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A novel risk score to predict early and late recurrence in solitary fibrous tumour

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Aims: Solitary fibrous tumours (SFTs) are rare mesenchymal neoplasms with recurrence rates of 10–30%. Current risk stratification systems for extrameningeal SFTs are based on cohorts with limited follow-up and are not suitable for prediction of late recurrences. In this study we aimed to develop a prognostic model accounting for both early and late recurrences using a relatively large patient cohort with long-term follow-up.

Methods and results: Clinicopathological factors were analysed in a cohort of 100 extrameningeal, STAT6-positive SFTs. Median follow-up for overall survival (OS) and recurrence-free interval (RFi) were 121 and 84 months, respectively. Disease relapse occurred in 31% of patients and median time to recurrence was 63 months. In univariate analysis mitotic count, necrosis, male gender and presence of severe atypia and pleomorphism were associated with inferior RFi. Mitotic count, necrosis and male gender were independent predictors of recurrence in multivariate analysis. Previously published risk models were also statistically associated with RFi in our cohort, but failed to reliably identify low-risk patients due to poor prediction of late recurrences. A novel risk score based on mitotic count, necrosis and gender was able to stratify patients into low-, intermediate- and high-risk groups for both early and late recurrences.

Conclusions: In this cohort of patients with extrameningeal SFT and long-term follow-up mitotic count, necrosis and gender were independent prognostic markers of recurrence. We propose a novel risk score based on these factors and accounting for late recurrences, which should be validated in external cohorts with sufficient follow-up time.

Keywords: prognosis, recurrence, risk stratification, solitary fibrous tumour, survival

Introduction

Solitary fibrous tumour (SFT) is a rare mesenchymal neoplasm defined as a tumour with a prominent haemangiopericytoma-like branching vascular pattern and fibroblastic differentiation.[1] SFT behaves predominantly as a benign neoplasm; however, aggressive behaviour in the form of local or distant recurrence may occur in 10–30%.[2–7] Established prognostic factors include mitotic count,[3,6–13] necrosis,[2,8,9,14] age,[3,7,8] tumour size,[2,5–10,15] tumour location,[5,16] Ki-67,[2,10,17] hypercellularity[9,13] and cellular atypia.[2,13] Although clinical and histopathological characteristics have been shown to predict outcome, the role of the above-mentioned variables in risk prediction is controversial.[18–20]

Scoring systems that include multiple prognostic factors have been created, aiming to improve prognostic accuracy. Demicco and co-workers developed a scoring system based on age, tumour size, mitotic

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count and necrosis to predict metastasis.[7,8] Salas and co-workers included mitotic count, age and tumour site to predict metastasis ($Salas^{MET}$), mitotic count and age for overall survival ($Salas^{OS}$) and age, tumour site and radiation therapy for local recurrence.[3] Other risk models based on pleuropulmonary SFT cohorts or cohorts without pleuropulmonary tumours have also been suggested.[9,13,18,21] A recently published comparison of the risk models demonstrated that the modified Demicco (mDemicco) and $Salas^{OS}$ models most accurately predicted recurrence.[22] However, nearly all the above-mentioned cohorts suffer from insufficient follow-up time. Recurrences occur relatively frequently more than 5 years after complete resection[2,3,5,7,9,23] and patients are still at risk of recurrence more than 10 years after primary treatment.[19,22] Notably, median follow-up in the studies by Demicco *et al.* and Salas *et al.* was 48 and 33 months, respectively.

Thus, the robustness of the existing stratification systems for the prediction of late recurrences is questionable. In this work, we aimed to develop a prognostic score accounting for both early and late recurrences using a relatively large patient cohort with long-term follow-up from a sarcoma reference centre.

Materials and methods

PATIENT COHORT

We searched our prospectively maintained, institutional clinical sarcoma database and our pathology database for patients treated with curative intent for localised extrameningeal SFT or haemangiopericytoma. One-hundred and eighty-three patients diagnosed between January 1983 and December 2018 were identified. To ensure a sufficient follow-up time, we excluded patients diagnosed after December 2015 (n = 30). Two patients treated with preoperative radiation and chemotherapy were excluded. Clinical records and pathology reports were collected for all cases. The project was approved by the Regional Ethics Committee in South East Norway (no. 2010-509).

HISTOPATHOLOGICAL EVALUATION

All available slides of surgical resection specimens were reviewed and classified according to the World Health Organisation (WHO) classification by two authors (T.G. and B.B), one of whom is an experienced soft tissue pathologist.[1] For inclusion, typical morphological criteria of SFT had to be present: ovoid-to-spindle tumour cells arranged in a patternless pattern, branching haemangiopericytoma-like vessels and alternating hypo- and hypercellular areas in a variably collagenised stroma. Signal transducer and activator of transcription 6 (STAT6) should be positive with immunohistochemistry.[1,24,25] Mitotic count was evaluated in the most mitotically active areas per 10 high-power fields (1 HPF = 0.2289 mm^2) and subgrouped according to Demicco *et al.* (0, 1–3, ≥4)[7] and Salas *et al.* (≤4, >4).[3] The extent of tumour necrosis was categorised according to Demicco *et al.* (<10%, ≥10%)[7] and Salas *et al.* (no, <50% and ≥50%).[3] Cellularity was graded as low, intermediate and high according to Demicco et al..[7] Atypia was categorised as the absence or presence of prominent cellular atypia and nuclear pleomorphism. Tumours were classified as superficial if located exclusively above the superficial fascia, otherwise deep-seated. Resection margins were assessed as negative (R0), microscopically (R1) and macroscopically (R2) positive.[26] Growth pattern was defined as infiltrative or 'pushing'.[27] Primary tumour size was grouped according to Demicco *et al.* (0.0–4.9, 5.0–9.9, 10.0–14.9, ≥15.0 cm).[7] The immunohistochemical analysis is described in Supporting information Data S1.

STATISTICAL ANALYSIS

Survival was calculated from the date of histopathological diagnosis either on core biopsy or resection specimen. For recurrence-free interval (RFi), distant metastasis or local recurrence was considered an event. For distant recurrence-free interval (D-RFi) metastasis was considered an event.[28] Patients without recurrence were censored at the date of last radiological examination of chest and/or abdomen for RFi and D-RFi, and death was not considered an event. For OS, date of death of any cause was collected from the National Registry of Norway and patients still alive were censored at 21 February 2019.

Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariate survival analysis was performed using the Cox proportional hazard regression model with backward, stepwise elimination of variables. Receiver operating characteristics (ROC) curves and area under the ROC curve (AUC) were used to measure the performance of prognostic systems. Associations between clinicopathological parameters were examined using the two-tailed Fisher's exact test and the Mann–Whitney U-test. A P-value < 0.05 was

considered significant. SPSS Statistics version 25.0 (SPSS Inc., Chicago, IL, USA) was used.

Results

PATIENT COHORT

After pathology review, 100 patients with extrameningeal SFT were included in the final cohort (Supporting information, Figure S1). The demographic and clinical characteristics are presented in Table 1. There were 53 females and 47 males. Median age at diagnosis was 60 years (range = 24–82). The most frequent tumour localisation was abdomen/retroperitoneum (28%), followed by pleuropulmonary tumours (22%) and tumours in extremities (20%). Median tumour size was 7 cm (range = 1–28 cm). Three patients (3%) underwent adjuvant radiation therapy.

HISTOPATHOLOGICAL CHARACTERISTICS

The histopathological characteristics are presented in Table 1. Twenty-four tumours (24%) had ≥4 mitotic figures per 10 HPF. Necrosis was present in 36 samples (36%), of which five tumours (5%) had ≥50% necrosis. Severe atypia and nuclear pleomorphism was observed in 14% of the tumours. Twenty-seven tumours (27%) were diffusely infiltrating. Cellularity was mostly moderate (47%) and high (47%). No cases were considered to have a de-differentiated component.[29] Strong nuclear STAT6 immunostaining was found in all included cases. CD34 was negative in four cases (4%). All CD34-negative tumours were MDM2-negative, excluding de-differentiated liposarcoma as a differential diagnosis.

A strong association between high mitotic count and presence of necrosis was found. In tumours with ≥4 mitoses, necrosis was present in 83% compared to 21% for tumours with mitotic count <4 ($P < 0.001$). An overview of the associations between the histopathological characteristics is presented in Supporting information, Table S1.

OUTCOME

Fourteen patients without follow-up for RFi were excluded from prognostic analysis. Median follow-up for OS was 121 months (range = 5–415) and median follow-up for RFi was 84 months (range = 1–243 months). Twenty-seven patients (31%) experienced disease recurrence after a median time of 63 months (range = 3–227). The median estimated RFi was 162 months. Distant metastasis was observed

Table 1. Demographic, clinical and histopathological characteristics

Characteristics	No. of patients (%)[1]
Age (at presentation), years	
Median (range)	60 (24–82)
Gender	
Male	47 (47)
Female	53 (53)
Site	
Head and neck	15 (15)
Extremity	20 (20)
Trunk wall	11 (11)
Pleuropulmonary	22 (22)
Abdomen/retroperitoneum	28 (28)
Other[2]	4 (4)
Tumour depth	
Deep-seated	79 (79)
Superficial	21 (21)
Tumour size, cm	
Median (range)	7 (1–28)
Resection margins	
R0	64 (64)
R1	34 (34)
R2	2 (2)
Mitotic count[3]	
Median (range)	2 (0–50)
<4	76 (76)
≥4	24 (24)
Necrosis	
Absent	64 (64)
<50%	31 (31)
≥50%	5 (5)
Atypia/pleomorphism	
No	86 (86)
Yes	14 (14)
Cellularity	

Table 1. *(Continued)*

Characteristics	No. of patients (%)[1]
Low	6 (6)
Moderate	47 (47)
High	47 (47)
Growth pattern	
Pushing	70 (70)
Infiltrating	27 (27)
Not determined	3 (3)

Total number of patients: 100.
[1]Unless otherwise specified.
[2]other tumour sites: prostate, labium majus, uterus, bladder.
[3]number of mitotic figures per 10 high-power fields.

in 21 patients (24%), and 15 tumours (17%) recurred locally. Lung was the most frequent first metastatic site (43%). Twenty-eight patients (28%) died during follow-up, 12 of whom died of SFT, seven for other reasons and nine of unknown cause. A summary of the outcome data is presented in Table 2.

PROGNOSTIC FACTORS

In univariate analysis, factors associated with inferior RFi were male gender ($P = 0.036$), necrosis ($P = 0.001$), mitotic count ($P < 0.001$) and the presence of severe atypia and pleomorphism ($P = 0.003$) (Table 3, Figure 1A–C). Estimated 10-year RFi for patients with tumours with ≥4 mitoses was 26% compared to 77% for the patients with a mitotic count <4. Patients with necrosis (<50% and ≥50%) had a 10-year survival of 46% compared to 75% for the patients with non-necrotic tumours. Males more often suffered from late recurrences and had poorer prognosis compared to females. Age, primary tumour location, surgical margin, cellularity, infiltrative growth pattern, tumour depth and tumour size did not influence RFi.

We performed a multivariate Cox analysis for RFi, including the variables that were significant in univariate analysis and adjusted for age. Atypia was not associated with RFi in this model ($P = 0.309$), and gender, necrosis and mitotic count were thus included in a revised model, also adjusted for age. Mitotic count ($P = 0.001$), necrosis ($P = 0.043$) and gender ($P = 0.046$) remained statistically significant as independent prognostic factors in the final model (Table 4).

Mitotic count ($P < 0.001$) and necrosis ($P = 0.005$) were also associated with inferior D-RFi in univariate analysis, whereas gender was not statistically significant ($P = 0.074$, Supporting information, Figure S2A–C). Factors associated with OS were age ($P = 0.019$), mitotic count ($P = 0.004$), necrosis ($P < 0.001$) and presence of severe atypia and pleomorphism ($P < 0.001$) (Table 3, Figure 2A–C). In multivariate analysis, age ($P = 0.048$), mitotic count ($P = 0.004$) and necrosis ($P = 0.002$) remained statistically significant (Table 4).

Table 2. Patient outcome

Characteristics	No. of patients (%)[1]
Follow-up for OS	
Median, months (range)	121 (5–415)
Follow-up for RFi	
Median, months (range)	84 (1–243)
Recurrence	27 (31)
Time to recurrence	
Median, months (range)	63 (3–227)
Local recurrence	15 (17)
Time to local recurrence	
Median, months (range)	86 (13–227)
Metastasis	21 (24)
Time to first metastasis	
Median, months (range)	65 (3–227)
Metastatic site[2]	
Lung	9 (43)
Liver	3 (14)
Peritoneum	4 (19)
Soft tissue	3 (14)
Other[3]	2 (10)

Total number of patients: 86.
OS, Overall survival; RFi, Recurrence-free interval.
[1]Unless otherwise specified.
[2]First site of metastasis.
[3]Other metastasis sites: bone, mediastinum.

VALIDATION OF ESTABLISHED RISK STRATIFICATION SYSTEMS

Data for risk assessment according to Demicco *et al.* and Salas *et al.* was available for all patients. According to the mDemicco risk model, 48 (56%) tumours

Table 3. Univariate analysis of recurrence-free interval and overall survival

	RFi, *n* = 86			OS, *n* = 100		
Variables	HR	95% CI	*P*-value[1]	HR	95% CI	*P*-value[1]
Age[2]	1.02	0.99–1.05	0.198	1.05	1.02–1.08	**0.003**
Gender	2.37	1.03–5.44	**0.042**	1.17	0.55–2.46	0.685
Tumour size[2]	1.04	0.99–1.10	0.136	1.05	0.995–1.01	0.075
Mitotic count[2]	1.11	1.06–1.15	**<0.001**	1.1	1.05–1.15	**<0.001**
Necrosis			**0.003**			**<0.001**
Absent	Ref	–	–	Ref	–	–
<50%	2.59	1.04–6.42	**0.040**	3.14	1.31–7.55	**0.010**
≥50%	8.76	2.53–30.32	**<0.001**	14.95	4.82–46.36	**<0.001**
Cellularity[3]	2.16	0.94–5.00	0.071	1.98	0.92–4.24	0.080
Growth pattern	2.13	0.98–4.63	0.055	2.1	0.97–4.39	0.060
Atypia/pleomorphism	3.40	1.48–7.84	**0.004**	4.15	1.85–9.34	**0.001**
Resection margins[3]	0.82	0.36–1.87	0.636	1.18	0.56–2.51	0.662
Tumour depth	1.84	0.43–7.83	0.410	1.83	0.63–5.28	0.266
Site[3]						
Head and neck/other	Ref	–	–	Ref	–	–
Extremity/trunk wall	1.38	0.34–5.49	0.652	1.02	0.29–3.62	0.981
Pleuropulmonary	1.17	0.34–4.04	0.801	1.61	0.45–5.72	0.464
Abdomen/retroperitoneum	1.52	0.47–4.93	0.483	1.83	0.59–5.74	0.297

OS, overall survival; RFi, recurrence-free interval; HR, hazard ratio; CI, confidence interval. Significant p-values are in bold.
[1]*P*-value was obtained from Cox regression analysis.
[2]age, tumour size and mitotic count were evaluated as continuous variables.
[3]R1 and R2, head and neck and other, extremity and trunk wall, low and moderate cellularity were grouped for analysis.

were identified as low risk, 18 (21%) as intermediate risk and 20 (23%) as high risk. The model predicted recurrence in our cohort ($P = 0.004$; Figure 1D) and the AUC value was 0.768. There were, however, six low-risk patients with recurrence, with a median time to recurrence of 92 months. Thirteen of 27 patients with recurrence were classified as high risk and had a median time to recurrence of 38 months. mDemicco also predicted metastasis with an AUC of 0.772 ($P = 0.004$, Supporting information, Figure S2D).

According to Salas^{OS} risk model, 36 (42%) patients were classified as low risk, 37 (43%) as intermediate risk and 13 (15%) as high risk. The model showed a significant association with RFi ($P < 0.001$; Figure 1E), with an AUC value of 0.691. Seven patients classified as low risk developed recurrence after a median time of 84 months. Ten of 13 high-risk patients recurred after a median time of 30 months. Salas^{MET} also predicted RFi in our cohort, but with marginally reduced performance compared to Salas^{OS} (data not shown). Both Salas^{OS} and Salas^{MET} predicted metastasis with an AUC of 0.618 ($P = 0.001$) and 0.580 ($P < 0.001$), respectively (Supporting information, Figure S2E,F).

DEVELOPMENT OF A NOVEL RISK STRATIFICATION SYSTEM

We included the variables that were independently associated with RFi in multivariate analysis. Because mitotic count and necrosis had a stronger prognostic impact than gender, we arbitrarily assigned 2 points to ≥4 mitoses and ≥50% necrosis, whereas male

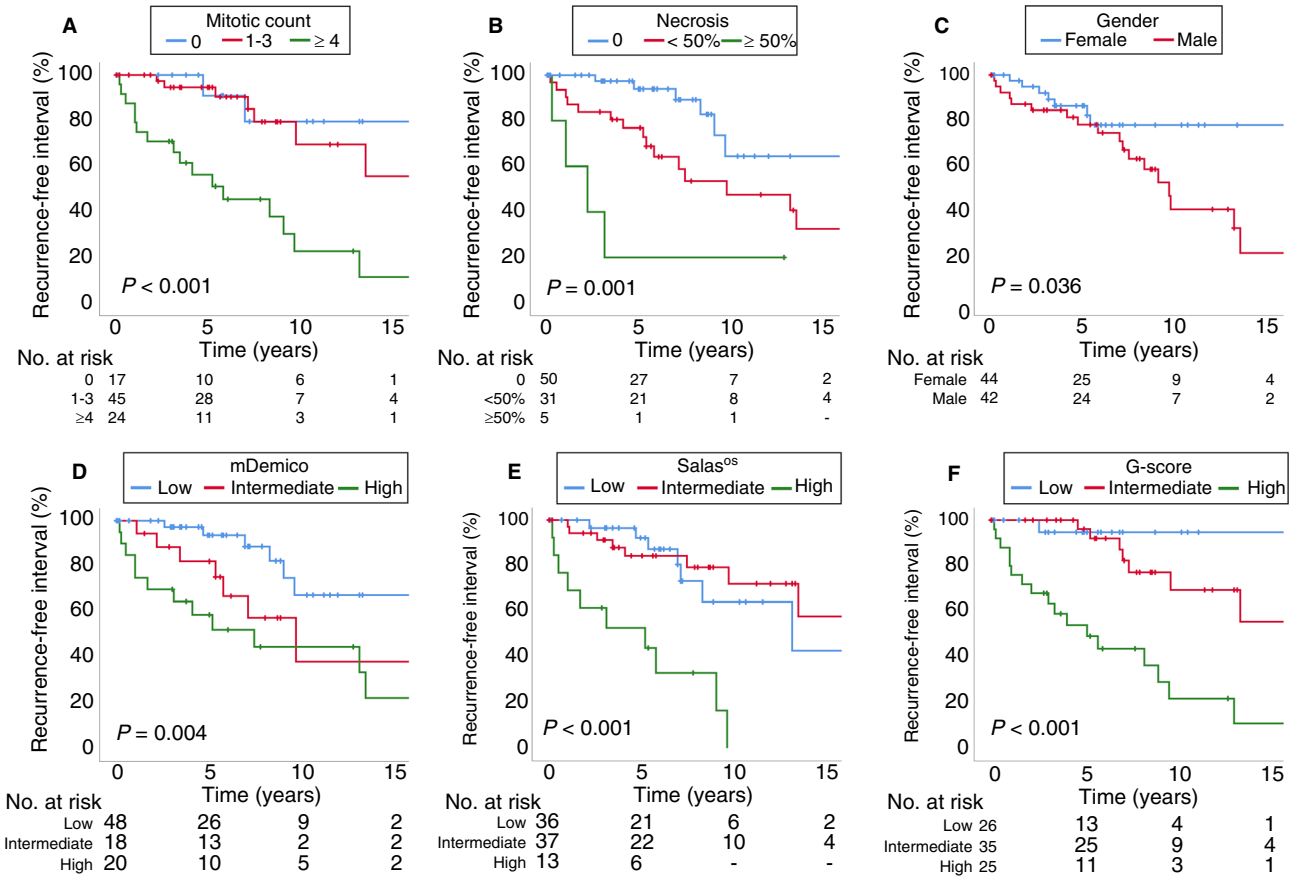

Figure 1. Prognostic factors and performance of risk stratification systems for recurrence-free interval. Kaplan–Meier survival curves of recurrence-free interval stratified based on (**A**) mitotic count, (**B**) necrosis, (**C**) gender, (**D**) modified Demicco's risk score, (**E**) Salas^{OS} risk score and (**F**) G-score as indicated.

Table 4. Multivariate analysis of recurrence-free interval and overall survival

	RFi, n = 86			OS, n = 100		
Variables	HR	95% CI	P-value[1]	HR	95% CI	P-value[1]
Age[2]	1.004	0.97–1.04	0.838	1.03	1.00–1.07	**0.048**
Gender	2.45	1.02–5.88	**0.046**	–	–	–
Mitotic count[2]	1.10	1.05–1.15	**<0.001**	1.08	1.02–1.13	**0.004**
Necrosis			**0.043**			**0.002**
Absent	Ref	–	–	Ref	–	–
<50%	1.79	0.67–4.77	0.244	1.83	0.71–4.72	0.209
≥50%	5.08	1.43–18.07	**0.012**	8.24	2.54–26.76	**<0.001**
Atypia/pleomorphism	–	–	–	2.07	0.75–5.69	0.160

OS, Overall survival; RFi, Recurrence-free interval; HR, Hazard ratio; CI, Confidence interval. Significant p-values are in bold.
[1]*P*-value was obtained from Cox regression analysis
[2]Age and mitotic count were evaluated as continuous variables.

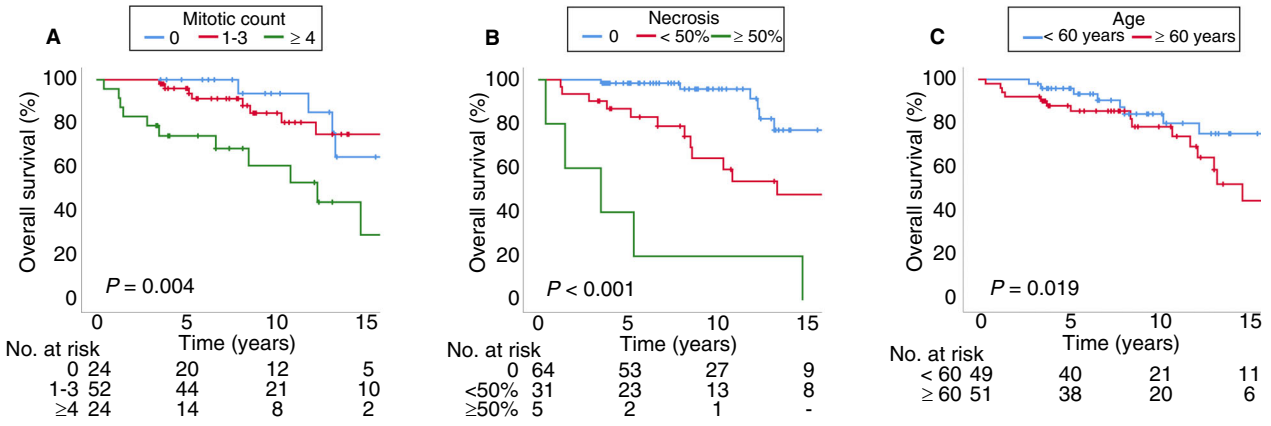

Figure 2. Prognostic factors for overall survival. Kaplan–Meier survival curves of overall survival stratified based on (**A**) mitotic count, (**B**) necrosis and (**C**) age, as indicated.

gender and <50% necrosis were assigned 1 point. Patients were subsequently stratified into three risk groups: low, 0 points; intermediate, 1–2 points; and high, 3–5 points (Table 5). Twenty-six patients (30%) were classified as low risk, 35 (41%) as intermediate risk and 25 (29%) as high risk. Our model, which we termed G-score, was able to clearly separate patients according to risk of recurrence (AUC = 0.828; $P < 0.001$; Figure 1F). Only one recurrence was observed in the low-risk group: the tumour was removed with positive surgical margins and a local recurrence occurred 32 months later. After re-excision the patient is still alive without metastasis after 62 months of follow-up. In the intermediate-risk group, eight of 35 (23%) tumours recurred, seven of which occurred >5 years after primary surgery. In the high-risk group, 18 of 25 (72%) patients developed disease recurrence, with a median time to recurrence of 40 months. G-score also clearly separated patients according to risk of distant recurrence, with an AUC of 0.837 for D-RFi ($P < 0.001$, Supporting information, Figure S2G).

There was a poor correlation between all three prognostic systems, with only 12 (14%) tumours scored as low risk, seven (8%) as intermediate risk and eight (9%) as high risk by all three models (Supporting information, Figure S3A–C).

Table 5. A novel risk stratification model (G-score) for prediction of recurrence in solitary fibrous tumour

Prognostic factors	Score
Mitotic count[1]	
<4	0
≥4	2
Necrosis	
Absent	0
<50%	1
≥50%	2
Gender	
Female	0
Male	1
Risk score	Total score
Low	0
Intermediate	1–2
High	3–5

[1]Mitotic figures per 10 high-power fields of the microscope.

Discussion

Late recurrences after curative intended treatment for SFT are common,[2,3,5,7,9,19,22,23] and prognostic models aiming to have clinical utility must be generated from cohorts with sufficient follow-up time. In the present cohort, with median RFi follow-up of 84 months and median OS follow-up of 121 months, median time to recurrence was 63 months. We demonstrate that mitotic count and necrosis are robust and independent prognostic factors for both early and late recurrences, and that male gender was associated with an increased risk of late recurrence. Previously established risk models also predicted RFi in our cohort, but incorrectly classified low-risk

patients. The absolute risk of recurrence in the low-risk groups using mDemicco[8] and Salas^{OS3} was 13 and 19%, respectively, and was mainly attributed to recurrences occurring between 5 and 10 years after primary treatment. In the high-risk groups, however, the median time to recurrence was 38 and 30 months. Thus, our data clearly demonstrate that mDemicco and Salas^{OS} models reliably identify patients at high risk of early recurrence, but that novel prognostic algorithms are needed to predict late recurrences.

Based on our findings, the new risk stratification system G-score was proposed, including mitotic count, necrosis and gender as prognostic variables. Our model reliably identified low-risk patients. Only one local recurrence and no distant metastases were observed in the 26 patients in the low-risk group. Patients in the intermediate-risk group had a significantly higher recurrence risk compared to the low-risk group. Notably, all but one recurrence in this group occurred more than 5 years after surgery, suggesting that these tumours are relatively indolent, yet able to metastasise. High-risk tumours were clearly more aggressive, with a median time to recurrence of 40 months and a 10-year RFi of 25% compared to 95% for low- and 75% for intermediate-risk patients.

High mitotic count and necrosis have been associated with more aggressive tumour behaviour in several studies,[3,7,8,10,12–14] and both mDemicco, Salas^{OS} and Salas^{MET} include mitoses as one of the factors. Mitotic count and >50% necrosis had the strongest prognostic impact in our cohort and was thus assigned more weight in the model than gender and necrosis <50%. An association between male gender and poor outcome has also been shown previously.[5,30] The biological explanation for this observation is, however, unknown. Demicco *et al.* included age and tumour size, and Salas *et al.* included age and tumour site in their models.[3,7] These variables were not associated with RFi in our cohort and were thus not included in our algorithm.

The poor correlation between the stratification systems is probably explained by the inclusion of different prognostic factors. It further illustrates that the models identify distinct and only partially overlapping subsets with dissimilar characteristics and outcome.

A strength of the present cohort is the long follow-up time allowing the analysis of prognostic factors for late recurrence. In addition, all patients with neoadjuvant therapy were excluded, implying that the histopathological variables reflect the tumours' biology and not response to treatment. Furthermore, a radiological examination of the chest and/or abdomen was required as a valid observation for RFi, reducing the risk of inappropriately censoring patients with an undetected recurrence. Finally, strong nuclear STAT6 immunostaining was observed in all cases, indicating the presence of the pathognomonic *NAB2–STAT6* gene fusion.[31,32]

As a complement to traditional clinicopathological parameters, novel prognostic factors should be explored to further improve the risk models. Barthelmess and co-workers found that tumours with a *NAB2*ex6-*STAT6*ex16/17 fusion had more aggressive clinical behaviour than tumours with a *NAB2*ex4-*STAT6*ex2 fusion.[33] The findings have not been confirmed;[34–37] however, the association should be investigated further in cohorts with adequate follow-up. We are currently performing molecular analysis of selected tumours in the current study, aiming to elucidate the impact of the different fusion types in our series.

Our study has certain limitations. We have not validated our findings in an independent cohort. As the G-score was developed using the data from this patient series, direct comparisons between previously published risk models and G-score would not be appropriate. We are currently validating the G-score in external cohorts with sufficient follow-up time. The final multivariate model included three variables adjusted for age. A higher number of events and cases is always beneficial; however, our model fits and estimated confidence intervals reflect appropriate variability for our data. Additional analyses with bootstrapped standard errors confirm that there are probably significant associations between mitotic count, necrosis and gender, adjusted for age and recurrence (data not shown). Even though data were obtained from a prospectively maintained database, some data had to be retrospectively collected. Oslo University Hospital serves as a tertiary sarcoma reference centre, and even though Norwegian national guidelines recommend that all cases should be referred to a sarcoma centre, a referral bias cannot be excluded. This could also explain the relatively high frequency of recurrences. Finally, despite a relatively large cohort with long-term and thorough follow-up, a larger sample size with a higher number of events and even longer follow-up time would have been advantageous.

In conclusion, we demonstrate that mitotic count, necrosis and gender reliably predicted both early and late recurrences of SFT. A novel risk score based on these factors and accounting for late recurrences was developed and should be validated in external cohorts with sufficient follow-up time.

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Conflicts of interest

The authors of the study declare that they have no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram of patient cohort.

Figure S2. Prognostic factors and performance of risk stratification systems for distant recurrence-free interval.

Figure S3. Correlation between risk stratification systems (Venn diagrams).

Table S1. Associations between histopathological characteristics.

Data S1. Immunohistochemistry (method).