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Uncommon and peculiar soft tissue sarcomas: Multidisciplinary review and practical recommendations for diagnosis and treatment. Spanish group for Sarcoma research (GEIS – GROUP). Part I

Javier Martínez-Trufero [a,*], Josefina Cruz Jurado [b], M.Carmen Gómez-Mateo [c], Daniel Bernabeu [d], Luis Javier Floría [e], Javier Lavernia [f], Ana Sebio [g], Xavier García del Muro [h], Rosa Álvarez [i], Raquel Correa [j], C.Nieves Hernández-León [k], Gloria Marquina [l], Nadia Hindi [m], Andrés Redondo [n], Virginia Martínez [n], Jose Manuel Asencio [o], Cristina Mata [p], Claudia M. Valverde Morales [q], Javier Martin-Broto [m]

[a] *Hospital Universitario Miguel Servet, Medical Oncology Department, Zaragoza, Spain*
[b] *Hospital Universitario Canarias, Medical Oncology Department, Santa Cruz de Tenerife, Spain*
[c] *Hospital Universitario Miguel Servet, Pathology Department, Zaragoza, Spain*
[d] *Hospital Universitario La Paz, Radiology Department, Madrid, Spain*
[e] *Hospital Universitario Miguel Servet, Orthopedic and Traumatology Department, Zaragoza, Spain*
[f] *Instituto Valenciano de Oncología, Medical Oncology Department, Valencia, Spain*
[g] *Hospital Universitario Santa Creu i Sant Pau, Medical Oncology Department, Barcelona, Spain*
[h] *Instituto Catalán Oncología Hospitalet, Medical Oncology Department, Barcelona, Spain*
[i] *Hospital Universitario Gregorio Marañón, Medical Oncology Department, Madrid, Spain*
[j] *Hospital Virgen de la Victoria, Radiation Oncology Department, Malaga, Spain*
[k] *Hospital Universitario Canarias, Pathology Department, Santa Cruz de Tenerife, Spain*
[l] *Hospital Universitario Clínico San Carlos, Medical Oncology Department, Madrid, Spain*
[m] *University Hospital "Fundacion Jimenez Diaz" Madrid, Medical Oncology Department, Madrid, Research Institute FJD-UAM, Madrid (Spain), TBsarc, CITIUS III, Seville, Spain*
[n] *Hospital Universitario La Paz, Medical Oncology Department, Madrid, Spain*
[o] *Hospital Universitario Gregorio Marañón, Surgery Department, Madrid, Spain*
[p] *Hospital Universitario Gregorio Marañón, Pediatric and Adolescent Hemato-oncology Department, Madrid, Spain*
[q] *Hospital Universitario Vall D'Hebron, Medical Oncology Department, Barcelona, Spain*

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* Corresponding autor at: Medical Oncology Department, Hospital Universitario Miguel Servet, Avda. Isabel La Católica 1-3, 50009 Zaragoza, Spain.
E-mail address: jmtrufero@seom.org (J. Martínez-Trufero).

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Introduction

Soft Tissue Sarcomas (STS) is a heterogeneous and complex group of mesenchymal tumors with an annual incidence of 50–60 new cases per million people and year, which means about 1% of malignancies [1]. In the last WHO classification of Sarcomas, there are 64 locally aggressive and/or malignant subtypes, and this number is increasing, since new advances in molecular diagnosis have diversified and split up tumors into new diagnostic categories [2]. There are some subtypes with higher incidence like GIST, liposarcoma, leiomyosarcomas, and undifferentiated sarcomas, on which most of guidelines are focused, and which share somehow a similar therapeutic approach [3,4]. Although the majority of sarcomas are considered rare cancer with an incidence lower than 6/10^6/year, most of individual subtypes have an incidence lower than 1/10^6/year. Recently, in the results of data extracted from French nationwide NETSARC registry with 25,172 sarcoma patients, it was clearly showed that the number of published phase II and III trials were significantly higher with sarcomas subtypes with an incidence above 1/10^6 per year [5]. In the other hand, the Connective Tissue Oncology Society has recently published an expert consensus, defining as ultra-rare sarcomas those with an incidence $\leq 1/10^6$ /year. There are 56 soft tissue STS subtypes, that that fulfill that requirement, where is extremely difficult to conduct well powered prospective clinical studies [6]. Besides that, taking into account clinically relevant features, other than gross incidence rates, it is obvious that there is more and more need to address most of sarcoma subtypes in a more customized approach. Almost all the subtypes included in our review belong to the ultra-rare sarcomas. But other subtypes, not so uncommon, as Kaposi Sarcoma and Myxofibrosarcoma, with uncertain incidence and specific different approach, have been also included in this review, since they share most of the clinical problems of ultra-rare subtypes.

The Spanish Group for Sarcoma Research (GEIS), according to its commitment to continuous medical education on sarcoma care, would like to provide an easy-to-handle tool in the form of "quick decision-making guide", which may help us when facing to these complex and peculiar cases. We have included a review of each entity, focusing on current research lines and open trials, trying to stimulate clinicians to actively participate in the improvement of the sarcoma knowledge.

We have divided our work in two parts. In this first part we have included the following sarcoma subtypes: Vascular tumors (Angiosarcoma, Haemangioendotheliomas, Kaposi Sarcoma) or related-to-vessels tumors (Intimal Sarcoma), and Fibroblastic/myofibroblastics tumors (Myxofibrosarcoma, Adult Fibrosarcoma, Infantile fibrosarcoma, Solitary Fibrous Tumor, Dermatofibrosarcoma Protuberans, Low Grade Fibromyxoid Sarcoma, Sclerosing Epithelioid Fibrosarcoma, Inflammatory Myofibroblastic Tumor and Fibroblastic Myxoinflammatory Tumor).

We are going to summarize, one by one, all subtypes, highlighting only the more relevant questions with clinical implications. We have also added some tables where main features related to radiology (Table 1), pathology and molecular biology (Tables 2 and 3), and systemic treatment (Table 4) are pointed out.

Local treatments (surgery and radiotherapy) are also considered. In many cases, general rules for surgery and radiotherapy (RT) applied to common sarcomas, are also applicable to these uncommon histotypes [3]. Because of this, we have tried to highlight only those specific peculiarities related with these treatments, which should be taken into account in each particular subtype.

As many of these subtypes are nowadays considered today orphan diseases, with few approved systemic systemic treatment options, as general recommendation we strongly recommend as a first option, not only the inclusion in clinical trials, but also to collaborate in their creation and design, through cooperation between different institutions. Knowing that, we present the available treatment options, but also we give some tips for clinical research. The recommendations reflected on Table 4 expect to be a multidisciplinary confluent expert decisions, being aware that the content can be debatable.

We have scored our relevant recommendations with levels of evidence (from I to V) and strength of recommendation (from A to C) gradings, adapted from those published by the Infectious Disease Society of America (Table 5) [7].

Vascular-related tumors

Angiosarcomas (AS)

AS are aggressive tumors that account for less than 2% of STS. They arise from vascular cells and may develop in previously irradiated tissues. The most common locations are skin (scalp, mostly) and breast but, a small group <20% has primary visceral location (lung, liver, heart, and kidney). Local extension and metastases are frequent. This aggressive behavior determines a short median survival between 15 and 30 months [8]. Worst outcome has been specially associated to radiation-induced cases and non-scalp locations [9]. Imaging shows a high vascular tumor with aggressive features: flow-void serpentine vessels, multicentricity, and rapid growing lesion with peripheral tissue invasion (Table 1).

AS is presented as a multinodular hemorrhagic mass. Microscopically, it varies from well-formed anastomosing vessels (low-grade) to solid epithelioid or spindle cell tumor without clear vasoformation (high-grade). The whole spectrum can be encountered within the same lesion. Vascular markers (CD34, CD31, FLI1 and ERG) can be useful as well as podoplanine [2]. Some AS with epithelioid morphology can expresses epithelial antigens (EMA and cytoqueratin). Post-radiation AS exhibit MYC overexpression [10]. Some molecular pathways have been linked to AS development and clinical behavior like VEGF and angiopoyetin-Tie in addition to RAS/RAf/MEK/Erk, PI3K/AKT/Mtor, p16 pathway among others [11]. Although there are different histological subtypes of AS (Table 2), it has no therapeutic implications.

The choice of treatment depends on the extent of the disease. For localized disease, the gold standard is surgery when possible. Achieving R0 excision is often impossible but efforts must be aimed to achieve a 3 cm margin or an anatomical barrier free of infiltration [2]. Complementary radiotherapy (RT) should be used in case of close margins or R1 surgery (IV, A) [3].

RT is effective for inoperable patients and reduces the risk of postoperative recurrence [12,13]. Low dose could be enough effective following resection of tumor within 3 weeks. Definitive RT has recently been used in unresectable tumors such as AS of the head and neck. Higher doses (>70 Gy) may improve local control and overall survival (OS) when treating with RT alone (IV, C) [14]. Although use of reirradiation in RT-induced AS has been controversial, most of authors agree that it can be used safely as part of combined management for locally recurrent AS, either in adjuvant or as unique treatment (IV, B) [15].

Neoadjuvant chemotherapy in AS has not been studied in prospective randomized trials, but a review retrospective data indicated a potential beneficial role of this approach on improving resection margins, especially in patients with cardiac or cutaneous AS. So, this treatment should be considered, provided the poor results achieved with surgery alone (IV, B) [16].

However, despite an adequate locoregional treatment, more than half of patients will develop metastases [17]. Although adjuvant or neoadjuvant chemotherapy has not been proved yet as beneficial, recent retrospective data are in favor of its use (IV, B) [18].

For locally advanced disease, or metastatic disease, the best option is systemic treatment, ideally within clinical trials. Eventually, local

Table 1
Main Radiological Characteristics Of Each Uncommon Sarcoma Subtypes.

TUMOR SUBTYPE	XR	CT	MRI	US	PET/CT
AS [200]	**Breast AS**-Mammography: solitary ill-defined uncalcified mass in primary AS. Secondary AS can appear as unspecific cutaneous thickening. **Cardiac AS:** Cardiomegaly. **Bone AS**: Destructive lytic lesion with aggressive pattern. Can be multicentric.	**Deep soft-tissue AS** (10%) can arise on extremities, chest wall, retroperitoneum, peritoneum and mediastinum. Rapidly growing palpable mass, irregular with heterogeneous enhancing when large because necrosis. Calcification into the tumor can occur. **Cardiac AS** shows highly vascularized atrial mass, usually with irregular margins. **Liver AS** with hypodense multiple lesions that in DCE-CT shows patchy enhancement in arterial phase with progressive centrifugal CE (reverse hemangioma).	**Primary cutaneous and soft-tissue AS:** intermediate to hypersignal on T1WI (hemorraghe) and heterogenous high signal on T2WI. Void-flow signal from serpentine vessels. **Breast AS** shows unspecific hyposignal T1WI and hypersignal T2WI with rapid CE and washout. **Cardiac AS** use to arise on right atrium as irregular lobulated "cauliflower" shape with flow-void vessels and "sunray" appearance of infiltrated pericardium. **Bone AS** shows aggressive nonspecific pattern with soft tissue extension, peripheral enhancement and sometimes fluid–fluid levels. **Lymphoedema-associated** (Stewart-Treves syndrome) and **post-radiation induced AS**: plaque-like subcutaneous mass in the background of lymphoedema. Low ADC values on Diffusion-MRI.	Unspecific hypoechoic irregular solid mass, solitary or multiple. Well vascularized.	Avid FDG uptake. Useful to detect multifocality.
EHE [201]	Expansive bone radiolucent lesion often with some cortical rim, septa, multifocal, and no periosteal reaction nor calcification. Pure cortical involvement can be seen. Unspecific soft tissue mass.	Expansive radiolucent bone lesion often with cortical disruption, and sometimes soft tissue extension. Homogeneous CE. **Lung lesions** appear as bilateral nodules on perivascular paths. **Liver lesions** are multiple, peripheral, with progressive centripetal CE (hemangioma-like), and "**lollipop sign**".	Bone and soft-tissue lesions show unspecific geographic T1&T2WI pattern. Heterogeneous CE, sometimes with **target sign**. In some cases, intratumoral blood filled cavities show hypointense or dark T2WI signal (deoxyhemoglobin).	Unspecific hypoechoic irregular solid mass, solitary or multiple.	Avid FDG uptake is usually seen. Useful to detect multifocality.
KS [202]	Bone lytic lesion without periosteal reaction of axial location in AIDS and posttransplant KS, and appendicular in classic and endemic KS. Unspecific soft tissue mass.	AIDS-related KS include pulmonary ill-defined nodules in a flame-shaped broncovascular distribution, with ground-glass opacities and pleural effusion; associated almost always to mucocutaneous disease. Enlarging retroperitoneal lymph nodes, liver masses hemangioma-like, and duodenum thickening. Lesions show CE.	Cutaneous forms show a diffuse ill-defined mass with hyposignal on T1WI and heterogeneous hyposignal on T2WI, with patchy areas of hypersignal. Uneven and patchy CE. Edema pattern can be seen at the boundaries of the lesion. Low signal on Diffusion-MRI.	Echogenic edema-like area in the subcutaneous tissue with ill-defined boundaries and prominent arteriovenous vascularization.	No enough data.
IS [76]	Cardiomegaly or without findings.	Hypodense mass with some CE in the pulmonary trunk or left atria. It can be mistaken for pulmonary embolism/thrombus. Infiltration to neighborhood structures.	Unspecific T1/T2WI signal mass into pulmonary trunk or left cavities, with infiltrative pattern and moderate CE. Pericardial effusion.	Cardiac or transesophageal US show a left atrial or pulmonary trunk mass	Avid FDG uptake.
MFS [203]	Unspecific soft tissue-mass or without findings.	Low attenuation mass in the soft tissue area of lower limbs.	Ill-defined infiltrative mass with variable MRI hypersignal on T2WI upon relative amount of myxoid/fibrous tissue, with a global heterogeneous pattern. Nodular and peripheral CE with a "tail sign" often seen, especially when tumors are superficial.	Irregular hypointense and heterogenous mass, with irregular vascularization.	Heterogeneous avid FDG uptake related to myxoid/solid distribution.
AF [204]	Unspecific soft tissue-mass or without findings.	Usually is seen as a deep lobulated well defined isodense mass, with the long axis parallel to the deep fascia. Mild to intense heterogeneous CE.	Unspecific signal on T1 and T2WI. Intermediate or low-grade tumors show areas with very low signal on T1 and T2WI from fibrous tissue. Mild to intense heterogeneous CE mostly peripheral, with a "spoke-wheel" like pattern in some cases. The 'tail-sign' may be present.	Hypointense mass with acoustic shadowing in deep areas because fibrous septa.	Avid FDG uptake in high-grade variants. Mild or poor uptake in the low-grade.
IFS [205]	Unspecific soft tissue-mass or without findings.	Unspecific soft tissue mass iso or slightly hypo attenuated related to muscle. Heterogenous CE.	Heterogeneous ST mass either with well-defined or infiltrative margins. Unspecific T1/T2WI signal pattern, sometimes with hyposignal foci from fibrous tissue, and multiples areas of flow-void signal secondary to vessels. Hemorrhagic component	Hypervascular and heterogenous mass that mimic hemangioma.	No data available.

(*continued on next page*)

treatment could be reassessed, in dependence of response to systemic treatment (IV, C).

Retrospective studies have not demonstrated a benefit of polychemotherapy over monochemotherapy in advanced disease, so that, in this moment the recommended treatment is chemotherapy (CT) with single agents. At present, in advanced disease, available options for first line include doxorubicin (DOX) 75 mg/m^2 every 21 days (IV-B) or weekly paclitaxel (PAC) 80 mg/m^2 weekly, 3 weeks every 28 days (IV-B). There are no significant differences between both treatments, perhaps a small difference in efficacy and toxicity in favor of PAC, mainly, in cutaneous disease and elderly people) [19]. The addition of antiangiogenic agents (bevacizumab) has not demonstrated benefit, so its use is not recommended [20,21].

After DOX and/or PAC failure, gemcitabine (GEM), vinorelbine (VNR) or tyrosine kinasa inhibitors (TKI) can be offered (III, C) [22–24]. In a retrospective study of patients with vascular sarcomas and in phase II and III EORTC trials, of which 77% were AS, responses to pazopanib (PZ), were described in 20% of patients with AS [25]. GEM as a single agent 1000 mg/m^2 days 1, 8 and 15 every 28 days demonstrated significant efficacy in a retrospective study on 25 patients with advanced AS, after progression to previous CT [26]. With limited experience in three patients with AS, after failure to previous CT, the combination of GEM with albumin-bound paclitaxel, has shown clinical benefit in all three [27]. The role of beta-blockers associated or not with metronomic CT [28,29], and/or immunotherapy [30] remains to be clarified.

Epithelioid Haemangioendothelioma (EHE)

Haemangioendotheliomas (HE) are a very heterogeneous group of vascular neoplasms from intermediate to malignant behavior. Six

Table 1 (*continued*)

TUMOR SUBTYPE	XR	CT	MRI	US	PET/CT
			appears on large masses. Heterogeneous CE.		
SFT [206]	Unspecific soft tissue-mass or without findings.	30% in thoracic cavity, 30% in abdominal region, 20% in H&N and 10% in soft-tissues. Cystic changes can be seen in large masses. Variable CE, 35% intense heterogeneous and 65% slight and progressive.	Low T1WI signal intensity and variable T2WI signal (upon collagenous components), but usually hyperintense. Characteristically flow voids sign on T2WI because of tumoral vascular supply. Small tumors show quick and strong CE, and large lesions show more heterogeneous and progressive CE (hypocellular and fibrous areas).	Well defined mass with heterogenous hypoechoic solid pattern that shows rich vascularization.	Avid 18F-FDG uptake is usually seen. Useful to detect multifocality.
DFSP [207]	Unspecific nodular subcutaneous mass or thickening, without calcifications.	Subcutaneous lesions with attenuation values similar to skeletal muscle. Moderate and heterogenous CE is noted.	Unspecific high signal on T2 and STIR, and low or intermediate signal on T1, with either uniform or patchy pattern of CE	Well-marginated, hypoechoic subcutaneous mass, with posterior enhancement and vascularization on doppler-color.	No enough data. Low grade tumors show limited benefit.
LGFMS [208]	Unspecific soft tissue-mass or without findings.	Heterogeneous mass with areas hypodense to skeletal muscle. Intratumoral calcifications can be seen.	Heterogeneous mass at MRI, because distinctive myxoid and fibrous zones disposed in alternate sheets giving it a striated appearance like "cerebriform gyri". Heterogeneous CE, either solid with cerebriform pattern or mixed solid/cystic with enhanced septa. Low ADC values are described.	Mass may have multinodular appearance within it. Some nodules showing a ringed target-like appearance.	Abnormal FDG uptake has been described. But low-grade tumors show limited benefit.
SEF [209]	Unspecific soft tissue-mass and/or bizarre periosteal reaction when next to long bones.	Well-defined mass isodense with muscle. Mild to intense heterogeneous CE. Bone periosteal reaction or destruction can be seen.	Unspecific signal on visceral lesions. Stellate central low signal on T1 and T2WI in large lesions. Mild to intense heterogeneous CE, mostly peripheral and in septa, with a "spoke-wheel" like pattern in some cases.	Hypointense mass with acoustic shadowing in deep areas because fibrous septa.	Variable FDG uptake from low to high. Related to histological grade.
IMT [210]	Soft tissue-mass that may have calcifications, or without findings.	Lobulated heterogenous mass that may have calcifications. In lung use to be peripheral, well defined with lower-lobe predominance. Intense and heterogenous CE with centripetal pattern, that persists on delayed images.	Isointense to muscle on T1WI, and variable T2 signal depending on the fibrous contents. Similar CE pattern as CT.	Unspecific hypoechoic mass in some case reports.	Avid FDG uptake
MIFS [211]	Unspecific soft tissue-mass or without findings.	No CT descriptions from case reports available.	Single lobulated nodule, or multiple ill-defined nodules along the fibrous connective tissue of fat, fascia, or tendon sheaths. Unspecific low signal on T1WI and high signal on T2WI. Variable CE with peripheral nodular pattern, and non-enhancing central areas.	Ovoid hypoechoic solid mass with slight posterior acoustic enhancement, and markedly increased vascularity.	Avid 18F-FDG uptake is usually seen. Useful to detect recurrence after treatment.

AS: Angiosarcomas; EHE: Epithelioid Haemangioendotheliomas; KS: Kaposi Sarcoma; IS: Intimal Sarcoma; MFS: Myxofibrosarcoma; AF: Adult Fibrosarcoma; IFS: Infantile Fibrosarcoma; SFT: Solitary Fibrous Tumor; DFSP: Dermatofibrosarcoma Protuberans; LGFMS: Low Grade Fibromyxoid Sarcoma; SEF: Sclerosing Epithelioid Fibrosarcoma; IMT: Inflammatory Myofibroblastic Tumor; MIFS: Myxoinflammatory Fibroblastic Tumor; XR: X-ray; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; US: Ultrasound; PET: Positron-Emision Tomography

different entities can be included under this rubric of HE (morphological and immunoprofiles are described in Table 2).

EHE is a rare (1/1,000,000) vascular tumor arising commonly in women and involving soft tissues and bones (limbs preferentially) and visceral organs (liver and lung) [31]. 5 year OS is reported between 59 and 100% [2]. On imaging, lesions show unspecific geographic pattern with heterogeneous contrast enhancement (CE), sometimes with target sign. Liver lesions use to be multiple, peripheral, with progressive centripetal CE (Table 1). It is characterized by epithelioid endothelial cells with intracytoplasmic vacuolation (occasionally fragmented

Table 2
Main Pathological and Molecular Characteristics of Vascular and Related-to vessels Sarcomas.

	MAIN MORPHOLOGICAL FEATURES		IMMUNOHISTOCHEMISTRY	MOLECULAR ALTERATIONS
KAPOSI SARCOMA	Stages: - patch: vascular channels - plaque-like: vascular and spindle- cell proliferation - nodular: spindle-cell proliferation Intracitoplasmatic hyaline globules Intravascular protrusion of spindle-cell		**HHV8+ (nuclear)** LANA-1 [212] CD31, D2-40 and CD34 +	11q13 (*FGF4* and *FGF3*) Loss Y chromosome (early phases) Changes in 16, 17, 21, X and Y (during tumor growth) *KRAS, TP53* [2]
HEMANGIOENDOTHELIOMAS	**KHE**	KHE and TA are considered a spectrum from deeper lesions to superficial dermal lesions.	HHV8 and GLUT1 -	
		Nodules of spindled endothelial cells surrounded by dilated crescentic lymphatic vessels	CD31, CD34, ERG +	
		Slit-like lumina with erythrocytes and microthrombi	D2-40 and lymphatic markers +	
	RH	Arborizing blood channels "retiform pattern"	CD34 ++ CD31 and ERG +	
		"Hobnail" endothelial cells	PROX1 +	
		No or very low mitotic ratio	D2-40 -/+	
	PILA	Intraluminal proliferation of hobnail endothelial cells within a lymphatic vascular proliferation	CD31, ERG ++ CD34 +/- D2-40 and lymphatic markers +	
	CHE	Admixture benign and malignant vascular components	CD31, ERG, Fli1 +	
		Subtype: neuroendocrine CHE	CD34, D2-40 + (50%) CAMTA – Neuroendocrine markers (subtype Neuroendocrine CHE)	
	PMHE	Plump spindle or epithelioid cells with vesicular chromatin and eosinophilic cytoplasm "myoid appearance!	**FOSB +**	*FOSB* gene rearrangements
		Loose fascicles or sheets pattern	Pan-CK, Fli1, ERG +	- *SERPINE1-FOSB* [213]
		Multifocal (different tissue planes)	CD31 + 50% CD34 -; INI1 + SMA+ 30%	- *ACTB-FOSB* [214,215] - *WWTR1-FOSB* [216]
	EHE	- Classic EHE: epithelioid endothelial cells with vacuolizated cytoplasmic. Cords or nested pattern in myxochondroid or hyaline stroma	**CAMTA1/TFE3 +**	- *WWTR1-CAMTA1* 90% [32]
		- EHE with *YAP1-TFE3* fusion: solid growth and vascular channel formation	CD34, CD31, D2-40, Fli 1 and ERG +	- *YAP1-TFE3 < 10%* [35]
		- <10%: atypical histological features	CK, SMA +/-	
ANGIOSARCOMAS	**CAS**	Histology varies from vascular infiltrating pattern to solid epithelioid or spindle-cell pattern.	CD34, CD31, Fli 1 and ERG +	*VEGFR 2 and 3* [2] Angiopoyetin-Tie *RAS/RAf/MEK/ Erk, PI3K/AKT/Mtor, P16* [2,10,11]
	ST-AS	Histology varies, but epithelioid morphology is common	**Keratins and EMA +/-** CD34, CD31, Fli 1 and ERG +	*CIC* gene abnormalities [2]
	AS POST-RT	Hemangioma or lymphangioma like appearance with anastomosing patterns	**C-Myc +** CD34, CD31, Fli 1 and ERG +	*C-MYC* amplification [2,10,11]
INTIMAL SARCOMA	Poorly differentiated spindled and pleomorphic cells	**MDM2 + (70%)** SMA, desmina ±	- *MDM2* amplification (100%) [2] - Other alterations (the most frequently reported): * Gains/amplifications of *CDK4, TSPAN31, GLI1 and 4q12* [2] * *HMGA2, DDIT3, KIT, PDGFRA, EGFR, CDKN2A* aberrations [80,81] - Fusions detected by NGS [80] * *PDE4DIP-NOTCH2* * *MRPS30-ARID2*	

KHE: Kaposiform Haemangioendothelioma; TA: Tufted Angioma; RH: Retiform Haemangioendothelioma; PILA: Papillary Intralymphatic Angioendothelioma; CHE: Composite Haemangioendothelioma; PMHE: Pseudomyogenic Hemangioendothelioma; EHE: Epithelioid Hemangioendothelioma; KHE: Kaposiform Haemangioendothelioma; CAS: Cutaneous Angiosarcoma; ST-AS: Soft Tissue Angiosarcoma; AS POST-RT: Angiosarcoma Postradiation; NGS: Next Generation Sequence.

Table 3
Main Pathological and Molecular Characteristics of Fibroblastic sarcomas.

	MAIN MORPHOLOGICAL FEATURES	IMMUNOHISTOCHEMISTRY	MOLECULAR ALTERATIONS
MYXOFIBROSARCOMA	Spectrum from low cellularity and scant atypia to solid hypercellular and pleomorphism Fibrous or myxoid stroma	MSA + SMA + CD34 frequently +	*NF1* mutation or deletion (10%) *RB1* and *CDKN2A/CDKN2B* mutation and *CDK6, CCND1* and *MDM2* amplification [2]
ADULT FIBROSARCOMA	Monomorphic spindle cells (mild-moderate atypia) in long fascicles "Herringbone pattern"	SMA + CD34, Cytokeratin, EMA, S100 and Desmin – Calponina ocasionally	Complex karyotype aberrations *STRN3-NTRK3* fusion [2]
INFANTIL FIBROSARCOMA	Hypercellular mass. Intersecting fascicles of primitive, round, ovoid or spindle cells. Focal herringbone pattern.	Nonspecific: Vimentin + Actin + focal Desmin + focal CD34+ S100+ Pan-TRK+	*ETV6-NTRK3, EML4-NTRK3* gene fusion. *NTRK1* fusion with *TPM3, LMNA, TPR, SQSTM1* and *MIR584F1*. *TFG-MET* fusion *NTRK2, MET* and *BRAF* fusions [2]
SFT	Spindled cells and staghorn vessels. Hyalinized or myxoid stroma.	CD34+ (90-95% of cases) STAT6+ GRIA2+	*NAB2/STAT6* gene fusion *P53* mutation/delections *TERT* mutation [2]
DFSP	Infiltrative diffuse pattern Uniform spindled cells Storiform, whorled or cartwheel growth pattern Low atypia and scant mitosis figures	CD34+ (classical DFSP) CD34 – (fibrosarcomatous DFSP) EMA, SMA +/-.	*COL1A1-PDGFB* *COL6A3-PDGFB* *EMILIN2-PDGFB* [2]
LGFMS	Bland spindle cells arranged in hypocellular and hypercellular areas with short fascicular pattern an variable myxoid and fibrous stroma Arcades of small vessels Giant collagen rosettes (30%)	**MUC4+** EMA+ (80%) SMA+ (30%)	*FUS-CREB3L2* *FUS-CREB3L1* *EWSR1-CREB3L1* *YAP1-KMT2A* *KMT2A-YAP1* *PRRX1-KMT2D*
SEF	Epithelioid fibroblast arranged in cords or nests within a prominent hyalinized stroma	**MUC4+** (80-90%) EMA, SMA + (40%) CK -	*KMT2D-PRRX1* [170,178,179]
INFLAMMATORY MYOFIBROBLASTIC TUMOR	Mixture of fibroblastic-myofibroblastic cells and inflammatory infiltrate. Three patterns: - loosely arranged cells in an oedematous background (granulation tissue-like) - fascicular proliferation with ganglion-like cells - collagen predominance and lower cellularity (scar-like proliferation) Epithelioid IMT: aggressive subtype composed of plump epithelioid cells with neutrophils and myxoid matrix	SMA, MSA, and desmin +/- ALK/ROS1 + (<50%)	***ALK* rearrangements** [182,183,185,217,218] *TPM3-ALK* *TPM4-ALK* *CLTC-ALK* *CARS-ALK* *ATIC-ALK* *RANBP2-ALK* *SEC31L1-ALK* *PPFIBP1-ALK* *DCTN1-ALK* *EML4-ALK* *PRKAR1A-ALK* *LMNA-ALK* *TFG-ALK* *FN1-ALK* ***ROS1* rearrangements** [183,185,218] *YWHAE-ROS1* *TFG–ROS1* *ETV6–NTRK3* ***PDGFRB* rearragments** [182] *NAB2-PDGFRB* ***RET* rearragments** [183]
MIFS	Matrix myxoid or fibrous Bland to bizarre epithelioid cells Mixed inflammatory infiltrate, hemosiderin, Macrophages, Touton- type giant cell and a mononuclear cell background.	Unhelpful (CD68+, CD34 +, SMA +)	*TGFBR3/MGEA5* Loss 3 and 13 chromosomes 3p rearrangements (*VGLL3* gene) *BRAF*-related fusions (1/3) [2,10]

erythrocytes within) and low nuclear grade, organized in cords embedded in a myxo-hyaline stroma. Vascular markers expression is common and epithelial antigens can be also observed. *WWTR1-CAMTA1* fusion is the hallmark of 90% of EHE [32–34]. A subset harboring *YAP1-TFE3* fusion displays higher-grade and a more vasoformative pattern [35,36]. Nuclear expression of CAMTA1 and TFE3 are respectively observed [37].

However, since indolent course is relatively common in most of them, watchful waiting is a reasonable option (IV, B) [38]. Symptomatic cases, or when critical organs are at risk, a complete resection is the treatment of choice, because in more than 75% of cases 5 years survival is expected [39]. There are practically not additional options beyond surgery.

Palliative resection is not recommended due to the aggressiveness of the tumor after resection. Extension to other organs does not contraindicate surgery but it has not impact on survival. For primary liver EHE, liver transplantation is indicated when liver resection is not feasible and the disease is limited to this orgean (IV, B) [40]. Risk factors of unfavorable outcome after liver transplantation are macroscopic vascular invasion, time on the waiting list greater than 120 days and lymph node positive [41] (IV, C).

RT is not standard treatment for EHE, but usually, RT after surgical resection is chosen for localized EHE to control potential residual disease. Adjuvant doses of 50–60 Gy in 25–30 fractions have been employed with good results in local control (V, C) [42,43]. RT may be used in cases where radical resection is not possible, although the benefit is unclear (V, C) [44]. Adjuvant systemic treatment is not indicated outside of clinical trials.

In advanced/metastatic disease watchful waiting is an option, in asymptomatic patients, and without critical organs involved at risk (V, B) [38]. The role of CT is very limited due to short experience and retrospective series with small number of patients. Adjuvant systemic treatment is not indicated outside of clinical trials. For metastatic disease, participation in a clinical trial, if available, is recommended, because DOX and PAC have demonstrated very limited efficacy in this setting (3% ORR, mPFS 5.5 months) (IV, C) [38]. Weekly paclitaxel showed 3% ORR with median PFS of 2.9 months [45]. In two retrospective cohorts PZ showed promising activity in EHE achieving clinical benefit in 6/10 and 3/12 patients with a median PFS of 26.3 and 2.9 months respectively (IV, C) [25,45]. Sorafenib also has been prospectively tested, showing 2 partial responses out of 15 patients, and a 9 months progression Free Survival (PFS) of 30.7% (III, B) [46]. Intriguingly, INF α 2b, resulted in an ORR of 7% and a m-PFS of 8.9 months, [45] and sirolimus, a mTOR inhibitor, showed an ORR of 10.8% with a m-PFS of 13 months [47], the best figures displayed by a systemic treatment.

Recently, a phase II with 42 patients in EHE treated with a MEK-pathway inhibitor (trametinib) has showed an ORR of 7%, with stabilization >6 months in 40% of patients[48].

Kaposi Sarcoma (KS)

KS is an angio-proliferative disease arising mostly in the skin but can also affect mucous, visceral sites and lymph nodes. Herpes human virus 8 is a necessary condition for developing KS, and immunosuppression is a risk factor. KS can be classified in classic, endemic (Sub-Saharan Africans), immune suppression related and AIDS-related. All four clinical types of KS show identical morphological characteristics [2], but with some different clinical and radiological behavior (Table 1). Classical KS rarely presents systemic involvement whereas endemic is more aggressive and skin lesions are rare. Immuno- and AIDS- related KS, both can develop skin and systemic lesions.

KS is more frequent in men (3:1 ratio) and approximately 1600 new cases per year are diagnosed in the European Union [49]. The prognosis of KS is nowadays very good, and 5-year OS varies from 85 to 100% [50].

For diagnosis and staging thorough physical examination and biopsy are mandatory. Gastrointestinal endoscopy, radiologic imaging or bronchoscopy can be performed when it is clinically indicated.

Histologically, KS is a vascular tumor with three stages: patch, plaque-like and nodular (Table 2). It is typical to find cytoplasmic PAS positive pink hyaline globules and spindle-cells protruding into vascular lumina. Immunoprofile and genetics are described in Table 2 but HHV8 nuclear expression is characteristic. The main differential diagnosis includes angiosarcoma and cellular haemangioma [51].

Treatment for KS depends on the extent of the disease. Patients with limited disease can be treated with local therapies such as RT (doses 30–40 Gy get better local control and hypofractionated regimes can also be used), surgical excision, cryotherapy, laser ablation, intralesional or topical therapy (II, C) [52–58].

In advanced /metastatic classic SK disease with and indolent course and asymptomatic patients, watchful waiting can be an option, in case of indolent and asymptomatic classic SK. In AIDS-related KS with no visceral involvement antirretroviral therapy (ART) alone can be effective in almost 50% of patients (II, A) [59]. Around 10% of AIDS-related KS responds initially to ART with disease progression, because of the immune reconstitution inflammatory syndrome (KS-IRIS). In these cases, systemic oncologic treatment must be early initiated, given an increased risk of mortality (IV, A) [60].

When systemic therapy is needed, the preferred first-line is pegylated liposomal doxorubicin (PLD) (I, B) [61]. For AIDS-related KS, PDL is combined with antiretroviral therapy (ART), achieving a response rate of 30–60% [62]. Refractory PLD patients might be treated with PAC achieving an overall response rate (ORR) of approximately 60% [63,64]. PAC has been proved as superior to etoposide in a randomized trial (II, A) [65]. Recently, the FDA has granted approval of pomalidomide, an anti-angiogenic and immunomodulator, for the treatment symptomatic KS patients after the results of a phase I/II study in which the ORR was 73% (60% in AIDS-related KS and 100% in HIV-uninfected patients) [66]. Other active CT agents are VNR [67] or etoposide(II, C)[68].

Experimental therapies with promising results include those targeting angiogenesis such as PZ [69] and bevacizumab [70] as well as mTOR inhibitors [71] PDGFR inhibitors [72] and inmunotherapy [73,74]

Intimal Sarcoma (IS)

IS is an undifferentiated and aggressive rare sarcoma arising in the tunica intima of large vessels of the pulmonary and systemic circulation. Pulmonary IS are more frequent than those of aortic origin and develop more frequently in females (3:1 ratio). Prognosis of IS is dismal with a median OS of 5–9 months for aortic and 8–13 for pulmonary IS [2].

Clinically and radiologically, pulmonary IS can mimic a pulmonary embolism obstructing the vessels. Aortic IS symptoms include back, abdomen and thoracic pain and claudication. Radiological imaging for IS may include echocardiogram, endobronchial ultrasound, CT scan and MRI for staging and planning the surgical procedure [75,76]. CT and PET-TC could help to differentiate IS from pulmonary embolism (Table 1) [77,78]. It is described a high risk of bleeding complications with conventional eco-guided biopsies, so endovascular catheter-guided forceps biopsy could be a safer procedure (IV, B) [79].

Macroscopically, IS appears as an endoluminal polypoid mass attached to the wall that can, potentially, seed tumor emboli to other organs. Histologically, IS is characterized by poorly differentiated spindled and pleomorphic cells. Expression of MDM2 nuclear staining is characteristic and SMA, desmin and focal keratin can be present but endothelial markers are usually negative. Immunophenotype and

SFT: Solitary Fibrous Tumor; DFSP: Dermatofibrosarcoma Protuberans; LGFMS: Low Grade Fibromyxoid Sarcoma; SEF: Sclerosing Epithelioid Fibrosarcoma; MIFS: Myxoinflamatory Fibroblastic Sarcoma

molecular alterations are described in Table 2 [80,81]. Differential diagnosis should be made with angiosarcoma, dedifferentiated liposarcoma (DDLS) and undifferentiated sarcoma.

The mainstay of treatment is surgical excision. However, surgery rarely leads to a cure as the tumor rapidly disseminates to other organs [82,83].

The value of perioperative CT and/or RT treatment has not been established although some authors suggest this multimodality approach could be beneficial [82,84]. Combination CT with anthracyclines plus Ifosfamide (IFO) has been used as perioperative treatment [85].

Regarding RT, in the postoperative setting, high doses (approximately 60 Gy) are needed, although this is unfeasible when treating critical structures. Highly conformal radiation techniques like 4D respiratory breathing technique can be used to reduce undesirable dose to moving structures (IV, C).

Regarding systemic therapies for advanced disease, DOX containing regimens have been reported to yield a 38% response rate, whereas with GEM-based and PZ regimes may achieve a response rate of 8% (V, C) [25,86].

Potential experimental therapies based on molecular alterations include targeted agents as PDGFR, MDM2, CDK4 or NOTCH inhibitors as well anti-EGFR therapies [80].

Table 5
Levels of evidence and Grades of recommendation.

Levels of evidence
I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for a bias) or *meta*-analyses of well-conducted randomised trials without heterogeneity
II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or *meta*-analyses of such trials or of trials with demonstrated heterogeneity
III Prospective cohort studies
IV Retrospective cohort studies or case–control studies
V Studies without control group, case reports, and experts' opinions
Grades of recommendation
A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…), optional

Fibroblastic/myofibroblastics tumors

Myxofibrosarcoma (MFS)

MFS is one of the most commonly STS in elderly patients, with the extremities and girdles being the most frequent sides, equal in men and women. It usually presents as a slow growing, often painless, deeply located mass in 30–60% of patients. Imaging features are summarized in Table 1. MFS is a malignant fibroblastic neoplasm with variable myxoid stroma, cellular pleomorphism and thin-walled curvilinear vessels. Superficial MFS is a multinodular lesion, with gelatinous or fibrous nodules but deep-seated MFS usually is a single large mass with infiltrative margins and necrotic foci [8]. Microscopically the lesion may show a spectrum from low cellularity and scant atypia to solid hypercellular and pleomorphism tumor with high mitotic index, even atypical mitosis and myxoid stroma. All these characteristics define the grade. Often a transition from low-grade to high-grade is encountered in high-grade tumor. The cells can be stellate or plump spindle with eosinophilic cytoplasm. Frequently the tumor has pseudolipoblasts. An epithelioid variant exists too. Immunohistochemistry profile is MSA and /or SMA and frequently CD34 positive [2]. Desmin and histiocyte-specific markers are negative [2]. This tumor has a complex karyotype without a specific rearrangement or mutation. In a 10% of MFS there is NF1 mutation or deletion and there is frequently alteration in P53 signaling [2,8]. *RB1* and *CDKN2A/CDKN2B* mutation and *CDK6, CCND1* and *MDM2* amplification have been described [2]. Some actionable genes in MFS are *ATRX, NRTK1* and *JAK1* [87].

High grade MFS and undifferentiated pleomorphic sarcoma (UPS) are found to be largely transcriptomic indistinguishable across multiple platforms, which may be of interest to include both entities in similar clinical trials [88]. Overall, grade correlates with the rate of metastasis. Grade 2 and 3 tumors develop metastasis to lung, bone, and lymph nodes in 15–35% of patients, compare to none in grade 1 ones [89].

MFS is one of the most frequently "unplanned" excised STS linked to involved surgical margins, especially if a previous multidisciplinary evaluation is not performed. It is not clear the importance of surgical margins, especially, in high grade and deep MFS, but a wide resection margin is required to reduce the incidence of local recurrence (II, A) [90]. For MFS a margin less than 10 mm is associated with a greater risk

Table 4
Proposed And Potential Systemic Treatments In Unresectable/Metastatic Uncommon Sarcoma Subtypes.

SARCOMA SUBTYPE	PREFERRED FIRST LINE	ALTERNATIVE/SUCCESIVE LINE	POTENTIAL FUTURE TREATMENTS
AS	PaclitaxelDoxorrubicin[19]	Gemcitabine [26]Pazopanib [25]	Beta –blokers[28,29]Metronomic CT [29] Inmunotherapy [30]
EHE*	Pazopanib [25,45]		Interferon α 2b [45]Trametinib [48]
KS*	Pegylated doxorrubicin [61,62]	Paclitaxel[63,64]Pomalidomide [66]	Antiangiogenic [69]m-TOR inhibitors [71] Inmunotherapy[73,74]
IS	Anthracycline –based CT[86]	Gemcitabine [25]Pazopanib[25]	MDM2 inhibitorsCDK4 inhibitorsNOTCH inhibitors[80]
MFS	Anthracycline –based CT[95]	Gemcitabine-based CT[96]TrabectedinPazopanib	Immunotherapy[97–99]
AF	Anthracycline –based CT[3]	Gemcitabine-based CT[3]	MMPs-inhibitors[110]Inmunotherapy [111]
IFS	Selective TRK inhibitors (TRK fusión +) [122] Anthracycline –based CT[121]	Pazopanib [126]	Adoptive cell therapy [127]
SFT	Pazopanib [149,150]Anthracycline –based CT (Only in D-SFT) [146]	Sunitinib[151]Temozolamide-bevacizumab[147] Axitinib[152]Regorafenib [153]	IGF1R inhibitorsImmunotherapy [155,156]
DFSP	Imatinib [165]	Sunitinib[167]Pazopanib [168]	
LG-FMS	Wait and see [173]	Pazopanib[174]Trabectedin[172]	
SEF	Wait and see [181]	Anthracyclyne –based CT [181]	
IMT	ALK –inhibitors(in ALK +)[187–189]	Anthracycline –based CTVinca alcaloids + Methotrexate[190]	
MIFS	Wait and see [192,193]		

AS: Angiosarcomas; EHE: Epithelioid Haemangioendotheliomas; KS: Kaposi Sarcoma; IS: Intimal sarcoma; MFS: Myxofibrosarcoma; AFS: Adult Fibrosarcoma; IFS: Infantile fibrosarcoma; SFT: Solitary Fibrous Tumor; D-SFT: dedifferentiated-SFT; DFSP: Dermatofibrosarcoma Protuberans; LG-FMS: Low Grade Fibromyxoid Sarcoma; SEF: Sclerosing Epithelioid Fibrosarcoma; IMT: Inflammatory Myofibroblastic Tumor; MIFS: Myxoinflammatory Fibroblastic Tumor; CT: chemotherapy.

* In some cases watchful waiting is an option as first choice

of local recurrence than other STS (17–54%) but it is important to achieve a good quality of fascial or periostal tissue margin [91,92].

Neoadjuvant/ adjuvant CT with or without RT in high grade MFS with IFO/anthracyclines especially, in younger patients, are not fully investigated in this rare entity, but generally recommended (II, C) [93]. RT may also be applied for recurrent, unresectable lesions or with positive resection margins, to reduce local recurrence and the risk of histologic progression, especially for high-grade MFS [94]. In advanced disease, conventional drugs for STS seem to work, DOX +/- IFO combination as first line [95] (II, B), and in second line combinations with GEM [96], (II, B) trabectedin (TRB) and/or PZ (I,B) are possible options with an uncertain outcomes, because few cases of MFS were included in the pivotal studies. Pembrolizumab in a case report was active in a MFS refractory to RT and conventional cytotoxic CT (V, B) [97]. MAGE-A3 mRNA and protein expression is associated with worse OS, just like UPS, and make this tumor a potential target for immunotherapy [98]. Moreover, presence of "T-cell inflamed" tumor microenvironment of MFS has been reported, supporting even more this hypothesis [99].

Expanding molecular profiling of MFS revealed potentially actionable targets, in a series of 26 patients. Mutational analysis by NGS demonstrated mutations in *TP53, PTEN, FGFR3, CDKN2A,* and *RB1* [100]. These findings support the use of expanded molecular profiling in MFS to detect drug-able targets, encouraging the inclusion of these patients in basket clinical trials. These findings support the use of expanded molecular profiling in MFS to detect drug-able targets, encouraging the inclusion of these patients in basket clinical trials.

Adult Fibrosarcoma (AF)

AF is classified as a highly malignant tumor and account for less than 1% of all adult sarcomas [2,101]. Most often, AF involves the deep soft tissue of extremities, trunk, head, and neck, and occasionally, visceral organs. The peak of incidence is between 30 and 60 years of age [102]. AF is a malignant fibroblastic tumor with variable collagen production, which presents as high-grade tumor in 80% of cases. The 10 year OS is conditioned by the grade of the tumor and ranges from 60% in low-grade to 30% in high-grade tumors. AF presents some characteristic radiological patterns (Table 3) [103,104]. It appears in deep soft tissues as a circumscribed firm and white mass. Hemorrhage and necrosis can be seen. AF are composed of monomorphic spindle cells with mild to moderate atypia, arranged in long fascicles in a herringbone pattern, occasionally storiform. The cells have tapered, darkly staining nuclei with or without nucleoli and scanty cytoplasm. Mitotic activity is always present but variable in intensity [2,105]. The stroma has variable collagen, even with hyalinization or sclerosis. It may express SMA or Calponin but CD34, Cytokeratin, EMA, S100 and Desmin are negative [106,107]. AF shows complex karyotype aberrations and *STRN3-NTRK3* fusions have been described [2,108]. Currently, the main treatment for early stage AF is wide surgical resection margin consisting of the pseudocapsule and a margin of normal tissue around the tumor to minimize the risk for local recurrence (II, A). For King et al. relatively low local recurrence rates can be achievable with planned close margins of less than 1 mm if a sarcoma specialist does the resection [109]. Even though the response rate of AF to RT and CT is very low, they are broadly used as a neoadjuvant and/or adjuvant tumor treatment: RT of 50.4 Gy (conventional fractionated irradiation) and CT with DOX in combination with other chemotherapeutic agents, mainly IFO (II, D). In advanced disease DOX in first line (I, A), TRB (I, B), PZ (I, B) and combinations with GEM in second line, are the alternative for palliation [3] (II, B).

As potential treatments, matrix metalloproteinases inhibitors (MMPI) as TIMP-1-GPI, have been postulated that they could lead to a better chemosensitivity in fibrosarcoma cells [110]. Based on immunogenic features immunotherapy also has been proposed as potential treatment [111].

Infantile Fibrosarcoma (IFS)

IFS is a rare paediatric malignancy, but the most common sarcoma in children under one year [112] (30–50% are present at birth) and cases develop almost exclusively within the first 2 years of life. IFS are usually located in deep soft tissues of upper or lower extremities, and less frequently in trunk or head [113]. It grows rapidly even to huge dimensions, rarely metastasizes and has a high survival rate (80–100%).

Imaging shows a heterogeneous, well-defined, or infiltrative mass, highly vascularize with flow void areas on MRI, which can mimic vascular malformation or hemangioma (Table 1).

Classified by WHO as an intermediate malignancy, IFS is a solitary poorly circumscribed lobulated, hypercellular mass, that sometimes presents infiltrative growth [2]. It is composed of intersecting fascicles of primitive, round, ovoid or spindle cells that form cords, bands, sheets or a focal herringbone pattern. Mitotic activity tends to be prominent. Zonal necrosis, hemorrhage, myxoid changes or dystrophic calcification may be seen. The immunophenotype is nonspecific (Table 3) [2,114].

IFS is characterized by the recurrent translocation t(12;15)(p13;q25) with the transcript *ETV6-NTRK3*, that is also seen in other tumors [8,114,115]. The existence of negative *ETV6-NTRK3* IFS is an open question and other possible diagnosis should be considered. As an example, morphological IFS features are shared with "Primitive myxoid mesenchymal tumor of infancy" (PMMTI), a more aggressive entity [116].

This tumor can be classified based on a postsurgical IRS (International rhabdomyosarcoma Study) Clinical Grouping classification. Briefly, IRS I (primary complete resection), IRS II (microscopic residual or primary complete resection but node involvement), IRS III (macroscopic residual) [117].

The mainstay of treatment for IFS is primary surgery with complete excision after biopsy when microscopically complete, non-mutilating excision is possible [118,119]. For patients with localized IFS with IRS I/II after surgery close surveillance is the recommendation [120]. However, secondary resection R0/R1 could improve outcome in adults, but not in infants with IRS group III [119]. Amputation has been considered as an alternative surgery in patients whose neurovascular structures are invaded by the tumor and cannot be operated with limb-sparing surgery. Any mutilating resection will probably be avoided in the near future, provided the irruption of new effective active systemic treatments as TRK inhibitors (TRKi).

Otherwise, a multidisciplinary approach includes neoadjuvant CT and more-conservative sparing operations [121]. Neoadjuvant CT with a free anthracyclines/alkylating regimen as Vincristine-Actinomycin D is highly effective, so it should be attempted first. More intensive regimens will be used only in the case of no response. The value of adjuvant CT is not clear.

Targeted therapy with selective TRKi has shown durable objective responses in patients with recurrent IFS allowing complete surgical resections. Larotrectinib [122] in a phase I/II trial in patients with advanced/metastatic IFS who harbored an NTRK fusion, all cases with IFS had objective response, allowing in 2 cases a microscopically complete surgical resection (III, A). Other TRKi are being tested in ongoing current clinical trials: selitrectinib [123], entrectinib [124,125]. Other potential treatments are PZ [126] and IMT [127].

Solitary Fibrous Tumor (SFT)

The incidence of SFT is low (1–2 case per million). Most of them are localized at diagnosis (90%), most frequently in abdominal (peritoneum) and thoracic cavities (pleura), meningeal, and limbs. Typically, it may be associated to Doege-Potter paraneoplastic Syndrome (2–4% of cases), characterized by hypoinsulinaemic hypoglycaemia, due to ectopic secretion of a prohormone of insulin-like growth factor 2 (IGF-2) [128]. It tends to disappear after resection [129]. The risk of metastases ranges between 35% and 45% [130]. Mitotic count has shown to be the

most consistent pathologic factor correlated with higher probability of metastases and with a worse OS in series with a long follow-up [131,132]. Imaging shows a large, well-defined, and heterogeneous mass with progressive enhanced pattern, and serpentine vessels on CT-arterial phase or MRI (Table 1).

SFT is a mesenchymal fibroblastic neoplasm of intermediate biological potential, which integrates different clinicopathological subtypes such as typical (T-SFT), malignant (M-SFT) and dedifferentiated (D-SFT). However, last WHO classification did not include SFT in other category different from intermediate behavior. Instead of dividing into benign or malignant, two risk stratification models have been proposed and followed in many clinical studies to select patients [2].

Microscopically it has a patternless pattern, with a differentiation alternating between hypocellular and hypercellular areas with characteristic staghorn vessels. Uniform atypical, spindled cells are in a collagenous stroma that can be hyalinized or have myxoid changes [2]. Perivascular hyalinization is also frequently seen [8]. Traditionally, when mitotic activity was $\geq$ 4/10 HPF with hypercellularity, atypia and/or necrosis, the term M-SFT has been used. A widely used model for metastatic risk incorporates mitotic count, patient age, tumor size and necrosis to classify tumors into low, intermediate and high-risk group [133]. Cases of standard SFT that abruptly change to another high-grade sarcoma area are called D-SFT. Immunohistochemically, SFT shows positivity for CD34 and nuclear STAT6 (see Table 3). This tumor is characterized by an intrachromosomal inversion 12q13.3 with *NAB2-STAT6* gene fusion. Mitotic index >4/10 HPFs and TERT promoter and/or *TP53* mutations have been considered variables that better correlate with aggressiveness [134].

Surgical resection with wide margins is the mainstay treatment in localized disease, with a 10 year-OS ranging from 54% to 89% in surgical series with clear margins [135–137] (II, A). Low recurrence rates can be achieved by close margins that are even less than 1 mm [134,138]. There are some studies that do not find a significant association between the existence of positive margins and local recurrence or the development of metastasis[132,139], in contrast to others that do [140]. Embolization of feeding arteries can allow safe surgical resection or biopsy of these hypervascular tumors [141]. As late relapses are found many years after surgery, 10 years of follow-up would be recommended [132]. It is noteworthy that the metastasis-free interval is significantly longer for T-SFT compared with M-SFT [132]. There is no evidence to support use of Neoadjuvant/Adjuvant CT, as in other STS. In localized disease, RT is recommended after wide excisional surgery, with no significantly higher toxicity than that with surgery alone (II, B) [142]. RT alone can be considered for patients refusing or unsuitable for surgery, and it can attain 30% to 60% control rate [143]. However, it is controversial if RT is therapeutic only for high-grade tumors or also for low-grade tumors [144]. Anecdotal reports of RT efficacy in some cases have been reported [145].

T-SFT presents a more indolent clinical course after metastatic spread than M-SFT, although both subtypes often behave unpredictably. Since the use of risk stratification model is so recent, we can guess that previous malignant categories (M-SFT and D-SFT) now correspond to the high risk WHO subgroup.

In advanced disease, retrospective series with conventional anthracycline-based CT reported RECIST-ORR and 6-months PFS rate of 20 and 20% respectively [146]. Temozolamide-bevacizumab showed and ORR of 21.4%, and a median PFS and OS of 17 and 45 months respectively [147]. Trabectedin has shown some activity with a reported 6-month PFS rate of 72.7% [148].

Recently many TKIs have been prospectively tested in SFT. PZ was explored in two different cohorts. In a phase II trial with M-SFT and D-SFT no response was seen in D-SFT. In M-STF and Choi-ORR of 51% was obtained, with a mPFS of 5.57 m and 24 months-OS of 73%. [149] In T-SFT Choi-ORR of 51% was reported, with a median Choi- PFS of 9.8 months, and median OS of 49.8 months [150].

Other TKIS that have shown relevant activity are sunitinib,axitinib and regorafenib. Sunitinib offered a Choi-ORR of 48%, 12 months-PFS and OS rate of 30% and 66% respectively [151]. Axitinib showed 54% Choi-ORR in M-SFT even after having received previously other TKI, with median Choi-PFS of 14.8 months, and median OS of 25.3 months [152]. In a recent study with 18 patients Regorafenib showed 42.9% Choi-ORR, median PFS 3.68 months, and Median OS of 15.7 months [153]. A combination of nivolumab-sunitinib is being explored. Preliminary results showed 4/6 long-term Choi responses in SFT [154]. Other drugs that are being investigated are the IGF1R inhibitors [155,156].

Based on all these data we recommend TKIs as first choice being PZ the drug with more evidence (II, A).

Dermatofibrosarcoma Protuberans (DFSP)

DFSP is a locally aggressive intermediate fibroblastic neoplasm, which arises in the dermis and involves subcutaneous tissues. Its estimated incidence ranges from 0.8 to 5 cases per million per year with a peak of incidence between 25 and 50 years, although congenital and pediatric cases are also observed. It is usually a low-grade neoplasm characterized by a slow growth and a high tendency to local recurrence, but very low metastatic potential. High-grade fibro-sarcomatous transformation is seen in 10% of cases. The common clinical presentation consists of a slowly progressive indurated cutaneous plaque or nodule, often of violet or brown color. DFSP arise commonly in the trunk and proximal upper limbs, followed by head and neck. MRI and CT could show a contrast-enhanced well-defined subcutaneous nodule (Table 1) [157].

Pathologically, DFSP presents with an infiltrative diffuse pattern of the dermis and subcutis that grows along the fibrous septa and interdigitate with fat lobules. DFSP is composed of uniform spindled cells with plump or elongated wavy nuclei arranged in a storiform, whorled or cartwheel growth pattern. Cytological atypia is minimal and mitotic activity is typically low [2,158]. Conventional DFSP show diffuse expression of CD34. DFSP is characterized in more than 90% of cases by the presence of supernumerary ring chromosomes that contain an occult translocation t(17:22) (q21.3;q13.1) with a fusion gene *COL1A1-PDGFB1*, that places the platelet-derived growth factor-B (PDGFB) under the control of the collagen 1A1 promoter [159]. This fusion gene encodes a protein that is processed to PDGFB ligand, producing stimulation of the PDGFB receptor expressed in tumor cells and driving to tumorigenesis [160].

In order to achieve the recommended goal of clear surgical margins, complete circumferential and peripheral deep margin assessment is recommended. Surgical procedures are mainly Mohs micrographic surgery (MMS), or wide local excision (WLE). Accepted peripheral margin is 2–4 cm, or even larger than 4 cm in more aggressive variants [161]. Traditionally, WLE had been considered the gold standard. However, recently, a *meta*-analysis reported that MMS is more efficacious in the cure rate and recurrence reduction of DFSP and should be recommended as the first line surgical attemp, especially in high recurrence prone zones (I, A) [162].

Postoperative RT may improve disease free survival in these patients [163]. Recently, a *meta*-analysis reported that patients undergoing postoperative RT had a lower recurrence rate compared with those undergoing surgery alone (II, B) [164]. The location and size of tumor, and the placement of surgical scar, determine the size of the radiation field. RT doses are usually 50 Gy/25 fractions to the tumor bed extended by 3–5 cm and with/without 10–16 Gy electron boost to the tumor bed extended by 1 cm for patients with positive or insufficient margins.

Imatinib, a PDGFRB inhibitor, with approved indication, has shown activity in patients with unresectable or metastatic DFSP or those requiring mutilating surgery, in two phase II trials [165]. The combined results of both trials, showing an ORR of 46% and a median PFS of 1.7 years, led to the approval of this agent for the treatment of DFSP (II, A). Imatinib, however, appears to be inactive in DFSP lacking t(17:22)

and in cases of fibro-sarcomatous transformation. Imatinib is also used as neoadjuvant therapy before surgery for large tumors, when surgical resection implies excessive functional impairment (II, B) [166]. Sunitinib has shown activity in imatinib resistant DFSP and can be considered a second-line therapy (IV, B) [167]. Recently PZ has also been explored in a small phase II trial showing a ORR of 30% (II, B) [168]. Patients with advanced fibro-sarcomatous transformation should be treated with standard CT for soft tissue sarcomas. (IV, B) [157].

Low Grade Fibromyxoid Sarcoma (LGFMS)

LGFMS is a very rare sarcoma subtype that arises predominantly in young adults, although it can be found in patients of any age. It is typically located in the extremities and trunk, but sometimes occurs in the head and neck and visceral organs. It is characterized by a long and indolent clinical course. However, higher rates of recurrences and metastases are observed in long-term follow-up. In a series of 31 patients with long follow-up, 21 patients had recurrence after intervals of up to 15 years, and 15 had metastases, mostly in the lungs and pleura, after periods of up to 45 years, with a median of 5 years [169]. Imaging shows a heterogeneous CE mass on MRI, because its myxoid component. On CT scan use to be hypodense to skeletal muscle, sometimes with small calcifications (Table 1).

Histologically, LGFMS is a banal-looking neoplasm consisting of bland spindle cells arranged in a short fascicular "whorling" pattern within an admixture of myxoid and fibrous stroma. Alternation of hypocellular and hypercellular areas with a peculiar vasculature of arcades of small vessels with a surrounding cellular condensation is characteristic [170]. MUC4, a transmembrane glycoprotein involved in cell growth signaling pathways, is typically overexpressed, therefore it is a highly sensitive and specific diagnostic marker [171]. Characteristically, most LGFMS harbor a *FUS-CREB3L2* fusion gene, while rare cases show *FUS-CREB3L1* or *EWSR1-CREB3L1* instead [169]. Some uncommon cases that have undifferentiated round cell morphology could have an aggressive clinical course [169]. Areas indistinguishable from sclerosing epithelioid fibrosarcoma (SEF) can be found (see below).

Treatment of localized LGFMS consisted of surgical resection with clear margins. However, it is commonly non-encapsulated and infiltrating, making complete excision difficult without a wide resection (IV, B). Local recurrence is estimated to occur in up to 64% of cases [169]. Experience with radiotherapy is limited but LGFMS is often considered not very radiosensitive, but it may be used as in other sarcomas (V, C) [172]. In metastatic patients, the activity of systemic chemotherapy seems to be disappointing. Only 2 patients treated with trabectedin achieved long-term stabilizations [172]. In a recent series of 7 patients treated with different types of CT, there were no responses and the mPFS survival was 1.8 months (V, C) [173]. Anecdotal responses have been reported with PZ [174].

Nevertheless, given the indolent course of the disease and the common long intervals between the primary treatment and the relapse, surgery of the metastatic disease, when feasible, could be the best and only option in selected patients.

Sclerosing Epithelioid Fibrosarcoma (SEF)

SEF is a very rare and aggressive soft tissue sarcoma subtype. It is usually seen in adults and elderly patients and affects mainly lower extremities, and less commonly upper extremities, trunk and head and neck. SEF is characterized by a high tendency to relapse and metastasize, with a poor outcome despite its misleading low aggressive histological appearance [175]. On imaging it shares some radiological features with AFS (Table 1). SEF is composed of epithelioid fibroblasts arranged in cords or nests within a prominent hyalinized stroma and shows MUC4 immunoreactivity in 80% of cases [176]. According to immunophenotype and molecular aberrations, a subset of SEF is closely related to LGFMS [177]. Most cases harbor *EWSR1-CREB3L1* fusions, but FUS or PAX5 (instead of EWSR1) and *CREB3L2, CREB3L3* or *CREM* (instead of *CREB3L1*) can be observed [178]. Recently, *YAP1-KMT2A* and *KMT2D-PRRX1* fusions have also been added [177–179].

Due to extreme rarity of this tumor, data about the clinical behavior and the effectiveness of the different treatments is very limited. Surgery, including wide excision with clear resection margins, remains the treatment mainstay (V, B). Inasmuch SEF is uncommon, difficult to diagnose on small biopsies, potentially benign appearing and often located where wide resection is not feasible, it is not surprising that many patients experience persistent disease or local recurrence [175]. Perioperative or postoperative radiotherapy can be used, which can help with local control, although its role is not established (V, C) [180]. It has been suggested that radiotherapy should only be administered in cases where surgery is impossible, and/or where there may be the potential to slow the progression of the disease. The role of systemic treatment remains unclear. A recent series suggests that chemotherapy appears to be of scarce benefit in this disease (IV, C) [181].

Inflammatory Myofibroblastic Tumor (IMT)

IMT is a mesenchymal neoplasm of rarely metastasizing intermediate malignant potential. It occurs in less than 1 for 1 million people. IMT mainly affects children and young adults, although it can be observed all over the adulthood. The most common anatomical locations are the abdominopelvic region, lung, head and neck and retroperitoneum, but it may arise anywhere in the body. IMT is characterized by an indolent clinical course with development of metastases in less than 5% of cases. Approximately, 30% of patients present with an associated inflammatory syndrome characterized with fever, weight loss and malaise, and laboratory alterations such as anemia, thrombocytosis and polyclonal hypergammaglobulinemia. This syndrome resolves when the tumor is excised. Imaging features are highly variables likely related to variations in the cellular and fibrous components of the tumor [2,8] (Table 1).

Pathologically, IMT is composed of fibroblastic-myofibroblastic cells and inflammatory infiltrate. Three histological patterns are described (see Table 3). Approximately in a half of the cases, IMT harbors a fusion involving the anaplastic lymphoma kinase (*ALK*) gene. However, other less frequent rearrangements have also been described: *ROS1, RET*, and *NTRK3* [182,183]. Immunohistochemically, overexpression of *ALK* or *ROS1* correlates with the presence of the respective rearrangement. Pathologic features do not have a clear correlation with clinical behavior, with the exception of the epithelioid IMT aggressive variant associated with *RANBP2-ALK* gene rearrangement [184]. IMT harboring this fusion and also ALK-negative IMT (mostly found in adults) have a higher tendency to develop metastases. To note, IMT should be differentiated from Ig G4-related sclerosing disease and inflammatory pseudotumors [2,185].

The standard treatment for localized cases consists of surgical excision with negative margins. Because of the proximity to vital structures, complete resection might not be always possible (IV, A) [186]. Recurrences are seen in less than a quarter of cases of extrapulmonary IMT and very rarely in those confined to the lung. They can be preceded by constitutional symptoms. In patients with advanced ALK-positive disease, ALK inhibitors have demonstrated activity and are the standard first-line treatment (II, A) [187–189]. Conventional CT also appears to be active in this disease regardless of ALK status. A recent retrospective study showed that treatment with either anthracycline-based regimens or methotrexate plus vinca alkaloids achieved responses in 47% and 53% patients, respectively [190]. Moreover, disease control with these chemotherapy regimens, especially with the second one, seems to be prolonged (IV, B). Other anecdotal responses have been reported with platinum-pemetrexed [191]. Interestingly, responses to CT were observed in ALK-positive cases and no association was observed between outcome and ALK status [190].

Myxoinflammatory Fibroblastic Sarcoma (MIFS)

MIFS is a locally aggressive, rarely metastasizing, slow-growing fibroblastic neoplasm that occurs in middle-age patients. MIFS arises mainly in distal extremities, more frequently in the subcutaneous tissue of hands and feet, and less often intramuscular. MIFS has a high propensity to local recurrence after surgery [192]. Occasionally, lymph nodes and even distant metastases may appear (<1% of cases) [2]. MIFS can mimic several benign and malignant entities on histopathology and imaging. On MRI it has nonspecific features, either suggestive of benign or malignant lesions [193] (Table 1). Pathologically, MIFS shows a prominent mixed inflammatory infiltrate, hemosiderin deposition, macrophages, Touton-type giant cells and a mononuclear cell background with variable degrees of nuclear atypia (bland to bizarre spindle or epithelioid cells with inclusion-like nucleoli (resemble vyrocites or Reed- Sternberg cells) and pseudolipoblasts). Recently, high-grade examples of MIFS and dedifferentiated tumors have been reported. MIFS may feature a t (1;10) (p22–23;q24–25) translocation involving *TGFBR3* and *MGEA5* genes that results in upregulation of the *FGF8* gene [194,195]. Other molecular features are described in Table 3.

Surgical resection with wide margins is the treatment of choice. It can be curative, but recurrences have been reported to occur in ranges from 22 to 67% (IV, A) [196]. Because of the high rate of recurrence after wide local excision, Mohs micrographic surgery could be considered as a reasonable treatment option (V, B) [197]. Amputation may be considered when wide resection fails to preserve a functional lower extremity, or in cases with multiple recurrences (V, B) [198].

RT, preoperative or postoperative, may have a role in the local control of this tumor, especially in those cases with positive margins (IV, B) [199]. Experience with CT is anecdotal, and currently there is no a clear recommendation for its use.

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