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*Annals of Oncology* 0: 1–9, 2017
doi:10.1093/annonc/mdx250

ORIGINAL ARTICLE

# Prediction of local and metastatic recurrence in solitary fibrous tumor: construction of a risk calculator in a multicenter cohort from the French Sarcoma Group (FSG) database

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Note: The data used in this publication were provided by the French Sarcoma Group database as part of the ConticaBase, the Conticanet database (www.conticabase.org).

**Background:** Solitary fibrous tumors (SFT) are rare unusual ubiquitous soft tissue tumors that are presumed to be of fibroblastic differentiation. At present, the challenge is to establish accurate prognostic factors.

**Patients and methods:** A total of 214 consecutive patients with SFT diagnosed in 24 participating cancer centers were entered into the European database (www.conticabase.org) to perform univariate and multivariate analysis for overall survival (OS), local recurrence incidence (LRI) and metastatic recurrence incidence (MRI) by taking competing risks into account. A prognostic model was constructed for LRI and MRI. Internal and external validations of the prognostic models were carried out. An individual risk calculator was carried out to quantify the risk of both local and metastatic recurrence.

**Results:** We restricted our analysis to 162 patients with local disease. Twenty patients (12.3%) were deceased at the time of analysis and the median OS was not reached. The LRI rates at 10 and 20 years were 19.2% and 38.6%, respectively. The MRI rates at 10 and 20 years were 31.4% and 49.8%, respectively. Multivariate analysis retained age and mitotic count tended to significance for predicting OS. The factors influencing LRI were viscera localization, radiotherapy and age. Mitotic count, tumor localization other than limb and age had independent values for MRI. Three prognostic groups for OS were defined based on

the number of unfavorable prognostic factors and calculations were carried out to predict the risk of local and metastatic recurrence for individual patients.

**Conclusion:** LRI and MRI rates increased between 10 and 20 years so relapses were delayed, suggesting that long-term monitoring is useful. This study also shows that different prognostic SFT sub-groups could benefit from different therapeutic strategies and that use of a survival calculator could become standard practice in SFTs to individualize treatment based on the clinical situation.

**Key words:** prognostic factors, solitary fibrous tumor, risk calculator, competing risks

## Introduction

Solitary fibrous tumors (SFT) are unusual ubiquitous soft tissue tumors categorized as having intermediate biological potential with a low risk of metastasis. Although most cases are considered as benign, they may behave unpredictably. About 10% behave aggressively with local and distant recurrence many years after primary resection. These rare tumors, which are presumed to be of fibroblastic differentiation, usually affect adults and can occur at any site. Typical SFTs show a patternless architecture characterized by a combination of hypocellular and hypercellular areas separated by thick bands of hyalinized, sometimes keloidal, collagen and thin-walled branching hemangiopericytoma-like vessels. Tumor cells are ovoid to spindle-shaped with limited pale cytoplasm having indistinct borders and dispersed chromatin within vesicular nuclei (WHO classification [1]. In 2013, two different teams simultaneously reported a *NAB2-STAT6* fusion transcript in most SFTs whatever their localization [2, 3]. The fusion leads to a nuclear relocation of the STAT6 protein and is detectable by immunohistochemistry. STAT6 immunohistochemistry has been shown to provide excellent sensitivity and specificity for routine histological diagnosis [4]. While these discoveries have improved the diagnosis, the challenge is to establish accurate prognostic factors. Few authors have searched for prognostic factors in large series of primary solitary fibrous tumors. The two largest series (110 and 243 patients) that had a rigorous statistical analysis was published by Demicco et al. and Pasquali et al. who identified clinicopathological prognostic factors and proposed a risk model assessment [5, 6]. The purpose of our study was to identify prognostic factors for overall survival (OS), local recurrence and metastatic recurrence in patients with SFT and to propose an individual risk calculator for clinical practice.

## Patients and methods

### Patient selection

From 15 December 1975 to 24 October 2014, 214 consecutive patients with extra-meningeal SFT were diagnosed for their first tumor event in 24 participating cancer centers and were entered into the European database (https://conticabase.sarcomabcb.org). Fifty-two of the 214 patients were excluded from this study because they had evidence of metastatic spread at the time of diagnosis (5 patients) or were not operable with a curative intent. We restricted our analysis to patients with local disease and absence of residual tumor after local treatment to obtain a more homogeneous population. Absence of residual tumor meant that the patients had no disease visible on imaging after surgery and radiotherapy. The diagnosis of SFT was confirmed in each case by collegial histological analysis and by STAT6 positivity on immunohistochemistry.

### Pathology review

Histological slides of all patients entered in this study were reviewed by the pathology subcommittee of the French Sarcoma Group (GSF). The subcommittee included 20 pathologists and a monthly slide review session was carried out. Histologic typing was based on the World Health Organization (WHO) classification of soft tissue tumors.

### Data collection

Data regarding patients' characteristics, tumor description, treatment modalities and their results and outcome were obtained from a retrospective review of medical records. These and histological data were entered into a centralized computerized database (https://conticabase.sarcomabcb.org). The following seven variables were analyzed for their potential prognostic value: age at presentation, sex, tumor size, tumor site, surgical margins (macroscopic incomplete as R2 resection; microscopic incomplete resection as R1 resection; microscopic complete resection as R0 resection), necrosis score, mitotic count (number of mitoses per 10 high-power fields according to the FNCLCC grading (1 HPF measures 0.1734 $mm^2$). Mitosis was analyzed as a continuous variable and the highest counts were adopted for final scoring. The scores used for necrosis were also from the FNCLCC grading system. Only tumor coagulative necrosis was recorded: 0 means no necrosis found; 1 means necrosis volume is $<$50% of the total tumoral volume; and 2 means $>$50%. Sites of primary tumors were categorized as soft tissue *versus* viscera (internal organs of the body: lung, liver etc.) and as limb, intra-abdominal/pelvic, trunk or pleural/intrathoracic. The status of resection margins in surgically treated patients was classified according to the UICC R classification [7]. The depth of the tumor could not be taken into account in the prognostic models because of the small number of events in the superficial tumor subgroup (no death, only one local recurrence and only one metastatic recurrence).

### Statistical analysis

*Definition of end points.* OS was computed from the date of initial diagnosis to the date of death (whatever the cause) or the date of last contact. Local recurrence incidence (LRI) and metastatic recurrence incidence (MRI) were computed from the date of initial diagnosis to the date of recurrence, or last contact, or death. Follow-up was censored at 20 years.

*Competing risks framework.* Local recurrence may be altered or precluded by metastatic recurrence or death, creating a context of competing risks. The analysis was limited to the first event occurring in the competing risks framework using the following quantities commonly used to summarize outcomes by event type: (i) the cause-specific hazard function, which for local recurrence can heuristically be considered the probability of local recurrence in a short time interval, given that no metastatic recurrence or death occurred before; and (ii) the cumulative incidence function, which for local recurrence corresponds to the probability of local recurrence in the presence of competing metastatic recurrence or death. Furthermore, metastatic recurrence may be precluded by death, and the same strategy was applied when MRI was considered.

*Statistics.* A descriptive analysis was carried out. Continuous variables were expressed as medians and categorical variables were expressed as numbers and percentages. Survival analysis was conducted using the Kaplan-Meier method and the Cox regression model to estimate hazard ratios (HR) and their 95% confidence intervals (95% CIs). Regarding the analyses of LRI and MRI, sub-distribution HR and their 95% CIs were estimated using the Fine and Gray model. Univariate analyses were carried out to identify prognostic factors, and all variables with a *P*-value <0.20 were included in the multivariate model. All multivariate models were systematically adjusted on age. Different prognostic groups were defined based on the number of unfavorable prognostic factors for the various end points. A prognostic model was constructed for LRI and MRI based on the variables that were selected for the multivariate models. All of the tests were two-sided. A *P*-value <0.05 was considered to be significant. The analysis was carried out using R Studio version 0.99.486 (RStudio 2015: Integrated Development for R. RStudio, Inc., Boston, MA; http://www.rstudio.com/). The R packages survival and cmprsk were used for survival and competing risk analyses, respectively [Bob Gray (2013). cmprsk: Sub-distribution Analysis of Competing Risks. R package version 2.2-6; http://CRAN.R-project.org/package=cmprsk]. An individual risk calculator was developed to quantify the risk of both local and metastatic recurrence, based on the estimated cumulative sub-distribution hazard obtained for the specified covariate values, depending on the individual's characteristics, obtained from the Breslow-type estimate of the underlying hazard and the estimated regression coefficients from the multivariate analyses.

## Assessment of validity of the model

*Internal validation.* The validity of the model was assessed using a bootstrap sample procedure. Bootstrapping involves generating a large number of datasets (1000 for this study), each with the same sample size as the original one, by resampling with replacement. The C-index and the D of Royston and Sauerbrei were estimated for each bootstrap sample, and results were pooled to obtain a single estimate.

*External validation.* A second external cohort of 92 patients was available [8]. This independent cohort was from the Rare Cancer Network consortium (http://www.rarecancer.net). The C-index and the D of Royston and Sauerbrei and their 95% CI were estimated for LRI and MRI in this cohort. Moreover, in the validation cohort, the probabilities of the occurrence of local and metastatic recurrence were estimated according to the risk models developed in the initial cohort. The HR and their 95% CI assessing the association between these probabilities and the occurrence of events in the validation cohort were estimated. Then, patients in the validation cohort were classified according to the median of the distribution of the predicted probabilities in the initial cohort. Cumulative incidences for local and metastatic recurrences were estimated in each of these subgroups and were compared with the Gray test [9].

# Results

## Patient and disease characteristics

Patient characteristics are listed in Table 1. The median age was 58.5 (range 15.6–87.4). Two-thirds of the 162 patients were female. Tumor localizations were as follows: limbs, 47 (29.0%); intra-abdominal/pelvic, 49 (30.3%); trunk/other, 30 (18.5); and pleural/intrathoracic, 36 (22.2%). One hundred twenty-four tumors occurred in soft tissue. The median largest diameter was 9.0 cm (range 1.8–33.0). Twenty-two patients (13.6%) had a previous history of another cancer.

**Table 1. Patient and disease characteristics at baseline**

| | *N*/median | Proportion/IQR |
|---|---|---|
| Gender | | |
| Female | 100 | 61.7% |
| Male | 62 | 38.3% |
| Age | 58.52 | 41.60–66.15 |
| Tumor's site | | |
| Intra-abdominal | 15 | 9.26% |
| Limb | 47 | 29.01% |
| Other | 12 | 7.41% |
| Pelvis | 16 | 9.88% |
| Pleura | 36 | 22.22% |
| Retroperitoneum | 18 | 11.11% |
| Trunk | 18 | 11.11% |
| Category of tumor's site | | |
| Soft-tissue | 124 | 76.54% |
| Viscera | 38 | 23.46% |
| Tumor's size | 90 | 60–130 |
| Significant previous history | | |
| No | 136 | 83.95% |
| Other | 3 | 1.85% |
| Previous cancer | 22 | 13.58% |
| NA | 1 | 0.62% |
| Mitotic count | 4 | 2–10 |
| Necrosis | | |
| 0 | 94 | 58.02% |
| 1 | 49 | 30.25% |
| 2 | 1 | 0.62% |
| NA | 18 | 11.11% |

## Pathological features

Necrosis was present in one third of the patients. The median mitotic count was 4 (range 0–50) per 10 high-power fields.

## Treatment characteristics

One hundred fifty-three (94.4%) patients had an initial surgical resection. Forty-four patients received additional radiotherapy which generally included photons or electrons with a median dose of 50 Grays. Surgery was followed by radiotherapy in 35 patients. Two patients received radiotherapy before surgery (one of whom also received neoadjuvant chemotherapy) and 7 patients received it after surgery and chemotherapy. Histological evaluation of surgical margins was available for 124 cases among the 153 patients who underwent first surgery (81.0%). Eighty-three patients (54.3%) had R0 resection, 40 (26.1) had R1 resection and 1 (0.7%) had R2 resection. Seventeen patients (10.5%) received chemotherapy as adjuvant or neoadjuvant treatment. All patients who received chemotherapy were treated with an anthracycline-containing regimen.

## Outcome

Median follow-up was 32.8 months (95% CI: 25.0–42.2).

*Recurrence.* At the end of follow-up, local recurrence had occurred in 20 (12.3%) patients and metastatic recurrence was observed in 27 (16.7%) patients. Moreover, 50% of local

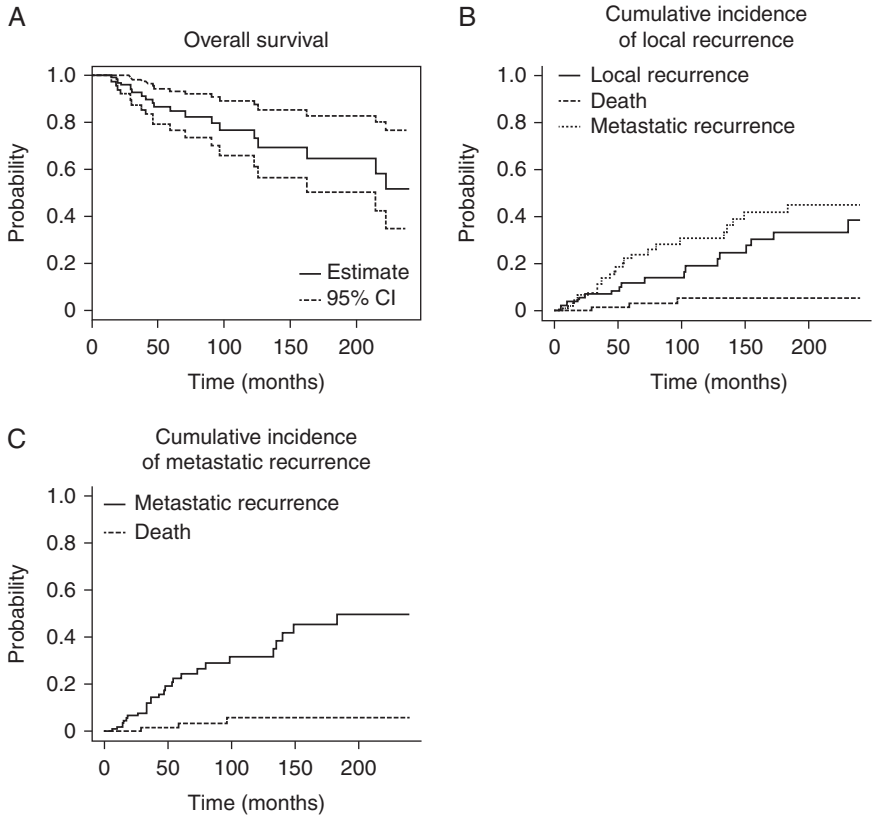


**Figure 1.** (A) Probability of overall survival of the 162 patients. (B) Probability of local recurrence in the 162 patients. (C) Probability of metastatic recurrence in the 162 patients.

recurrence and metastases occurred after 4.3 and 3.6 years, respectively, after initial resection.

*OS, local and MRI rates.* OS, LRI and MRI of the 162 patients are shown in Figure 1A–C. The OS rates at 10 and 20 years were 76.8% and 51.7%, respectively. The LRI rates at 10 and 20 years were 19.2% and 38.6%, respectively. The MRI rates at 10 and 20 years were 31.4% and 49.8%, respectively. Twenty patients (12.3%) were deceased at the time of analysis, so the median OS was not reached. The rate of tumor mortality was 75.0%. Other causes of death were unspecified in 6 (30.0%) cases.

## Prognostic factors

*Prognostic factors of OS.* The factors influencing OS in univariate analysis were age ($P = 0.002$) and mitotic count ($P = 0.013$) with a better outcome for the patients under 60 years and a poorer outcome for tumor with high mitotic count. In the multivariate analysis, age (HR = 1.06; 95% CI = 1.02–1.11; $P = 0.007$) remained statistically significant and mitotic count tended to significance (HR = 1.03; 95% CI = 01.00–1.07; $P = 0.060$) (Table 2).

*Prognostic factors of LRI.* In univariate analysis, viscera localization ($P = 0.012$) and radiotherapy ($P = 0.044$) had a significant impact on LRI. In multivariate analysis, viscera localization (HR = 3.25; 95% CI = 1.32–7.93; $P = 0.010$), radiotherapy (HR= 0.30; 95% CI = 0.11–0.83; $P = 0.021$) and age (HR= 0.97; 95%CI = 0.946–0.998; $P = 0.032$) remained statistically significant (Table 3).

*Prognostic factors of MRI.* Univariate analysis showed that three variables were statistically associated with MRI: age ($P = 0.024$), mitotic count ($P < 0.001$) and necrosis ($P = 0.011$). Multivariate analysis retained mitotic count (HR = 1.05; 95%CI = 1.02–1.08; $P < 0.001$) tumor localization other than limb (HR = 0.41; 95% CI = 0.18–0.96; $P = 0.040$) as prognostic factors of MRI. Age was included in the multivariate model even if its effect was not statistically significant in our study (HR = 1.02; 95%CI = 1.00–1.05; $P = 0.150$), considering its known prognostic role from literature data (Table 4).

## Risk stratification model

To develop the risk stratification model, we had to dichotomize the mitotic count and age. The cut-off of 4 was retained for mitotic count and 60 for age (corresponding to the observed median). When considering the dichotomized mitotic count and age, the results were the followings for the OS univariate analysis: mitotic count (>4): HR = 2.70 [1.31–5.54], *P*-value =0.007; age (≥60): HR = 1.87 [1.05–3.35], *P*-value =0.034 and the results were the followings for the OS multivariate analysis: mitotic count (>4): HR = 2.66 [1.28–5.50], *P*-value =0.008; age (≥60): HR = 2.75 [1.33–5.68], *P*-value =0.006. Age was considered for the risk stratification model as we chose to systematically adjust all analyses. Thus, three prognostic groups for OS (good, fair and poor prognosis) were defined according to the number of unfavorable prognostic factors (age ≥ 60; mitotic count >4). Four prognostic groups for local recurrence were defined based on the number of unfavorable prognostic factors (age <60, viscera

**Table 2. Univariate and multivariate analysis for prognostic factors in overall survival**

| | *N* at risk | *N* events | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Gender | | | | | | | | |
| Female | 100 | 11 | 1 | | | | | |
| Male | 62 | 9 | 1.20 | [0.49–2.90] | 0.69 | | | |
| Age | 162 | 20 | 1.06 | [1.02–1.10] | <0.01 | 1.06 | [1.02–1.11] | <0.01 |
| Category of tumor's site | | | | | | | | |
| Soft-tissue | 124 | 17 | 1 | | | | | |
| Viscera | 38 | 3 | 0.54 | [0.16–1.83] | 0.32 | | | |
| Tumor's site | | | | | | | | |
| Limb | 47 | 6 | 1 | | | | | |
| Other | 115 | 14 | 0.71 | [0.27–1.87] | 0.49 | | | |
| Tumor's size | | | | | | | | |
| Above the median | 78 | 11 | 1 | | | | | |
| Below the median | 68 | 6 | 1.02 | [0.37–2.81] | 0.97 | | | |
| Mitotic count | 143 | 17 | 1.05 | [1.01–1.08] | 0.01 | 1.03 | [1.00–1.07] | 0.06 |
| Necrosis | | | | | | | | |
| 0 | 94 | 8 | 1 | | | | | |
| 1/2 | 50 | 9 | 2.62 | [0.93–7.39] | 0.07 | | | |
| Margins | | | | | | | | |
| R0 | 85 | 11 | 1 | | | | | |
| R1 | 45 | 4 | 0.51 | [0.16–1.64] | 0.26 | | | |
| Radiotherapy | | | | | | | | |
| No | 118 | 12 | 1 | | | | | |
| Yes | 44 | 8 | 1.53 | [0.62–3.81] | 0.36 | | | |
| Chemotherapy | | | | | | | | |
| Adjuvant or neoadjuvant | 17 | 5 | 1 | | | | | |
| No | 145 | 15 | 0.42 | [0.15–1.20] | 0.11 | | | |

localization, no additional radiotherapy). Finally, a 4-tiered score stratifying our population by risk of metastatic recurrence (very low, low, moderate, or high) was developed. Scores were assigned for age (<60 or ≥60), mitotic count (≤4 or >4) and tumor localization (limb versus others), and total scores were tabulated to determine the risk of aggressive disease. Figure 2A shows OS curves in patients with 0 or 1 and 2 unfavorable prognostic factors, respectively. Figure 2B and C shows the cumulative incidence of local or metastatic recurrence according to the different prognostic groups.

## Survival calculator: personalized risk prediction for local and metastatic recurrence

Calculations were carried out to predict the risk of local and metastatic recurrence for individual patients. For example, a 65-year-old patient with a soft tissue SFT who did not receive additional radiotherapy had a 12.1% risk of local recurrence at 10 years while a 65-year-old patient with a soft tissue SFT who received additional radiotherapy had a 3.8% risk of local recurrence at 10 years. A 65-year-old patient with a limb SFT and high mitotic count (5) had a risk of metastatic recurrence at 5 and 10 years of 35.9% and 52.4%, respectively, while a 50-year-old patient with an SFT localized elsewhere than a limb and with low mitotic count (2) had a risk of metastatic recurrence at 5 and 10 years of 11.0% and 17.7%, respectively (supplementary Tables S1 and S2, available at *Annals of Oncology* online).

## Results of assessment of validity of the model

*Internal validation.* The means *c*-index were 0.71789 (95%CI = 0.5781–0.8359) and 0.7337 (95%CI = 0.5680–0.8679) for LRI and MRI, respectively. The means D of Royston and Sauerbrei were 1.2737 (95%CI = 0.6543–1.9621) and 1.5222 (95%CI = 0.7561–2.3921) for LRI and MRI, respectively.

*External validation.* The clinical data of this independent cohort have already been published by Krengli et al. [8]. The *c*-index was 0.58 (95% CI = 0.49–0.67) and 0.72 (95%CI = 0.59–0.87) for LRI and MRI, respectively. The means D of Royston and Sauerbrei were 0.47 (95%CI = 0- 0.97) and 1.02 (95%CI = 0–2.07) for LRI and MRI, respectively. The HR describing the association between predicted probabilities of events and the occurrence of events in the validation cohort were 3.10 [0.84–11.41] for LRI and 11.23 [1.57–80.06] for MRI. The cumulative incidence of LRI and MRI was higher in patients with a high predicted event risk ($P = 0.03$ for LRI and $P = 0.02$ for MRI).

## Discussion

This is the largest series of non-metastatic SFT ever published to determine the prognostic factors of these rare tumors (cohort of 162 patients and external validation cohort of 92 patients). We identified the prognostic factors of OS, LRI and MRI by

**Table 3. Univariate and multivariate analysis for prognostic factors in local recurrence incidence**

| | *N* at risk | *N* events | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Gender | | | | | | | | |
| Female | 100 | 10 | 1 | | | | | |
| Male | 62 | 10 | 1.62 | [0.68–3.83] | 0.28 | | | |
| Age | 162 | 20 | 0.98 | [0.96–1.01] | 0.14 | 0.97 | [0.95–1.00] | 0.03 |
| Category of tumor's site | | | | | | | | |
| Soft-tissue | 124 | 11 | 1 | | | 1 | | |
| Viscera | 38 | 9 | 2.90 | [1.26–6.65] | 0.01 | 3.25 | [1.32–7.99] | 0.01 |
| Tumor's site | | | | | | | | |
| Limb | 47 | 2 | 1 | | | | | |
| Other | 115 | 18 | 3.27 | [0.76–14.10] | 0.11 | | | |
| Tumor's size | | | | | | | | |
| Above the median | 78 | 10 | 1 | | | | | |
| Below the median | 68 | 4 | 0.64 | [0.20–2.05] | 0.46 | | | |
| Mitotic count | 143 | 10 | 1.02 | [0.97–1.06] | 0.47 | | | |
| Necrosis | | | | | | | | |
| 0 | 94 | 10 | 1 | | | | | |
| 1/2 | 50 | 5 | 0.79 | [0.28–2.24] | 0.65 | | | |
| Margins | | | | | | | | |
| R0 | 85 | 8 | 1 | | | | | |
| R1 | 45 | 6 | 1.35 | [0.51–3.64] | 0.55 | | | |
| Radiotherapy | | | | | | | | |
| No | 118 | 17 | 1 | | | 1 | | |
| Yes | 44 | 3 | 0.30 | [0.09–0.97] | 0.04 | 0.30 | [0.11–0.83] | 0.02 |
| Chemotherapy | | | | | | | | |
| Adjuvant or neoadjuvant | 17 | 3 | 1 | | | | | |
| No | 145 | 17 | 1.00 | [0.30–3.33] | >0.99 | | | |

considering the competing risks and these risk factors were validated in an independent cohort. The OS rate at 10 years was similar to that of Demicco et al. for patients without metastasis at the time of diagnosis [5]. As in other series, this relatively poor survival is probably due to a referral bias at a major sarcoma treatment center with a population skewed toward more aggressive tumors. In our study, OS rates decreased to 51.7% at 20 years. This confirms the poor prognosis of these tumors in the long term and the need for protracted follow-up. Otherwise, LRI and MRI rates increased between 10 and 20 years so relapses were delayed. This suggests that long-term monitoring is useful and that complementary therapies are probably necessary for some patients, although their benefit in the first years is not easy to demonstrate. However, metastasis occurred in 16.7% of the patients. This rate is higher than the 10% rate in the series of Demicco and we had adequate follow-up time to determine metastatic frequency. We were able to compile margin status in 81% of cases and found no significant association between positive margins and eventual metastasis or local recurrence, as did Demicco et al. but in contrast to Gold et al. [10]. However, surgical margins have prognostic value in many other histologic types of soft tissue sarcomas. These controversial findings may be explained partially by the difficulty to evaluate surgical margins in retrospective studies. Regarding prognostic factors, tumor size was not predictive of poor prognosis in multivariate analysis although previous studies have suggested that tumor size >10 cm is a prognostic factor of metastasis-free survival [5, 10, 11]. However, in our series, patients also tended to have larger tumors than those reported in the literature [5, 10, 12–16]. In multivariate analysis, age under 60 years old was statistically associated with longer survival and a low MRI, as already demonstrated by Demicco et al. [5]. In contrast, age under 60 years old was a negative prognostic factor for local recurrence. Recently, the identification of different *NAB2–STAT6* gene fusion transcripts according to different clinical settings emphasized the impact of age, some fusion variants being more common in older patients [3, 17]. For example, *NAB2* exon *4-STAT6* exon 3 fusion correlated with classic fibrous morphology, older age, pleural localization and low mitotic activity [18], while *NAB2* exon6-*STAT6* exon16/17 was found in much younger patients [19]. Furthermore, the biological processes leading to metastasis or local recurrence are different.

The anatomic site of primary tumors has also been reported to predict outcome. In our work, tumors in limbs behaved more aggressively with a significant difference in MRI in multivariate analysis. This may seem surprising because these localizations seem easier to operate than other localizations, so local control of the disease could be assumed to limit the metastatic process as in other mesenchymal tumors. It is unclear, however, whether these differences are due to biological or to surgical management differences.

The use of radiotherapy in these tumors is controversial. Van Houdt et al. found no significant beneficial effects of adjuvant

**Table 4. Univariate and multivariate analysis for prognostic factors in metastatic recurrence incidence**

| | *N* at risk | *N* events | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Gender | | | | | | | | |
| Female | 100 | 16 | 1 | | | | | |
| Male | 62 | 11 | 1.12 | [0.53–2.37] | 0.77 | | | |
| Age | 162 | 27 | 1.03 | [1.00–1.05] | 0.02 | 1.02 | [0.99–1.05] | 0.15 |
| Category of tumor's site | | | | | | | | |
| Soft-tissue | 124 | 20 | 1 | | | | | |
| Viscera | 38 | 7 | 1.09 | [0.45–2.62] | 0.85 | | | |
| Tumor's site | | | | | | | | |
| Limb | 47 | 9 | 1 | | | 1 | | |
| Other | 115 | 18 | 0.60 | [0.28–1.31] | 0.20 | 0.41 | [0.18–0.96] | 0.04 |
| Tumor's size | | | | | | | | |
| Above the median | 78 | 12 | 1 | | | | | |
| Below the median | 68 | 7 | 0.97 | [0.39–2.44] | 0.95 | | | |
| Mitotic count | 143 | 24 | 1.06 | [1.06–1.09] | <0.01 | 1.05 | [1.02–1.08] | <0.01 |
| Necrosis | | | | | | | | |
| 0 | 94 | 10 | 1 | | | | | |
| 1/2 | 50 | 14 | 2.77 | [1.26–6.09] | 0.01 | | | |
| Margins | | | | | | | | |
| R0 | 85 | 15 | 1 | | | | | |
| R1 | 45 | 7 | 0.70 | [0.29–1.67] | 0.42 | | | |
| Radiotherapy | | | | | | | | |
| No | 118 | 16 | 1 | | | | | |
| Yes | 44 | 11 | 1.36 | [0.65–2.88] | 0.41 | | | |
| Chemotherapy | | | | | | | | |
| Adjuvant or neoadjuvant | 17 | 6 | 1 | | | | | |
| No | 145 | 21 | 0.55 | [0.20–1.50] | 0.24 | | | |

radiotherapy on LRI or MRI in 19 patients [20]. Recently, Bishop et al. reported that treatment of soft tissue SFT using combined surgery and radiotherapy in 31 patients (preoperative radiotherapy in 14 patients and postoperative radiotherapy in 17 patients) resulted in excellent local control with no local relapse at the end of follow-up. In our series, postoperative radiotherapy was a good prognostic factor of LRI. Our results and those of Bishop et al. suggest that radiotherapy should be part of the therapeutic strategy, although only a prospective randomized trial taking account of prognostic factors could confirm the beneficial effect of radiotherapy in SFT.

The histological prognostic factors of SFT remain to be defined. The WHO classification of soft tissue tumors recognizes a malignant category of SFT but with some subjective parameters and no well-defined cut-off such as 'hypercellularity, variable atypias' combined with mitotic count >4/10 high-power fields, necrosis and/or infiltrative margins. For this reason, we did not include hypercellularity and variable atypias in our model unlike Pasquali et al. [6]. While FNCLCC histologic grade is an independent predictive factor for metastatic development in most adult STS, it is not applicable for SFT in because the degree of cellular differentiation is not evaluable [21].

The prognostic value of necrosis is controversial. Gold et al. found that it had a prognostic value in univariate analysis only for time to recurrence and that it was not a compulsory parameter for malignancy [10]. Like Demicco et al., we found that it was a prognostic factor of MRI and OS in univariate analysis. Unlike Demicco et al. we did not use it in our risk assessment model since it had no prognostic value in multivariate analysis. In contrast, Tapias et al. used the item necrosis or hemorrhage in their scoring system for pleural SFT recurrence [22].

Our data confirm that mitotic activity is the best histological prognostic factor for SFTs whatever their localization. Mitotic count analyzed as a continuous variable or with a cut-off of four or more mitotic figures/10 high-power fields was a strong prognostic factor for MRI and OS in univariate analysis and for MRI only in multivariate analysis in our study. The prognostic value of mitotic count was reported in most series with a cut-off of four or more mitoses [5, 6, 20, 22] or strictly more than four mitoses per 10 high power fields [1, 10, 23]. This raises the issue of a separate group of patients with high mitotic score who could potentially benefit from more aggressive therapeutic strategies. Mitotic count should therefore be included in any standardized pathological report.

This study clearly shows that different prognostic SFT subgroups could benefit from different therapeutic strategies and the main question now is how they should be managed. Should patients with good prognostic factors for local recurrence and metastasis be considered to have less risk of recurring after surgery and thus be monitored exclusively with a long follow-up? Or could patients with more aggressive tumors benefit from radiotherapy and/or systemic treatment? If these results are confirmed in larger

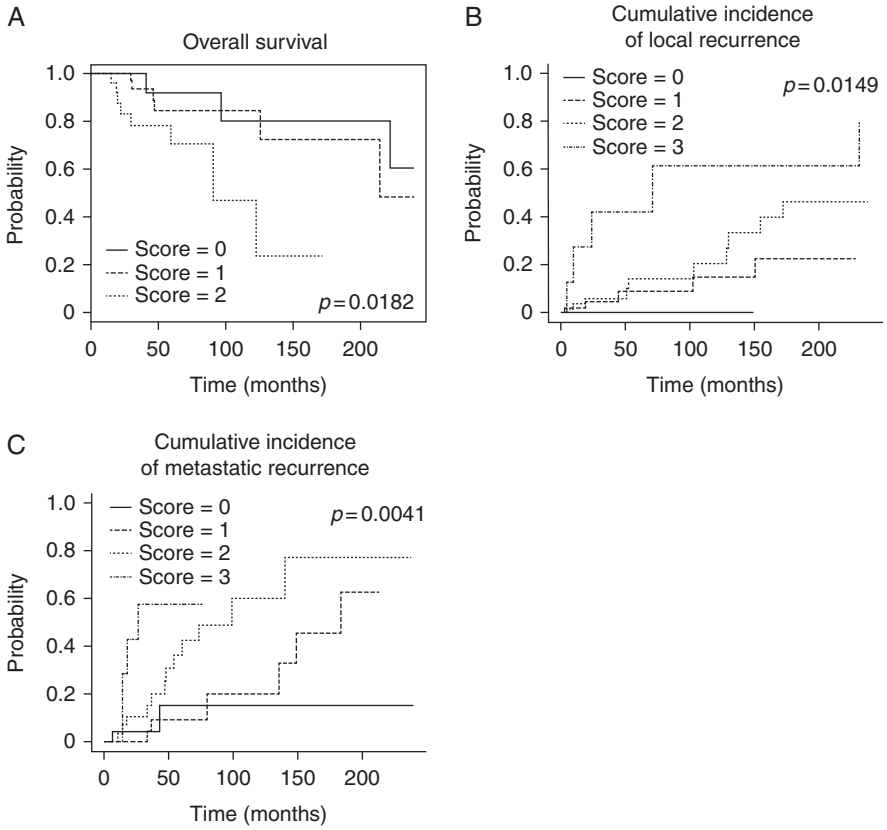


**Figure 2.** (A) Effects of number of prognostic factors on overall survival. (B) Effects of number of prognostic factors on local recurrence incidence (LRI). (C) Effects of number of prognostic factors on metastatic recurrence incidence (MRI).

studies, our risk assessment model could be useful for stratifying patients in randomized trials. Moreover, the survival calculator could become standard practice in SFTs to individualize treatment based on the clinical situation. Use of an individual risk calculator to quantify the risk of local recurrence could help in making a decision about whether or not the patient should be treated with additional radiotherapy. For example, is it necessary to treat a 65-year-old patient with radiotherapy to decrease the risk of recurrence by 12.1%–3.8% at 10 years, given the toxicity of the treatment? Finally, this investigation could be the starting point for studies incorporating biomarkers such as *NAB2/STAT6* fusion transcript types in the risk assessment model.

## Acknowledgement

We are grateful to R. Cooke for editing the English.

## Funding

None declared.

## Disclosure

The authors have declared no conflicts of interest.

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