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Identification of low-risk tumours in histological high-grade soft tissue sarcomas

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ABSTRACT

In more than one-third of patients with a histological high-grade malignant soft tissue sarcoma metastasis develops despite local control of the primary tumour. Hence, adjuvant chemotherapy is increasingly used for these relatively chemoresistant tumours which requires improved prognostication to exclude low-risk patients from overtreatment. We assessed the value of stepwise prognostication in a series of 434 histological high-grade STS of the extremity and trunk wall. Vascular invasion was used as the first discriminator whereafter the risk factors tumour necrosis, size (>8 cm) and infiltrating growth pattern were used to discriminate high- and low-risk tumours. We identified a high-risk group with a cumulative incidence of metastasis >0.4 at 5 years, and a low-risk group, comprising half of the tumours, with a cumulative incidence of metastasis <0.15. The model was validated in an independent material of 175 patients. This model improved prognostication in STS and is of value for identifying patients who probably should not receive adjuvant chemotherapy.

1. Introduction

One-third of adult patients with soft tissue sarcomas (STS) of the extremity and trunk wall without detectable metastases at the time of diagnosis will die of metastatic disease despite local control of the primary tumour.[1,2] Therefore, adjuvant chemotherapy is increasingly used in patients considered having highly malignant tumours. However, there is no consensus on how to best identify high-risk tumours; several systems have been suggested, but few have been validated. The two most commonly used, and also validated, systems are the French FNCLCC system and the American AJCC/UICC system.[3–5] Patients with localised tumours at diagnosis but with the highest risk for metastasis (Stage III) in the AJCC/UICC system comprise half of the STS population with about 50% metastatic risk,[4] the corresponding figure in the FNCLCC (Grade 3) is about half the sarcoma population with almost a 60% risk of metastatic disease.[3] These patients are often considered for chemotherapy. In both systems almost half of the tumours are classified as Stage II/Grade 2 with a 30%

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risk for metastasis; whether these patients should be candidates for adjuvant systemic treatment is unclear.

We constructed a prognostic system based on a stepwise use of risk factors; first vascular invasion and thereafter a combination of the risk factors tumour size, necrosis and growth pattern was applied in the remaining tumours without demonstrated vascular invasion. This system was established in a series of 434 histological high-grade STS of the extremities and trunk wall and was then validated in an independent material of 175 tumours. Our aim was to improve the identification of patients who manage well without chemotherapy despite having histological high-grade soft tissue sarcomas.

2. Patients and methods

2.1. Patients

Common for all patients in all series was >15 years of age, primary, pathology peer-reviewed histological high-grade soft tissue sarcoma of the extremity or trunk wall, no metastases, treatment at a sarcoma centre, no chemotherapy and complete follow-up (Table 1).

2.1.1. Test series

This series included 434 patients treated between 1986 and 2004 at tumour centres in Sweden and Norway.[6] The surgical resection margin was wide or marginal in 398 (92%), and intralesional in 36 (8%) tumours. Radiotherapy was administered to 119 (27%) patients. Metastases developed in 135 (31%) patients and a local recurrence occurred in 87 (20%) patients. The median follow-up time for survivors without metastasis was 10 years.

2.1.2. Validation series

The prognostic system suggested from the test series was validated in an independent series of 175 tumours: 122 patients treated at the Lund University hospital, Sweden, 1988–2001 and 53 patients treated at the The Norwegian Radium Hospital 1998–2001 (series A and B, Table1). The Swedish series has previously been published as part of 140 STS comprising of 18 histologically low-grade malignant tumours and the 122 high-grade malignant tumours.[7]

The surgical resection margin was wide or marginal in 168 tumours and intralesional in 7 tumours. Radiotherapy was administered to 70 (40%) patients. Metastasis developed in 64 (37%) patients and 28 (16%) had a local recurrence. The median follow-up for survivors without metastasis was 5 years.

The present study was approved by the Lund University Ethics Committee.

2.2. Pathology review

The peer review in the test series of 434 tumours focused principally on subtyping the sarcoma and on attributing a histological malignancy grade and was based on small tumour sections (7–10 slides per tumour). Appropriate immunohistochemical panels were used for establishment of cell lineage and also cytogenetic techniques, and sometimes electron microscopy.[8–10] Malignancy grading used a IV-tiered grading system based on cellularity, pleomorphism, nuclear atypia, tumour necrosis and mitotic activity. In this system, Grades III–IV corresponds roughly to Stages II–III in the AJCC/UICC system and to Grade 3 in the FNCLCC system.[3,11,12] Necrosis was determined as present or not, the amount of necrosis was not quantified and thus we could not grade our tumours according to the FNCLCC system.

The 53 tumours in the Norwegian part of the validation series were reviewed by two of the authors (B.B. and P.R.) and necrosis, vascular invasion and growth pattern were determined on multiple tumour sections (10–15 slides per tumour).

The 122 tumours in the Swedish part of the validation series had been histologically evaluated using 7–10 small sections for immunohistochemical staining and whole-tumour sections, i.e. entire tumour planes had been thoroughly assessed for vascular invasion and presence of necrosis.[7] This means that the most intense search for necrosis and vascular invasion using most tumour material (whole tumour sections) was performed in this series.

2.3. Definition of prognostic factors

Tumour size was measured as the maximum diameter (cm) on the fresh surgical specimen in the test series and in series C, but in series B on a formalin fixed surgical specimen.

Tumour necrosis was defined as the presence of amorphous cellular debris, usually associated with a neutrophil polymorphonuclear cell response, or clustering of dead cells and apoptotic bodies or cell ghosts. We employed no lower limit of a necrotic area, but areas of hyalinosis or oedema, fibrin exudates lacking tumour cells or acellular areas of fibrosis were not defined as necrosis.

Vascular invasion of tumour cells was defined as the presence of tumour cells within any space having an obvious endothelial lining, whether within the tumour or in the tumour rim. The tumour cells had to be adherent to the vessel wall, or associated with adherent fibrin, red blood cells, or leucocytes. Bulging of tumour into a vessel with intact endothelial lining was not accepted as intravascular tumour growth.

Peripheral tumour growth pattern was microscopically assessed in the tumour periphery on an entire tumour plane if a whole-tumour section had been performed (validation series A), and from serial small sections from the tumour in the test series and validation series B. The growth pattern was classified as pushing if no sign of infiltrative growth could be seen, and as infiltrating if the tumour rim was seen infiltrating into the surrounding tissues.

2.4. Modelling the prognostic system

The purpose of our study was to find a prognostic system that separates patients with histological high-grade STS but with a low risk for metastasis without chemotherapy from high-risk patients. The patients age at diagnosis was high and thus death due to any cause was considered a competing event to the end-point metastasis.[13] Very few metastases occurred after 5 years, and hence the cumulative incidence of metastases at 5 years was chosen as the end-point.[13] Hazard ratios for

Table 1 – Clinical-pathological characteristics in histological high-grade STS. Test series (n = 434) and validation series A (*n* = 122) and B (*n* = 53)

Factor	Test series *n* (%)	Series A	Series B
Sex			
Male	225 (52)	70 (57)	26 (49)
Female	209 (48)	52 (43)	27 (51)
Age			
Median (range)	69 (16–96)	71 (16–94)	69 (21–93)
Site			
Lower extremity	277 (64)	88 (72)	32 (60)
Upper extremity	104 (24)	24 (20)	15 (28)
Trunk wall	53 (12)	10 (8)	6 (11)
Depth			
Subcutaneous	253 (58)	44 (36)	35 (66)
Deep-seated	181 (42)	78 (64)	18 (34)
Histopathological diagnosis			
MFH and myxofibrosarcoma	220 (51)	34 (28)	30 (57)
Leiomyosarcoma	107 (25)	45 (37)	12 (23)
Liposarcoma	44 (10)	8 (7)	2 (4)
Synovial sarcoma	37 (9)	8 (7)	2 (4)
Other types	26 (6)	27 (22)	6 (11)
Histological malignancy grade			
III	162 (37)	24 (20)	25 (47)
IV	272 (63)	98 (80)	28 (53)
Tumour size median (range) (cm)	6 (1–30)	8 (2–28)	5 (1–25)
⩽5	213 (49)	34 (28)	26 (50)
>5	221 (51)	88 (72)	26 (50)
1–8	319 (74)	65 (53)	36 (68)
>8	115 (26)	57 (47)	17 (32)
Vascular invasion			
Identified	36 (8)	49 (40)	9 (17)
Not found	398 (92)	73 (60)	44 (83)
Tumour necrosis			
Identified	235 (54)	82 (67)	26 (49)
Not found	199 (46)	40 (33)	27 (51)
Tumour growth pattern			
Infiltrative	340 (78)	95 (78)	44 (83)
Pushing	94 (22)	27 (22)	9 (17)
Local recurrence	87 (20)	24 (20)	4 (8)
Metastasis	135 (31)	52 (43)	12 (23)

the prognostic factors were determined using univariate Cox models.

The test series of 434 patients was used to develop a prognostic system based on the risk factors size, depth, vascular invasion, necrosis and growth pattern. Vascular invasion was the strongest prognostic factor for metastasis. Tumours with identified vascular invasion constituted a small group with a high absolute risk for metastasis. However, vascular invasion may be hard to find, and hence a non-finding is not as informative as a finding. This led us to allocate patients with vascular invasion to a high-risk group and to use the other factors in the patients without an identified vascular invasion. The best prognostic model was found when necrosis, growth pattern and size (>8 cm versus ⩽8 cm) were used for separation of high- and low-risk tumours.

As the risk for metastasis increases with increasing tumour size,[14] we investigated different cut-off levels and found that 8 cm was the best in the group of tumours without identified vascular invasion (data not shown). We also analysed incorporating tumour depth instead of tumour growth pattern, but found less prognostic accuracy when depth was included (data not shown).

The stepwise model was evaluated in an independent validation material. It was also compared with two other prognostic systems, the SIN system used in Scandinavia and the American AJCC/UICC system.[1,15]

3. Results

3.1. *Test series, 434 patients*

Vascular invasion was the strongest prognostic factor for metastasis; it was found in 36/434 tumours (8%) of which 21/36 (58%) metastasised (hazard ratio 3.14) (Fig. 1a, Table 2).

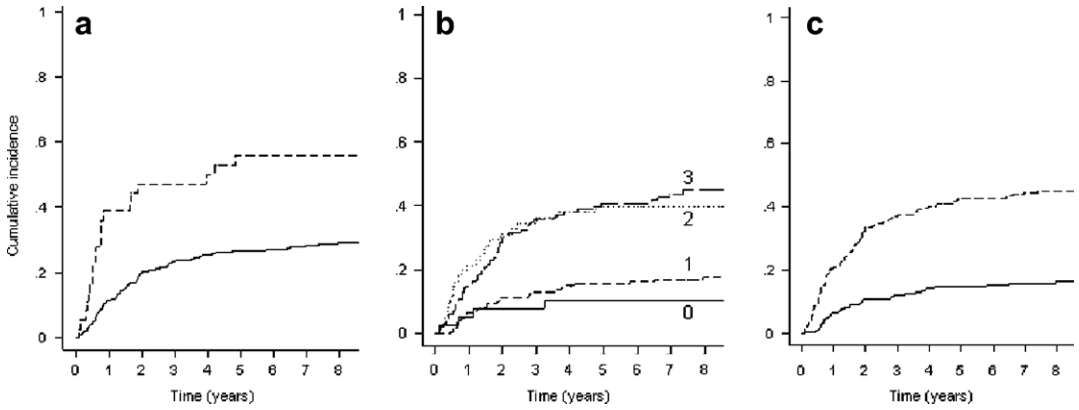

Fig. 1 – Cumulative incidence of metastasis in the test series of 434 histological high-grade STS: (a) tumours with (*n* = 36, dashed line) versus without identified vascular invasion (*n* = 398, solid line); (b) Tumours without vascular invasion (*n* = 398). Curve figures (0–3) denote number of risk factors (size >8 cm, necrosis and infiltrative growth). 3 risk factors (*n* = 61), 2 risk factors (*n* = 130), 1 risk factor (*n* = 169), and 0 risk factor (*n* = 38); and (c) All tumours (*n* = 434). High-risk group (vascular invasion or presence of 2–3 risk factors, *n* = 227), versus low-risk group (without vascular invasion and 0–1 risk factors, *n* = 207).

The remaining 398 tumours, without identified vascular invasion, could be separated in a high- and a low-risk group based on the number of the risk factors size >8 cm, necrosis, and infiltrative growth that were present. The high-risk group, with two or three risk factors, comprised 191/398 (48%) tumours with a cumulative incidence of metastasis at 5 years (metastasis rate) of about 0.4, the low-risk group, with none or one risk factor, comprised 207/398 (52%) tumours with a metastasis rate of 0.15 (Fig. 1b).

The combined set of the 36 tumours with identified vascular invasion and the 191 tumours subsequently classified as high risk by the presence of 2–3 of the other factors, formed a high-risk group of 227/434 (53%) tumours with a metastasis rate of 0.43. The remaining 207/434 (47%) tumours, classified as low-risk tumours, had a metastasis rate of 0.15 (Fig. 1c).

One-third (72/227) of the tumours in the high-risk group were small (<5 cm) and one-third (66/207) of the tumours in the low-risk group were large.

3.2. *Validation series, 175 patients*

In this series vascular invasion was detected in 58/175 (33%) tumours, and 42/58 (72%) metastasised (Fig. 2a). In the remaining 117 tumours without identified vascular invasion we applied the risk stratification determined in the test series based on the presence of 0–1 or 2–3 risk factors (size >8 cm, necrosis, growth pattern). This resulted in identification of a high-risk group of 57/117 (49%) and a low-risk group of 60/117 (51%) tumours (Fig. 2b). The combined high-risk group of 115 tumours (58 tumours with vascular invasion and the 57

Table 2 – Prognostic factors and cumulative incidence of metastasis at 5-years in 434 histological high-grade STS (test series)

Factor	Proportion	Cumulative incidence of metastasis 5 years (95% CI)	Hazard ratio (95% CI)
Size related factors			
Tumour size 1–5 cm	0.49	0.19 (0.14–0.25)	1
>5 cm	0.51	0.39 (0.33–0.46)	2.78 (1.93–3.98)
Tumour size 1–8 cm	0.74	0.23 (0.19–0.29)	1
>8 cm	0.26	0.45 (0.36–0.54)	2.50 (1.77–3.54)
Deep-seated	0.42	0.40 (0.33–0.47)	2.25 (1.60–3.16)
Superficial	0.58	0.21 (0.17–0.27)	1
Vascular invasion			
Identified	0.08	0.56 (0.38–0.70)	3.14 (1.97–5.00)
Not found	0.92	0.27 (0.23–0.31)	1
Tumour necrosis			
Identified	0.54	0.40 (0.33–0.46)	2.85 (1.95–4.15)
Not found	0.46	0.17 (0.12–0.23)	1
Tumour growth pattern			
Infiltrative	0.78	0.31 (0.27–0.36)	1.47 (0.93–2.32)
Pushing	0.22	0.22 (0.14–0.30)	1

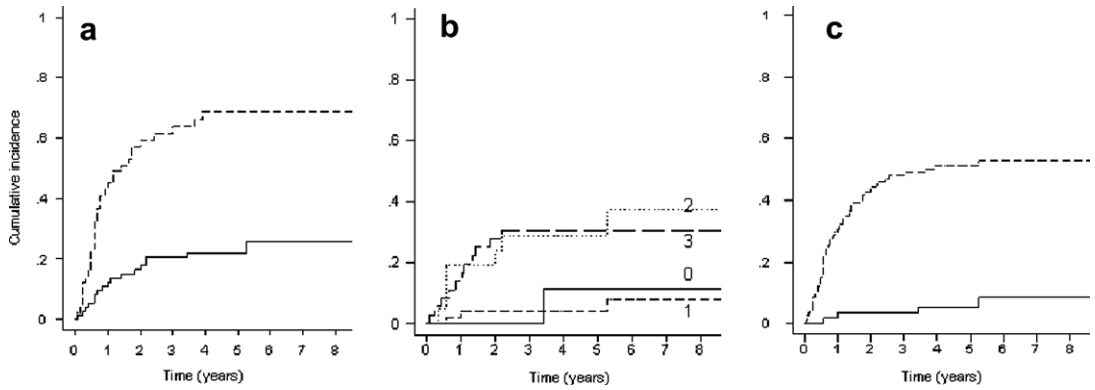

Fig. 2 – Cumulative incidence of metastasis in 175 histological high-grade STS (validation series): (a) tumours with (*n* = 58, dashed line) versus without (*n* = 117, solid line) identified vascular invasion. (b) tumours without vascular invasion (*n* = 117). Curve figures (0–3) denote number of risk factors. Three risk factors (*n* = 21), 2 risk factors (*n* = 36), 1 risk factor (*n* = 50), and 0 risk factor (*n* = 10). (c) All tumours (*n* = 175). High-risk group (vascular invasion or presence of 2–3 risk factors, *n* = 115), versus low-risk group (without vascular invasion and 0–1 risk factors, *n* = 60).

tumours with 2 or 3 of risk factors had a metastasis rate of 0.51). The remaining low-risk group (no vascular invasion and 0–1 risk factors) comprised 60/175 (34%) tumours with a metastasis rate of 0.05 (Fig. 2c and Table 3). In the validation material 81/175 (46%) tumours were deep seated and large (>5 cm), i.e. Stage III tumours in the AJCC/UICC system and had a metastases rate of 0.44. The stepwise risk stratification was applied in the 79 subcutaneous and 96 deep-seated tumours, respectively, and was in these subsets found to clearly separate high-risk and low-risk groups with a metastasis rate of 50% in the high-risk groups, and 11% in the low-risk groups. Thus, prognostication was not dependent of tumour depth.

We also applied the stepwise evaluation separately to the two tumour series A and B in the validation material and found similar results with clear separation of high-risk and low-risk groups in each series (data not shown).

3.3. *Prognostic accuracy compared with other systems*

We compared our system with two other systems: the SIN system used in Scandinavia for selecting patients with histological high-grade STS for adjuvant chemotherapy, in which the presence of two or three of the risk factors, size >8 cm, vascular invasion and necrosis constitutes high-risk criteria

Table 3 – Cumulative incidence of metastasis at 5 years using three different prognostic systems in 175 histological high-grade STS (validation series)

Prognostic system	*n* patients	Proportion	Cumulative incidence of metastasis 5 year (95% CI)
Stepwise evaluation			
High-risk group	115	0.66	0.51 (0.41–0.60)
Low-risk group	60	0.34	0.05 (0.01–0.13)
SIN system			
High-risk group	84	0.48	0.56 (0.45–0.66)
Low-risk group	91	0.52	0.16 (0.09–0.24)
AJCC			
High-risk group (Stage III)	81	0.46	0.46 (0.35–0.56)
Low-risk group (Stage II)	94	0.54	0.26 (0.18–0.35)

Table 4 – Proportion of metastasis in concordant and discordant low-risk and high-risk groups using three different prognostic systems in 175 histological high-grade STS (validation series)

Prognostic system	Risk group, *n* patients	SIN system		AJCC/UICC	
		Low-risk, *n* = 91	High-risk, *n* = 84	Low-risk, Stage II; *n* = 94	High-risk, Stage III; *n* = 81
Step-wise model	Low-risk, *n* = 60	4/60 (7%)	0	3/49 (6%)	1/11 (9%)
	High-risk, *n* = 115	11/31 (35%)	49/84 (58%)	23/45 (51%)	37/70 (53%)

and the AJCC/UICC system (6th ed.) in which Stage III (high-grade, deep and >5 cm) was considered high risk.

We used the validation material of 175 patients for this comparison and found that the stepwise model classified a higher proportion of patients as high risk, 115/175 (66%), than the SIN system, 84/175 (48%). All 31 discordantly classified patients were classified as low-risk in the SIN system and high risk by our model and 11/31 of these metastasised (Table 4).

Compared to the AJCC system, 56/175 (32%) tumours were discordantly classified. Eleven tumours were classified as high risk in the AJCC/UICC system but as low-risk by our model and 1/11 metastasised. There were 45 tumours classified as low risk by the AJCC/UICC system, and as high risk by our model and of these 23 metastasised (Table 4).

4. Discussion

We have developed a stepwise prognostication model for histological high-grade malignant STS of the extremity and trunk wall. Hereby, we confirmed the strong prognostic importance of tumour size and necrosis as well as the importance of vascular invasion and tumour growth pattern. We validated the model in an independent patient material with good separation of low-risk and high-risk tumours and believe that our findings may improve the identification of low-risk patients not suited for adjuvant chemotherapy.

Meta-analyses have demonstrated only a small survival benefit of adjuvant chemotherapy in adult STS.[16,17] Despite this, chemotherapy is increasingly used in patients with histological high-grade STS. Its limited benefit calls for improved identification of low-risk patients who can be spared the toxic anthracyclin-based regimes often used.

Several prognostic systems for adult non-visceral STS are in use.[4,18–21] With all systems there are difficulties in identifying truly high- and low-risk patients. Most systems are based on combinations of histological malignancy grade, tumour size, necrosis, mitotic frequency and degree of differentiation. The latter three factors are incorporated in histological malignancy-grading systems which confounds analyses of the prognostic strength of different factors versus malignancy grade. Therefore, we did not analyse the prognostic importance of histological malignancy-grade III versus IV in the IV-tiered grading system we have used.

We excluded from our study two subsets of patients with extremely poor and good prognoses, respectively, i.e. patients with a metastatic disease detected at the time of diagnosis of the primary tumour, which occurs in less than one-tenth of all patients,[1] and patients with histological low-grade tumours. Of 116 low-grade tumours (grades I and II in the IV-tiered system) excluded from our test series, 10 developed metastases. These metastatic low-grade tumours could not be identified by the use of our prognostic model (data not shown). The low-grade tumours comprise about 20% of all STS of the extremity and trunk wall in population-based data from Sweden.[1] These figures are similar in the AJCC/UICC system and the FNCLCC system in which histological low-grade tumours comprise about 15% and are associated with a 10% metastasis risk.[3,4] Thus, the histopathological classification of a low-grade malignant sarcoma seems to be consistent and of value for the identification of low-risk patients.

The three tumour series we used for this study were selected for pathology review from larger population-based tumour series. A larger proportion of our tumours were superficial than to the rate of one-third found in population-based studies.[12] We have no explanation for this difference but do not believe that it makes our findings limited to our patients since we did not use tumour depth for prognostication. Furthermore, the outcome in a defined subset of our patients, i.e. those who had large and deep-seated tumours, was similar to that in other reports in which about 40% metastasise.[3,4] We acknowledge that the strength and type of risk factors probably vary between different tumour histotypes, but although large, our series did not allow meaningful subgroup analyses.

Tumour size has repeatedly been demonstrated to be a strong prognostic factor in STS.[3,19,22,23] Size is readily measured, and is continuously associated with an increasing risk but is most often dichotomised for prognostication as we also did. The cut-off point is often set at 5 cm but we found 8 cm better, supporting our previous findings.[1,15] Although a strong risk factor, size alone was inadequate for prognostication in our high-grade malignant tumours; in the validation material one-third of high-risk tumours were small (<5 cm) and one-third of the low-risk tumours were large. Size is also closely related to tumour depth and the rationale for including both size and depth in a prognostic system has been questioned.[24,25] We found no value of including depth among the other risk factors we used as these two factors provided similar prognostic information (Table 2). When superficial and deep-seated tumours were analysed separately in the validation material, the stepwise prognostication clearly identified high-, and low-risk groups irrespective of tumour depth.

Also *tumour necrosis* has repeatedly been shown to be a strong prognostic factor in STS.[1,22,26,27] It is, using varying cut-off levels, incorporated in all histological malignancy-grading systems. The precise determination of the amount of necrosis in a tumour is difficult. We, and others, have previously shown good prognostic value of necrosis dichotomised into present (irrespective of amount) or not,[15,22] and we used the same classification in this study. This classification of necrosis may be more reproducible than classification of vascular invasion; in our three series the rate of necrosis varied less than that of vascular invasion (see below), but was highest in the series were whole-tumour sections were analysed. We have previously found a good reproducibility in the identification of necrosis but also of vascular invasion.[15] However, that study was performed by a group of dedicated pathologists whose main task at review was to identify necrosis and vascular invasion.

We have also recently demonstrated that infiltrative peripheral *tumour growth pattern* (versus pushing growth) is strongly linked to the risk of local recurrence and metastasis.[7] The importance of an invasive growth pattern has previously been suggested by Mandard in a series of mixed STS.[27] A non-invasive, pushing growth pattern is present in about one-fifth of histological high-grade STS with less propensity for metastasis.[7]

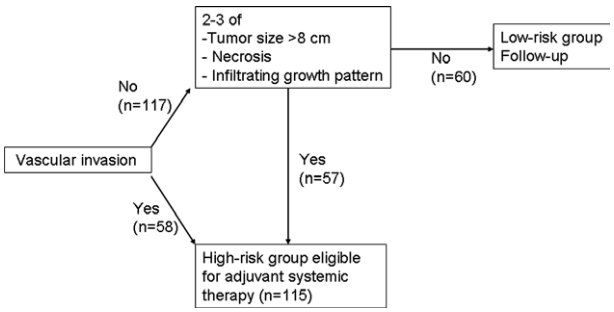

Fig. 3 – A treatment algorithm for histological high-grade STS of the extremities and trunk wall based on vascular invasion, tumour necrosis, tumour size >8 cm and an infiltrative growth pattern. The figures are based on the 175 tumours in the validation series.

Vascular invasion by tumour cells has been shown to be a strong prognostic factor for metastasis in several previous studies of STS.[1,3,7,15,27,28] Despite this, vascular invasion is not included in any of the most commonly used malignancy-grading systems.[29] The reported rate of vascular invasion in histological high-grade STS varies between 10% and 40%.[1,7,30] The reasons for this variation may be difficulties identifying vascular invasion, depending on the amount of tumour tissue examined, as the highest rate reported (40%) was based on examining whole-tumour sections.[7] We found the same variation in our three tumour groups, the lowest rate of vascular invasion was found in the test series where vascular invasion was not specifically searched for and a limited amount of tumour was examined whereas the highest rate was found in the series in which whole-tumour sections were used for identification of vascular invasion. A contributing factor may also be that pathologists pay less attention to vascular invasion since it is not included in current histological malignancy-grading systems. Given the repeatedly demonstrated strong prognostic importance of vascular invasion we decided to test a model in which this factor was taken into account when positive (vascular invasion found) whereas its absence was considered non-informative and such tumours were then subjected to further prognostic assessment.

When the stepwise model was compared to the SIN system and the AJCC/UICC system, all three systems identified high-risk tumours with a risk of metastasis of about 40–50%. However, when assessing discordantly classified tumours, the discrimination between low-risk and high-risk tumours was clearly improved using the stepwise prognostication, which more accurately identified real low-risk tumours (Table 4). Our model can be used as a treatment algorithm for histological high-grade malignant STS and identifies a large subset of patients with low-risk tumours that probably should be exempted from adjuvant chemotherapy (Fig. 3).

Conflicts of interest statement

There are no financial or scientific conflicts of interest for any of the authors, which have bearing on the present work.

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