Cancer Treatment Reviews 99 (2021) 102260

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Uncommon and peculiar soft tissue sarcomas: Multidisciplinary review and practical recommendations. Spanish Group for Sarcoma research (GEIS –GROUP). Part II

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

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

ARTICLE INFO

Keywords:
Sarcomas
Rare Sarcomas
Uncommon Sarcomas
Alveolar Soft Part Sarcoma
Epithelioid Sarcoma
Clear Cell Sarcoma
Desmoplastic Small Round Cell Tumor
Rhabdoid Tumor
Phyllodes Tumor
Tenosynovial Giant Cell Tumors
Myoepithelial Tumor
Perivascular Epithelioid Cell Neoplasms (PEComas)
Extraskeletal Myxoid Chondrosarcoma
NTRK-fusions Sarcomas

ABSTRACT

Among all Soft Tissue sarcomas there are some subtypes with low incidence and/or peculiar clinical behaviour, that need to be consider separately. Most of them are orphan diseases, whose biological characteristics imply a clearly different diagnostic and therapeutic approach from other more common sarcoma tumors. We present a brief and updated multidiciplinary review, focused on practical issues, aimed at helping clinicians in decision making. In this second part we review these subtypes: Alveolar Soft Part Sarcoma, Epithelioid Sarcoma, Clear Cell Sarcoma, Desmoplastic Small Round Cell Tumor, Rhabdoid Tumor, Phyllodes Tumor, Tenosynovial Giant Cell Tumors, Myoepithelial Tumor, Perivascular Epithelioid Cell Neoplasms (PEComas), Extraskeletal Myxoid Chondrosarcoma, NTRK-fusions Sarcomas. Most of them present their own radiological and histopathological feautures, that are essential to know in order to achieve early diagnosis. In some of them, molecular diagnosis is mandatory, not only in the diagnosis, but also to plan the treatment. On the other hand, and despite the low incidence, a great scientific research effort has been made to achieve new treatment opportunities for these patients even with approved indications. These include new treatments with targeted therapies and immunotherapy, which today represent possible therapeutic options. It is especially important to be attentive to new and potential avenues of research, and to promote the conduct of specific clinical trials for rare sarcomas.

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

https://doi.org/10.1016/j.ctrv.2021.102260
Received 18 April 2021; Received in revised form 3 July 2021; Accepted 6 July 2021
Available online 16 July 2021

Introduction

In this second part of the "Uncommon and peculiar soft tissue sarcomas: multidisciplinary review and practical recommendations" from Spanish Group for Research on Sarcoma (GEIS –group), we will review, in a multidisciplinary way, another group of uncommon sarcoma subtypes, with the same objectives and rules we set up in the first part. We will analyze here the following subtypes: alveolar soft part sarcoma, epithelioid sarcoma, clear cell sarcoma, desmoplastic small round cell tumor, rhabdoid tumor, phyllodes tumor, tenosynovial giant cell tumors, myoepithelial tumor, perivascular epithelioid cell neoplasms (PEComas), extraskeletal myxoid chondrosarcoma, and a new emerging group of NTRK-rearranged sarcomas.

We will highlight the most relevantsubtypes, highlighting the more relevant questions with clinical implications. Provided our multidisciplinary approach, to facilitate understanding, we show separately differential radiological (Table 1) and pathological (Table 2) characteristics of each sarcoma subtype,as well as a summary table of systemic treatment (Table 3).

As we did in part I, levels of evidence and strength of recommendation gradings are those adapted from those published by the Infectious Disease Society of America (Table 4) [1].

Alveolar soft part Sarcoma (ASPS)

ASPS involve about 1% of all STS, and usually occur in adolescents and young adults, with a male/female ratio of 1:2. ASPS generally appear in skeletal muscles of lower limbs. The natural history of this tumor is characterized by a relative indolent behavior, but metastatic disease is a common event, predominantly to the lungs [2]. Patients with ASPS can develop metastasis in unusual sites, as brain in up to 19% metastatic patients. Local recurrence occurs in 20–30% of cases, and prognosis depends mainly on initial presentation (localized versus metastatic), tumor size and age [3]. 56% of 5 years Overal survival rate has been reported in these tumors [4]. Radiological features include a lobulated well-defined mass, highly vascularized, with intense contrast enhancement (CE) (Table 1).

The most distinctive microscopic feature is the organoid or nesting growth pattern, frequently discohesive with focal central necrosis, giving the so-called pseudoalveolar appearance. Cells are uniform in size and shape. In most cases intracytoplasmic PAS diastase-resistant crystals may be observed but in variable amount. Strong nuclear staining for TFE3 (C-terminus antibody) and diffuse cathepsin K is characteristic. Epithelial and melanocytic markers are consistently negative [2,4].

ASPS is defined by a specific translocation t(X;17) (p11;q25) that originates the gen fusion ASPSCR1-TFE3 [4,5]. Partners other than ASPSCR1 have been recently described [6]. RT-PCR or FISH for TFE3-rearrangements (more sensitive than immunohistochemical stain) are robust methods for molecular diagnosis purposes [2,4-6]. Differential diagnosis includes renal cell carcinoma and PEComas due to the morphology and molecular overlap.

Several signaling pathways are involved in tumorigenesis, and potentially useful as therapeutic targets. One is overexpression of the MET tyrosine receptor kinase, induced by the ASPSCR1-TFE3 fusion protein. This leads to intracellular activation of the promitotic growth kinases AKT and MEK1/2. Other targets include the VEGF tyrosine kinase receptor and its ligand, as well as tumor cell receptor tyrosine kinases [7]. It has been proposed that ASPS translocation may engender immunogenicity, leading to explore the activity of immuno check-points inhibitors (ICIs) in these tumors [8].

Currently, the main local treatment for ASPS is wide surgical resection, including the pseudocapsule and a cuff of normal tissue around the tumor to minimize the risk for local recurrence [9,10]. Resection of metastases may play a role of metastatic disease, even when located outside the chest [11].

There is a paucity of data regarding the use of radiation therapy (RT). In one small retrospective series with 11 patients with localized disease, adjuvant radiation seems to offer favorable results (IV, B) [12].

ASPS are not sensitive to conventional cytotoxic chemotherapy (CT). Anthracycline-based treatments have shown disappointing results with overall response rate (ORR) lower than 10% (IV, C) [13,14]. Similarly, trabectedin has shown limited activity in a small retrospective study [15].

In the absence of clinical trial options, there is enough evidence to support the use of antiangiogenic tirosin-kinasa inhibitors (TKIs) as first choice (II, B). Cediranib is a VEGFR 1,2,3 inhibitor, that has shown in a recent randomized phase II trial significant higher ORR than placebo (21.4 vs 0%) [16]. Sunitinib (PDGFRB, VEGFR2 and RET inhibitor) has shown in retrospective studies ORR between 28 and 55%, and median progresion free survival (mPFS) between 17 and 41 months [17–19]. Pazopanib (PZ) (VEFGR 1,2,3 inhibitor) has presented activity with 35% ORR, and mPFS of 13 months [20]. Anlotinib (VEGFR, FDGFR, PDGFR and KIT inhibitor) is also a treatment option with an ORR of 46% and mPFS of 21 months described in a phase II trial [21].

Interestingly, combination of antiangiogenic agents and immunotherapy has recently been tested with very promising results in 2 phase II trials. Axitinib plus pembrolizumab has shown activity in a cohort of 12 patients with ASPS, with 7 of them showing partial response with a 6-month PFS of 38.1% [22]. Nivolumab plus sunitinib also has shown activity a partial response in 2 of 3 patients with ASPS included in a phase II trial [23]. Inmunotherapy as monotherapy has been showed as useful in recent works. Recently, in a phase II trial with pembrolizumab as single agent has been reported a 50% of patients achieving partial responses and a median PFS of 7.5 months in 14 patients with ASPS [24]. An ORR of 37.2% and 37% have also been described in both phase II trials with 44 and 37 patients respectively treated with atezolizumab [25] or geptanolimab (GB226), anti PD-1 antibody [26]. A retrospective review of data from a world-wide registry with different Inmuno checkpoint inhibitors shows an ORR of 40.4% [27].

Currently, ongoing clinical trials in ASPS are focused mainly on TKIs and ICIs, and their combinations [28–30]. AKT pathway and microphthalmia transcription factor (MiT) are also being explored in this disease [31,32].

Epithelioid Sarcoma (ES)

ES is an ultra-rare sarcoma, with less than 0.2 [33] and 0.5 new cases/million inhabitants/year [34] in Europe and the US, respectively.

ES has a high rate of loco-regional and distant relapse. Lymph node involvement is very characteristic of this entity and has been described in 29–48% of cases [34–36]. 5-year specific overall survival (OS) was 68% in the Surveillance, Epidemiology and End Results (SEER series), and age <16 years, negative node involvement, localized stage at diagnosis and resectability of primary disease were predictive factors of survival [34]. Radiological features include a lobular infiltrative mass with frequent central necrosis and intense CE. Attention must be paid to fascial spread (Table 1). Proportion of necrosis has been related to metastasis at diagnosis.

ES has two main variants: classical and proximal [4,37]. Classical type is nodular patterned and constituited by a mixture of moderately atypical spindle and eosinophilic epithelioid cells with variable nuclear atypia and low mitotic activity. These nodules may show central granuloma-like necrosis [37], dystrophic calcification and metaplastic bone formation [4]. Proximal type shows a multinodular pattern with predominance of large epithelioid cells with severe atypia, prominent nucleoli, and frequent mitosis. Rhabdoid features and necrosis can be present. Some cases show hybrid features [4]. Immunohistochemically both show EMA, cytokeratins (keratins 8 and 19 but keratin 5/6 are typically negative) and vimentin positivity. CD34 is observed in approximately half of the cases. ERG can be positive. Loss of nuclear expression of SMARCB1 (INI1) is presented in both types (90% of ES) [4,38]. Genetically rearrangement of 22q11 that included inactivation

Table 1
Main Radiological Characteristics of Each Uncommon Sarcoma Subtypes.

Tumor	XR	CT	MRI	US	PET
ASPS [190]	Unspecific soft tissue-mass, sometimes with small calcifications.	Well-defined lobulated contours with infiltrative pattern in poles, where large vessels are present. Homogeneous and slightly reticular CE pattern. Central necrosis and calcifications can be seen.	Mass slightly hyperintense to muscle on T1WI and hyperintense on T2WI. Many serpiginous flow void vessels (>5) are present at both poles, periphery and center of the tumor. Homogeneous and slightly reticular CE, sometimes peripheral if central necrosis.	Non-specific slightly lobulated hypoechoic mass, sometimes with a punctate hyperechoic background. Great vascularization on doppler-US, especially on poles, that show low resistive index (RI).	Intense 18FDG-uptake with $SUV_{max} > 6$.
ES [191]	Unspecific soft tissue-mass or without findings.	Isodense or slightly hypodense lobular mass with infiltrative margins. Heterogeneous CE. Nodal involvement is often seen.	Lobulated infiltrative mass located either deeply, or cutaneous ulcer-like. Unspecific heterogeneous signal on T1WI and T2WI reflecting variable degree of necrosis and hemorrhage. Surrounding edema is common, as well as fascial and tendon spread. Regional lymph nodes must be included in staging.	Hypoechoic myxoid pattern with well-defined or mild infiltrative margins. Well vascularized on doppler-US, but necrotic areas.	Avid 18FDG-uptake with heterogeneous or irregular ring pattern. Recommended for nodal staging.
CCS [192]	Unspecific soft tissue-mass, that can erode bone without periosteal reaction; or without findings.	Isodense well-defined mass or slightly heterogeneous with hyperdense areas, and mild CE. It can erode adjacent bones up 10%. Calcifications are rather rare.	Well defined or lobulated lesion that use to be located on deep fascia, tendons or aponeurosis, with slow growing rate. It is isointense or mild hyperintense on T1WI (melanin) and heterogeneously hyperintense on T2WI, with strong CE. Nodal spread is common.	Non-specific heterogeneous hypoechoic mass, in same locations as described in MRI, with mild vascularization on doppler-US.	Mild or avid heterogeneous 18FDG-uptake. Recommended for nodal staging.
DSRCS [193]	Abdominal mass effect with fixed or displaced bowel loops.	Bulky omental disease with multiple lesions, with a dominant one in most cases. Cystic changes in large masses with heterogeneous enhancement after contrast. Calcifications in 20% and ascites in 30%. Lymph node involvement can be seen up 50%.	Because it uses to be an abdominal tumor, MRI is the next alternative to CT. It has an hypointense T1WI and hyperintense T2WI pattern, with heterogeneous enhancement after gadolinium.	Lobulated peritoneal masses with variable echogenicity. Dystrophic intratumoral calcification in 20%. Thickened peritoneum. Ascites. Serosal hepatic metastases are often seen.	Intensely avid 18FDG-uptake with $SUV_{max} > 6$. Recommended for nodal and metastatic staging.
RT [194]	Unspecific soft tissue-mass. Extra-pleural features on Chest-XR.	Large hypodense masses with heterogeneous CE. RTK use to have subcapsular hematoma and renal vein invasion. Calcifications are possible.	Lobulated mass with unspecific features (hypointense T1WI / heterogeneous hyperintensity on T2WI). Heterogeneous CE with hypovascular areas of necrosis.	Solid lobulated heterogeneous mass, with moderate vascularization. Acoustic shadows when calcifications.	Intense 18FDG-uptake with $SUV_{max} > 6$. Staging and response evaluation.
PT [195]	High-density round and well defined noncalcified mass on mammography. Irregular or indistinct margins can be seen, as well as a lucent halo sign from fat. It may mimic a fibroadenoma.	Not useful in local imaging.	Ovoid mass with sharp margins. Isointense on T1WI and heterogeneous hyperintensity on T2-WI/STIR. Heterogeneous internal CE. Neither Diffusion-MRI, nor DCE-MRI patterns are helpful to distinguish PT from fibroadenoma.	Oval homogeneous hypoechoic tumor with parallel orientation of echoes (also described in fibroadenomas). Internal fluid filled spaces and heavy posterior acoustic enhancement help to differentiate PT from fibroadenoma.	Only casual or metastasis reports. Mild or avid heterogeneous 18FDG-uptake.
TGCT [196]	Soft tissue mass that may show bone erosion with smooth margins (slow growing). Joint effusion.	Soft tissue mass hypo/isodense to muscle, next to tendons or joints. Synovial thickening and/or tenosynovial/joint effusion. Bone erosion with low aggressiveness pattern.	Either localized, well defined mass, and diffuse form are described. It shows low signal on T1WI and heterogeneous slightly hyperintense T2WI signal. On gradient sequences it shows patchy hypointense areas secondary to hemosiderin deposits. Strong and homogeneous CE. Slow values of ADC on Diffusion-MRI.	Nodular hypoechoic masses around, or next to tendon sheaths and/or joints. Well vascularized on doppler-color.	Homogeneous avid 18FDG-uptake in located forms and more heterogeneous avid uptake in diffuse form.
MT [197]	Unspecific soft tissue-mass, that can infiltrate cortical bone; or without findings.	Homogeneously isodense to muscle mass with mild CE. Bone erosion may be seen.	Well-defined lobular or slightly infiltrative soft-tissue mass. Heterogeneous T1WI signal	Well-defined heterogeneous mass. Irregular hypoechoic	Most cases with avid 18FDG-uptake.

(*continued on next page*)

Table 1 (*continued*)

Tumor	XR	CT	MRI	US	PET
		Most descriptions in head&neck locations.	with occasional bleeding areas; heterogeneous T2WI/STIR signal with peripheral hyperintensity. Heterogeneous CE.	areas from necrosis or myxoid changes may be seen.	
PEComas [198]	Abdominal mass effect with displaced bowel loops if large enough.	Retroperitoneal and genitourinary predilection. Large and well-defined mass hypodense to muscle, with significant CE, mostly heterogeneous. Fat density foci when associated to AML. Hepatic PEComa may mimic focal nodular hyperplasia.	Unspecific low signal on T1WI and high signal on T2WI. Areas of fat hypersignal on T1WI if secondary to AML. Renal location may have cystic appearance with thick septa and hemorrhagic changes. Intense heterogeneous CE.	Well-defined heterogeneous echogenic mass, with hypoechoic areas if necrosis. Mild vascularization on Doppler-US.	Moderate-intensely avid 18FDG-uptake. Can help to differentiate malignant from the benign counterpart (low or absent 18FDG uptake).
EMC [199]	Unspecific soft tissue-mass, that can infiltrate cortical bone; or without findings.	Lobulated hypodense mass. Heterogeneous mild CE, mostly peripheral and septa, sometimes nodular.	Lobulated well-defined mass with myxoid pattern: iso/ hypointense to muscle on T1WI and high hyperintense on T2WI, with hypointense T2 internal septa. Peripheral and clearly septal CE, very heterogeneous, sometimes with "spoke on wheel" pattern.	Very hypoechoic mass with lobulated well-defined margins. Septa can appear slightly echogenic. Low to mild vascularization on doppler-US.	Variable 18FDG-uptake related to myxoid (low uptake) / cellular (high uptake) ratio.

ASTS: Alveolar soft tissue sarcoma; ES: Epithelioid Sarcoma; CCS: Clear Cell Sarcoma; DSRCS: Desmoplatic Small Round Cell Sarcoma; RT: Rhabdoid Tumors; PT: Phyllodes tumor; TGCT: Tenosynovial Giant Cell Sarcoma; MT: Myoepithelial Tumors; PEComas: Perivascular Epithelioid Cell Neoplasms; EMC: Exytrasqueletal Myxoid Chondrosarcomas; XR: X-ray; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; US: Ultrasound; PET: Positron-Emision Tomography; CE: contrast enhancement.

of SMARCB1 because of mutation or deletions, as well as 8q gains have been implicated.

ES exhibits aggressive local invasiveness. Wide surgical resection is the mainstay of treatment. Microscopically free margins are the most important prognostic factor for recurrence [39]. Because distal sites are often affected, amputation has to be considered as an option in selected patients, especially after the first local disease relapse [40]. Sentinel lymph node biopsy/regional lymphadenectomy are not routinely recommended [41]. Perioperative RT is indicated for improving local control in primary and recurrent cases [42], with favorable results in local control compared to amputation, without impact in OS (IV, A) [43]. CT is generally not recommended in the localized setting due to lack of evidence on its activity.

Anthracycline-based regimens have showen activity in the advanced setting, with ORR of 22% and mPFS of 6 months (IV, A) [33]. Gemcitabine-based (ORR of 27%, mPFS of 4 months) and PZ (mPFS of 3 months) could be options for second and further lines (IV, B) [44]. Tazemetostat (EZH2 inhibitor) has recently been approved by the FDA for advanced ES [45]. A phase II trial showed ORR of 15% with some long-lasting responses and median OS of 18 months and should be offered as second line if available (III, A) [46].

Recently, 20% of responses have been reported with pembrolizumab. But the role of immunotherapy is still under research [47–49].

Clear cell sarcoMA (CCS)

CCS is another ultra-rare sarcoma, with an estimated incidence of 0.06–0.14 new cases/million inhabitants/year in US [50].

CCS is an aggressive entity, usually presenting as deep-soft tissue masses in the extremities (with predominance in low limbs) [4,51]. Lymph node and/or regional involvement is frequent, being present in 16–33% of cases in the biggest series [50,52–54]. Brain metastasis can be developed, and central nervous system image can be considered for staging [55]. The estimated 5-year disease-specific survival is 62–67% [56]. The presence of necrosis, tumor size, stage at diagnosis, regional lymph node involvement and local recurrence have been described as prognostic factors [50,51,57]. They are well-defined or lobulated lesions that use to be located on deep fascia, tendons or aponeurosis, with slow growing. Main MRI features include slightly hyperintense T1WI (melanin), and heterogeneously hyperintense T2WI signal (Table 1).

This entity frequently shows melanocytic differentiation, and the main differential diagnosis is made with malignant melanoma [4]. It grows in a nested pattern separated by collagenous bands. The cells present epithelioid, and less frequently, spindle-cell morphology, with clear or pale eosinophilic cytoplasm. Multinucleate giant cells are often present. Gastrointestinal CCS sometimes has more eosinophilic cytoplasm and giant cells are infrequent. Immunohistochemically, CCS shows positivity for S100, HMB45 and MITF. The genetic hallmark of CCS is a reciprocal translocation t(12;22) (q13;q12) with EWSR1-ATF1 fusion in $>$ 90% of cases. The most common is exon 8 of EWSR1 fused in-frame with ATF1 codon 65. In a 6% of cases the translocation is t(2;22) (q32;q12) with EWSR1- CREB1 fusion [4], more specific of gastrointestinal CCS but it can also be present in some soft-tissue CCS. In cases where EWSR1-rearrangement is detected without partner, CREM should be considered [58].

Treatment for early-stage CCS is wide surgical resection with negative margins (IV, A) [59]. Routine use of sentinel node biopsy is not recommended, however it is suggested in the presence of suspicious lymph nodes during staging, although impact on OS has not been demonstrated (IV, B) [60]. Isolated limb perfusion (ILP) with high-dose tumor necrosis factor-alpha (TNF-a) and melphalan could be considered for local control in locally advanced unresectable tumors or in patients with concomitant metastatic disease (IV, A), after discussion in multidisciplinary tumor board [61,62]. The benefit from ILP seems lower in patients with in-transit metastasis (IV, C) [63]. There is no specific data about the role of adjuvant RT in this subtype; so general recommendations for sarcomas should be applied (IV, C). There is no evidence of any role of adjuvant CT in this subtype, so it is not recommended (IV, C).

Local treatment of metastatic disease can be considered following general principles for STS. CCS is considered as a not very responsive entity to classic cytotoxic agents. In a series of 11 patients treated with anthracycline-based regimens 2 short-lasting responses were described) (IV, B) [63]. Antiangiogenics such as anlotinib (III, A) [21], PZ (III, B) [65] or sunitinib (V, A) [66] have been reported as active in this entity and could be offered as upfront line if available. Crizotinib, a MET inhibitor, was evaluated in a multicohort phase II trial, showing moderate

Table 2
Main pathological and molecular characteristics.

	Main morphological features	Immunohistochemistry	Molecular alterations
ASPS	Organoid or nesting growth pattern, frequently discohesive with focal central necrosis, giving the so-called pseudoalveolar appearance.	– TFE3+ – Cathepsin K+	– *ASPSCR1-TFE3* [4] – *HNRNPH3-TFE3* [6] – *DVL2-TFE3* [6] – *PRCC-TFE3* [6]
ES	– Classical type: atypical spindle and eosinophilic epithelioid cells. Central granuloma-like necrosis – Proximal type: Large epitheloid cells with severe atypia, rabdoid features. Focal necrosis.	– EMA+ – CKs (CK8 and 19 + but CK 5/6-) – CD34+(50%) – Loss of expression of INI1 (90%)	Inactivation of *SMARCB1* [4] 8q gains [4]
CCS	Epithelioid and spindle-cell, with clear or pale eosinophilic cytoplasm. Multinucleate giant cells	S100, HMB45 and MITF+	– *EWSR1- ATF1* (90%) [4] – *EWSR1- CREB1* [4] – *CREM* [58]
DSRCS	Uniform small round cells arranged in nests within a prominent desmoplastic stroma	Co-expression: – epithelial (CK and EMA) – mesenchymal (vimentin) – myogenic (desmin, 75% dot-like pattern) – neural markers (NSE and CD56). – WT1 + (C-terminal) – CD99+/-	– *EWRS1-WT1* [4]
ERT	Rhabdoid cells" organized in sheets or solid discohesive trabecular pattern.	– Co-expression of vimentin and epithelial markers (CKAE1AE3, EMA +) – INI1 -	– Loss of *SMARCB1* (*INI1/SNF5/BAF47*) [94] – Mutation and/or loss of *SMARCA4* (*BRG1*) [97]
PT	Benign, borderline or malignant based on [4]: – presence of stromal cellular atypia, – mitotic activity, – well-defined vs. infiltrative margins – presence of stromal overgrowth.	– CD34 + (majority of PT, decrease in malignant PT) – CD117 + (10% OF PT) – p53+ (more common in malignant PT) – β- catenin + (nuclear, more often in benign PT, not useful for diagnosis) – P63, p40 and CK + focal in malignant PT	*MED12, RARA, TERT, FLNA, SETD2* and *KMT2D* mutations *PIK3CA, RB1, TP53, PTEN, BRAF and EGFR* promote progression to borderline and malignant PT. [4,107,111,112]
TGCT	Variable proportions of mononuclear cells, osteoclast-like giant cells, foamy macrophages and siderophages within a collagenized stroma Subclassification: – Site: intra-articular extra-articular – Growth pattern and behavior: localized type * diffuse type	– large mononuclear cells: clusterin, D2-40 and desmin (50%) + – small histyocites: CD68, CD163, CD45 +	– *COL6A3-CSF1* [126,128,200] – *CSF1-S100A10* [129]
MT	Reticular, trabecular, nested, or solid pattern with myxoid or hyalinized stroma. Tumor cells are epithelioid, spindled or plasmocytoid.Myoepithelial carcinoma shows severe nuclear atypia, with high mitotic rate and necrosis.	– Broad-spectrum keratins, S100 and calponin. – They can show EMA, GFAP, SMA and p63. – Loss of expression of INI1 – SOX10 (in myoepithelial tumor, not in myoepithelial carcinoma)	– *EWSR1-POU5F1, EWSR1-PBX1, EWSR1-PBX3, WRSR1-ATF1, EWSR1-ZNF444*, EWSR1*-VGLL1* – *PLAG1* rearrangement (mixed tumor) – *FUS* and *SRF-E2F1* rearrangements [4,37,144,145]
PEComa family	AML: benign neoplasm composed of thick-walled blood vessels, smooth muscle cells and adipose tissue. LAM: pulmonary interstitial infiltrate of myoid cells associated with dilated lymphatics and cystic changes CCST: clear epithelioid cells, with a nested pattern and prominent vasculature PEComas: admixture of uniform epithelioid and spindled cells arranged in radial fashion around blood vessels	– Co-expression of melanocytic (HMB45, S100) and muscle markers (SMA, desmin) – TFE3+ (subset)	– Loss of function mutation in TSC*1* or *TSC2* genes. – *TFE3* gene rearrangements [155]
EMC	Multilobular architecture Uniform cells with reticular pattern within chondromyxoid stroma	– Vimentin + – S100, EMA, CD117, synaptophysin and NSE ± – INI1 – (in cases with rabdoide features)	– *EWSR1-NR4A3* [166,167] – *RBP56-NR4A3* [166] – *TAF15-NR4A3* [166,167] – *TFG-NR4A3* [166,167] – *TCF12-NR4A3* [166,167] – *FUS-NR4A3* [166,168]

(*continued on next page*)

Table 2 (*continued*)

	Main morphological features	Immunohistochemistry	Molecular alterations
NTRK-rearranged Sarcomas	Morphological spectrum with prominent bundles of collagen and perivascular keloid-like hyalinization – low grade monomorphic spindled neoplasm (so called LPF-NT) – highly cellular proliferation (hemangiopericytoma-like or MPNST-like)	– S100 +/- – CD34 +/- – anti-pan-TRK + cytoplasmic or nuclear – H3K27me3 retained	NTRK-rearrangements [178]

ASPS: Alveolar Soft Part Sarcoma; ES: Epithelioid Sarcoma; CCS: Clear Cell Sarcoma; DSRCT: Desmoplastic Small Round Cell Tumor; ERT: Extrarenal Rhabdoid Tumor; PT: Phyllodes Tumor; TGCT: Tenosynovial Giant Cell Tumors; MT: Myoepithelial Tumor; EMC: Extraskeletal Myxoid Chondrosarcoma; LPF-NT: Lipofibromatosis-Like Neural Tumor; MPNST: Malignant Peripheral Nerve Sheat Tumor; CK: cytokeratin.

activity in CSS (III, B) [67].

Desmoplastic small round cell tumor (DSRCT)

DSRCT is a rare and aggressive tumor that predominantly occurs in male adolescents, and young adults, with an estimated incidence between 0.2 and 0.5 cases per million [68,69]. It typically presents with multiple intra-abdominal tumors, involving the pelvis, retroperitoneum, omentum and mesentery [68–72]. Prognosis for this disease is poor, with a reported median survival ranging from 17 to 25 months and 3 and 5-year survival rates from 44% to 15–25% respectively [73,74]. Computer tomography is the preferred imaging study, frequently showing a bulky omental disease with heterogeneous CE, that may have calcifications (Table 1).

Histologically, it is characterized by monotonous small round cells arranged in nests, very often with peripheral palisading and central necrosis, surrounded by a prominent stromal desmoplasia. These poorly differentiated cells have small hyperchromatic nuclei, scant cytoplasm and indistinct cytoplasmic borders. Nuclear molding or glandular or rosette patterns can be found. A subset of tumors may present intracytoplasmic eosinophilic rhabdoid inclusions or larger cells. Mitosis and apoptosis are frequent [4,72,75]. The typical immunohistochemical profile is characterized by co-expression of epithelial (keratin and EMA), muscular (desmin), and neural markers (NSE and CD56) as well as WT1 (C-terminus antibody). Recurrent translocation of EWRS1-WT1 is seen in virtually all cases [4,71].

DSRCT often presents as advanced abdominal disease with nodal and synchronous liver involvement. Lung, splenic and bone metastases are also possible [69,72].

The standard of care for patients presenting without extra-abdominal metastases is multimodal therapy with multiagent intensive CT and aggressive debulking surgery (IV, B) [68,71,74,77].

The most effective chemotherapeutic regimen still is debated. Most combinations are based on alkylating agents, similar to those in Ewing sarcomas and included combinations of doxorubicin, vincristine, dactinomycin, cyclophosphamide, ifosfamide, and etoposide (IV,A) [69–71,77]. Metronomic therapy with cyclophosphamide/vinblastine correlated with prolonged time to relapse in one series [78]. Experiences with High dose CT Autologous Stem Cell Transplant has been explored especially in patients in first complete remission, with no clear conclusive results, so it is not recommended as standard [79].

The value of consolidative whole abdomen RT at dose of 30 Gy, with or without a focal boost has been explored in several retrospective series. Its added value in terms of survival is unclear, and it has been associated to significant hematological and gastrointestinal toxicities [79,81]. Other groups have reported disease-free survival of less than 1 year with mostly, intraperitoneal relapses (V, C) [81,82].

Once cytoreduction is completed, the role of hyperthermic peritoneal perfusion with CT (HIPEC) using cisplatin, remains unclear (V, C) [68,71,74,77].

Topoisomerase-containing regimens such as temozolomide/irinotecan or cyclophosphamide/topotecan, high-dose ifosfamide, and gemcitabine/docetaxel, are common second- and third-line regimens in recurrent DSRCT (V, B) [70–74].

Trabectedin has demonstrated clinical activity in some retrospective reports [83,84]. There are data on clinical activity with

Table 3
Proposed and potential systemic treatments in unresectable/metastatic uncommon sarcoma subtypes.

Sarcoma subtype	Preferred first line	Alternative/ Successive Line	Potential future treatments
ASTS	Pazopanib [20] Cediranib [16]	Sunitinib [17–19]	Immunotherapy [22–28]
ES	Anthacycline-based CT [33] Tazemetostat [45,46]	Gemcitabine [44] Pazopanib [44]	Immunotherapy [47–49]
CCS	Antiangiogenic TKIs [21,65,66]	CT [64]	MET-inhibitors Immunotherapy [67]
DSRCS	Poli-CT (similar to Ewing-sarcoma) [69–71,77]	Metronomic –CT [78] Antiangiogenic [70,72,85] Trabectedin [83,84]	Antiangiogenic TKIs + CT [69,71,86] Androgenic-blockade [87] Immunotherapy [86] IGFR1 antibody [88]
RT	Poli-CT [101]		EZH2 inhibitors [104] HDACs inhibitors [104] Inmunotherapy [105,106]
PT	Anthracycline-based CT [107,108]		Antiangiogenic TKIs [122]
TGCT	Pexidartinib [136]	Imatinib [138,139]	
MT	Anthracyclyne-based CT [149]		
PEComa	mTOR-inhibitors [160–162]	Antiangiogenic TKIs [161] CT [161]	
EMC	Pazopanib [174]	Sunitinib [175,176] Anthracycline-based CT [172,173]	Immunotherapy [177]
NTRK-rearranged sarcomas	TRK inhibitors [188,189]	Classic treatment according to histological subtype	Second generation TRK inhibitors [185,186]

ASTS: Alveolar Soft Tissue Sarcoma; ES: Epithelioid Sarcoma; CCS: Clear Cell Sarcoma; DSRCS: Desmoplatic Small Round Cell Sarcoma; RT: Rhabdoid Tumors; PT: Phyllodes tumor; TGCT:Tenosynovial Giant Cell Sarcoma; MyoT: Myoepithelial Tumors; PEComas: Perivascular Epithelioid Cell Neoplasms; EMC: Exytrasqueletal Myxoid Chondrosarcomas; CT: chemotherapy ; TKIs: Tirosin-Kinase-Inhibitors.

Table 4
Levels of evidence and Grades of recommendation.

Levels of evidence
I Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for a bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II Small randomized trials or large randomized 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

several targeted treatments, especially TKIs such as sunitinib, sorafenib or PZ with or without mTOR inhibitors [70,72,85]. New therapies under investigation include targeting angiogenesis blockade in combination with irinotecan and temozolomide, and immunotherapies that target DSRCT specific surface antigens (V,C) [69,71,86]. Other potential targets that have been investigated are androgen receptor blockade and type-1 insulin-like growth factor receptor antibody [86–88].

Rhabdoid tumor of the kidney and soft tissue extracranial malignant rhabdoid tumOR (RTK/ EMRT)

RTK/ EMRT are rare and highly aggressive malignant tumors occurring predominantly in children younger than three years, with the higher incidence in infants younger than one year [89]. They receive different names depending on the location: atypical teratoid/rhabdoid tumor (AT/RT) in the central nervous system (65%), rhabdoid tumor of the kidney (RTK) (9%) and the soft tissue extracranial extrarenal rhabdoid tumor (EMRT) (26%) that may arise at any site. RTK tends to present early, usually in the first year of life, is frequently associated with hypercalcemia and tends to develop brain metastasis [90].

RTK imaging features include a hypodense lobulated mass on computer tomography, often with necrosis and subcapsular haematoma (Table 1) [91].

RTK tends to present early, usually in the first year of life, is frequently associated with hypercalcemia and tends to develop brain metastasis [90].

EMRT is an extremely aggressive tumor with trend to recur and metastasize. Stage and age at diagnosis are the main prognostic factors, being those patients with metastatic disease at diagnosis (about 30% of patients) and those younger than 24 months or older than 18 years those with the worst prognosis (IV) [92]. Most EMRTs appear in the trunk and upper abdomen as large hypodense lesions with heterogeneous contrast enhancement on computer tomography, and unspecific US and MRI features (Table 1).

They are characterized by the presence of homogenous "rhabdoid cells" (eosinophilic cytoplasm and eccentric nuclei with prominent nucleoli), organized in sheets or solid discohesive trabecular pattern. Mitotic figures are frequently observed. Foci of undifferentiated small round cells can be present [4]. Immunophenotype shows characteristically, loss of SMARCB1 (INI-1). Most tumors also express epithelial markers (keratins and EMA) and could also express CD99, synaptophysin, ERG, SALL4 and glypican-3 among others [93,94]. All these tumors are related to tumor suppressor role for the SWI/SNF (SWItch/Sucrose Non-Fermenting) complex involved in the remodeling of chromatin. As consequence of this, the main oncogenic event in RT formation is loss of SMARCB1 expression, SMARCB1 (INI1/SNF5/BAF47) [96]. This event can be identified by the loss of INI-1 staining in IHC. Rare tumors with retained SMARCB1 expression (5%) are characterized by mutation and/or loss of SMARCA4 (BRG1) gene [96,97]. Recently, new entities of thoracic SMARCA4 deficient carcinomas and sarcomas have been characterized with gene profiling distinct from lung carcinomas but more related to EMRTs, although there is already a paucity of data about their clinical behaviour and therapeutic implications[98,99].

Germline mutations of SMARCB1, rarely SMARCA1 are present in 25–35% of patients, constituting a "rhabdoid tumor predisposition syndrome" inherited in an autosomal dominant manner (incomplete penetrance). Up to a 35% of the "sporadic" cases have a de novo germline SMARCB1 pathogenic variant [100].

In 2010 the European Rhabdoid Registry (EU-RHAB) was created aimed to homogenize treatment throughout Europe [101]. In recent years specific trials with multimodal regimens combining surgery, RT and CT have been developed, showing improvements in survival rates. The current therapeutic standard approach, following the European Rhabdoid Registry (EU-RHAB) recommendation is gross total resection, multidrug conventional CT (including anthracyclines and alkylating agents, combining DOX-ICE-VCA cycles), intrathecal methotrexate and permissive use of myeloablative chemotherapy (CARBO-TT) with stem cell rescue, and RT.

Upfront complete wide resection of the primary tumor is the recommended choice. Radical resection with sufficient margins often implies nephrectomy in kidney and anatomical resections for other locations. All visible tumor sites should be resected or at least biopsied (V, B) [102].

Current data suggest the benefit of early RT, as benefits in survival have been reported [103]. EU-RHAB recommendation is to start RT as soon as feasible in patients older than 18 months. In case of primary metastatic disease RT may be delayed until the end of intensive CT. Doses varies depending on the residual disease after surgery (36–50,4 Gy for EMRT, less for RTK). Doses greater than 25 Gy were associated with better outcome (IV, B) [92].

Despite aggressive intensive multidrug therapy, long-term survival remains unsatisfactory (15–50%) and activity of conventional therapy is insufficient, especially in refractory tumors and for patients with initial poor prognosis risk factors.

Novel targets therapies such as EZH2 inhibitors (tazemetostat), histone deacetylase (HDACs) inhibitors (vorinostat, valproic acid), CDK4/6 inhibitors, Gli 1 inhibitors and aurorakinase (alisertib), are being developed currently in ongoing clinical trials. Immunotherapy has also become a research topic with agents as the PDL-1 antibody atezolizumab [104]. In regards to SMARCA4 deficient thoracic tumors, both chemoterapy and inmunotherapy have showed promising activity in isolated cases both in monotherapy and combining schemes [105,106].

Phyllodes tumor (PT)

PT is an infrequent subtype of fibroepithelial breast tumor that constitutes less than 1% of breast tumors, and has a broad spectrum of biological behavior, from tumors quite similar to fibroadenomas to those that resemble high-grade sarcomas [107,108].

WHO sub-classified them histologically as benign, borderline, or malignant. Benign tumors are more frequent (35–64%)while malignant cases comprise about 25% of cases.

PT is included in this review as its management and biological behavior is closer to sarcomas than epithelioid tumors.

In malignant PT, the stromal component frequently shows a sarcomatous pattern and constitutes the main neoplastic component while the epithelial component is benign. Heterologous differentiation may be present in the form of chondrosarcoma, osteosarcoma, liposarcoma, or rhabdomyosarcoma. Recent studies have shown that PT and non-angiosarcoma breast sarcomas have mutations in MED12 and TERT genes, supporting the hypothesis that they have the same origin [109]. The majority of PT appear in women, and it has been associated with Li-Fraumeni syndrome [110].

Classical presentation includes an enlarging painless, well defined breast mass, mobile and with variable size. Most PTs are classified in mammography and US as BIRAD-3. Main features include a smooth and polylobulated mass on XR, and a solid, well defined and hypoechoic mass, with cystic foci, on US (Table 1). Misdiagnosis with fibroadenomas is common, but a rapidly progressing course is useful in the differential diagnosis [107,108,111].

PT shows a prominent intracanalicular architectural pattern with leaf-like stroma fronds, capped by luminal epithelial and myoepithelial cell layers, with stromal hypercellularity [4]. They are classified in benign, borderline, and malignant [4]. Malignant phyllodes are diagnosed when the tumor has all these features: marked stromal atypia, stromal overgrowth (absence of epithelial elements in 40x magnification), ≥10 mitosis/10 HPF, increase stromal cellularity and infiltrative borders or when malignant heterologous component is present even in the absence of the previous features. When some but not all histological characteristics are seen, a diagnosis of borderline PT is made [4]. PT has implicated mutations in MED12, RARA, TERT, FLNA, SETD2 and KMT2D [4,111,112]. Others like PIK3CA, RB1, TP53, PTEN, BRAF and EGFR have been described and related with promotion of progression to borderline and malignant PT [108,113].

Since surgical approach differs substantially according to histological classification, an accurate expert-based pathological diagnosis is mandatory previous to establish any treatment. Most patients with benign or borderline PT are cured by surgery alone with just conservative procedures, since the risk of recurrence is low and does not appear to affect prognosis [114]. In malignant cases where, the survival rates decrease to 60–80%,initial surgical treatment consists of wide local excision with tumor free margins, with conservative surgery (partial mastectomy), whenever possible. Mastectomy is the choice in tumors that cannot be resected with negative margins using conservative surgery (III, B). Positive surgical margins should be avoided due to the higher risk of local relapse[107,110,115]. Adequate margin width is controversial: although most advocate a surgical margin of 1 cm, recent studies suggest that tumor free margins (3 mm) may be adequate to prevent recurrence (IV, B) [115]. Due to the infrequency of lymph node involvement prophylactic axillary lymphadenectomy is not indicated (V, B) [107,110,115].

The administration of adjuvant RT in benign PT after extensive surgery is not recommended (III, B). The role of adjuvant RT in malignant PT remains controversial: it could improve local control, with no clear survival benefit (III, B) [115,117]. A recent metanalysis suggested a role of RT in prevention of metastasis [118].

Adjuvant CT is not a standard treatment, without randomized studies available. This might be evaluated on an individual-case basis in selected patients with large, high-risk malignant PT or after recurrence (III, C) [107,110]. Two observational studies showed no impact of adjuvant CT on OS [108,118]. Hormone therapy is not recommended despite the existence of hormonal receptors in the epithelial component (V, B) [107,119].

In case of local recurrence, wide excision with or without adjuvant RT is recommended (V, B). Patients with metastatic disease should be treated following treatment guidelines for patients with metastatic STS (V, B) [107,108].

Some genomic alterations with potential clinical interest have been identified, such as the fusions KIAA1549-BRAF or FGFR3-TACC3 [120,121]. Angiogenesis may play a role in oncogenesis and prognosis, so antiangiogenic treatments also may been explored in this entity [122].

Tenosynovial giant cell tumORS (TGCT)

TGCT is a group of lesions of synovial origin, which involve joints, tendon, sheaths, and bursae. They may be intra- or extra-articular and, according to growth pattern and behavior, they are classified as localized-type (L-TGCT) and diffuse-type (D-TGCT). D-TGCT was previously called pigmented villonodular synovitis (PVNS), term no longer recommended [4].

TGCT has a female predominance (2:1) occurring at any age but usually at 30–50 years with an earlier onset in the diffuse type (<40 years). L-TGCT is the most common subset, presenting as a painless swelling small well-circumscribed mass, mostly monoarticular and commonly seen in small joints (fingers). D-TGCT presents with monoarticular pain, swelling and limited joint motion. It is commonly large (>5 cm), counts with an infiltrative pattern affecting larger joints (knee) and has high propensity for recurrence [4,123]. MRI features include a diffuse or nodular mass that usually has patchy areas of hypointensity in all sequences, especially gradient ones; and homogeneous CE (Table 1).

Histologically, apart from the growing pattern, both forms are similar, composed by variable number of mononuclear cells, osteoclast-like giant cells, inflammatory cells, foamy macrophages and siderophages within a collagenized stroma. Two type of mononuclear cells are present: the larger ones are positive for clusterin and can also express desmin while the smaller histyocite-like cells show CD68 and CD45 expression [4]. Malignant transformation in diffuse type (coexistence of benign forms with malignant areas or by recurrence as a sarcoma) occurs in less than 3% of cases [124]. Metastases with benign histology have also been reported [125].

TGCT are characterized for harboring Colony Stimulating Factor 1 (CSF-1) gene rearrangements in a minority of the cells leading to aberrant expression of CSF-1. One of the most frequent is translocation t(1;2)(p11;q36-37) (COL6A3-CSF1) [126]. Other multiple partners for CSF1 have also been depicted, along with CBL gene mutations, that lead to increased CSF1/CSF1R signaling and are involved in the characteristic inflammatory changes frequently described in these tumors [127,128].

Surgery is the most common approach to treat L-TCGT. Primary resection may be total or subtotal synovectomy. In localized forms, recurrence rate is less than 10%. Disease control is achieved with either arthroscopic or open surgical approach (IV, C) [130]. Most authors report low recurrence rates (10%) with arthroscopic synovectomy, excellent functional results and no local complications. Extensive en-bloc surgery is not indicated [131].

Treatment of diffuse forms is more complex, given its infiltrative growth pattern, and recurrences are common within several years of primary diagnosis [123].

To date, a randomized controlled trial comparing arthroscopic versus open synovectomy has not been performed. We recommend performing a complete open synovectomy if the option of an arthroscopic resection is not available (IV, B) [132]. Intraarticular radionuclides have been used in the past as an antiproliferative measure for recurrence of disease, although its role is not established (V, C) [123,133].

External beam radiation within 3–4 months from surgery has been used in some patients with persistent recurrence of disease, extra-articular involvement, or residual disease (total recommended doses 30–36 Gy) achieving recurrence rates lower than 20% [134].

RT could be discussed as primary treatment for inoperable disease, but its role in TCGT diffuse type is currently unclear, especially with the development of systemic therapies (IV, C) [135].

Medical oncology approach in TCGT has historically offer symptom palliation with analgesics, anti-inflammatory drugs or steroids. Pexidartinib (PLX3397), a small molecule inhibitor of CSF1 Receptor, is currently approved by the FDA for the treatment of symptomatic TGCT associated with severe morbidity or functional limitations not amenable to improve with a further surgical procedure (I,A) [136]. However, this drug has currently no marketing authorization in Europe, based on its potential hepatic toxicity [137]. Imatinib has also been used in TCGT not amenable for surgery, and may be useful, as an alternative to pexidartinib while this drug is not available in Europe (V, B) [138,139]. Other CSF1 inhibitors are currently in clinical development in this entity [140].

Myoepithelial tumor (MT)

MT of the soft tissue is an uncommon STS and although it is considered a different entity from myoepithelial carcinoma that arises from salivary glands, they share many molecular features [141]. It typically presents as a palpable mass in the superficial or deep soft tissue of the limbs or head and neck of both children and adults [4,142]. Imaging features are summarized in Table 1.

MT is usually a well-circumscribed tumor showing a broad morphological spectrum: reticular, trabecular, nested, solid pattern with myxoid or hyalinized stroma. Tumor cells can be epithelioid, spindled or plasmocytoid. These tumors could show cartilaginous or osseous differentiation and, occasionally, squamous or adipocytic metaplasia [4]. Myoepithelial carcinoma shows severe nuclear atypia, often with high mitotic rate and necrosis [4]. High-grade cytology, with moderate to severe nuclear atypia, remains the best predictor of aggressiveness [4,37].

Broad-spectrum keratins, S100 and calponin are widely expressed; EMA, GFAP, SMA and p63 can also be expressed. They may be SOX10 positive [143]. EWSR1 gene rearrangement has been identified in 45–50% of cases (EWSR1-POU5F1, EWSR1-PBX1, EWSR1-PBX3, ERSR1-ATF1, EWSR1-ZNF444, EWSR1-KLF17, and EWSR1-VGLL1 fusions) [4,37,144]. Homozygous deletions of SMARCB1, PLAG1, FUS and SRF-E2F1 rearrangements have also been identified [4,37,145].

Standard treatment for localized soft-tissue MT is surgical resection following sarcoma principles [145,146]. The majority of lesions behave in an indolent fashion. Recurrences are observed in 17–20%, but metastases are rare, thus complete surgical excision with negative margins is recommended [4,147]. No clinical or histological features predictive of local recurrence have been identified [148]. However, myoepithelial carcinomas should be managed in high volume centers with expertise in the treatment of such rare cases.

A systematic review of 691 patients (including patients with head and neck and soft tissue tumors), studied the efficacy of perioperative RT, showing that RT (adjuvant or neoadjuvant) significantly decreased locoregional relapses in patients with worse risk factors [148]. In an analysis of 234 cases from the SEER Registry, RT showed an OS benefit in patients with high-grade tumors. Thus RT should be proposed. (IV, B).

In unresectable recurrences, some activity from doxorubicin has been reported, but the identification of further active options of systemic therapy is an unmet need (IV, C) [142,149].

Malignant perivascular epithelioid cell neoplasms (PEComas)

PEComas are rare tumors having hybrid smooth muscle and melanocytic characteristics, which may derive from distinctive perivascular epithelioid cells. The PEComa family encompasses a variety of diagnoses such as angiomyolipoma (AML), lymphangioleiomyomatosis (LAM), pulmonary clear cell "sugar" tumour (CCST), primary extrapulmonary sugar tumor (PEST), clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres (CCMMT), abdominopelvic sarcoma of PECs, and other group of tumors arising in different sites also termed as PEComas [4,150–153].

AML is a benign neoplasm that arises in the kidney and less frequently in the liver, composed of thick-walled blood vessels, smooth muscle cells and adipose tissue, admixed in variable proportions. Renal epithelioid AML often behave in a malignant fashion, particularly if atypia and necrosis is present [150,152,153].

LAM is found almost exclusively in pre-menopausal women, characterized by a pulmonary interstitial infiltrate of myoid cells associated with dilated lymphatics and cystic changes. It may also arise as a tumoral mass (lymphangiomyoma) in lymph nodes, retroperitoneum, pelvis and mediastinum [150].

CCST is a benign pulmonary neoplasm of clear epithelioid cells, with a nested pattern and prominent vasculature [150].

Malignant PEComas should be considered as a spectrum of their benign counterparts, and many of the imaging features of benign PEComa are applicable to the malignant PEComa (Table 1).

PEComas show an admixture of uniform epithelioid and spindled cells with clear cytoplasm in a fascicular or nested pattern, showing a characteristic radial fashion arrangement around blood vessels [4,150]. 15% of cases have densely collagenous stroma (sclerosing PEComas) [151]. Although criteria for malignancy have not been established yet, Folpe's classification in 3 categories is the best available approach [151,154]. Malignant tumors should have two or more worrisome features (>5 cm, infiltrative, high nuclear grade and cellularity, mitotic rate > 1/50HPF, necrosis, vascular invasion) [150].

Co-expression of melanocytic (HMB45, the most sensitive, and Melan A) and smooth muscle markers such as SMA (smooth muscle actin) is the characteristic immunoprofile [151].

Conventional PEComas frequently harbor inactivating mutations and loss of heterozygosity of TSC2 gene (tuberin) or more rarely of TSC1 (hamartin) gene and can be associated with tuberous–sclerosis complex or be sporadic. TSC1 and TSC2 gene products contribute to a molecular complex, which negatively regulates the mTOR complex 1 (mTORC1) [156]. As a consequence of TSC1 or TSC2 alterations, the mTOR pathway is constitutively activated. Another subset of PEComas (23%) harbors TFE3 gene rearrangements correlating with strong nuclear immunoreactivity. Both pathogenic pathways are distinct and mutually exclusive. The most common described fusion partner is SFPQ (PSF), but new partners are being described (DVL2, NONO and RBMX) [155,156]. Recently, FLCN mutations under LOH have been also described [157]. In addition, novel RAD51B gene rearrangements have been identified in 8% of uterine PEComas [155].

Primary treatment for localized PEComa is wide surgical resection (IV, B). Although some PEComas carry biological features that favor the use of RT, evidence on RT is based on isolated cases and its role remains unclear (IVB) [158]. RT has been used both pre and postoperatively, and even SBRT for unresectable liver PEComas [159]. The used doses range 45–60 Gy in the case of adjuvant RT and 50 Gy in neoadjuvant. CT seems to have no benefit in the adjuvant setting (V, B) [160].

PEComas usually show benign behavior and do not recur following complete resection. However, nearly 20% of newly diagnosed patients are advanced and up to 70% of localized malignant PEComa will develop local recurrence and metastatic disease. In this setting, the traditional cytotoxic CT has shown limited efficacy. Anthracycline-based and gemcitabine-based CT have shown, in retrospective studies, disease control rates of 56.5 and 33.3 % and mPFS of 3.2 and 3.4 months respectively (IV, B). Antiangiogenic agents can result in disease stabilization in some patients. In PEComas with TFE3 translocations the treatment with VEGFR inhibitors such as pazopanib or sunitinib could be an option (IV, B) [161,162].

Case reports and retrospective case series patients treated with mTOR inhibitors (sirolimus, temsirolimus or everolimus) have showed durable tumor responses including complete responses in several cases, especially with sirolimus. For this reason, although there are no specifically approved drugs for the treatment of advanced PEComa, mTOR inhibitors are currently recommended in some guidelines (III, B) [161,162].

The AMPECT study, a single-arm phase 2 trial with a new intravenous nanoparticle albumin-bound mTOR inhibitor called nab-sirolimus (ABI-009) is the first and only prospective clinical trial developed for advanced PEComa. The trial showed an independently assessed ORR of 39% (95% CI 22–58%) with durable responses (50% of patients with ongoing responses lasting more than 25 months; range: 6.5 to 42.4+ months) and acceptable safety profile. This trial suggests that Nab-sirolimus may be a good option in advanced PEComas (III, B) [162]. Recently, addition of antiestrogen treatment to mTOR inhibition has been postulated as beneficial, although in a small retrospective series of patients (III, C) [163].

Extraskeletal myxoid chondrosarcoma (EMC)

EMC arises more frequently in males (2:1). Extremities are the most frequent site for primary tumor, although they can appear at any site. The course of the disease is usually indolent, with a progressive slow growth. The distant recurrence-free survival and OS rates at 10 years were 58% and 65%, respectively, and late relapses can occur [164]. Metastases can appear in lungs, but also in lymph nodes and soft tissues. Imaging features include hypodense CT mass, and myxoid MRI pattern with hypointense septa in T2WI. Heterogeneous peripheral and septal contrast enhancement (Table 1).

EMC is a malignant neoplasm of uncertain differentiation, characterized by multilobular architecture of uniform cells arranged in cords, clusters, trabecular or reticular pattern within an abundant chondromyxoid hypovascular stroma. No evidence of true cartilaginous differentiation is seen. Mitotic figures are scarce. Some tumors could display rhabdoid appearance, hypercellularity and even higher grade epithelioid morphology [4]. Immunophenotype is unspecific (S100, EMA, CD117, synaptophysin and NSE in 20–30%). Tumors with rhabdoid features may lose INI1 expression [165].

EMC is characterized by specific NR4A3 (CHN, TEC or NOR1) rearrangements in more than 90% of cases. Partners involved are EWRS1 (>75%), RBP56, TAF15, TCF12, TFG or FUS4 [166,167]. EMCs with non-EWSR1-NR4A3 fusions could behave more aggressively [167,168].

Treatment of localized disease is based in radical resection. Both margin status and radiation therapies are associated with better local control rates (IV, B) [169]. Although this tumor has been considered radioresistant, general recommendations of the European Society of Medical Oncology (ESMO) support adjuvant RT for those tumors larger than 5 cm and high-intermediate grade, given their high local recurrence rate. Several retrospective studies have reported better local control with adjuvant RT. A SEER review of 156 patients with localized disease, observed better specific cancer survival at 3 and 5 years for the combined arm of surgery and RT compared with only resection (97% and 85% vs 94% and 85% respectively). In another analysis of 172 patients included in the SEER database, 5-year cancer specific survival were improved in those who received adjuvant RT (95% vs 85%) [170]. Based in these data, perioperative RT could be considered (IV, B). In contrast adjuvant CT is not recommended in this subtype (V, C) [171].

EMC had been considered a tumor with limited chemosensitivity. However, retrospective series showed activity of antracycline-based CT in this entity (ORR 40–50%), although its impact in survival is unclear (IV, C) [172,173]. The better available evidence supports the activity of TKI antiangiogenics in this subtype, with promising data coming from a phase II trial and a retrospective series. Recently, the first clinical trial developed in EMC has been published. Twenty-three patients with advanced/unresectable molecularly confirmed ECM (87% with NR4A3-EWSR1 and 13% with NR4A3-TAF15 fusions) were treated with pazopanib (800 mg daily) and included in the efficacy analysis. ORR and stable disease were 18% and 73%, respectively, and mPFS was 19 months (19.4 in EWSR1-NR4A3 and 4.1 in NR4A3-TAF15 fusions) [174]. The 4 tumors that experienced partial response had EWSR1-NR4A3 fusion, and the 3 with progression disease had NR4A3-TAF15 fusion. With this data and given the modest benefit of conventional CT, pazopanib should be considered as the preferred treatment for advanced EMC (III, B).

A small series of 10 patients treated with sunitinib (37.5 mg on a continuous daily dosing schedule) showed ORR of 60% and stable disease of 20%. All responders had EWSR1-NR4A3 fusion, whereas non-responders had TAF15-NR4A3 fusion [175]. The updated results showed a mPFS of 34 months, while OS had not been reached [176].

A phase Ib/II study testing the combination of sunitinib with nivolumab in several sarcoma subtypes, showed 3 objective responses (1 complete and 2 partial) among the 4 ECM patients included [177].

NTRK-rearranged sarcomas

Oncogenic fusions involving neurotrophic receptor tyrosine kinase (NTRK) genes have been recently identified in a wide range of tumors including sarcomas. Especially interesting are the discovery of NTRK1 and NTRK3 fusions, where NTRK inhibitors have shown remarkable activity.

There is no accurate data about what percentage of sarcomas are associated with NTRK-rearrangements, but overall, it is thought to be present in less than 1%. Tumor harboring NTRK-rearrangement had been previously described in the case of Infantile fibrosarcoma, defined by the ETV6-NTRK3 fusion. This spindle cell sarcoma, with typical herring-bone pattern, typically is presented in children younger than 2 years (described in part I of our work). NTRK fusions have also been identified in some cases of adult fibrosarcoma, either on soft tissues or viscera, with not specific histologic pattern [178].

Apart from fibrosarcomas, NTRK-rearranged spindle cell neoplasms have shown a wide morphological spectrum. At one side tumors are formed of monomorphic spindle cells, with low mitotic count, no necrosis and an infiltrative growth pattern, the so-called lipofibromatosis-like neural tumor (LPF-NT). At the other end highly cellular pattern less proliferation showing hemangiopericytoma-like or Malignant Peripheral Nerve Sheat Tumor (MPNST) –like patterns have been described. Some clues to suspect NTRK rearrangements are the presence of prominent bundles of collagen and perivascular keloid-like hyalinization. Most NTRK–related tumors show coexpression of S100, CD34, and anti-pan-TRK cytoplasmic or nuclear positivity, with H3K27me3 retained [179].

NTRK1 fusion-positive STS are associated more frequently to tumors arising in children and with benign behavior. NTRK3-fusions have been associated to more malignant course and typically fibrosarcoma or MPNST-like features [179].

A recent experts consensus panel has proposed a three different risk groups of sarcomas with different priority for testing NTRK fusions: 1) High priority (Infantile fibrosarcomas and ALK and ROS1 fusion-negative inflammatory myofibroblastic tumors), 2) Intermediate priority (Complex-genomic sarcomas and wild-type GIST) and 3) Low priority (Sarcomas with canonical oncogene alterations) [180].

Surgery is the mainstay of therapy in localized resectable tumors, but beyond that, identification of NTRK fusions has become of heightened importance, particularly in advanced tumors, due to the recent availability of selective and highly effective targeted therapies. NTRK fusions can be targeted with TRK inhibitors (TRKi), including larotrectinib and entrectinib, which are well tolerated and effective in about 75% of patients with NTRK-translocated tumors, often producing durable responses [181,182].

A specific review of activity of larotrectinib of 71 adult and paediatric patients with TRK fusion sarcomas, enrolled in three trials, showed an ORR of 87% (77–94) with a mPFS of 28.3 months (95% CI 16.8–NE) [183]. Another study analyzed activity of entrectinib in 13 patients with TRK-fusion STS on other three trials, showing and ORR of 46.2 % with a mPFS of 11.0 months [184].

Despite the remarkable efficacy of TRKI the development of resistance is common. This can occur through the development of mutations of the NTRK gene, mutations of MAPK pathway genes such as BRAF (V600E) and KRAS (G12D), and the amplification of MET. However, second-generation TRK inhibitors have been developed, such as selitrectinib and repotrectinib, which have shown activity in these patients [185-187].

In unresectable or advanced disease, provided that recent FDA and EMA approval of NTRK targeted treatments, these inhibitors are the first choice of therapy (III, A) [188,189].

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Reference

[1] Dykewicz CA. Centers for Disease C, Prevention. Infectious Diseases Society of A. American Society of B, Marrow T Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001;33(2):139–44. https://doi.org/10.1086/321805.

[2] Jaber OI, Kirby PA. Alveolar soft part sarcoma. Arch Pathol Lab Med 2015;139 (11):1459–62. https://doi.org/10.5858/arpa.2014-0385-RS.

[3] Portera Jr CA, Ho V, Patel SR, et al. Alveolar soft part sarcoma: clinical course and patterns of metastasis in 70 patients treated at a single institution. Cancer 2001;91(3):585–91. https://doi.org/10.1002/10970142(20010201)91:3<585::aidcncr1038>3.0.co;2-0.

[4] Fletcher CDM, Baldini EH, Blay JY, Gronchi A, et al. WHO Classification of Tumours of Soft Tissue and Bone. Fifth Edition. WHO 2020; IARC WHO Classification of Tumours, No 3. ISBN-9789283245025.

[5] Zhong M, De Angelo P, Osborne L, Keane-Tarchichi M, Goldfischer M, Edelmann L, et al. Dual-color, break-apart FISH assay on paraffin-embedded tissues as an adjunct to diagnosis of Xp11 translocation renal cell carcinoma and alveolar soft part sarcoma. Am J Surg Pathol 2010;34:757–66. https://doi.org/10.1097/PAS.0b013e3181dd577e.

[6] Dickson BC, Chung CT, Hurlbut DJ, Marrano P, Shago M, Sung YS, et al. Genetic diversity in alveolar soft part sarcoma: A subset contain variant fusion genes, highlighting broader molecular kinship with other MiT family tumors. Genes Chromosomes Cancer 2019 Aug 21. https://doi.org/10.1002/gcc.22803.

[7] Mitton B, Federman N. Alveolar soft part sarcomas: molecular pathogenesis and implications for novel targeted therapies. Sarcoma 2012;2012:428789. https://doi.org/10.1155/2012/428789.

[8] Paoluzzi L, Maki RG. Diagnosis, prognosis, and treatment of alveolar soft-part sarcoma: A review. JAMA Oncol 2019 Feb 1;5(2):254–60. https://doi.org/10.1001/jamaoncol.2018.4490.

[9] Lin YK, Wu PK, Chen CF, Chen CM, Tsai SW, Chih-Hsueh P. Alveolar soft part sarcoma: Clinical presentation, treatment, and outcome in a series of 13 patients. J Chin Med Assoc 2018;81:735–41. https://doi.org/10.1016/j.jcma.2018.01.006.

[10] Kayton ML, Meyers P, Wexler H, Gerald WL, LaQuaglia P. Clinical presentation, treatment, and outcome of alveolar soft part sarcoma in children, adolescents, and young adults. J Pediatic Surg 2006;41:187–93. https://doi.org/10.1016/j.jpedsurg.2005.10.023.

[11] Pennacchioli E, Fiore M, Collini P, Radaelli S, Dileo P, Stacchiotti S. Alveolar soft part sarcoma: clinical presentation, treatment, and outcome in a series of 33 patients at a single institution. Ann Surg Oncol 2010;17:3229–33. https://doi.org/10.1245/s10434-010-1186-x.

[12] Daigeler A, Kuhnen C, Hauser J, et al. Alveolar soft part sarcoma: clinicopathological findings in a series of 11 cases. World J Surg Onc 2008;6:71. https://doi.org/10.1186/1477-7819-6-71.

[13] Liu YP, Jin J, Wang WH, Wang SL, Song YW, Fang H, et al. A retrospective analysis of lung metastasis in 64 patients with alveolar soft part sarcoma. Clin Transl Oncol. 2015;17(10):803–9. https://doi.org/10.1007/s12094-015-1308-9.

[14] Reichardt P, Lindner T, Pink D, Thuss-Patience PC, Kretzschmar A, Dörken B. Chemotherapy in alveolar soft part sarcomas. What do we know? Eur J Cancer. 2003;39(11):1511–6. https://doi.org/10.1016/s0959-8049(03)00264-8.

[15] Stacchiotti S, Mir O, Le Cesne A, et al. Activity of pazopanib and trabectedin in advanced alveolar soft part sarcoma. Oncologist 2018;23(1):62–70. https://doi.org/10.1634/theoncologist.2017-0161.

[16] Judson I, Morden JP, Kilburn L, Leahy M, Benson C, Bhadri V, et al. Cediranib in patients with alveolar soft-part sarcoma (CASPS): a double-blind, placebo-controlled, randomised, phase 2 trial. Lancet Oncol 2019;20(7):1023–34. https://doi.org/10.1016/S1470-2045(19)30215-3.

[17] Jagodzińska-Mucha P, Świtaj T, Kozak K, et al. Long-term results of therapy with sunitinib in metastatic alveolar soft part sarcoma. Tumori 2017;103(3):231–5. https://doi.org/10.5301/tj.5000617.

[18] Li T, Wang L, Wang H, et al. A retrospective analysis of 14 consecutive Chinese patients with unresectable or metastatic alveolar soft part sarcoma treated with sunitinib. Invest New Drugs 2016;34(6):701–6. https://doi.org/10.1007/s10637-016-0390-3.

[19] Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. Ann Oncol. 2011;22(7):1682–90. https://doi.org/10.1093/annonc/mdq644.

[20] Liu J, Fan Z, Li S, Gao T, Xue R, Bai C, et al. Target therapy for metastatic alveolar soft part sarcoma: a retrospective study with 47 cases. Ann Transl Med 2020;8 (22):1493. https://doi.org/10.21037/atm-20-6377.

[21] Chi Y, Fang Z, Hong X, et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. Clin Cancer Res 2018;24(21):5233–8. https://doi.org/10.1158/1078-0432.CCR-17-3766.

[22] Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. Lancet Oncol 2019;20(6):837–48. https://doi.org/10.1016/S1470-2045(19)30153-6.

[23] Martin-Broto J, Hindi N, Grignani G, et al. Immunosarc: a collaborative spanish (GEIS) and italian (ISG) sarcoma groups phase I/II trial of sunitinib plus nivolumab in advanced soft tissue and bone sarcomas: results of the phase II soft tissue sarcoma cohort CTOS Meeting 2019 Tokio, abst: 3255157.

[24] Blay YI, Penel N, Ray-Coquard IL, et al. High clinical activity of pembrolizumab in chordoma, alveolar soft part sarcoma (ASPS) and other rare sarcoma histotypes: The French AcSé pembrolizumab study from Unicancer. J Clin Oncol 2021;39 (suppl 15; abstr 11520). https://doi.org/10.1200/JCO.2021.39.15_suppl.11520.

[25] Naqash AR, O'Sullivan GH, Coyne NM, et al. Phase II study of atezolizumab in advanced alveolar soft part sarcoma (ASPS). J Clin Oncol 2021;39(15_suppl): 11519. https://doi.org/10.1200/JCO.2021.39.15_suppl.11519.

[26] Shi Y, Cai Q, Jiang Y, Huang G, et al. Activity and Safety of Geptanolimab (GB226) for Patients with Unresectable, Recurrent, or Metastatic Alveolar Soft Part Sarcoma: A Phase II, Single-arm Study. Clin Cancer Res 2020;26(24): 6445–52. https://doi.org/10.1158/1078-0432.CCR-20-2819.

[27] Hindi N, Rosenbaum E, Jonczak E, et al. Retrospective world-wide registry on the efficacy of immune checkpoint inhibitors in alveolar soft part sarcoma: Updated results from sixty patients. J Clin Oncol 2021;39(suppl 15; abstr 11564). https://doi.org/10.1200/JCO.2021.39.15_suppl.11564.

[28] Trial of Sunitinib Plus Nivolumab After Standard Treatment in Advanced Soft Tissue and Bone Sarcomas (ImmunoSarc). https://clinicaltrials.gov/ct2/show/NCT03277924. Accessed April 24, 2020.

[29] A phase III trial of anlotinib in metastatic or advanced alveolar soft part sarcoma, leiomyosarcoma and synovial sarcoma (APROMISS). https://clinicaltrials.gov/ct2/show/ NCT03016819. Accessed April 24, 2020.

[30] Atezolizumab in treating patients with newly diagnosed and metastatic alveolar soft part sarcoma that cannot be removed by surgery. NCT03141684. https://clinicaltrials.gov/ct2/show/ NCT03141684. Accessed April 24, 2020.

[31] A Trial of Perifosine in Patients With Chemo-Insensitive Sarcomas. https://clinicaltrials.gov/ct2/show/NCT00401388. Accessed April 24, 2020.

[32] Phase 2 Study in Patients With MiT Tumors. https://clinicaltrials.gov/ct2/show/NCT00557609. Accessed April 24, 2020.

[33] Frezza AM, Botta L, Pasquali S, et al. An epidemiological insight into epithelioid sarcoma (ES): the open issue of distal-type (DES) versus proximal type (PES). ESMO Annual Meeting, Madrid, Spain, September, 2017 ;Ann Oncol 28, v525. https://doi.org/10.1093/annonc/mdx387.013.

[34] Jawad MU, Extein J, Min ES, Scully SP. Prognostic factors for survival in patients with epithelioid sarcoma: 441 cases from the SEER database. Clin Orthop Relat Res 2009;467(11):2939–48. https://doi.org/10.1007/s11999-009-0749-2.

[35] Baratti D, Pennacchioli E, Casali PG, et al. Epithelioid sarcoma: prognostic factors and survival in a series of patients treated at a single institution. Ann Surg Oncol 2007;14(12):3542–51. https://doi.org/10.1245/s10434-007-9628-9.

[36] Wolf PS, Flum DR, Tanas MR, Rubin BP, Mann GN. Epithelioid sarcoma: the University of Washington experience. Am J Surg. 2008;196(3):407–12. https://doi.org/10.1016/j.amjsurg.2007.07.029.

[37] Dei Tos AP. Intermediate malignant and malignant tumors of soft tissue featuring a spindle cell morphology. Soft tissue sarcomas. A pattern-based approach to diagnosis. United Kingdom. Cambridge. 2019. 578–591. ISBN 978-1-107-04080-9.p157-169.

[38] James AW, Dry SM. Diagnostically challenging epithelioid soft tissue tumors. Surg Pathol Clin 2015;8(3):309–29. https://doi.org/10.1016/j.path.2015.05.002.

[39] Maeda K, Asano N, Kikuta K, et al. Classic-type epithelioid sarcoma arising from the sciatic nerve: A case report [published online ahead of print, 2019 Sep 16]. J Orthop Sci 2019; S0949-2658(19) 30268-4. https://doi:10.1016/j.jos.2019.08.017.

[40] Hurren JS, Cormack GC. The application of the rotation flap to the dorsum of the hand. Br J Plast Surg 2000;53(6):491–4. https://doi.org/10.1054/bjps.2000.3376.

[41] Maduekwe UN, Hornicek FJ, Springfield DS, et al. Role of sentinel lymph node biopsy in the staging of synovial, epithelioid, and clear cell sarcomas. Ann Surg Oncol 2009;16(5):1356–63. https://doi.org/10.1245/s10434-009-0393-9.

[42] Callister MD, Ballo MT, Pisters PW, et al. Epithelioid sarcoma: results of conservative surgery and radiotherapy. Int J Radiat Oncol Biol Phys 2001;51(2): 384–91. https://doi.org/10.1016/s0360-3016(01)01646-7.

[43] Wolf PS, et al. Epithelioid Sarcoma: the University of Washington experience. CTOS annual meeting presentation; 2005.

[44] Frezza AM, Jones RL, Lo Vullo S, et al. Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma: A Multi-institutional Case Series. JAMA Oncol 2018;4(9). https://doi.org/10.1001/jamaoncol.2018.0219.

[45] First EZH2 Inhibitor Approved-for Rare Sarcoma. Cancer Discov 2020; 10(3): 333–334. https://doi:10.1158/2159-8290.CD-NB2020-006.

[46] Stacchiotti S, Schoffski P, Jones R et al. Safety and efficacy of tazemetostat, a first-in-class EZH2 inhibitor, in patients (pts) with epithelioid sarcoma (ES) (NCT02601950). J Clin Oncol 37, 2019 (suppl; abstr 11003). https://doi: 10.1200/JCO.2019.37.15_suppl.11003.

[47] Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1–2 trial. Lancet Oncol 2020;21(1):121–33. https://doi.org/10.1016/S1470-2045(19)30671-0.

[48] Paoluzzi L, Cacavio A, Ghesani M, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res 2016; 6: 24. Published 2016 Dec 30. https://doi:10.1186/s13569-016-0064-0.

[49] Blay JY, Chevret S, Penel N, et al. High clinical benefit rates of single agent pembrolizumab in selected rare sarcoma histotypes: First results of the AcSé Pembrolizumab study. ESMO Meeting 2020. September 19-20, 2020. Abstract 1619O.

[50] Li AB, Jiang BJ, Wang HH, et al. Prognostic factors for survival in patients with clear cell sarcoma: an analysis of the Surveillance, Epidemiology, and End Results (SEER) database. Med Sci Monit 2019; 25: 6950–6956. Published 2019 Sep 15. htpps://doi:10.12659/MSM.916705.
[51] Markku Miettinen. Modern soft tissue pathology. Tumors and non neoplastic conditions. Cambrigde medicine; 2010.
[52] Keung EZ, Chiang YJ, Voss RK, et al. Defining the incidence and clinical significance of lymph node metastasis in soft tissue sarcoma. Eur J Surg Oncol 2018;44(1):170–7. https://doi.org/10.1016/j.ejso.2017.11.014.
[53] Jacobs AJ, Morris CD, Levin AS. Synovial sarcoma is not associated with a higher risk of lymph node metastasis compared with other soft tissue sarcomas. Clin Orthop Relat Res. 2018;476(3):589–98. https://doi.org/10.1007/s11999.0000000000000057.
[54] Sherman KL, Kinnier CV, Farina DA, et al. Examination of national lymph node evaluation practices for adult extremity soft tissue sarcoma. J Surg Oncol. 2014; 110(6):682–8. https://doi.org/10.1002/jso.23687.
[55] Casali PG, Abecassis N, Aro HT, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4). https://doi.org/10.1093/annonc/mdy321.
[56] Blazer 3rd DG, Lazar AJ, Xing Y, et al. Clinical outcomes of molecularly confirmed clear cell sarcoma from a single institution and in comparison with data from the Surveillance, Epidemiology, and End Results registry. Cancer 2009; 115(13):2971–9. https://doi.org/10.1002/cncr.24322.
[57] Gonzaga MI, Grant L, Curtin C, Gootee J, Silberstein P, Voth E. The epidemiology and survivorship of clear cell sarcoma: a National Cancer Database (NCDB) review. J Cancer Res Clin Oncol. 2018;144(9):1711–6. https://doi.org/10.1007/s00432-018-2693-6.
[58] Segawa K, Sugita S, Aoyama T, et al. Detection of specific generearrangements by fluorescence in situ hybridization in 16 cases of clear cell sarcoma of soft tissue and 6 cases of clear cell sarcoma-like gastrointestinal tumor. Diagn Pathol. 2018; 13(1):73. https://doi.org/10.1186/s13000-018-0752-6. Published 2018 Sep 15.
[59] Ibrahima RM, Jensenb SS, Jacob JJ. Clear cell sarcoma. A review. J Orthopaedics 2018;15:963–6. https://doi.org/10.1016/j.jor.2018.08.039.
[60] Bianchi G, Charoenlap C, Cocchi S, Rani N, Campagnoni S, Righi A, et al. Clear cell sarcoma of soft tissue: A retrospective review and analysis of 31 cases treated at Istituto Ortopedico Rizzoli. J Cancer Surg 2014;40:505–10. https://doi.org/10.1016/j.ejso.2014.01.016.
[61] Grabellus F, Kraft C, Sheu-Grabellus SY, et al. Tumor vascularization and histopathologic regression of soft tissue sarcomas treated with isolated limb perfusion with TNF-α and melphalan. J Surg Oncol. 2011;103(5):371–9. https://doi.org/10.1002/jso.21724.
[62] Gutman M, Inbar M, Lev-Shlush D, et al. High dose tumor necrosis factor-alpha and melphalan administered via isolated limb perfusion for advanced limb soft tissue sarcoma results in a >90% response rate and limb preservation. Cancer 1997;79(6):1129–37. https://doi.org/10.1002/(sici)1097-0142(19970315)79:6<1129::aid-cncr11>3.0.co;2-1.
[63] Pennacchioli E, Deraco M, Mariani L, et al. Advanced extremity soft tissue sarcoma: prognostic effect of isolated limb perfusion in a series of 88 patients treated at a single institution. Ann Surg Oncol. 2007;14(2):553–9. https://doi.org/10.1245/s10434-006-9251-1.
[64] Stacchiotti S, Palassini E, Negri T, et al. Clear cell sarcoma (CCR): Clinical behavior and response to chemotherapy. J Clin Oncol 2010;28(15_suppl). 10096–10096.
[65] Urakawa H, Kawai A, Goto T, et al. Phase II trial of pazopanib in patients with metastatic or unresectable chemoresistant sarcomas: A Japanese Musculoskeletal Oncology Group study. Cancer Sci. 2020;111(9):3303–12. https://doi.org/10.1111/cas.14542.
[66] Stacchiotti S, Grosso F, Negri T, et al. Tumor response to sunitinib malate observed in clear-cell sarcoma. Ann Oncol. 2010;21(5):1130–1. https://doi.org/10.1093/annonc/mdp611.
[67] Schöffski P, Wozniak A, Stacchiotti S, et al. Activity and safety of crizotinib in patients with advanced clear-cell sarcoma with MET alterations: European Organization for Research and Treatment of Cancer phase II trial 90101 'CREATE' [published correction appears in Ann Oncol. 2019 Feb 1;30(2):344] [published correction appears in Ann Oncol. 2019 Feb;30(2):344]. Ann Oncol 2017; 28(12): 3000–3008. htpps://doi:10.1093/annonc/mdx527.
[68] Honore C, Delhorme JB, Nassif E, Faron M, et al. Can we cure patients with abdominal Desmoplastic Small Round Cell Tumor? Results of a retrospective multicentric study on 100 patients. Surg Oncol. 2019;29:107–12. https://doi.org/10.1016/j.suronc.2019.04.002.
[69] Bulbul A, Fahy BN, XIu J, Rashad S, et al. Desmoplastic small round blue cell tumor: A review of treatment and potential therapeutic genomic alterations. 1278268 Sarcoma 2017;2017. https://doi.org/10.1155/2017/1278268.
[70] Dufresne A, Cassier P, Couraud L, Marec-Bérard P, et al. Desmoplastic small round cell tumor: current management and recent findings. Sarcoma 2012;2012. https://doi.org/10.1155/2012/714986. 714986.
[71] Hayes- Jordan A, LaQuaglia MP, Modak S. Management of desmoplastic small round cell tumor. Semin Pediatr Surg. 2016;25(5):299–304. https://doi.org/10.1053/j.sempedsurg.2016.09.005.
[72] Thway K, Noujaim J, Zaidi S, et al. Desmoplastic small round cell tumor: pathology, genetics, and potential therapeutic strategies. Int J Surg Pathol. 2016; 24(8):672–84. https://doi.org/10.1177/1066896916668637.
[73] Lal DR, Su WT, Wolden SL, Loh KC, Modak S, La Quaglia MP. Results of multimodal treatment for desmoplastic small round cell tumors. J Pediatr Surg. 2005;40(1):251–5. https://doi.org/10.1016/j.jpedsurg.2004.09.046.
[74] Subbiah V, Lamhamedi-Cherradi SE, Cuglievan B, Menegaz BA, et al. Multimodality treatment of desmoplastic small round cell tumor: chemotherapy and complete cytoreductive surgery improve patient survival. Clin Cancer Res. 2018 Oct 1;24(19):4865–73. https://doi.org/10.1158/1078-0432.CCR18-0202.
[75] Chang F. Desmoplastic small round cell tumors: cytologic, histologic, and immunohistochemical features. Arch Pathol Lab Med. 2006 May;130(5):728–32. https://doi.org/10.1043/1543-2165(2006)130[728:DSRCTC]2.0.CO;2.
[77] Kushner BH, LaQuaglia MP, Wollner N, et al. Desmoplastic small round-cell tumor: prolonged progression-free survival with aggressive multimodality therapy. J Clin Oncol. 1996;14(5):1526–31. https://doi.org/10.1200/JCO.1996.14.5.1526.
[78] Scheer M, Vokuhl C, Blank B, Hallmen E, et al. Desmoplastic small round cell tumors: Multimodality treatment and new risk factors. Cancer Med. 2019;8(2): 527–42. https://doi.org/10.1002/cam4.1940.
[79] Forlenza CJ, Kushner BH, Kernan N, et al. Myeloablative chemotherapy with autologous stem cell transplant for desmoplastic small round cell tumor. Sarcoma. 2015;2015:269197. https://doi.org/10.1155/2015/269197.
[81] Desai NB, Stein NF, LaQuaglia MP, et al. Reduced toxicity with intensity modulated radiation therapy (IMRT) for desmoplastic small round cell tumor (DSRCT): an update on the whole abdominopelvic radiation therapy (WAP-RT) experience. Int J Radiat Oncol Biol Phys. 2013;85(1):e67–72. https://doi.org/10.1016/j.ijrobp.2012.09.005.
[82] Osborne EM, Briere TM, Hayes-Jordan A, et al. Survival and toxicity following sequential multimodality treatment including whole abdominopelvic radiotherapy for patients with desmoplastic small round cell tumor. Radiother Oncol. 2016;119(1):40–4. https://doi.org/10.1016/j.radonc.2015.10.016.
[83] Verret B, Honore C, Dumont S, Terrier P, Adam J, Cavalcanti A, et al. Trabectedin in advanced desmoplastic round cell tumors: a retrospective single-center series. Anticancer Drugs. 2017;28(1):116–9. https://doi.org/10.1097/CAD.0000000000000435.
[84] Brunetti AE, Delcuratolo S, Lorusso V, Palermo L, Di Giorgio A, Pisconti S, et al. Third-line trabectedin for a metastatic desmoplastic small round cell tumour treated with multimodal therapy. Anticancer Res. 2014 Jul;34(7):3683–8.
[85] Loktev A, Shipley JM. Desmoplastic small round cell tumor (DSRCT): emerging therapeutic targets and future directions for potential therapies. Expert Opin Ther Targets. 2020;24(4):281–5. https://doi.org/10.1080/14728222.2020.1738392. Epub 2020 Mar 11.
[86] Bexelius TS, Wasti A, Chisholm JC. Mini-review on targeted treatment of desmoplastic small round cell tumor. Front Oncol. 2020;10:518. https://doi.org/10.3389/fonc.2020.00518. Published 2020 Apr 21.
[87] Fine RL, Shah SS, Moulton TA, Yu IR, Fogelman DR, Richardson M, et al. Androgen and c-Kit receptors in desmoplastic small round cell tumors resistant to chemotherapy: novel targets for therapy. Cancer Chemother Pharmacol. 2007;59: 429–37. https://doi.org/10.1007/s00280-006-0280-z.
[88] Tap WD, Demetri G, Barnette P, Desai J, Kavan P, Tozer R, et al. Phase II study of ganitumab, a fully human anti-type-1 insulin-like growth factor receptor antibody, in patients with metastatic ewing family tumors or desmoplastic small round cell tumors. J Clin Oncol. 2012;30:1849–56. https://doi.org/10.1200/JCO.2011.37.2359.
[89] Sultan I, Casanova M, Al-Jumaily U, Meazza C, Rodriguez-Galindo C, Ferrari A. Soft tissue sarcomas in the first year of life. Eur J Cancer. 2010;46(13):2449–56. https://doi.org/10.1016/j.ejca.2010.05.002.
[90] Vujanić GM, Sandstedt B, Harms D, Boccon-Gibod L, Delemarre JF. Rhabdoid tumour of the kidney: a clinicopathological study of 22 patients from the International Society of Paediatric Oncology (SIOP) nephroblastoma file. Histopathology 1996;28(4):333–40. https://doi.org/10.1046/j.1365-2559.1996.d01-436.x.
[91] Han TI, Kim MJ, Yoon HK, Chung JY, Choeh K. Rhabdoid tumour of the kidney: Imaging findings. Pediatr Radiol. 2001;31(4):233–7. https://doi.org/10.1007/s002470000417.
[92] Sultan I, Qaddoumi I, Rodríguez-Galindo C, Nassan AA, Ghandour K, Al-Hussaini M. Age, stage, and radiotherapy, but not primary tumor site, affects the outcome of patients with malignant rhabdoid tumors. Pediatr Blood Cancer. 2010;54(1):35–40. https://doi.org/10.1002/pbc.22285.
[93] Kohashi K, Nakatsura T, Kinoshita Y, Yamamoto H, Yamada Y, Tajiri T, et al. Glypican 3 expression in tumors with loss of SMARCB1/INI1 protein expression. Hum Pathol. 2013 Apr;44(4):526–33. https://doi.org/10.1016/j.humpath.2012.06.014.
[94] Kohashi K, Yamada Y, Hotokebuchi Y, Yamamoto H, Taguchi T, Iwamoto Y, et al. ERG and SALL4 expressions in SMARCB1/INI1-deficient tumors: a useful tool for distinguishing epithelioid sarcoma from malignant rhabdoid tumor. Hum Pathol. 2015 Feb;46(2):225–30. https://doi.org/10.1016/j.humpath.2014.10.010.
[96] Oda Y, Biegel JA, Pfister SM. Extrarenal rhabdoid tumour. World Health Organization Classification of Tumors. 5th ed. Lyon: IARC Press; 2020, pags. 309-311.
[97] Schneppenheim R, Frühwald MC, Gesk S, Hasselblatt M, Jeibmann A, Kordes U, et al. Germline nonsense mutation and somatic inactivation of SMARCA4/BRG1 in a family with rhabdoid tumor predisposition syndrome. Am J Hum Genet. 2010;86:279–84. https://doi.org/10.1016/j.ajhg.2010.01.013.
[98] Le Loarer F, Watson S, Pierron G, et al. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. Nat Genet. 2015 Oct;47(10):1200–5. https://doi.org/10.1038/ng.3399.
[99] Nambirajan A, Dutta R, Malik PS, et al. Cytology of SMARCA4-deficient thoracic neoplasms: comparative analysis of SMARCA4-deficient non-small cell lung

carcinomas and SMARCA4-deficient thoracic sarcomas. Acta Cytol. 2021;65(1): 67–74. https://doi.org/10.1159/000510323.
[100] Nemes K, Bens S, Bourdeaut F, Hasselblatt M, Kool M, Johann P, et al. Rhabdoid tumor predisposition syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® Seattle (WA): University of Washington, Seattle; 1993-2020.2017 Dec 7.
[101] A multinational registry for rhabdoid tumors of any anatomical site. European Rhabdoid Registry (EU-RHAB)v2.2010. Michael C Frühwald, Principal investigator. Principal Investigator Coordination Centre: Klinik für Kinder und Jugendliche, Klinikum Augsburg, Germany eurhab@uni-muenster.de.
[102] Garcés-Iñigo EF, Leung R, Sebire NJ, McHugh K. Extrarenal rhabdoid tumours outside the central nervous system in infancy. Pediatr Radiol. 2009;39(8): 817–22. https://doi.org/10.1007/s00247-009-1288-4. Epub 2009 May 19.
[103] Puri DR, Meyers PA, Kraus DH, Laquaglia MP, Wexler LH, Wolden SL. Radiotherapy in the multimodal treatment of extrarenal extracranial malignant rhabdoid tumors. Pediatr Blood Cancer. 2008;50(1):167–9. https://doi.org/10.1002/pbc.20947.
[104] Nemes K, Frühwald MC. Emerging therapeutic targets for the treatment of malignant rhabdoid tumors. Expert Opin Ther Targets. 2018;22(4):365–79. https://doi.org/10.1080/14728222.2018.1451839. Epub 2018 Mar 20. PMID: 29528755.
[105] Iijima Y, Sakakibara R, Ishizuka M, Honda T, Shirai T, Okamoto T, et al. Notable response to nivolumab during the treatment of SMARCA4-deficient thoracic sarcoma: a case report. Immunotherapy. 2020 Jun;12(8):563–9. https://doi.org/10.2217/imt-2019-0142. Epub 2020 May 3.
[106] Kawachi H, Kunimasa K, Kukita Y, et al. Atezolizumab with bevacizumab, paclitaxel and carboplatin was effective for patients with SMARCA4-deficient thoracic sarcoma. Immunotherapy. 2021 Jul;13(10):799–806. https://doi.org/10.2217/imt-2020-0311. Epub 2021 May 25.
[107] Telli ML, Horst KC, Guardino AE, Dirbas FM, Carlson RW. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. J Natl Compr Canc Netw. 2007;5 (3):324–30. https://doi.org/10.6004/jnccn.2007.0027.
[108] Strode M, Khoury T, Mangieri C, Takabe K. Update on the diagnosis and management of malignant phyllodes tumors of the breast. Breast. 2017;33:91–6. https://doi.org/10.1016/j.breast.2017.03.001.
[109] Lim SZ, Ng CCY, Rajasegaran V, Guan P, Selvarajan S, Thike AA, et al. Genomic profile of breast sarcomas: a comparison with malignant phyllodes tumours. Breast Cancer Res Treat 2019;174(2):365–73. https://doi.org/10.1007/s10549-018-5067-5. Epub 2018 Dec 3.
[110] Khosravi-Shahi P. Management of non metastatic phyllodes tumors of the breast: review of the literature. e143-8 Surg Oncol. 2011;20(4). https://doi.org/10.1016/j.suronc.2011.04.007.
[111] Zhang Y, Kleer CG. Phyllodes tumor of the breast: histopathologic features, differential diagnosis, and molecular/genetic updates. Arch Pathol Lab Med. 2016;140(7):665–71. https://doi.org/10.5858/arpa.2016-0042-RA.
[112] Krings G, Bean GR, Chen YY. Fibroepithelial lesions; The WHO spectrum. Semin Diagn Pathol. 2017;34(5):438–52. https://doi.org/10.1053/j.semdp.2017.05.006.
[113] WHO Classification of Tumours Editorial Board. Breast tumours. Lyon (France): International Agency for Research on Cancer; 2019. 5th ed; vol 2. ISBN: 9789283245001.
[114] Spitaleri G, Toesca A, Botteri E, et al. Breast phyllodes tumor: a review of literature and a single center retrospective series analysis. Crit Rev Oncol Hematol 2013;88(2):427–36. https://doi.org/10.1016/j.critrevonc.2013.06.005.
[115] Neron M, Sajous C, Thezenas S, et al, French Sarcoma Group (CSF-GETO). Surgical margins and adjuvant therapies in malignant phyllodes tumors of the breast: A multicenter retrospective study. Ann Surg Oncol 2020 Jan 27. https://doi:10.1245/s10434-020-08217-y.
[117] Barth RJ, Wells WA, Mitchell SE, et al. A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. Ann Surg Oncol 2009;16:2288–94. https://doi.org/10.1245/s10434-009-0489-2.
[118] Chao X, Chen K, Zeng J, et al. Adjuvant radiotherapy and chemotherapy for patients with breast phyllodes tumors: a systematic review and meta-analysis. BMC Cancer 2019;19:372. https://doi.org/10.1186/s12885-019-5585-5.
[119] Morales-Vásquez F, Gonzalez-Angulo AM, Broglio K, et al. Adjuvant chemotherapy with doxorubicin and dacarbazine has no effect in recurrence-free survival of malignant phyllodes tumors of the breast. Breast J. 2007;13(6):551–6. https://doi.org/10.1111/j.1524-4741.2007.00510.x.
[120] Nozad S, Sheehan CE, Gay LM, Elvin JA, et al. Comprehensive genomic profiling of malignant phyllodes tumors of the breast. Breast Cancer Res Treat. 2017;162 (3):597–602. https://doi.org/10.1007/s10549-017-4156-1. Epub 2017 Feb 17.
[121] Piscuoglio S, Ng CK, Murray M, Burke KA, Edelweiss M, Geyer FC, et al. Massively parallel sequencing of phyllodes tumours of the breast reveals actionable mutations, and TERT promoter hotspot mutations and TERT gene amplification as likely drivers of progression. J Pathol. 2016;238(4):508–18. https://doi.org/10.1002/path.4672. Epub 2016 Jan 25.
[122] Ho SK, Thike AA, Cheok PY, Tse GM, Tan PH. Phyllodes tumours of the breast: the role of CD34, vascular endothelial growth factor and β-catenin in histological grading and clinical outcome. Histopathology 2013 Sep;63(3):393–406. https://doi.org/10.1111/his.12177. Epub 2013 Jun 18. PMID: 23772632.
[123] Giant Cell Tumor of Tendon Sheath/Pigmented Villonodular Synovitis. In: Murray F. Brennan, Cristina R. Antonescu, Kaled M. Alektiar. Second edition. Switzerland: Springer International Publishing; 2016. p. 361-362.
[124] Nakayama R, Jagannathan JP, Ramaiya N, et al. Clinical characteristics and treatment outcomes in six cases of malignant tenosynovial giant cell tumor: initial experience of molecularly targeted therapy. BMC Cancer. 2018;18(1):1296. https://doi.org/10.1186/s12885-018-5188-6. Published 2018 Dec 29.
[125] Chen EL, de Castro CM4th, Hendzel KD, et al. Histologically benign metastasizing tenosynovial giant cell tumor mimicking metastatic malignancy: A case report and review of literature. Radiol Case Rep 2019; 14(8): 934–940. Published 2019 May 24. https://doi:10.1016/j.radcr.2019.05.013.
[126] West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci U S A. 2006;103(3):690–5. https://doi.org/10.1073/pnas.0507321103.
[127] Ho J, Peters T, Dickson BC, Swanson D, et al. Detection of CSF1 rearrangements deleting the 3' UTR in tenosynovial giant cell tumors. Genes Chromosomes Cancer. 2020 Feb;59(2):96–105. https://doi.org/10.1002/gcc.22807.
[128] Möller E, Mandahl N, Mertens F, Panagopoulos I. Molecular identification of COL6A3-CSF1 fusion transcripts in tenosynovial giant cell tumors. Genes Chromosomes Cancer. 2008;47(1):21–5. https://doi.org/10.1002/gcc.20501.
[129] Panagopoulos I, Brandal P, Gorunova L, Bjerkehagen B, Heim S. Novel CSF1-S100A10 fusion gene and CSF1 transcript identified by RNA sequencing in tenosynovial giant cell tumors. Int J Oncol. 2014;44(5):1425–32. https://doi.org/10.3892/ijo.2014.2326.
[130] Staals EL, Ferrari S, Donati DM, Palmerini E. Diffuse-type tenosynovial giant cell tumour: Current treatment concepts and future perspectives. Eur J Cancer. 2016; 63:34–40. https://doi.org/10.1016/j.ejca.2016.04.022.
[131] Gouin F, Noailles T. Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented villonodular synovitis). Orthop Traumatol Surg Res. 2017;103(1S):S91–7. https://doi.org/10.1016/j.otsr.2016.11.002.
[132] Mastboom MJL, Palmerini E, Verspoor FGM, et al. Surgical outcomes of patients with diffuse-type tenosynovial giant-cell tumours: an international, retrospective, cohort study. Lancet Oncol. 2019;20(6):877–86. https://doi.org/10.1016/S1470-2045(19)30100-7.
[133] Gortzak Y, Vitenberg M, Frenkel Rutenberg T, Kollender Y, Dadia S, Sternheim A, et al. Inconclusive benefit of adjuvant 90Yttrium hydroxyapatite to radiosynovectomy for diffuse-type tenosynovial giant-cell tumour of the knee. Bone Joint J. 2018;100-B(7):984–8. https://doi.org/10.1302/0301-620X.100B7.BJJ-2017-0867.R3.
[134] Heyd R, Micke O, Berger B, et al. Radiation therapy for treatment of pigmented villonodular synovitis: results of a national patterns of care study. Int J Radiat Oncol Biol Phys. 2010;78(1):199–204. https://doi.org/10.1016/j.ijrobp.2009.07.1747.
[135] O'Sullivan B, Cummings B, Catton C, et al. Outcome following radiation treatment for high-risk pigmented villonodular synovitis. Int J Radiat Oncol Biol Phys. 1995;32(3):777–86. https://doi.org/10.1016/0360-3016(95)00514-Y.
[136] Tap WD, Wainberg ZA, Anthony SP, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. N Engl J Med. 2015;373(5):428–37. https://doi.org/10.1056/NEJMoa1411366.
[137] https://www.esmo.org/oncology-news/ema-recommends-refusal-of-the-marketing-authorisation-for-pexidartinib. Last accessed October 2020.
[138] Blay JY, El Sayadi H, Thiesse P, Garret J, Ray-Coquard I. Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). Ann Oncol. 2008;19(4):821–2. https://doi.org/10.1093/annonc/mdn033.
[139] Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer 2012;118(6):1649–55. https://doi.org/10.1002/cncr.26409.
[140] Cannarile MA, Weisser M, Jacob W, Jegg AM, Ries CH, Rüttinger D. Colony-stimulating factor 1 receptor (CSF1R) inhibitors in cancer therapy. J Immunother Cancer. 2017;5(1):53. https://doi.org/10.1186/s40425-017-0257-y. Epub 2020 Feb 7.
[141] Suurmeijer AJH, Dickson BC, Swanson D, Zhang L, Sung YS, Fletcher CD, et al. A morphologic and molecular reappraisal of myoepithelial tumors of soft tissue, bone, and viscera with EWSR1 and FUS gene rearrangements. Genes Chromosomes Cancer. 2020;59(6):348–56. https://doi.org/10.1002/gcc.22835. Epub 2020 Feb 7.
[142] Mostly Benign/Rarely Metastasizing - Myoepithelial Tumors of Soft Tissue. In: Murray F. Brennan, Cristina R. Antonescu, Kaled M. Alektiar. Second edition. Switzerland: Springer International Publishing; 2016. p. 361-362.
[143] Miettinen M, McCue PA, Sarlomo-Rikala M, et al. Sox10–a marker for not only schwannian and melanocytic neoplasms but also myoepithelial cell tumors of soft tissue: a systematic analysis of 5134 tumors. Am J Surg Pathol. 2015;39(6): 826–35. https://doi.org/10.1097/PAS.0000000000000398.
[144] Komatsu M, Kawamoto T, Kanzawa M, et al. A novel EWSR1-VGLL1 gene fusion in a soft tissue malignant myoepithelial tumor. Genes Chromosomes Cancer. 2020;59(4):249–54. https://doi.org/10.1002/gcc.22823.
[145] Jo VY, Fletcher CD. Myoepithelial neoplasms of soft tissue: an updated review of the clinicopathologic, immunophenotypic, and genetic features. Head Neck Pathol. 2015;9(1):32–8. https://doi.org/10.1007/s12105-015-0618-0.
[146] LeBlanc RE, Taube J. Myofibroma, Myopericytoma, Myoepithelioma, and Myofibroblastoma of Skin and Soft Tissue. Surg Pathol Clin. 2011;4(3):745–59. https://doi.org/10.1016/j.path.2011.08.003.
[147] Gleason BC, Hornick JL. Myoepithelial tumours of skin and soft tissue: an update. Diagnostic Histopatol. 2008;14(11):552–62.
[148] Miccio JA, Oladeru OT, Yang J, Xue Y, Hoda ST, Ryu S, et al. The role of radiation therapy. A case report and analysis of data from the Surveillance, Epidemiology,

and End Results (SEER) registry. J Pediatr Hematol Oncol 2016 May;38(4):274–8. https://doi.org/10.1097/MPH.0000000000000508.
[149] Chamberlain F, Cojocaru E, Scaranti M, et al. Adult soft tissue myoepithelial carcinoma: treatment outcomes and efficacy of chemotherapy. Med Oncol. 2019; 37(2):13. https://doi.org/10.1007/s12032-019-1335-4. Published 2019 Dec 27.
[150] Hornick JL, Fletcher CD. PEComa: what do we know so far? Histopathology 2006; 48:75–82. https://doi.org/10.1111/j.1365-2559.2005.02316.
[151] Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol. 2005;29(12):1558–75. https://doi.org/10.1097/01.pas.0000173232.22117.37.
[152] Thway K, Fisher C. PEComa: morphology and genetics of a complex tumor family. Ann Diagn Pathol. 2015;19:359–68. https://doi.org/10.1016/j.anndiagpath.2015.06.003.
[153] Weiss SW, Goldblum JR. Enzinger and Weiss's Soft Tissue Tumors. 7th ed. Philadelphia, PA: Elsevier; 2020.
[154] Martignoni G, Pea M, Reghellin D, Zamboni G, Bonetti F. PEComas: the past, the present and the future. Virchows Arch. 2008;452:119–32. https://doi.org/10.1007/s00428-007-0509-1.
[155] Agaram NP, Sung YS, Zhang L, Chen CL, Chen HW, Singer S, et al. Dichotomy of Genetic Abnormalities in PEComas With Therapeutic Implications. Am J Surg Pathol. 2015;39:813–25. https://doi.org/10.1097/PAS.0000000000000389.
[156] Argani P, Zhong M, Reuter VE, Fallon JT, Epstein JI, Netto GJ, et al. TFE3-fusion variant analysis defines specific clinicopathologic associations among Xp11 translocation cancers. Am J Surg Pathol. 2016 Jun;40(6):723–37. https://doi.org/10.1097/PAS.0000000000000631.
[157] Akumalla S, Madison R, Lin DI, Schrock AB, Yakirevich E, Rosenzweig M, et al. Characterization of clinical cases of malignant PEComa via comprehensive genomic profiling of DNA and RNA. Oncology. 2020;98(12):905–12. https://doi.org/10.1159/000510241. Epub 2020 Sep 23.
[158] Bleeker JS, Quevedo JF, Folpe AL. "Malignant" perivascular epithelioid cell neoplasm: risk stratification and treatment strategies. Sarcoma. 2012;2012: 541626. https://doi.org/10.1155/2012/541626.
[159] Kirste S, Kayser G, Zipfel A, Grosu AL, Brunner T. Unresectable hepatic PEComa: a rare malignancy treated with stereotactic body radiation therapy (SBRT) followed by complete resection. Radiat Oncol. 2018;13(1):28. https://doi.org/10.1186/s13014-018-0974-5.
[160] Ben-Ami Eytan, Hornick Jason L, Wagner Andrew J. The potential of emerging new therapeutics for the treatment of perivascular epithelioid cell tumors (PEComa). Expert Opin Orphan Drugs 2018;6(9):537–43. https://doi.org/10.1080/21678707.2018.1493376.
[161] Sanfilippo R, Jones RL, Blay JY, et al. Role of Chemotherapy, VEGFR Inhibitors, and mTOR Inhibitors in Advanced Perivascular Epithelioid Cell Tumors (PEComas). Clin Cancer Res 2019;25(17):5295–300. https://doi.org/10.1158/1078-0432.CCR-19-0288.
[162] Wagner AJ, Ravi V, Grigorian B, Schmid A.N, Hou S, Harris K, et al. Long-term follow-up from ampect, an open-label phase 2 registration trial of nab-sirolimus for patients with advanced malignant perivascular epithelioid cell tumors (PECOMA). Paper #29, 3463014. CTOS 2020.
[163] Sanfilippo R, Fabbroni C, Fucà G, Fumagalli E, Morosi C, Sbaraglia M, et al. Addition of antiestrogen treatment in patients with malignant PEComa progressing to mTOR inhibitors. Clin Cancer Res 2020 Jun 30. doi: 10.1158/1078-0432.CCR-20-1191. Epub ahead of print. PMID: 32605908.
[164] Drilon AD, Popat S, Bhuchar G, et al. Extraskeletal myxoid chondrosarcoma: a retrospective review from 2 referral centers emphasizing long-term outcomes with surgery and chemotherapy. Cancer 2008;113(12):3364–71. https://doi.org/10.1002/cncr.23978.
[165] Panagopoulos I, Mertens F, Isaksson M, et al. Molecular genetic characterization of the EWS/CHN and RBP56/CHN fusion genes in extraskeletal myxoid chondrosarcoma. Genes Chromosomes Cancer. 2002;35(4):340–52. https://doi.org/10.1002/gcc.10127.
[166] Agaram NP, Zhang L, Sung YS, Singer S, Antonescu CR. Extraskeletal myxoid chondrosarcoma with non-EWSR1-NR4A3 variant fusions correlate with rhabdoid phenotype and high-grade morphology. Hum Pathol. 2014;45(5):1084–91. https://doi.org/10.1016/j.humpath.2014.01.007.
[167] Benini S, Cocchi S, Gamberi G, et al. Diagnostic utility of molecular investigation in extraskeletal myxoid chondrosarcoma. J Mol Diagn. 2014;16(3):314–23. https://doi.org/10.1016/j.jmoldx.2013.12.002.
[168] Broehm CJ, Wu J, Gullapalli RR, Bocklage T. Extraskeletal myxoid chondrosarcoma with a t(9;16)(q22;p11.2) resulting in a NR4A3-FUS fusion. Cancer Genet. 2014;207(6):276–80. https://doi.org/10.1016/j.cancergen.2014.06.024.
[169] Bishop AJ, Bird JE, Conley AP, et al. Extraskeletal myxoid chondrosarcomas: combined modality therapy with both radiation and surgery improves local control. Am J Clin Oncol. 2019;42(10):744–8. https://doi.org/10.1097/COC.0000000000000590.
[170] Kemmerer EJ, Gleeson E, Poli J, Ownbey RT, Brady LW, Bowne WB. Benefit of radiotherapy in extraskeletal myxoid chondrosarcoma: A propensity score weighted population-based analysis of the SEER database. Am J Clin Oncol 2018; 41(7):674–80. https://doi.org/10.1097/COC.0000000000000341.
[171] Stacchiotti S, Baldi GG, Morosi C, Gronchi A, Maestro R. Extraskeletal myxoid chondrosarcoma: state of the art and current research on biology and clinical management. Cancers (Basel). 2020;12(9). https://doi.org/10.3390/cancers12092703. E2703.
[172] Stacchiotti S, Dagrada GP, Sanfilippo R, et al. Anthracycline-based chemotherapy in extraskeletal myxoid chondrosarcoma: a retrospective study. Clin Sarcoma Res. 2013;3(1):16. https://doi.org/10.1186/2045-3329-3-16. Published 2013 Dec 18.
[173] Chiusole B, Le Cesne A, Rastrelli M, Maruzzo M, Lorenzi M, Cappellesso R, et al. Extraskeletal myxoid chondrosarcoma: clinical and molecular characteristics and outcomes of patients treated at two institutions. Front Oncol. 2020;10:828. https://doi.org/10.3389/fonc.2020.00828.
[174] Stacchiotti S, Ferrari S, Redondo A, et al. Pazopanib for treatment of advanced extraskeletal myxoid chondrosarcoma: a multicentre, single-arm, phase 2 trial [published correction appears in Lancet Oncol. 2019 Oct;20(10):e559]. Lancet Oncol 2019;20(9):1252–62. https://doi.org/10.1016/S1470-2045(19)30319-5.
[175] Stacchiotti S, Pantaleo MA, Astolfi A, et al. Activity of sunitinib in extraskeletal myxoid chondrosarcoma. Eur J Cancer. 2014;50(9):1657–64. https://doi.org/10.1016/j.ejca.2014.03.013.
[176] Provenzano S, et al. Sunitinib (SM) in advanced extraskeletal myxoid chondrosarcoma (EMC): Updated analysis in 11 patients (pts). J Clin Oncol 2016; 34(suppl; abstr 11059).
[177] Martin-Broto J, Hindi N, Grignani G, Martinez-Trufero J, Redondo A, Valverde C, et al. Nivolumab and sunitinib combination in advanced soft tissue sarcomas: a multicenter, single-arm, phase Ib/II trial. J Immunother Cancer. 2020;8(2). https://doi.org/10.1136/jitc-2020-001561. e001561.
[178] Suurmeijer AJ, Antonescu CR. NTRK-rearranged spindle cell neoplasm ((emerging). World Health Organization Classification of Tumors. 5th ed. Lyon: IARC Press; 2020.
[179] Antonescu CR. Emerging soft tissue tumors with kinase fusions: An overview of the recent literature with an emphasis on diagnostic criteria. Genes Chromosomes Cancer 2020 Apr 3. https://doi: 10.1002/gcc.22846.
[180] Demetri GD, Antonescu CR, Bjerkehagen B, et al. Diagnosis and management of tropomyosin receptor kinase (TRK) fusion sarcomas: expert recommendations from the World Sarcoma Network. Ann Oncol. 2020;31(11):1506–17. https://doi.org/10.1016/j.annonc.2020.08.2232. Epub 2020 Sep 3.
[181] Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378(8):731–9. https://doi.org/10.1056/NEJMoa1714448.
[182] Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. Lancet Oncol. 2020 Feb;21(2): 271–82. https://doi.org/10.1016/S1470-2045(19)30691-6.
[183] Demetri GD, Albert CM, Tan DSW, Bielack S, Orbach D, DuBois SG, et al. Larotrectinib Efficacy and Safety in Patients with TRK Fusion Sarcomas. CTOS Meeting 2019 Tokio, abst: 3254588.
[184] Liu SV,1 Paz-Ares L, Hu J, Wolf J, Cho BC,Krzakowski M, et al. Entrectinib in NTRK Fusion-Positive Sarcoma: Integrated Analysis of Patients Enrolled in STARTRK-2, STARTRK-1 and ALKA-372-001. . CTOS Meeting 2019 Tokio, abst: 3255999.
[185] Drilon A, Nagasubramanian R, Blake JF, Ku N, Tuch BB, Ebata K, et al. A next-generation TRK kinase inhibitor overcomes acquired resistance to prior TRK kinase inhibition in patients with TRK fusion-positive solid tumors. Cancer Discov 2017;7:963–72.
[186] Drilon A, Ou SI, Cho BC, Kim DW, Lee J, Lin JJ, et al. Repotrectinib (TPX-0005) Is a Next-Generation ROS1/TRK/ALK Inhibitor That Potently Inhibits ROS1/TRK/ALK Solvent- Front Mutations. Cancer Discov. 2018;8:1227–36.
[187] Cocco E, Schram AM, Kulick A, Misale S, Won HH, Yaeger R, et al. Resistance to TRK inhibition mediated by convergent MAPK pathway activation. Nat Med. 2019;25:1422–7.
[188] Al-Salama ZT, Keam SJ. Entrectinib: First Global Approval. Drugs. 2019;79(13): 1477–83. https://doi.org/10.1007/s40265-019-01177-y.
[189] Scott LJ. Larotrectinib: First Global Approval. Drugs 2019;79(2):201–6. https://doi.org/10.1007/s40265-018-1044-x.
[190] Crombé A, Brisse HJ, Ledoux P, Haddag-Miliani L, Bouhamama A, Taieb S, et al. Alveolar soft-part sarcoma: can MRI help discriminating from other soft-tissue tumors? A study of the French sarcoma group. Eur Radiol 2019;29(6):3170–82. https://doi.org/10.1007/s00330-018-5903-3.
[191] McCarville MB, Kao SC, Dao TV, Gaffney C, Coffin CM, Parham DM, et al. Magnetic resonance and computed tomography imaging features of epithelioid sarcoma in children and young adults with pathological and clinical correlation: a report from Children's Oncology Group study ARST0332. Pediatr Radiol 2019;49 (7):922–32. https://doi.org/10.1007/s00247-019-04389-2.
[192] De Beuckeleer LH, De Schepper AM, Vandevenne JE, Bloem JL, Davies AM, Oudkerk M, et al. MR imaging of clear cell sarcoma (malignant melanoma of the soft parts): a multicenter correlative MRI-pathology study of 21 cases and literature review. Skeletal Radiol 2000;29(4):187–95. https://doi.org/10.1007/s002560050592.
[193] Thomas R, Rajeswaran G, Thway K, Benson C, Shahabuddin K, Moskovic E. Desmoplastic small round cell tumour: the radiological, pathological and clinical features. Insights Imaging 2013;4(1):111–8. https://doi.org/10.1007/s13244-012-0212-x.
[194] Abdullah A, Patel Y, Lewis TJ, Elsamaloty H, Strobel S. Extrarenal malignant rhabdoid tumors: radiologic findings with histopathologic correlation. Cancer Imaging. 2010;10(1):97–101. https://doi.org/10.1102/1470-7330.2010.0010. Published 2010 Mar 18.
[195] Plaza MJ, Swintelski C, Yaziji H, Torres-Salichs M, Esserman LE. Phyllodes tumor: review of key imaging characteristics. Breast Dis 2015;35(2):79–86. https://doi.org/10.3233/BD-150399.
[196] Schvartzman P, Carrozza V, Pascual T, Mazza L, Odesser M, San Román JL. Radiological features of pigmented villonodular synovitis and giant cell tumor of

tendon sheath. Rev Argentina Radiol 2015;79(1):4–11. https://doi.org/10.1016/j.rard.2014.10.005.
[197] Rekhi B, Joshi S, Panchwagh Y, et al. Clinicopathological features of five unusual cases of intraosseous myoepithelial carcinomas, mimicking conventional primary bone tumours, including EWSR1 rearrangement in one case. APMIS. 2016;124(4):278–90. https://doi.org/10.1111/apm.12506.
[198] Phillips CH, Keraliya AR, Shinagare AB, Ramaiya NH, Tirumani SH. Update on the imaging of malignant perivascular epithelioid cell tumors (PEComas). Abdom Radiol [Internet]. 2016;41(2):368–76. https://doi.org/10.1007/s00261-015-0568-8.
[199] Kapoor N, Shinagare AB, Jagannathan JP, Shah SH, Krajewski KM, Hornick JL, et al. Clinical and radiologic features of extraskeletal myxoid chondrosarcoma including initial presentation, local recurrence, and metastases. Radiol Oncol. 2014;48(3):235–42. https://doi.org/10.2478/raon-2014-0005.
[200] Cupp JS, Miller MA, Montgomery KD, Nielsen TO, O'Connell JX, Huntsman D, et al. Translocation and expression of CSF1 in pigmented villonodular synovitis, tenosynovial giant cell tumor, rheumatoid arthritis and other reactive synovitides. Am J Surg Pathol. 2007;31:970–6. https://doi.org/10.1097/PAS.0b013e31802b86f8.