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Extra-meningeal solitary fibrous tumor: an evolving entity with chameleonic morphological diversity, a hallmark molecular alteration and unresolved issues in risk stratification assessment

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Summary. Solitary fibrous tumor (SFT) is a rare type of mesenchymal lesion with variable clinical presentation in which specific clinicopathologic factors have been related to patient outcome. SFT shares an important morphologic and immunohistochemical overlap with other sarcomas, hence the differential diagnosis is challenging. Although molecular studies provide significant clues, especially in the differential diagnosis with other neoplasms, a thorough hematoxylin and eosin analysis and the integration of phenotypical, clinical, and radiological features remain an essential tool in SFT diagnosis. In this review, we discuss some emerging issues still under debate in SFT.

Key words: Non-small cell lung cancer, circTADA2A, miR-214-3p, EIF4A3, MAPK8

Introduction

Solitary fibrous tumor (SFT) is an uncommon mesenchymal tumor with unpredictable clinical evolution (Huang and Huang, 2019; Demicco et al., 2020; Georgiesh et al., 2022). Changes in diagnostic terminology and site-specific classification over the past few decades have resulted in a disjointed literature (Huang and Huang, 2019; Bianchi et al., 2020; Demicco et al., 2020; Anderson and Doyle, 2021). First recognized in the pleura, SFT was previously referred to by several other names, including hemangiopericytoma (HPC) (Brunnemann et al., 1999; Cardillo et al., 2000; Demicco et al., 2020; Alexeiv et al., 2021; Baneckova et al., 2022). The current WHO blue book defines SFT as neoplasm of uncertain behaviour, rarely-metastasizing, showing fibroblastic differentiation (Demicco et al., 2020). SFT usually affects adults, with no gender predilection and can occur at any anatomical site (extra-meningeal or meningeal) (Liu et al., 2008; Cranshaw et al., 2009; Demicco et al., 2012; Lahon et al., 2012; Lococo et al., 2012; Rao et al., 2013; Feasel et al., 2018; Smith et al., 2017; Friis et al., 2018; Ng et al., 2018; Kinslow et al., 2020; Bianchi et al., 2021; Devins et al., 2022). Extra-meningeal sites include the intrathoracic cavity (pleura and lung), retroperitoneum/pelvis, and head and neck, and is always more frequent in deep soft tissue than in superficial soft tissue (Liu et al., 2008; Cranshaw et al., 2009; Demicco et al., 2012; Lahon et al., 2012; Kinslow et al., 2020; Bianchi et al., 2021; Devins et al., 2022). Meningeal forms are not infrequent, although clinical evolution seems to be different to the extra-meningeal counterpart (Brunnemann et al., 1999; Cranshaw et al., 2009; Huang and Huang, 2019; Demicco et al., 2020). At histopathological level, a patternless proliferation of bland spindle/ovoid cells accompanied by variable collagenous stroma and typical hemangiopericytoma-like pattern is the usual morphology, although atypical forms with rare histological subtypes are emerging (Furusato et al., 2011; Kao et al., 2016; Huang and Huang, 2019; Bianchi

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et al., 2020, Demicco et al., 2020; Guillou et al., 2020; Machado et al., 2020a,b, 2021; Choi and Ro, 2021; Tariq et al., 2021; Kazazian et al., 2022; Suster et al., 2023).

The detection of fusion gene *NAB2::STAT6* (intrachromosomal inversion at 12q13.3) confirms a morphological diagnosis, particularly in cases with unconvincing STAT6 immunoexpression by immunohistochemistry (Mohajeri et al., 2013; Robinson et al., 2013; Barthelmeß et al., 2014; Akaike et al., 2015; Park et al., 2019; Vogels et al., 2019; Salguero-Aranda et al., 2021; Smrke et al., 2021; Krskova et al., 2022). STAT6 nuclear immunoreactivity has become a satisfactory molecular surrogate, and is systematically employed as an accurate method for SFT diagnosis (Doyle et al., 2014; Koelsche et al., 2014; Yoshida et al., 2014; Demicco et al., 2015, 2020; Huang and Huang, 2019; Dermawan et al., 2021). Specific gene fusions have been related to prognosis and tumor location, although they have not been extensively applied in follow-up or treatment decisions (Barthelmeß et al., 2014; Huang and Huang, 2019; Demicco et al., 2020; Salguero-Aranda et al., 2021). The clinical evolution of SFT is often uncertain and while most cases evolve in a benign fashion, a small group can progress towards local and/or distant recurrences (Cardillo et al., 2000; Liu et al., 2008; Smith et al., 2017; Cranshaw et al., 2019; Demicco et al., 2020; Alexiev et al., 2021). Several risk stratification systems (RSS) have been proposed to predict recurrence in localised, extra-meningeal SFT (Tapias et al., 2015; Pasquali et al., 2016; Demicco et al., 2017, 2019, 2020; Gholami et al., 2017; Salas et al., 2017; Reisenauer et al., 2018; Huang and Huang , 2019; Riedel, 2019; Georgiesh et al., 2020, 2022; Thompson et al., 2021; Liu et al., 2022; Machado et al., 2022; Sugita et al., 2022). Demicco et al. developed a risk stratification model based on mitotic count, age, tumor size and necrosis, however, the stratification systems are not able to reliably identify low-risk patients due to poor prediction of late recurrences (Demicco et al., 2017, 2019, 2020). Recently, Georgiesh T et al. developed a novel risk model (G-score) mainly constructed on a well-characterised large patient cohort with long-term follow-up, which included mitotic count, necrosis and gender as independent prognostic factors (Georgiesh et al., 2022). In the present review, we aim to update the clinical, pathological, and molecular findings, the newly-implemented risk stratification systems, as well as clinical outcome and treatment approach in extra-meningeal SFT.

Is there any particular clinical presentation in SFT?

SFT, previously designated hemangiopericytoma, typically occurs in middle-aged adults without gender predilection (Brunnemann et al., 1999; Cardillo et al., 2000; Demicco et al., 2020; Alexeiv et al., 2021; Baněčková et al., 2022). It may arise in the extra-meningeal or meningeal areas (Huang and Huang, 2019; Demicco et al., 2020). We will focus this review on extra-meningeal SFT which can arise at almost any location, including intra-thorax/pleura, intra-abdomen/pelvis, extremities/trunk, and head and neck area (Demicco et al., 2020; Alexiev et al., 2021; Baněčková et al., 2022; Devins et al., 2022). Around 25% to 30% of cases arise intrathoracically, with the pleura being the most common single site (Cardillo et al., 2000; Huang and Huang, 2019; Demicco et al., 2020; Kazazian et al., 2022). Intra-abdominal and pelvic SFT constitute the largest site-related group in most series of extra-pleural SFT (Demicco et al., 2020). In addition, some cases may arise in visceral locations (lung, liver, pancreas, kidney) among others (Huang and Huang, 2019, Demicco et al., 2020). Cutaneous SFTs are extremely rare and can be primary or an extension of superficial soft tissue SFT (Feasel et al., 2018). In our retrospective study of 97 SFTs, the primary tumor locations were mainly soft tissue from intrathoracic and abdominopelvic sites, some with visceral involvement, while location in the extremities was rare (Machado et al., 2020b) The majority of SFTs manifest as a well-delimited, slow-growing, painless tumor. Clinical presentation may be asymptomatic or trigger compression symptoms depending on the tumor size and anatomic site (Liu et al., 2008; Cranshaw et al., 2009; Demicco et al., 2012, 2020; Lahon et al., 2012; Lococo et al., 2012; Rao et al., 2013; Feasel et al., 2018; Smith et al., 2017; Friis et al., 2018; Ng et al., 2018; Kinslow et al., 2020; Bianchi et al., 2021; Devins et al., 2022). Paraneoplastic syndromes are a constellation of symptoms and signs that are mediated by a substance excreted by tumor cells or by an immune response against the tumor that cross-react with other normal cells (Chang et al., 2001; Meng et al., 2014, Huang and Huang, 2019; Demicco et al., 2020; Anderson et al., 2021). SFT is associated with multiple paraneoplastic syndromes, including hypoinsulinemic hypoglycemia, due to ectopic secretion of a prohormone of insulin-like growth factor 2 (IGF-2) (Doege-Potter syndrome), neurological disorders, hypertrophic pulmonary osteoarthropathy (Pierre-Marie-Bamberger syndrome), and elevated beta human chorionic gonadotropin, hence the clinician must be aware of these rare clinical presentations of SFT (Meng et al., 2014; Huang and Huang, 2019; Demicco et al. 2020). The majority of SFTs are benign with 10-30% of them exhibiting aggressive and malignant features (Tapias et al., 2015; Pasquali et al., 2016; Demicco et al., 2017, 2019, 2020; Gholami et al., 2017; Salas et al., 2017; Reisenauer et al., 2018; Huang and Huang, 2019; Riedel, 2019; Georgiesh et al., 2020, 2022; Thompson et al., 2021; Liu et al., 2022; Machado et al., 2022; Sugita et al., 2022). The aggressiveness of this type of tumor is not completely associated with its histological features, which makes surgical resection the treatment of choice (Pasquali et al., 2016; Demicco et al., 2017, 2019, 2020; Salas et al., 2017; Huang and Huang, 2019; Georgiesh et al., 2020, 2022; Liu et al., 2022; Machado et al., 2022; Sugita et al., 2022).

Can radiological images provide clues in the diagnosis of SFT or suggest dedifferentiation?

Radiologically, SFTs are variable and generally nonspecific, while given their abundant vascularity a prominent blood supply is frequently demonstrated (Gangly et al., 2006; Wignall et al., 2010; Garcia-Bennett et al., 2012; Papathanassiou et al., 2013; Liu et al., 2014). Computed tomography (CT) scan is the standard imaging modality for detecting SFT, which usually reveals a well-demarcated mass that is often isodense to the skeletal musculature with prominent avid blood vessels and heterogeneous contrast enhancement (Figs. 1-3). CT scans usually show a well-circumscribed isodense mass invading skeletal muscle with contrast enhancement in highly vascularized tumors. SFTs are often characterized by the presence of low-signal-intensity foci on T1- and T2-weighted magnetic resonance imaging (MRI), corresponding to the collagen content (Fig. 2B) (Gangly et al., 2006; Wignall et al., 2010; Garcia-Bennett et al., 2012, Papathanassiou et al., 2013; Liu et al., 2014). Larger or malignant cases may present with a more heterogeneous appearance due to fibrosis, haemorrhage, necrosis, myxoid and cystic degeneration or calcifications (Figs. 1-3). The increased uptake on fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography may be worrisome for malignant SFT, and PET hypermetabolism should raise suspicions of a malignant SFT or dedifferentiated SFT, although its imperfect sensitivity limits its diagnostic utility (Gangly et al., 2006; Wignall et al., 2010; Garcia-Bennett et al., 2012, Papathanassiou et al., 2013; Liu et al., 2014). Radiologists may guide the Tru-Cut biopsy in cases with suspicion of dedifferentiation (Liu et al., 2014).

Do gross features correlate with the radiological findings?

Grossly, SFTs are generally well-circumscribed, solid or cystic tumors with or without fibrous pseudo-capsules and have a soft, elastic to firm consistency depending on the relative proportion of cellularity to the collagenous stroma (Fig. 3C,D) (Liu et al., 2008; Huang and Huang, 2019; Demicco et al., 2020; Bianchi et al., 2021; Kazazian et al., 2022). The cut section surfaces are often tan-white, solid, firm, unencapsulated, and lobulated multinodular masses with infrequent secondary myxoid changes, while areas of haemorrhage and necrosis with fleshy appearance are more common in malignant cases (Lococo et al., 2012; Rao et al., 2013; Smith et al., 2017) (Fig. 3). Radiological findings are

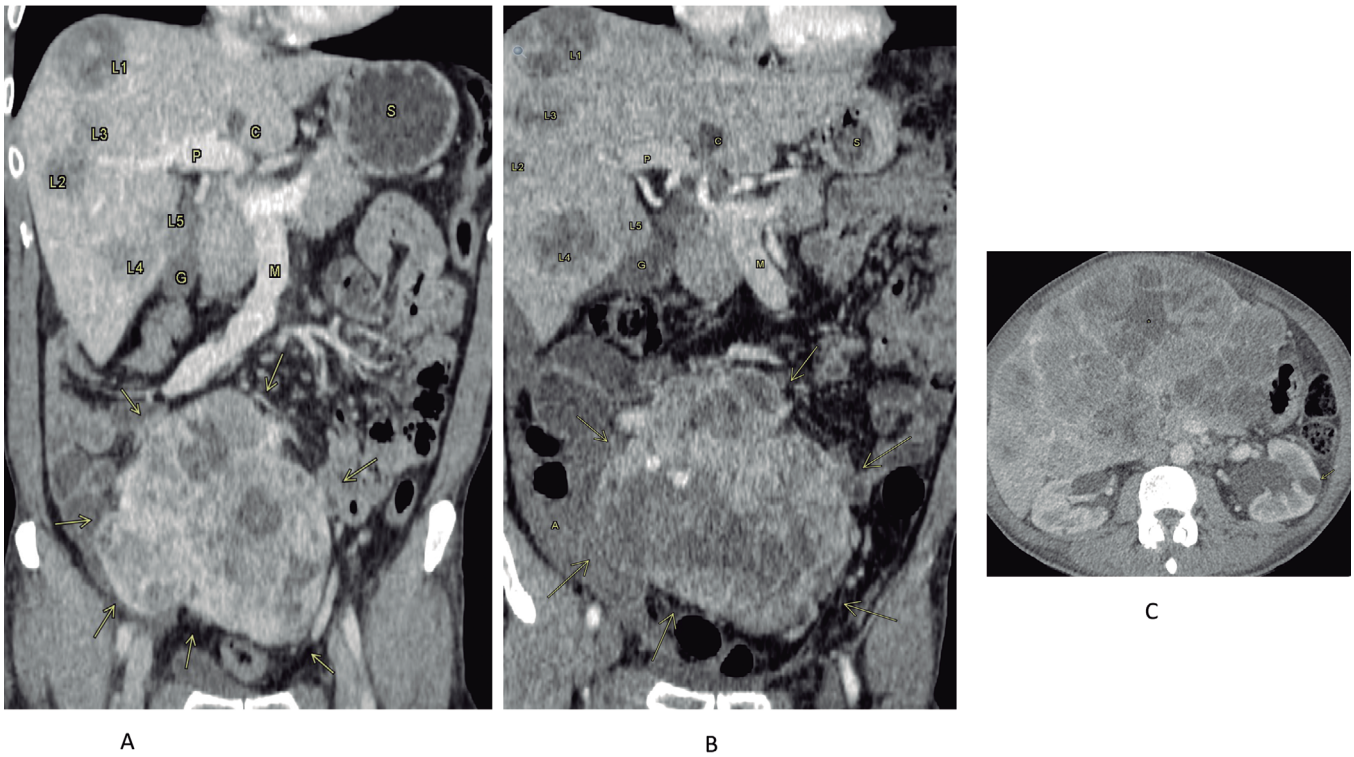

Fig. 1. A and B. Coronal CT reconstruction shows a heterogeneous pelvic mass probably attached to the mesenteric root (arrows) with more extensive necrotic areas, and multiple liver metastases (L1 a L5), some of them confluent, different from a liver cyst. Note the presence of ascites (A) on the right side near the pelvic mass, and normal gallbladder (G) and stomach (S), also portal (P) and mesenteric (M) venous structures. **C.** CT: Multiple liver metastases appearing as multinodular hypovascular and confluent focal lesions with central necrosis (*) with preservation of only a small segment on VI, near the kidney. Note a small left kidney cyst (arrow).

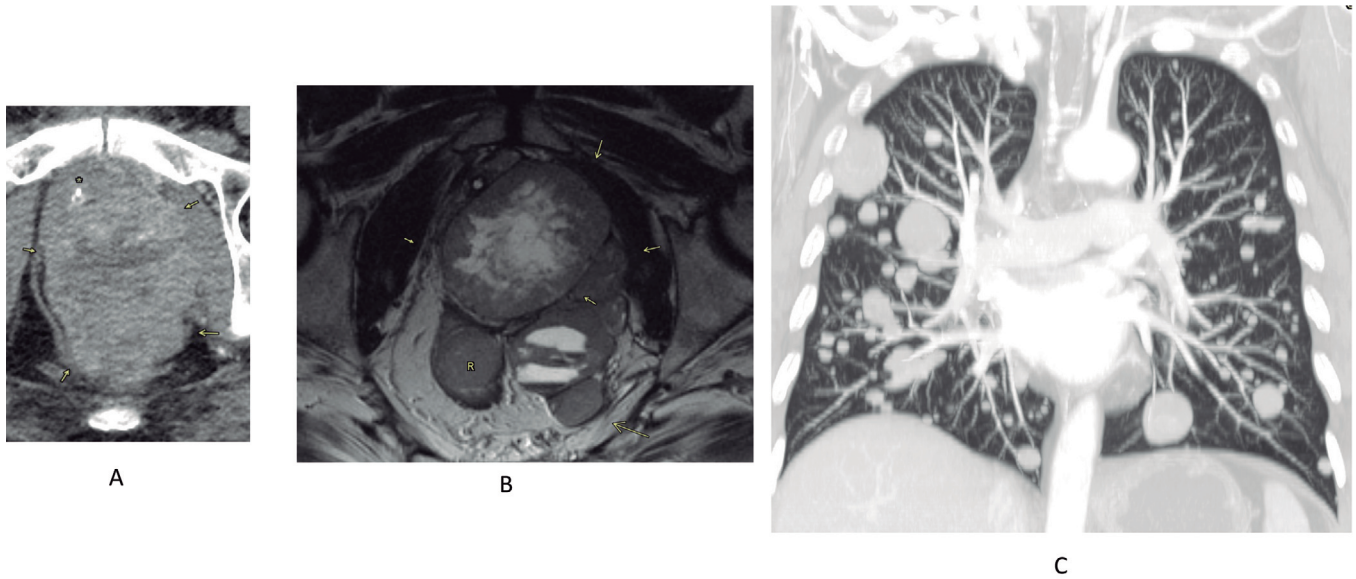

Fig. 2. A. CT. Soft tissue heterogeneous mass (arrows), hypervascular and central necrosis mass on prostatic bed, after prostatectomy growing and displacing the uretra. Note vesical device inside (*). **B.** Axial T2 MRI showing multiple relapsing pelvic masses, one of them looking like a polypoid rectal mass (R). **C.** Coronal CT reconstruction with lung window setting, showing multiple lung metastases.

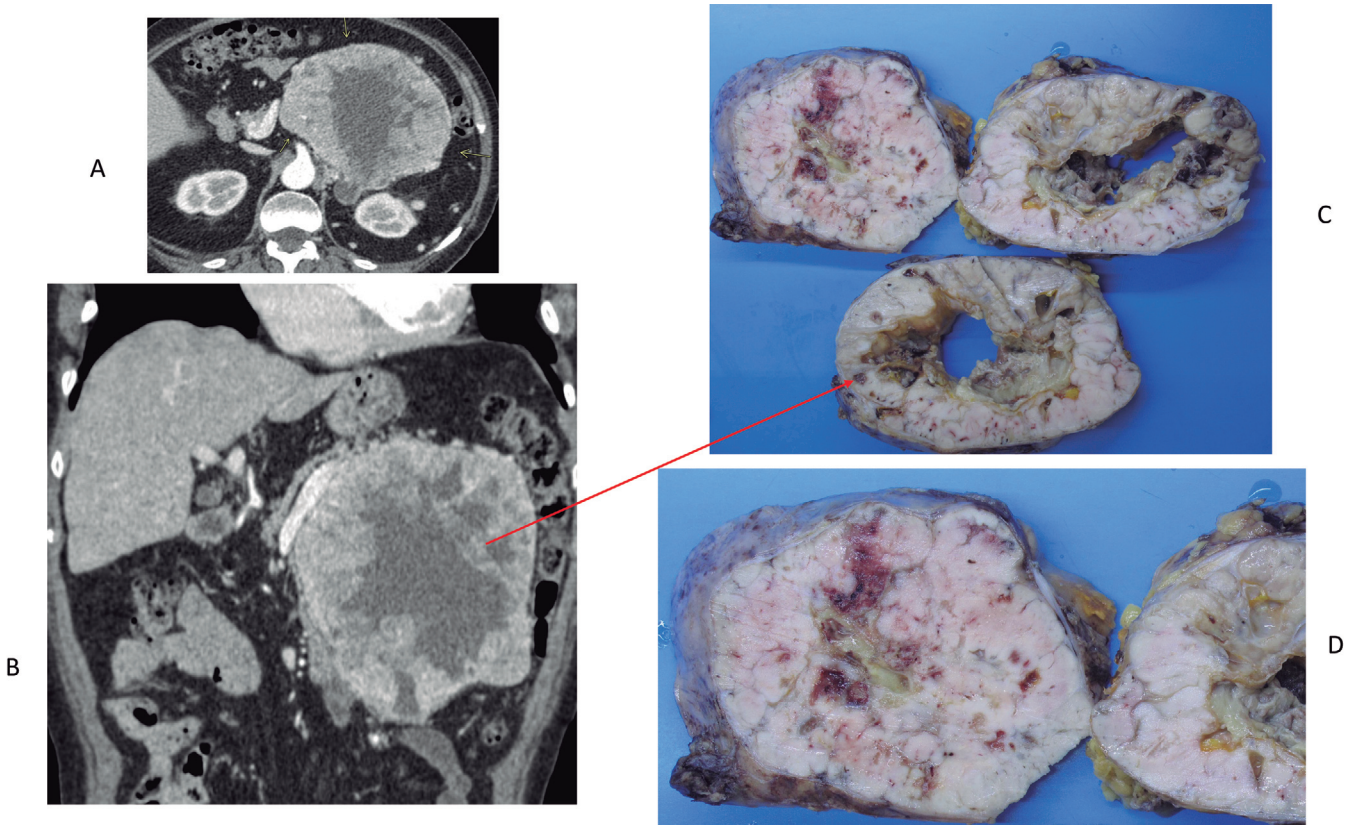

Fig. 3. A. Axial CT showing a well-defined, enlarged and necrotic soft tissue mass, probably originating in the left adrenal gland, which enhances strongly in the most peripheral solid tissue. Left kidney is not invaded and vascular structures are displaced. **B.** Coronal reconstruction. **C and D.** Macroscopic correlation. High risk solitary fibrous tumor with necrosis.

usually correlative with macroscopic features (Gangly et al., 2006; Wignall et al., 2010; Garcia-Bennett et al., 2012, Papathanassiou et al., 2013; Liu et al., 2014) (Fig. 3). The size of SFT ranges widely and is related to the tumor site (Huang and Huang, 2019; Demicco et al., 2020). SFT in the abdominopelvic region and retroperitoneum are the largest followed by the intrathoracic and somatic soft tissue tumors (Liu et al., 2008; Cranshaw et al., 2009; Demicco et al., 2012, 2020; Lahon et al., 2012; Lococo et al., 2012; Rao et al., 2013; Feasel et al., 2018; Smith et al., 2017; Friis et al., 2018; Ng et al., 2018; Kinslow et al., 2020; Bianchi et al., 2021; Devins et al., 2022).

The histopathological spectrum of SFT is unceasingly expanding.

SFT comprises a histologic spectrum ranging from "classic" hypocellular fibrous SFT, to hypercellular tumors previously recognized as "hemangiopericytoma," and anaplastic SFT with frank sarcomatous transformation (Mosquera and Fletcher, 2009; Furusato et al., 2011; Subramaniam et al., 2011; Collini et al., 2012; Thway et al., 2013; Kurisaki-Arakawa et al., 2014; Schulz et al., 2014; Dagrada et al., 2015; Kao et al., 2016; Schneider et al., 2017; Huang and Huang, 2019; Bianchi et al., 2020; Demicco et al., 2020; Guillou et al., 2020; Machado et al., 2020a,b, 2021; Choi and Ro, 2021; Tariq et al., 2021; Kazazian et al., 2022; Suster et al., 2023). The distinctive histopathological finding in conventional SFT is a patternless or haphazard growth pattern due to proliferation of ovoid to spindle-shaped tumor cells with prominent branching (Fig. 4), thin-walled, forming an hemangiopericytoma-like pattern of blood vessels (Huang and Huang, 2019; Bianchi et al., 2020, Demicco et al., 2020; Machado et al., 2020a; Choi and Ro, 2021; Tariq et al., 2021; Kazazian et al., 2022; Suster et al., 2023). The plump spindle to ovoid tumor cells have scant pale or eosinophilic cytoplasm, indistinct borders, usually vesicular nuclei and frequent inconspicuous nucleoli (Huang and Huang, 2019; Bianchi et al., 2020, Demicco et al., 2020; Tariq et al., 2021; Kazazian et al., 2022; Suster et al., 2023). Some nuclear variability is common, but marked pleomorphism is rare (Figs. 4, 5). The amount of intervening collagenous stroma is variable, tumors with abundant collagen/sclerosis are easier to classify as SFT than tumors with scant collagen stromal tissue and hypercellularity where it is sometimes hard to recognize this lesion as SFT (Huang and Huang, 2019; Bianchi et al., 2020; Demicco et al., 2020; Machado et al., 2020a; and Ro, 2021; Tariq et al., 2021; Kazazian et al., 2022; Suster et al., 2023) (Fig. 4). Storiform growth patterns may predominate in a subset of SFTs, and the formation

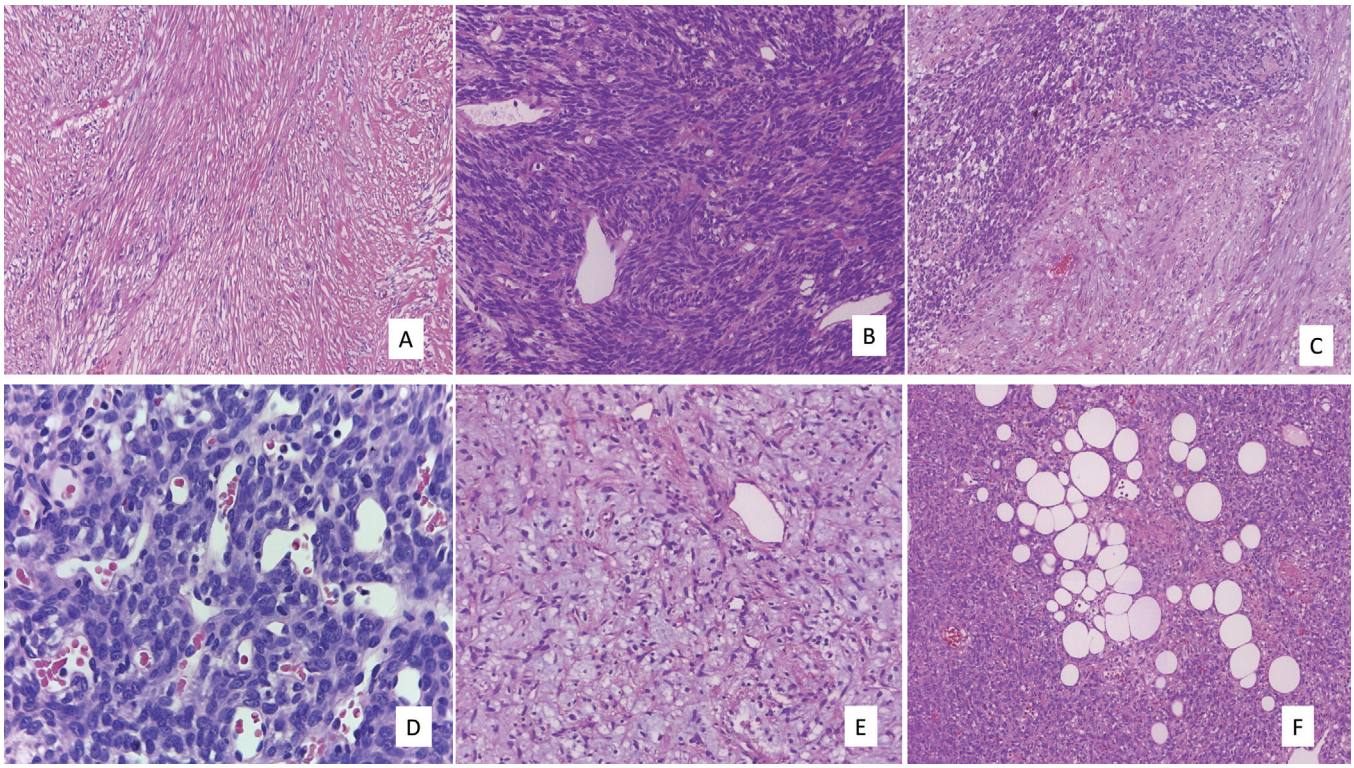

Fig. 4. A. Paucicellular solitary fibrous tumor (SFT) with abundant collagen. Hematoxylin and eosin (H&E). **B.** Hypercellular SFT with scant collagen deposit. H&E. **C.** SFT with paucicellular and hypercellular areas. H&E. **D.** SFT with classic hemangiopericytic pattern. H&E. **E.** SFT with predominant myxoid pattern. H&E. **F.** Fat-forming SFT. H&E. A-C, F x 20; D, E, x 40.

of pseudo-papillae is unusual and may be confused with other mesenchymal or even epithelial neoplasms. Other patterns include corded, fascicular, trabecular, nested, microcysts, myxoid background, and extensive hyalinization (Fig. 5). Vasculature may include thin-walled branching "staghorn", thick-walled, and hyalinized vessels or dilated anastomosing vascular channels (Figs. 4-6). Less frequently, SFT may reveal multinucleated giant cells (Fig. 6), epithelioid morphology, myxoid stroma (Fig. 4E), clear cells, leiomyoma-like morphology, prominent angiomatoid cystic changes, fibroadenomatous or adenofibromatous appearance and fat-forming patterns (Fig. 4F) (Guillou et al., 2000; Furusato et al., 2011; Lee and Fletcher, 2011; Feasel et al., 2018; Huang and Huang, 2019; Bianchi et al., 2020, 2021; Demicco et al., 2020; Choi and Ro, 2021; Devins et al., 2022; Suster et al., 2023). Regarding the fat-forming variant, although adipocytic cells may vary in the amount and degree of maturation, most fat-forming SFT exhibit mature adipocytes amid bland-appearing spindle cells (Fig. 4F), without notable differences in location, age or gender, and usually follow a favourable clinical course, except in rare cases that may have poor evolution (Lee and Fletcher, 2011; Huang and Huang, 2019; Bianchi et al., 2020, Demicco et al., 2020; Guillou et al., 2020).

Struggling with dedifferentiation and/or trans-differentiation in SFT

Dedifferentiated SFT is the most aggressive form of this tumor, it may be de novo or occur during clinical evolution in recurrences or metastases (Mosquera and Fletcher, 2009; Subramaniam et al., 2011; Collini et al., 2012; Thaway et al., 2013; Kurisaki-Arakawa et al., 2014; Schulz et al., 2014; Dagrada et al., 2015). De-differentiation is a histological phenomenon characterised by abrupt transition of histology to a sarcomatous component with high-grade malignant potential in SFT (Fig. 7). This high-grade component may have anaplastic/pleomorphic, round cell morphology, but always has a poorly-differentiated component with high mitotic index, usually necrosis and occasionally a myxoid component. In addition, hetero-logous, rhabdomyosarcomatous, angio-sarcomatous (Fig. 7F) chondrosarcomatous/osteo-sarcomatous dedifferentiation as well as neuroendocrine, squamous cell carcinomatous histology or teratocarcinosarcoma-like and adamantinoma-like SFT have been also reported (Mosquera and Fletcher, 2009; Subramaniam et al., 2011; Collini et al., 2012; Thaway et al., 2013; Kurisaki-Arakawa et al., 2014; Schulz et al., 2014; Dagrada et al., 2015). A recent phenomenon

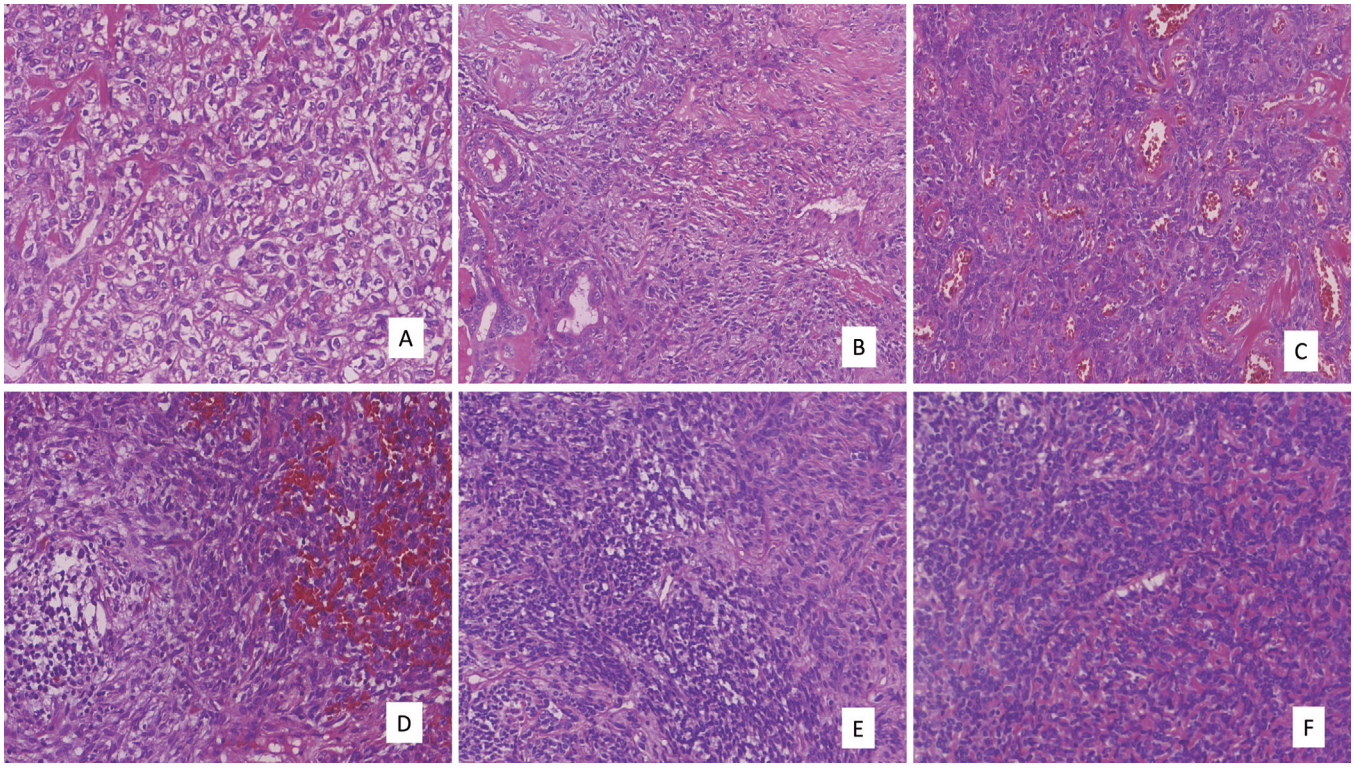

Fig. 5. A. SFT with clear and epithelioid cells. H&E. **B.** SFT with transdifferentiation, see both components, the mesenchymal and non-mesenchymal counterpart. H&E. **C.** Glomangioma-like SFT. H&E. **D.** SFT with lymphoid infiltration and blood vessels and hemorrhage. H&E. **E.** SFT with round and spindle cells. H&E. **F.** SFT with predominant round cell component mimicking a round/ovoid cell sarcoma. H&E. A, x 40; B-F, x 20.

characterized by transdifferentiation in the head and neck area has also been reported. In the transdifferentiation process, SFT acquired the morphologic appearance of tumors originating in the oral minor salivary glands, the base of the tongue, and sinonasal tract and closely resembled either hyalinizing clear cell carcinoma of the salivary gland, adenocarcinoma not otherwise specified, or biphenotypic sinonasal sarcoma (Baněčková et al., 2022) (Fig. 5B). This phenomenon highlights a much broader histologic diversity than previously known for neoplasms with *NAB2::STAT6*.

Do immunohistochemical ancillary methods still provide important clues in diagnosis and prognosis in SFT?

Many years ago, the diagnosis of SFT typically relied on the expression of CD34 combined with bcl-2, and CD99 (Fig. 8) and although this represents a non-specific panel, it can aid in the diagnosis of many SFTs in an appropriate histological and clinical context (Doyle et al., 2014; Yoshida et al., 2014; Demicco et al., 2015, 2020; Huang and Huang, 2019; Dermawan et al., 2021; Devins et al., 2022). Diffuse CD34 positivity is very suggestive of SFT, although the tumor cells may lose CD34 positivity or may be patchy, particularly in dedifferentiated SFT (Doyle et al., 2014; Yoshida et al., 2014; Demicco et al., 2015, 2020; Huang and Huang, 2019). Nowadays, STAT6 immunoreactivity (Fig. 8) is well implemented practically worldwide in the diagnosis of SFT and may be a surrogate for the hallmark genetic translocation that characterizes SFT (*NAB2:STAT6*). As a matter of fact, although acceptably sensitive, STAT6 expression is not perfectly specific for SFT and may be detected in other mesenchymal tumors with genetic alteration near the STAT6 chromosome region, for example, liposarcomas with MDM2 amplification or GLI1-amplified tumors (Yoshida et al., 2014; Demicco et al., 2015, 2020; Huang and Huang, 2019). Luckily this expression is almost always cytoplasmic and completely different in intensity when compared with the strong nuclear expression in SFT. ALDH1 and GRIA2 are frequently positive in SFT, but with the implementation of STAT6 the use of these antibodies has declined (Bouvier et al., 2013; Vivero et al., 2014). To variable degrees, SFT may express epithelial markers (pan-CK/AE1/AE3 and EMA) (Fig. 8F), CD10, TLE1, PAX8 (abdominopelvic location) and β-catenin immuno-reactivity. S100, SOX10, melanic, vascular and muscle markers are usually negative (Doyle et al., 2014; Yoshida et al., 2014; Demicco et al., 2015, 2020; Huang and Huang , 2019; Machado et al., 2020a; Dermawan et al., 2021; Devins et al., 2022), although some cases with dedifferentiation or transdifferentiation may reveal some of these markers depending on the nature of the dedifferentiated component (Mosquera and Fletcher,

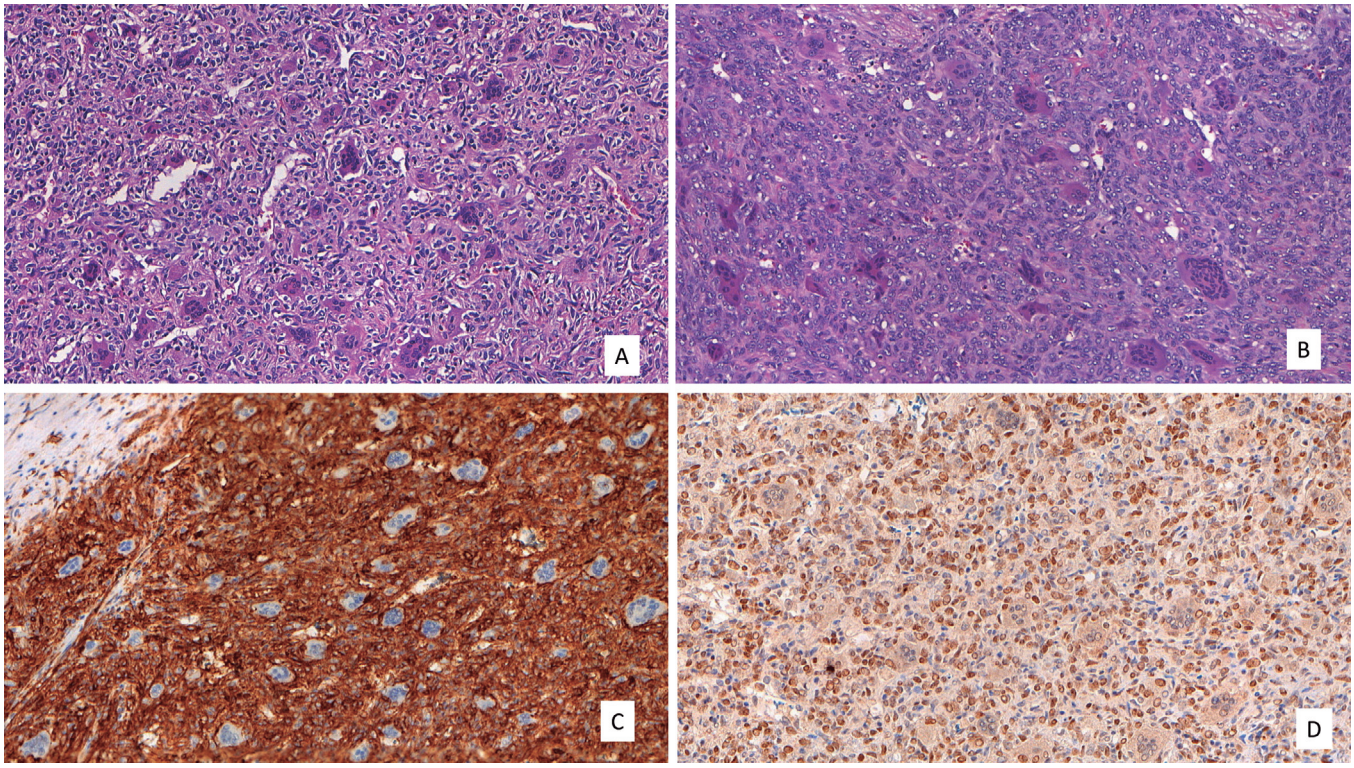

Fig. 6. A and B. Giant-cell rich SFT. H&E. **C.** Strong and diffuse CD34 immunoreactivity in stromal cells (Giant-cell rich SFT). **D.** Strong and diffuse STAT6 immunoexpression in tumor cells. A, C, D, x 20; B, x 40.

2009; Subramaniam et al., 2011; Collini et al., 2012; Thaway et al., 2013; Kurisaki-Arakawa et al., 2014; Schulz et al., 2014; Dagrada et al., 2015; Baněčková et al., 2022). p53 overexpression and HTER immunoreactivity are usually associated with poor evolution. HTER and p53 overexpression may confer poor prognosis in SFT, but this association has been better confirmed by molecular studies on HTER and p53 genes (Chirosi et al., 2008; Bahrami et al., 2016; Demicco et al., 2018; Lin et al., 2018; Park et al., 2019; Bouvier et al., 2019; Smrke et al., 2021; Karskova et al., 2022). The Ki-67 labelling index in the high-intermediate risk group (median, 10%) is usually higher than in the low-risk group (median, 3%) (Sugita et al., 2022; Machado et al., 2022).

Compared with the classical SFT component, CD34 and STAT6 expression often decreases in the dedifferentiated component, adding another level of complexity in the diagnosis, hence molecular demonstration of the specific *NAB2:STAT6* gene fusion is usually mandatory in such cases (Mosquera and Fletcher, 2009; Subramaniam et al., 2011; Collini et al., 2012; Thaway et al., 2013; Kurisaki-Arakawa et al., 2014; Schulz et al., 2014; Dagrada et al., 2015). As expected, dedifferentiated SFT evolves as a high-grade sarcoma with higher rates of recurrence, metastasis and death from disease and is concordant with a high mitotic rate (≥4/10 high-powered field), necrosis and multinodular growth pattern in this variant. p16 and/or p53 overexpression and Rb protein loss are significantly associated with dedifferentiation (Mosquera and Fletcher, 2009; Subramaniam et al., 2011; Collini et al., 2012; Thaway et al., 2013; Kurisaki-Arakawa et al., 2014; Schulz et al., 2014; Dagrada et al., 2015).

Ki-67 surrogating mitotic count, does it provide new prognostic information?

Among the histological predictive factors of aggressiveness in SFT, high mitotic counts with a general agreement of ≥4/10 HPFs represent the strongest predictor of malignant behaviour (Huang and Huang, 2019; Demicco et al., 2020; Georgiesh et al., 2022; Machado et al., 2022). Nevertheless, mitotic assessment may have some limitations because mitotic figures may be overlooked due to tissue artifacts, necrosis or abundant apoptotic figures (Diebold et al., 2017; Sugita et al., 2022). In order to address these limitations, Sugita et al. recently published an RSS that replaces mitotic count with Ki-67 assessment (Sugita et al., 2022). Nevertheless, we found in a recent study that applying an RSS incorporating the Ki-67 index does not provide any better risk stratification in comparison with the Demicco RSS (Demicco et al., 2017), and testing both

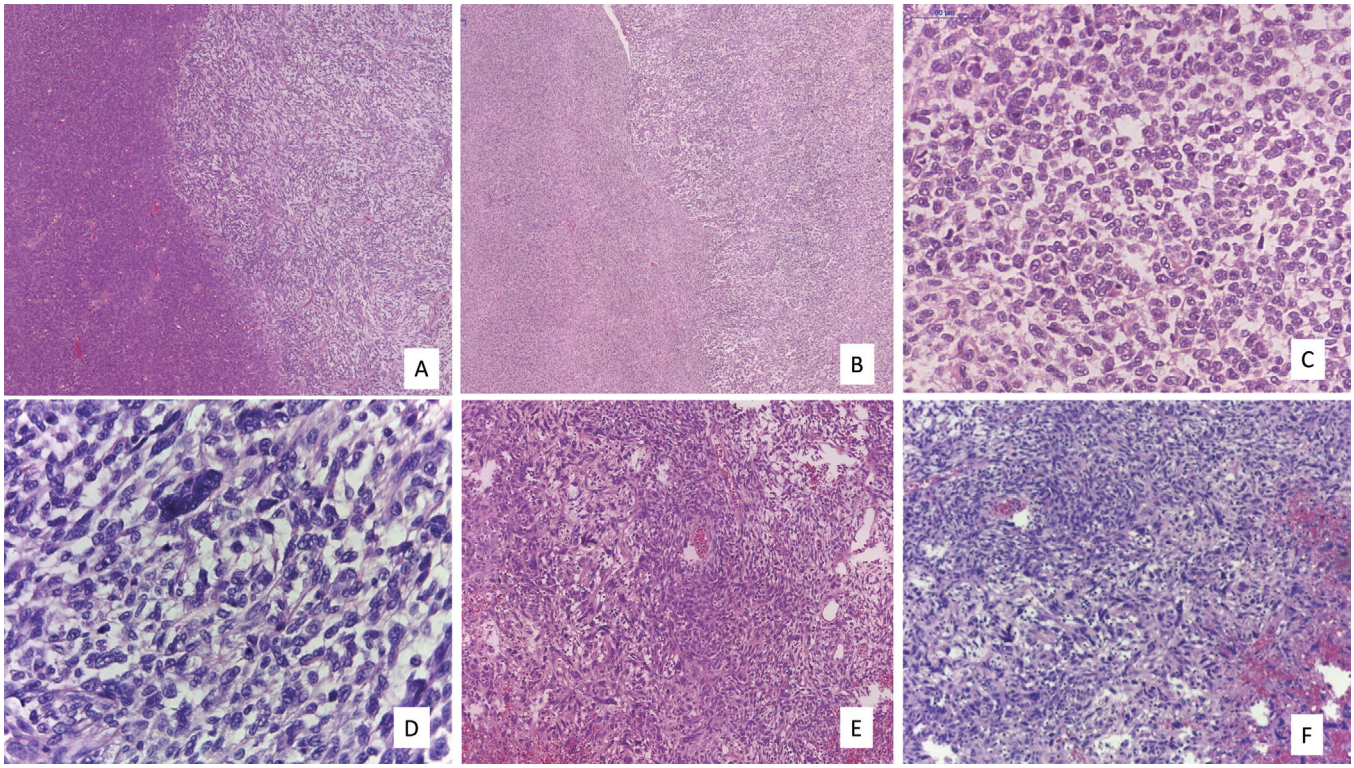

Fig. 7. Dedifferentiation in SFT. **A and B.** Abrupt transition between well differentiated and dedifferentiated area. H&E. **C.** Dedifferentiated SFT with Ewing-like morphology. H&E. **D.** Dedifferentiated SFT with spindle and giant tumor cells. H&E. **E.** Dedifferentiated SFT with area like pleomorphic sarcoma. H&E. **F.** Angiosarcoma-like dedifferentiated. SFT H&E. A, E, F, x 20; B, x 10; C, D, x 40.

RSS in our series produced similar survival data (Machado et al., 2022). In addition, accurate and reliable Ki 67 index assessment requires whole tissue sections and digital pathology or morphometry methods are not always available in all hospitals (Diebold et al., 2017; Sugita et al., 2022).

How difficult is the differential diagnosis, particularly in atypical or unusual histological subtypes of SFT?

SFT has been considered the "great simulator" of soft-tissue neoplasms due to its many differential diagnoses and variable morphologic appearance (Mosquera and Fletcher, 2009; Subramaniam et al., 2011; Collini et al., 2012; Thaway et al., 2013; Kurisaki-Arakawa et al., 2014; Schulz et al., 2014; Dagrada et al., 2015). The differential diagnoses of SFT cover a broad range of benign to malignant histological mimics, and is better approached in the context of the combination of anatomical locations: intrathoracic, intraabdominal, visceral, superficial, bone as well as the dominant stromal background: myxoid, collagen-rich, vessel-rich stromal tissue, fat-forming (Fig. 4F), heterologous components/osteoid matrix and finally the histological pattern/cellular morphology: spindle/ovoid, round (Fig. 5E,F), epithelioid, clear cells, giant-cell (Fig. 6), anaplastic/pleomorphic predominant (Fig. 7) (Kao et al., 2016; Huang and Huang, 2019; Bianchi et al., 2020, Demicco et al., 2020; Machado et al., 2020a,b, 2021; Choi and Rao, 2021; Tariq et al., 2021; Kazazian et al., 2022; Suster et al., 2023). Nevertheless, when the option of SFT is borne in mind in any tumor with any morphology, a strong and diffuse nuclear STAT6 immunoreactivity should basically resolve almost all diagnostic challenges with the exception of cases with loss of CD34 and/or STAT6 expression due to dedifferentiation (Mosquera and Fletcher, 2009; Subramaniam et al., 2011; Collini et al., 2012; Thaway et al., 2013; Kurisaki-Arakawa et al., 2014; Schulz et al., 2014; Dagrada et al., 2015).

In the differential diagnosis of SFT, tumors normally originating from intrathoracic or abdominopelvic cavities such as carcinosarcomas, desmoplastic mesothelioma, monophasic synovial sarcoma, desmoplastic small round cell tumors, and dedifferentiated liposarcoma should be kept in mind. These tumors may have abundant collagen matrix, hemangiopericytoma-like pattern or, rarely, STAT6 immunoreactivity, resulting in morphological overlap (Yoshida et al., 2014; Demicco et al., 2015, 2020; Kao et al., 2016; Huang and Huang, 2019; Bianchi et al., 2020, Choi and Rao, 2021; Machado et al., 2021; Tariq et al., 2021; Kazazian et al.,

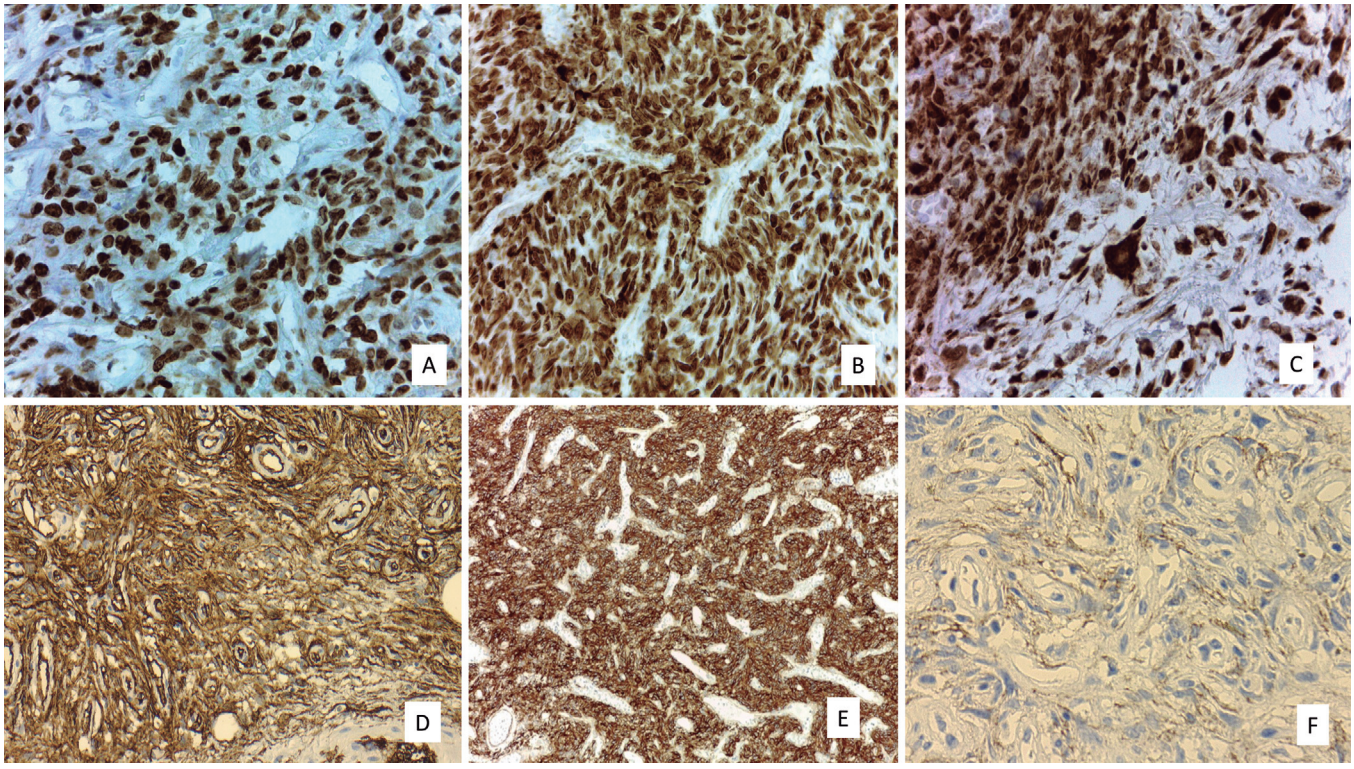

Fig. 8. A and B. Strong and diffuse STAT6 nuclear overexpression in conventional SFT. **C.** Strong and diffuse STAT6 nuclear immunoreactivity in dedifferentiated SFT (conventional and dedifferentiated areas show immunoexpression). **D.** Strong and diffuse cytoplasmic CD34 immunoexpression in SFT. **E.** Strong and diffuse membranous CD99 immunoexpression in SFT. **F.** Moderate and patchy cytoplasmic EMA immunoreactivity in SFT. A, E, F, x 20.; B, C, x 40; D, x 10.

2022; Suster et al., 2023). Fortunately, in these cases the STAT6 expression is almost always cytoplasmic and rarely nuclear and with less staining intensity than observed in SFT.

In some scenarios, the differential diagnosis is particularly difficult with those tumors belonging to the category of CD34-positive mesenchymal neoplasms (mammary-type myofibroblastoma, cellular angiofibroma, dermatofibrosarcoma protuberans, superficial CD34 tumors, fat-poor spindle cell/pleomorphic lipoma), some of which may have Rb loss, although nuclear STAT6 immunoreactivity has not been reported as far as we know (Yoshida et al., 2014; Demicco et al., 2015, 2020; Kao et al., 2016; Huang and Huang, 2019; Bianchi et al., 2020, Choi and Rao, 2021; Machado et al., 2021; Tariq et al., 2021; Kazazian et al., 2022; Suster et al., 2023).

Some other mesenchymal neoplasms with similar stromal background and/or pattern/cellular morphology may prompt excluding the possibility of SFT. The most frequent includes monophasic/undifferentiated synovial sarcoma with ovoid or round cells, mesenchymal chondrosarcoma, Ewing sarcoma, Ewing-like sarcoma, gastrointestinal stromal tumor (GIST), malignant peripheral nerve sheath nerve (MPNST), phosphaturic mesenchymal tumor, endometrial stromal sarcoma and NTRAK-rearranged sarcomas (ref). Individually, all these tumors have particular morphologic, phenotypic and molecular hallmarks that may usually allow an accurate differential diagnosis (Yoshida et al., 2014; Demicco et al., 2015, 2020; Kao et al., 2016; Huang and Huang, 2019; Bianchi et al., 2020, Choi and Rao, 2021; Machado et al., 2021; Tariq et al., 2021; Kazazian et al., 2022; Suster et al., 2023). SYT/SSX1 immunoreactivity has not been reported in SFT. Although mesenchymal chondrosarcoma may have aberrant STAT6 expression (Yoshida et al., 2014; Demicco et al., 2015, 2020; Huang and Huang, 2019) and usually has HPC-like vessels, mature cartilage islands have not so far been described in SFT. Furthermore, both tumors have different gene fusions. NKX2.2, PAX7, ETV4, DUX4, BCOR or CCNB3 immunoreactivity have not been reported in SFT, hence the differential diagnosis with Ewing or Ewing-like sarcomas in cases of SFT with predominant round/ovoid cell and scant stromal tissue may be less complicated. While CD34 expression in GIST is not exceptional, they also express CKIT and DOG1 (Yoshida et al., 2014; Demicco et al., 2015, 2020; Huang and Huang, 2019). MPNST have a peculiar clinical presentation and the loss of H3K27me aided by a lack of nuclear STAT6, especially in high grade tumors, may support their diagnosis (Huang and Huang, 2019). Phosphaturic mesenchymal tumor is almost always negative for CD34 and STAT6, hence the differential diagnosis with SFT may be easier. Occasionally, SFT may express CD10 and may resemble endometrial

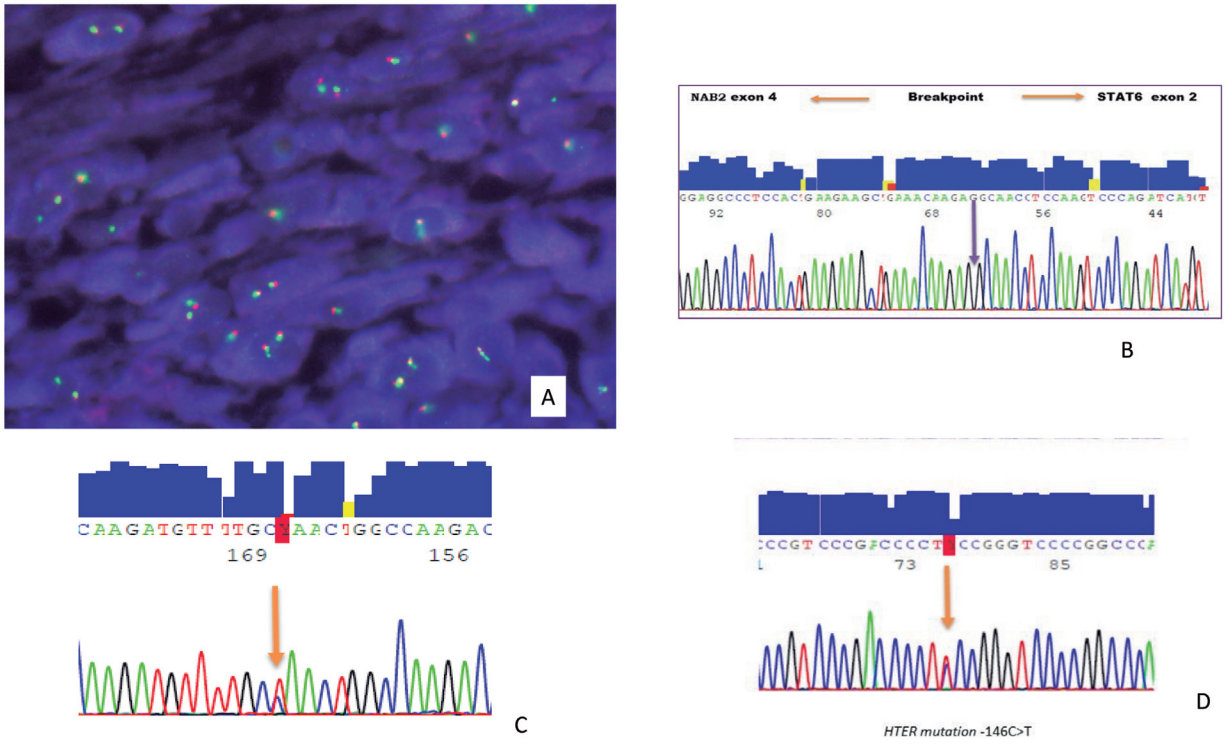

Fig. 9. A. FISH for STAT6 reveal paired signal (red/green), no translocation. **B.** RT-PCR with NAB2 (exon 4)::STAT6 (exon 2) gene fusion positive in SFT, **C and D.** Dedifferentiated SFT with TP53 and HTER mutations. A, x 100.

stromal sarcoma and a subset of NTRAK-rearranged sarcomas may exhibit high-grade round cells, HPC-pattern and CD34 expression (Devins et al., 2022) showing a histological resemblance to cellular SFT, nevertheless strong STAT6 nuclear expression has not been described in these tumors.

In the case of intra-abdominal, retroperitoneal or pelvic locations the differential diagnosis of SFT may be confused with some mesenchymal tumors such as dedifferentiated liposarcoma, intimal sarcoma, GLI1-altered neoplasm (Yoshida et al., 2014; Demicco et al., 2015, 2020; Kao et al., 2016; Huang and Huang, 2019; Bianchi et al., 2020, Choi and Rao, 2021; Machado et al., 2021; Tariq et al., 2021; Kazazian et al., 2022; Suster et al.,2023). Such tumors may display cytoplasmic STAT6 immunoreactivity since the *MDM2*, *CDK4* and *GLI1* genes are in the vicinity of the *STAT6* chromosome region. Nevertheless, with the exception of dedifferentiated SFT, the morphology of conventional SFT is quite different to liposarcoma, intimal sarcoma or GLI1-altered neoplasms. In addition, *MDM2* or *GLI1* amplification is usually unexpected in SFT (Huang and Huang, 2919; Demicco et al., 2020, Machado et al., 2022).

Myxoid change in SFT may be focal or extensive, and when diffuse the differential diagnosis with a myxoid mesenchymal neoplasm such as myxofibrosarcoma, myxoid synovial sarcoma, myoepithelial carcinomas, *CIC* or *BCOR* sarcoma with myxoid areas may be difficult. Absence of intense STAT6 nuclear immunoreactivity and specific molecular alterations can provide valuable information in challenging cases (Yoshida et al., 2014; Demicco et al., 2015, 2020; Kao et al., 2016; Huang and Huang, 2019; Bianchi et al., 2020, Choi and Rao, 2021; Machado et al., 2021; Tariq et al., 2021; Kazazian et al., 2022; Suster et al., 2023).

Despite the high sensitivity and specificity of STAT6 nuclear expression, nuclear STAT6 immunostaining is occasionally observed in other tumors such as low-grade fibromyxoid sarcoma, deep fibrous histiocytoma, nodular fasciitis and undifferentiated pleomorphic sarcoma (Yoshida et al., 2014; Demicco et al., 2015, 2020; Kao et al., 2016; Huang and Huang, 2019; Bianchi et al., 2020; Choi and Rao, 2021). Fortunately, the clinical presentation, histopathology, immunoprofile and molecular alteration of these neoplasms are very different from SFT. Finally, some cases of SFT may be negative for STAT6, in such cases, while GRIA2 and ALDH1 can be expressed in many SFTs, they are quite unspecific (Bouvier et al., 2013; Vivero et al., 2014) and the molecular detection of *NAB2:STAT6* carries more weight than the detection of these antibodies.

Does mandatory molecular diagnosis in all SFTs provide additional prognostic and/or therapeutic information?

The diagnosis of SFT is established by the combination of clinical, pathological, immunohistochemical, and molecular features. Identification of the *NAB2* (NGFI-A-binding protein 2)::*STAT6* (signal transduction and activator of transcription 6) fusion oncogene has emerged as a specific cytogenetic hallmark for SFT (Chmielecki et al., 2013; Mohajeri et al., 2013; Barthelmeß et al., 2014; Akaike et al., 2015; Salguero-Aranda et al., 2021; Smrke et al., 2021; Krskova et al., 2022). SFTs are characterized by a paracentric inversion involving chromosome 12q13.3, resulting in the juxtaposition of the *NAB2* and *STAT6* genes (Akaike et al., 2015; Salguero-Aranda et al., 2021; Smrke et al., 2021; Krskova et al., 2022).

In practice, the detection of the NAB2:STAT6 fusion gene with fluorescent in situ hybridization (FISH) is impossible due to the small size of the inverted sequence and the proximity of the *NAB2* and *STAT6* loci (Chmielecki et al., 2013; Mohajeri et al., 2013; Barthelmeß et al., 2014; Akaike et al., 2015; Huang and Huang, 2019; Demicco et al., 2020; Salguero-Aranda et al., 2021; Smrke et al., 2021; Krskova et al., 2022) (Fig. 9A). In addition, the diversity of *NAB2:STAT6* breakpoints requires RT-PCR or next generation sequencing (NGS) to provide adequate sensitivity. Nevertheless, RT-PCR or NGS are not able to consistently detect all intronic fusions, hence the demonstration of the *NAB2::STAT6* fusion (Fig. 9B) is not an absolute requirement for the diagnosis of SFT (Barthelmeß et al., 2014; Akaike et al., 2015; Huang and Huang , 2019; Demicco et al., 2020; Salguero-Aranda et al., 2021; Smrke et al., 2021; Krskova et al., 2022). In fact, strong and diffuse nuclear positivity in the absence of cytoplasmic expression on immunohisto-chemical staining for STAT6 c-terminal epitopes is sensitive and specific for these rearrangements and is widely used as a surrogate to the molecular determination (Yoshida et al., 2014; Demicco et al., 2015, 2020; Machado et al., 2021).

Many different fusion types involving different exons, introns, or 50 untranslated regions of these genes have been reported. It is thought that the different fusion types may contribute to the variation in phenotype and location of SFT, since most SFTs arising in the pleura show fusions of *NAB2* exon 4 with *STAT6* exon 2 or 3, whereas in SFTs arising in extrathoracic locations, fusions of NAB2 exon 5, 6, or 7 to STAT6 exons 16, 17, or 18 are more common (Akaike et al., 2015; Huang and Huang, 2019; Demicco et al., 2020; Salguero-Aranda et al., 2021; Krskova et al., 2022). Among all fusion subtypes reported to date, *NAB2ex4::STAT6ex2* and *NAB2ex6::STAT6ex16/17* represent the two predominant variants, accounting for approximately 70% of cases (Akaike et al., 2015; Huang and Huang, 2019; Demicco et al., 2020; Salguero-Aranda et al., 2021). The former exhibits preponderance in intrathoracic sites (up to 80%) of the elderly, with greater size and indolent behavior, while the latter is consistently associated with younger age, hypercellular histology, and extrathoracic locations, but variably related with higher mitotic counts and smaller size (Akaike et al., 2015). However, other studies have failed to demonstrate a clear impact of fusion variants on prognosis, probably due to a short

follow-up that did not consider late recurrences (Huang and Huang, 2019; Demicco et al., 2020; Salguero-Aranda et al., 2021). In a recent retrospective cohort with long-term follow-up, Georgiesh et al. investigated the clinicopathological and prognostic impact of the STAT6-Full (intact STAT6 domains) and STAT6-TAD (contains only the STAT6 TAD domain) variants by RNA sequencing (Georgiesh et al., 2021). Patients with STAT6-TAD tumors had a worse prognosis, with a higher mitotic count and a 10-year recurrence-free survival rate of 25% (vs. 78% for STAT6-Full patients) (Georgiesh et al., 2021). These promising results need further confirmation in prospective trials to confirm their prognostic value.

Additional mutations or genetic alterations have been reported to possibly contribute to SFT progression, including *TP53* mutations or loss of Rb in anaplastic SFT and *TERT* promoter mutations in long-standing tumors diagnosed in older patients (Chirosi et al., 2008; Bahrami et al., 2016; Demicco et al., 2018; Lin et al., 2018; Park et al., 2019; Vogels et al., 2019; Smrke et al., 2021; Karskova et al., 2022). *TERT* promoter mutations are strongly associated with older age, larger tumor size, higher risk classification, and poorer event-free survival. These associations of the *TERT* promoter mutation (Fig. 9) with adverse clinicopathological factors and a worse prognosis are partly similar to a recent large study in which significance was only observed in the prediction of shorter metastasis-free survival in intermediate risk category SFT with imperfect risk prediction (Demicco et al., 2018). Whole-genome sequencing has revealed a very low mutation burden in SFT (Chmielecki et al., 2013; Demicco et al., 2020). However, deletions or mutations of the *TP53* gene locus (Fig. 9) at 17p13 have been described in dedifferentiated or malignant SFTs, and *PDGFRB* mutation has also been occasionally observed in classic conventional SFTs (Chirosi et al., 2008; Subramaniam et al., 2011; Park et al., 2019; Salguero-Aranda et al., 2021; Smrke et al., 2021). Some patients have *FGFR1* gene fusion and *MET* gene fusion, which may be potential therapeutic targets (Huang and Huang, 2019; Demicco et al., 2020). We observed in our SFT series (n=97) that cases with both *HTER* and *TP53* mutation are associated with poor evolution (Machado et al., 2021) although we also found several cases categorized as low-risk by the Demicco system, but with *HTER* mutation.

The concept of benign or malignant in SFT and the progressive evolution of risk stratification systems (RSS).

Overall, SFTs are relatively indolent tumors with good prognosis after surgery, but recurrence/metastases can occur in up to 10-30% (Friss et al., 2018; Bianchi et al., 2020, 2021; Georgiesh et al., 2020; Demicco et al., 2020). While the most aggressive tumors tend to metastasize within the first 5 years after primary presentation, more indolent or low-risk tumors have been reported, with metastases arising after 10 or even 20 years. Preferential metastatic sites include lungs,

Table 1.

Prognostic factor	Demicco et al., 2017		Sugita et al., 2022		Georgiesh et al., 2022 G-Score	
Mitoses (per 10 HPF)	Points	Value			Points	Value
	0	0				
	1	1-3			0	<4
	2	≥4			2	≥4
Ki-67			Points	Value		
			0	<1		
			1	1-10		
			2	≥10		
Age (years)	0	<55	0	<55		
	1	≥55	1	≥55		
Tumor size (cm)	0	0-4.9	0	0-4.9		
	1	5-9.9	1	5-9.9		
	2	10-14.9	2	10-14.9		
	3	≥5	3	≥5		
Necrosis	0	<10%	0	<10%	0	Absent
	1	≥10%	1	≥10%	1	<50%
					2	≥50%
Gender					0	Female
					1	Male
Scoring	Points	Risk	Points	Risk	Points	Risk
	0-3	Low	0-3	Low	0	Low
	4-5	Intermediate	4-5	Intermediate	1-2	Intermediate
	6-7	High	6-7	High	3-5	High

liver, and bone (Huang and Huang, 2019; Demicco et al., 2020).

A key update for SFT classification is the development of risk stratification models that has resulted in improved prognostication over the traditional benign/malignant distinction that is now avoided (Tapias et al., 2015; Demicco et al., 2017, 2019; Diebold et al., 2017; Gholami et al., 2017; Salas et al., 2017; Reisenauer et al., 2018; Riedel, 2019; Georgiesh et al., 2020, 2022; Thompson et al., 2021; Liu et al., 2022; Machado et al., 2022; Sugita et al., 2022). Traditionally, SFTs were defined as "benign" or "malignant," based on criteria initially developed for pleural SFTs. Most series incorporated mitotic activity (>4 mitoses/10 high power fields [HPF]) in the definition of malignancy (Demicco et al., 2017, 2019, 2020; Diebold et al., 2017; Gholami et al 2017; Salas et al., 2017; Huang and Huang, 2019; Georgiesh et al., 2020, 2022; Liu et al., 2022; Machado et al., 2022), whereas additional tumor characteristics, such as tumor size and necrosis were consistently omitted (Table 1).

Among those RSS models that integrate several clinicopathologic variables to predict the individual risk of metastatic recurrence, the Demicco model is the most widely used in clinical practice and is applicable to SFTs of all extra-meningeal sites (Demicco et al., 2017). It is based on age at presentation, tumor size, mitotic count and necrosis to classify SFTs with a low, moderate, or high risk of developing a metastatic recurrence. This model has been validated both for soft tissue SFTs and pleural SFTs. The Demicco RSS is specifically designed to predict metastasis. Although it is of great value in the prediction of early metastasis or death, it is unable to predict local recurrence and may under-predict late metastasis and recurrence. While it can be used to predict overall survival, it is not designed for this purpose (Demicco et al., 2017). Only one group has published a series of extrameningeal SFT with median follow-up of greater than 6 years (Georgiesh et al., 2022). In this study, Georgiesh et al. (G-Score) found that a model incorporating sex as a predictive feature, with men being at higher risk than women, together with high mitotic rate and the presence of extensive necrosis was predictive of both early and late local and distant recurrence, with high-risk tumors having a median time to recurrence of 40 months and a 10-year recurrence-free rate of 25%, compared with a 10-year recurrence-free rate of 95% for low-risk tumors (Georgiesh et al., 2022). Hence, G-Score RRS is apparently much stricter in its classification of low-risk SFT. As a caveat for all RSS, the histologic assessment of mitotic figures and necrosis depends on adequate tumor sampling and is predisposed to subjectivity (Demicco et al., 2017, 2019, 2020; Diebold et al., 2017; Gholami et al 2017; Salas et al., 2017; Huang and Huang, 2019; Georgiesh et al., 2020, 2022; Liu et al., 2022; Machado et al., 2022). Given that the evaluation of mitotic figures tends to differ between observers, Sugita et al. developed a grading system that substitutes mitotic count with Ki-67 index (Sugita et al., 2020) but we were unable to find significant differences in plot survival curves when comparing this model with the Demicco RSS in a series of 97 SFT (Machado et al., 2022).

An additional problem when dealing with RSS in SFTs is that there is also poor concordance between scoring systems as to which specific tumors fall into low-, intermediate-, or high-risk categories (Demicco et al., 2017, 2019, 2020; Diebold et al., 2017; Gholami et al 2017; Salas et al., 2017; Huang and Huang, 2019; Georgiesh et al., 2020, 2022; Liu et al., 2022; Machado et al., 2022). As a result, some investigators have recommended scoring risk in extrameningeal SFT using multiple systems and basing risk on concordance of results. For example, we classified a series of 28 SFTs using various RSS (Machado et al., 2021) and found that all patients with tumors classified as high risk by multiple systems (Pasquali, Demicco, Diebold and Salas RSSs) (Pasquali et al., 2016; Demicco et al., 2017; Diebold et all., 2017; Salas et al., 2017) developed recurrence, whereas patients with tumors classified as low risk by multiple systems remained free of disease.

As a matter of fact, one of the most important unsettled issues is that some low-risk SFTs may have late recurrence/metastasis leading to uncertainty among clinicians regarding the specificity of the RSS (Pasquali et al., 2016; Demicco et al., 2017, 2020; Diebold et al., 2017; Salas et al., 2017; Huang and Huang, 2019; Machado et al., 2022). In our large series of SFTs we observed that many cases classified by Demicco RSS as low risk were changed to intermediate risk when classified using the new system (G-score RSS), thus the total number of low-risk SFTs was reduced when using this new RSS. Kaplan-Meier survival plots in the present series using the Demicco system (Machado et al., 2022) showed three well-defined groups: low-risk, intermediate-risk and high-risk SFT, this last being the group with poor evolution. However, using G-Score RSS (Georgiesh et al., 2022), low-risk and intermediate-risk SFTs had a similar evolution that contrasted with the more aggressive high-risk group (Machado et al., 2022). Hence, although the G-score system (Georgiesh et al., 2022) is apparently much stricter when classifying tumors as low risk, the evolution for the low and intermediate-risk groups was similar, at least in this series (Machado et al., 2022). Perhaps increasing the sample size in future prospective international studies could potentially better delineate the evolution for the low and intermediate-risk groups. In the same study, we also found that incorporating the Ki-67 index does not provide any better risk stratification in comparison with the Demicco RSS (Demicco et al., 2017), and testing both RSS in our series produced similar Kaplan-Meier survival data (Machado et al., 2022). Nevertheless, half the tumors categorized as low-risk by the Demicco et al. system but which had a worse evolution (late recurrence or metastasis) showed Ki-67 $\geq$ 10 (Machado et al., 2022).

While clinical and histological parameters have been

used to develop various RSS, molecular findings have not been included in any of the RSS in use so far (Tapias et al., 2015; Demicco et al., 2017, 2019; Diebold et al., 2017; Gholami et al., 2017; Salas et al., 2017; Reisenauer et al., 2018; Riedel, 2019; Georgiesh et al., 2020, 2022; Thompson et al., 2021; Liu et al., 2022; Machado et al., 2022; Sugita et al., 2022). In our last study, all six cases of SFT classified as high-risk by both the Demicco and G-score RSS revealed recurrence/metastasis, and half showed both *TP53* and *HTER* mutations (Machado et al., 2022). Previous publications have recommended including *TERT* promoter mutation status and/or *TP53* mutational status as an aid in risk assessment, particularly for tumors scored as intermediate risk (Bahrami et al., 2016; Demicco et al, 2018; Lin et al., 2018; Park et al., 2019; Volgels et al., 2019), aiming to provide further evidence of probable aggressive behaviour. Importantly, dedifferentiation remains unpredictable by all these RSSs.

In conclusion, risk assessment and RSSs remains debatable in SFT stratification and final outcome. Nevertheless, the integration of all clinicopathological and molecular findings may improve risk stratification of SFT and may potentially aid designing risk-adjusted treatment and scheduled follow-up. The G-score RSS has more accurately identified low-risk patients so far, but a long-term follow-up is recommended (Georgiesh et al. 2022), even in low-risk cases given the possibility of late recurrence/metastasis.

Is a surgical approach the best strategy in localized SFT?

Patients with SFT should be managed within sarcoma reference centers, and each case should be discussed by a specialized multidisciplinary tumor board to determine the best individualized therapeutic strategy (Sung et al., 2005; Park et al., 2011; Stacchiotti et al., 2010, 2012, 2013, 2014, 2017, 2019, 2021; Constantinidou et al., 2012; Park et al., 2013; Tazzari et al., 2014; van Doorn et al., 2015; Spagnuolo et al., 2016; Bishop et al., 2018; Haas et al., 2018; de Lemos et al., 2019; Martin-Broto et al., 2019; Bonvalot et al., 2020, Haas et al., 2020; Krengli et al., 2020; Martin-Broto et al., 2020; Zhou et al., 2020; Wang et al., 2021; de Bernardini et al., 2022; Mondaza et al., 2022; Ozaniak et al., 2022). To date, surgical intervention with adequate margins and long-term follow-up still remains the standard care in managing patients with SFT (Sung et al., 2005; Martin-Broto et al., 2019; Stacchiotti et al., 2019, 2021; Bonvalot et al., 2020, Haas et al., 2020; Krengli et al., 2020; Martin-Broto et al., 2020; Zhou et al., 2020; Wang et al., 2021; de Bernardini et al., 2022; Mondaza et al., 2022; Ozaniak et al., 2022). Pretreatment biopsy is ideal, but not always diagnostic, and resection may be required to finalize the diagnosis (Bonvalot et al., 2020, Haas et al., 2020; Krengli et al., 2020; Martin-Broto et al., 2020; Zhou et al., 2020; Stacchiotti et al., 2021; Wang et al., 2021; de Bernardini et al., 2022; Mondaza et al., 2022).

The potential benefit of perioperative radiation therapy in extrameningeal SFT should be discussed by the multidisciplinary team (Bishop et al., 2018; Haas et al., 2018; de Lemos et al., 2019; Martin-Broto et al., 2019; Stacchiotti et al., 2019; Bonvalot et al., 2020; Haas et al., 2020; Krengli et al., 2020). Preoperative RT may be considered in order to facilitate negative microscopic margins or even to render as resectable those tumors that are deemed unresectable or borderline resectable (Bishop et al., 2018; Haas et al., 2018; de Lemos et al., 2019; Martin-Broto et al., 2019; Stacchiotti et al., 2019; Bonvalot et al., 2020, Haas et al., 2020; Krengli et al., 2020). In isolated case reports, neoadjuvant radiotherapy aiming at tumor shrinkage has been used to control local symptoms or enable surgical excision (Bishop et al., 2018; Haas et al., 2018; Bonvalot et al., 2020; Haas et al., 2020).

Chemotherapy has typically been used in the advanced or metastatic setting for patients with SFT, and the potential role of adjuvant chemotherapy following resection of SFT is unclear (ref). Recently, several tyrosine kinase inhibitors (TKIs) have been prospectively assessed in patients with advanced SFT who have progressed on prior therapy (Stacchiotti et al., 2010, 2012, 2013, 2014, 2017, 2019, 2021; Park et al., 2013; Tazzari et al., 2014; van Doorn et al., 2015; Spagnuolo et al., 2016; Martin-Broto et al., 2019; Krengli et al., 2020; Martin-Broto et al., 2020; Zhou et al., 2020; Wang et al., 2021; de Bernardini et al., 2022; Mondaza et al., 2022; Ozaniak et al., 2022). Pazopanib and other TKIs shown to have some activity in SFT are sunitinib, axitinib, and regorafenib (Martin-Broto et al., 2019, 2020).

State of the art treatment and immunotherapy in SFT.

IGF-1 is overexpressed in SFT, and treatment regimens using figitumumab, a fully human IgG2 anti-IGF-1 (IGF-1R) monoclonal antibody, have demonstrated tumor response in a few patients with advanced SFT (Stacchiotti et al., 2010; Tazzari et al., 2014; van Doorn et al., 2015; Smrke et al., 2021; Ozaniak et al., 2022). Immunotherapy seems to be another promising approach for SFT, although available data on the SFT immune microenvironment has come mainly from retrospective studies (Stacchiotti et al., 2010; Tazzari et al., 2014; Boothe et al., 2017; Ozaniak et al., 2022). On the basis of the results in the entire cohort, the authors suggested that T-cell immune infiltrate might be less frequent in translocation-associated sarcomas, such as SFT (Stacchiotti et al., 2010; Tazzari et al., 2014; Boothe et al., 2017; Smrke et al., 2021; Ozaniak et al., 2022). Overall, some studies suggest that antiangiogenic therapies such as pazopanib could be of interest for first-line treatment, while data on the efficacy of immunotherapy remain scarce and more results are needed. Recently, a Spanish group found that ISG15 is a prognostic factor in malignant SFT,

regulating the expression of CSC-related genes and CSC maintenance (Mondaza-Hernandez et al., 2022). They suggested that ISG15 could be a novel therapeutic target in SFT, which could improve the efficacy of the currently available treatments (Mondaza-Hernandez et al., 2022). Prospective clinical trials are needed to confirm this hypothesis.

Conclusion

SFTs are a unique subtype of mesenchymal lesion, featuring intense vascularity, well-circumscribed margins and a clinical course that is often relatively indolent. Description of the characteristic NAB2::STAT6 gene fusion has facilitated accurate diagnosis. Optimal management of SFTs is focused on complete resection, and the existing risk stratification systems can be used to estimate risk of recurrence following the procedure. The accuracy of the RSS is expected to increase as the diagnosis of SFT improves and with the potential incorporation of molecular information. Long-term follow-up is recommended due to the possibility of late recurrence even in low-risk tumors. Although the efficacy of targeted therapies for SFT awaits further investigation, the improvement in molecular characterization may cooperatively lead to the potential incorporation of molecular signatures into risk stratification and future identification of more druggable targets. International collaborative studies and additional clinical trials are undoubtedly needed to achieve this goal.

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