Soft-tissue sarcoma of the thigh

Surgical margin influences local recurrence but not survival in 152 patients

Søren Vraa, Johnny Keller, Ole Steen Nielsen, Anne Grethe Jurik and Olaf Myhre Jensen

Center for Bone and Soft-tissue Sarcoma, University Hospital of Aarhus, DK-8000 Aarhus C, Denmark
Tel +45 8949 4114. E-mail: keller@aaa.dk. Correspondence: Dr. J Keller
Submitted 00-01-12. Accepted 00-09-20

ABSTRACT – Between 1979 and 1998, 152 patients with a soft-tissue sarcoma arising in the thigh were surgically treated in the Sarcoma Center in Aarhus, Denmark. We studied clinicopathologic factors prognostic for local recurrence and survival. 27 patients (18%) had a low-grade tumor, 26 (17%) an intermediate-grade and 99 (65%) a high-grade tumor.

27 patients (18%) were amputated and 125 (82%) had a local resection. 21 (14%) underwent a marginal resection, 82 (54%) a wide resection and 49 (32%) a compartmental resection. 32 patients were also given radiotherapy, 11 of these had a marginal resection.

The 5-year local recurrence-free rate was 91%. Multivariate analysis selected marginal resection and histological high grade as unfavorable prognostic factors for local recurrence. The 5-year survival rate was 68%. High age and histological high grade were unfavorable prognostic factors for survival in a multivariate analysis. Surgical margin influenced local recurrence, but not the overall survival.

■

Soft-tissue sarcomas are rare tumors, comprising only approximately 1% of all malignancies (Mouridsen et al. 1990). About one third of all sarcomas are located in the thigh. Numerous studies have analyzed prognostic factors concerning local control and survival (Collin et al. 1987, Alho et al. 1989, Berlin et al. 1990, Stotter et al. 1990, Gaynor et al. 1992, Gustafson 1994, Singer et al. 1994, Coindre et al. 1996, Pisters et al. 1996, Li et al. 1996, Guillou et al. 1997). Histological grade and tumor size are agreed to be of importance for survival. Radical surgery results in a better local control (Alho et al. 1989, Mandard et al. 1989, Berlin et al. 1990, Stotter et al. 1990, Gaynor et al. 1992, Coindre et al. 1996, Pisters et al. 1996), but few studies have found an improved survival in patients treated with radical surgery (Stotter et al. 1990, Singer et al. 1994, Coindre et al. 1996, Vraa et al. 1998). Most authors have included a heterogeneous group of patients with soft-tissue sarcomas located in both upper and lower extremities and the trunk wall. To analyze the effect of surgical treatment in an anatomic more homogeneous group of sarcoma patients, we included only patients with tumors arising in the thigh.

Patients and methods

The Sarcoma Center of Aarhus covers a population of about 1.5 million people. From this area, patients with extremity related sarcomas are referred and treated at the Center. All patients surgically treated for a soft-tissue sarcoma at the Center have been registered and followed since 1979. Our database consists of basal patient data, specific data on tumor characteristics regarding size, histological type and location (anatomical, compartmental and tumor depth), as well as information about the treatment. Between January 1, 1979 and January 1, 1998, 508 patients received surgical treatment for a localized, nonmetastatic soft-tissue sarcoma. Only the 152 patients (31%) presenting with a tumor in the thigh were included in the present study. There were 82 (54%) women.

Table 1. Histological types of soft-tissue sarcomas

Histological type	Number	%
MFH	44	29
Liposarcoma	37	24
Leiomyosarcoma	24	16
Fibrosarcoma	4	3
Malignant schwannoma	8	5
Synovial sarcoma	8	5
Angiosarcoma	3	2
Extraskeletal osteosarcoma	8	5
Other types	16	11
Total	152	100

The median age was 56 (range 18–87) years.

The histopathological evaluation was performed at the University Department of Pathology by the same pathologist. MFH and liposarcoma were by far the commonest types (Table 1). The histological analysis of the resected specimen determined the resection margin and the tumor grade. The surgical margin was defined, using the classification of Enneking et al. (1980a) with a subdivision of the wide margin. If tumor cells were seen at the margin, the surgery was classified as a marginal resection. A wide margin meant removal of the tumor and approximately 1 cm of normal tissue or intact fascia or periosteum. The histopathological grading was based on mitotic activity, cellularity, anaplasia and necrosis, using a three-grade scale. High-grade tumors were further subdivided into grade 3A and 3B based on the number of mitoses alone (Myhre Jensen et al. 1983, Jensen et al. 1991) (Table 2). The median tumor diameter was 8 (1–27) cm.

82 patients (54%) were referred to the Sarcoma Center without previous treatment, 19 patients (12%) were referred after a biopsy and 51 (34%) after an inadequate resection. Almost all surgery at the Center was performed by two surgeons according to the same principles. 21 patients (14%) had a marginal resection, 82 (54%) a wide resection and 49 (32%) a compartmental resection. 27 patients (18%) had an amputation, but the number of amputations has been reduced during the study. In the first third of the period, 28% of the patients were amputated, but in the last third, only 12% underwent amputations.

Table 2. Actuarial local recurrence-free rates and survival rates according to various clinical factors

Factors	No. of patients	Local recurrence-free rate 5-year	P-value	Survival rate 5-year	P-value
Age, years					
0–55	71 (47%)	0.92	0.5	0.81	<0.0001
≥ 55	81 (53%)	0.90		0.53	
Sex					
Male	70 (46%)	0.92	0.9	0.70	0.3
Female	82 (54%)	0.90		0.63	
Duration of symptoms					
≤1 year	121 (80%)	0.89	0.5	0.65	0.3
>1 year	31 (20%)	0.97		0.72	
Tumor size					
≤8 cm	78 (51%)	0.93	0.4	0.71	0.06
>8 cm	72 (49%)	0.88		0.60	
Tumor depth					
Superficial	42 (28%)	0.93	0.9	0.71	0.3
Deep	110 (72%)	0.90		0.66	
Histological grade					
Grade 1	27 (18%)	1.00	0.08	1.00	0.10
Grade 2	26 (17%)	0.88	0.9	0.91	0.02
Grade 3A	47 (31%)	0.93	0.1	0.62	0.01
Grade 3B [b]	52 (34%)	0.83		0.39	
Compartmentalization					
Intra	117 (77%)	0.91		0.71	
Extra	35 (23%)	0.90		0.57	
Surgical treatment					
Local excision	125 (82%)	0.89	0.1	0.72	0.004
Amputation	27 (18%)	1.00		0.45	
Surgical margin					
Marginal	21 (14%)	0.79	0.02	0.60	0.6
Wide	82 (54%)	0.95	0.08	0.73	0.06
Compartmental	49 (32%)	0.89		0.59	
Local recurrence					
Yes	14 (9%)			0.43	0.04
No	138 (91%)			0.72	

[a] Data missing for 2 patients.
[b] Including 9 patients with a high-grade tumor not otherwise specified.

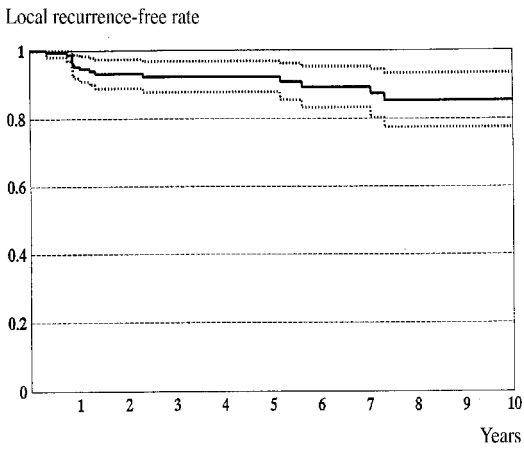

Figure 1. Soft-tissue sarcoma. Local recurrence-free rate of 152 patients with sarcomas in the thigh. 95% confidence intervals.

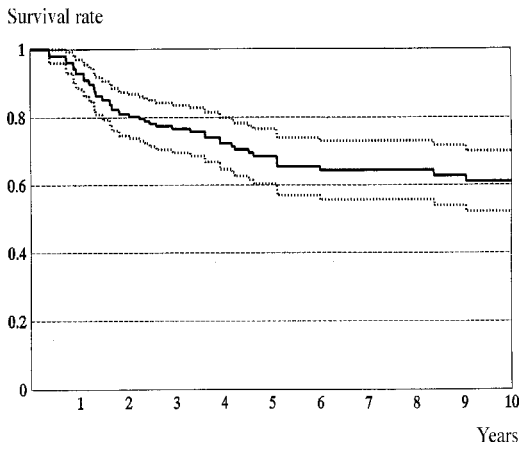

Figure 2. Soft-tissue sarcoma. Survival rate of 152 patients with sarcomas in the thigh. 95% confidence intervals

32 patients received adjuvant radiotherapy, 19 preoperatively and 13 postoperatively. Adjuvant radiotherapy was given to 11 of the marginally-treated patients, 17 treated with a wide margin and 4 who underwent compartmental surgery. Most patients received a total dose of 50 Gy in 25 fractions. 4 patients (3%) had adjuvant chemotherapy.

Patients were usually seen regularly up to 10 years after primary treatment. In this study, they were followed until January 2000 or until they died. The minimum follow-up period was 24 months or until death (median 52 months for all patients, 81 months for survivors). Only 2 patients were followed less than 3 years. A physical examination and chest radiographs were performed in patients with grades 2 and 3 tumors at every follow-up visit.

Statistics

Local recurrence and survival rates were estimated with the Kaplan-Meier method. To evaluate the significance of individual factors, the log-rank test was used. The possible prognostic factors were included in a Cox proportional hazards model for multivariate analysis.

Results

Univariate analysis

14 patients (9%) developed a local recurrence. All patients but 1 had the recurrence surgically removed and 5 patients received adjuvant radiotherapy. The patients with local recurrence had a significantly poorer survival than those without local recurrence.

49 patients developed distant metastases, of whom 32 had lung metastases, 9 other metastases (primarily bone metastases) and 8 both lung metastases and other types. The metastases were diagnosed at a median of 10 (2–104) months after the primary surgery. 43 of the 49 patients with distant metastases died because of tumor, 5 are still alive and 1 patient died of another disease.

50 patients had a tumor-related death (following treatment, due to tumor or metastases or from an intercurrent disease with tumor or metastases), 17 patients died of other causes, with no signs of tumor.

Using univariate analysis, the local recurrence risk was associated with the surgical margin (marginal vs wide) and the survival rate to age, histological grade, compartmentalization, surgical treatment (local excision vs amputation) and local recurrence (Table 2).

Multivariate analysis

The 5-year local control was 91% (Figure 1). Using multivariate analysis, surgical margin and the histological grade were found to be independent prognostic factors for local recurrence (Table 3).

The 5- and 10-year survival rates were 67% and

Table 3. Multivariate analysis of unfavorable prognostic factors for local control and survival

	Local recurrence			Survival		
Factors	RR	95% CI	P-value	RR	95% CI	P-value
High-grade	2	1.0–4	0.04	3	2–4.6	<0.001
Marginal resection	11	1.2–8.9	0.04	1	0.4–2	0.8
High age (≥ 55 years)	1	0.98–1.0	0.5	3	1.4–6	0.002

RR risk ratio, CI confidence interval.

62%, respectively (Figure 2). Multivariate analysis selected age and histological grade as independent prognostic factors for survival (Table 3). The multivariate analysis was also performed in a selected group consisting of 99 patients with a high-grade tumor (3A and 3B). This analysis selected the surgical margin as the only prognostic factor for local control. Age and histological grade were selected as prognostic factors for survival.

Discussion

We analyzed prognostic factors for local recurrence and survival in 152 patients with soft-tissue sarcoma located in the thigh. Most previous studies have included patients with sarcoma located in both extremities and the trunk wall. To our knowledge very few studies have selected patients with tumor present only in the thigh (Enneking et al. 1981, Karakousis et al. 1998).

The 5-year survival rate in our study was 67%. In a similar study (Karakousis et al. 1998) which included only thigh sarcomas, the 5-year survival rate was 66%. Studies including sarcoma patients in general had better survival rates (Tsujimoto et al. 1988, Ueda et al. 1988, Pisters et al. 1996). We have previously shown (Vraa et al. 1998) that patients with soft-tissue sarcomas in the lower extremities had the worst prognosis. Pisters et al. (1996) found a worse prognosis for patients with tumors in the thigh. Many deep-seated sarcomas in the thigh are not detected for a longer time than tumors in, e.g., the upper extremity, and therefore they are usually larger and may have had a greater risk of dissemination. The histogical grade is generally agreed to be the most significant prognostic factor for survival and our study confirms this. Similar to some studies (LeVay et al. 1993, Coindre et al. 1996), we also found histological grading to be a prognostic factor for local recurrence, but this has not been confirmed by others (Stotter et al. 1990, Gaynor et al. 1992). Many studies (Stotter et al. 1990, Berlin et al. 1990, Gaynor et al. 1992, Coindre et al. 1996), including ours have not found tumor size important for local control. Most (Collin et al. 1987, Mandard et al. 1989, Stotter et al. 1990, Gaynor et al. 1992, Gustafson 1994, Singer et al. 1994, Coindre et al. 1996, Li et al. 1996, Pisters et al. 1996, Vraa et al. 1998) have shown tumor size to be a prognostic factor for survival, but our study did not confirm this. The reason could be that deep-seated thigh tumors are usually larger than extremity and trunk wall sarcomas. Thigh tumors in our database are, on the average, 10 cm in diameter while tumors in other anatomic sites measure 6 cm. We found high age to be an unfavorable prognostic factor for survival. This has also been reported by others (Collin et al. 1987, Berlin et al. 1990, Gustafson 1994, Singer et al. 1994, Li et al. 1996, Guillou et al. 1997), but not noted in a number of studies (Stotter et al. 1990, Gaynor et al. 1992, Coindre et al. 1996, Pisters et al. 1996).

The 5-year local recurrence risk was 9%, which is low (Lindberg et al. 1981, Berlin et al. 1990, LeVay et al. 1993, Pisters et al. 1996). Like most others (Alho et al. 1989, Mandard et al. 1989, Berlin et al. 1990, Stotter et al. 1990, Gaynor et al. 1992, Coindre et al. 1996, Pisters et al. 1996), we found a lower local recurrence rate in patients treated with a wide surgical margin than in those treated with a marginal resection. In the literature, a wide margin is simply defined as an en bloc excision with a margin of normal tissue around the tumor removed (Enneking et al. 1980a, b). How-

ever, the separation between marginal and wide is based on several qualitative judgments. The reactive zone is not well defined. The risk of local spread may be related to the type of tissue, localization, distance and type of sarcoma. The distance must be based on a peroperative assumption, since the soft tissue will retract after removal of the tumor. Due to these problems with definition of the surgical margin, it is difficult to compare the effect of the surgical margin on local recurrence and survival. An intact fascia, periosteum or a normal tissue cuff of minimum 1 cm (peroperative judgment) may be a more precise definition of a wide excision.

We included only patients with tumors in the thigh, because we aimed to investigate the importance of the surgical procedure in a possibly more homogeneous anatomical area. Despite this, we found no significant improvement in survival among patients treated with radical surgery than in those treated with wide surgery or among patients treated with wide surgery compared to marginal surgery. To exclude bias from other factors, we also analyzed a subgroup of patients with high-grade tumors, but again without finding that the surgical margin significantly improved the overall survival. Other studies (Collin et al. 1987, Mandard et al. 1989, Li et al. 1996, Pisters et al. 1996) have shown a connection between surgical margin and survival, but many others have not confirmed this (Stotter et al. 1990, Singer et al. 1994, Coindre et al. 1996).

Supported by grants from the Clinical Research Unit of the Danish Cancer Society, Department of Oncology, Aarhus University Hospital.

Alho A, Alvegard T A, Berlin O, Ranstam J, Rydholm A, Rooser B Stener B. Surgical margin in soft tissue sarcoma. The Scandinavian Sarcoma Group experience. Acta Orthop Scand 1989; 60: 687-92.

Berlin O, Stener B, Angervall L, Kindblom L G, Markhede G, Oden A. Surgery for soft tissue sarcoma in the extremities. A multivariate analysis of 6-26-year prognosis in 137 patients. Acta Orthop Scand 1990; 61: 475-86.

Coindre J M, Terrier P, Bui N B, Bonichon F, Collin F, Le Doussal V, Mandard A M, Vilain M O, Jacquemier J, Duplay H, Sastre X, Barlier C, Henry Amar M, Mace Lesech J, Contesso G. Prognostic factors in adult patients with locally-controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol 1996; 14: 869-77.

Collin C, Godbold J, Hajdu S, Brennan M. Localized extremity soft tissue sarcoma: an analysis of factors affecting survival. J Clin Oncol 1987; 5: 601-12.

Enneking W F, Spanier S S, Goodman M A. Current concepts review. The surgical staging of musculoskeletal sarcoma. J Bone Joint Surg (Am) 1980a; 62: 1027-30.

Enneking W F, Spanier S S Goodman M A. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980b; 153: 106-20.

Enneking W F, Spanier S S, Malawer M M. The effect of the anatomic setting on the results of surgical procedures for soft parts sarcoma of the thigh. Cancer 1981; 47: 1005-22.

Gaynor J J, Tan C C, Casper E S, Collin C F, Friedrich C, Shiu M, Hajdu S I, Brennan M F. Refinement of clinicopathologic staging for localized soft tissue sarcoma of the extremity: a study of 423 adults. J Clin Oncol 1992; 10: 1317-29.

Guillou L, Coindre J M, Bonichon F, Bui N B, Terrier P, Collin F, Vilain M O, Mandard A M, Doussal V L, Leroux A, Jacquemier J, Duplay H, Sastre-Garau X, Costa J. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 1997; 15 (1): 350-62.

Gustafson P. Soft tissue sarcoma. Epidemiology and prognosis in 508 patients. Acta Orthop Scand (Suppl 259) 1994; 65: 1-31.

Jensen O M, Hogh J, Ostgaard S E, Nordentoft A M, Sneppen O. Histopathological grading of soft tissue tumours. Prognostic significance in a prospective study of 278 consecutive cases. J Pathol 1991; 163: 19-24.

Karakousis C P, Kontzoglou K, Driscoll D L. Anterior compartment resection of the thigh in soft-tissue sarcomas. Eur J Surg Oncol 1998; 24: 308-12.

LeVay J, O'Sullivan B, Catton C, Bell R, Fornasier V, Cummings B, Hao Y, Warr D, Quirt I. Outcome and prognostic factors in soft tissue sarcoma in the adult. Int J Radiat Oncol Biol Phys 1993; 27: 1091-9.

Li X Q, Parketh S G, Rosenberg A E, Mankin H J. Assessing prognosis for high-grade soft-tissue sarcomas: search for a marker. Ann Surg Oncol 1996; 3 (6): 550-7.

Lindberg R D, Martin R G, Romsdahl M M, Barkley H T J. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer 1981; 47: 2391-7.

Mandard A M, Petiot J F, Marnay J, Mandard J C, Chasle J, de Ranieri E, Dupin P, Herlin P, de Ranieri J, Tanguy A, Boulier N, Abbatucci J S. Prognostic factors in soft tissue sarcomas. A multivariate analysis of 109 cases. Cancer 1989; 63: 1437-51.

Mouridsen H T, Dombernowsky P, Jensen O M, Johansen H, Lund B, Nordentoft A, Poulsen H S, Schiodt T, Sneppen O. Sarcoma treatment in Denmark. Ugeskr Laeger 1990; 152: 989-92.

Myhre Jensen O, Kaae S, Madsen E H, Sneppen O. Histopathological grading in soft-tissue tumours. Relation to survival in 261 surgically-treated patients. Acta Pathol Microbiol Immunol Scand A 1983; 91: 145-50.

Pisters P W, Leung D H, Woodruff J, Shi W, Brennan M F. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996; 14: 1679-89.

Singer S, Corson J M, Gonin R, Labow B, Eberlein T J. Prognostic factors predictive of survival and local recurrence for extremity soft tissue sarcoma. Ann Surg 1994; 219: 165-73.

Stotter A T, A'Hern R P, Fisher C, Mott A F, Fallowfield M E, Westbury G. The influence of local recurrence of extremity soft tissue sarcoma on metastasis and survival. Cancer 1990; 65: 1119-29.

Tsujimoto M, Aozasa K, Ueda T, Morimura Y, Komatsubara Y, Doi T. Multivariate analysis for histologic prognostic factors in soft tissue sarcomas. Cancer 1988; 62: 994-8.

Ueda T, Aozasa K, Tsujimoto M, Hamada H, Hayashi H, Ono K, Matsumoto K. Multivariate analysis for clinical prognostic factors in 163 patients with soft tissue sarcoma. Cancer 1988; 62: 1444-50.

Vraa S, Keller J, Nielsen O S, Sneppen O, Jurik A G, Jensen O M. Prognostic factors in soft tissue sarcomas: the Aarhus experience. Eur J Cancer 1998; 34 (12): 1876-82.