Solitary Fibrous Tumor

Subjects: Oncology

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Solitary fibrous tumor (SFT) is a malignant condition that exhibits different clinical behaviors ranging from low to high aggressive SFT. Even when surgery alone provides curation rates above 60%, recurrences do occur in a fraction of patients where surgery is unable to provide disease control. Among the systemic therapeutic options, antiangiogenic compounds have shown higher efficacy than chemotherapy by indirect comparisons.

Keywords: solitary fibrous tumor ; anti-angiogenics ; tumor biology

1. Introduction

Solitary fibrous tumor (SFT) has an age-adjusted incidence rate of 0.61 and 0.37 per million persons per year for extrameningeal [1] and meningeal [2] cases, respectively; in other words, we can assume an age-adjusted yearly incidence of 1 new case per million people. The 2013 WHO classification integrated under the SFT nomenclature the former hemangiopericytoma denomination, [3] and the 2020 WHO classification eluded the terms of “typical” or “malignant” as typical SFT was not necessarily synonymous with benign disease [4]. Instead, risk stratification models were recommended as a better tool to determine prognosis in SFT. The risk of metastatic spread can be as high as 35–45%, or even greater, in series with a longer follow-up period [5][6]. One of these series reported a 5-year metastasis-free rate of 74%, while for the 10-year metastasis-free rate, this figure decreased by 55%. Recurrences beyond 10 years were seen in up to 10% of the SFT patients [7]. Even with a longer follow-up, the relapse-free survival can be as low as 18% at 20 years [8].

2. Clinical Aspects

SFT is considered a fibroblastic tumor with ubiquitous allocation affecting adult patients, usually from 20 to 70 years. In the largest series, the extrameningeal SFT cases were distributed as follows: abdominal cavity 31%, limbs 29%, pleura 22%, trunk 11% and others 7% (including head and neck but not meninges) [9]. The median age reported in the largest series ranged from 50 to 60 years [6][9]. Clinically, SFTs present as a well-defined mass, which is more silent in primary pleural locations than extra-pleural primary sites.

3. Pathogenesis and Pathology

3.1. Morphological Features

An SFT is comprised of randomly arranged cells with spindle or ovoid shape, within a collagenous stroma, intermixed with blood vessels with a characteristic staghorn shape. The disposition of cellular and stromal components in SFT is called “patternless pattern” and the intercellular collagen bands, if we may be so bold, could be said to evoke Van Gogh lines. The histological spectrum goes from a paucicellular context with abundant stromal collagen to highly cellular tumors where stroma is hardly detected. The mitotic count is more frequently low, and it is crucial for establishing a recurrence risk. Other pathologic findings that could have some influence on recurrence risk are nuclear pleomorphism, necrosis and cellularity. Fat-forming SFT carries a component of mature adipose tissue, and it is more frequently seen in the context of more indolent SFT. Yet, some aggressive SFTs have been also described with this feature, where the presence of lipoblasts and an atypical lipomatous tumor is seen with higher frequency than in low risk or more indolent SFTs [10]. Giant cell-rich SFT, formerly known as giant cell angiofibroma, shows features of SFT admixed with multinucleated giant cells within the stroma [11]. This characteristic SFT is more frequently, but not exclusively, found in the head and neck region. Dedifferentiated SFT constitutes the most aggressive SFT subtype. Histologically, it exhibits an abrupt transition zone to high-grade sarcoma that could contain heterologous elements such as, for instance, rhabdomyosarcoma or osteosarcoma (Figure 1) [12].

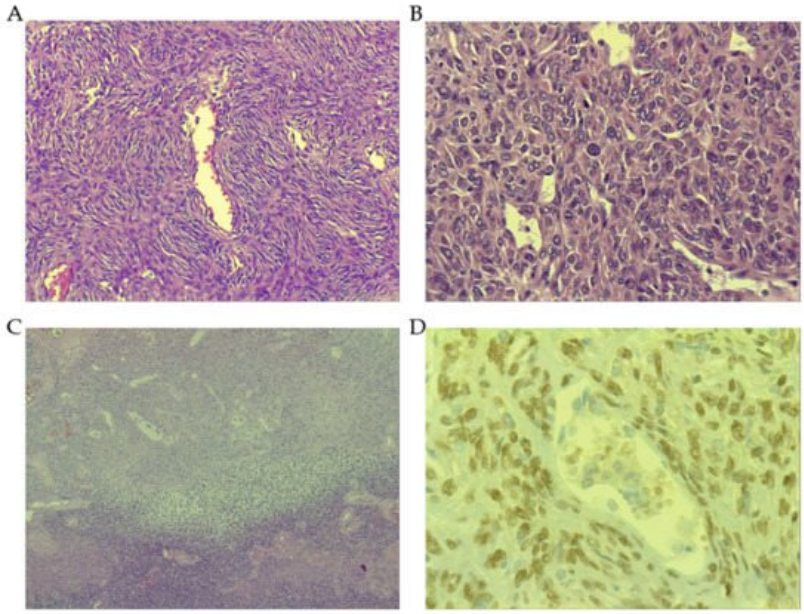

Figure 1. Histopathological features of solitary fibrous tumor (SFT). (**A**) Low-grade SFT showing a patternless pattern, with spindle cells, low number of mitosis (or lack of) and vessels with “staghorn” appearance (Magnification 40×). (**B**) High-grade SFT showing hypercellularity with nuclear pleomorphism, high number of mitotic figures (Magnification 200×). (**C**) Dedifferentiated SFT with an abrupt transition from conventional SFT to high-grade sarcoma (Magnification 10×). (**D**) STAT6 positive nuclear immunostaining (Magnification 400×).

3.2. The Role of Signal Transducer and Activator of Transcription 6 (STAT6)

Immunohistochemically, strong nuclear staining of signal transducer and activator of transcription 6 (STAT6) has become characteristic of SFT. As explained below, the underlying transcript between NGFI-A binding protein 2 (EGR1 binding protein 2) (*NAB2*) and *STAT6* is formed after the replacement of at least one repressor domain of *NAB2* with a transactivation domain of *STAT6*, which results in an overexpression of EGR1, a main target of the *NAB2* gene. The *STAT6* gene encodes a cytoplasmic protein (in a continuous shuttling to the nucleus), which acts as a transcription factor, in contrast to *NAB2*, that normally functions as a transcriptional repressor through its interaction with EGR1 and is localized in the nucleus. The transcript *NAB2–STAT6* acts as transcriptional activator, inducing the expression of EGR1 target genes. Interestingly, the transcript translocates to the nucleus resulting in a high level of expression of the transcript (*NAB2* is also a target of EGR1) compared with other tumors or normal tissues. This is the rationale for the characteristic nuclear STAT6 immunostaining, which is tremendously helpful for the diagnosis of SFT [13]. Of note, in the presence of a higher genomic instability and cell reprogramming observed in dedifferentiated SFT, the expression of oncoprotein transcript *NAB2–STAT6* can be lost [14]. It is unclear whether *STAT6* acts as a key player in the pathogenesis of SFT or rather plays a secondary role. Intriguingly, *STAT6* can induce fibrosis in the interactive network context of wound healing between macrophages, CD4 (Th2) and fibroblasts, signalizing through IL-13 [15]. As this latter cytokine signal by *STAT6*, a nexus with EGR1 and PDGF has been established in the pulmonary context, in the subepithelial fibrosis of distal airways [16]. However, these IL-13 mediated actions have been described in the context of wild-type *STAT6*, hence it is doubtful whether this is displayed in SFT in the same way. In any case, it seems judicious to consider STAT6 as a potential key protein in the SFT pathogenesis as well. The fact that EGR1 is target of both *NAB2* as a transcriptional repressor and *STAT6* as a transcription factor results in an interesting meeting point even when something other than the canonical IL-13/STAT6 pathway, which induces phosphorylation and posterior dimerization of STAT6 to enter in the nucleus, will be required. Further, as *NAB2* and *STAT6* are involved in the regulation of inflammation, collagen production, fibroblast activation and vessel formation, a deeper microenvironment study is needed in SFT to deconvolute the mechanisms due to each one.

Besides, strong nuclear staining for STAT6 has been observed in other mesenchymal tumors (Table 1), including well-differentiated and dedifferentiated liposarcoma (WD/DD-LPS) [17]. In the latter, STAT6 overexpression could be related to the amplicon intricately linked to WD/DD-LPS pathogenesis given the fact that *STAT6* is located at chromosomal region 12q13 [18]. In all of these tumors, the strong nuclear immunostaining of STAT6 concurrently occurred with strong cytoplasmic expression, indicating a higher than normal shuttling of STAT6 between the cytoplasm and nucleus.

Table 1. Immunohistochemical markers commonly expressed in solitary fibrous tumors.

Marker	Normal Tissues/Precursors	Mesenchymal Benign Entities	Mesenchymal Malignant Tumors
CD 34	-Early hematopoietic stem cells -Mesenchymal stem cells -Small-vessels endothelial cells -Embryonic fibroblasts -Endoneurial cells, dermal dendritic interstitial fibroblastic cells -Adipocitic cells	- Giant cell fibroblastoma - Lipoma	-SFT * -Kaposi sarcoma -Low-grade myofibroblastic sarcoma -Inflammatory myofibroblastic tumors -DFSP -GIST
bcl 2	-Stem cells -Endocrine tissue -Long-lived cells	-Schwannoma -Spindle cell lipoma -Dendritic fibromyxolipoma -Neurofibromas (focal)	-SFT * -Fibrosarcoma -Low-grade myxofibrosarcoma -Dedifferentiated liposarcoma -Synovial sarcoma -DFSP -GIST -Kaposi sarcoma -MPNST
CD99	-Bone marrow cells -Leukocytes	-Fibroma -Giant cell angiofibroma	-SFT * -Ewing sarcoma -Synovial sarcoma -Rhabdomyosarcoma -Osteosarcoma
STAT 6			-SFT * -Unclassified sarcomas of spindle cell or epithelioid morphology (12%) -Desmoid tumors (8%) -Neurofibromas (5%) -Clear cell sarcoma (5%) -Well-diff./dedifferentiated liposarcoma

** Expression can be lost in dedifferentiated solitary fibrous tumors (SFT); DFSP: Dermatofibrosarcoma protuberans; GIST: Gastrointestinal stromal tumors; MPSNT: Malignant peripheral stealth nerve tumors.*

3.3. Other Immunohistochemical Markers

Other unspecific supportive immunostaining markers used in SFT diagnosis are CD34, bcl-2 and CD99. The expression of CD34 is strong and diffuse in more than 80% of SFT tumors, but its expression can be lost in the most aggressive SFTs [19][20]. CD34 is a glycoprotein of the cellular membrane, which is expressed in several normal tissues: hematopoietic precursors, endothelial, endoneurial or fibroblastic cells (Table 1). Interestingly, several low-grade fibroblastic and myofibroblastic tumors apart from SFT can also show diffuse and strong CD34 immunostaining (Table 1).

Even when the molecular structure of CD34 is well recognized, its function is far from being completely understood. In hematopoiesis, CD34 has roles of cytoadhesion and the regulation of cell differentiation. $CD34^+$ cells represent a proportion of the total mesenchymal stem cells (MSCs), and are associated with high colony forming efficiency and long-term proliferative capacity [21][22]. Moreover, $CD34^+$ MSCs have exhibited a propensity for endothelial transdifferentiation. Thus, $CD34^+/CD90^+$ cells of human adipose tissue were able to form a sphere cluster and be differentiated in endothelial cells that form capillary-like structures producing a high level of VEGF [23]. A diffuse cytoplasmic with perinuclear enhancement of bcl-2 staining has been constantly described in SFT [24]. The level of bcl-2 positivity ranges from 70 to 86% in the largest series of SFT [19][25]. Of note, bcl-2 immunostaining was positive in benign conditions with spindle cellularity (Table 1). Further, apart from SFT, it is expressed in some fibroblastic spindle cell sarcomas and in the spindle component of DD-LPS or in synovial sarcoma. A close relationship of CD34 staining is seen with bcl-2, being coincident in several tumors such as SFT, dermatofibrosarcoma protuberans, Kaposi sarcoma or gastro-intestinal stromal tumor (GIST), as well as in other previously mentioned benign conditions [26]. In SFT, bcl-2 expression was seen regardless of the mitotic activity or the cellularity. Analyses in mammalian tissues determined that bcl-2 protein expression is common in stem cells, endocrine tissue, and long-lived cells [27]. Considered together, this raises the possibility that the pathogenesis of SFT could be explained as a result of neoplastic transformation of a fibroblastic precursor $CD34^+/bcl\text{-}2^+$. In addition, bcl-2 expression could be induced by STAT6 through IL-4. This mechanism is physiologically activated in lymphocytes where this signaling pathway would maintain the T cells activated, avoiding apoptosis [28]. The overexpression of bcl-2 in SFT could explain the chemo-resistance seen in this entity. Additionally, the bcl-2 expression detected in synovial sarcoma could be explained by the characteristic translocation t (X, 18) that would affect the bcl-2 gene allocated in chromosome 18 [29]. The positive expression of bcl-2 seen in neural neoplasms could be due to the fact that these tumors stem from the neural crest cell lineage, which also expresses bcl-2. The protein expression of CD99 is extensively present in SFT, showing strong membranous predominant staining, or membranous cytoplasmic, in more than 80% of cases. The glycosylated transmembrane protein CD99 is implicated in several cellular functions such as cell adhesion, migration, differentiation, endo and exocytosis among others [30]. In malignancy, CD99 has been demonstrated to have a remarkable role in migration, invasion and metastasis. In this sense, CD99 has behaved as an oncogene in several tumors including some sarcomas such as Ewing sarcoma, synovial sarcoma or rhabdomyosarcoma. However, there is an increasing number of tumors in which CD99 expression is diffuse in an early stage or in benign conditions, but is lacking or reduced in an advanced stage or in the malignant counterpart [31][32]. In this latter subset of tumors, which includes osteosarcoma, CD99 acts as a suppressor gene. In addition, two isoforms of CD99 (wild type and truncated forms) have been described with opposite functions. While $CD99^{wt}$ inhibits migration, metastasis, anoikis resistance and anchorage-independent growth, the truncated form exhibits the opposite functions [33]. CD99 is highly expressed in $CD34^+$ bone marrow cells and in leukocytes, whatever the lineage, and it is a determinant in the orientation of immune response [34]. As CD99 expression is usually lost in the dedifferentiated SFT (in the DD zones), it is probable that CD99 would act also as a tumor suppressor in the context of SFT [35].

In all, one might speculate that precursor cells of SFT would harbor an early expression of CD34+ and bcl-2, probably a progenitor of fibroblasts or myofibroblasts, along with CD99+ upon which other genetic early hits had been added, such as the characteristic NAB2–STAT6 transcript. The latter would ultimately facilitate proliferation through EGR1 signaling.

4. Dedifferentiated SFT (DD-SFT)

Dedifferentiation can occur at the end of the transforming histological stage of SFT, reflecting that new genetic hits have emerged in the tumor or that dedifferentiated clones have evolved from the initial malignant process, until they govern the tumor biology. This dedifferentiation process is not exclusive to SFT, rather it is observed in a wide spectrum of malignancies, such as melanomas, carcinomas or even other sarcomas (DD-LPS or chondrosarcomas, for instance). This subtype can be underestimated when core biopsies do not reach the dedifferentiated component or after a resection of bulky SFT if the sampling is not complete. DD-SFT can be diagnosed de novo or following a recurrence of indolent or aggressive SFT. Characteristically, DD-SFT is diagnosed if an abrupt area of high grade sarcomatous or anaplastic cells appears in the SFT bed. As previously mentioned, some protein expressions are frequently lost in DD-SFT, such as CD34, [20][36][37] CD99 [38] and STAT6 [14][39]. It is not yet clear which are the mechanisms underlying the loss of

expression of the previous proteins, but a kind of post-translational control through ubiquitination has been postulated, at least for the loss of STAT6 nuclear expression [14]. The mutation of *TP53*, and accordingly, a nuclear positive immunostaining, has been found in some high-grade SFTs and in many DD-SFTs. This finding was reported a long time ago [20][40] and corroborated in recent times by comparative genomic hybridization, demonstrating the loss of 17p, always involving *TP53,* in high-grade and DD-SFT [14][41][42]. Another onco-suppressor, *RB1*, is also frequently lost in DD-SFT, something supported by the disappearance of previously verified nuclear immunostaining and by the most frequent copy number abnormalities, the loss of 13q, always affecting *RB1* [14]. Interestingly, in the transit towards higher dedifferentiation, SFT cells display a complex cytogenetic profile with numerous copy number alterations, indicating an increase in genomic instability [14]. Oxidative stress (ROS) could also contribute to this instability via EGR1, which is a transcriptional activator of *NOX4*. In some disease contexts, such as diabetic kidney disease, *EGR1, NOX4* and *ROS* have been found as critical components [43]. Interestingly, *NOX4* is overexpressed in SFT. These genomic gains and losses are nonrandom events, likewise other dedifferentiation processes observed in sarcoma, such as DD-LPS or DD chondrosarcoma, where recurrent genomic events are detected. The critical genomic events that induce different SFT subtypes from one precursor or maybe convert low-grade SFT into high-grade SFT and then to DD-SFT, changing from *NAB2–STAT6* addiction to other genomic drivers, are just being explored from recent times.

Insulin-like growth factor 2 (IGF2) and insulin-like growth factor 2 receptor (IGF2R) are overexpressed in a substantial proportion of SFT cases, and this overexpression is detected by immunohistochemistry [44]. In fact, the serum increase in IGF2 would be responsible for the hypoglycemic syndrome (Doege–Potter syndrome). Hypoglycemia has been proposed as an independent prognostic marker in SFT for a higher probability of metastatic recurrence and death [45]. Along the same lines, early reports already related the appearance of hypoglycemia to a larger tumor diameter and more aggressive behavior [46]. However, some controversies still remain regarding the prognostic implications and functionality of IGF2R. Additionally, the overexpression of interferon-stimulated gene 15 (*ISG15*) significantly correlated with worse PFS and OS in translational research of a phase II clinical trial exploring pazopanib as first line of antiangiogenesis in advanced/metastatic SFT [47]. *ISG15* has been implicated in stemness, cancer survival and drug resistance [48].

The presence of *TERT* promoter mutation had a worse prognostic role in some series [49][50] but not in others [51]. Therefore, further investigation is needed to know its real prognostic impact.

5. Molecular Biology

The identification of *NAB2–STAT6* fusion within chromosome 12, communicated in 2013 by three different research groups, was an important milestone in terms of understanding this entity [52][53][54]. According to some authors, the key dysfunction in the transcript *NAB2–STAT6* lies in the disturbed function of *NAB2*, rather than *STAT6* deregulation. The reason is based on the fact that all the genomic fusions between *NAB2–STAT6* entail a protein transcript that exchanged at least one repressor domain from NAB2 for an activation domain from STAT6. This results in a dysregulation of early growth response (EGR) signaling. NAB2 is constituted, on the one hand, by an N-terminal binding domain (NAB2 conserved domain 1-NCD1) that interacts with EGR1, and NCD2 which is important for transcriptional repression and, on the other hand, the carboxy-terminal, which includes a chromodomain helicase DNA-binding protein 4 (CHD4) interacting domain (CID), important for transcriptional repression as well. CHD4 is a subunit of the nucleosome remodeling and histone deacetylase complex (NuRD) with enzymatic function (Figure 2).

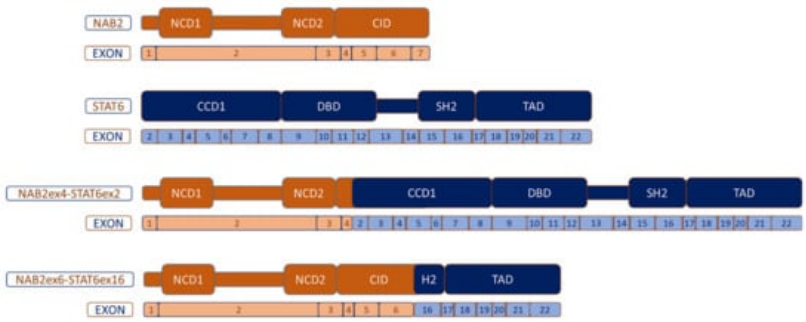

Figure 2. Most common *NAB2–STAT6* fusion variants. NCD: NAB-conserved domain; CID: CHD4-interacting domain; CCD1: Coiled-coil domain 1; DBD: DNA-binding domain; SH2: Src homology 2 and TAD: transcriptional activator domain.

As the EGR1-interacting NCD1 is always present in the fusion protein, an enhancement of the expression of EGR1-target genes is expected in SFT. EGR1 is one of four cysteine-rich zinc finger transcription factors. *EGR1* expression is activated by different factors such as cytokines, hormones or growth factors such as TGF-β. This gene has been implicated in

cancer, inflammation or fibrosis. Of note, *NAB2* is a target of EGR1 and *EGR1* is a target of NAB2. This latter regulation is produced by the binding of ERG1 to the R1 inhibitory domain and through CHD3 and CHD4 proteins that have enzymatic function and belong to NuRD, a remodeling chromatin complex with relevance in transcription regulation [55]. As the wild type *NAB2* gene is a repressor of EGR1 transcription activity, and in the context of the *NAB2–STAT6* transcript, where the carboxi-terminal parts of *NAB2* (relevant for transcriptional repression) have been exchanged, an increase in transcription for *EGR1* target genes could be expected. However, this was not found in some investigations [54]. This could be explained by the fact that *NAB2* sometimes potentiates rather than represses *EGR1* transcription. In any case, EGR1′s effects are not fully characterized. Among those EGR1 target genes found to be dysregulated in SFT, several are involved in fetal development. Thus, *HOX* genes (class I homeobox genes) have been shown to be overexpressed in SFT, except for *HOXD* [53][54].

Of note, NuRD also has a relevant prominence for the normal differentiation of embryonic stem cells by downregulating the expression of *ZFP42*, *TBX3*, *KLF4*, and *KLF5* genes. Intriguingly, some of these genes are downregulated in SFT [54]. In other words, in the context of SFT, NuRD's function is to restrict these pluripotency genes. It should be questioned if in DD-SFT some of the NuRD complex functions are lost, such as the *Mbd3*, since the mutation of this gene induced the overexpression of the pluripotency genes mentioned above [56].

On the other hand, the *STAT6* gene is a member of the *STAT* family encoding cytoplasmic transcription factors, which regulate gene expression, transmitting signals to the nucleus and binding to certain DNA promoters. The *STAT6* gene consists of 23 exons and functionally has the following structure: N-terminal, coiled-coil domain (CCD), DNA binding domain (DBD1), a linker domain (LD), a Src-homology 2 domain (SH2), a tyrosine phosphorylation site (pY) and a C-terminal transcriptional activation domain (TAD). The SH2 domain is critical for binding to a receptor (IL-4R or IL-13R) and consecutive activation of STAT6 through the phosphorylation of tyrosine residues with the intervention of Janus kinases (JAK), specifically Jak1 and Jak3. After the phosphorylation of receptors, STAT6 binds to them and is phosphorylated by Jak and TyK2 kinases on tyrosine residue Y641 located at the C-terminus of the SH2 domain, as indicated above. This entails the homodimerization of STAT6, which thereby translocates to the nucleus and efficiently binds to DNA sequences through the DBD, acting as a transcription factor (Figure 1) [57].

Even when at least 12 different *NAB2–STAT6* fusion variants have been described according to their breakpoints [58], the two most recurrent variants are: the *NAB2 exon4–STAT6 exon2* (N4S2), which is the most frequent, and the *NAB2 exon6–STAT6 exon16/17* (N6S16/17). N4S2 entails the fusion between NAB2 that lacks the CID domain and partially lacks the NCD2 domain, and the almost complete STAT6 part. This fusion correlates with a distinctive phenotype: primary tumors are derived mostly from the thoracic cavity, patients are older than in other breakpoint variants, tumors are significantly larger in diameter (median 10 cm) and they exhibit the appearance of a predominantly fibrotic and paucicellular tumor context. In contrast, the N6S16/17 fusion transcript contains almost all the NAB2 portion, except for exon 7 of CID, and a truncated STAT6 protein keeping TAD and part of the C-terminal of the SH2 domain. This N6S16/17 fusion is harbored more commonly by patients with pelvic, meningeal or extremity SFT, younger age than N4S2, smaller tumors (median 4.3 cm) and more tumor cellularity in comparison to N4S2 [58][59]. The prominent fibrosis seen in N4S2 could be related to the lack of CID (less repression on EGR1), and possibly to the presence of the almost entire STAT6 portion in the chimeric protein. Differential transcriptome analysis between the two most frequent fusion variants revealed that N4S2 exhibited a gene signature enriched for genes involved in DNA binding, gene transcription and nuclear localization, whereas the N6S16/17 signature was enriched for genes involved in tyrosine kinase signaling, cell proliferation and cytoplasmic localization [60]. Despite the fact that N4S2 correlates more frequently with less aggressive SFT, there is no convincing study demonstrating an unequivocal significant prognostic correlation among the fusion variants [51]. Larger studies analyzing homogeneous populations (i.e., completely resected localized tumors, or from metastatic spread) with enough follow-up are required. Additionally, the median tumor size of N4S2 was also greater, which would compensate the apparent better prognosis.

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