

# Prognostic factors for local recurrence and mortality in adult soft tissue sarcoma of the extremities and trunk wall

## A cohort study of 922 consecutive patients

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**Background and purpose** — Previous studies of soft tissue sarcoma (STS) have identified a number of possible prognostic factors; however, the majority of these include highly selected populations, with unclear validation of data and insufficient statistical methods. We identified prognostic factors in a validated, population-based 30-year series of STS treated at a single institution, using an advanced statistical approach.

**Patients and methods** — Between 1979 and 2008, 922 adult patients from western Denmark were treated at the Aarhus Sarcoma Center for non-metastatic STS in the extremities or trunk. The endpoints were local recurrence (LR) and disease-specific mortality (DSM). Prognostic factors were analyzed using a proportional hazard model, including continuous variables as cubic splines. Directed acyclic graphs were used to depict the causal structure.

**Results** — The 5-year LR was 16% and the 5-year DSM was 24%. Important prognostic factors for both LR and DSM were age, duration of symptoms, tumor size, grade, margin, and radiotherapy, while anatomical location (upper, lower extremity, trunk) was prognostic for DSM.

**Interpretation** — In this population-based series of adult, non-metastatic STS, we included directed acyclic graphs, cubic splines, and a competing risk model in order to minimize bias, and demonstrated that these statistical methods are feasible. Using these statistical methods on a large, validated dataset, we excluded depth as a prognostic factor and established that age, duration of symptoms, size, grade, margin, and radiotherapy were important prognostic factors for both local recurrence and disease-specific mortality.

Over the past 3 decades, numerous studies on soft tissue sarcoma (STS) have investigated prognostic factors for local recurrence and survival (Pisters et al. 1996, Kattan et al. 2002, Stojadinovic et al. 2002, Zagars et al. 2003, Weitz et al. 2003, Gronchi et al. 2005, Gutierrez et al. 2007, Jebsen et al. 2008, Biau et al. 2011, 2012). While the prognostic value of some factors, e.g. grade and surgical margin, are generally accepted, the value of other factors such as age and location is still uncertain.

To investigate this discrepancy between previous studies, we reviewed the literature and 3 core problems emerged: small sample sizes, heterogeneity of study populations, and differences in statistical methods used.

The rarity of STS, with an incidence of 1.4 per 100,000 (Maretty-Nielsen et al. 2013), makes a sufficient sample size challenging to obtain, and studies are often based on few patients. Thus, these studies may not have sufficient power to identify prognostic factors, or may identify them by chance.

The heterogeneity of study populations in the literature— inclusion of selected subtypes only, high-grade tumors, or patients from centers with major tertiary referral practices and a larger proportion of large, high-grade, recurrent, or otherwise complicated sarcomas—results in possible selection bias and low generalizability. Few authors (e.g. Gustafson 1994) have used population-based data, and when they have, the validity of data sources has not been described or is unknown.

The statistical approaches used to analyze data may introduce several problems, including a substantial overestimation of the failure risk if competing risk is not taken into account, biased estimates if the proper confounding variables are not

included in the adjusted analyses, and risk of over-optimized or irreproducible estimates and residual confounding if the data are analyzed using categorical variables instead of continuous variables (Fine and Gray 1999, Royston et al. 2006, Shrier and Platt 2008). Previously, statistical methods for handling these problems were not easy to use; however, recent implementations in statistical software have made it feasible to address these problems properly.

The aim of this study was to identify prognostic factors in a validated, population-based series of adult STS, using an improved statistical approach with cubic spline regression in a competing risk setting.

## Patients and methods

The Danish healthcare system provides tax-funded, free-of-charge healthcare for all residents. Since 1968, all the citizens of Denmark have been assigned a unique 10-digit civil personal registration number (CPR number). These numbers are used in all Danish administrative registries and clinical databases. This allows linkage of databases at the level of the individual patient and ensures complete follow-up.

### Practice at the Aarhus Sarcoma Center (ASC)

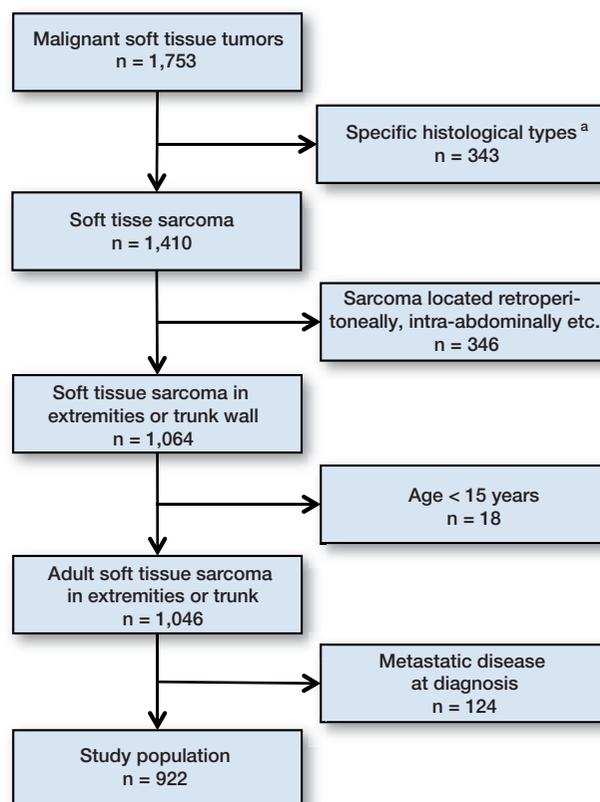
Since 1979, treatment of sarcoma in western Denmark (with 2.5 million inhabitants) has been centralized at the Sarcoma Center of Aarhus University Hospital (ASC). The diagnostic program follows international guidelines and includes a clinical examination, diagnostic imaging, biopsy, and histopathological evaluation conducted by an experienced multidisciplinary team (Co-operative Cancer Departments 2007). In the study period, a 3-tiered malignancy-grading system based on cellularity, necrosis, anaplasia, and number of mitoses was used (Jensen et al. 1991).

The primary treatment is surgery aiming at a wide margin (including radical margins), according to the principles of Enneking et al. (1980). Low-grade tumors are mainly treated with marginal or wide margins (1 cm surrounding cuff of normal tissue), while deep intermediate and high-grade tumors are treated with wide margins and postoperative radiotherapy. The radiotherapy consists of fractions of 2 Gy to a total dose of 50–60 Gy.

Patients are followed for a minimum of 5 years after the last treatment, with intervals ranging from 3 to 6 months. Follow-up visits include clinical examination and chest radiography (intermediate- and high-grade tumors only), with MRI scans for patients with deep-seated tumors in recent years.

### Study population

Between January 1979 and December 2008, 1,753 consecutive patients were treated for STS at the ASC and registered in the Aarhus Sarcoma Registry (ASR) (Vraa et al. 1998). The ASR has recently been systematically validated by reviewing



<sup>a</sup> Dermatofibrosarcoma protuberans, rhabdomyosarcoma, extrasosseous osteosarcoma, kaposi sarcoma, atypical fibroxanthoma, malignant phyllodes tumor, extrasosseous giant cell tumor, subcutaneous low-grade liposarcoma, or if the pathologist was unable to determine whether sarcoma or other malignancy

Figure 1. Flow chart of patients treated for a malignant soft tissue tumor at Aarhus Sarcoma Center in the period 1979–2008, with number of patients (n), reasons for exclusion, and the study population of adult patients with non-metastatic soft tissue sarcoma in the extremities or trunk wall.

the medical files (gold standard) for all patients registered in the ASR using standardized forms. The completeness of the ASR was > 85% for western Denmark in 1979–2008, when compared with the Danish Cancer Registry at the patient level (Maretty-Nielsen et al. 2013). The ASR collects basic patient data, specific data on tumor characteristics and treatment, and data on follow-up, local recurrence, distant metastasis, and death. The completeness of registered data is > 99%. Patients were excluded if they had certain histological types, if they had tumors not located in the extremities or trunk wall, if they were younger than 15 years, or if they had metastases at diagnosis (Figure 1). The study population thus comprised 922 adult patients with non-metastatic STS of the extremity or trunk.

### Prognostic factors

Based on a literature search, possible prognostic factors were selected and prioritized before the data analysis. Based on

the number of events in the study (i.e. in order to have sufficient statistical power), the following factors were included: age at diagnosis, duration of symptoms, tumor size, location, depth, grade, surgical margin, radiotherapy, and calendar year of diagnosis. Directed acyclic graphs were used to depict a possible causal relationship between the prognostic factors selected, possible confounding variables, and the outcomes (Figure 2, see Supplementary data).

Tumor size was recorded as the largest diameter (in cm), based on the fixed pathological specimen. However, if patients were not treated surgically or if the pathology report was insufficient, diagnostic images were used to determine size. Tumors located in the shoulder and gluteal area were classified as trunk tumors. Margins were defined, based on the pathological specimen, as intralesional/marginal if the incision was within the tumor or the pseudocapsule, or as wide if the tumor was surrounded by a cuff of normal tissue.

### Statistics

Descriptive statistics are reported as median and proportions; they were compared using the Kruskal-Wallis test and the chi-squared test. The outcomes assessed were local recurrence (LR) and disease-specific mortality (DSM). DSM was defined as death from sarcoma (including patients with locally advanced tumors) or death from metastatic disease. Patients were followed from the date of diagnosis (DSM analysis) or the date of their last primary treatment (LR analysis) to date of outcome, emigration, or end of the study period. The LR and DSM were estimated as cumulative incidence rates, with 95% confidence intervals (CIs) based on the pseudo-value approach (Fine and Gray 1999, Graw et al. 2009).

The possible prognostic factors were analyzed using a Cox proportional hazard model, estimating both crude and adjusted hazard ratios (HRs) with CI. The confounding variables, as given in Tables 3 and 4 and Figure 2 (see Supplementary data), were selected based on the approach described by Shrier and Platt (2008). Age, duration of symptoms, and tumor size were analyzed continuously as 4-knotted cubic splines, with the twenty-fifth percentile as reference (Smith 1979). Adjusted cumulative incidence curves were constructed using the Stata command *stcurv* (Cleves 2000). The proportional hazard assumption was tested for all the variables included, both crude and adjusted, using log-minus-log plots and no contradictions were found. Competing risks were death from all causes in the analyses of LR and death from causes other than sarcoma in the analyses of DSM. Only patients who were macroscopically disease-free (i.e. with no macroscopic residual tumor) after primary treatment ( $n = 879$ ) were included in the analyses of LR. All tests were two-sided and any  $p$ -value  $\leq 0.05$  was considered significant. Analyses were performed using Stata statistical software, version 13.1.

### Ethics

The study was conducted in accordance with the Helsinki

Declaration. It was approved by the Danish Data Protection Agency (2007-58-0010) and the Danish Health and Medicines Authority (7-604-04-2/262/KWH).

## Results

### Patient and tumor characteristics

Overall, 922 adult patients in western Denmark were diagnosed with non-metastatic STS of the extremity or trunk wall from 1979 through 2008. The median age was 60 (15–95) years and 52% were males (Table 1). Over the study period, an increasing proportion of patients were referred without previous treatment and for primary diagnostics. At the same time, the proportion of patients treated with amputations decreased and the proportion of patients treated with radiotherapy increased. The proportion of wide resections decreased in the final 10-year period. The most frequent tumor types were malignant fibrous histiocytoma, liposarcoma, and leiomyosarcoma (Table 2). After primary treatment, 95% of the patients were macroscopically disease-free. The median follow-up time was 7 (0–34) years. The median follow-up time for patients who were still alive at the end of the study period was 13 (3–34) years.

### Local recurrence (Figures 3–5 and Table 3)

The 5-year LR rate was 16% (CI: 13–18). The correlation between age and the risk of LR was approximately linear with a constant risk from 15 to 55 years, after which the risk increased successively. The relationship between the risk of LR and symptom duration was “J”-shaped, where an increase in the duration of symptoms in the first 12 months was associated with a pronounced drop in the risk of LR, but after that the risk of LR increased steadily the longer the duration of symptoms. An increasing tumor size, for tumors  $\leq 5$  cm or  $\geq 15$  cm, was associated with an increasing risk of LR. In the confounder-adjusted analyses, age  $> 55$  years (vs. 45 years), duration of symptoms  $< 3$  months (vs. 3 months), tumor size 5–7 cm or  $> 20$  cm (vs. 4 cm), grade 3, and intralesional/marginal excision were adverse prognostic factors, while duration of symptoms  $> 3$  months and  $< 24$  months (vs. 3 months), tumor size  $< 4$  cm (vs. 4 cm), and treatment with radiotherapy were favorable prognostic factors.

### Disease-specific mortality (Figures 3, 4, and 6, and Table 4)

The 5- and 10-year DSM rates were 24% (CI: 21–27) and 29% (CI: 26–32). The risk of DSM was nearly constant between 15 and 45 years, after which it increased. Increasing duration of symptoms was associated with a decreasing risk within 9 months, but after that it was approximately constant. Increasing tumor size was associated with an increasing risk, and this was most pronounced for tumors  $\leq 5$  cm. Adverse prognostic factors were age  $> 45$  years (vs. 45 years), tumor size  $> 4$  cm (vs. 4 cm), trunk and lower extremity location, grade 2–3

**Table 1.** Characteristics of adult patients treated for a non-metastatic soft tissue sarcoma in the extremities or trunk wall at the Sarcoma Center of Aarhus University Hospital according to calendar year of diagnosis (n = 922). Unless otherwise stated, values are number (%)

	1979–1988	1989–1998	1999–2008	Total	p-value <sup>a</sup>
Sex					
Female	104 (49)	147 (50)	190 (46)	441 (48)	0.6
Male	110 (51)	148 (50)	223 (54)	481 (52)	
Age at diagnosis, years					
Median (range)	61 (15–95)	57 (15–92)	60 (15–93)	60 (15–95)	0.06
Duration of symptoms, months					
Median (range) <sup>b</sup>	9 (1–672)	7 (1–600)	6 (1–732)	6 (1–732)	0.06
Treatment before referral					
None	55 (26)	135 (46)	238 (58)	428 (46)	< 0.001
Biopsy	32 (15)	34 (12)	32 (8)	98 (11)	
Surgery, insufficient <sup>c</sup>	115 (54)	120 (41)	135 (33)	370 (40)	
Surgery, sufficient <sup>c</sup>	12 (6)	6 (2)	8 (2)	26 (3)	
Reason for referral					
Primary diagnostic	184 (86)	284 (96)	397 (96)	865 (94)	< 0.001
Local recurrence	30 (14)	11 (4)	16 (4)	57 (6)	
Tumor size, cm					
Median (range) <sup>d</sup>	6 (1–30)	6 (1–28)	7 (1–35)	7 (1–35)	0.7
Depth					
Superficial	60 (28)	72 (24)	130 (31)	262 (28)	0.1
Deep	154 (72)	223 (76)	283 (69)	660 (72)	
Grade					
1	36 (17)	44 (15)	67 (16)	147 (16)	0.001
2	40 (19)	55 (19)	47 (11)	142 (15)	
3	129 (60)	196 (66)	292 (71)	617 (67)	
Unclassifiable	9 (4)	0 (0)	7 (2)	16 (2)	
Surgical treatment	207 (97)	286 (97)	401 (97)	894 (97)	1.0
Type <sup>e</sup>					
Resection	153 (77)	226 (81)	368 (92)	747 (85)	< 0.001
Amputation	47 (24)	54 (19)	31 (8)	132 (15)	
Margin <sup>f</sup>					
Wide	157 (79)	223 (79)	256 (64)	636 (72)	< 0.001
Intralesional/marginal	43 (22)	59 (21)	143 (36)	245 (28)	
Radiotherapeutic treatment	28 (13)	107 (36)	161 (39)	296 (32)	< 0.001
Chemotherapeutic treatment	9 (4)	2 (1)	12 (3)	23 (2)	0.03
Macroscopically disease-free	202 (94)	283 (96)	394 (95)	879 (95)	0.7

<sup>a</sup> Based on the Kruskal-Wallis test and the chi-square test.  
<sup>b</sup> 33 missing values.  
<sup>c</sup> Assessed at the Aarhus Sarcoma Center. Sufficient surgery was defined as wide resections, whereas insufficient surgery was defined as intralesional/marginal resections.  
<sup>d</sup> 15 missing values.  
<sup>e</sup> Only patients treated with surgery (n = 894) included. 15 missing values.  
<sup>f</sup> Only patients treated with surgery (n = 894) included. 13 missing values.

or unclassifiable, and intralesional/marginal excision, while duration of symptoms  $\geq 15$  and  $\leq 30$  months, tumor size  $< 4$  cm (vs. 4 cm), and treatment with radiotherapy were favorable prognostic factors. Depth was not a prognostic factor.

## Discussion

In this population-based study, using systematically validated data, we found a 5-year LR rate of 16% and a 5-year DSM of 24%. Important prognostic factors for both LR and DSM were age, duration of symptoms, tumor size, grade, margin, and radiotherapy, while anatomical location was prognostic for DSM.

## Methodological considerations

The main strengths of the present study include the large sample size, the population-based design with complete follow-up, and the statistical methods used to minimize bias.

The validity of the ASR has been reported in detail in a previous paper (Maretty-Nielsen et al. 2013). The overall completeness of patient registration in the ASR is  $> 85\%$ ; however, the completeness differed according to calendar year at diagnosis, residency, and age. The completeness was lower in patients diagnosed before 1994, in patients from the southern region of Denmark, and in patients over 60 years of age. These differences may introduce a selection bias if the association between the factors investigated and the outcome is different for patients not registered in the ASR. Based on this,

**Table 2.** Distribution of non-metastatic soft tissue sarcomas in the extremities and trunk wall according to histological types in adult patients treated at the Aarhus Sarcoma Center from 1979 to 2008 (n = 922)

Type	n	%
MFH <sup>a</sup>	280	30
Liposarcoma	185	20
WD/DD <sup>b</sup>	71	7.8
MRC <sup>c</sup>	66	7.2
Pleomorphic	46	5.0
Unknown	2	0.2
Leiomyosarcoma	164	18
Synovial sarcoma	65	7.1
MPNST <sup>d</sup>	61	6.6
Fibrosarcoma	47	5.1
Angiosarcoma	22	2.4
Epithelioid sarcoma	18	2.0
Malignant hemangiopericytoma	11	1.2
Fibromyxoid sarcoma	8	0.9
Extraosseous chondrosarcoma	8	0.9
Spindle cell sarcoma	3	0.3
Malignant mesenchymoma	3	0.3
Others	11	1.2
Unclassifiable	36	3.9

Classified according to the WHO classification of tumors of soft tissue and bone, 3rd edition, 2002.

<sup>a</sup> Malignant fibrous histiocytoma (undifferentiated, pleomorphic sarcoma according to the 4th edition, 2013).

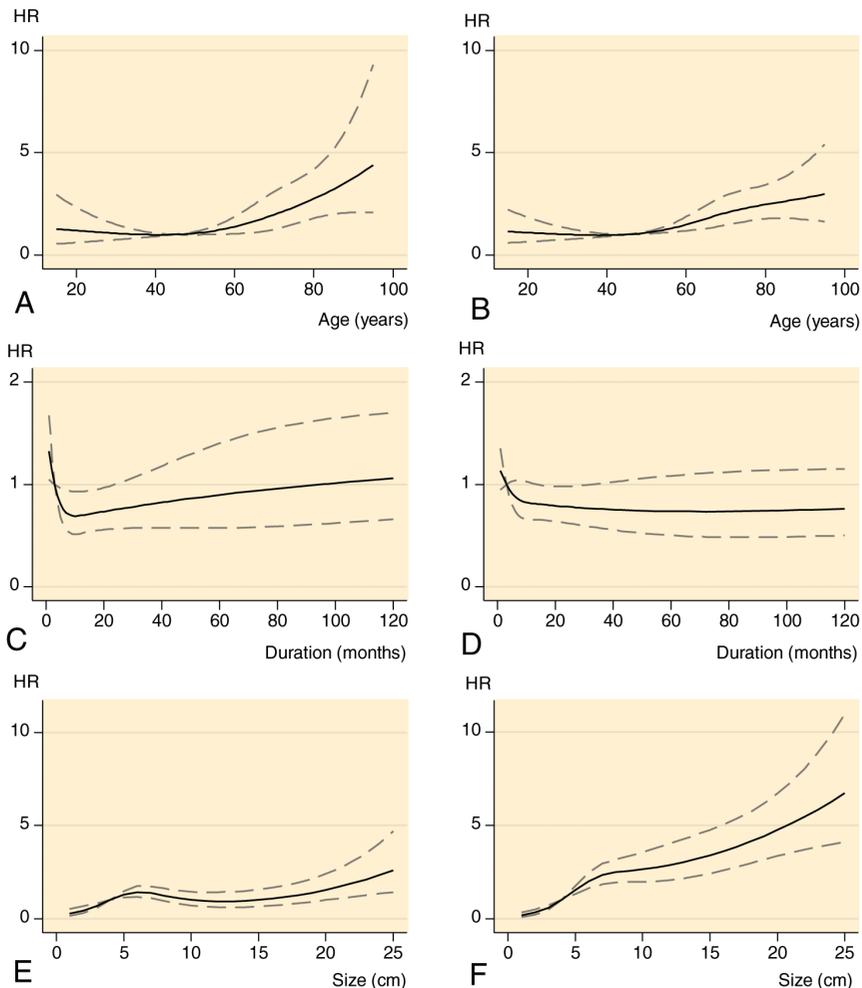
<sup>b</sup> Well-differentiated/dedifferentiated.

<sup>c</sup> Myxoid round cell tumor.

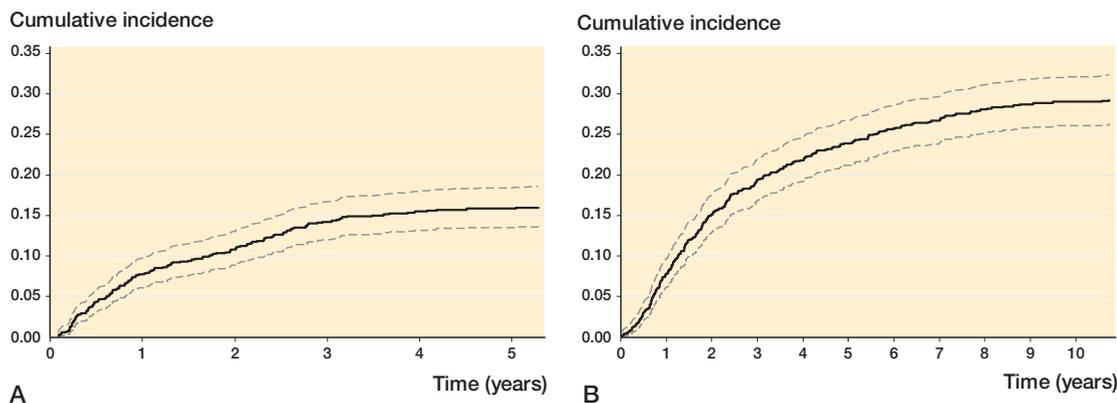
<sup>d</sup> Malignant peripheral nerve sheath tumor.

we would expect any selection bias to have been minor.

The possible prognostic factors we investigated were selected based on a literature search, and they were specified before the data analysis. When selecting the possible



**Figure 4.** Adjusted hazard ratios (HR (solid line)) with 95% confidence intervals (dashed lines) for local recurrence (panels A, C, and E) and disease-specific mortality (B, D, and F) according to age, duration of symptoms, and tumor size, based on Cox proportional hazard analyses. Adjustment covariates were selected based on Figure 2 (see Supplementary data); no covariates were included in the analysis of age; duration of symptoms was adjusted for age and grade; tumor size was adjusted for duration of symptoms and grade.



**Figure 3.** Cumulative incidence rate (solid black line) of local recurrence (panel A) and disease-specific mortality (panel B) with 95% confidence intervals (dotted gray lines).

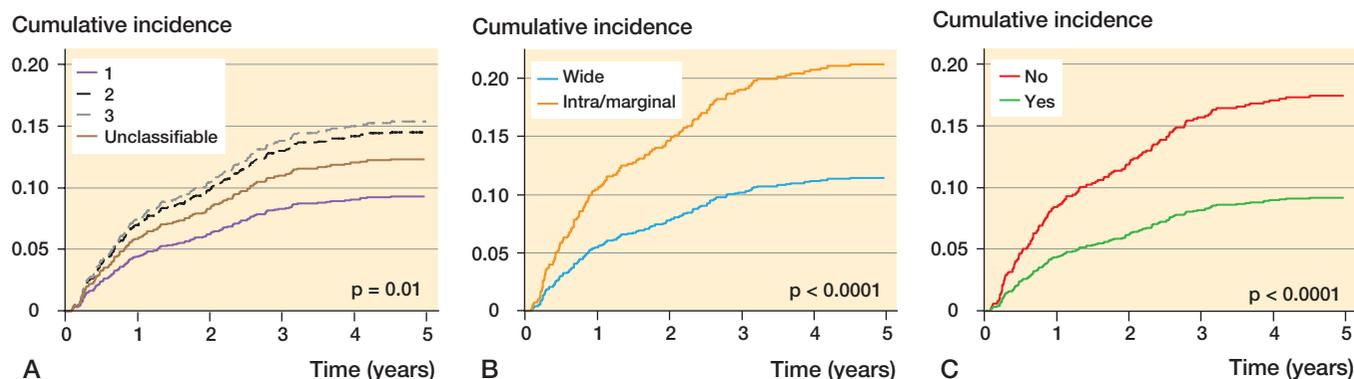


Figure 5. Adjusted cumulative incidence of local recurrence by grade (A), surgical margin (B), and radiotherapy (C) based on a Cox proportional hazard regression. Grade was adjusted for age and histological subtype; margin was adjusted for age, size, depth, location, compartmentalization, grade, and year of diagnosis; and radiotherapy was adjusted for age, depth, grade, margin, and year of diagnosis.

Table 3. Crude and confounder-adjusted Cox proportional hazard analyses of possible prognostic factors for local recurrence in adult patients with non-metastatic soft tissue sarcoma in the extremity or trunk wall (n = 879)

Factor	n (%)	LR rate 5-year, %	Crude HR (95% CI)	Adjusted <sup>a</sup> HR (95% CI)
Anatomical location				
Upper extremity	150 (17)	19	1	1
Trunk	255 (29)	20	1.09 (0.71–1.68)	1.18 (0.76–1.82)
Lower extremity	474 (54)	12	0.71 (0.47–1.08)	0.89 (0.58–1.36)
Depth				
Superficial	259 (29)	14	1	1
Deep	620 (71)	17	1.31 (0.92–1.86)	0.80 (0.53–1.21)
Grade				
1	145 (17)	9	1	1
2	137 (16)	15	1.48 (0.79–2.76)	1.61 (0.85–3.03)
3	585 (67)	18	2.32 (1.40–3.86)	2.00 (1.16–3.44)
Unclassifiable	12 (1)	8	1.82 (0.42–7.90)	1.76 (0.39–7.86)
Surgery (excision) <sup>b</sup>				
Wide	636 (73)	12	1	1
Intralesional/marginal	237 (27)	25	2.29 (1.67–3.14)	2.01 (1.41–2.85)
Radiotherapy				
No	598 (68)	17	1	1
Yes	281 (32)	14	0.84 (0.60–1.19)	0.47 (0.32–0.71)
Calendar year of diagnosis				
1979–1988	202 (23)	19	1	1
1989–1998	283 (32)	14	0.86 (0.57–1.28)	0.86 (0.57–1.28)
1999–2008	394 (45)	15	0.85 (0.58–1.24)	0.85 (0.58–1.24)

LR: local recurrence; HR: hazard ratio.

<sup>a</sup> Confounding variables were selected based on the directed acyclic graph depicted in Figure 2 (see Supplementary data): location was adjusted for histological type; depth was adjusted for duration of symptoms, size, and histological type; grade was adjusted for age and histological type; margin was adjusted for age, size, depth, location, compartmentalization, grade, and year of diagnosis; radiotherapy was adjusted for age, depth, grade, margin, and year of diagnosis; no adjustments were included in the analysis of year of diagnosis.

<sup>b</sup> Only patients treated with surgery (n = 876) included. 3 missing values.

confounding factors that should be included in the adjusted analyses, many studies have used variations of forward selection, backward elimination, or simply inclusion of all factors; however, this can result in biased estimates with CIs that are too narrow and p-values that are too low. To our knowledge, this is the first study of prognostic factors in STS in which

directed acyclic graphs have been used to depict causal relationships in order to select possible confounding factors and thus minimize bias.

The continuous variables were included as cubic splines (Smith 1979). When evaluating the results from other studies, these variables are often analyzed categorically with one cut-off point or continuous linearly (Royston et al. 2006). As seen in Figure 4, neither of these approaches is adequate, with the categorical method resulting in residual confounding and the continuous linear method being a false assumption. Furthermore, when selecting cut-points the method is often not specified, or the “optimal” cut-point method is used, leading to over-optimized and irreproducible estimates. Likewise, different cut-points are often used, impairing the generalizability.

The WHO classification, which was used to classify STS in this study, has recently been updated, resulting in the change of some histological subtypes, e.g. malignant fibrous histiocytoma, now called

undifferentiated pleomorphic sarcoma, and fibrosarcoma, which is becoming increasingly rare due to classification as other more specific types (Fletcher et al. 2002). The pathology of the STS patients reported in this study has not been reviewed, which may have caused misclassification when compared to the new WHO classification. However, a histo-

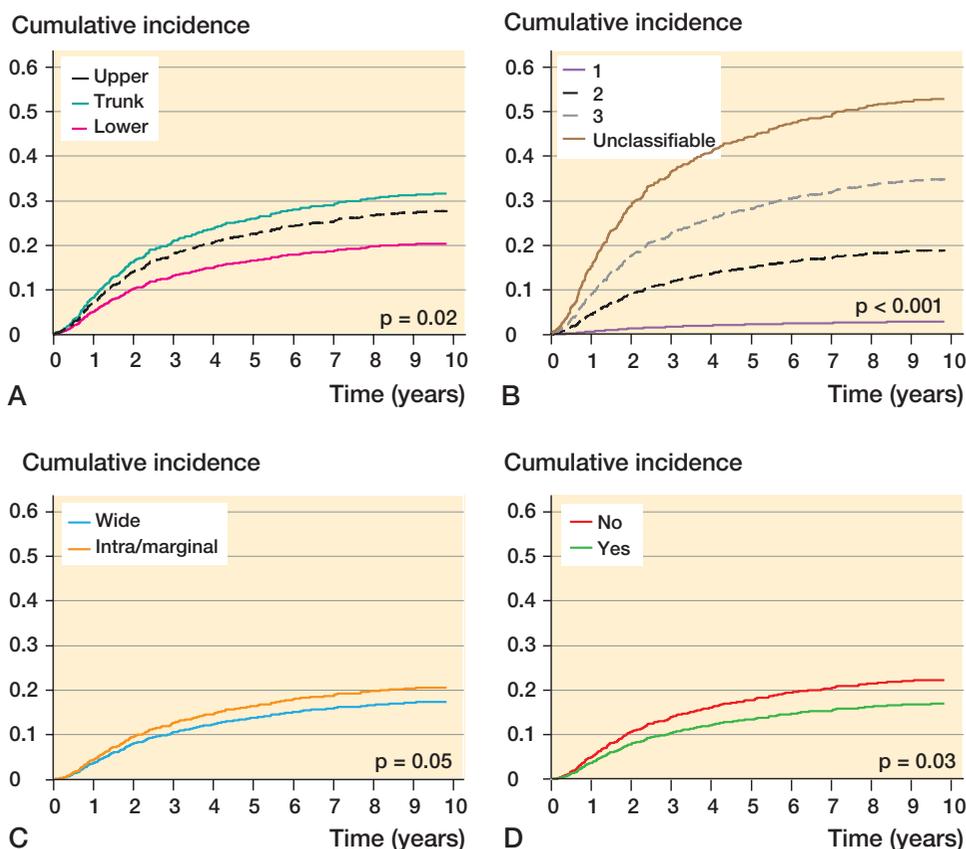


Figure 6. Adjusted cumulative incidence of disease-specific mortality by location (A), grade (B), surgical margin (C), and radiotherapy (D) based on Cox proportional hazard regression. Location was adjusted for histological subtype; grade was adjusted for age and histological subtype; margin was adjusted for age, size, depth, location, compartmentalization, grade, and year of diagnosis; and radiotherapy was adjusted for age, depth, grade, margin, and year of diagnosis.

pathological evaluation according to the (at that time) relevant classification was performed at the time of diagnosis by an experienced sarcoma pathologist, for all patients referred to or diagnosed/treated at the Aarhus Sarcoma Center. Furthermore, during the study period only 2–3 pathologists performed these evaluations, ensuring that the classification was consistent throughout the study period. For this reason, misclassification would be expected to be minor and of no significance to our study, where several histological types were considered together.

The comparability with other prognostic studies may have been complicated by the grading system used in the ASR (Jensen et al. 1991). This is primarily based on the number of mitoses, taking the cellularity, necrosis, and anaplasia into account, with some specific histopathological subtypes pre-specified, e.g. rhabdomyosarcoma and extrasosseous osteosarcoma as grade 3. Currently, the most common grading systems are the National Cancer Institute (NCI) system and the Fédération Nationale des Centres de Lutte contre le Cancer (FNCLCC) system (Costa et al. 1984, Trojani et al. 1984). These grading systems are based on the same principles as in

the system we used. STS patients at the ASC have been registered according to the FNCLCC system since January 2009, and based on the limited discrepancies in grading that we have found before and after January 2009, we would expect comparability issues to be minor.

We assessed the outcomes LR and DSM using a competing risk model, which was not done in most previous studies. In cases in which the competing event is frequent, not using a competing risk model can lead to overestimation of the failure outcome (Fine and Gray 1999). Establishment of the correct cause of death is essential in DSM, and even though we used validated data on the cause of death, this can be problematic in elderly patients, where comorbidity is frequent.

During the study period, some changes in the treatment of patients at ASC were observed. Consistent with reports from other sarcoma centers, the proportion of patients treated with amputation decreased from 24% in the period 1979–1988 to 8% in the period 1999–2008 (Gronchi et

al. 2005, Jebsen et al. 2008, Biau et al. 2011, 2012). Overall, it appears that there has been a shift in treatment regime, with a tendency towards “closer” surgical removal and adjuvant treatment with radiotherapy. However, this shift did not affect the LR rate or the DSM rate, as seen in the insignificance of calendar year of diagnosis in our analyses.

### Overall rates

The LR and DSM rates presented in our study were in overall agreement with those in previously published studies (Gustafson 1994, Pisters et al. 1996, Stojadinovic et al. 2002, Zagars et al. 2003, Gutierrez et al. 2007, Jebsen et al. 2008, Biau et al. 2011). Such studies have found 5-year LR rates between 8% and 22%, whereas there tended to be higher LR rates previously, which is possibly explained by the non-competing risk setting. The majority of previous studies found 5-year DSM rates between 20% and 45%, as compared to our results of 24%. The lower rates observed might also be explained by the fact that surgical treatment during the study period was performed by a small number of experienced oncology surgeons working in close collaboration.

**Table 4.** Crude and confounder-adjusted Cox proportional hazard analyses of possible prognostic factors for disease-specific mortality in adult patients with non-metastatic soft tissue sarcoma in the extremities or trunk (n = 922)

Factor	n (%)	DSM rate (%)		Crude HR (95% CI)	Adjusted <sup>a</sup> HR (95% CI)
		5-year	10-year		
<b>Anatomical location</b>					
Upper extremity	152 (16)	18	25	1	1
Trunk	275 (30)	29	33	1.52 (1.04–2.22)	1.72 (1.18–2.52)
Lower extremity	495 (54)	23	28	1.24 (0.87–1.78)	1.49 (1.03–2.14)
<b>Depth</b>					
Superficial	262 (28)	11	14	1	1
Deep	660 (72)	29	35	2.91 (2.07–4.11)	1.31 (0.88–1.97)
<b>Grade</b>					
1	147 (16)	3	3	1	1
2	142 (15)	9	17	7.06 (2.47–20.24)	7.23 (2.51–20.79)
3	617 (67)	32	37	19.71 (7.33–52.97)	15.75 (5.78–42.93)
Unclassifiable	16 (2)	50	57	35.52 (10.93–115.40)	30.60 (9.20–101.78)
<b>Surgery (excision)<sup>b</sup></b>					
Wide	636 (72)	20	25	1	1
Intralesional/marginal	245 (28)	29	34	1.59 (1.22–2.06)	1.32 (1.00–1.76)
<b>Radiotherapy</b>					
No	626 (68)	22	27	1	1
Yes	296 (32)	28	34	1.28 (1.00–1.64)	0.64 (0.48–0.86)
<b>Calendar year of diagnosis</b>					
1979–1988	214 (23)	26	33	1	1
1989–1998	295 (32)	22	27	0.93 (0.68–1.26)	0.93 (0.68–1.26)
1999–2008	413 (45)	24	29	0.93 (0.69–1.25)	0.93 (0.69–1.25)

DSM: disease-specific mortality; HR: hazard ratio.

<sup>a</sup> Confounding variables were selected based on the directed acyclic graph depicted in Figure 2 (see Supplementary data): grade was adjusted for age and histological type; location was adjusted for histological type; depth was adjusted for duration of symptoms, size, and histological type; margin was adjusted for age, size, depth, location, compartmentalization, grade, and year of diagnosis; radiotherapy was adjusted for age, depth, grade, margin, and year of diagnosis; no adjustments were included in the analysis of year of diagnosis.

<sup>b</sup> Only patients treated with surgery (n = 894) included. 13 missing values.

### Prognostic factors

Age > 45–55 years was associated with higher LR and DSM. The important effect of age on DSM, when analyzed continuously, has not been described before. Two recent studies investigated the prognostic value of age when analyzed using cubic splines: Gronchi et al. (2005) reported no independent effect on either LR or DSM, while Biau et al. (2011) found a statistically significantly higher LR rate with increasing age. Studies have shown increased LR and mortality with increasing age, even when reporting DSM; however, the majority of these have reported age as a binomial categorical variable (Kattan et al. 2002, Weitz et al. 2003, Zagars et al. 2003, Gutierrez et al. 2007).

Size, grade, and margin were important prognostic factors for both LR and DSM, which is supported by the previous literature (Pisters et al. 1996, Kattan et al. 2002, Stojadinovic et al. 2002, Zagars et al. 2003, Weitz et al. 2003, Gronchi et al. 2005, Jebsen et al. 2008, Biau et al. 2011, 2012). Unexpectedly, we found a tendency of unclassifiable tumors being associated with higher mortality than even high-grade tumors. One explanation could be that this group represents the most undifferentiated sarcomas with high aggressiveness.

Very few studies have analyzed duration of symptoms in a confounder-adjusted setting, and only as a categorical variable. Previous results have been highly contradictory; some studies found no prognostic effect of duration of symptoms (Rougraff et al. 2007), others found that short duration of symptoms was associated with increased mortality (Saithna et al. 2008, Urakawa et al. 2013), and finally others found that short duration of symptoms was associated with reduced mortality (Nakamura et al. 2011). One possible explanation of these contradictions might be that the correlation between duration of symptoms and mortality is “J”-shaped, as an expression of rapid increase in size of high-grade tumors—and thus short duration of symptoms—while low-grade tumors grow slowly and in the end may de-differentiate into higher grades. This is further supported by the findings of Maguire et al. (1994), namely that the effect of duration of symptoms on survival was not linear. In accordance with this, we found that both curves were almost “J”-shaped, with higher LR and DSM rates at both ends of the symptom-duration spectrum.

The literature regarding the prognostic value of depth on mortality is controversial. In contrast to the majority of published studies (Pisters et al. 1996, Kattan et al. 2002, Weitz et

al. 2003, Gronchi et al. 2005), our data did not support depth as a prognostic factor for DSM, which is supported by a few studies, including a recent study comparing the sixth and the seventh version of the American joint committee's staging system, where depth is no longer included (Rydholm and Gustafson 2003, Maki et al. 2013). In line with our study, most studies have found that anatomical location is an important prognostic factor for mortality (Pisters et al. 1996, Kattan et al. 2002, Stojadinovic et al. 2002, Zagars et al. 2003, Gutierrez et al. 2007). In concordance with the majority of published studies (Pisters et al. 1996, Weitz et al. 2003, Jebsen et al. 2008), but not all (Stojadinovic et al. 2002, Biau et al. 2011, 2012), we found that location and depth were not prognostic factors for LR.

Most studies (Jebsen et al. 2008, Biau et al. 2011, 2012), like ours, found that radiotherapy reduces the LR rate; however, the characteristics of tumors for which radiotherapy is beneficial vary. Kaytan et al. (2003) reported an effect only in high-grade tumors, while Jebsen et al. (2008) reported effects in low-grade tumors also. Very few studies have investigated the effect of radiotherapy on survival, and while some found a significant impact (Gronchi et al. 2005, Gutierrez et al. 2007), others found the opposite (Weitz et al. 2003). A retrospective study involving 6,960 patients showed that radiotherapy improved survival for high-grade tumors, while no improvement was seen for low-grade tumors. (Koshy et al. 2010). Based on the local practice at the Aarhus Sarcoma Center, subgroup analyses were not obtainable in our study.

### Conclusion

We conducted a large study including 922 consecutive adult non-metastatic STS patients, representing the "reality" seen in everyday clinics. Since results have a direct impact on future treatment strategies as well as the prognosis given to our patients, obtaining unbiased results is essential. In order to properly address a wide range of biases we included directed acyclic graphs, cubic splines and a competing risk model, and showed that these statistical methods are feasible. Using these improved statistical methods on a large, validated dataset, we excluded depth as an independent prognostic factor, and established that duration of symptoms and radiotherapy were important prognostic factors for DSM. Moreover, the method confirmed the importance of several prognostic factors for LR and DSM previously identified in studies with major tertiary referral practices.

### Supplementary data

Figure 2 is available at Acta's website ([www.actaorthop.org](http://www.actaorthop.org)), identification number 6776.

KMN: collected clinical data, performed statistical analyses, and wrote the manuscript. NAP: collected clinical data, contributed to the statistical analyses, and proofread the manuscript. AS and JK: planned the study, treated the patients included, collected clinical data, and proofread the manuscript. PHJ

and BHH: operated the patients included, collected clinical data, and proofread the manuscript. SB: examined the pathological materials, collected clinical data, and proofread the manuscript. ABP: planned the study, contributed to statistical evaluation, and proofread the manuscript.

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