# Validation of a novel risk score to predict early and late recurrence in solitary fibrous tumour

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ARTICLE

Clinical Studies

# Validation of a novel risk score to predict early and late recurrence in solitary fibrous tumour

Tatiana Georgiesh[1,2], Ninna Aggerholm-Pedersen[3], Patrick Schöffski[4], Yifan Zhang[5], Andrea Napolitano[6], Judith V. M. G. Bovée[7], Åse Hjelle[8], Gordon Tang[9], Mateusz Spalek[10], Margherita Nannini[11], David Swanson[12], Thomas Baad-Hansen[13], Raf Sciot[14], Asle C. Hesla[15], Paul Huang[16], Desiree Dorleijn[17], Hans Kristian Haugland[18], Maribel Lacambra[19], Jacek Skoczylas[10], Maria A. Pantaleo[20], Rick L. Haas[21], Leonardo A. Meza-Zepeda[2,22], Florian Haller[23], Anna M. Czarnecka[10], Herbert Loong[19], Nina L. Jebsen[8], Michiel van de Sande[17], Robin L. Jones[6], Felix Haglund[5], Iris Timmermans[4], Akmal Safwat[3], Bodil Bjerkehagen[1,24] and Kjetil Boye[2,25]✉



**BACKGROUND:** Current risk models in solitary fibrous tumour (SFT) were developed using cohorts with short follow-up and cannot reliably identify low-risk patients. We recently developed a novel risk model (G-score) to account for both early and late recurrences. Here, we aimed to validate the G-score in a large international cohort with long-term follow-up.

**METHODS:** Data were collected from nine sarcoma referral centres worldwide. Recurrence-free interval (RFi) was the primary endpoint.

**RESULTS:** The cohort comprised 318 patients with localised extrameningeal SFTs. Disease recurrence occurred in 96 patients (33%). The estimated 5-year RFi rate was 72%, and the 10-year RFi rate was 52%. G-score precisely predicted recurrence risk with estimated 10-year RFi rate of 84% in low risk, 54% in intermediate risk and 36% in high risk ($p < 0.001$; C-index 0.691). The mDemicco ($p < 0.001$; C-index 0.749) and Salas$^{OS}$ ($p < 0.001$; C-index 0.674) models also predicted RFi but identified low-risk patients less accurate with 10-year RFi rates of 72% and 70%, respectively.

**CONCLUSIONS:** G-score is a highly significant predictor of early and late recurrence in SFT and is superior to other models to predict patients at low risk of relapse. A less intensive follow-up schedule could be considered for patients at low recurrence risk according to G-score.

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## BACKGROUND

Solitary fibrous tumour (SFT) is a rare fibroblastic tumour characterised by *NAB2-STAT6* gene fusion [1], with a reported annual incidence of 3.5 cases per million [2]. Both distant and local recurrences are observed after surgical resection, and recurrence rates of 10–30% in patients with localised SFT have been reported [3–9]. Late recurrences are frequent, and patients continue to be at risk at least 10 years after surgery [3–6, 9–13]. Several risk systems have been proposed to predict recurrence in localised, extrameningeal SFT. Demicco and colleagues developed a risk stratification model based on mitotic count, age, tumour size and necrosis [6, 14] (Supplementary Table S1). Salas and colleagues designed a risk calculator including mitotic count and age for the prediction of overall survival (Salas$^{OS}$), mitotic count, age and

[1]Department of Pathology, Oslo University Hospital, Oslo, Norway. [2]Department of Tumour Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway. [3]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark. [4]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium. [5]Department of Oncology-Pathology, Karolinska Institutet and Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden. [6]Sarcoma Unit, The Royal Marsden Hospital and The Institute of Cancer Research, London, UK. [7]Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands. [8]Department of Oncology, Haukeland University Hospital, Bergen, Norway. [9]Department of Clinical Oncology, Prince of Wales Hospital, Hong Kong SAR, China. [10]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland. [11]Division of Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. [12]Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway. [13]Department of Orthopedic Surgery, Aarhus University Hospital, Aarhus, Denmark. [14]Department of Pathology, University Hospitals Leuven, Leuven, Belgium. [15]Department of Molecular Medicine and Surgery, Karolinska Institutet and Clinical Orthopaedics, Karolinska University Hospital, Stockholm, Sweden. [16]Division of Molecular Pathology, The Institute of Cancer Research, London, UK. [17]Department of Orthopedic Surgery, Bone and Soft Tissue Tumor Unit, Leiden University Medical Center, Leiden, The Netherlands. [18]Department of Pathology, Haukeland University Hospital, Bergen, Norway. [19]Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong SAR, China. [20]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy. [21]Department of Radiotherapy, the Netherlands Cancer Institute, Amsterdam, The Netherlands and Department of Radiotherapy, the Leiden University Medical Center, Leiden, The Netherlands. [22]Department of Core Facilities, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway. [23]Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany. [24]Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [25]Department of Oncology, Oslo University Hospital, Oslo, Norway. ✉email: kjetil.boye@rr-research.no

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tumour site for metastasis (Salas$^{MET}$) and age, tumour site and radiation therapy for local recurrence (Salas$^{LR}$) [3] (Supplementary Table S1). In the later validation studies, the modified Demicco (mDemicco) and Salas$^{OS}$ models have shown the best performance [9, 13]. However, the stratification systems were not able to reliably identify low-risk patients due to poor prediction of late recurrences [9].

Based on a well-characterised large patient cohort with long-term follow-up, we recently developed a novel risk model, termed G-score, which included mitotic count, necrosis and gender as independent prognostic factors [9] (Supplementary Table S1). G-score was designed to account for both early and late recurrences and was shown to precisely predict recurrence risk.

In the present study, we aimed to validate the G-score and compare it with previously proposed risk models. We collected data from nine tertiary sarcoma referral centres worldwide and analysed the performance and clinical utility of the risk models to predict both early and late recurrences.

## MATERIALS AND METHODS

### Patient cohort

We established a collaboration at the Forum for Translational Research in Sarcomas (FORTRESS) meeting in January 2020 and retrospectively collected data from patients with localised, extrameningeal solitary fibrous tumours from nine sarcoma referral centres (Supplementary material). Data were collected under GDPR institutional approvals, pseudonymised and transferred to Oslo University Hospital for central analysis. Four patients treated with preoperative radiation and chemotherapy were excluded. The project was approved by the Regional Ethics Committee in South-East Norway (#2010-509).

### Histopathological evaluation

Mitotic counts per 10 high-power fields (HPF) were classified according to G-score (<4, ≥4), mDemicco (0, 1–3, ≥4) and Salas$^{OS}$ (≤4, >4). The extent of necrosis was categorised as absent (0%), <50% and ≥50%. To calculate the mDemicco score, where 10% necrosis was used as a cut-off, we classified cases with no necrosis as <10% and cases with necrosis (<50% and ≥50%) as ≥10%. Resection margins were evaluated as negative (R0), microscopically (R1) and macroscopically (R2) positive [15]. Tumour size was categorised according to mDemicco (0.0–4.9, 5.0–9.9, 10.0–14.9, ≥15.0 cm).

### Statistical analysis

Survival was calculated from the date of primary surgery. For recurrence-free interval (RFi) distant metastasis or local recurrence was considered an event. For local recurrence-free interval (L-RFi) local recurrence was considered an event, and for the distant recurrence-free interval (D-RFi), distant metastasis was considered an event [16]. Recurrence was verified on biopsy, surgical resection or indisputable on imaging. Patients without recurrence were censored at the date of last radiological examination of the chest and/or abdomen or last clinical follow-up. Survival was estimated using the Kaplan–Meier method and compared by the log-rank test. Median follow-up was calculated using the reverse Kaplan–Meier method. Time to recurrence was categorised as early (<5 years after surgery) or late (≥5 years after surgery). Associations between clinicopathological factors and time to recurrence were assessed using the two-tailed Fisher´s exact test and the Mann–Whitney *U*-test. Kaplan–Meier survival curves and C-index were used to analyse outcomes and compare the risk models. A *p*-value <0.05 was considered significant. SPSS Statistics, version 27.0 (SPSS Inc., Chicago, IL, USA) and R (survival package version 3.2-13) [17, 18] were used.

## RESULTS

### Patient cohort

The cohort comprised 318 patients, of whom 162 were female and 156 male (Table 1). The median age at diagnosis was 59 years (range 0–88). Extremities and trunk wall were the most frequent tumour location, followed by pleura/lung, head and neck and retroperitoneum/abdomen. Median tumour size was 8.5 cm (range 0.4–30.0 cm). Forty-one patients (14%) underwent adjuvant radiation therapy, and one patient received adjuvant chemotherapy.

**Table 1.** Demographical, clinical and histopathological characteristics.

| Characteristics | No. of patients (%)[a] |
|---|---|
| Age (at presentation), years | |
| Median (range) | 59 (0–88) |
| Gender | |
| Male | 156 (49) |
| Female | 162 (51) |
| Primary tumour site | |
| Head and neck | 40 (13) |
| Extremity and trunk wall | 117 (37) |
| Pleura/lung | 101 (32) |
| Retroperitoneum/abdomen | 40 (13) |
| Other[b] | 20 (6) |
| Tumour size, cm | |
| Median (range) | 8.5 (0.4–30) |
| Resection margins | |
| R0 | 195 (61) |
| R1 | 60 (19) |
| R2 | 23 (7) |
| n/a | 40 (13) |
| Mitotic count[c] | |
| Median (range) | 3 (0–70) |
| <4 | 163 (51) |
| ≥4 | 112 (35) |
| n/a | 43 (14) |
| Necrosis | |
| Absent | 160 (50) |
| Present | 92 (29) |
| n/a | 66 (21) |
| Extent of necrosis | |
| <50% | 67 (73) |
| ≥50% | 6 (7) |
| n/a | 19 (21) |

Total number of patients: 318.
[a]Unless otherwise specified.
[b]Other tumour sites: prostate, uterus, bladder, vesicula seminalis, pelvis, n/a.
[c]Number of mitotic figures per 10 high-power fields.

### Histopathological characteristics

Data on mitotic count and necrosis were available for 275 and 251 tumours, respectively (Table 1). One hundred and twelve cases (35%) had ≥4 mitotic figures per 10 HPF. Necrosis was present in 92 tumours (29%), of which 67 (73%) had <50%, 6 (7%) had ≥50% necrosis and 19 (21%) had unknown percentage. STAT6 immunostaining was performed in 148 cases (47%), of which 146 (99%) were positive.

### Outcome

Thirty patients without follow-up for RFi were excluded from the survival analysis. Median follow-up for OS was 65 months (range 1–407), and the median follow-up for RFi was 64 months (1–407). Ninety-six patients (33%) experienced disease recurrence, and the median time to recurrence was 36 months (range 2–210 months). Thirty-one percent of the recurrences occurred ≥5 years after

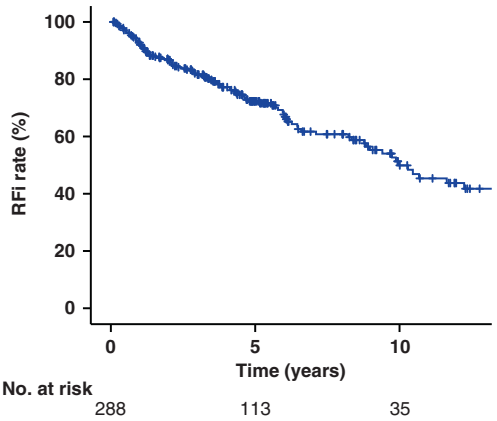


**Fig. 1 Recurrence-free interval after surgery for localised, extrameningeal SFT.** RFi recurrence-free interval.

primary surgery. The estimated 5-year RFi rate was 72%, and the 10-year RFi rate was 52% (Fig. 1). Local recurrence was observed in 55 cases (19%), and the median time to local recurrence was 41 months (range 3–193). The estimated 5-year L-RFi rate was 83%, and the 10-year L-RFi rate was 69% (Supplementary Fig. S1A). Distant metastasis was observed in 70 patients (24%), and the median time to distant recurrence was 43 months (range 2–298). The estimated 5-year D-RFi rate was 80%, and the 10-year D-RFi rate was 67% (Supplementary Fig. S1B). The most frequent first site of metastasis was the lung, followed by multiple sites, liver and bone. A summary of the outcome data is presented in Supplementary Table S2.

### Prediction of recurrence risk using G-score

Data for risk assessment according to G-score were available for 211 (73%) patients. Forty-nine (23%) patients were identified as low risk, 90 (43%) as intermediate and 72 (34%) as high risk. G-score was a highly significant predictor of recurrence ($p < 0.001$, C-index 0.691; Fig. 2a). Only three recurrences (6%) were observed in the low-risk group and occurred after 52, 56 and 62 months. Twenty-seven patients (30%) in the intermediate group developed recurrence with a median time to recurrence of 50 months (range 4–147 months). In the high-risk group, 35 of 72 tumours (49%) recurred with a median time to recurrence of 16 months (range 2–193 months). The estimated 10-year RFi rate was 84%, 54% and 36% for the low-, intermediate- and high-risk groups, respectively. G-score was also a significant predictor for L-RFi ($p = 0.001$, C-index 0.711; Supplementary Fig. S2A) and D-RFi ($p = 0.003$, C-index 0.676; Supplementary Fig. S2D).

### Prediction of recurrence risk using the mDemicco model

Data for risk assessment according to mDemicco were available for 224 (78%) patients. One hundred and twenty-five patients (56%) were categorised as low risk, 58 (26%) as intermediate and 41 (18%) as high risk. The model was a highly significant predictor of recurrence ($p < 0.001$, C-index 0.749; Fig. 2b). However, 17 low-risk patients (14%) had disease relapses. The estimated 10-year RFi rate was 72%, 52% and 13% for the low-, intermediate- and high-risk groups, respectively. mDemicco score was also significantly associated with L-RFi ($p < 0.001$, C-index 0.682; Supplementary Fig. S2B) and D-RFi ($p < 0.001$, C-index 0.787; Supplementary Fig. S2E).

### Prediction of recurrence risk using the Salas models

Data for risk assessment according to Salas$^{OS}$ were available for 248 (86%) patients. Ninety patients (36%) were classified as low risk, 110 (44%) as intermediate and 48 (19%) as high risk. The model significantly predicted recurrence ($p < 0.001$, C-index 0.674; Fig. 2c). Nevertheless, 18 low-risk patients (20%) had local or distant relapse. The estimated 10-year RFi rate was 70%, 60% and 25% for the low-, intermediate- and high-risk groups, respectively. Salas$^{OS}$ was also able to predict L-RFi ($p < 0.001$, C-index 0.661; Supplementary Fig. S2C) and D-RFi ($p < 0.001$, C-index 0.678; Supplementary Fig. S2F). Salas$^{LR}$ was not associated with RFi, L-RFi or D-RFi (Supplementary Fig. S3A, C, E). Salas$^{MET}$ was a significant predictor of recurrence but showed marginally poorer performance than Salas$^{OS}$ (Supplementary Fig. S3B, D, F).

### Correlation between risk models

There was a poor correlation between G-score, mDemicco and Salas$^{OS}$. There were 200 cases with a risk score calculated by all three models, of which 23 (12%) were scored as low risk, 15 (8%) as intermediate and 21 (11%) as high-risk models (Fig. 3a–c). G-score identified only 23% of patients as low risk, whereas mDemicco classified more than half of the patients as low risk (56%). The intermediate group was the largest, using Salas$^{OS}$ (44%) and G-score (43%). G-score classified 34% as high risk, compared to 18% by mDemicco and 19% by Salas$^{OS}$.

### Prognostic factors for early and late recurrence

Since there were large variations in time to recurrence, we explored whether clinicopathological factors could predict early or late recurrence. High mitotic count and high age at diagnosis were significantly associated with early recurrence (Supplementary Table S3). The median mitotic count for patients with early recurrence (<5 years after surgery) was 7 per 10 HPF, compared to 3 per 10 HPF for patients with late recurrence (≥5 years after surgery) ($p = 0.003$). Tumour size, necrosis, gender and tumour location were not associated with time to recurrence (Supplementary Table S3).

## DISCUSSION

In the present study, we have validated the G-score, our recently proposed recurrence risk score in extrameningeal SFT, using a large worldwide patient cohort. We demonstrate that G-score is a highly significant predictor of tumour recurrence and can precisely identify patients at both low and high risk of disease relapse. G-score more accurately identified low-risk patients than previously published risk models, possibly due to better prediction of late recurrences.

Our data confirm that late recurrences are common in SFT, and patients continue to be at risk of recurrence even ten years after surgery. Nearly one-third of the recurrences occurred after more than 5 years. G-score clearly delineated the low-, intermediate- and high-risk groups, also taking into account late recurrences. Among 49 low-risk patients, only three recurrences were observed, and all occurred after four years of follow-up. Intermediate- and high-risk patients experienced both early and late recurrences, but the median time to recurrence was considerably shorter in the high-risk group (16 vs 50 months). Thus, in addition to recurrence risk prediction, G-score might indicate the risk of early versus late recurrence.

The performance of the G-score was compared to the previously established prognostic systems mDemicco [6, 14] and Salas$^{OS3}$. We observed a poor correlation between the models. G-score had a smaller low-risk group and a larger high-risk group, reflecting that the low-risk criteria in the G-score are strict, i.e. no necrosis, mitotic count <4 and female gender. This strict definition of low risk resulted in a more precise selection of patients truly at low risk of recurrence. As an example, a tumour with ≥4 mitoses and ≥10% necrosis would be classified as low risk using mDemicco in the absence of other risk factors, whereas it would be considered high-risk using G-score. Our data indicate that no risk factors should be present to classify a tumour as low risk. On the other hand, all three systems performed well to identify high-risk patients both in our initial series [9] and in the present

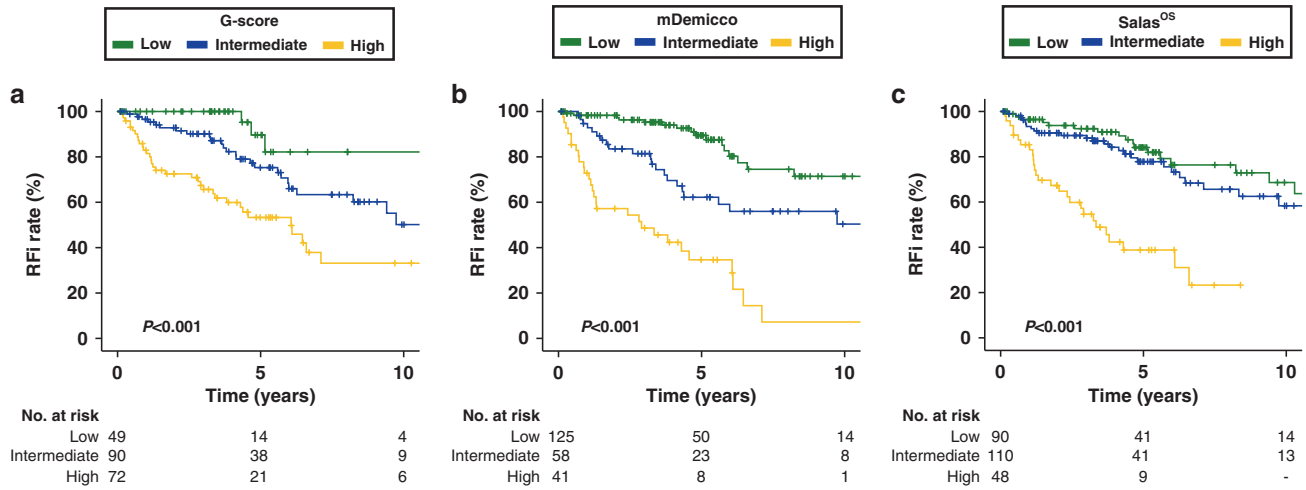


**Fig. 2 Prediction of recurrence risk using G-score, mDemicco and Salas$^{OS}$.** Kaplan–Meier survival curves of recurrence-free interval stratified based on **a** G-score, **b** modified Demicco risk score, **C** Salas$^{OS}$ risk score as indicated. RFi recurrence-free interval.

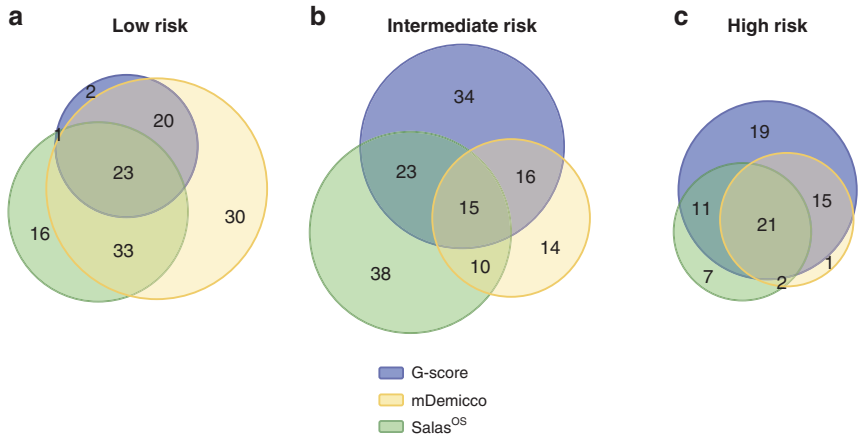


**Fig. 3 Correlation between risk stratification systems.** Venn diagrams showing **a** low risk, **b** intermediate risk and **c** high risk based on G-score, mDemicco and Salas$^{OS}$ risk models as indicated.

validation cohort. mDemicco had a higher C-index compared to G-score and Salas$^{OS}$ for both RFi and D-RFi, probably due to a better selection of high-risk patients. However, C-index is only a measure of discrimination, and the models´ performance should also be based on clinical utility [19].

An accurate risk stratification system is necessary to inform clinical decision-making regarding adjuvant treatment and follow-up strategies [20]. Low-risk patients, according to G-score, have a good prognosis and are not candidates for adjuvant radiotherapy or adjuvant chemotherapy. A less intensive follow-up could be considered for this group, as recurrences are infrequent and occur late. A suggested follow-up schedule based on the G-score is provided in Table 2, considering the risk of distant and local recurrence over time in each of the risk groups. We emphasise that this is a suggested empirical strategy based on our data, and not based on prospective evidence. High-risk patients, identified by all three models, have a poor prognosis and could benefit from (neo)adjuvant treatment. Many centres recommend adjuvant radiotherapy following the same principles as for other soft tissue sarcomas [21]. L-RFi rate for high-risk patients was <50% at 10 years for all risk models, supporting the use of adjuvant radiotherapy in this group. There is no evidence of adjuvant chemotherapy for SFT. Our data show that more than half of the high-risk patients will develop distant metastasis and thus potentially benefit from adjuvant systemic therapy. In fact, the 2-year D-RFi rate for mDemicco high-risk patients was only 56%, which is similar to other high-grade soft tissue sarcomas. Ideally, a phase 3 study investigating the benefit of adjuvant chemotherapy should be performed, but it is questionable whether such a trial is realistic considering the low incidence and limited benefit of chemotherapy in advanced disease in SFT. Taken together, we believe adjuvant chemotherapy should not be routinely offered in the absence of formal evidence.

There is a need for improved prediction of prognosis in patients with intermediate risk. According to the current model, they are at significant risk of recurrence, but the risk probably does not justify considering adjuvant treatment. None of the clinicopathological factors collected was able to improve stratification in this project (data not shown). We have previously shown that *NAB2-STAT6* fusion variants have a prognostic impact [22], and whether fusion status could improve risk stratification of the intermediate group should be addressed in future studies.

The present study is a result of a worldwide multicentre collaboration formed at the FORTRESS meeting in 2020. SFT is a rare tumour, and international efforts are of vital importance for such rare diseases. Despite the low incidence, we managed to collect a sufficiently large cohort with long-term follow-up to validate the G-score and compare the risk models. The present cohort may also serve as a resource for the sarcoma community in future projects in localised, extrameningeal SFT.

The study has certain limitations. The data were collected retrospectively, and we did not perform a central pathology

**Table 2.** Suggested follow-up schedules based on G-score[a].

| | Year 1–2 | Year 3–5 | Year 6–10 | After year 10 |
|---|---|---|---|---|
| Low risk | Every 12 months | Every 12 months | Every 12 months | Consider yearly FU[b] |
| Intermediate risk | Every 6 months | Every 6 months | Every 12 months | Consider yearly FU[b] |
| High risk | Every 3 months | Every 6 months | Every 12 months | Consider yearly FU[b] |

*FU* follow-up, *MRI* magnetic resonance imaging, *CT* computed tomography.
[a]All FU visits should include imaging of the primary tumour site with MRI or CT as indicated and imaging to detect distant metastasis, with CT of the chest, abdomen and pelvis as recommended imaging modality.
[b]Continued FU after 10 years can be considered on an individual basis.

review. Mitotic count and necrosis appear to be the most important predictors and both rest upon the evaluation of the local pathologists. Thus, differences between centres and between pathologists may exist. STAT6 staining was performed only in 47% of the cases. However, the data were collected from sarcoma tertiary referral centres, and the diagnosis is expected to be correct in most cases. We observed a higher recurrence rate than in the previously reported series. This could be explained by longer follow-up, but we cannot exclude referral bias.

In conclusion, we have validated in a large worldwide cohort that G-score could be used to predict recurrence risk in patients with localised, extrameningeal SFT. Compared to mDemicco and Salas$^{OS}$, G-score more precisely identifies patients at low risk of recurrence. All three models reliably identify high-risk patients. Improved classification of intermediate-risk patients is needed, and *NAB2-STAT6* fusion variants could be investigated as a prognostic biomarker in this group. Finally, we confirm that late recurrences are common in SFT and that patients are at risk of relapse at least ten years after surgical resection.

## DATA AVAILABILITY

The data are available from the corresponding author upon reasonable request.

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## AUTHOR CONTRIBUTIONS

TG collected and organised the data, performed data analysis, interpreted the results and drafted the manuscript; NAP, PS, YZ, AN, JVMGB, ÅH, GT, MS, MN, DS, TBH, RS, ACH, PH, DD, HKH, ML, JS, MAP, RLH, AMC, HL, NLJ, MS, RLJ, FH, IT and AS acquired and organised the data and revised the manuscript; LAMZ, FH and BB conceptualised the work and revised the manuscript; KB conceived, designed and guided the study, collected and organised the data, performed data analysis, interpreted the results and drafted the manuscript. All the authors have read the manuscript and agreed with the submission of the article in its present form.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Regional Ethics Committee in South-East Norway (#2010-509) and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent to participate.

## CONSENT FOR PUBLICATION

Not applicable.

## ADDITIONAL INFORMATION

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**Correspondence** and requests for materials should be addressed to Kjetil Boye.