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Review Article

Exploring Rare Mesenchymal Neoplasms: Morphological Features, Molecular Pathways, Diagnostic Challenges, and Therapeutic Perspectives

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Abstract

Pattern less mesenchymal neoplasia with branching, staghorn-like vessels represent a diagnostically challenging group of lesions in which solitary fibrous tumor (SFT) is the principal entity. SFT may arise in nearly any organ or soft-tissue compartment and displays a wide range of clinical behavior, from slowly enlarging localized masses to recurrent or metastatic disease. Its defining molecular event is the NAB2::STAT6 fusion, which alters transcriptional regulation and provides the biological basis for the characteristic nuclear STAT6 immunostaining pattern. Morphologically, tumors show spindle or ovoid cells in variably collagenized stroma, with alternating cellularity and a branching vascular network. Cellular, lipomatous, giant cell-rich, myxoid, malignant, and dedifferentiated patterns broaden the diagnostic spectrum. Because these appearances overlap with numerous fibroblastic, perivascular, adipocytic, and other spindle-cell neoplasms, diagnosis requires correlation of architecture, cytology, immunophenotype, imaging, and, when needed, molecular testing. Nuclear STAT6 is the most useful immunohistochemical marker, while CD34 and selected secondary markers provide supporting evidence. Prognostic assessment should incorporate age, tumor size, mitotic activity, necrosis, margins, site, and histological grade rather than relying on a simple benign–malignant distinction. Complete resection with negative margins remains the preferred treatment for localized disease. For unresectable or metastatic tumors, antiangiogenic agents have shown activity, whereas conventional chemotherapy and immunotherapy have more limited or evolving roles. This review integrates the clinicopathological spectrum, diagnostic strategy, risk assessment, and current management principles relevant to these uncommon neoplasms.

Keywords: Fibroblastic Neoplasm; NAB2::STAT6 Fusion; STAT6 Immunohistochemistry; Staghorn Vasculature; Spindle-Cell Lesions; Risk Stratification; Targeted Therapy

INTRODUCTION

Solitary fibrous tumor (SFT) represents a distinctive fibroblastic neoplasm characterized by a prominent vascular network composed of thin-walled, branching vessels. These vessels frequently exhibit a characteristic staghorn configuration, historically associated with hemangiopericytoma. Although the tumor was initially identified in the pleura, subsequent investigations established its occurrence in numerous extrapleural anatomical locations, including the extremities, abdominal cavity, retroperitoneum, head and neck, visceral organs, and skeletal structures. The clinicopathological characteristics of pleural tumors contributed substantially

to the early understanding of this entity and its subsequent recognition as a distinct mesenchymal neoplasm [1].

Historically, the terminology surrounding SFT was complicated by the widespread use of the term hemangiopericytoma. Many lesions previously classified under this designation were subsequently recognized as fibroblastic tumors rather than neoplasms originating from true pericytes. Advances in tumor classification gradually established SFT as a unified diagnostic category encompassing several previously separate morphological entities [2].

A major development in understanding SFT occurred with the identification of the recurrent NAB2::STAT6 gene fusion. This molecular alteration provided an important explanation for the shared biological characteristics of tumors previously classified as pleural SFT and extrapleural hemangiopericytoma. Subsequent genomic investigations confirmed the recurrent nature of this fusion and demonstrated its diagnostic significance [3,4]. Additional molecular characterization identified different fusion variants and their potential associations with histological appearances and clinical behavior [5].

Despite these molecular advances, establishing an accurate diagnosis remains challenging because SFT exhibits substantial morphological variation and overlaps with several spindle-cell, fibroblastic, vascular, and soft tissue neoplasms. Nuclear expression of signal transducer and activator of transcription 6 (STAT6) has consequently become an important diagnostic feature because it reflects the underlying NAB2::STAT6 rearrangement. The incorporation of STAT6 immunohistochemistry into routine pathological assessment has substantially improved diagnostic reliability [6].

The clinical importance of SFT extends beyond its characteristic histological appearance. Although many tumors demonstrate relatively indolent behavior, some develop local recurrence, distant metastasis, or high-grade transformation. Consequently, understanding the relationship between molecular alterations, histological findings, and clinical outcomes is essential for establishing appropriate management strategies.

This review provides an integrated discussion of SFT, covering its historical development, epidemiology, clinical presentation, radiological characteristics, molecular mechanisms, histopathological subtypes, immunohistochemical profile, differential diagnosis, prognostic assessment, and available therapeutic approaches.

LITERATURE REVIEW

Historical Development and Evolution of Classification

The classification of SFT has undergone substantial changes as pathological and molecular knowledge has progressed. Early descriptions focused primarily on pleural lesions characterized by spindle-shaped cells and branching vascular structures. The terminology of hemangiopericytoma was subsequently applied to tumors believed to originate from specialized perivascular cells. However, the presumed pericytic origin could not be consistently established through ultrastructural examination or immunohistochemical findings. Furthermore, tumors previously classified as hemangiopericytomas displayed considerable morphological and biological variation.

The discovery of the NAB2::STAT6 fusion provided molecular evidence supporting the unification of conventional SFT and most extrapleural tumors previously diagnosed as hemangiopericytoma. The updated classification eliminated the traditional separation of these two entities in most anatomical locations. Nevertheless, certain lesions previously included under the hemangiopericytoma designation remain distinct. Infantile hemangiopericytoma is considered within the spectrum of infantile myofibromatosis, whereas sinonasal glomangiopericytoma represents a separate neoplasm demonstrating perivascular myoid differentiation.

Epidemiology and Anatomical Distribution

SFT predominantly affects adults, with the greatest frequency occurring between the fourth and seventh decades of life. Both sexes are affected at approximately similar rates, although variations in sex distribution have been documented in certain anatomical locations and morphological subtypes. Extrapleural tumors account for a substantial proportion of reported cases. Common anatomical distributions include the extremities, deep abdominal and pelvic soft tissues, retroperitoneum, trunk, and head and neck region. The tumor may also develop within the gastrointestinal, genitourinary, endocrine, respiratory, and central nervous systems. Comprehensive clinicopathological investigations have demonstrated that anatomical location considerably influences clinical presentation and subsequent management [7].

Within the female genital tract, SFT has been identified in the vulva, vagina, and cervix, predominantly among adult women. These lesions demonstrate morphological characteristics similar to those observed in other

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anatomical locations, supporting the concept of a site-independent tumor entity [8].

Thoracic involvement most frequently originates from the visceral or parietal pleura, although intrapulmonary and pericardial lesions have also been described. Central nervous system involvement is uncommon and generally manifests as a dural-based tumor. Such lesions have historically been classified as meningeal hemangiopericytomas before being incorporated into the broader SFT classification [9,10].

Clinical Presentation

The clinical manifestations of SFT depend largely on the anatomical location, tumor dimensions, and relationship with adjacent structures. Most patients present with a slowly enlarging, painless mass that may remain clinically silent for an extended period.

Abdominopelvic lesions may produce abdominal enlargement, constipation, urinary difficulties, or early satiety. Tumors involving the respiratory system can remain asymptomatic until substantial growth produces cough, respiratory discomfort, or chest pain. Head and neck lesions may present with nasal obstruction, recurrent epistaxis, hoarseness, or localized swelling. Orbital tumors can cause proptosis, diplopia, displacement of the globe, and visual disturbances. Intracranial lesions may produce headaches, neurological deficits, seizures, or manifestations associated with increased intracranial pressure.

A clinically important manifestation of certain large or biologically aggressive tumors is paraneoplastic hypoglycemia. This condition, known as Doege-Potter syndrome, results from inappropriate production of insulin-like growth factor 2 (IGF2) by tumor tissue. The resulting hypoglycemia may occasionally accompany other metabolic manifestations [11].

Radiological Characteristics

Radiological examination is valuable for determining tumor location, evaluating surrounding anatomical structures, identifying vascularity, and planning surgical intervention. However, imaging findings are generally nonspecific and cannot independently establish the diagnosis.

Computed tomography (CT) frequently demonstrates a well-defined, occasionally lobulated soft tissue mass with enhancement following contrast administration. Prominent feeding vessels may be visible because of the tumor's extensive vascular network.

Magnetic resonance imaging (MRI) generally demonstrates intermediate signal intensity on T1-weighted sequences and variable signal intensity on T2-weighted images. Dense collagenous components commonly produce relatively low T2 signals, whereas cellular and myxoid regions may show increased signal intensity. Larger tumors may demonstrate internal heterogeneity resulting from hemorrhage, fibrosis, necrosis, or cystic degeneration. In the thoracic region, pleural-based masses frequently exhibit well-defined margins. Intracranial tumors may resemble meningiomas because of their dural attachment and contrast-enhancement characteristics.

Although positron emission tomography may demonstrate increased metabolic activity in aggressive tumors, substantial overlap between biologically different lesions limits its ability to distinguish malignant from indolent SFT reliably. Imaging findings should therefore be interpreted alongside pathological and molecular results [12-19].

Molecular Pathogenesis and Genetic Characteristics

The molecular hallmark of SFT is the recurrent NAB2::STAT6 gene fusion, generally resulting from a paracentric inversion involving chromosome 12q13. This alteration combines NAB2, which normally functions as a transcriptional repressor, with STAT6, a transcriptional activator.

The resulting fusion protein modifies normal transcriptional regulation and promotes constitutive activation of early growth response 1 (EGR1)-associated signaling. This molecular event influences the expression of downstream genes involved in cellular proliferation, growth, and survival. The fusion also contributes to increased expression of several growth-associated molecules, including IGF2 and fibroblast growth factor receptor 1 (FGFR1). These molecular interactions provide a biological explanation for certain clinical manifestations and may contribute to tumor development and progression.

Different NAB2::STAT6 fusion variants have been identified. Their structural differences may influence tumor morphology and biological characteristics. Certain fusion patterns are more frequently associated with conventional, less cellular tumors, whereas others occur more commonly in cellular or clinically aggressive variants. However, fusion subtype alone cannot reliably predict the clinical course of an individual patient. Additional molecular alterations have been associated with tumor progression and aggressive behavior. These include mutations involving the TERT promoter and TP53,

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together with abnormalities involving p16-associated cell-cycle regulation. Nevertheless, no single secondary molecular alteration consistently distinguishes all indolent tumors from malignant lesions.

TERT promoter mutations have been investigated as potential indicators of aggressive biological behavior and may contribute to the molecular characterization of high-risk SFT [20].

The importance of integrating molecular findings with conventional pathological assessment is particularly evident in tumors showing unusual morphology, high-grade transformation, or loss of conventional immunohistochemical markers. These developments have broadened the understanding of SFT beyond its original morphological definition (Figure 1).

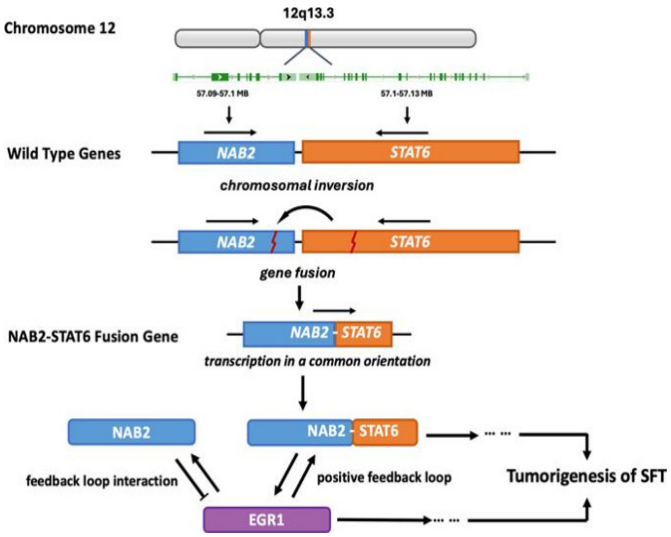


Figure 1: Molecular Mechanism and Biological Significance of NAB2::STAT6 Fusion.

GROSS AND HISTOPATHOLOGICAL FEATURES

Macroscopic Appearance

SFTs generally present as well-circumscribed, solid masses of variable dimensions. Their size ranges from relatively small lesions measuring approximately 1 cm to extensive tumors exceeding 25 cm.

The cut surface may appear firm and white when collagen deposition is prominent, whereas highly cellular tumors frequently exhibit a fleshy, tan, or pinkish-gray appearance. Hemorrhage, necrosis, calcification, and cystic degeneration may be identified, especially in larger lesions.

Tumors arising from serosal surfaces may demonstrate exophytic growth, while some intracavitary lesions exhibit a polypoid configuration attached by a fibrous stalk. Pleural tumors occasionally contain prominent feeding vessels within their pedicles.

Microscopic Appearance

Conventional SFT is characterized by a patternless growth arrangement, consisting of alternating hypercellular and hypocellular areas. The tumor cells are generally spindle-shaped to ovoid, with relatively uniform nuclei, pale eosinophilic cytoplasm, and indistinct cellular boundaries.

The intervening stroma contains variable amounts of collagen, ranging from delicate fibers to extensive hyalinized material. A prominent network of branching, thin-walled vessels is frequently present and represents one of the most recognizable morphological characteristics. The vessels may demonstrate perivascular hyalinization, while tumor cells are distributed irregularly between collagen bundles or arranged in short fascicles and occasional storiform configurations.

Conventional lesions generally demonstrate limited mitotic activity and minimal nuclear atypia. Additional findings may include hemorrhage, myxoid degeneration, cyst formation, multinucleated giant cells, and occasional epithelioid or rhabdoid cellular components. The combination of cellularity, stromal composition, and vascular architecture is important for recognizing the morphological spectrum of SFT [13].

HISTOPATHOLOGICAL VARIANTS

Cellular Solitary Fibrous Tumor

The cellular variant demonstrates increased cellular density with closely packed spindle-shaped, ovoid, or rounded tumor cells. Intervening collagenous stroma is relatively limited, while branching vascular channels remain prominent. These lesions historically correspond to tumors classified as hemangiopericytoma. Hemorrhage may be observed, and some cases demonstrate necrosis or increased mitotic activity.

Lipomatous solitary fibrous tumor

Lipomatous SFT, previously associated with the term lipomatous hemangiopericytoma, is characterized by the presence of mature adipose tissue within the tumor. The adipocytic component occurs alongside conventional SFT morphology, including spindle cells, collagen deposition, and branching vasculature. Although most reported examples demonstrate relatively indolent behavior, malignant histological characteristics have also been documented. The presence of mature adipose tissue

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may create diagnostic confusion with other adipocytic neoplasms [14,15].

Giant Cell-Rich Solitary Fibrous Tumor

This uncommon variant was historically recognized as giant cell angiofibroma. It contains conventional SFT-like spindle cells together with numerous multinucleated giant cells.

The giant cells may be scattered throughout the stromal component or arranged along pseudovascular spaces. Alternating cellular and sclerotic regions are frequently present, accompanied by branching vascular structures [16].

Myxoid Solitary Fibrous Tumor

Myxoid SFT demonstrates extensive mucin-rich stromal alteration, which may involve most of the tumor. The neoplastic cells are generally relatively bland and show reduced cellularity. The prominent myxoid matrix may obscure the conventional architectural characteristics and create diagnostic overlap with other myxoid mesenchymal neoplasms [17].

Malignant Solitary Fibrous Tumor

Malignant SFT is associated with one or more adverse histological features, including increased cellularity, marked nuclear atypia, elevated mitotic activity, necrosis, and infiltrative growth.

Increased mitotic activity is an important indicator of aggressive behavior. Tumors demonstrating more than four mitoses per 10 high-power fields have historically been associated with malignant classification. Contemporary

Immunohistochemical marker	Approximate positivity	Diagnostic relevance
STAT6	More than 95%	Strong, diffuse nuclear expression; surrogate for NAB2::STAT6 fusion
CD34	81–95%	Frequently positive in conventional SFT
ALDH1	75–95%	Supplementary diagnostic marker
GRIA2	60–80%	Additional marker supporting SFT diagnosis
CD99	Approximately 70%	Frequently expressed but nonspecific
SMA	20–35%	Variable or focal positivity
Desmin	Less than 5%	Usually, negative
S100 protein	Approximately 15%	Occasionally focal; requires differential assessment
EMA	20–35%	Variable expression
Cytokeratins	Less than 10%	Usually negative or focally positive
PAX8	Approximately 40%	Potential diagnostic pitfall in visceral lesions
BCL2	Approximately 30%	Nonspecific expression
TLE1	Less than 10%	Limited diagnostic value
p53	Variable	Abnormal expression may accompany aggressive disease
p16	Variable	Overexpression may be associated with adverse behavior

Table 1: Immunohistochemical Characteristics of Solitary Fibrous Tumors.

Abbreviations: STAT6, signal transducer and activator of transcription 6; CD34, cluster of differentiation 34; ALDH1, aldehyde dehydrogenase 1; GRIA2, glutamate ionotropic receptor AMPA type subunit 2; SMA, smooth muscle actin; EMA, epithelial membrane antigen; PAX8, paired box protein 8; BCL2, B-cell lymphoma 2; TLE1, transducin-like enhancer of split 1.

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reporting should express mitotic activity in mitoses per square millimeter, taking microscope field area into account.

Dedifferentiated Solitary Fibrous Tumor

Dedifferentiation is an uncommon but clinically important transformation characterized by an abrupt transition from conventional SFT morphology into a high-grade sarcomatous component. The dedifferentiated area may exhibit marked pleomorphism, increased mitotic activity, and loss of conventional immunophenotypic characteristics, including nuclear STAT6 expression. Heterologous differentiation, including osteogenic or rhabdomyoblastic features, has occasionally been documented. These tumors demonstrate an increased likelihood of recurrence and metastasis, contributing to their unfavorable prognosis [18].

Immunohistochemical Characteristics

Immunohistochemistry is fundamental to the pathological identification of SFT. Strong, diffuse nuclear STAT6 staining represents the most useful diagnostic finding because it reflects the underlying NAB2::STAT6 fusion. CD34 is another commonly expressed marker and generally demonstrates cytoplasmic and membranous staining. However, its expression may decrease or disappear in high-grade and dedifferentiated tumors (Table 1).

Additional immunohistochemical markers include:

- **ALDH1:** Frequently expressed and potentially useful when differentiating SFT from selected spindle-cell mimics.
- **GRIA2:** An additional diagnostic marker identified through gene-expression profiling.
- **CD99 and BCL2:** May demonstrate positivity but lack sufficient specificity for independent diagnosis.
- **SMA:** Shows variable expression, frequently with focal staining.
- **Desmin:** Generally negative or only occasionally positive.
- **S100 and SOX10:** Usually absent or limited to focal expression.
- **EMA and cytokeratins:** May demonstrate variable or occasional focal positivity.
- **PAX8:** Can occasionally be expressed and may create diagnostic confusion in visceral tumors.

Although diffuse nuclear STAT6 staining strongly supports SFT, exceptions occur. STAT6 expression can be encountered in selected other mesenchymal neoplasms, while dedifferentiated SFT may demonstrate reduced or absent expression.

Therefore, immunohistochemical findings should always be interpreted alongside morphological features and, when necessary, molecular investigations [6].

Diagnostic Approach

Accurate identification of SFT requires an integrated assessment of clinical history, tumor location, radiological findings, microscopic architecture, immunohistochemistry, and molecular characteristics.

The initial pathological examination should focus on the overall tumor architecture, cellular distribution, stromal composition, and vascular configuration. Recognition of the patternless growth pattern, collagen-rich background, and branching vascular structures provides important clues. STAT6 and CD34 are generally included in the initial immunohistochemical panel. Strong, diffuse nuclear STAT6 expression, particularly when accompanied by CD34 positivity, supports the diagnosis.

When findings are inconclusive, additional markers such as GRIA2 and ALDH1 may provide supplementary information. Other markers should be selected according to the suspected morphological differential diagnosis. Molecular methods, including fluorescence in situ hybridization and next-generation sequencing, can help identify NAB2::STAT6 rearrangements in diagnostically difficult cases. These techniques are especially valuable when evaluating unusual morphological appearances, high-grade transformation, or loss of conventional marker expression. A combination of morphological assessment, immunophenotypic characterization, and molecular confirmation provides the strongest basis for a reliable diagnosis (Table 2).

Histological Differential Diagnosis

The differential diagnosis of SFT is extensive because several mesenchymal neoplasms demonstrate overlapping spindle-cell morphology and prominent vascular patterns.

A comprehensive assessment of the morphological spectrum and the diagnostic contribution of immunohistochemistry and molecular testing is necessary to avoid misclassification [19].

Important differential diagnoses include:

Spindle cell lipoma: This benign lesion contains bland

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Differential diagnosis	Characteristic morphology	Important distinguishing findings
Spindle cell lipoma	Bland spindle cells, adipocytes, rope-like collagen	RB1 loss; STAT6 negative
Nodular fasciitis	Tissue culture-like fibroblastic proliferation	USP6 rearrangement; SMA positive
Desmoid fibromatosis	Long sweeping fascicles	Nuclear β-catenin; CTNNB1/APC alterations
Cellular angiofibroma	Bland spindle cells and thick-walled vessels	RB1 loss; STAT6 negative
Angiofibroma of soft tissue	Branching thin-walled vessels	AHRR::NCOA2 fusion
Dermatofibrosarcoma protuberans	Storiform spindle-cell arrangement	COL1A1::PDGFB fusion
Deep fibrous histiocytoma	Storiform or fascicular spindle cells	PRKCB or PRKCD rearrangements
Myopericytoma	Concentric perivascular cellular arrangement	SMA and caldesmon positivity
Sinonasal glomangiopericytoma	Perivascular myoid growth	CTNNB1 mutation; nuclear β-catenin
Dedifferentiated liposarcoma	Spindle-cell or pleomorphic sarcomatous component	MDM2 and CDK4 amplification
Gastrointestinal stromal tumor	Spindle or epithelioid morphology	CD117 and DOG1 positivity
Malignant peripheral nerve sheath tumor	Fascicular spindle cells and necrosis	SOX10 expression; possible H3K27me3 loss
Synovial sarcoma	Monophasic or biphasic growth	SS18::SSX fusion
Phosphaturic mesenchymal tumor	Spindle cells and grungy calcification	FN1::FGFR1 fusion
Mesenchymal chondrosarcoma	Primitive cells and cartilage islands	HEY1::NCOA2 fusion

Table 2: Major Histological Mimics of Solitary Fibrous Tumor and Their Distinguishing Features.

spindle cells, mature adipocytes, and rope-like collagen. Although CD34 expression may overlap with SFT, loss of RB1 expression and the absence of nuclear STAT6 help establish the distinction.

Nodular fasciitis: A benign fibroblastic or myofibroblastic proliferation characterized by a tissue culture-like growth pattern and frequently associated with USP6 rearrangement. SMA expression is common, whereas STAT6 expression is absent.

Desmoid fibromatosis: Demonstrates infiltrative growth and long sweeping fascicles of fibroblastic cells. Nuclear beta-catenin expression and alterations involving CTNNB1 or APC help distinguish it from SFT.

Cellular angiofibroma: A vascular fibroblastic neoplasm containing numerous thick-walled vessels. Loss of RB1 expression may be observed, while nuclear STAT6 expression is absent.

Angiofibroma of soft tissue: Characterized by delicate branching vessels within a myxoid or collagenous background. Its vascular architecture can resemble SFT, but nuclear STAT6 expression is generally absent.

Dermatofibrosarcoma protuberans: Demonstrates a storiform spindle-cell arrangement and infiltrative growth into surrounding adipose tissue. COL1A1::PDGFB-associated molecular alterations support its diagnosis.

Deep fibrous histiocytoma: May contain monomorphic spindle cells and prominent branching vessels. STAT6 negativity helps differentiate this lesion from SFT.

Myopericytoma: Characterized by concentric perivascular arrangement of spindle cells and expression of smooth

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muscle-associated markers, particularly SMA.

Sinonasal glomangiopericytoma: Demonstrates perivascular myoid differentiation, commonly accompanied by nuclear beta-catenin expression and CTNNB1 alterations.

Dedifferentiated liposarcoma: May resemble SFT, especially when adipocytic differentiation is inconspicuous. MDM2 and CDK4 amplification and corresponding immunohistochemical findings provide important diagnostic evidence.

Gastrointestinal stromal tumor: Can show spindle-cell morphology and CD34 expression. Positive CD117 and DOG1 staining, together with the absence of typical nuclear STAT6 expression, supports GIST.

Malignant peripheral nerve sheath tumor: Frequently demonstrates fascicular spindle-cell architecture, necrosis, and variable expression of S100 and SOX10. Loss of H3K27me3 may provide additional diagnostic evidence.

Synovial sarcoma: The monophasic spindle-cell variant may closely resemble cellular SFT. SS18::SSX fusion-associated immunohistochemical or molecular findings help establish the diagnosis.

Phosphaturic mesenchymal tumor: Often contains bland spindle cells, a rich vascular network, and characteristic grungy calcification. FGF23-associated molecular alterations support this diagnosis.

Mesenchymal chondrosarcoma: Demonstrates undifferentiated round cells together with islands of hyaline cartilage. The characteristic HEY1::NCOA2 fusion differentiates it from SFT. The differential diagnosis is particularly important in limited biopsy specimens because sampling may not capture the characteristic vascular architecture or the more representative regions of a heterogeneous tumor.

Prognostic Assessment and Clinical Behavior

SFT demonstrates a wide range of clinical outcomes. Although many cases remain localized following surgical treatment, a subset develops local recurrence or distant metastasis. Recurrence may occur several years after the initial diagnosis, highlighting the importance of prolonged surveillance. Conventional benign and malignant classifications do not adequately represent the complete spectrum of biological behavior. Therefore, multivariable prognostic models have been developed to estimate the probability of recurrence and metastatic progression.

Important prognostic parameters include:

- Patient age at diagnosis.
- Maximum tumor diameter.
- Mitotic activity.
- Presence and extent of tumor necrosis.
- Anatomical location.
- Infiltrative growth and dedifferentiation.

Molecular alterations involving TERT and TP53 have also been investigated in relation to aggressive tumor progression.

The modified Demicco risk model incorporates patient age, tumor size, mitotic activity, and necrosis to improve prediction of metastatic potential. Validation and comparison studies have demonstrated the value of using multivariable systems rather than relying exclusively on traditional histological classification [21,22].

Central nervous system SFTs require additional prognostic assessment because they may exhibit delayed recurrence and metastatic progression. Histological grading systems incorporating mitotic activity and necrosis help identify patients at increased risk [23].

Orbital SFTs also represent a clinically important subgroup because local recurrence may occur even after initial treatment. Tumor extent, surgical margins, and histological characteristics contribute to subsequent clinical behavior [24].

Multivariable prognostic assessment has further supported the development of risk-calculation approaches for identifying patients who require closer follow-up. Such models provide a more structured basis for clinical decision-making and postoperative surveillance (Figure 2) [25].

Therapeutic Management

Treatment selection depends on tumor location, dimensions, respectability, histological characteristics, and metastatic status. Management is preferably undertaken through a multidisciplinary team familiar with soft tissue and sarcoma pathology.

Surgical Treatment

Complete surgical removal with negative margins represents the preferred treatment for localized SFT. En bloc resection is generally recommended whenever technically feasible. When margins are positive, additional

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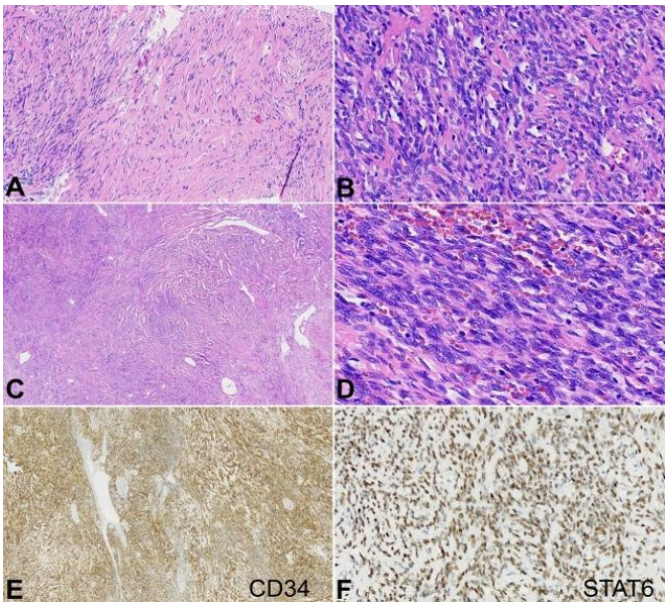


Figure 2: Integrated Diagnostic Algorithm for Solitary Fibrous Tumor.

surgery may be considered according to the anatomical location and expected functional consequences. Adjuvant radiotherapy may be appropriate for selected patients with high-risk tumors or incomplete surgical margins. Evidence from combined surgical and radiotherapeutic treatment suggests improved local control in appropriately selected patients, although a consistent survival advantage from postoperative radiation has not been established [26].

Conventional Chemotherapy

Conventional cytotoxic chemotherapy has generally demonstrated limited effectiveness against advanced SFT. Anthracycline-based regimens have been employed in patients with unresectable or metastatic disease, but responses are inconsistent and progression-free survival remains limited [27]. Dacarbazine-containing treatment has demonstrated activity in selected cases, supported by retrospective clinical observations and preclinical investigations [28]. Trabectedin has also been evaluated as a systemic treatment option for advanced malignant SFT, particularly in patients requiring additional therapeutic approaches following disease progression [29].

Antiangiogenic Therapy

SFT frequently demonstrates extensive vascularity, providing a biological rationale for investigating antiangiogenic treatment strategies.

Agents targeting vascular endothelial growth factor-associated signaling pathways have demonstrated encouraging activity in advanced disease. Pazopanib, sunitinib, and sorafenib have been investigated, with some patients achieving partial responses or disease stabilization. The increasing use of antiangiogenic agents represents an important development in the management of unresectable or metastatic SFT [30].

Sorafenib has demonstrated clinical activity in selected patients with progressive malignant tumors, supporting the therapeutic relevance of vascular signaling inhibition [31]. Sunitinib-based treatment has also been investigated, including combinations with agents targeting the insulin-like growth factor pathway. These findings provide a basis for further research into molecularly guided systemic treatment [32].

Immunotherapy

Evidence supporting immune checkpoint inhibition in SFT remains limited. Nevertheless, isolated reports have documented sustained responses following programmed cell death protein 1 (PD-1) blockade in refractory disease [33]. Clinical investigations of immunotherapy in soft tissue sarcomas have also explored the relationship between PD-1 signaling, macrophage infiltration, and immune-associated pathways. These findings provide a rationale for further evaluation of immunotherapeutic strategies in selected SFT populations [34].

Future Research Directions

Further research is required to establish more reliable relationships between the molecular characteristics of SFT and its clinical behavior. Although NAB2::STAT6 fusion is a defining molecular alteration, the prognostic significance of its individual variants remains incompletely understood. The contribution of secondary genetic abnormalities to tumor progression and dedifferentiation also requires additional investigation. Molecular profiling may help identify alterations associated with aggressive disease and potentially useful therapeutic targets. Prospective multicenter studies are needed to improve the reliability of existing prognostic models and determine whether molecular information can provide additional predictive value beyond established clinicopathological parameters.

Advances in digital pathology and artificial intelligence may also support quantitative evaluation of tumor cellularity, mitotic activity, stromal composition, and vascular characteristics. Such applications require independent validation before they can be incorporated into routine prognostic assessment. Emerging molecular investigations have emphasized the importance of combining genomic findings with clinical and pathological information to

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improve disease characterization and future therapeutic development [35,36].

CONCLUSION

Solitary fibrous tumor is a rare fibroblastic neoplasm with a broad anatomical distribution, diverse histological appearances, and clinical behavior that cannot be predicted reliably from morphology alone. Recognition of the characteristic patternless architecture, collagen-rich stroma, branching vasculature, and nuclear STAT6 expression is central to diagnosis, while molecular testing can resolve selected atypical cases. The differential diagnosis includes several spindle-cell and vascular tumors that share overlapping features but differ in immunophenotype and genetic profile. Prognostic assessment should incorporate tumor size, mitotic activity, age, necrosis, anatomical site, and dedifferentiation rather than relying on a benign–malignant label alone. Complete resection with negative margins remains the preferred treatment for localized disease; selected patients with advanced tumors may benefit from antiangiogenic agents. Long-term surveillance is warranted because recurrence or metastasis may occur years after treatment. Future studies should integrate molecular data and validated risk models to improve individualized care and clarify the prognostic value of individual NAB2::STAT6 fusion variants and emerging immunotherapeutic approaches.

References

1. England DM, Hochholzer L, McCarthy MJ. Localized benign and malignant fibrous tumors of the pleura: a clinicopathologic review of 223 cases. Am J Surg Pathol. 1989; 13:640–658.
2. Guillou L, Fletcher JA, Fletcher CD, Mandahl N. Extrapleural solitary fibrous tumour and haemangiopericytoma. In: Fletcher CD, Unni KK, Mertens F, editors. World Health Organization classification of tumours: pathology and genetics of tumours of soft tissue and bone. 3rd ed. Lyon: IARC Press; 2002. p. 86–90.
3. Robinson DR, Wu YM, Kalyana-Sundaram S, et al. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet. 2013; 45:180–185.
4. Chmielecki J, Crago AM, Rosenberg M, et al. Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. Nat Genet. 2013; 45:131–132.
5. Mohajeri A, Tayebwa J, Collin A, et al. Comprehensive genetic analysis identifies a pathognomonic NAB2/STAT6 fusion gene, nonrandom secondary genomic imbalances, and a characteristic gene expression profile in solitary fibrous tumor. Genes Chromosomes Cancer. 2013; 52:873–886.
6. Doyle LA, Vivero M, Fletcher CD, Mertens F, Hornick JL. Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. Mod Pathol. 2014; 27:390–395.
7. Martin-Broto J, Mondaza-Hernandez JL, Moura DS, Hindi N. A comprehensive review on solitary fibrous tumor: new insights for new horizons. Cancers (Basel). 2021; 13:2913.
8. Yang EJ, Howitt BE, Fletcher CD, Nucci MR. Solitary fibrous tumour of the female genital tract: a clinicopathological analysis of 25 cases. Histopathology. 2018; 72:749–759.
9. Rao N, Colby TV, Falconieri G, Cohen H, Moran CA, Suster S. Intrapulmonary solitary fibrous tumors: clinicopathologic and immunohistochemical study of 24 cases. Am J Surg Pathol. 2013; 37:155–166.
10. Mena H, Ribas JL, Pezeshkpour GH, Cowan DN, Parisi JE. Hemangiopericytoma of the central nervous system: a review of 94 cases. Hum Pathol. 1991; 22:84–91.
11. Fukasawa Y, Takada A, Tateno M, et al. Solitary fibrous tumor of the pleura causing recurrent hypoglycemia by secretion of insulin-like growth factor II. Pathol Int. 1998; 48:47–52.
12. Keraliya AR, Tirumani SH, Shinagare AB, Zaheer A, Ramaiya NH. Solitary fibrous tumors: 2016 imaging update. Radiol Clin North Am. 2016; 54:565–579.
13. Hasegawa T, Hirose T, Seki K, Yang P, Sano T. Solitary fibrous tumor of the soft tissue: an immunohistochemical and ultrastructural study. Am J Clin Pathol. 1996; 106:325–331.
14. Folpe AL, Devaney K, Weiss SW. Lipomatous hemangiopericytoma: a rare variant of hemangiopericytoma that may be confused with liposarcoma. Am J Surg Pathol. 1999; 23:1201–1207.
15. Guillou L, Gebhard S, Coindre JM. Lipomatous hemangiopericytoma: a fat-containing variant of solitary fibrous tumor? Clinicopathologic, immunohistochemical, and ultrastructural analysis of a series in favor of a unifying concept. Hum Pathol. 2000; 31:1108–1115.
16. Dei Tos AP, Seregard S, Calonje E, Chan JK, Fletcher CD. Giant cell angiofibroma: a distinctive orbital tumor in adults. Am J Surg Pathol. 1995; 19:1286–1293.
17. de Saint Aubain Somerhausen N, Rubin BP, Fletcher CD. Myxoid solitary fibrous tumor: a study of seven cases with emphasis on differential diagnosis. Mod Pathol. 1999; 12:463–471.
18. Vallat-Decouvelaere AV, Dry SM, Fletcher CD. Atypical and malignant solitary fibrous tumors in extrathoracic locations: evidence of their comparability to intrathoracic tumors. Am J Surg Pathol. 1998; 22:1501–1511.
19. Tariq MU, Din NU, Abdul-Ghafar J, Park YK. The many faces

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of solitary fibrous tumor: diversity of histological features, differential diagnosis and role of molecular studies and surrogate markers in avoiding misdiagnosis and predicting the behavior. Diagn Pathol. 2021; 16:32.

20. Demicco EG, Wani K, Ingram D, et al. TERT promoter mutations in solitary fibrous tumour. Histopathology. 2018; 73:843–851.
21. Demicco EG, Wagner MJ, Maki RG, et al. Risk assessment in solitary fibrous tumors: validation and refinement of a risk stratification model. Mod Pathol. 2017; 30:1433–1442.
22. Demicco EG, Griffin AM, Gladdy RA, et al. Comparison of published risk models for prediction of outcome in patients with extrameningeal solitary fibrous tumour. Histopathology. 2019; 75:723–737.
23. Macagno N, Vogels R, Appay R, et al. Grading of meningeal solitary fibrous tumors/hemangiopericytomas: analysis of the prognostic value of the Marseille grading system in a cohort of 132 patients. Brain Pathol. 2019; 29:18–27.
24. Yang P, Liu HC, Qiu E, et al. Factors for postoperative recurrence of orbital solitary fibrous tumor: an analysis of long-term clinical follow-up results from a Chinese tertiary hospital. BMC Ophthalmol. 2021; 21:61.
25. Salas S, Resseguier N, Blay JY, et al. Prediction of local and metastatic recurrence in solitary fibrous tumor: construction of a risk calculator in a multicenter cohort from the French Sarcoma Group database. Ann Oncol. 2017; 28:1979–1987.
26. Bishop AJ, Zagars GK, Demicco EG, Wang WL, Feig BW, Guadagnolo BA. Soft tissue solitary fibrous tumor: combined surgery and radiation therapy results in excellent local control. Am J Clin Oncol. 2018; 41:81–85.
27. Constantinidou A, Jones RL, Olmos D, et al. Conventional anthracycline-based chemotherapy has limited efficacy in solitary fibrous tumour. Acta Oncol. 2012; 51:550–554.
28. Stacchiotti S, Tortoreto M, Bozzi F, et al. Dacarbazine in solitary fibrous tumor: a case series analysis and preclinical evidence vis-a-vis temozolomide and antiangiogenics. Clin Cancer Res. 2013; 19:5192–5201.
29. Khalifa J, Ouali M, Chaltiel L, et al. Efficacy of trabectedin in malignant solitary fibrous tumors: a retrospective analysis from the French Sarcoma Group. BMC Cancer. 2015; 15:700.
30. de Bernardi A, Dufresne A, Mishellany F, Blay JY, Ray-Coquard I, Brahmi M. Novel therapeutic options for solitary fibrous tumor: antiangiogenic therapy and beyond. Cancers (Basel). 2022; 14:1064.
31. Valentin T, Fournier C, Penel N, et al. Sorafenib in patients with progressive malignant solitary fibrous tumors: a subgroup analysis from a phase II study of the French Sarcoma Group. Invest New Drugs. 2013; 31:1626–1627.
32. Stacchiotti S, Negri T, Palassini E, et al. Sunitinib malate and figitumumab in solitary fibrous tumor: patterns and molecular bases of tumor response. Mol Cancer Ther. 2010; 9:1286–1297.
33. Boothe JT, Budd GT, Smolkin MB, Ma PC. Durable near-complete response to anti-PD-1 checkpoint immunotherapy in a refractory malignant solitary fibrous tumor of the pleura. Case Rep Oncol. 2017; 10:998–1005.
34. Toulmonde M, Penel N, Adam J, et al. Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas: a phase 2 clinical trial. JAMA Oncol. 2018; 4:93–97.
35. Vogels R, Macagno N, Griewank K, et al. Prognostic significance of NAB2-STAT6 fusion variants and TERT promoter mutations in solitary fibrous tumors/hemangiopericytomas of the CNS: not (yet) clear. Acta Neuropathol. 2019; 137:679–682.
36. Ren C, D'Amato G, Hornicek FJ, Tao H, Duan Z. Advances in the molecular biology of the solitary fibrous tumor and potential impact on clinical applications. Cancer Metastasis Rev. 2024; 43:1337–1352.

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