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European Journal of Cancer 39 (2003) 1568–1576

European Journal of Cancer

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Prognostic information in soft tissue sarcoma using tumour size, vascular invasion and microscopic tumour necrosis—the SIN-system

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Received 6 August 2002; received in revised form 14 April 2003; accepted 15 April 2003

Abstract

We have earlier devised a system for soft tissue sarcoma (STS), based on three negative prognostic features: large tumour size, vascular invasion, and microscopic tumour necrosis, the SIN-system. Tumours which exhibit 2 or 3 of these features are categorised as high-risk, the others as low-risk. We have now tested this system for reproducibility both as regards recognition of its components, and as regards prognostic strength in patients from another institution. We have also compared it with the American Joint Committee on Cancer (AJCC) system. 200 patients with STS were analysed, all had been treated by surgery, in 97 patients combined with radiotherapy. The median follow-up for the 117 survivors was 10 (1.5–27) years. Without knowledge of the clinical data, three groups of pathologists independently reviewed original slides from all of the tumours. Based on the factors, the tumours were classified as high-risk or low-risk. The prognostic strength was compared using the results obtained by the different observers. Concordance in recognition of vascular invasion, tumour necrosis, and overall grading was seen in 156 (78%), 154 (77%), and 167 (84%) of the 200 tumours, respectively. Based on the different observers' grading, the cumulative 5-year metastasis-free survival rate (MFSR) varied for patients with low-risk tumours between 0.85 and 0.80, and for patients with high-risk tumours between 0.48 and 0.43. The Kappa-value for grading between all three groups of observers was 0.77. The SIN-system gave more clinically useful prognostic information than the AJCC system. Useful prognostic information in STS can be obtained by using tumour size, vascular invasion and microscopic tumour necrosis. This system provides two distinct prognostic groups, and has a high reproducibility.

Keywords: Soft tissue sarcoma; Size; Necrosis; Vascular invasion; Prognosis; Grading

1. Introduction

There is no consensus as regards the value of adjuvant chemotherapy in the treatment of patients with soft tissue sarcoma (STS). Until reliable methods exist to identify beforehand those who both need and respond to chemotherapy, it seems logical to give chemotherapy only to those with a sufficiently poor prognosis to justify this potentially toxic treatment. In this situation, presently available prognostication systems, some based mainly on histological grading (the two best known of which are the National Cancer Institute (NCI) [1] and the French Federation of Cancer Centers (FNCLCC) [2] systems), and some based on a combination of histological and clinical data (the two best known of which are the American Joint Committee on Cancer (AJCC) [3] and the Surgical Staging System [4]) give limited help. These systems identify between three and eight prognostic groups, often with a large intermediate group(s), and with small groups at the extremes of the prognostic spectrum. Their clinical usefulness is thus open to dispute; the clinician may derive useful prognostic information in only a small fraction of the patients, i.e. those whose prognosis sufficiently deviates from that of the general STS patient to justify adjuvant

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doi:10.1016/S0959-8049(03)00369-1

chemotherapy for example. In addition, the reproducibility of many systems has not been formally analysed. An exception is the system proposed by the French Sarcoma Group (FNCLCC) in which the proportion of agreement as regards grading was 75% [5]. Reproducibility is important as it facilitates multicentre studies and also allows comparison between different studies.

To meet the need of a reproducible two-group prognostication system in STS, we have devised a system based on tumour size, vascular invasion, and microscopic tumour necrosis, the "SIN-system". This system was based on an analysis of 508 patients from the population-based database of the Musculoskeletal Tumor Center in Lund. Several potential prognostic factors were multivariately evaluated, and we found that tumour size >10 cm, vascular invasion and microscopic tumour necrosis (originally defined as greater than 4 mm in extent) were strong and independent factors—even stronger than histological malignancy grade; each factor had a relative risk between 2 and 3. We constructed a system based on the number of these factors present; patients whose tumours were characterised by none or only one of these factors (two thirds of the patients) formed a low-risk group with 81% 5-year metastasis-free survival (MFSR). The other patients (one third) with tumours displaying two or three risk factors had 32% 5-year MFSR. Thus, the system seemed to identify a relatively large group of patients with a poor prognosis [6].

We now report upon the reproducibility of a slightly modified version of this system in three ways; (1) inter-observer variation in the assessment of the histological variables, (2) the prognostic strength of the system when applied by different observers, and (3) the applicability of the system in a series of STS from another institution where treatment as well as histopathological methodology may show some differences. We have also compared the SIN-system to the AJCC system.

Table 1
Descriptive data on 200 surgically treated patients with soft tissue sarcoma of the extremity and trunk wall

	Lund, $n=100$	Bordeaux, $n=100$	Both series combined
Years of diagnosis	1967–1993	1980–1995	1967–1995
Median age (range) at diagnosis	63 (17–96)	53 (17–87)	59 (17–96)
Localisation			
Trunk wall	8	17	25
Upper extremity	15	10	25
Lower extremity	77	73	150
Depth			
Subcutaneous	21	17	38
Deep-seated	79	83	162
Median tumour size (range) in cm	8 (1–25)	7 (1–25)	7 (1–25)
Original histological classification			
MFH	45	21	66
Liposarcoma	13	20	33
Leiomyosarcoma	18	12	30
Synovial sarcoma	13	10	23
MPNST	1	7	8
STS NOS	2	12	14
Other STS	8	18	26
Local treatment			
Inadequate	15	16	31
Adequate	85	84	169
Adjuvant chemotherapy			
Preoperative	0	0	0
Postoperative	15	33	48
None	85	67	152
Number of patients with metastases	37	34	71
Number of tumour-related deaths	32	25	57
Local recurrence rates			
Inadequate loc. tr.	5/15	4/16	9/31
Adequate loc. tr.	11/85	9/84	20/169
5-year metastasis-free survival rate	0.63	0.73	0.68
5-year tumour-related survival rate	0.72	0.77	0.75

MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumour; STS NOS, soft tissue sarcoma non otherwise specified. Inadequate local treatment (loc. tr.) = intralesional surgery with or without adjuvant radiotherapy or marginal surgery without adjuvant radiotherapy. Adequate local treatment = marginal surgery with adjuvant radiotherapy or wide or radical surgery with or without adjuvant radiotherapy.

2. Patients and methods

2.1. Patients

From each centre (Lund and Bordeaux), 100 adult patients (age >17 years) were included. We intended to obtain a consecutive series, but this was not possible since only patients with blocks large enough for the preparation of new slides could be included. The patients had all been treated for STS of the extremity or trunk wall, all but 3 patients with pulmonary metastases had no metastases at diagnosis of the primary tumour, and had follow-up (Table 1). The Lund patients were treated between 1967 and 1993, and the median follow-up time for the 47 survivors was 13 (4.5–27) years. The Bordeaux patients were treated between 1980 and 1995, and the median follow-up time for the 70 survivors was 7 (1.5–17) years. All surgical margins were reassessed at the respective institution according to modern definitions.

The 2 series were comparable as regards patient age, tumour localisation, and distribution of histotypes. The median tumour size was larger in the Lund patients than in the Bordeaux patients, 8 cm and 7 cm, respectively. In 39 of the Lund patients, and in 31 of the Bordeaux patients the tumour size exceeded 8 cm. The cumulative 5-year MFSR was 0.63 in the Lund series and 0.73 in the Bordeaux series. This difference may be explained by the slightly larger tumours and longer minimum follow-up time in the Lund series (Table 1).

All patients were treated by surgery, in 97 (Lund $n=20$, Bordeaux $n=77$) of them combined with radiotherapy (RT). Fifteen patients were operated upon with an intralesional margin (in 12 combined with RT), 52 with a marginal margin (36 RT), 125 with a wide margin (48 RT), and 8 patients were operated upon with a radical margin (1 RT). RT was given if the treating doctor deemed it necessary to achieve local control, and the decision was based on tumour and patient features and the surgical margin obtained. Forty-eight (Lund $n=15$, Bordeaux $n=33$) patients were also given adjuvant chemotherapy with different regimens. No patient was given adjunctive therapy of any kind prior to surgery. Local recurrence was diagnosed in 29 patients, and metastases developed in 71 patients.

All procedures in this study were done in accordance with the ethical standards of the Helsinki Declaration of 1975.

2.2. Definition of prognostic factors

The slides of all 200 tumours, stained with haematoxylin and eosin (H&E), and ranging in number from 1 to 41 (median 6 per tumour, and median 0.9 sections per cm of tumour diameter) were independently reviewed in the absence of outcome data for the presence or absence of vascular invasion and microscopic tumour necrosis by (I) Åkerman and Willén in cooperation, (II) Fletcher and (III) Coindre. No use was made of special stains or of immunohistochemistry in order to highlight vascular invasion. No attempt was made to reassess the original histopatological subclassification, although all tumours were verified as STS. For the statistical analyses, no attempts to reach a consensus were made. After closure of the review and statistical analysis, a meeting was held where the discordant classifications were reviewed and discussed.

2.2.1. Tumour size

Defined as the largest diameter reported by the original pathologists in the surgical specimen and in all statistical analyses was assumed to be the same for all observers.

In the original description of the system, we dichotomised tumour size at 10 cm [6], but for this study, we have changed the size cut-off point to 8 cm. The reason for this adjustment was to use a cut-off point closer to the median tumour size observed in a population-based series of STS, where it was 6.5 cm [6]. This adjustment had no effect on the prognostic strength of tumour size (data not shown). In all analyses in this study, tumour size was dichotomised as 1–8 cm versus larger than 8 cm.

2.2.2. Vascular invasion

When present, could be seen within the tumour (in most cases), or in the adjacent tissues close to the tumour and was defined as the presence of tumour within any space having an obvious endothelial lining. Such tumour either had to be adherent to the luminal aspect of the vessel wall or, if free-floating, had to be associated with adherent fibrin, red blood cells, or leucocytes (Fig. 1a and b). If the tumour was covered by an intact layer of endothelium, if the involved space had no discernable endothelial lining or if the tumour invaded the vessel wall (but not the lumen) then this was not accepted within the definition of vascular invasion (Fig. 1c and d). In all analyses in this study, vascular invasion was classified simply as absent versus present.

2.2.3. Microscopic tumour necrosis

Defined as the presence of amorphous cellular debris, usually associated with a neutrophil polymorphonuclear cell response. Dead cells were generally arranged in sheets, often with ghost nuclear outlines (Fig. 2a and b). Individual cell death, apoptotic bodies, areas of hyalinosis or oedema, areas of fibrinoid exudate lacking tumour cells, and areas of acellular fibrosis were not accepted within the definition of necrosis (Fig. 2c and d).

In the original description of the system, we dichotomised microscopic tumour necrosis at 4 mm [6], but for this series, we have changed the classification to absent versus present (regardless of the extent). This adjustment had no effect on the prognostic strength of microscopic tumour necrosis, and in fact concordance in classification increased (data not shown). In all analyses in this study, microscopic tumour necrosis was therefore classified simply as absent versus present (regardless of the extent).

2.3. Definition of prognostic groups

For prognostication of metastatic risk, the patients were divided into either a low-risk group (none or only one of the following three factors tumour size >8 cm, vascular invasion, or microscopic tumour necrosis) or into a high-risk group (two or three of these factors).

2.4. Comparison of metastasis-free survival rates

5-year MFSR with the new definitions of prognostic factors ranged from 0.91 to 0.87 with none of the above factors, 0.80 to 0.72 with 1 factor, 0.53 to 0.46 with 2 factors and 0.36 to 0.34 with 3 factors. The corresponding numbers with the old definitions, and calculated in the 354 patients forming the original patient group [6] were 0.89 with none of the factors, 0.68 with 1 factor, 0.34 with 2 factors and 0.23 with 3 factors.

2.5. Analysis of reproducibility

We analysed reproducibility in three ways;

1. Concordance in classification of vascular invasion and microscopic tumour necrosis. The rate

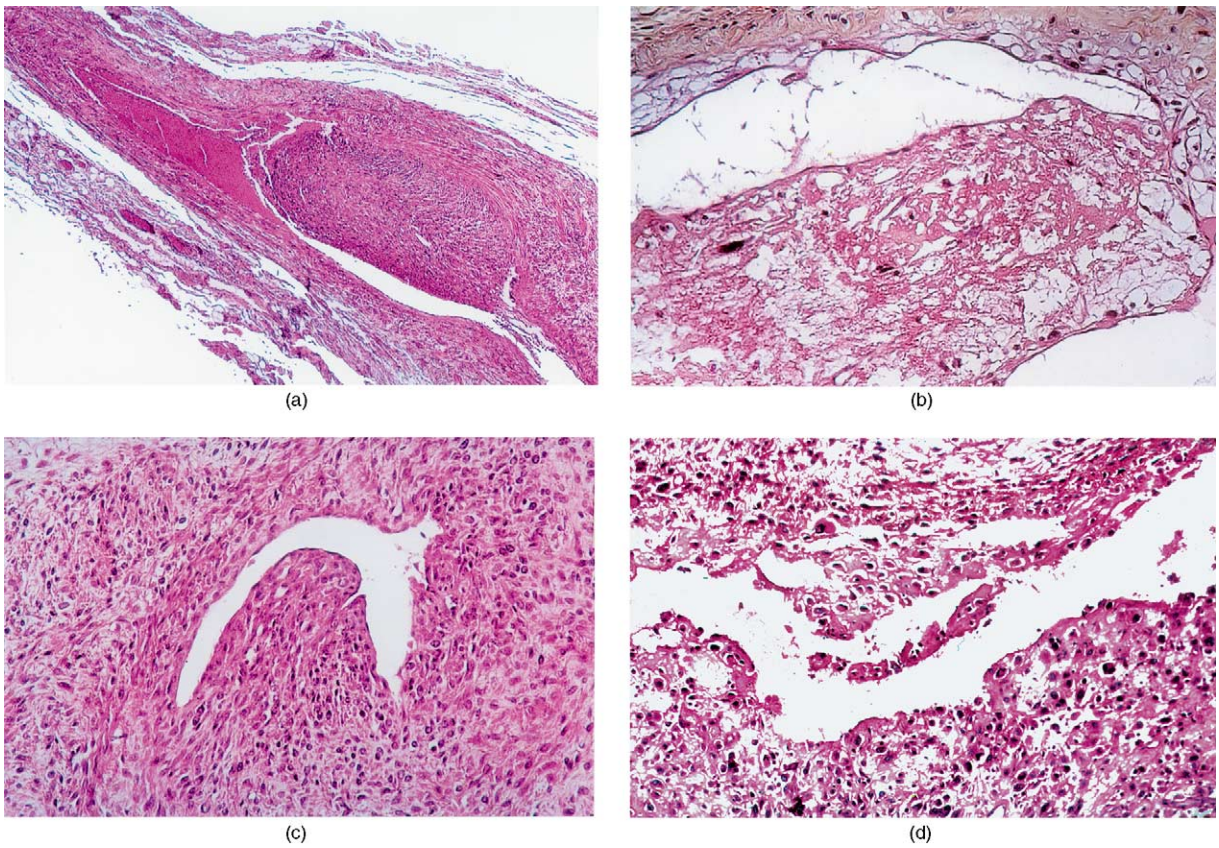

Fig. 1. (a) Typical vascular invasion. Hematoxylin-eosin staining (HES). Original magnification ×10. (b) Free-floating tumour with adherent fibrin. HES. Original magnification ×25. (c) Tumour pouting into, but not invading vessel. HES. Original magnification ×64. (d) Preparation artefact mimicking vessel. HES. Original magnification ×25.

of agreement between the three separate pathological assessments was evaluated by Kappa analysis.

2. Prognostic strength based on grading. The 5-year MFSR for each group of pathologists were calculated using the Kaplan–Meier technique. The positive and negative predictive values were calculated.
3. Prognostic strength was compared between the separate series from Lund and Bordeaux when graded by all of the observers. This analysis was done to evaluate whether the prognostication system, originally based on Lund patients only, is equally applicable to a series of STS patients from another institution.

2.6. Comparison with the AJCC system

For the comparison with the AJCC system (5th edition), Coindre also classified histopathological malignancy grade in all 200 patients according to the updated FNCLCC system [7]. Histopathological malignancy grade 1 in the FNCLCC was called low-grade in the AJCC system, and correspondingly grades 2 and 3 were called high-grade. The patients were then staged according to the AJCC system using grade, tumour size, nodal involvement and metastasis.

3. Results

3.1. Identification of necrosis, vascular invasion and grading (200 tumours)

Concordance between the three groups of pathologists as regards vascular invasion was found in 156 (78%) tumours, and as regards microscopic tumour necrosis in 154 (77%) tumours. The Kappa values for overall agreement were 0.64 and 0.68, respectively. Concordance as regards overall grading in low-risk or high-risk groups was found in 167 (84%) of the tumours, and the Kappa value was 0.77 (Table 2).

3.2. Prognostic strength

3.2.1. Combined series (n = 200)

The cumulative 5-year (10-year) MFSR for the low-risk group varied among the three groups of pathologists between 0.85 (0.82) and 0.80 (0.78), and for the

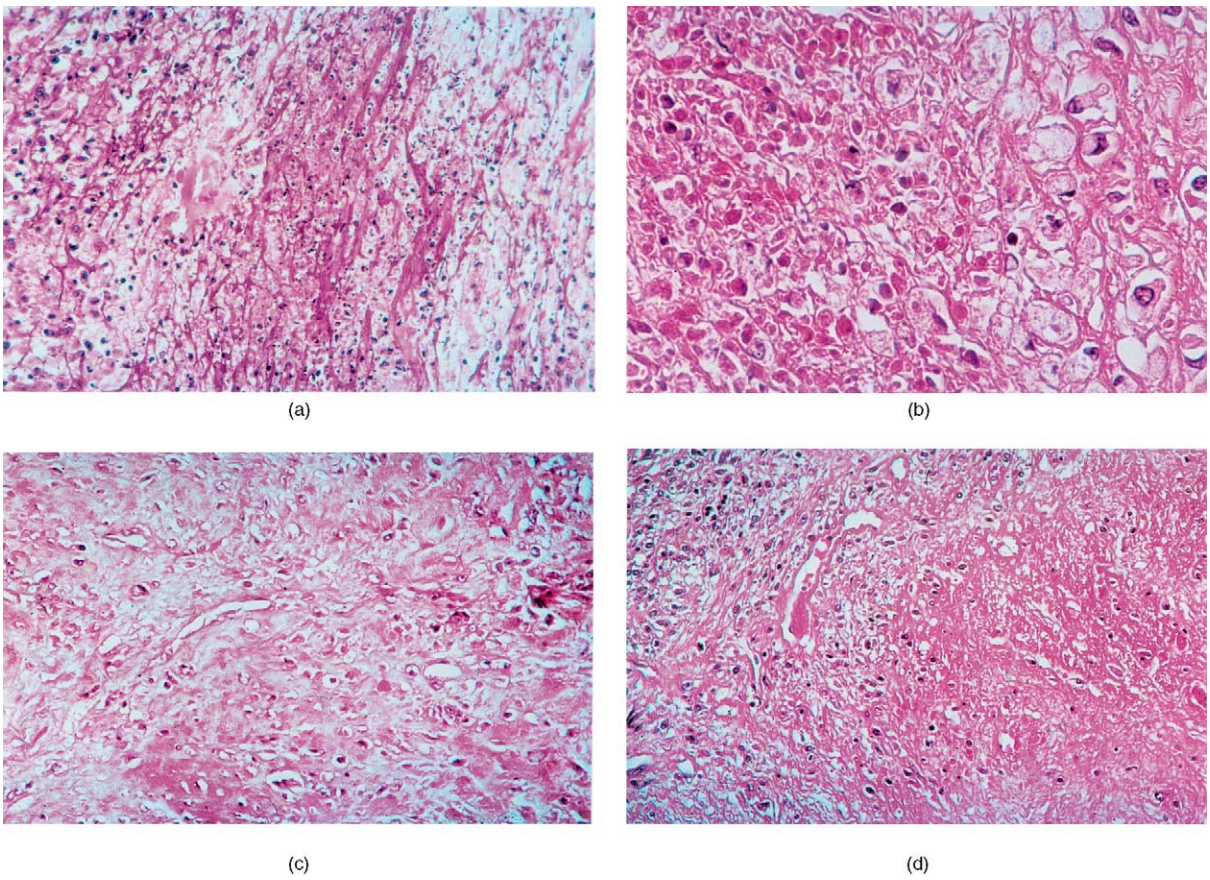

Fig. 2. (a) Typical microscopic necrosis. HES. Original magnification ×64. (b) Dead cells arranged in sheets, and with ghost nuclear outlines. HES. Original magnification ×160. (c) Hyalinised tumour area mimicking necrosis. HES. Original magnification ×64. (d) Fibrinoid exudate lacking tumour cells mimicking necrosis. HES. Original magnification ×10.

high-risk group between 0.48 (0.34) and 0.43 (0.30), *P* values in all instances were <0.0001 (Table 3, Fig. 3b). The positive predictive values for metastasis (how often the presence of metastasis could correctly be predicted) were 58%, 59%, and 61% for Bordeaux, Boston and Lund, respectively, and the corresponding negative predictive values (how often the absence of metastasis could correctly be predicted) were 80%, 80%, and 83%, respectively (Table 3).

3.2.2. Separate series

The system was just as effective when applied to Bordeaux patients as to Lund patients, irrespective of the observer (Table 3). Similarly, the system showed comparable prognostic strength in the major histological subtypes (malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma) (data not shown), but the actual sample size in each histologic group was too small to permit a detailed statistical analysis.

3.3. Comparison with the AJCC system

Staging according to the AJCC system gave survival curves comparable to those previously reported [3].

Table 2
Concordance in assessment of vascular invasion, microscopic tumour necrosis and grading in 200 surgically treated patients with soft tissue sarcoma of the extremity and trunk wall. Grading in low-risk (no or one of the factors) and high-risk (two or three of the factors) group using tumour size >8 cm, vascular invasion, and microscopic tumour necrosis

	Lund series	Bordeaux series	Both series
Tumour size[a]			
Vascular invasion	79/100	77/100	156/200
Kappa-value			0.64
Microscopic tumour necrosis	77/100	77/100	154/200
Kappa-value			0.68
Grading (low-risk versus high-risk)	84/100	83/100	167/200
Kappa-value			0.77
Size of low-risk/high-risk groups[b]			
Lund pathologists	50/50	65/35	115/85
Bordeaux pathologists	53/47	66/34	119/81
Boston pathologists	56/44	64/36	120/80

[a] Tumour size as measured by original diagnostic pathologists assumed to be the same between observers.
[b] As assessed by different observers.

Fifteen of the 200 patients were stage I; their 5-year MFSR was 1.00. Seventy-three patients were stage II, with a 5-year MFSR of 0.78, and 109 were stage III with a 5-year MFSR of 0.58. Three patients were stage IV (Fig 3a). In the SIN-system, 120 patients were classified as low-risk with a 5-year MFSR of 0.83, and 80 patients as high-risk with a 5-year MFSR of 0.43, P value <0.0001 (figures based on the grading by Fletcher) (Fig 3b).

Table 3
Prognostic values expressed as 5-year metastasis-free survival rates (MFSR) and predictive values in 200 surgically treated patients with soft tissue sarcoma of the extremity and trunk wall. Grading in low-risk (no or one of the factors) and high-risk (two or three of the factors) group using tumour size >8 cm, vascular invasion and microscopic tumour necrosis

	Lund series	Bordeaux series	Both series
Tumour size (1–8 cm/larger than 8 cm)	0.71/0.51	0.78/0.61	0.74/0.56
Vascular invasion (no/yes)			
Lund	0.81/0.35	0.83/0.44	0.82/0.39
Bordeaux	0.76/0.34	0.77/0.59	0.76/0.46
Boston	0.76/0.27	0.79/0.51	0.77/0.38
Microscopic tumour necrosis (no/yes)			
Lund	0.85/0.50	0.88/0.62	0.86/0.55
Bordeaux	0.79/0.53	0.92/0.61	0.85/0.57
Boston	0.83/0.50	0.86/0.61	0.85/0.55
Grading (low-risk/high-risk)			
Lund	0.83/0.43	0.88/0.45	0.85/0.43
Bordeaux	0.78/0.46	0.83/0.53	0.80/0.48
Boston	0.83/0.37	0.84/0.52	0.83/0.43
Predictive values (%) (positive/negative)			
Lund	56/82	69/85	61/83
Bordeaux	53/77	65/82	58/80
Boston	59/80	58/80	59/80

Tumour size is assumed to be the same between observers. Predictive values; positive = the ability to correctly predict the occurrence of metastasis, negative = the ability to correctly predict the absence of metastasis.

4. Discussion

Unlike the situation for osteosarcoma and Ewing's sarcoma, a clear and undisputed survival benefit from adjuvant chemotherapy has not been shown for STS patients, although a recent large meta-analysis of over 1500 STS patients showed a positive trend [8]. There may be several reasons for this earlier lack of evidence; for example, it may be that none of the tested chemotherapy regimens were sufficiently effective, or there may have been difficulties in selecting appropriate patients for chemotherapy trials. Only patients with a high risk for metastasis should be enrolled into such studies, but clear parameters for identifying this subgroup of patients have been hard to define. A further reason may have been a lack of statistical power; the patients may have been too few if a number of "general STS" patients from one institution were included within a reasonable time-span. Inclusion of patients with a good prognosis is disadvantageous for two reasons; firstly, chemotherapy may give serious side-effects and, secondly, a positive effect of chemotherapy may be difficult to reveal if the study group is diluted by low-risk patients.

Prognostication in classical osteosarcoma and Ewing's sarcoma is easy; essentially all tumours are by definition highly malignant, with a high risk for metastatic spread. The opposite holds true for STS; in this heterogenous group of tumours, there is as yet no clear-cut association between histotype and prognosis in many cases. Several prognostication systems are in use; the Surgical Staging System based on histopathological

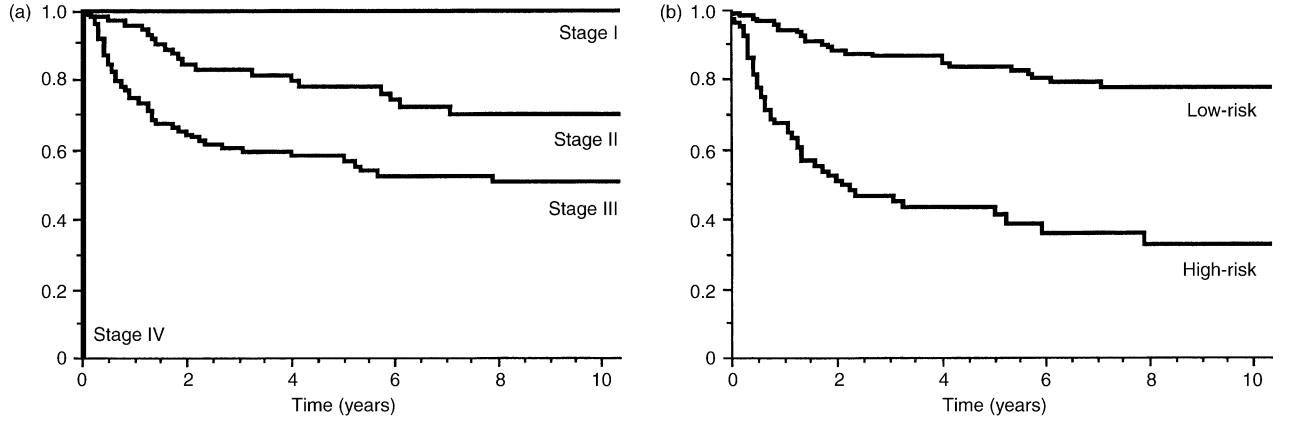

Fig. 3. (a) Cumulative metastasis-free survival in 200 adult patients with soft tissue sarcoma of extremity and trunk wall using the American Joint Committee on Cancer (AJCC) system. Stage I had 15 patients, stage II 73 patients, stage III 109 patients and stage IV had 3 patients. (b) Cumulative metastasis-free survival in 200 adult patients with soft tissue sarcoma of extremity and trunk wall using the SIN-system. Low-risk group consisted of 120 patients and the high-risk group of 80 patients. P value <0.0001. SIN, see Methods for description.

malignancy grade and compartmentalisation [4]; the AJCC system based on histopathological malignancy grade, tumour depth and tumour size [3]; the modified AJCC system proposed by Ramanathan and colleagues. [9]; the NCI system based on histological subtype and macroscopic necrosis [1]; the FNCLCC system based on differentiation, mitotic count and microscopic tumour necrosis [2]; the system of Myhre-Jensen based on cellularity, anaplasia, necrosis, histogenetic type and subtype of tumour [10]; the European Organisation for Research and Treatment of Cancer (EORTC) system based on mitotic count, macroscopic tumour necrosis and tumour size [11]; the system of Tomita and colleagues based on histological grade and clinical factors in combination [12]; and the system devised by Hajdu, based on histological features [13]. All these systems suffer from weaknesses; they give between three and eight prognostic groups, most of them can not specify a group of patients without detectable metastases at presentation, but with a really poor prognosis, and/or they have not been tested for reproducibility. The issue of the number of prognostic groups can be discussed, but from a clinical point of view it is advantageous to have as few prognostic groups as possible, since this simplifies decision-making with regard to adjuvant therapy (adjuvant (chemo)therapy or not). The issue of how poor a prognosis the patients in the poor prognosis group should have is subjective; no clear-cut guidelines or recommendations exist, but in oncological practice, it is generally considered that the expected survival for a poor prognosis group should not exceed 50%, this to minimise patients receiving potentially hazardous treatment when they do not need this therapy. As regards reproducibility, this is a clear-cut requirement of a prognostication system. STS is an uncommon tumour, and the need for multicentre cooperation is clear, therefore a reproducible system is especially desirable.

We believe that the patient series used in the present study can be regarded as representative for STS of the extremity and trunk wall in general. In a large population-based study, Gustafson [6] found a median age of 64 years (in this study it was 59 years), a median size of 6.5 cm (in this study it was 7 cm), and approximately one third (in this study it was one fifth) of subcutaneous tumours, and the survival between the studies is also comparable. In fact, the proportion of subcutaneous tumours in a series, and the median size are two fairly sensitive indicators of representativeness [6]. We included only sarcomas of the extremity and trunk wall. Most tumours in these localisations can be controlled by surgery, if necessary combined with radiotherapy; death because of tumour is in most cases due to metastatic disease. By contrast, in head and neck or retroperitoneal STS, it is often difficult to eradicate the primary tumour, and many patients die from uncontrollable local disease without metastases. We did not analyse the type of treatment for the primary tumour and its relationship to local recurrence and metastases. It has repeatedly been shown that there is no, or only a weak, association between the type of treatment for the primary tumour and outcome as regards metastatic disease. It appears that in most cases local recurrence is more a marker of intrinsic biological aggression than a cause of metastases [6,14–17].

We found concordance in grading in excess of 80%. This corresponded to a Kappa value of 0.77, which reflects substantial agreement [18], and compares favourably with studies in other tumour types. The prognostic strength, tested both with different observers classifying the same series of tumours, and the same observers classifying different series of tumours, was powerful, allowing a clear separation into only two groups of patients with markedly different outcomes.

Although interobserver variation is a well-recognised problem in the pathological assessment of many tumour types, the concordance obtained in the assessment of vascular invasion and microscopic tumour necrosis in the present study (admittedly using experienced STS pathologists) was remarkably good. We believe that the histological parameters described herein could also be used fairly easily by other pathologists. One possible caveat is that we often found vascular invasion to be present *within* the tumours themselves, which contrasts with that seen in some other malignancies (e.g. thyroid or testicular cancers) and which, since it may be ''submerged'' in the surrounding tumour, therefore may be harder to identify unless special care is taken.

Vascular invasion is a well-known prognostic factor in many malignant neoplasms, although data on this phenomenon in STS are relatively limited [2,19–22]. In this study, we found that vascular invasion was of prognostic importance, and that its identification was adequately reproducible (with a concordance in 78% of the tumours). We reanalysed our discordant cases after the study was completed, and found two major reasons for discordance; first was the failure to identify a single involved vessel, due to presumed observer inattention while reviewing a large number of slides, and second was the tendency by each observer to occasionally overinterpret tumour ''bulging'' into a vascular lumen while retaining an intact endothelial lining.

Several authors have reported the strong prognostic importance of necrosis in STS, although the definition of necrosis varies widely between reports [1,2,19,23]. By using simply presence or absence of necrosis, as was also advocated by the EORTC group [11], we found concordance between the observers in the estimation of necrosis of 77%. When we reanalysed our discordant specimens after the study was completed, we found two major reasons for discordance; first was the failure to identify tiny foci (<1 mm) of necrosis due to presumed observer inattention when viewing a large number of

slides, and second was overinterpretation by one observer of isolated degenerate or apoptotic cells as necrosis. A corollary of the reappraisal of discordant cases was the realisation that any necrosis (however small) was of prognostic relevance in this series (data not shown).

It is possible that the relative strength of tumour size, vascular invasion and microscopic tumour necrosis varies between different histological types of STS. Although our series comprises 200 tumours, it is not sufficiently large to allow for such analyses because of the many histotypes present. However, histotype-specific analyses face the problem of determining the histological classification of STS, with a poor reproducibility among pathologists [5,24]. Notably, this problem refers especially to what is often regarded as today's commonest histotype, i.e. malignant fibrous histiocytoma, which increasingly has been acknowledged to consist of a wide variety of tumour types with different outcomes. However, there is no consensus yet as to how these lesions should be better subclassified, nor as to how much effort or expense should be devoted to this task [25]. Until these classification problems are solved, it may be advantageous to use a prognostication system which is not dependent on the exact histotype.

We believe that the SIN-system is applicable to most adult STS (at least the more common histotypes) occurring in the limbs and trunk wall. However, we would caution that the system can only be applied to thoroughly sampled resection specimens and can not be used on small biopsies. Furthermore, in common with all other grading systems, the SIN-system can not be used in patients receiving preoperative adjunctive therapy because of the resulting alterations in the resected tumour size and extent of necrosis.

As compared with the AJCC system, the SIN-system may give prognostic information that could facilitate decision-making; the SIN low-risk group is larger and has a better prognosis than the corresponding group (stage II) in the AJCC system, and the SIN high-risk group is smaller and has a worse prognosis than the corresponding group in the AJCC system (stage III). In this regard, we have not considered the very small stage I and IV groups of the AJCC system. The clear and binary separation in the SIN-system may offer an important advantage over the AJCC system.

We have demonstrated herein the validity of a new system for predicting outcome in STS, the SIN-system. This system provides prognostication for adult patients with STS of the extremities and trunk wall, using tumour size, vascular invasion and microscopic tumour necrosis as parameters. This system meets the clinical requirements of a prognostication system; it gives two distinct groups (with sufficiently poor prognosis for the poor prognosis group), and it is reproducible. We believe that this system may be a valuable tool in selecting patients for chemotherapy trials, and that it may facilitate multicentre analyses, something that must always be considered due to the relative scarcity of STS.

Acknowledgements

This study was supported by grants from the Swedish Cancer Society, the Nordic Cancer Union, The Swedish Medical Research Council (project 09509), the Medical Faculty Lund University, Malmöhus Läns Landsting, and Stiftelsen för bistånd åt vanföra i Skåne. All data are avilable from the authors.

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