Prognosis and Treatment of Primary Deep Soft Tissue Sarcomas

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Abstract. *The objective of this study was to define the prognostic factors for survival of patients with soft tissue sarcomas (STS) of the extremities located below the muscular fascia. Patients and Methods: One hundred and twenty-seven consecutive patients, resected in our Institution between March 1988 and December 2002, were reviewed. Results: On univariate analysis, the prognostic factors for survival were tumor size, nodal status, adequate surgery, tumor malignancy grade and administered chemotherapy. Additionally, local failure, metastasis after resection and residual tumor after incomplete resection followed by complete resection were adverse prognostic factors for survival. The tumor size, nodal status and metastasis after resection were factors indicating worse survival on multivariate analysis. Conclusion: Our results indicate that most factors influencing the course of the disease cannot be controlled by the surgeon. Complete resection is imperative for local control and allows the patient the chance of a cure. New treatment procedures should be evaluated in prospective trials to optimize therapy. Surgery without sufficient information on the malignancy or expansion of the tumor might be detrimental for the patient.*

Soft tissue sarcomas (STS) are rare, accounting for 1% of all malignant tumors (1). Even after implementation of radiation, chemotherapy and hyperthermia therapies, surgical tumor resection remains the only curative treatment. For subfascial tumors, whether the optimal surgical procedure performed should be compartmental or wide resection has not definitely been solved in the literature, but it is beyond doubt that clean surgical margins are the crucial factors for the prevention of local recurrrence. Positive resection margins are correlated with a high risk of local recurrence (2-4); some studies have reported a higher risk of metastasis, while other studies have contradicted this thesis (2, 3, 5). Surgery alone, however, cannot guarantee freedom from recurrence and metastasis. The tumor biology has an impact at least as crucial as the tumor size and location (2, 3, 6). Former practices promoting extensive, sometimes mutilating resections have been abandoned for an individualized therapy including ratiation, chemotherapy or hyperthermia whenever feasible (7, 8). Adjuvant radiation therapy following radical, but limb and function preserving surgery, has been shown to achieve local tumor control and freedom from metastasis at a rate similar to ablative surgery (9-11).

Unfortunately, the diagnosis is often delayed because the patient attributes a palpable tumor to a trauma or other cause and seeks medical advice only at an advanced stage of the disease. Furthermore, the degree of tumor malignancy is often not perceived by the doctor leading to inadequate surgery, and consequent referral to a specialized center after confirmation of the diagnosis. These patients are reported to have a higher risk of local recurrence and may benefit from re-resection, since they have a high incidence of residual tumor in the tumor bed (12).

The purpose of this study was to evaluate prognostic factors for survival for deep, subfascial extremity sarcomas in patients treated at a single institution.

Patients and Methods

Between March 1988 and December 2002, 127 consecutive patients presented at our Institution with a STS of an extremity. All 127 patients presented with a primary tumor, including 61 patients (48%) transferred to our Institution for immediate re-resection after a suspected benign tumor had been resected elsewhere and final histology revealed an STS.

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Fifty-seven patients (44.9%) were treated with a compartmental resection while the remaining 70 patients (55.1%) were treated with a so-called "wide resection", in which resection of the tumor included adjacent muscles, but without resection of the whole muscular compartment. The decision whether to perform a compartmental resection or not was made individually, based on tumor site, size and infiltrated tissue.

The quality of resection was determined according to the UICC R-classification (13). All tumors were classified by one experienced pathologist (A.G.).

All data were collected prospectively in a computerized database. The patients were followed up by us until December 31, 2005.

Statistical analysis. To explore the prognostic factors for the survival of patients with primary deep STS, an univariate analysis with the Kaplan-Meier method was used to estimate the survival curves and a two-sided log-rank test was applied to test the significance between the survival curves of each potential risk factor. A stepwise multivariable Cox regression survival model was adjusted to test the independent prognostic relevance of the variables. The limit for reverse selection procedures was $p \leq 0.05$ for entry and $p \leq 0.10$ for removal by the likelihood ratio test. The proportionality assumption for all variables was assessed with the log-negative-log survival distribution functions. All statistical analyses were performed with the statistical program SPSS for Windows (SPSS Inc., Version: 12.0, 2001).

Results

Characteristics. Detailed characteristics of the study population are shown in Table I. The mean age of the patients was 50.8 (15-86) years.

Site of primary tumor. Eighty-five (85.9%) out of the 99 tumors located in the lower extremities were proximal to the knee, and 20 (71.4%) of the 28 tumors of the upper extremities were located proximal to the elbow.

Operative treatment. Resection of the tumor was achieved in all 127 patients, but in 6 patients (4.7%), the tumor reached the resection margins or the tumor capsula was opened during the operation (R1). In the other 121 patients the tumor was resected completely (R0) and no patient with visible tumor left in the tumor bed (R2).

In 23 (37.7%) out of the 61 re-resection patients tumor tissue was found in the re-resection specimen. In 20 (87%) of these patients, tumor-free margins could be confirmed (R0), while in three patients (13%) resection margins were not free or the tumor capsula was opened during the course of the operation.

A regional lymphadenectomy was performed in patients in whose clinical presentation or imaging procedures had revealed lymph nodes suspicious of tumor cell infiltration.

Histology. Malignant fibrous histiocytoma (MFH, n=32) and liposarcoma (n=27) accounted for 46.5% of all the tumors, followed by malignant peripheral nerve sheath tumor (MPNST, n=19) leiomyosarcoma (n=12) and synovial sarcoma (n=10). Other histologies were rare and accounted for 27 tumors altogether (Table I).

Table I. *Clinical characteristics of the study population.*

	n	%
Patients	127	100
Age, yr (Mean±SD)	50.8	±17.1
Gender		
male	77	60.6
female	50	39.4
Site of primary tumor		
lower extremity	99	78.0
upper extremity	28	22.0
Histology of tumor		
Liposarcoma	27	21.3
Malignant fibrous histocytoma	32	25.2
Malignant peripheral nerve sheath tumor	19	15.0
Other*	49	38.6
Tumor size, cm		
≤5 (T1)	26	20.5
>5 (T2)	101	79.5
Tumor grade		
G1	27	21.3
G2/3	99	78.0
Presence of positive regional lymph nodes		
yes	6	4.7
no	121	95.3
Distant metastases at diagnosis		
yes	4	3.1
no	123	96.9
Resection quality		
R0	121	95.3
R1	6	4.7
Compartmental resection		
yes	57	44.9
no	70	55.1
Re-resection		
yes	61	48.0
no	66	52.0
Residual tumor in re-resection patients		
yes	23	37.7
no	38	62.3
Adjuvant radiation therapy		
yes	43	33.9
no	84	66.1
Adjuvant chemotherapy		
yes	25	19.7
no	102	80.3
Local recurrence		
yes	19	15.0
no	108	85.0
Metastasis		
yes	64	50.4
no	63	49.6

*Leiomyosarcoma (12), synovial sarcoma (10), fibrosarcoma (6), chondrosarcoma (6), osteosarcoma (5), hemangiopericytoma (3), epitheloid sarcoma (2), and others.

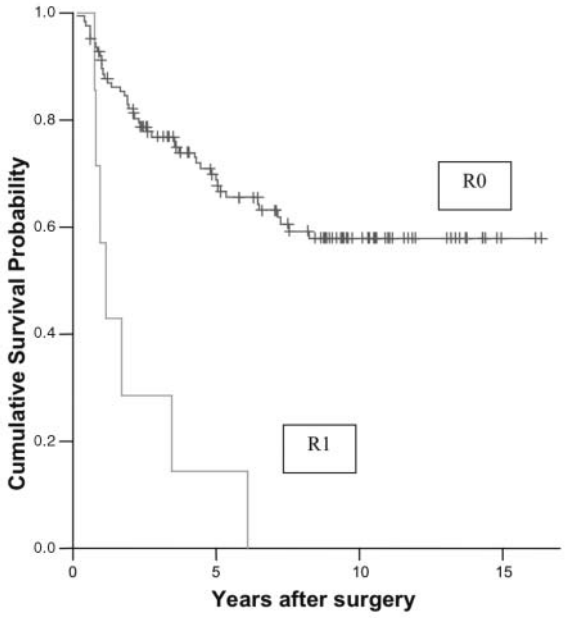

Figure 1. *Overall survival according to R-status ($p<0.001$). R, resection; R0, tumor free margins; R1, tumor reached resection margins or tumor capsula opened during surgery.*

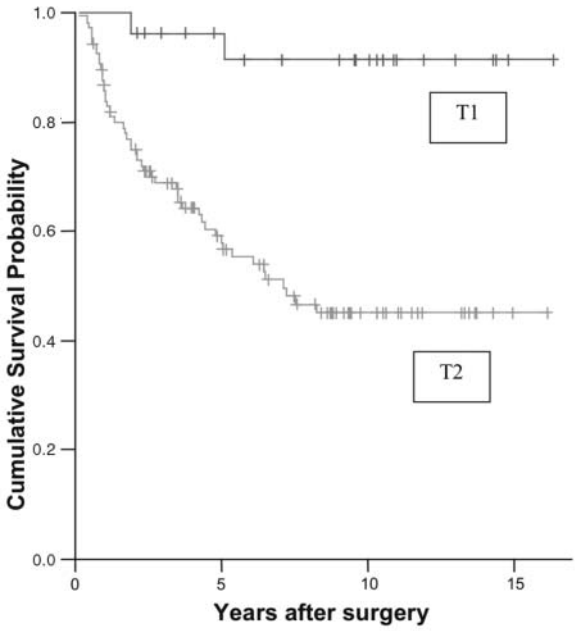

Figure 2. *Survival according to tumor size ($p<0.001$). T1, tumor ≤5 cm; T2, tumor >5 cm.*

Tumor grading was according to the three-level grading system. Sixty-six tumors (52%) were of poor differentiation (G3), 33 (26%) were of moderate (G2) and 27 (21.3%) of good differentiation. Grading of one patient could not be obtained.

In six patients (4.7%), consistently with T2 tumors of the lower extremity, 5 proximal and one distal to the knee, tumor cells were found in the resected lymph nodes (N1). One of these six patients had distant metastases at the time of diagnosis of the primary tumor, the remaining five patients developed metastases after a median of 4.6 (2-7) months. All six N1-patients died after a median of 18.7 months (range 6-42, SD 14.6). The tumor histology of these patients was leiomyosarcoma, hemangiopericytoma, fibrosarcoma, liposarcoma, MFH and clear cell sarcoma.

Four patients presented in an advanced tumor stage and had distant metastases diagnosed before or within four weeks after resection of their primary tumor.

Postoperative treatment. All patients were presented to our interdisciplinary soft tissue sarcoma team, where adjuvant treatment strategies were determined based on histology, staging, and surgical treatment results. Twenty-eight patients (22.1%) received adjuvant radiation therapy alone, 10 (7.9%) adjuvant chemotherapy and 15 (11.8%) both (see Table I). Wherever possible, patients were enrolled in EORTC studies, mostly EORTC # 62931 (a randomized phase III trial of adjuvant chemotherapy with high-dose doxorubicin, ifosfamide and lenograstim in high grade soft tissue sarcoma).

Prognostic factors for survival. After a median follow-up of 81.1 months (2-217), 60 patients (47.2%) were alive with no evidence of disease. Fifty-five patients (43.3%) died from their tumor disease. The median survival time was 42.2 months (range 2-217).

The 49 patients who died from their tumor disease after complete tumor resection lived for a median of 43.9 (2-217) months after the resection. All six patients with incomplete resection and all six patients with positive lymph nodes died, making N and R status strong prognostic factors (both $p \leq 0.0001$), shown for R in Figure 1. The six patients with incomplete local control lived for a maximum of 74.5 months (median 28 months), and the six patients with positive lymph nodes lived for a maximum of 42 months (median 18.7 months).

Five out of the 26 patients with a T1 tumor (19.2%), but 50 out of the 101 patients with a T2 tumor (49.5%, $p<0.001$) died (Figure 2). Patients with a tumor of low malignancy grade had a better prognosis than patients with a tumor of high or intermediate malignancy grade ($p<0.006$, Figure 3). The incidence of recurrent disease, metastatic or local, proved to be a significant factor for worse prognosis ($p<0.001$ and $p<0.008$). The presence of tumor cells in the resected mass of the patients who had to undergo re-resection after incomplete resection elsewhere indicated a worse prognosis ($p<0.036$).

In the multivariate analysis T ($p=0.002$), N ($p=0.001$), and tumor malignancy grade ($p=0.008$) were independent

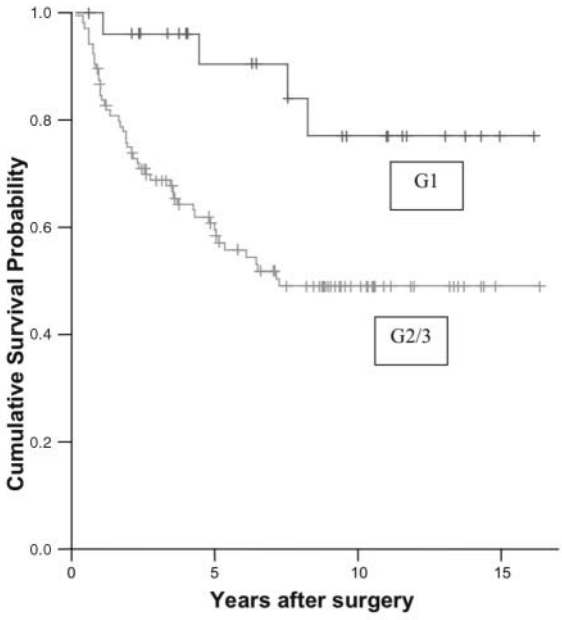

Figure 3. *Survival according to tumor grade (p=0.0056).*

Table II. *Univariate analysis by the Kaplan-Meier method.*

Parameter	Total	Tumor death	*p*-value (log-rank test)
Tumor size, cm			
≤5 (T1)	26	2	0.0003
>5 (T2)	101	48	
Tumor grade			
G1	27	4	0.0056
G2/3	100	46	
Presence of positive regional lymph nodes			
yes	6	6	0.0001
no	121	44	
Distant metastases at diagnosis			
yes	4	3	0.0051
no	123	47	
Resection quality			
R0	121	44	0.0001
R1	6	6	
Residual tumor			
yes	23	14	0.0358
no	104	36	
Local recurrence			
yes	19	14	0.0083
no	108	36	
Metastasis			
yes	64	50	0.0001
no	63	0	

prognostic factors. These results are displayed in detail in Tables II and III.

Discussion

Complete resection remains the gold standard of therapy for STS of any site, including deep sarcomas of the extremities. Most factors influencing the course of the disease, however, cannot be controlled by the surgeon. Tumor size and malignancy grade are the major elements determining the aggressiveness of the tumor and require a therapeutic approach that goes beyond resection.

In this study, poor surgical margins had an adverse effect on survival, reflecting the prerequisite of adequate surgery. However, the power for the statistical analysis was weak, since only six out of 127 patients had positive margins.

All six patients with positive margins had a sarcoma of high or intermediate malignancy grade, and patients with G1 sarcoma had better survival. The adverse survival profile of these six patients might also have been due to the high or intermediate malignancy grade of their tumors.

All six patients with regional lymph node metastases at the time of resection of the primary tumor had a large tumor (T2) of the lower extremity, in 5/6 cases proximal to the knee, and all of them developed distant metastases. A STS can grow to a size of more than 5 cm in diameter very easily in a thigh of a man or woman of average size without causing pain or a loss of function, but this will hardly ever occur in the upper extremity. When a large STS is diagnosed or suspected an extended diagnostic process is compulsory and should include, in our opinion, besides a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the primary tumor site, a CT scan of the lungs and a whole-body positron emission tomography (PET) scan. The efficacy of the PET scan to detect a tumor mass that cannot be identified by conventional diagnostic techniques is widely accepted (14). Regional lymph node

Table III. *Cox regression analysis for survival.*

Parameter	Coefficient (β)	Relative risk (RR)	95% CI for RR	*p*-value
Tumor size >5 cm	2.215	9.158	2.212-37.925	0.002
Presence of positive regional lymph nodes yes	1.662	5.271	2.136-13.011	0.001
Tumor grade G2/3	1.404	4.072	1.454-11.398	0.008

metastasis is indicative of an advanced tumor stage and demands adjuvant therapy. Results from a phase II study have advocated neoadjuvant chemotherapy combined with regional hyperthermia for locally advanced primary soft-tissue sarcomas (15). Whether or not neoadjuvant therapy improves the prognosis of a patient with suspected regional lymph node metastasis should be evaluated in prospective randomized studies.

Residual tumor after re-resection following inadequate surgery was found in 23 out of 61 patients (37.7%) in this study, a number comparable to the 45 to 49% in other studies (12, 16, 17). Since local control is mandatory for a cure, this data reinforces the demand for re-resection whenever adequate surgery is in doubt. The patients who had residual tumor in the resected tissue, had a worse survival, but the reason was unclear. Probably only those patients with a large, deep-seated tumor were referred to our institution for re-resection, thus triggering a selection bias. Our data emphasize, however, the need for an accurate diagnosis before surgery since in patients, who had received inadequate surgery, the option of a neoadjuvant therapy was no longer possible. Surgery without sufficient information on the malignancy or expansion of the tumor might be detrimental for the patient.

Since metastasis and disease-specific survival strongly depend on tumor histotype, size and malignancy grade, surgery alone cannot control the spread of the disease (5, 18-20). This is particularly true for sarcomas of high or intermediate malignancy grade. In our patients adjuvant treatment strategies were determined based on histology, staging and surgical treatment results. Randomised trials have not shown conclusively whether or not adjuvant chemotherapy is beneficial for patients with resectable STS. Doxorubicin-based adjuvant chemotherapy appears to significantly improve time to local and distant recurrence and overall recurrence-free survival in adults with localised resectable STS (21). Compartment resection whenever possible or extensive *en bloc* resection, followed by radiotherapy in the event of unclear margins and/or high grade tumour even in small sarcomas has been suggested (22) and should be performed.

In this study patients who received adjuvant chemotherapy demonstrated a worse survival, which was clearly due to a selection bias. Ongoing trials concentrating on the implementation of adjuvant therapies such as hyperthermic isolated limb perfusion or radio-hyperthermo-chemotherapy have reported promising results (23-29).

In the presented study, we were able to avoid any limb amputations. It is likely that amputations will be performed even less frequently when all sarcoma patients are seen in a center where the potential of an interdisciplinary approach for therapy is fully exploited. In order to receive the best treatment, the patient must be managed in a specialized sarcoma center. In the future, the choice of individual treatments will be based more and more on morphological and molecular findings. Before surgery, treatment options such as neoadjuvant radiation or chemotherapy, possibly combined with hyperthermia, must be considered for selected subgroups, and need to be evaluated in prospective, randomized studies.

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