leiomyosarcomas, 19 neurosarcomas, 13 dedifferentiated sarcomas, and 62 others. Each patient's data were prospectively entered into a sarcoma database, including, but not restricted to, patient's perceived length of symptoms of the tumor, size of the tumor in greatest dimension, grade of the tumor, stage of disease at the time of diagnosis, age at the time of diagnosis, and eventual oncologic outcome. The study size was determined by including every patient during the data collection time frame (no patients were excluded). No patients had missing data. The length of symptoms was interpreted from each patient by direct questioning of the patient by the lead author and recorded as weeks. All patients with their families were able to give accurate times when they first noticed a mass, new extremity pain, or unexplained swelling. We had no instance of a patient or family unable to give an accurate onset of the first symptom. For the purposes of this article, the terms length of

symptoms and delay of diagnosis are used interchangeably. The time from the first symptom until the date of initiation of treatment was defined in weeks as the length of symptoms. Minimum followup in surviving patients was 1 month (mean, 57 months; median, 59 months, range, 1–201 months). Of the patients with less than 5 years of followup, 96.1% were seen within the calendar year (2010) of the study. Fifteen patients were lost to followup between 1 to 42 months after treatment, 13 owing to failure to return for a clinic visit and two owing to relocation. No patients were recalled specifically for this study; all data were obtained from our prospective database.

Before biopsy confirmation, the patients were staged initially with MRI of the primary mass, chest radiographs, and chest CT. We used the staging system of the American Joint Committee on Cancer which is based on size, grade and presence of metastatic disease [5]. Forty-one of the 381 patients (10.8%) presented with metastatic disease. Chemotherapy was offered to 41 patients with metastatic disease at the time of diagnosis and 37 patients with selected tissue types [3] (extraskeletal osteosarcoma, extraskeletal Ewing's sarcoma, and some large high-grade soft tissue sarcomas).

Surgery, with or without radiation, was the primary treatment modality. One hundred thirty patients received radiation. All procedures were performed by the lead author.

After treatment, followup was directed by the lead author with 14 routine physical examinations looking for lymphadenopathy and palpable nodules in the operative site and chest radiographs every 3 months for 2 years, every 4 months for the third postoperative year, and every 6 months for the fourth and fifth postoperative years. In addition, yearly chest CT was performed for 5 years and MRI after 1 year and whenever there was suspicion of a palpable mass or swelling in the operative site. Chest CT was also performed any time there was any concern on a routine chest radiograph. Two of the authors (BTR, JL) were present at each patient interview to confirm and document these data and avoid bias. Tumor size was based on the MRI at the time of diagnosis, recording the largest dimension of the tumor mass.

Kaplan-Meier survival analysis and Cox proportional-hazards regression comprise the primary analysis in our study, using a method similar to that used in our 2007 study [24]. We compared the results of patients with one SD greater than the mean in terms of length of symptoms with the results of all other patients. We performed multivariable Cox proportional-hazards regression to quantitate the hazard ratio for significant variables (including length of symptoms) affecting 5-year overall survival or disease-free survival. Time was defined as date of diagnosis, the most recent event, or date of last followup. Duration of symptoms before diagnosis was analyzed as a continuous variable and

in quartiles. Failure events were new metastatic disease or local recurrence. Nonevent outcomes were continuous disease-free survival and death by another cause. The reported *p* values are Wilcoxon and log-rank statistics resulting from the sequence of the forward stepwise selection procedure, which was analyzed as a stratification variable. Length of symptoms was examined extensively, and length of symptoms by quartile (as defined by interquartile ranges Q1, Q2, Q3, and Q4) is reported. Wilcoxon rank sums, logistic regression, and ANOVA were used in the appropriate circumstances. All statistical analyses were performed with SAS® (SAS Institute Inc, Cary, NC, USA). The sample size at the time of the study was adequate to detect, in the worst case, a 9% difference in any factor affecting survival at 5 years with power of 0.85 and a probability of Type II error of 0.15 at a significance level of 0.025 (nQuery, Cork, Ireland).

Results

The 5-year overall survival was 64.7% and the disease-free survival was 54.5%. The 10-year overall survival was 47.6% and disease-free survival was 35.7% (Fig. 1). Size of tumor correlated to overall survival ($p < 0.001$) and disease-free survival ($p < 0.001$), with larger tumors having worse outcome. Likewise, presence of metastatic disease at the time of diagnosis was associated with overall survival ($p < 0.001$) and disease-free survival ($p < 0.001$) (Fig. 2). Younger patient age was not associated with better overall survival ($p = 0.960$) and disease-free survival ($p = 0.980$).

The median length of symptoms for all sarcoma patients was 20 weeks from first symptom until diagnosis, and the average was 66.6 weeks. Length of symptoms did not correlate with size of the tumor at the time of diagnosis

Fig. 1 This Kaplan-Meier survivorship curve shows overall survival and disease-free survival as a function of time from diagnosis for 381 patients with high-grade soft tissue sarcoma. Oncologic failure was defined as death from disease for the overall survival and tumor recurrence for the disease-free survival. The 5-year overall survival was 64.7% and the disease-free survival was 54.5%. The 10-year overall survival was 47.6% and disease-free survival was 35.7%. Bars = 95% CIs.

Fig. 2 This Kaplan-Meier survivorship curve shows the survival as a function of time from diagnosis for 381 patients with high-grade soft tissue sarcoma separated by patients with isolated disease at presentation (no mets at DX) versus patients with identifiable metastatic disease at presentation (mets at DX). Oncologic failure was defined as death from disease. Presence of metastatic disease at the time of diagnosis was associated with survival. Bars = 95% CIs.

Fig. 3 This Kaplan-Meier survivorship curve shows the survival as a function of time from diagnosis for 381 patients with high-grade soft tissue sarcomas separated according to their length of symptoms before diagnosis. The patients were grouped by quartiles with the shortest length of symptoms in Quartile 1 (Q1) and the longest length of symptoms in Quartile 4 (Q4), with Quartiles 2 and 3 (Q2 and Q3) in between. Q1, Q2, and Q3 were grouped for comparison with Q4. Length of symptoms did not predict survival. Bars = 95% CIs.

($p = 0.910$). Length of symptoms did not predict overall survival (overall, $p = 0.381$; by length of symptoms quartile, Q1: $p = 0.535$, Q2: $p = 0.858$, Q3: $p = 0.983$) or disease-free survival (overall, $p = 0.131$; by length of symptoms quartile, Q1: $p = 0.865$, Q2: $p = 0.985$, Q3: $p = 0.969$) (Fig. 3). Finally, there was no difference ($p = 0.637$) in the length of symptoms between those patients who presented with detectable metastases and those who did not.

One hundred seventeen of the 381 patients (30.1%) had subcutaneous sarcomas. The average length of symptoms was 73.3 weeks and the median was 26 weeks. These subcutaneous sarcomas were not diagnosed any sooner or later ($p = 0.261$) than their deep counterparts (average, 64.3 weeks; median, 20 weeks).

Discussion

It is commonly assumed patients with high-grade soft tissue sarcomas who are diagnosed and treated quickly after the first onset of symptoms fare better than those with longer symptom duration before treatment. The literature does not support this assumption, although no other study has been limited to high-grade soft tissue sarcomas. We therefore determined (1) what prognostic factors exist for high-grade soft tissue sarcoma, (2) whether the time from first symptom to diagnosis has an impact on survival or disease-free survival, and (3) whether subcutaneous sarcomas are diagnosed more quickly than deep sarcomas.

There are several limitations of this study. First, the reason for the delay in diagnosis was not initially documented in our database. These data are available for all patients since 2006 and will be available for survival analysis in 5 to 10 years. Therefore, we were not able to address differences between patient- and physician-related

delays. However, this issue was recently addressed by Clark and Thomas [8]. They defined a delay in diagnosis as a delay of 3 months or longer and reported a delay in diagnosis in 31 of 159 patients (20%). They found 13 delays were the fault of the primary physician, two the hospital, seven the referring specialist, and nine multifactorial. Any other delays would be attributable to the patient. Unfortunately, they did not correlate the delay in diagnosis to survival data or presence of metastatic disease at the time of ultimate treatment. Second, we had no comparison group of incidentally diagnosed sarcomas. During the 15-year time frame of this study, all patients were diagnosed after they perceived symptoms of the sarcoma. Third, we did not use morbidity as an end point. The focus of this paper was oncologic impact and to include the impact of morbidity would have broadened the scope of the paper excessively. Likewise, this study was not designed to address inappropriate surgical intervention before diagnosis. This impact has been studied previously with bone sarcoma [2] and with soft tissue sarcoma [14, 25]. Reasons for increased surgical morbidity are multifocal and complex. Impact of delay on diagnosis on surgical morbidity can have serious implications, such as need for amputation or extensive local treatment, which can impact ultimate function and quality of life. Fourth, the assessment of time to diagnosis relies on a patient's perception of first symptoms. We took the task of defining the patient's first time of clinical symptom seriously to obtain the most precise time as possible and the data were collected in a prospective fashion. Two of us (BTR, JL) were consistently present at the time of data collection for every patient. We want to emphasize our study was not a chart review of data from hospital records by varying individuals who may or may not have had interest in the project. The database was prospectively collected by two of us (BTR, JL) without review of hospital records. Finally, we did not consider

margins as a potentially confounding variable. The database does not allow us to address this point, and we therefore cannot say whether the presence of positive or negative margins would influence survival in this patient population.

Our study supports the hypothesis that the time to diagnosis of patients with high-grade soft tissue sarcoma does not predict outcome. This finding is supported by several oncology studies in other cancer models [4, 6, 10, 11, 13, 16, 18–21, 26] and three sarcoma studies [23, 24, 27]. In 2007, we published our findings of bone and soft tissue sarcoma [24]. We included high- and low-grade sarcomas and found no difference in length of symptoms for bone or soft tissue sarcomas. That study included only 278 high-grade soft tissue sarcomas (624 total patients of all types of sarcoma). The finding that metastatic disease identified at the time of diagnosis was not associated with increased time to diagnosis from first symptom is strongly suggestive that high-grade sarcomas are highly variable in their timing of metastasis and growth. There does not appear to be a critical size that these sarcomas must reach before vascular invasion and tumor spread occurs. Tumors that have the biologic capability to grow to large size before treatment do carry a worse prognosis, but this has no correlation to the time from first symptom and the time of diagnosis and treatment. It may seem to be more appropriate to address the rate of growth of sarcoma, but this is confounded by different anatomic locations and differing local factors that allow for variable tumor growth and size before diagnosis. For example, most subcutaneous sarcomas are diagnosed when they are less than 8 cm, whereas deep buttocks or thigh sarcomas are rarely diagnosed when they are that small. Likewise, deep sarcomas have easier access to large draining veins that could make metastatic spread easier as compared to subcutaneous sarcomas. We found length of symptoms was not shorter for patients with subcutaneous sarcomas compared to deep sarcomas. Perhaps subcutaneous tumors have a less favorable environment for growth and do not grow as rapidly as deep sarcomas.

This lack of correlation of time to diagnosis with outcome and, more profoundly, stage of disease is at odds with the lay perception of cancer and may be disturbing to the medical community, which remains optimistic about improved early cancer referrals and treatment through better education. We are not in any way condoning intentional delay in treatment of patients with sarcoma. Smaller soft tissue sarcomas are easier to resect with good margins and with less surgical morbidity. Every oncologic surgeon prefers to treat patients with high-grade sarcoma as quickly and expeditiously as possible. However, there are other biologic factors that are far more important in predicting survivability than the time from first symptom and the time

of initial treatment for patients with high-grade soft tissue sarcoma.

We found the median time to diagnosis was 5 months of onset of symptoms, but the average time to diagnosis was 16.5 months. The large discrepancy between the median and mean is due to the large number of patients with very long time to diagnosis, which skewed the data. Even these skewed patients in the fourth quartile of (longest) length of symptoms had no differences in incidence of metastatic disease or survival. These findings are confirmed by other studies [23, 24].

We were unable to demonstrate a correlation between length of symptoms before diagnosis of sarcoma and tumor size, disease-free survival, overall survival, or stage at diagnosis. Therefore, we found no evidence that patient- or physician-related delays in treatment affected sarcoma oncologic outcome.

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