Analysis of Staging and Management of Patients with Sarcoma

A Ten-year Experience

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Over ten years, 70 patients with soft tissue sarcoma were treated for their primary tumors at the hospital of The Fox Chase Cancer Center. The clinical characteristics of these tumors are correlated with the outcome of various management efforts. The results of these evaluations identify three groups that can provide the basis for future treatment decisions and stratification for randomized studies of management options. The first group of patients, those with small well differentiated tumors, have no systemic spread regardless of the treatment modality used. The second group, those with large (>5 cm) tumors that are moderately or poorly differentiated, do uniformly poorly despite the management techniques used. An intermediate group, those with high grade or large size but not both, have outcomes which may be corrected to treatment modalities.

APPROPRIATE MANAGEMENT OF SOFT tissue sarcoma is a confusing and controversial issue and multidisciplinary therapy is becoming increasingly common.[9,11–13,18,24–26] Many cancer centers have espoused different treatment philosophies, and have demonstrated rationale for their conclusions by published results that show diminished local recurrence rates for particular procedures.[3,4,7,8,14–17,20,21] Reports of systemic therapy given at the time of initial treatment have been conflicting and are in need of interpretation in the light of the known biology of these tumors.[9,12,18] We report our experience with 70 patients who had at least part of their initial treatment at the American Oncologic Hospital (AOH); the biologic characteristics of both the population and the tumors are assessed. The mathematical models and techniques to define the clinical characteristics of the study patients are explained.

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Supported in part by the Junior Faculty Clinical Fellowship of the American Cancer Society.

Submitted for publication: November 12, 1979.

Diagnostic and treatment techniques were not uniformly applied to this population, yet philosophies of approach and therapy were held constant. A function sparing tumor resection was done whenever possible. Irradiation was used as a planned adjuvant in a limited number of cases. A variety of diagnostic procedures have been added over the ten years of this study and therefore have not been uniformly applied.

This is a retrospective review of a patient population and not a prospective inquiry about treatment alternatives. Nonetheless, a description of a defined population of patients treated at one institution can provide the basis for identifying important biologic and clinical information if these data are optimally managed.

Materials and Methods

The medical records of all patients with soft tissue sarcomas seen at the AOH since its opening in 1968 at Fox Chase until July, 1978 were reviewed in this study. Of the 127 cases, the 70 patients who had all or part of their initial treatment given at the AOH form the basis of this report. If radiation therapy or chemotherapy was part of a patient's initial treatment and was given prior to a clinical recurrence, these data were included.

Complete clinical data at the time of the initial treatment were not available, thus we could not correlate outcomes to preoperative apparent size, fixation of the lesion, rate of growth of the presenting mass, pain or other symptoms. Tumors were routinely measured by the pathologist and his measurements of the surgical specimen were used for this study whenever it was

0003-4932/80/0400/0488 $00.80

available. Histologic categorization and grade of each tumor were reviewed by one of the authors (T.R.). Carconisarcomas, mesotheliomas, Kaposi's Sarcoma and angiosarcomas were deleted from this study.

A variety of diagnostic procedures and treatment techniques were applied to these patients. Some patients were referred by their primary physicians for a specific modality, and occasionally a patient or his family refused the initially offered therapeutic options. Nonetheless, a common management philosophy was applied to most patients. Whenever possible, a function sparing resection was employed. Local excisions were defined in this study as a removal of the tumor and a small amount of surrounding normal tissue. Wide excision implied the removal of 4–5 cm of normal tissue around the tumor. This was supported by frozen section analysis of the specimen. No formal muscle group excisions were performed. Amputations were required when the anatomic location of the primary tumor involved bone, nerve, or blood vessel, or restricted other surgical options.

Patients were followed by their surgeons or referring physicians. Family physicians provided information about recent clinical status if this was not available on the medical records. No patients were lost to follow-up though some had moved to remote areas. Site and time of initial recurrence from treatment were recorded and defined as indicators of treatment failure.

The date of death and the relation of death to either the primary tumor or to its treatment were recorded. In the case in which the relationship between tumor and death was in doubt, a tumor related death was computed. Five patients dying of nontumor related causes were considered lost to follow-up. Curative treatment of localized or isolated recurrence was occasionally possible, but the results of these procedures could not be accurately assessed as they were not always done at the AOH.

The data were analyzed using the cox proportional hazards model[5] for failure time data, a generalization of exponential and Weibull regression models. In this model the covariates are assumed to act multiplicatively on the underlying hazard function. A computer program supplied by Dr. Norman Breslow at the University of Washington was used to generate the maximum likelihood estimates of the regression parameters.

We used the model to test whether factors presented in the literature (size, grade, etc.) affected failure in our series. Covariates, presumed to affect survival or time to recurrence were recoded to −1 for those not at risk and 0 for those at risk. For each covariate the program computes a regression parameter, B. Then an estimate of the relative hazard (RH) associated with a covariate is very conveniently expressed as exp (B), under the assumption that all covariates act multiplicatively.

Results

Of the 70 patients in the study, 37 have been treated within the past five years.

The age range of the 31 males and 39 females was 2–86 years at the time of diagnosis with a mean age of 55.9 years. Age was not related to a particular histologic diagnosis, grade, time to recurrence, or survival. The age of these patients reflects the population seen at the AOH. As pediatric malignancies are not emphasized at the AOH, there are fewer patients in this age group than in other similar studies. The sex, race, and geographic and occupational distribution of these patients reflects the referral patterns to this hospital, *i.e.*, a dominance of white, middle class families living in an urban industrial area.

Because of changes in terminology of histologic classification over 10 years, six tumors have been reclassified, but this was done without without knowledge of the follow-up information. In two cases, the tumor grade became more aggressive on subsequent recurrences, but the basic histologic diagnosis did not change during the course of observation. Table 1 presents the distribution of histologic diagnoses. The location of the tumors (Table 2) in this series were unremarkable. Neither the histologic diagnosis nor the site of occurrence was correlated with either local or systemic spread. It should be noted that 20 patients in this series had either dermatofibrosarcoma protuberance or well differentiated (myxoid) liposarcomas; none of the patients with dermatofibrosarcoma protuberance recurred locally or systemically. Operative resection was the only treatment given for 46 patients, radiation alone for four, chemotherapy alone for one, and 19 people received combination therapy.

There has been either a local or systemic recurrence in 28 patients. Any recurrence whether local or distant was considered a treatment failure. Influences on survival were computed by the Cox proportional hazards model; five patients dying of nontumor related deaths were considered lost to follow-up at death.

Three clinical variables, grade of the tumor, size of the tumor, and fever were found by the Cox model to be correlated with survival. Since the grade and size of the tumor so highly correlated with outcomes, stratification of the patient population into three stages based on grade and size could not isolate any other independent factors in either the analysis of survival or time to recurrence.

Thirty-three (47%) patients had low grade tumors (grade I), 13 (19%) had moderate to poorly differentiated

TABLE 1. *Distribution of Histologic Diagnosis*

Category Label	ICDO Histology Code	Absolute Frequency	Relative Frequency (%)
Sarcoma not otherwise specified	8800.	2	1.8
Fibrosarcoma	8810.	8	11.4
Fibrous histiocytoma	8830.	6	8.6
Dermatofibrosarcoma protuberances	8832.	9	12.9
Myxosarcoma	8840.	6	8.6
Liposarcoma not otherwise specified	8850.	5	7.1
Well differentiated liposarcoma	8851.	3	4.3
Myxoid liposarcoma	8852.	8	11.4
Pleomorphic liposarcoma	8854.	2	2.9
Leiomyosarcoma	8890.	14	20.0
Pleomorphic rhabdomyosarcoma	8901.	1	1.4
Embryonal rhabdomyosarcoma	8910.	1	1.4
Endometrial stromal sarcoma	8930.	1	1.4
Mesenchymoma	8990.	1	1.4
Synovial cell sarcoma	9040.	1	1.4
Schwannoma	9560.	2	2.9
Total		70	100.0

tumors (grade II) and 23 (33%) had anaplastic lesions (grade III). One tumor (1%) could not be graded and was classed as high grade. The size of tumors ranged from 0.7 to 67 cm (mean: 9.4 and SD: 10.3).

Two of the 33 patients with low grade tumors recurred locally, three had regional recurrences, and one recurred systemically; two low grade tumors contributed to the patients' death. There were 13 patients with intermediate grade tumors of which two recurred locally, four regionally, and one systemically. Six patients with intermediate grade tumors died because of sarcoma. Twenty-three patients with high grade tumors had seven local and eight regional or distant first recurrences. Fifteen patients with high grade tumors have had tumor related deaths.

The thirty-three patients with small (5 cm or less) tumors had four local and one distant recurrences and three tumor related deaths. In the 37 patients with tumors greater than 5 cm, there were seven local, nine regional, and seven distant recurrences and 20 of these patients died because of tumor related causes. Patients with high grade tumors had approximately a four-fold increase in hazard relative to patients with low grade tumors. Patients with large tumors had a seven-fold estimated relative increase in hazard.

TABLE 2. *Location of Primary Sarcoma*

Category Label	Absolute Frequency	Relative Frequency (Per Cent)
Head–Neck	12	17.1
Trunk other than viscera	16	22.9
Viscera (includes 4 in uterus)	10	14.2
Upper extremity:		
proximal	3	4.3
distal	3	4.3
Lower extremity:		
proximal	18	25.7
distal	8	11.4
Total	70	100.0

Table 3 shows the joint distribution of grade and size of tumor. The corrected chi square statistic and inspection of the data show the grade and size were not independent factors. Low grade tumors tended to be smaller than high grade ones. Therefore, the joint hazard of large and high grade relative to small size and low grade is less than the product of the individual hazards, *i.e.*, less than 4×7. The concomitant effect of grade and size on recurrence and survival is shown in Table 4. The rationale for this prognostic division of sarcoma patients based on grade and size is also graphically presented in Figure 1. There is one group who always do well, another who always do poorly, and an intermediate group.

Seven patients (10%) presented with fever unrelated to infection; all had high grade tumors and six of seven had tumors larger than 5 cm. Although all these patients have recurred and fever is prognostic of poor survival, it is a proxy for large high grade tumors. However, there was no association between fever and the type of recurrence (local, regional, or metastatic) in patients who recurred.

Although a function sparing philosophy dominated the approach, initial treatment of these tumors varied considerably. Local excision alone was the only treatment for 20 patients and local excision combined with radiation therapy was used for 10 patients. Wide excision alone was used on 18 and was combined with radiation therapy six times. Radiation therapy was the only therapy in four cases. Chemotherapy was used alone once and in combination with surgery or radiation therapy four times. Five amputations were done because of anatomical considerations. In retrospect, two patients had incomplete excisions. No curative therapy was given to only one patient. She had a 12 cm, low grade leiomyosarcoma; after palliative radiation she was alive 62 months postdiagnosis.

Local excisions, either alone or with radiation therapy, were done on 30 patients. Table 5 shows 21 patients have had no recurrence, six have recurred locally, two regionally, and one had distant recurrence. Seventeen patients were alive at last contact, ten died of their diseases, and three deaths were due to other causes. Table 6 shows 15 of these tumors were low grade, six were intermediate grade, and nine were high grade. The tumors were evenly divided by size with 15 small and 15 large lesions. The age dis-

tribution of this group of patients is of note: all three youths in the study received local excisions, as did six of nine patients over 75 years of age.

Ten of 24 patients receiving a wide excision have recurred, while two of five patients who had amputations for grade 2 or 3 tumors have recurred systemically and both of these have died. There are four patients whose luminal visceral sarcomas were treated by bowel resection only, and three of these had abdominal recurrences leading to their eventual deaths.

Radiation therapy, either alone or with surgery or chemotherapy, was given as treatment to 22 patients. Fourteen have not recurred while two each have recurred locally and regionally, and four have systemically recurred. Twelve are alive, eight died of their disease or treatment toxicity, and two have died of other causes. Table 7 shows the joint distribution of size and grade of tumor receiving radiation. Of 19 patients also receiving surgery with radiation, a majority, 10 had only local excisions.

Chemotherapy was added to initial therapy in five patients and four of these are free of distant recurrence. Of these, three were large low grade tumors, and the other two were high grade lesions.

Discussion

The management of sarcoma patients continues to be a challenging clinical problem. Extremity sarcomas have been shown to require aggressive treatments, such as major amputations or a combination of resection with high dose radiotherapy.[3,4,7,8,10–19] En bloc resections including the origin and insertion of the involved muscle groups and sparing function of the extremity, have found their place in the treatment of sarcomas.[1,2,4,16,17,20,21] Yet the problem of distant metastasis continues to limit the success of a regional treatment regimen for a very high proportion of patients.

Staging systems have been recently devised for this diverse group of histologic tumors which will aid the treatment selection and evaluation of prognosis.[19] These systems rely more on the size and the grade of tumor rather than the histologic category or the determination of the cell of origin. This may contribute to a more unified approach to therapy for this diverse group of tumors.

The records of patients with sarcomas treated at the AOH were retrospectively reviewed to determine the value of sarcoma staging systems and the individual items that enter into them. These factors were correlated with specific treatments directed toward the primary tumor to identify areas of appropriate or inappropriate treatment philosophy.

TABLE 3. *Comparison of Grade and Size of Tumor*

	Size		Row Total
	≤50 mm	>50 mm	
Grade			
Low	21	12	33
High	12	25	37
Total	33	37	70

Corrected chi square: 5.62107 with 1° of freedom. Significance = 0.0177 *i.e.*, grade and size are not independent covariates.

The patient population with sarcoma seen at the AOH was comparable to most reported groups. Age of initial diagnosis ranged from the third to the sixth decade[4,16–17,22,23] in many reported series with peaks in the fifth decade.[4,19,21] Our age range coincided with that reported by Gerber[7] whose peak was also in the sixth decade.

The anatomic location of the tumor was similar in the AOH series to that reported in other series.[10,14] The number of proxial and distal extremity lesions was as expected, and as was shown by Suit et al.[18,24,25] and others, proximal lesions were more likely to be large, have a higher grade, and a worse prognosis.

The grade of the sarcoma has long been recognized as an important indicator of metastatic potential and survival.[17,19,24] A 1965 study of Werf-Messing[27] correlated mitotic indices in the primary with later metastasis. If there were no mitoses per 10 HPF, metastasis occurred in only 25% of the patients. This percentage increased in the stepwise fashion to 100% of the patients with greater than 11 mitosis per 10 HPF. The addition of size to the grade in a staging system was shown to be effective by Russell et al [19] In his system, grade is the major discriminating factor, with size identifying a significant subgroup of patients with high grade lesions.

In our series, size had a higher relative hazard (RH = 7) than grade (RH = 4). However, since grade and size interact, we adopted a three group sarcoma staging system. Low stage tumors were well differentiated and smaller than 5 cm. An intermediate stage included tumors with either high grade or large size, but not both. High stage tumors had both high grade

TABLE 4. *Differential Survival and Type of Recurrence for Small, Low Grade Lesions and Large, High Grade Lesions*

	Small, Low Grade (n = 21)	Large, High Grade (n = 25)
Local recurrence	1	5
Regional or distant recurrence	0	12
Died of sarcoma	0	18

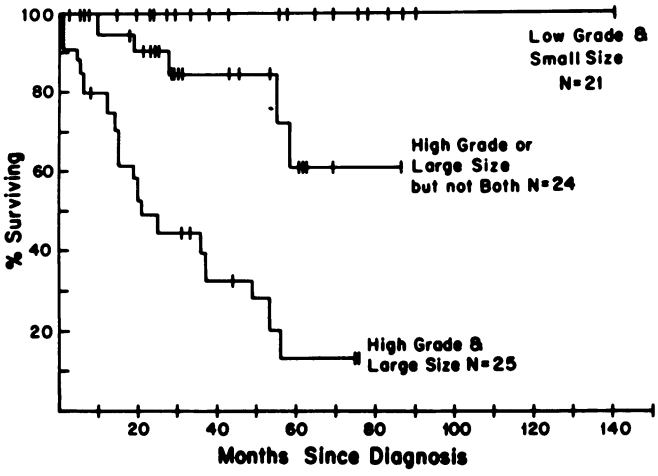

FIG. 1. Low grade is grade I, High grade II or III. A small tumor is 5 cm or less, a large tumor is greater than 5 cm. Data from patients who died of nontumor related causes are censored.

and large size. These divisions showed marked difference in outcome regardless of type of treatment given.

The Cox model of proportional hazards is intended for use in analyses of censored data. Censored data means that in the sample not all of patients have failed, *i.e.*, either recurred or died of sarcoma, its spread, or the effects of its treatment. At the close of the study (12/1/78), 40 of 70 (57%) were still living; their survival data is therefore censored. Five additional patients had censoring of their survival data because they died of other causes. At the close of this study, 41 of 70 (59%) had not recurred, thus their disease free interval is censored. Using censored data to estimate the failure rate is a familiar problem.

We have confirmed that the grade and size of soft tissue sarcomas are the principle components in staging. We have also shown that these covariates are not independent. Since the Cox model assumes independence among covariates, its use for this and similar analyses of clinical data sets must be tempered by

TABLE 5. *Comparison of Type of Operation and Recurrence*

Treatment	Type of Recurrence				
	None	Local	Regional	Metastatic	Total
None	0	0	3	2	5
Local excision	21	6	2	1	30
Wide excision	14	5	1	4	24
Amputation	3	1	0	1	5
Bowel resection	1	0	3	0	4
Incomplete excision	2	0	0	0	2
Total	41	12	9	8	70

TABLE 6. *Type of Operation Compared to Grade of Tumor (Cell Per Cent is Per Cent of Row)*

Operation	Grade Unknown	Low	Intermediate	High	Total
None	0 (0.0)	2 (40.0)	0 (0.0)	3 (60.0)	5 (7.1)
Local excision	0 (0.0)	15 (50.0)	6 (20.0)	9 (30.0)	30 (42.9)
Wide excision	1 (4.2)	13 (54.2)	4 (16.7)	6 (25.0)	24 (34.3)
Amputation	0 (0.0)	0 (0.0)	1 (20.0)	4 (80.0)	5 (7.1)
Bowel resection	0 (0.0)	1 (25.0)	2 (50.0)	1 (25.0)	4 (5.7)
Incomplete excision	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (2.9)
Total	1 (1.4)	33 (47.1)	13 (18.6)	23 (32.9)	70 (100.0)

such realization. However, the Cox model remains the best currently available for estimating a failure rate from censored data.

It was interesting that seven patients were identified in this series as having fever unrelated to infection when their primary tumor was being treated. There has been a clinical recurrence in each of these patients. Though this was a striking, unexpected, and previously unreported finding, the poor response to treatment could have been predicted in this small group of patients by use of the grade and size of the tumor alone. Nonetheless, it is our feeling that a fever related to tumor rather than infection in patients with soft tissue sarcoma should suggest the strong possibility of systemic spread and should influence the treatment plans.

Unlike many previous investigators, we have not found that all or a majority of soft tissue sarcomas treated with local excisions recur. A considerable number of low grade, small sarcomas do not require extensive excisions. On the basis of our review, staging information can identify patients for whom limited excisions are appropriate. Stratified groups based on these staging factors can be used in other investigations attempting to show synergistic association of excision and high dose radiation or other adjuvant

TABLE 7. *Comparison of Grade and Size for Patients Receiving Radiation*

Grade	Size	
	<5 cm	>5 cm
Low	4	5
High	3	10

programs. A group of patients can be identified prospectively that has a very low rate of treatment failure. Selective use of function sparing approaches to the treatment of soft tissue sarcomas would also appear justified in the light of this review.

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