Pergamon

European Journal of Cancer, Vol. 35, No. 12, pp. 1705–1710, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00152-5

Original Paper

Epidemiological Aspects of Soft Tissue Sarcomas (STS)—Consequences for the Design of Clinical STS Trials*

P.H.A. Nijhuis,[1] M. Schaapveld,[2] R. Otter,[2] W.M. Molenaar,[3] W.T.A. van der Graaf[4] and H.J. Hoekstra[1]

[1]Department of Surgical Oncology, Groningen University Hospital, P.O. Box 30.001, 9700 RB Groningen; [2]Comprehensive Cancer Center North-Netherlands (CCCN); [3]Department of Pathology; and [4]Department of Medical Oncology, Groningen University Hospital, Groningen, The Netherlands

The purpose of the study was to gain insight into epidemiological aspects of soft tissue sarcomas (STS), based on the population-based cancer registry of the Comprehensive Cancer Center North-Netherlands (CCCN), and to provide data for the development of future STS clinical trials. 456 primary STS (Kaposi, urogenital and gastro-intestinal STS excluded), registered from 1989 to 1995 by the cancer registration of the Comprehensive Cancer Center North-Netherlands (CCCN), were analysed. The annual, age-adjusted, STS incidence was 3.6 per 100 000. Incidence increased with age. Half of the patients were over the age of 65 years. Malignant fibrous histiocytomas and liposarcomas were most frequently encountered. At presentation, nodal involvement was rare (3–8%). Distant metastases were more frequently encountered (9–14%), and appeared to be related to tumour size and site. Above 70 years of age, 16% of patients received no treatment at all, especially for metastatic disease. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: soft tissue sarcoma, sarcoma, incidence, histology, cancer registry, metastases
Eur J Cancer, Vol. 35, No. 12, pp. 1705–1710, 1999

INTRODUCTION

SOFT TISSUE sarcomas (STS) are relatively rare tumours of different mesenchymal derivation, which account for less than 1% of all cancers in adults, and for approximately 7% of all childhood malignancies [1–3]. In adults the most common histological types are liposarcomas (21%), malignant fibrous histiocytomas (MFH) (20%), leiomyosarcomas (20%), fibrosarcomas (11%), and tendosynovial sarcomas (10%) [4]. In children, 70% of all STS are rhabdomyosarcomas, and in 20% of the remaining non-rhabdomyosarcomas the histological subtype remains unclassified [2, 3].

Tumour size, histology, primary site, grade, and the presence of metastatic disease appear to be the most important prognostic factors in the treatment of STS [4]. Only a few descriptive epidemiological studies on STS have been published in recent years [4–10].

Correspondence to H.J. Hoekstra, e-mail: h.j.hoekstra@chir.azg.nl
Received 6 Jul. 1998; revised 31 May 1999; accepted 20 Jun. 1999.
*Presented at the joint meeting of the SSO and WFSOS, 25–29 March 1998, San Diego, U.S.A.

PATIENTS AND METHODS

For a 6-year period (1989–1995), data on the incidence of primary STS were derived from the population-based cancer registry of the CCCN, which covers an area of 2.1 million inhabitants. Cancer registration at the CCCN started in 1986, but full coverage of the whole area encompassed by the CCCN was only achieved from 1 January 1989. The main sources for the CCCN cancer registry are the computerised pathology databank (PALGA) of the nine pathology laboratories within the CCCN area. Another important source in the CCCN area is the hospital discharge databank to which the 19 hospitals annually provide information on all discharge diagnoses of admitted patients. Specially trained CCCN members register the data from the patients' clinical records. Completeness of records, data consistency and the possibility of duplicate records are continously and extensively checked. Based on the outcomes of studies on the completeness of the cancer registry databanks in other regional cancer registries in The Netherlands which operate on the same basis, the overall completeness of the cancer registry databank is estimated to be approximately 95% [11, 12].

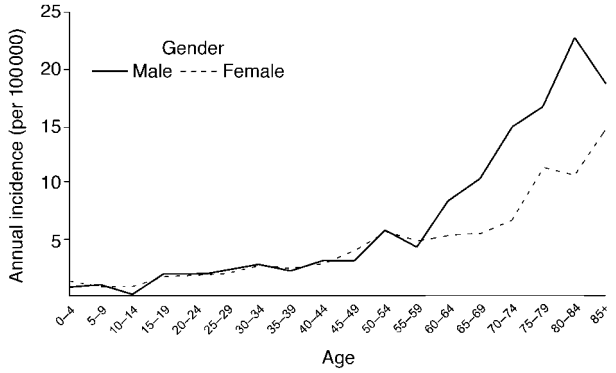

Figure 1. Incidence of soft tissue sarcomas according to age and gender.

Table 1. *Distribution of STS according to localisation and gender*

Localisation	Total *n* (%)	Male *n* (%)	Female *n* (%)
Head and neck	60 (13)	36 (15)	24 (11)
Upper limb and shoulder	70 (15)	45 (19)	25 (12)
Thorax	48 (11)	22 (9)	26 (12)
Abdomen	56 (12)	24 (10)	32 (15)
Trunk	10 (2)	4 (2)	6 (3)
(Retro)peritoneum	38 (8)	19 (8)	19 (9)
Pelvis	33 (7)	19 (8)	14 (6)
Lower limb and hip	133 (29)	64 (27)	69 (32)
Overlapping sites and NOS	8 (2)	6 (3)	2 (1)
Total	456 (100)	239 (100)	217 (100)

NOS, No other specification.

In this study, information on primary STS was used, with the exception of Kaposi sarcomas, urogenital and gastro-intestinal STS, thus encompassing ICD-O codes 171.0–171.9, 173.0–173.9, 174.0–174.9, and 158.0 for topography and ICD-O codes 8800–8933, 8963, 8990–8991, 9020–9044, 9120–9134, 9141–9340 and 9540–9581 for morphology.

For calculation of crude and age-specific incidence rates, the population structure of the CCCN area on 1 January 1992 was used. Age-adjusted rates were calculated using the European Standard Population [13]. Differences in histology, tumour size, number of patients presenting with regional or distant metastasis at time of diagnosis and primary treatment received were analysed according to anatomical subsite and/or gender using the Chi-square test.

Tumours were staged according to UICC Tumour Node Metastasis (TNM) Classification [14]. For pathological TNM classification, histological confirmation was required. For clinical TNM classification, a set of minimal requirements was used to determine a clinical tumour (cT), clinical node (cN) and clinical metastases (cM). For cT and cN, physical examination, ultrasonography, computed tomography (CT)-scan or magnetic resonance imaging (MRI) were required. To determine cM, physical examination, plain chest X-ray and determination of liver function tests were minimal requirements. Where no TNM classification was available (STS of skin and breast) or TNM classification was incomplete, the extent of disease (EoD), from clinical and/or pathological information from the patients' medical records, was used. Surgery, as described below, included different types of primary tumour resection, but excluded incisional biopsy.

RESULTS

From 1 January 1989 until 1 January 1995, 456 new primary STS (Kaposi sarcomas ($n = 32$), urogenital ($n = 79$) and gastro-intestinal STS ($n = 59$) excluded) were registered by the CCCN cancer registry. Of these STS, 239 were diagnosed in males (52%) and 217 in females (48%). At initial diagnosis, 225 (49%) patients were aged between 50 and 74 years (49%), 118 (26%) between 25 and 49 years, 53 (12%) were younger than 25 years and 60 (13%) were $\geq$75 years. Figure 1 shows, for both sexes, the incidence of STS according to age. The incidence of STS was 3.6/100 000/year (age-adjusted). For males and females these figures were 4.0/100 000/year and 3.2/100 000/year, respectively. The incidence of STS strongly increased with age.

Table 1 presents the distribution of STS according to anatomical site and gender. Most STS were situated in the

Table 2. *Distribution of STS according to histology and gender*

Morphology	Total *n* (%)	Male *n* (%)	Female *n* (%)
MFH (ICD 8830)	83 (18)	48 (20)	35 (16)
Liposarcoma (ICD 885)	82 (18)	44 (18)	38 (18)
Leiomyosarcoma (ICD 889)	70 (15)	34 (14)	36 (17)
Rhabdomyosarcoma (ICD 890)	23 (5)	11 (5)	12 (6)
Dermatofibrosarcoma (ICD 8832)	65 (14)	32 (13)	33 (15)
Fibrosarcoma (ICD 881)	30 (7)	18 (8)	12 (6)
Hemangiosarcoma (ICD 912, 913, 915)	9 (2)	5 (2)	4 (2)
Other sarcoma	94 (21)	47 (20)	47 (22)
Sarcoma NOS (ICD 880)	34 (7)	18 (8)	16 (7)
Phyllodes tumour (ICD 9020)	11 (2)	–	11 (5)
Synovial sarcoma (ICD 904)	17 (4)	11 (5)	6 (3)
Clear cell sarcoma (ICD 9044)	2 (0.5)	2 (1)	–
Mesenchymal chondrosarcoma (ICD 9240)	3 (1)	3 (1)	–
Malignant giant cell tumour of soft parts (ICD 9251)	5 (1)	3 (1)	2 (1)
Ewing's sarcoma (ICD 9260)	3 (1)	2 (1)	1 (0.5)
Malignant peripheral nerve sheath tumour (ICD 9540 + 9560)	17 (4)	8 (3)	9 (4)
Alveolar soft part sarcoma (ICD 9581)	2 (0.5)	–	2 (1)
Total	456 (100)	239 (100)	217 (100)

MFH, malignant fibrous histiocytoma.

extremities ($n = 203$, 45%), especially the lower limb and hip region ($n = 133$, 29%). Gender differences in distribution according to anatomical site were small and statistically non-significant.

The most common histological tumour types were MFH and liposarcoma (both 18%), followed by leiomyosarcoma (15%), dermatofibrosarcoma (14%), fibrosarcoma (7%), and rhabdomyosarcoma (5%) (Table 2). The distribution of histological tumour types varied for the various primary anatomical sites. The most striking differences were a high incidence of leiomyosarcomas in the retroperitoneum (20/38), and a high incidence of MFH in the lower limb (33/118).

The occurrence of the histological subtypes was age-dependent (Figure 2). Rhabdomyosarcomas were most frequently diagnosed in children and adolescents (Figure 2d), whereas leiomyosarcomas were not seen in the juvenile group, but were frequently encountered in the elderly (Figure 2c). The incidence of the most frequent STS (MFH and liposarcomas) increased with age (Figures 2a,b).

The distribution of T, N, and M stage is presented in Table 3. Skin and breast STS ($n = 88$) were excluded, since no TNM classification applies to these tumours. Overall, 33% of the patients presented with a T1-tumour, 48% with a T2-tumour, whereas in the remaining 19% T-stage was unknown. Notwithstanding the existence of staging guidelines in the CCCN region [15], the presence or absence of lymph node involvement was unknown in 210 patients (57%). 12 of 158 patients with a documented N-stage (8%) had lymph node metastases at initial presentation. However, using a 'best-case-scenario', in which all unknown N-stages are to be considered as node-negative, the overall incidence of nodal involvement would be 3%.

Table 3. TNM-distribution (STS of skin and breast excluded) ($n = 368$)

	n (%)
T-stage	
T1	121 (33)
T2	177 (48)
Unknown	70 (19)
N-stage	
N –	146 (40)
N +	12 (3)
Unknown	210 (57)
M stage	
M –	205 (56)
M +	34 (9)
Unknown	129 (35)

5 patients had both lymph node involvement and distant metastases at presentation.

The M-stage was not recorded in 129 patients (35%). At presentation, 34 of 239 patients (14%) with documented M-stage had distant metastases. Using the 'best-case-scenario', the overall incidence of distant metastatic disease would be 9%. 5 patients (1%) had both lymph node and distant metastases.

Lymph node involvement was not related to tumour size (T1: 3.3%, T2: 3.4%, unknown T-stage: 1.4%). Distant metastases, however, were significantly related to T-stage ($P < 0.01$; Table 4). Five per cent (4/83) of patients with a T1-tumour and a documented M-stage had distant metastases at presentation, in contrast to 17% (23/136) of patients with a T2-tumour and a documented M-stage.

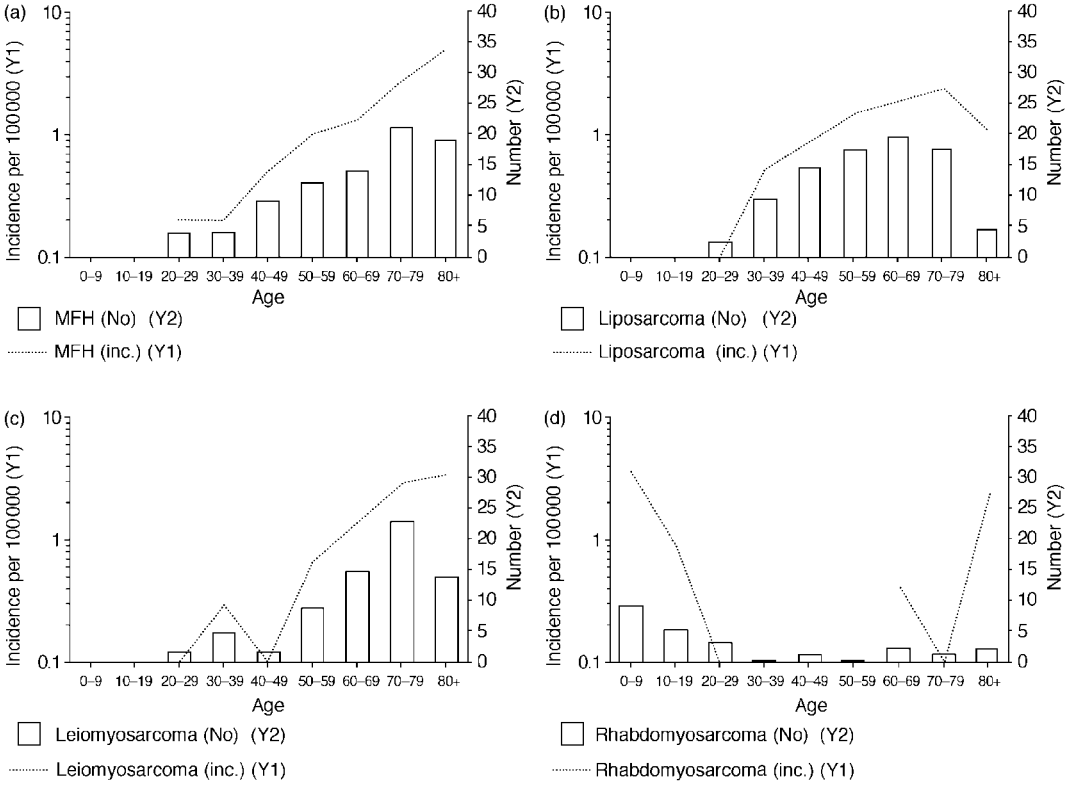

Figure 2. Histological distribution of soft tissue sarcomas according to age.

Table 4. Tumour size and distant metastases (STS of skin and breast excluded)

T-stage	M – *n* (%)	M + *n* (%)	M-unknown *n* (%)
T1 (*n* = 121)	79 (65)	4 (3)	38 (31)
T2 (*n* = 177)	113 (64)	23 (13)	41 (23)
unknown (*n* = 70)	13 (19)	7 (10)	50 (71)

A site-specific description of TNM classification is presented in Table 5. 27 (75%) of documented head/neck STS were T1-tumours, whereas all documented retroperitoneal STS (*n* = 31) were T2-tumours. There was no site-specific difference in lymph node involvement, in contrast to distant metastases, which were encountered in 21% of retroperitoneal STS, 14% of lower limb and hip STS, but were absent in head/neck STS. Tumour grade was documented in only 104 patients (23%).

Table 6 and 7 present the initial treatment according to the extent of disease, for all 456 patients, and for patients under 20 years of age, respectively. Overall, 371 patients (81%) received surgical treatment, 42 patients (9%) were non-surgically treated, and 43 patients (9%) received no treatment at all. The proportion of patients that received no treatment was 3% in children and adolescents (≤20 years), 7% in those aged 21–69 years, and 16% in patients above 70 years.

DISCUSSION

There are only a few epidemiological reports on STS, which are not centred-based [5–10]. The CCCN registry used in this study is population based, that is it contains information about all patients diagnosed and treated in a defined area. One of the major advantages of a population-based registry is the avoidance of selection bias, caused by referral to specialised centres.

The annual incidence of STS (Kaposi sarcomas, urogenital and gastrointestinal STS excluded) was 3.6 per 100 000

Table 5. TNM-stage and localisation (STS of skin and breast excluded)

Localisation	T1 *n* (%)	T2 *n* (%)	N + * *n* (%)	M + † *n* (%)	T-unknown *n* (%)	N-unknown *n* (%)	M-unknown *n* (%)
Head/neck (*n* = 60)	27 (45)	9 (15)	2 (10)	0	24 (40)	39 (65)	35 (58)
Upper limb/shoulder (*n* = 70)	26 (37)	14 (20)	2 (9)	1 (3)	30 (43)	48 (69)	40 (57)
Trunk (*n* = 10)	4 (40)	5 (50)	0	2 (22)	1 (10)	7 (70)	1 (10)
(Retro)peritoneum (*n* = 38)	0	31 (82)	0	5 (21)	7 (18)	28 (74)	14 (37)
Lower limb/hip (*n* = 133)	40 (30)	66 (50)	5 (7)	13 (14)	27 (20)	65 (49)	40 (30)

*Rate of lymph node metastases in patients with a documented N-stage. †Rate of distant metastases in patients with a documented M-stage.

Table 6. Primary treatment of STS according to extent of disease (EoD)

		Localised disease		Regional metastases		Distant metastases		EoD unknown	
	Total	0–69 yrs	70 + yrs	0-69 yrs	70 + yrs	0–69 yrs	70 + yrs	0–69 yrs	70 + yrs
Treatment	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Surgery	262 (57)	155 (62)	78 (64)	2 (33)	1 (50)	6 (22)	–	14 (54)	6 (38)
Surgery + radiotherapy	82 (18)	53 (21)	25 (21)	–	–	–	–	4 (15)	–
Surgery + chemotherapy	18 (4)	8 (3)	4 (3)	1 (17)	–	5 (19)	–	–	–
Surgery + radiotherapy + chemotherapy	9 (2)	9 (4)	–	–	–	–	–	–	–
Radiotherapy	12 (3)	2 (1)	5 (4)	–	1 (50)	2 (7)	1 (13)	1 (4)	–
Chemotherapy	23 (5)	8 (3)	1 (1)	3 (50)	–	7 (26)	2 (25)	2 (8)	–
Radiotherapy + chemotherapy	7 (2)	4 (2)	–	–	–	3 (11)	–	–	–
No treatment	43 (9)	10 (4)	9 (7)	–	–	4 (15)	5 (63)	5 (19)	10 (63)
Total	456 (100)	249 (100)	122 (100)	6 (100)	2 (100)	27 (100)	8 (100)	26 (100)	16 (100)

Table 7. Primary treatment of STS according to extent of disease (EoD) in children and adolescents

Treatment	Total *n* (%)	Localised disease *n* (%)	Regional metastases *n* (%)	Distant metastases *n* (%)	EoD unknown *n* (%)
Surgery	14 (41)	11 (48)	–	–	3 (75)
Surgery + radiotherapy	3 (9)	3 (13)	–	–	–
Surgery + chemotherapy	3 (9)	2 (9)	–	1 (25)	–
Surgery + radiotherapy + chemotherapy	–	–	–	–	–
Radiotherapy	–	–	–	–	–
Chemotherapy	7 (21)	2 (9)	3 (100)	1 (25)	1 (25)
Radiotherapy + chemotherapy	6 (18)	4 (17)	–	2 (50)	–
No treatment	1 (3)	1 (4)	–	–	–
Total	34 (100)	23 (100)	3 (100)	4 (100)	4 (100)

inhabitants, demonstrating the rarity of these tumours. In accordance with other reports, there was a slight male predominance [6, 7, 16]. Nearly half of our patients were older than 65 years ($n = 187$), with the highest age-specific rates seen in patients over the age of 70 years, indicating that most sarcomas are tumours of the elderly (Figure 1). Most STS (45%) were located at the extremities, predominantly the lower extremity and hip region (29%). Similar findings have been published by Pollock and colleagues [10]. A higher rate of limb STS (59.5%) was reported by Lawrence and colleagues [17], but in his nationwide, multicentre study, anatomical sites such as bone, lymphoid organs and lymph nodes, viscera and the central nervous system were excluded. Moreover, the study was centre-based, which might have led to selection bias.

As reported by others [4, 6, 9, 10, 18], the most common histological types in our study were MFH and liposarcoma (both 18%). Other histological types conformed more or less to modern reports [4, 7, 9]. However, in the Swedish population-based Cancer Registry, Gustafson [6] encountered more MFH (41%) and less liposarcomas (10%). In the latter registry, only STS of limb and trunk wall were included, whereas dermatofibrosarcomas were excluded.

The most obvious age differences in histogenetics were the higher incidence of rhabdomyosarcomas in children and adolescents, and the absence of leiomyosarcomas in this age group. During childhood and adolescence, the frequency of rhabdomyosarcomas is equal to or greater than that of the other types of STS combined [19]. In the current series, 14 out of 34 juvenile STS were rhabdomyosarcomas. As rhabdomyosarcomas are very rare tumours beyond adolescence, the registration of rhabdomyosarcomas at middle and late age (Figure 2d) might have been caused by misdiagnosis. The other histological types showed an increasing incidence with increasing age (Figure 2a–c), as demonstrated by others [9].

The relationship between tumour site and tumour size can be explained by the fact that palpation of relatively small tumours is easier in the head/neck region than in the retroperitoneum and lower extremity. Most reports on STS of the retroperitoneum and (especially the upper part of the) lower extremity confirm the high incidence of large tumours at presentation [6, 20, 21].

At initial presentation, the rate of lymph node involvement in STS appears to be between 3 and 8%. With regard to lymph node metastasis, the 'best-case-scenario' seems valid because many pathological reports tend not to mention normal findings, and because the STS types that were encountered most frequently are rarely associated with nodal involvement at initial presentation [4, 6, 18, 22, 23], whereas relatively rare STS, such as epithelioid sarcomas, angiosarcomas, synovial sarcomas and rhabdomyosarcomas, have a higher incidence of early lymph node involvement [4, 17, 23].

Fourteen per cent of patients with a documented M-stage had distant metastases at initial presentation. With regard to distant metastatic disease, the 'best-case-scenario' seems less reliable, as reported data show a relatively high incidence of distant metastases at presentation (7–25%) [4, 6, 18, 20, 22]. Nevertheless, it is very difficult to compare these data. The best comparable data come from the population-based study of Gustafson, who reported 13% distant metastases at initial presentation [6]. In a nationwide multicentre survey, Lawrence and colleagues encountered 23% distant metastatic disease at initial presentation [18]. However, they also used a 'best-case-scenario', as in 49% of the patients the M-stage was unknown. Other, centre-based series, reported 25% distant metastases at initial presentation, but these series mainly comprised STS of the lower extremity [20], or included visceral STS [4], both of which are associated with a much larger tumour size, and a higher frequency of metastatic disease. The lowest reported incidence was from a centre-based study by Gaakeer and coworkers, who encountered distant metastases in 12 of 183 patients (7%) [22]. However, as 80% of their patients were referred after initial surgery in another hospital, this figure seems to be selection-biased.

The most obvious treatment differences were found between children and adolescents ($\leq$20 years) and patients aged above 70 years. In contrast to localised disease, where no treatment difference was demonstrated, treatment in (regional and/or distant) metastatic disease was different between both age groups. In case of metastatic disease, at least 50% of the older patients were not treated at all and only 20% received some form of chemotherapy, in contrast to the young patients, who were all treated with, at least, chemotherapy.

One of the major contributing factors is the age difference in histogenetics, especially the higher incidence of rhabdomyosarcomas in children and adolescents, tumours which are relatively highly radio- and chemosensitive. Also, in the elderly, their general health is often weakened due to increasing co-morbidity, thus increasing the risk of morbidity and mortality following treatment. Only 5% of patients aged over 70 years received chemotherapy, in contrast to 12% of patients aged of 21–69 years and 47% in children and adolescents. Many chemotherapeutic (doxorubicin- and/or ifosfamide-based) STS treatment protocols exclude patients over the age of 65–70 years. In this study, no less than 33% of all patients was older than 70 years, 41% of which was even older than 80 years. Another contributing factor is the anatomical site of the tumour at initial presentation. By far the highest age-specific incidence of STS of trunk, lower extremities and retroperitoneum is encountered in patients aged above 70 years (9, 6, and 3/100 000, respectively). Tumours at these anatomical sites are known to be large at presentation, and are associated with a higher incidence of metastatic disease [4, 20, 21]. Moreover, their size and specific location at presentation often makes radical tumour excision difficult or even impossible [21]. Especially in retroperitoneal STS, radical surgical excision often necessitates removal of adjacent organs such as kidneys (25–70%), colon (20–25%), adrenals (12–25%) or pancreas (8%), and in rare cases even segmental resection of major vessels, exenterations or hemipelvectomy [21]. Most of the older patients with a retroperitoneal sarcoma are not candidates for this kind of extended surgical resection, although current improvements in anaesthetic techniques and intensive care treatment have decreased treatment-related morbidity and mortality. In the present study, the influence of primary tumour site on treatment regimen was obvious in patients over the age of 70 years. When the STS was situated in the retroperitoneum, no less than 44% of these patients received no treatment at all, in contrast to 18% for trunk STS, 14% for lower extremity STS, 8% for upper extremity STS, and 3% for head–neck STS.

Data on STS, derived from this population-based cancer registry, revealed interesting aspects that may be important for the design of future clinical trials on STS. Sarcomas are rare tumours, with an annual incidence of 3.6/100 000,

increasing with age. At initial presentation, lymph node involvement is rare (3–8%), whereas distant metastases are encountered more frequently (9–14%). As it is extremely difficult to attain a final diagnosis, even by experienced pathologists [8], and as STS staging generally is not well performed, notwithstanding staging guidelines, centralisation of STS diagnosis and staging seems advisable. As most of the progress in STS treatment is to be expected from multi-modality treatment protocols, it is important to realise that nearly half of the patients with a newly diagnosed STS are over the age of 65 years. These patients should receive an extensive work-up and a tailored treatment, according to primary tumour site, extent of disease, and co-morbidity, in order to improve overall survival and quality of life [24].

1. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics 1998. *CA Cancer J Clin* 1998, **48**, 6–29.
2. Marina NM, Krance R, Ribeiro RC, Crist WM. Diagnosis and treatment of the most common solid tumours in childhood. *Primary Care* 1992, **19**, 871–889.
3. Flamant F, Habrand J-L, Lacombe MJ, Revillon Y. Malignant mesenchymal tumours in childhood. In Peckham M, Pinedo HM, Veronesi U, eds. *Oxford Textbook of Oncology*. Oxford, Oxford University Press, 1995, 1939–1953.
4. Torosian MH, Friedrich C, Godbold J, Hajdu SI, Brennan F. Soft-tissue sarcoma: initial characteristics and prognostic factors in patients with and without metastatic disease. *Semin Surg Oncol* 1988, **4**, 13–19.
5. Clemente C, Orazi A, Rilke F. The Italian registry of soft-tissue tumours. *Appl Pathol* 1988, **6**, 221–240.
6. Gustafson P. Soft tissue sarcoma. Epidemiology and prognosis in 508 patients. *Acta Orthop Scand* 1994, **65**(Suppl. 259), 1–31.
7. Coebergh JWW, van der Heijden LH, Janssen-Heijnen MLG. Cancer of the soft tissues. In Coebergh JWW, van der Heijden LH, Janssen-Heijnen MLG, eds. *Cancer Incidence and Survival in the Southeast of The Netherlands 1955–1994. A Report from the Eindhoven Cancer Registry*. ISBN 90-5001-007-5. Eindhoven, The Netherlands, 1995, 46–47.
8. Harris M, Hartley AL, Blair V, *et al.* Sarcomas in North West England. I. Histopathological peer review. *Br J Cancer* 1991, **64**, 315–320.
9. Hartley AL, Blair V, Harris M, *et al*. Sarcomas in North West England. II. Incidence. *Br J Cancer* 1991, **64**, 1145–1150.
10. Pollock RE, Karnell LH, Menck HR, Winchester DP. The National Cancer Data Base Report on soft tissue sarcoma. *Cancer* 1996, **78**, 2247–2257.
11. Berkel J. General practitioners and completeness of cancer registry. *J Epidemiol Comm Health* 1990, **44**, 121–124.
12. Schouten LJ, Höppener P, Van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 1993, **22**, 369–376.
13. Waterhouse JAH, Muir C, Correa P, Tomatis L. Cancer incidence in five continents, Vol. III. *IARC Scientific Publications* No. 15. Lyon International Agency for Research on Cancer, 1976, 453–459.
14. Hermanek P, Sobin LH, eds. TNM classification of malignant tumours. UICC/*International Union Against Cancer*, 4th edn, 2nd revision. Berlin, Springer, 1992, 90–92.
15. Van Geel AN, Van Unnik JAM, Keus RB. Diagnosis and treatment of soft tissue tumours: the Dutch nationwide-accepted consensus. *Sarcoma* 1998, **2**, 183–191.
16. Jane MJ, Hughes PJ. Disease incidence and results of extremity lesion treatment: Mersey Region soft tissue sarcomas (1975–1985). *Sarcoma* 1998, **2**, 89–96.
17. Lawrence W Jr, Hays DM, Heyn R, *et al.* Lymphatic metastases with childhood rhabdomyosarcoma. *Cancer* 1987, **60**, 910–915.
18. Lawrence W Jr, Donegan WL, Natarajan N, Mettlin C, Beart R, Winchester D. Adult soft tissue sarcomas. *Ann Surg* 1987, **205**, 349–359.
19. Hays DM. Rhabdomyosarcoma. *Clin Orthop* 1993, **289**, 36–49.
20. Shiu MH, Castro ELB, Hajdu I, Fortner JG. Surgical treatment of 297 soft tissue sarcomas of the lower extremity. *Ann Surg* 1975, **182**, 597–602.
21. Van Dam PA, Lowe DG, McKenzie-Gray B, Shepherd JH. Retroperitoneal soft tissue sarcomas: a review of the literature. *Obstet Gynaecol Surv* 1990, **45**, 670–682.
22. Gaakeer HA, Albus-Lutter ChE, Gortzak E, Zoetmulder FAN. Regional lymph node metastases in patients with soft tissue sarcomas of the extremities, what are the therapeutic consequences? *Eur J Surg Oncol* 1988, **14**, 151–156.
23. Weingrad DW, Rosenberg SA. Early lymphatic spread of osteogenic and soft tissue sarcomas. *Surgery* 1978, **84**, 231–240.
24. Ham SJ, van der Graaf WTA, Pras E, Molenaar WM, van der Berg E, Hoekstra HJ. Soft tissue sarcomas of the extremities. A multi-modality diagnostic and therapeutic approach. *Cancer Treatment Reviews* 1998, **24**, 373–391.