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Tumor Size/Symptom Duration Ratio as a Prognostic Factor in Patients with High-grade Soft Tissue Sarcomas

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Abstract—*Two hundred sixty-seven patients with high-grade (G_2,G_3) soft tissue sarcomas but without distant metastases, were studied retrospectively with respect to their duration of symptoms and size of tumor. Prognosis was significantly related to the size of the tumor* (P = 0.0039). *Small tumors* (5 cm *or less*) *had a* 5*-year survival rate of* 49% *compared to* 28% *for large tumors* (*more than* 5 cm *in diameter*). *Symptom duration was not related significantly to survival time* (P = 0.2490). *The ratio of the size of the tumor* (*greatest diameter, recorded in* cm) *to duration of symptoms* (*recorded in months*), *reflecting the growth rate of the tumor, is introduced as a potentially important prognostic variable. Analysis revealed a highly significant relation between an increasing size/duration ratio and shorter overall survival time* (P < 0.0001) *and time to distant metastases* (P = 0.0034). *Moreover, an optimal cut-off point of* 1.0 *for the size/duration ratio offers prognostic information independent of the G-TNM classification and other prognostic factors.*

INTRODUCTION

THE clinical behavior of high-grade (G_2,G_3) soft tissue sarcomas (STS) and the fate of patients after definitive surgical treatment are difficult to predict. STS are both locally and systemically aggressive malignant tumors. Death from this type of malignancy is due primarily to distant metastases, and much less frequently to uncontrollable local progression of the primary tumor. For prognostic purposes and treatment planning, as well as for research purposes, the G-TNM staging scheme is very useful. In patients with all types of sarcomas, the differences in survival rates are clearly emphasized between low and high grade tumors, between those with and those without invasion of vessels, nerves or bone, as well as between small (5 cm or less) and large (more than 5 cm) STS [1, 2]. But in high grade STS the staging system is not as useful for prediction of the clinical course of the disease [3]. In all of these patients, except for rare cases with lymph node metastases, the size of the tumor is only one differentiating variable (stage IIa and IIIa vs. stage IIb and IIIb). In the majority of reports the prognostic value of the diameter of STS has been noted, and its importance for survival and local control of the sarcoma has been accepted [4–8]. Of the other predictive variables, not included in the TNM classification, symptom duration has failed to reveal any considerable influence on survival [9, 10]. In other words delay of treatment is not correlated with a lower overall survival rate [11]. The probable explanation for this observation is that although prolonged duration of symptoms prior to definitive treatment may, in itself, adversely affect survival, for patients presenting with this long history without clinical evidence of metastatic disease, the adverse effects of the delay in diagnosis may be compensated for by a lower tendency, on average, for such tumors to metastasize. Other factors, such as location of the sarcoma, local recurrence, and therapy probably have a more significant impact on prognosis [8, 12–14].

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However, there are also reports that tumor doubling time and, although controversial, duration of disease-free period to local recurrence or to lung metastases after definitive surgery of primary sarcoma have a relation with overall survival time [15–20]. Moreover, a clinical impression not infrequently used in everyday surgical practice is that the fate of a patient with a long history of high-grade sarcoma is more favorable than that of a patient with a short history of illness. It was found that for patients with late appearing (more than 1 year) slow-growing metastases or local recurrences, surgical treatment should be considered with curative intent [1, 16].

The purpose of the present study was to determine whether a relationship between duration of symptoms and size of the sarcoma with high-grade malignancy in the absence of distant metastases might exist before definitive surgery, and whether this interdependence can provide additional predictive information to other prognostic factors.

MATERIALS AND METHODS

Between January, 1950 and December, 1984, 285 patients with high-grade STS were operated on for 'cure' in the Department of Surgical Oncology, Institute of Oncology, Warsaw. According to the definition of STS [1, 2], tumors arising within the confines of dura mater, in parenchymatous organs and hollow viscera, fibromatosis aggressive intra- and extraabdominalis, dermatofibrosarcoma protuberans and Kaposi's sarcoma were not considered as STS. Further, patients with retroperitoneal and thoracic wall sarcomas were not entered into the study, as they present clinicopathological features and surgical problems different from other sarcomas.

All patients underwent a complete staging work-up: history and physical examination, radiographic study of the chest and standard laboratory tests. After this routine work-up 13 patients were found to have distant metastases and were excluded from further sudy. Also excluded were four patients under the age of 15 and one patient with synchronous breast cancer. Therefore, the basic series consisted of 267 patients with high grade sarcomas. All of these patients were operated on at the same institution; hence, they were treated with the same policy regarding surgical procedure. The majority of patients (188/267, 70%) were treated with surgery alone and only 30% (79/267) underwent surgery combined with other nonrandomized treatment (47 received pre- or postoperative radiotherapy, 25 received pre- or postoperative chemotherapy, and seven received both). The small number of subjects in the various adjuvant treatment groups, and the nonrandomized nature of this treatment, precludes any further discussion of treatment.

The extremities were the most common location (232/267, 87%) while the fewest tumors occurred in the trunk and head and neck area (5% and 8% respectively).

Details of history of illness, symptoms and signs at admission to the Institute, treatment details and follow-up information were collected from the patients' records. The type of sarcoma was determined from standard pathologic reports. In questionable cases, histological slides were reviewed by two pathologists, Ludwika Sikorowa, M.D., Ph.D., and Danuta Pietrow, M.D.

The tumor size was determined at the time of admission, before definitive operation, and was defined to be the greatest diameter of the palpable tumor upon physical examination, recorded in centimeters. For multifocal type growth, the largest diameter of the largest tumor was used.

The extent of surgical procedure, irrespective of type of procedure (limb sparing resection or amputation) was defined as marginal in 134 patients and wide in 133 cases. As in the classification by Simon and Enneking [13], the term marginal refers to marginal and intralesional margins, while the designation wide include all cases with wide or radical margin.

The duration of symptoms, recorded in months, of patients with primary sarcoma was defined as the time from first clinically apparent symptoms and/or signs to the date of definitive surgery, according to the patient's own account (anamnesis). In the majority of these patients a lump was the first and only symptom of disease. In some cases, the date of trauma was taken to be the beginning of disease, if the patient was convinced that the appearance of the tumor was linked with the injury. For patients referred to the Institute for locally recurrent tumor, duration of symptoms was defined to be the time from the previous operation performed elsewhere (or the last one for repeated recurrences) to the date of definitive surgery in the Institute. Thus, the date of the last unsuccessful operation performed elsewhere with curative intent was simultaneously taken to be the initial date of appearance of recurrent disease.

The tumor size/duration of symptoms (S/D) ratio was introduced as a simple index reflecting the growth rate of clinically apparent STS [21]. Of course, the S/D ratio would not be expected to have a linear relationship with the actual growth rate since the relationship between the diameter of a tumor and its volume is not linear.

Survival time was calculated from the date of definitive surgery to the date of death (from relapse, unrelated cause or in the postoperative period) or to the date of the last observation (alive without evidence of disease or with disease). Local (distant) recurrence-free time was measured from the date of

surgery to the date of first local (distant) relapse following that surgery. Disease-free survival time was measured from the date of surgery to the date of recurrence or death, whichever came first.

Estimates of survival time and recurrence-free time curves were obtained by the method of Kaplan and Meier [22]. Comparisons of survival or recurrence-free curves were carried out using Cox's proportional hazards model or the log-rank test [23].

RESULTS

Patient characteristics

There were 35 cases with bone infiltration (stage IVa) and 27 patients with regional lymph node metastases (stage IIIc).

The median age at presentation was 45 years with a range of 15–88 years. There were 144 males and 123 females. The lower extremities were by far the most common tumor location (152/267, 57%), followed by upper extremities (80/267, 30%). One hundred and forty-one patients were operated on for primary tumor while 126 cases were treated for local recurrence. Other details of the patient characteristics are shown in Table 1.

Follow-up information was available on 262 of the 267 cases. Two hundred and seventeen patients underwent surgery before 1981, which allowed for 5 years or more of follow-up in 81% of the cases. Sixty-five patients were alive 5 years or more, and 164 (63%) had died in less than 3 years. The estimated 5 year and 10 year survival rates for the entire group of patients were 34% and 27% respectively, with a median survival time of 30 months.

Size

The size of tumor could be determined in 265 patients. There were 84 tumors with the size of 5 cm or less and 181 were more than 5 cm. Analysis of these 265 patients using Cox's proportional hazards model revealed that increasing size is significantly related to decreased survival time ($P = 0.0034$). The estimated median survival time was 60 months for tumors 5 cm or less, and 25 months for those greater than 5 cm. The estimated 5 year and 10 year survival rates for patients with small tumors were 49% and 39%, while for cases with large sarcomas they were 28% and 21% respectively.

In 84 patients with small sarcomas ($\leq$5 cm) there were 40 cases with symptom duration 6 months or less and 44 cases with duration of disease before definitive treatment 7 months or more. The majority of patients (123/180, 68%) with large sarcomas (>5 cm) had symptom duration longer than 6 months.

Table 1. Patient characteristics—high-grade soft tissue sarcomas

Total	267
Sex male/female	144/123
Age mean/median	46/45
Stage:	
IIab + IIIab	205
IIIc	27
IVa (bone infiltration only)	35
Site:	
head and neck	22
trunk	13
extremities	232
upper	80
lower	152
distal (knee/elbow or below)	107
proximal (with limb girdles)	125
Duration of symptoms:	
0–6 months	97
7–12 months	81
13 and more months	88
unknown	1
Size of the tumor:	
5 cm or less	84
more than 5 cm	181
unknown	2
Type of tumor:	
primary	141
recurrent	126
Type of surgical margin:	
marginal	134
wide	133
Histology:	
undifferentiated sarcoma	33
fibrosarcoma	39
malignant fibrohistiocytoma	14
liposarcoma	19
leiomyosarcoma	10
synovial sarcoma	61
epithelioid sarcoma	8
clear cell sarcoma	2
angiosarcoma	9
malignant hemangiopericytoma	9
neurofibrosarcoma	47
(in von Recklinghausen disease)	(+8)
other sarcomas	8

Symptom duration

The duration of patients' symptoms before definitive treatment (in most cases a painless mass) was estimated in 266 cases. The mean symptom duration was 17 months, with a range of 1 month to 200 months. Ninety-seven patients (36%) had been symptomatic 6 months or less, 81 (30%) had a duration of illness of 7–12 months, and 88 (33%) had a duration of more than 12 months. The analysis of the impact of symptom duration (treated as a continuous variable) on prognosis showed no significant relationship to overall survival time ($P = 0.2490$). The estimated 5 year survival rates for symptom duration 6 months or shorter and more than 6 months were 33% and 35% respectively.

Size/duration ratio

The growth rate of a tumor provides evidence of its biologic aggressiveness. The change of the tumor size over a period of time divided by the time provides clinical evidence of the growth rate of the tumor. Since it is difficult to estimate the actual volume of a tumor, the greatest tumor diameter has been accepted, and used clinically as an indicator of the actual size. Therefore, the S/D ratio (with size measured in cm and duration measured in months) was introduced as an indicator of tumor growth with possible prognostic implications. The cumulative distribution for S/D ratio available for 259 patients is shown in Fig. 1. To determine whether there was a significant relationship between the S/D ratio and survival time, an analysis using Cox's proportional hazards model was performed. The *P*-value for this analysis was less than 0.0001, indicating a highly significant relationship between an increase in S/D ratio and shorter survival time.

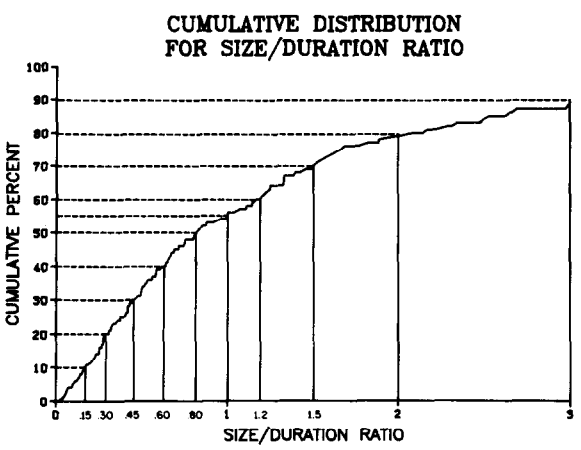

Fig. 1. Cumulative distribution for size/duration ratio in 259 patients with STS.

A series of exploratory analyses was performed to determine an 'optimal' cut-off point for the S/D ratio for distinguishing between good and poor prognosis. For each of 10 potential cutpoints (Fig. 1), survival analyses were performed to compare patients with S/D ratios below the cutpoint to those with ratios above the cutpoint. The cut-off points and corresponding *P*-values are shown in Table 2. The 1.0 cut-off point gave the smallest *P*-value, 0.0002. The median survival time for patients with a S/D ratio <1.0 was 49 months, compared with 21 months for cases with a S/D ratio >1.0. Hence, all further analyses used the 1.0 cut-off point. The survival curves corresponding to this cutpoint are shown in Fig. 2.

Determination of the S/D ratio is equally useful for patients with either primary sarcoma or recurrent tumor (Fig. 3). The estimated 5 year survival rates for patients with primary sarcomas and a S/D ratio ≤1 is 41%, while it is 28% for those with an S/D ratio >1 ($P = 0.0223$). For patients with recurrent sarcomas, the respective figures are 43% and 21% ($P = 0.0015$).

Table 2. Cut-off points and P-values for S/D ratio

Cut-off point	*P*-value
0.15	0.0218
0.30	0.0255
0.45	0.0045
0.60	0.0206
0.80	0.0018
1.0	0.0002
1.2	0.0005
1.5	0.0029
2.0	0.0073
3.0	0.0498

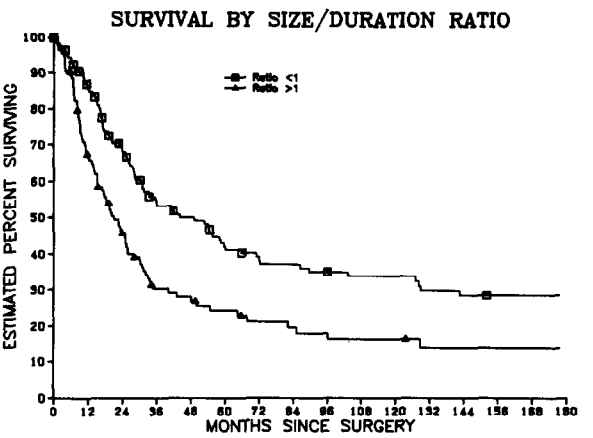

Fig. 2. Survival time distributions for patients with small and large size/duration ratios.

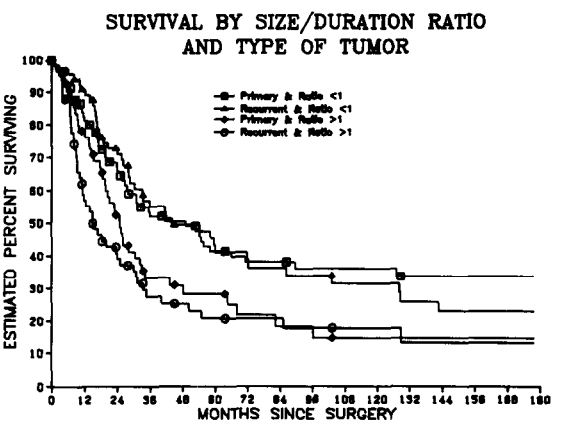

Fig. 3. Survival time distributions by size/duration ratio and type of tumor.

Moreover, patients with S/D ratio >1.0 revealed unfavorable prognosis with respect to disease-free survival time. Among them, the median time to failure was 8 months with a 5-year disease-free survival rate of 31% compared to 40 months of disease-free survival time and 45% disease-free survival rate in cases with S/D ratio ≤1.0 ($P = 0.019$). Treatment failure rates appeared to be due mainly

to distant metastases, as the analysis according to local recurrence failed to reveal considerable differences ($P = 0.687$), whereas the analysis of the time to distant metastases indicates that patients with unfavorable S/D ratio >1.0 were much more likely to have earlier distant metastases than cases with S/D ratio ≤1.0 ($P = 0.0034$). The estimated 5 year distant metastasis free rates were 28% and 44% respectively, and median free times were 17 and 48 months respectively.

Finally, if the size/duration ratio is to be truly useful, it should be significantly related to survival time, even after adjusting for the effect of other prognostic factors, including the size and stage of the STS, the type of tumor (primary or recurrent), the type of surgical margin, and the year of surgery (which may reflect changes in general medical care). That is, the S/D ratio should provide prognostic information in addition to these factors.

A multivariate proportional hazards model for survival time using tumor size (treated as a continuous variable), stage (IIa,b + IIIa,b vs. IIIc vs. IVa), type of tumor (primary vs. recurrent), the type of surgical margin (marginal vs. wide), the year of surgery, and the S/D ratio (with the 1.0 cut-off point) revealed that the S/D ratio was significantly related to survival time ($P = 0.0005$) even after adjusting for the effect of the other prognostic factors. Therefore, the S/D ratio offers independent prognostic information above and beyond that given by the size of the tumor, the stage of the patient, or the other factors considered.

DISCUSSION

The S/D ratio provides a simple, quick, and intuitively appealing method at the first clinical examination for preliminary prediction of the final postoperative fate of a patient with high-grade soft tissue sarcoma. Of course, the simplicity of this measure is obtained at the expense of its precision. The size of the tumor can be measured more precisely from a CT scan, for example, than from a simple physical examination. Further, a patient's prognosis is more likely related to the volume of the tumor than simply to its largest diameter. Hence, a more accurate predictor of survival time might be obtained by another measure of tumor burden, such as the maximum diameter^3 (which would give the volume if the tumor were actually a cube), or equivalently, $\pi/6 \times$ the maximum diameter^3 (which would give the volume if the tumor were actually a sphere). The analyses described above were repeated, therefore, using the maximum diameter^3/duration of disease as the prognostic variable. The median value of this measure for the patients studied was approx. 50; and with this cut-off point the results were quantitatively similar to those given above for S/D ≤ 1 vs. S/D > 1. Since the latter quantity is easier to compute and since the cut-off point of 1.0 is easy to interpret, the results for S/D have been presented.

Similarly, the duration of disease as defined here is admittedly arbitrary and might be improved upon. A patient's recollection of past events is subject to error, and therefore the duration of disease for patients presenting with a primary tumor probably cannot be measured accurately. It can also be argued that the denominator of the S/D ratio, as defined, does not reflect the same phenomenon for primary and recurrent patients.

Despite these shortcomings, the S/D ratio, as defined, provides significant independent prognostic information concerning the ultimate fate of these patients, even after adjusting for many other prognostic factors. The fact that the S/D ratio was found to be significantly related to survival time for both primary and recurrent tumors, and that the relationship appeared to be similar for the two groups (see Fig. 3), suggests that it may indeed be measuring a similar phenomenon for the two types of patients.

The presented results indicate that survival time is significantly better for patients characterized by numerically larger duration of symptoms than maximal size of the tumor, i.e. S/D ratio ≤ 1.0, in comparison with cases who have numerically shorter duration of illness than diameter of sarcoma, i.e. S/D ratio >1.0. It seems that this latter group represents patients with a high chance of development of distant metastases in the postoperative period. If the doubling time of a sarcoma is related to its tendency to metastasize, then the S/D ratio could be correlated, at least in part, with the growth of high grade sarcomas [24, 25].

The prognostic significance of the tumor size has been confirmed by many authors and was also observed in our series. The patients with large high-grade sarcomas fared significantly worse than patients with small tumors (5 cm or less). The introduction of the S/D ratio for clinical pretreatment evaluation of patients with sarcomas larger than 5 cm allows one to identify a group with especially high risk of failure. In our series, 81% of the cases with large sarcomas growing in relatively short time i.e. S/D ratio >1.0, did not survive more than 5 years.

The size/duration ratio, despite its shortcomings, reflects dynamic characteristics of the biological behavior of sarcomas, in contrast to other prognostic factors which are mainly based on static, anatomic features of these tumors. The knowledge of new factors which determine prognosis can be very useful, because the early diagnosis or suspicion of distant dissemination of sarcomas in subclinical forms is a fundamental step toward improvement of treatment results. So far, however, the fate of individual patients with high-grade soft tissue sar-

coma after definitive surgical treatment is much less predictable than in other malignant tumors. We feel that the S/D ratio provides a useful step towards a more accurate prediction of prognosis with this disease.

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