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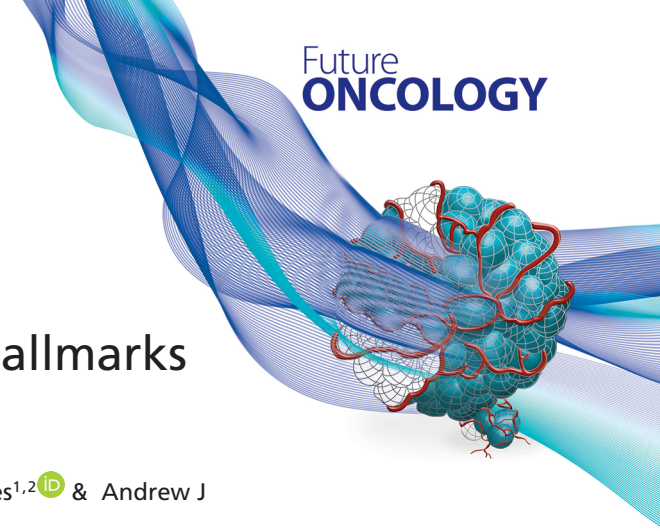

# Solitary fibrous tumor: molecular hallmarks and treatment for a rare sarcoma

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Solitary fibrous tumor (SFT) is a rare soft tissue sarcoma subtype which mainly affects adults in the fifth and sixth decades of life. Originally part of a spectrum of tumors called hemangiopericytomas, classification has been refined such that SFTs now represent a distinct subtype. The identification of *NAB2-STAT6* fusion in virtually all SFTs has further aided to define this rare subgroup. SFTs have a spectrum of behavior from benign to malignant, with evidence suggesting risk of metastases related to age at diagnosis, extent of necrosis, mitotic rate and tumor size. The standard treatment for localized disease is surgical excision with or without radiotherapy. Retrospective and prospective evidence suggests antiangiogenic treatment is effective for unresectable disease. Further translational work is required to understand the biology driving the differential behavior and identify more effective treatments for patients with metastatic disease.

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Solitary fibrous tumor (SFT) is a fibroblastic mesenchymal tumor which has been described to occur in virtually any site within the body [1]. It is a rare subtype of soft tissue neoplasm, with incidence of 0.1 per 100,000 person years [2]. SFTs emerged from a historical group of neoplasms described as hemangiopericytomas [3], first reported by Stout and Murray in 1942 [4]. Based on a subsequent review of 25 additional 'hemangiopericytoma' cases, Stout stated that understanding the variations between seemingly similar cases of hemangiopericytomas seemed a 'hopeless' task and that these neoplasms showed variable malignant potential [5]. His important key observation was that all of the tumors were united by profuse proliferation of capillaries surrounded by a thin or thick connective tissue sheath [5]. However, the diagnosis remained challenging, as hemangiopericytomatous features are seen in a number of other malignancies, including synovial sarcoma, mesenchymal chondrosarcoma and infantile fibrosarcoma [3]. Increasing understanding via clinicopathological correlations subsequently led to the grouping of these tumors as SFTs. In contemporary classification, the term hemangiopericytoma has been replaced by SFT and its variants [1].

Given the rarity of SFTs, much of the literature focuses on case reports or small retrospective cohorts, with few randomized trials. Here we review the molecular pathogenesis and approach to treatment of SFTs.

## Pathological classification

Histologically, SFTs are variably cellular neoplasms typically comprising patternless arrays of uniform ovoid to spindle-shaped cells in variably collagenous stroma. Vascularity is typically prominent, with interspersed large, dilated, thin-walled 'stag horn' (hemangiopericytic) vessels [1]. Immunohistochemically, SFT typically exhibits diffuse CD34, CD99 and BCL2 expression. Nuclear β-catenin can be present in approximately 40% of cases, and HHF35, neuron-specific enolase, LEU7 and GFAP can be focally positive [1]. Desmin and S100 protein are typically negative. Importantly, diffuse and strong nuclear STAT6 is sensitive for the diagnosis of SFT, although not completely specific [6]. A large study across mesenchymal tumors demonstrated that 85% (n = 204/240) of SFTs had strong nuclear STAT6 positivity, whereas strong expression was seen in a minority of desmoid fibromatosis (n = 14/184; 5%), liposarcomas (n = 49/408; 12%) and unclassified sarcomas (n = 8/65; 12%) [6]. In addition

**Table 1. Four-point risk stratification for solitary fibrous tumors.**

| Risk factor | Score | | |
|---|---|---|---|
| Age (years) | | | |
| • <55 | 0 | | |
| • ≥55 | 1 | | |
| Tumor size (cm): | | | |
| • <5 | 0 | | |
| • 5 to <10 | 1 | | |
| • 10 to <15 | 2 | | |
| • ≥15 | 3 | | |
| Mitotic count (/10 HPF): | | | |
| • 0 | 0 | | |
| • 1–3 | 1 | | |
| • ≥4 | 2 | | |
| Tumor necrosis: | | | |
| • <10% | 0 | | |
| • ≥10% | 1 | | |
| **Risk class** | | **Patients (n = 132)[†], n (%)** | **10-year metastasis-free survival** |
| Low | 0–3 | 65 (50%) | 100% |
| Intermediate | 4–5 | 45 (34%) | 50–90% |
| High | 6–7 | 22 (16%) | 0–27% |

[†]82 patients in the test set and 50 patients in the validation set.
HPF: High-powered fields.

to the presence of vessels, VEGFR1 and VEGFR2 have been shown to be expressed by immunohistochemistry [7]. Patient-derived xenograft models have shown PDGFRB and VEGFR2 expression [8].

While the majority of SFTs are benign, around 5–45% show aggressive clinical behavior leading to local recurrence and/or metastatic disease [9–13]; therefore it is important to identify the malignant potential of SFTs to inform clinical management. In addition to the typical SFT morphology, malignant SFTs variably demonstrate infiltrative margins, loss of CD34 expression, hypercellularity, necrosis, some degree of pleomorphism and a mitotic index greater than 4/10 high-powered fields (HPF) [1]. An initial risk assessment model developed based on the outcome of 103 patients identified that older age at diagnosis (>55 years), large tumor (>15 cm) and high mitotic rate (≥4/10 HPF) correlated with a higher rate of metastasis and death [14]. Based on this model, patients with high-risk SFTs had 10-year metastasis- and disease-free survival rates of 15 and 0%, respectively, while none of the patients with low-risk SFTs had experienced recurrent disease or died over a median follow-up of 50 months [14]. Interestingly, in this cohort, necrosis predicted tumors with higher risk of metastasis, but did not predict tumor-related death. Demicco *et al.* further refined their model with additional patients to include necrosis (Table 1) [11]. The addition of necrosis increased discrimination between groups. Congruent with the authors' earlier model, patients with low-risk tumors had 100% 10-year metastasis-free survival, while patients with high-risk tumors had a significant risk of recurrence at 10 years, between 78 and 100% [11]. Such a risk assessment model is a key tool for multidisciplinary treatment of SFTs.

More rarely, SFTs can also dedifferentiate to an anaplastic, high-grade morphology [15,16]. Dedifferentiated SFT had an approximately 0.8% incidence (n = 8/948) in primary SFTs reported by Mosquera and Fletcher over a 20-year period at a tertiary referral centre [16]. Dedifferentiation occurred in SFTs across multiple sites, ages (range: 40–76 years) and sizes (range: 3.4–20 cm) [16]. The hallmark of these cases is abruptly juxtaposed areas of high-grade sarcoma within typical and 'benign'-appearing SFT [16]. The dedifferentiated areas often show loss of CD34 expression with variable preservation of CD99. Expression of p53 and p16 was seen in the majority of dedifferentiated areas, but not in areas of typical-appearing SFT. Importantly, STAT6 expression has been shown to be frequently lost in the dedifferentiated components, but retained in malignant and classical-type SFT [17].

## Molecular hallmarks

The heterogeneity of SFTs led to an interest in exploring whether translational molecular sequencing could identify a unifying driver. Robinson *et al.* first identified a *NAB2-STAT6* fusion in a 44-year-old woman with a meningeal malignant SFT as part of an institutional clinical sequencing program [18]. Remarkably, a *NAB2-STAT6* fusion was then detected in 100% of further SFTs tested (n = 27), including tumors histologically described as benign and malignant. While there was variation in the *NAB2* or *STAT6* exons involved in the fusion breakpoint, the repressor domain of NAB2 was truncated in all cases [18]. The presence of a nearly ubiquitous *NAB2-STAT6* fusion was also reported by a separate independent group which performed whole exome sequencing on DNA isolated from SFTs from 17 patients [19]. In the classical fusion, the highly variable portion of *STAT6* replaces the carboxy-terminal repressor domain of *NAB2* found between exons 5–7 [20]. While *STAT6* and *NAB2* are physically close to each other on chromosome band 12q13, fusion events require an inversion, as the genes are transcribed in different orientations. Interestingly, based on extensive molecular testing, it is thought that the inversion required for the *NAB2-STAT6* fusion may develop due to simultaneous inter- and intra-chromosomal rearrangements [20]. Wild-type NAB2 functions as a negative regulator of a family of four early growth response (EGR) zinc finger DNA transcription factors via a homeostatic loop [19,21]. Activation of NAB2 is complex, involving extracellular stimuli and intimately related to the activation of EGR transcription factors themselves [22]. The N-terminal EGR1-binding domain of NAB2 binds with EGR1, leading to a cascade of events causing nuclear differentiation and proliferation [18,20,23]. Cell lines with high *NAB2-STAT6* expression have shown significantly higher rates of proliferation compared with those with low or no *NAB2-STAT6* expression [20]. Furthermore, the inhibition of proliferation seen in the high-expression *NAB2-STAT6* cell lines occurred with knockdown of *EGR1* [20]. Taken together, this work demonstrated the key role of the pathognomonic fusion in the development of SFT [20]. Congruently, the downstream activation of EGR1 is further demonstrated through increased *in vitro* expression of EGR1-responsive genes (*IGF2, FGF2, PDGFD, NAB1*) in SFTs with *NAB2-STAT6* fusions compared with other tumor types [18]. However, expression of *EGR1* and downstream genes has been shown to lead to negative regulation of NAB2 via the carboxy-terminal domain and subsequent decreased NAB2 expression [18,20,23]. Thus the *NAB2-STAT6* fusion leads to constitutive activation of *NAB2* through the loss of the negative regulatory carboxy-terminal domain of STAT6 [18,20]. This in turn generates a fusion with unopposed EGR activation and oncogenesis.

In a large group of SFTs, the majority had detectable fusions (n = 73/80) by RT-PCR [24]. Interestingly, nearly all (n = 6/7) of the so-called fusion-negative cases had STAT6 nuclear expression by immunohistochemistry. This suggests they may also have had occult *STAT6* fusions not detected by RT-PCR, especially given the complex mechanisms required for fusion formation requiring an inversion. The most common fusions were *NAB2ex4-STATex2* (n = 33/73), *NAB2ex6-STATex16* (n = 16/73) and *NAB2ex6-STAT6ex17* (n = 16) [24]. *NAB2ex4-STATex2/4* fusions were associated with larger tumors, older patients and lower mitotic indices. However, in this study, no specific fusions were associated with prognosis or malignant potential [24]. This finding requires further exploration in larger studies, but if fusion type does not correlate with clinical outcome, there are likely additional molecular mechanisms acquired by SFTs with malignant features or dedifferentiation which explain their aggressive clinical behavior.

Importantly, while dedifferentiated SFTs have been shown to retain the *NAB2-STAT6* fusion gene, they have reduced or lost expression of the chimeric protein, leading to STAT6 loss on immunohistochemistry [17]. This underscores the importance of molecular diagnostics as standard of care for patients with soft tissue sarcomas. Patients with *de novo* dedifferentiated SFT or sampling of the dedifferentiated component may have pathological appearances of a high-grade sarcoma if assessed by only immunohistochemistry, and molecular testing is required to find the diagnostic *STAT6* fusion.

## Clinical presentation

SFT has no gender predilection and most often presents in the fifth or sixth decade of life [13,14,25], with a significant number of tumors found incidentally [25]. SFTs have been reported at virtually every site [1], but in large retrospective series, common sites of presentation are pleura, abdomen/pelvis, extremities, and head and neck [14,25]. Patients with thoracic tumors are often older [14]. The majority of patients are diagnosed with localized disease, with few (4.5–6.4%) presenting with metastatic disease at diagnosis [14,25].

SFT are highly angiogenic tumors, which is evident on imaging and as an operative finding. The tumors have both intrinsic and extrinsic neovascularization, demonstrating intense enhancement on CT scan and MRI on imaging with intravenous contrast. This is seen within the tumor itself (Figure 1A) but also in large, tortuous extra-

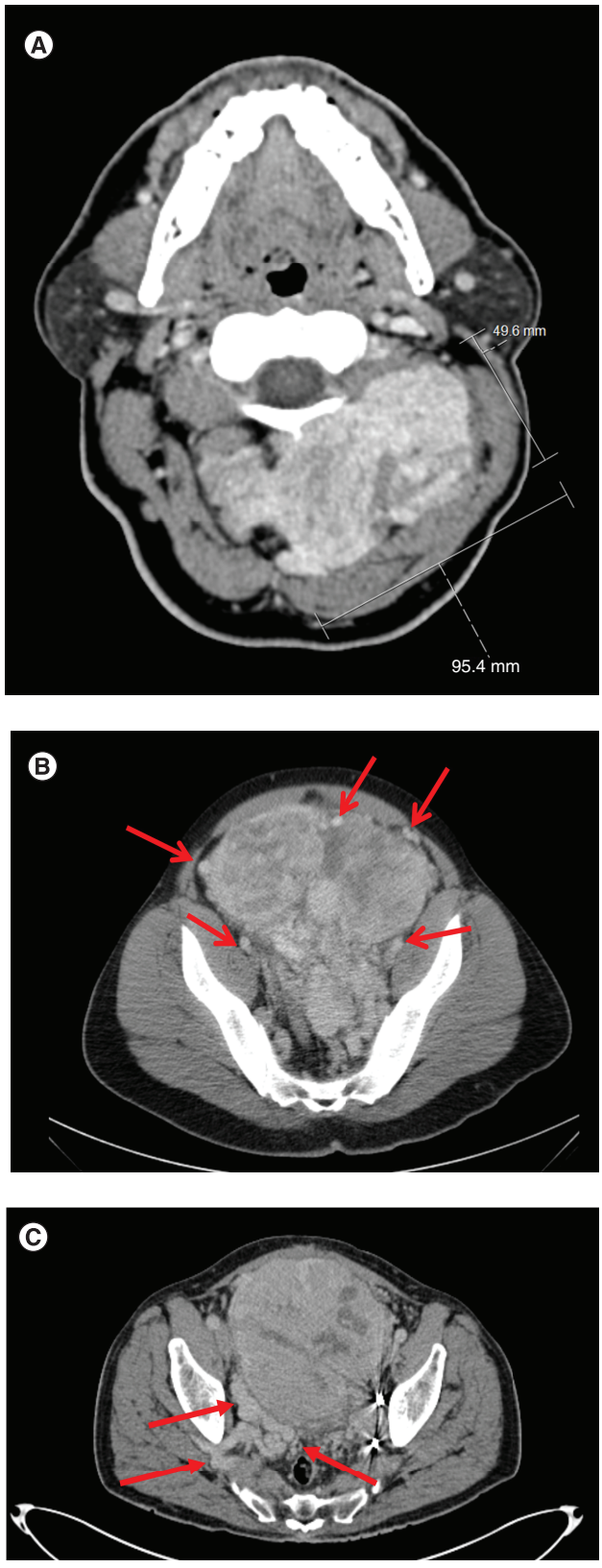


**Figure 1. Vascularization of solitary fibrous tumors demonstrated by contrast-enhanced computed tomography. (A)** Solitary fibrous tumor in the neck with intrinsic neovascularization. **(B & C)** Massive pelvic solitary fibrous tumors with multiple tortuous surrounding vessels (arrows).

anatomical blood vessels that surround the tumor (Figure 1B & C). At surgery these blood vessels are extremely friable, which can make surgery particularly hazardous for large tumors in confined anatomical spaces such as the pelvis. In the future, functional imaging may play a role in assessment of SFTs. However, the relationship between fluorodeoxyglucose PET/CT avidity and natural history of SFTs is poorly understood. Improved understanding of the prognostic nature of fluorodeoxyglucose avidity in SFT is required before PET/CT becomes a key tool in multidisciplinary management [26]. For example, PET/CT may prove particularly relevant in the preoperative setting for biopsy-confirmed tumors whose malignant potential cannot be classified [27,28].

In less than 5% of cases [25,29], patients can present with non-islet-cell tumor hypoglycemia, which was first described by Doege [30] and Potter [31] and eponymously termed Doege–Potter syndrome. Hypoglycemia results from secretion of high-molecular-weight IGF2. This IGF2 is unable to form the usual islet cell-produced IGF2 ternary complex and instead forms a binary complex. This leads to hypoglycemia by inhibiting hepatic gluconeogenesis and increasing peripheral glucose uptake through direct interaction with insulin-like growth factor and insulin receptors [29,32].

## Clinical presentation

### Localized disease

The standard treatment for localized disease is resection. Recurrence rates for an unselected population are high (57%) in large retrospective studies, with figures for local and distant recurrence of 26.7 and 30.2%, respectively [25]. Patients with intra-abdominal, retroperitoneal or pelvic tumor sites have been shown to have increased risk of local recurrence [13]. However, these findings must be interpreted with caution, as the patients within this study have heterogeneous recurrence risk. Risk models developed by Demicco *et al.* [11,14] suggest a wide spectrum of recurrence risk (Table 1), and thus it is difficult to extrapolate the true recurrence risk in an unselected population. Large retrospective studies have also demonstrated that disease-free survival is significantly associated with high mitotic rate (>4/10 HPF), hypercellularity and high levels of pleomorphism [33].

Based on the Demicco risk stratification, patients with intermediate- to high-scoring tumors have a high risk of recurrence. A recent international retrospective cohort of patients with non-meningeal SFTs demonstrated, using propensity score matching for margin status and mitotic count, that oncologic resection and radiotherapy (50 Gy; neoadjuvant or adjuvant) significantly reduced the risk of local recurrence compared with oncologic resection alone [34]. There was no difference in overall survival between the two groups. Given the rarity of SFTs, it is unlikely that randomized trials will be completed to more definitely conclude on the benefit of radiotherapy for resectable disease. Therefore, based on this evidence, perioperative radiotherapy should be considered as part of multidisciplinary management for patients with resected SFTs, particularly those with microscopic disease at margins (R1 resection) or those with high mitotic counts. Another potential benefit of preoperative radiotherapy is that the intense neovascularization seen in this tumor is often reduced after radiotherapy. This effect can be ongoing for some months after completion of radiotherapy (Figure 2). Accordingly, there can be clinical benefit in planning surgery after a slightly longer interval than the standard 6–8 weeks after completion of radiotherapy to ensure that maximum benefit in minimizing surgical risk is achieved.

After oncologic resection with or without radiotherapy, patients with intermediate or high risk of recurrence should have radiological follow-up in accordance with local practice [35]. Notably, late recurrences (>10 years after diagnosis) have rarely been reported [36].

For patients with localized but unresectable disease, an international retrospective study has shown good local control rates for patients treated with curative intent radiotherapy [37]. Based on 15 patients, objective response rate was 67% (n = 9; two complete response, seven partial response [PR]); 27% of patients (n = 4) had stable disease (SD) and only one patient had progressive disease (PD). Importantly, long-term benefit was seen, with 81.3% 5-year local control and a 5-year overall survival rate of 87.5% [38].

### Metastatic disease

While there are limited published data related to SFT's predilection for particular metastatic sites, one small study identified lung (31%), liver (24%) and bone (15%) as common sites of metastasis [39]. Other sites have been reported, including mediastinum, colonic mesentery, soft tissue [12] and kidney [39]. Taken together, this suggests that the mechanism of metastasis is hematogenous spread. There is limited prospective evidence to guide the treatment of metastatic SFT. Retrospective cohorts have shown half of patients treated with anthracycline-based chemotherapy had progressive disease, with only 6–20% PR [25,40,41]. Median progression-free survival with

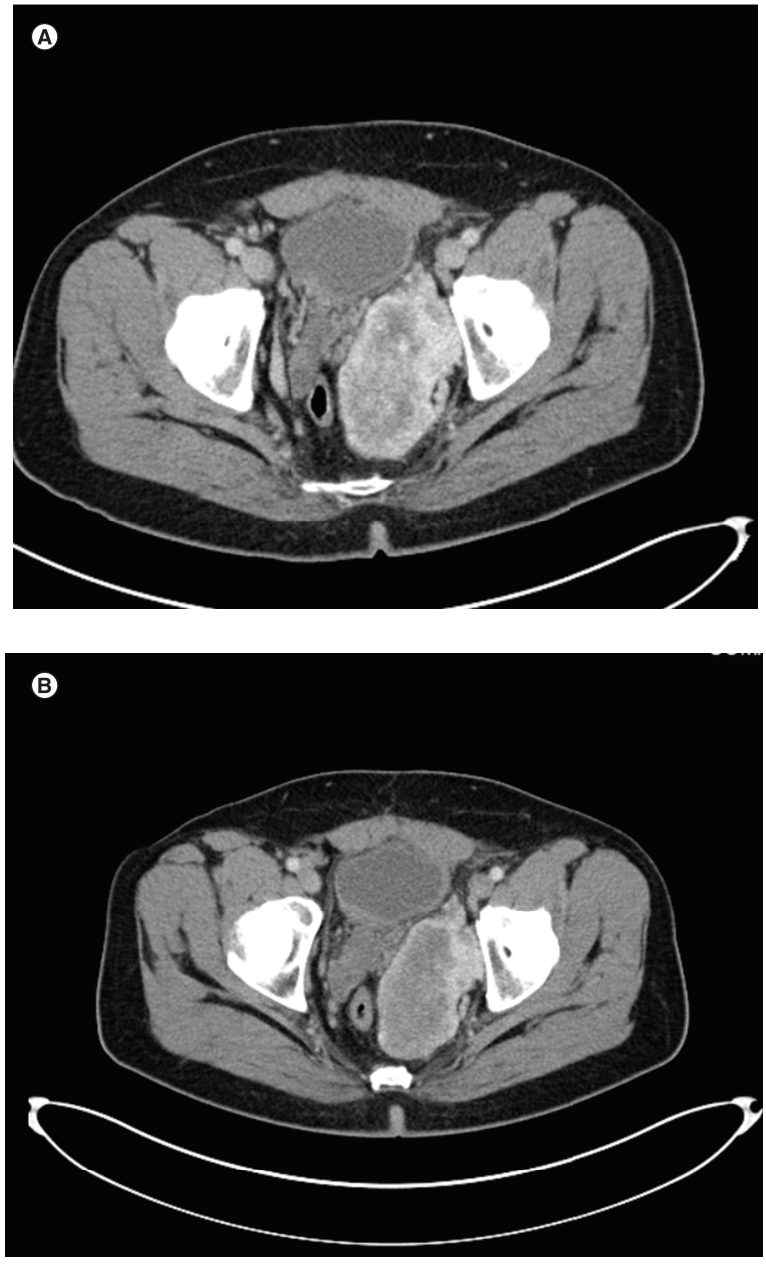


**Figure 2. Neoadjuvant radiotherapy decreases enhancement of pelvic solitary fibrous tumor on computed tomography with contrast.**
**(A)** Pre-radiotherapy. **(B)** Post-radical radiotherapy.

conventional sarcoma chemotherapy is short at 4–4.2 months [40,41]. A small retrospective cohort of eight patients treated with dacarbazine showed 38% PR (n = 3/8), 50% SD (n = 4/8) and 12% PD (n = 1/8) [42].

Given both its vascular nature on imaging and its expression of angiogenic markers, antiangiogenic agents have been explored in SFT. In initial retrospective studies, systemic therapies inhibiting angiogenesis, including pazopanib [25,39,43], sunitinib [43,44] and temozolomide–bevacizumab [45] showed promising response rates compared with those observed for standard chemotherapy. To explore the benefit of antiangiogenic agents in a prospective manner, the Italian, French and Spanish sarcoma groups conducted a single-arm, Phase II trial of pazopanib in patients whose metastatic or unresectable SFT had progressed within 6 months [38,46]. Notably, the trial was amended to exclude patients with dedifferentiated SFT, as there were two patients with rapid progression early in the study [38]. For 31 patients with typical SFT, based on central radiology review, 6% (n = 2/31) and 94% (n = 29/31) had PR and SD by the Response Evaluation Criteria In Solid Tumors (RECIST; v1.1), respectively. Median progression-free survival was 12.1 months. An Italian sarcoma group Phase II study of axitinib showed similar responses, with 5.9% PR (n = 1/17), 82% SD (n = 14/17) and 12% PD (n = 2/17) [47]. In addition, there are

currently two actively recruiting trials for patients with SFT: a Phase II single-arm study of eribulin (ERASING) [48] and a Phase II randomized study of trabectedin versus doxorubicin and dacarbazine (STRADA) [49] with results expected in 2023 and 2024, respectively. The results of these studies will further elucidate the role of 'STS-type' chemotherapy for this rare STS subtype.

Given the vascular nature of SFT, contemporary studies have also used the Choi criteria to assess response [38,39,44,46,48,49]. For patients with gastrointestinal stromal tumor, the Choi criteria have been shown to be more sensitive for response to treatment than traditional RECIST [50,51]. While retrospective studies have compared the predictive role of RECIST 1.1 and Choi response [52] for neoadjuvant therapy for high risk soft tissue sarcoma, there is limited understanding of the predictive role of the Choi criteria in SFT, and therefore Choi response should be interpreted with caution.

For patients with progressive SFTs requiring systemic treatment, evidence suggests treatment with an antiangiogenic, with no single treatment favored. In clinical practice, the choice of agent is often dictated by access to therapy. Prospective cohorts have demonstrated that patients may respond to more than one antiangiogenic therapy, suggesting a sequential approach may be used [46,47]. Chemotherapy can be considered, including dacarbazine; however, given the modest response rates, toxicity must be carefully balanced with realistic expectations of clinical benefit. For patients with dedifferentiated SFT, pazopanib was shown to be ineffective in two patients [38], and there is unfortunately little evidence to guide clinicians in treating this aggressive SFT variant.

Multidisciplinary care is key for patients with sarcoma, particularly those with metastatic disease. With limited retrospective and prospective data to guide treatment, local treatments can be considered within the context of a multidisciplinary team. For example, surgical treatment of metastatic disease could be considered for fit patients with a relatively long disease-free interval. In addition, radiotherapy is an important consideration for patients with metastatic disease. An international retrospective cohort study has demonstrated a response rate for radiotherapy of 38% (n = 9), with SD in 57% (n = 13) and only one patient having PD. Even with palliative doses for metastatic disease (3–39 Gy), the 5-year local control rate and overall survival were 62.5 and 54.2%, respectively.

## Conclusion

SFTs represent a rare subtype of STS with a variable natural history. The *NAB2-STAT6* fusion is pathognomonic, however further work is required to understand the spectrum of biology exhibited by SFTs. Risk stratification scores can identify those at high risk of recurrence, however surgery and radiotherapy remain the mainstay of curative-intent treatment. Current evidence demonstrates that antiangiogenic therapy is an important target for patients with unresectable or metastatic disease.

## Future perspective

For this rare subtype, a multidisciplinary approach is key to optimal outcomes for patients. Identification of the hallmark *NAB2-STAT6* fusion has laid the foundation for future translational work to identify subtype-specific therapy for the subset of SFTs that require systemic treatments. In order to provide meaningful results, trial design must take into account the heterogeneity within SFTs, and incorporate established risk stratification systems. Further work is need to focus on dedifferentiated SFT, which remains poorly understood, and there is no contemporary evidence to guide treatment of this ultra-rare, but aggressive subtype.

### Executive summary

**Pathological classification**

- Solitary fibrous tumors are a rare sarcoma subtype which can occur at virtually any anatomical site.

**Molecular hallmarks**

- Translational work has been key to identifying the hallmark *NAB2-STAT6* fusion that is present in the vast majority of solitary fibrous tumors.

**Clinical presentation**

- Surgery with or without radiotherapy is the established standard of care for localized disease.
- There is limited evidence to guide treatment of metastatic disease and a multidisciplinary approach is key.
- Further translational work is required to identify novel therapies and treatment strategies to improve outcomes for patients with recurrent or metastatic disease.

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