STANDARD CLINICAL PRACTICE RECOMMENDATIONS FOR PATIENTS WITH NON-RHABDOMYOSARCOMA SOFT TISSUE SARCOMAS AND OTHER RARE SOFT TISSUE NEOPLASMS

DOCUMENT VERSION 1.0 23.03.2026

DISCLAIMER:

These ESCP guidance documents were produced by the relevant tumour group or specialist committee as recommendations on current best practice. The ESCP guidance documents are not clinical trial protocols.

The interpretation and responsibility of the use of ESCP guidance documents lies fully with the user who retains full responsibility for the use of these guidance documents and his actions and (treatment) decisions based thereon, such as, but without limitation thereto: checking and prescribing certain doses, checking prescriptions, etc. A user should never base its decision solely on the content of these guidance documents and should always check any other relevant medical information that is available and make appropriate use of all relevant medical information.

These guidance documents have been made publicly available by SIOP Europe – the European Society of Paediatric Oncology and the European Reference Network for Paediatric Oncology (ERN PaedCan). It is the responsibility of the user who downloads these documents to make sure that:

- their use within the Paediatric Clinical Unit / Hospital is approved according to the local clinical governance procedures.

The ERN PaedCan received funding by the European Union's Health Programme (2014-2020), grant agreement nr. 847032.

- appropriate document control measures are in place to ensure that the most up to date locally approved versions are considered.

- any anomalies or discrepancies within the documents are immediately brought to the attention of the relevant special interest group chair and the European Clinical Study Group who has developed the ESCP guidance document.

Every care has been taken whilst preparing these documents to ensure that they are free of errors. Nonetheless, SIOP Europe and ERN PaedCan cannot be held liable for possible errors or mistakes in these guidance documents, nor can SIOP Europe and ERN PaedCan be held liable for any kind of damage resulting out of the use of these guidance documents.

INTRODUCTORY PAGES

- Paediatric Non-Rhabdomyosarcoma Soft Tissue Sarcoma
- Other rare Soft Tissue Neoplasms
- Document version 1.0, 23.03.2026

This document has been developed by:
Writing Committee: Eva Brack, Monika Sparber-Sauer and Andrea Ferrari (paediatric oncology)
Collaborators: Gabriela Guillén (Surgery), Laura Hiemcke (Pathology), Herve Brisse (Imaging), Martin Ebinger and Daniel Orbach (Paediatric Oncology) and Akmal Safwat (Radiotherapy)

Planned review date: TBD

Table of contents

1. BACKGROUND AND RATIONALE

1.1 Background

Non-Rhabdomyosarcoma soft tissue sarcomas (NRSTS) form a heterogeneous group of malignancies of presumed mesenchymal origin. The World Health Organization (WHO) classification of NRSTS comprises around 80 different entities, based on distinct histological, morphological, immune-histochemical and molecular features[1]. Although NRSTS only account for less than 1% of malignancies in the general population, they represent about 3-4% of all malignancies in children and adolescents[2]. Seventy-five percent of all NRSTS that occur in children and adolescents are diagnosed in the older age group between 15 and 19 years[3,4]. The most common histologic subtypes are infantile fibrosarcoma in infants, whereas, synovial sarcoma, malignant peripheral nerve sheath tumour and malignant fibrous histiocytoma, now called “undifferentiated pleomorphic sarcoma” (UPS) are the most common entities in the older age group of adolescents[5,6,7].

Prognostic factors and outcome vary between the different subgroups but the most common factors that influence survival include age, extent and stage of disease, histotype, pathology grading, tumour size and tumour site[8-11]. Therefore, due to these multiple varying factors and the resulting heterogeneity of STS, it is only possible to provide a general statement on curability and survival of children and adolescents diagnosed with NRSTS: Overall, survival rate is around 70%[12].

The clinical presentation can be very heterogeneous and varies depending on the primary tumour site. NRSTS can occur in any part of the body; however, the most common localizations are the extremities, followed by the trunk. Delay of diagnosis is unfortunately common due to this heterogeneous clinical presentation[13].

Regional lymph node involvement is also infrequent, occurring in about 3-6% of most NRSTS, though again this varies depending on the specific tumour type. Notably, clear cell sarcoma and epithelioid sarcoma exhibit higher rates, with lymph node involvement observed in up to 18% and 14-22% of cases, respectively[14-16]. Presence of lymph node involvement significantly worsens prognosis[17-22]. However, patients with isolated LN metastases have a high 5-year OS (approximately 85%) and should be treated with curative intent[23].

Primary metastases are uncommon in NRSTS (approximately 5%), and the lung is their most common localization (60%)[9,10,24,25]. However, prevalence of metastatic disease reaches 5-15% in the more aggressive subtypes of “adult-type” NRSTS and synovial sarcoma[25-28].

Historically, therapeutic approaches in children have been based on experiences extrapolated from rhabdomyosarcoma (RMS) studies and from experiences in adult patients. So far, two large prospective international clinical trials, namely COG ARST0332 and E*p*SSG NRSTS 2005 have generated data on the systematic treatment and outcome of children with NRSTS. In addition, data from two large-scale prospective European trials have been recently published, CWS-96 and CWS-2002P [29]. This guideline is based on these four trials.

2. PATIENT MONITORING AND ASSESSMENT

2.1 Patient Group

The clinical practice guideline should be used in patients with a pathologically confirmed diagnosis of NRSTS and other rare soft tissue neoplasms. Due to the complexity of these tumours, only the most common subtypes can be discussed here (see section Histopathology) [30]:

Further, the guideline is valid for patients

- With localized or metastatic disease
- At first diagnosis
- At relapse/recurrence
- With NRSTS as secondary malignancy
- Who are pre-treated or
- With cancer predisposition syndromes

In patients with NRSTS as a secondary malignancy, in pre-treated patients with pre-existing illnesses or a cancer predisposition syndrome, a treatment adaptation may be needed considering the treatment already delivered and the pre-existing morbidities. The treating-physician may need to adapt the guideline correspondingly.

2.2 Diagnostic Criteria

Histology and biology of paediatric Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS)

NRSTS encompass a heterogeneous group of malignancies in children and adolescents, varying significantly in histology, biology, and clinical behaviour. Paediatric NRSTS presents unique challenges in diagnosis, treatment, and prognostication due to this diversity. Recent advances in the molecular understanding of NRSTS have paved the way for classification that is more refined and prognostic systems, as well as the identification of potential therapeutic targets [31-35]

Classification and Grading of NRSTS

The World Health Organization (WHO) has recently updated its classification of soft tissue and bone tumours, providing a more precise categorization that reflects the unique molecular and histologic features of these tumours[1,36]. The new WHO classification recognizes specific subtypes within NRSTS, many of which are defined by particular genetic alterations and molecular profiles. This classification assists clinicians in tailoring treatment approaches and in identifying tumours with distinct clinical behaviours, enabling a more personalized approach to patient care[34,36] .

Tumour grading has a crucial role in predicting outcomes and guiding therapeutic decisions in NRSTS[37]. Histological grading assesses parameters such as cellular differentiation, mitotic activity, and necrosis to stratify tumours into low, intermediate, and high grades. The French grading system (Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)), widely applied in the

evaluation of paediatric soft tissue sarcomas, categorizes tumours based on three main factors: degree of differentiation, mitotic count, and the presence of necrosis. Scores for each parameter are combined to classify tumours into grades I, II, or III, providing prognostic information and aiding in therapeutic stratification [38] .

Biology and Molecular Characterization

NRSTS comprises a wide array of biologically distinct tumours, each defined by unique genetic and molecular profiles. Molecular characterization has revealed a spectrum of alterations, from simple translocations leading to specific fusion proteins to complex genomic profiles with numerous mutations and structural changes. Key molecular pathways involved in NRSTS include abnormalities in cell cycle regulation, growth factor signalling, and chromatin remodelling, with each subtype of NRSTS often associated with characteristic genetic mutations or translocations. For instance, synovial sarcomas typically harbour the *SS18::SSX* fusion gene, the main driver of tumourigenesis[39,40].

Understanding these molecular drivers of NRSTS has implications beyond classification. Identifying specific genetic mutations and expression profiles contributes to knowledge of tumorigenesis and allows researchers to uncover new molecular prognostic variables. These prognostic variables can potentially stratify patients more accurately, tailoring treatment plans to individuals based on molecular risk factors[31-33,35].

Toward a Molecular Approach: Tumorigenesis and Targeted Therapy

Ongoing research into the tumorigenesis of NRSTS aims to identify molecular targets that could lead to novel therapeutic options. Identifying pathways essential to tumour survival and progression, which could be disrupted and halt disease progression is the main goal. As the understanding of NRSTS biology expands, new prognostic markers will likely emerge, allowing for more refined risk stratification.

The identification of molecular targets also opens avenues for targeted therapies, which can inhibit specific signalling pathways or genetic alterations involved in tumour growth. Examples include NTRK inhibitors targeting TRK fusion in infantile fibrosarcoma or ALK inhibitors in inflammatory myofibroblastic tumours[41-43, 44]. These targeted approaches, combined with traditional therapies, may offer new hope for improving outcomes in paediatric NRSTS patients, especially those with high-grade or refractory disease.

2.3 Initial Assessment

The following assessments and procedures should be performed prior to start of treatment and might need to be adopted depending on final diagnosis and the facilities at the specific centre. Pre-treatment work-up, should be completed as soon as possible to avoid any delay of the beginning of treatment. A full medical history, including personal and family history (including potential cancer predisposition syndromes as NF-1, TP53 pathogenic variant or other syndromes) is mandatory. Physical examination

should be thoroughly taken, including vital signs, height, weight, and assessment of specific clinical signs at the tumour site and potential lymph node involvement.

The prevailing standard approach necessitates the categorization of NRSTS patients based on pivotal prognostic indicators. These include the detection of distant and nodal metastases, histologic grade, size of the primary tumour (≤5 cm versus >5 cm), and the extent of surgical resection. Through this approach, a risk-adapted stratification is achieved, enabling the delineation of appropriate indications for various multimodal therapeutic interventions[45].

2.3.1 Imaging Modalities

The imaging investigations listed below are based on the current INSTRuCT - imaging working group recommendations [46] and need to be adapted to the given tumour type and situation:

1. Local Investigations: Initial imaging often begins with an ultrasound, which is typically the first examination. It can be a useful tool to plan the diagnostic biopsy or to monitor certain lesions, but has no role in monitoring treatment response.

   MRI Scan: MRIs should also be conducted for detailed local assessment. In NRSTS this the main imaging modality. The field of view should include loco-regional lymph nodes and the expected loco-regional extension of the tumour (for extremities, this means the whole limb needs to be examined). Besides routine T1 and T2 weighted sequences and post Gadolinium sequences, diffusion-weighted MRI images should be taken[47,48]. Imaging of the primary site should include tumour volume measurement and examination of regional lymph nodes especially if not evaluable clinically or if clinically suspicious.

2. Distant Metastasis Assessment: For assessing distant metastases, a lung CT is recommended as a primary imaging modality. Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG-PET/CT) scans are valuable for evaluating broader metastatic spread. Bone scintigraphy is only recommended when 18F-FDG-PET/CT is unavailable. Additional imaging, such as brain MRI or bone CT, may be considered for specific clinical indications:

   Brain MRI: At the staging phase, patients diagnosed with alveolar soft part sarcoma, clear-cell sarcoma, and angiosarcoma are advised to undergo brain MRI as part of their evaluation process.

   Whole Body MRI: In patients with myxoid liposarcomas, staging with whole body MRI is recommended.

   Chest CT scan/radiography: Chest CT is the primary method for detecting pulmonary metastases in clinical practice and is recommended for a better characterization when suspicious pulmonary lesions are found on chest-x ray. However, for patients with low-risk NRSTS - defined as FNCLCC grade 1 or 2, small tumour size (< 5 cm), and/or complete

resection at diagnosis (IRS I) - a chest x-ray in two orthogonal planes may suffice instead of chest CT, due to the very low risk of lung metastasis. Periodic monitoring of pulmonary nodules should be conducted using chest CT in patients with previous lung metastases and with x-ray in patients without pulmonary nodules. 1 mm to max 1.5 mm slice thickness of the CT scan are acceptable and images in axial and coronal plane should be taken. In order to improve sensitivity, maximum intensity projections should be taken in high-grade NRSTS[49].

FDG-PET-CT/MRI or whole-body MRI: For all NRSTS patients presenting with lung metastases, irrespective of grade, screening with 18F-FDG-PET CT is strongly recommended to ascertain the presence of extra-pulmonary disease. Furthermore, in cases of FNCLCC grade 3 NRSTS; including those without lung metastases, the multidisciplinary team may consider staging with 18F-FDG-PET CT. In small, low grade NRSTS 18F-FDG-PET CT imaging is not recommended. The images should be done according to current European Association of Nuclear Medicine (EANM) guidelines[50].

Interpretation of radiological findings

A thorough assessment and interpretation of the radiological findings is crucial not only for staging purposes, to discuss the tumour resectability at any time of treatment but also for treatment response control and remission status evaluation.

The images should be interpreted at least using the RECIST 1.1 guideline for a proper response monitoring and discussed in national/international tumour-boards [51]. The method of assessment should be the same in all successive imaging to assure the greatest reproducibility.

Primary tumour site

On cross-sectional images, all lesions must be measured by utilizing either one-dimensional (1D) or three-dimensional (3D) methodologies. However, considering the current evidence, there are no conclusive recommendations regarding the preference for either 1D or 3D measurements. Therefore, it is advisable to adhere to protocol recommendations until further evidence emerges. Furthermore, irrespective of the measurement method employed, it is imperative to maintain consistency in the measurement methodologies[46,52].

Lymph nodes

Locoregional and distant lymph node assessment may be critical for staging. Although involvement of locoregional lymph nodes in NRSTS is generally uncommon, with incidence rates for the whole group ranging from 3% to 4% [25,30] , routine assessment is not warranted for most histological subtypes[23]. However, the likelihood of locoregional lymph node involvement varies depending on tumour histology and biological characteristics, reaching as high as 18% in clear cell sarcoma (CCS) and 14–22% in epithelioid sarcoma, [14,27,53-57]. Therefore, evaluation of locoregional lymph nodes is recommended for these diagnoses. Furthermore, assessment of locoregional lymph nodes is advised for paediatric patients with extra cranial malignant rhabdoid tumour due to its propensity for nodal metastases[58]. On the other hand, spread to lymph nodes is much rarer in alveolar soft part sarcoma (ASPS) and

angiosarcoma [14,27,53-57] . In some histotypes, lymph node spread is essentially never present (liposarcoma, leiomyosarcoma …) and therefore any clinical suspicion should be pathologically confirmed to assure appropriate tumour staging.
Discrimination between pathological and normal lymph nodes (LN) on imaging can be challenging. MRI and FDG PET-CT/MRI scans are the best imaging tools; however, US imaging can also be very helpful here if performed by an experienced radiographer. Furthermore, ultrasound can be useful in assessing whether lymph node architecture is normal or disrupted. On MRI, pathologic lymph nodes must measure at least 15 mm in short axis. Loco-regional nodes smaller than 15 mm which show only peripheral enhancement (necrotic centre) are likely to be involved by tumour as well.
On FDG PET-CT/MRI visual assessment using the Deauville-score, with liver uptake as reference tissue, is recommended. In addition, FDG positive lymph nodes with a short axis smaller 15 mm should be considered suspicious.
It is highly recommended, that all doubtful or suspected lymph nodes undergo a lymph-node sampling if technically feasible and without major risks[59]. Given the low incidence of nodal disease in NRSTS, routine random lymph node sampling or sentinel node biopsy without radiological/clinical suspicion is not mandatory [60], except in cases of clear cell sarcoma (CS), epithelioid sarcoma (ES), extra cranial malignant rhabdoid tumour and angiosarcoma where it is considered mandatory [23,60].
Regional lymph nodes are those appropriate to the site of the primary tumour: see appendix 3“Definition of Sites”.

Pulmonary lesions

Assessment of pulmonary lesions is critical for proper staging and can be very challenging, as without tissue a distinction between benign unspecific lesions and lung metastases may be impossible[61,62].
Although no international consensus exists how to define metastatic disease in NRSTS,
the EpSSG criteria for defining lung disease can be used:

- No metastatic disease, defined as no pulmonary lesions present.
- Pulmonary metastases, defined, in the absence for other causes of the lesion/radiological explanation, as the presence of either:
  One or more pulmonary nodules of 10 mm or more diameter
  Or two or more well-defined nodules of 5 to 10 mm diameter
  Or five or more well-defined nodules of less than 5 mm
- 4 or nodules smaller 5 mm at diagnosis will not be considered as pulmonary metastatic disease and are classified as “non-specific pulmonary lesions”[63].

As in rhabdomyosarcoma (RMS), a recent European study evaluated the clinical significance of indeterminate pulmonary nodules, defined as no more than four pulmonary nodules measuring less than 5 mm each, or a single nodule measuring between 5 and less than 10 mm, detected by CT scan

in NRSTS. The investigators found, that survival outcomes did not differ between patients presenting with indeterminate pulmonary nodules and those without pulmonary nodules[64,65].
In case of doubt, a pathology confirmation before any therapy should be discussed through surgical resection or transthoracic imaging guided biopsy.

2.3.2 Other

Laboratory analyses and organ function

1. Complete full blood count (Haemoglobin Hb, White blood cells (WBC), platelets, lymphocytes, neutrophils),

3. Creatinine and serum electrolytes

4. Liver function tests (ALAT (GPT), ASAT (GOT), GGT, bilirubin), Serum albumin

5. TSH and fT4, and IGF-1, IGF-BP3, ACTH/Cortisol for patients with huge skull base primary

6. Coagulation screen (INR, PT)

7. Serum virology according to local policies

8. Cardiac function tests if chemotherapy planned

9. Pregnancy test for female patients of childbearing age

Fertility considerations

Semen cryopreservation before treatment should be offered to post-pubertal male patients and ovarian cortical tissue harvesting or egg cryopreservation to female patients who are likely to receive pelvis radiation or chemotherapy according to local standard practice[66,67].

2.4 Tumour Biopsy

2.4.1 Primary tumour site

It is crucial, that the primary biopsy is done in the same expert oncology centre where the definitive resection is foreseen. If a sarcoma is suspected, a biopsy first of the suspected lesion should be performed, without any attempt of immediate primary resection before any final diagnosis. In very rare cases and in very small tumours that can be easily resected with expected microscopic negative margins without mutilating consequences a primary resection can be considered after multidisciplinary discussion[68,69].

To ensure proper diagnostics and obtain enough tissue for biology studies and biobanking, enough tumour material needs to be obtained via an image-guided coaxial core needle, incisional, or endoscopic biopsy. Image-guided core needle biopsy (CNB), using a 14/16 Gauge needle, obtaining a minimum of 4 to 8 cores, is the preferred approach. CNBs should be the method of choice over an incisional biopsy (IB) as both procedures deliver similar results and a CNB brings fewer complications compared to IB[70]. Major neurovascular structures should not be touched. The biopsy must be carefully planned in order to include the scar and biopsy track in the definitive surgical resection or radiotherapy field. IB on

extremities should be longitudinal to the limb, avoiding the needle traversing several tissue compartments. If not necessary, drains should be avoided and if needed, the drain tract needs to be in the definitive surgical resection area. Fine needle biopsies are discouraged.

2.4.2 Lymph node biopsy [18,19,60,71]

If lymph node involvement is suspected, clinically or radiologically, lymph node biopsy should be performed if feasible, and this can be achieved surgically or with image-guided core-needle biopsy. Sentinel lymph node dissection (SLND) might be helpful for those histologies with a high incidence of nodal disease, although evidence is very limited. LN cyto-aspiration may be useful if positive.

2.4.3 Bone marrow biopsy

Evaluation of a potential bone marrow involvement should no longer be performed, as it rarely occurs in NRSTS.

2.4.4 Lumbar puncture

Although very rare, in parameningeal head and neck tumours, or tumours surrounding the spine (paraspinal), a lumbar puncture should be done for cerebral spinal fluid examination with cell count and cytospins to search for tumour cells (in the case of a spinal tumour compression, a lumbar puncture is a clear contraindication and must be avoided). Further, according to the histotype further imaging of the spine, liver, kidneys and CNS is indicated (Rhabdoid or primary thoracic myofibroblastic tumours).

3. STAGING

So far, no staging system has systematically been validated in NRSTS in children. Mostly NRSTS are staged according to the Intergroup Rhabdomyosarcoma Study Group surgical-pathological grouping system (IRS) and the International Union Against Cancer staging system[72]. Most specialists agree to use both staging systems to determine the degree of disease. They can be found in Appendix 1

4. TUMOUR ENTITIES BACKGROUND AND TREATMENT RECOMMENDATIONS

The term NRSTS describes a very heterogeneous group of malignant tumours arising from mesenchymal, extra skeletal tissues with a spectrum of clinical behaviour, which ranges from relatively benign to highly malignant[1]. In this guideline, not every NRSTS can be discussed and the focus lies on the most common NRSTS in children and adolescents. The summary here is no comprehensive review, but shall provide an overview of the histopathological background and biology of the discussed entities. For more details, please refer to Enzinger & Weiss, Diagnostic Soft Tissue Pathology, and WHO Classification of Tumours of Soft Tissue and Bone[73-75].

Historically, a subgroup of NRSTS were grouped into “adult-type NRSTS” [9] with the idea to group certain entities, which were homogeneous in their clinical behaviour[9] and to be able to give treatment

recommendations. A better understanding of the molecular background and biology of these tumours has led to a revision of the classification and was adopted in the E*p*SSG NRSTS 2005 protocol[30,63].

The classification and management of adult-type NRSTS have evolved considerably over the years, guided by multidisciplinary collaboration and international consensus efforts. Not every entity mentioned here, will be further discussed in more detail. Adult-type NRSTS requiring the same therapeutic approach include synovial sarcoma, malignant peripheral nerve sheath tumour (MPNST), adult-type fibrosarcoma, epithelioid sarcoma, leiomyosarcoma, liposarcoma, angiosarcoma and undifferentiated high-grade pleomorphic sarcoma. Contrasted with these are the group of adult-type NRSTS requiring a distinct and specific therapeutic approach like alveolar soft part sarcoma, clear cell sarcoma, and dermatofibrosarcoma protuberans. Besides these adult-type NRSTS other malignant soft tissue tumours (rhabdoid tumour, desmoplastic small round cell tumour, undifferentiated soft part sarcoma, undifferentiated sarcoma of the liver, BCOR family/CIC-rearranged undifferentiated sarcomas) and tumours of intermediate malignancy (desmoid-type fibromatosis (DTF), infantile fibrosarcoma (IFS), inflammatory myofibroblastic tumours (IMT), epithelioid hemangioendothelioma) all requiring specific therapeutic approaches can be distinguished[9,11,30].

4.1 Adult-type NRSTS

Adult-type NRSTS encompasses a broad spectrum of histological subtypes, each characterized by unique clinical and pathological features, as well as variable responses to treatment (Table1). These sarcomas typically manifest as localized masses in soft tissues of the extremities, trunk, or retroperitoneum, with occasional involvement of deeper structures such as viscera or bone. Despite advances in diagnostic techniques and therapeutic modalities, adult-type NRSTS remain a therapeutic challenge due to their heterogeneity and propensity for local recurrence and distant metastasis.

Histological subtyping and grading, molecular profiling, and risk stratification are pivotal in tailoring treatment strategies, which often include a combination of surgery, radiotherapy, and chemotherapy. However, optimal management approaches continue to evolve, driven by ongoing research endeavours aimed at elucidating the underlying molecular mechanisms driving tumorigenesis and therapeutic resistance.

Adult-type NRSTS (with same and distinct therapeutic approach) and other malignant and intermediate STS

Surgery remains the mainstay of treatment. Targeted therapy (e.g. ALK inhibitors) may be effective in advanced disease.			
Histotype	**Peak of Incidence**	**Molecular Finding**	**Clinical Characteristics**
Adult-type NRSTS requiring the same therapeutic approach			

Synovial sarcoma	2nd-3rd decade	*SS18::SSX1/SSX2* fusion (t(X;18)(p11;q11))	Most frequent NRSTS histotype in paediatric age. Often arises near joints (extremities), possible axial location (worse prognosis). Metastatic potential (mainly to the lungs); more sensitive to chemotherapy (ifosfamide-doxorubicin) than other NRSTS.
Malignant peripheral nerve sheath tumour (MPNST)	3rd-4th decade	Loss of rearrangement of 10p, 11q, 17q and 22q, complex karyotype	Relatively frequent in paediatric age. Aggressive tumour, often associated with neurofibromatosis type 1, developing on a pre-existing plexiform neurofibroma. Axial location. Tends to occur along major nerves. Marked local invasiveness and scarce response to chemotherapy. Frequent lung metastases.
Epithelioid sarcoma	3rd decade	SMARCB1/INI1 mutation, P13 K-Akt-mTOR signalling pathway alteration	Painless, slow-growing mass often in distal extremities (e.g. fingers). High risk of lymph node metastasis and local recurrence
Fibrosarcoma (adult-type)	4th-5th decade	Rare, but sometimes NTRK1 rearrangements, t (2;5) and t (7;22)	Typically presents as a deep-seated soft tissue mass. May be aggressive with a tendency for local recurrence.
Angiosarcoma	7th decade	VEGF signalling pathway alterations	Very aggressive vascular tumour often involving skin, breast, liver, or deep tissues. Frequently metastasizes early. Poor prognosis. Could be primary tumour or a secondary malignancy after radiotherapy
Leiomyosarcoma	6th decade	Complex karyotype; no specific fusion	Typical of adults, rare in paediatric age. Malignant smooth muscle tumour, often arising from uterus, retroperitoneum, or blood vessels. High propensity for haematogenous spread.
Liposarcoma	6th-7th decade	Amplifications MDM2, CDK4 in well-/dedifferentiated types, t (12;16), t (12;22) in myxoid subtype	Typical of adults, rare in paediatric age. Arises most commonly in the deep soft tissues of limbs or retroperitoneum. Behaviour varies greatly depending on histologic subtype.
Undifferentiated high-grade pleomorphic sarcoma	6th-7th decade	Complex genetic alterations; no specific translocation	Highly aggressive soft tissue sarcoma presenting as a rapidly enlarging mass.

			Frequent distant metastasis, mainly to the lungs.
Adult-type NRSTS requiring a distinct and specific therapeutic approach			
Alveolar Soft Part Sarcoma	3rd decade	*ASPSCR1::TFE3* fusion (t (X;17) (p11;q25))	Rare, slow-growing but highly metastatic tumour, often affecting the deep soft tissues of extremities. Characterized by vascular metastases to lungs and brain. Standard chemotherapy is generally not effective. Promising data with immune checkpoint inhibitors and tyrosine kinase inhibitors.
Clear cell sarcoma	3rd-4th decade	*EWSR1::ATF1* fusion (t (12 ;22) (q13 q12)), t (9;22)	Melanoma-like tumour arising in tendons and aponeuroses. High risk of local recurrence, nodal disease and distant metastasis. Standard chemotherapy is generally not effective. Promising data with immune checkpoint inhibitors.
Extra-cranial rhabdoid tumour	First 5 years	SMARCB1 (INI1) mutations/deletions	Typical of young children. Highly aggressive tumour seen in kidneys, liver or soft tissues. Poor prognosis despite intensive multidrug therapy.
Desmoplastic small round cell tumour	2nd-3rd decade	*EWSR1::WT1* fusion (t(11;22)(p13;q12))	Very aggressive intra-abdominal tumour. Multiple peritoneal, hepatic, lymph node and distant metastasis common at diagnosis. Poor prognosis.
Undifferentiated soft part sarcoma	Variable	No specific genetic finding	Heterogeneous group of aggressive sarcomas without clear line of differentiation. Clinical behaviour similar to high-grade sarcomas.
Undifferentiated sarcoma of the liver (UES)	Paediatric onset	Often associated with complex karyotypes and cytogenetic aberration in chromosome 19q13.4	Rare liver tumour in children characterized by aggressive behaviour and symptoms (pain, fever) with negative tumour markers. Relatively good response to conventional chemotherapy [76,77].
BCOR family / CIC-rearranged undifferentiated sarcomas	Adolescents and young adults	*BCOR::CCNB3* or BCOR -ITD (for BCOR sarcoma); *CIC::DUX4* (for CIC sarcoma)	Highly aggressive sarcomas with poor prognosis. Tend to arise in deep soft tissues or viscera, often with early metastasis.
Soft tissue tumours of intermediate malignancy requiring specific therapeutic approaches			

Dermatofibrosarcoma protuberans	3rd-5th decade	*COL1A1::PDGFB* fusion (t(17;22)(q22;q13))	Slow-growing cutaneous tumour, often on the trunk. High local recurrence rate but rarely metastasizes. Specific surgical treatment (Mohs technique). Discuss imatinib in case of unresectable tumour.
Desmoid-type fibromatosis	3rd-4th decade	CTNNB1 or APC mutations	Locally aggressive fibroblastic neoplasm with no metastatic potential. High risk of local recurrence, often requiring multimodal treatment. Wait-and-see strategy adopted in non-evolving disease. Low-morbidity systemic treatment is the first choice in evolving disease.
Infantile Fibrosarcoma	1st year	*ETV6::NTRK3* fusion (t(12;15)(p13;q25))	Soft tissue tumour of infants with rapid growth but favourable prognosis. Responsive to chemotherapy and to targeted therapies like TRK inhibitors.
Inflammatory myofibroblastic tumours	Children, young adults	ALK rearrangements (~50%); also, ROS1, NTRK fusions	Spindle cell tumour with inflammatory infiltrate. Surgery remains the mainstay of treatment. Targeted therapy (e.g. ALK inhibitors) is effective in advanced disease.
Epithelioid hemangioendothelioma	Young to middle-aged adults	*WWTR1::CAMTA1* or *YAP1::TFE3* fusions	Vascular tumour of intermediate malignancy, often involving liver, lung, or bone. Clinical behaviour ranges from indolent to aggressive.

Table 1: “Adult-type” soft tissue sarcomas and other malignant and intermediate soft tissue sarcomas with their peak incidence, molecular findings and clinical characteristics.

4.1.1 Treatment approach to adult-type NRSTS

The multidisciplinary team(MDT) should discuss the patients’ individual treatment, ideally before any surgical procedure, considering the specific pathology of the disease, the patient’s age, the anatomical site and extent of the tumour. Treatment might consist of one modality or the combination of several, depending on the treatment group the patient has been assigned to. Current E*p*SSG recommendations divide patients into four treatment groups based on: surgical stage according to the Intergroup Rhabdomyosarcoma Study (IRS) post-surgical group classification[78], tumour size, nodal involvement, and histopathological tumour grade (tumour site is added as a criterion for synovial sarcoma)[24]. Please see table 2 for a comprehensive overview.

Adult-type NRSTS are mostly insensitive towards chemotherapy with response rates less than 50%[79]. Radiotherapy is another treatment possibility; however, indications should take into consideration the inherent higher risk of severe late effects. Surgery is still the standard treatment for many subtypes, but also needs thorough discussion in a MDT beforehand.

Treatment group	Histotypes	Variables	Treatment
SURGERY ALONE group	synovial sarcoma	IRS group I, tumor size ≤5 cm	initial resection only no adjuvant treatment
	"adult-type" NRSTS	IRS group I, ≤5 cm, any tumor grade	
		IRS group I, >5 cm, G1	
		IRS group II, any size, G1	
ADJUVANT RADIOTHERAPY group	"adult-type" NRSTS	IRS group I, >5 cm, G2	radiotherapy 50.4 Gy
		IRS group II, ≤5 cm, G2-G3	radiotherapy 54 Gy
		IRS group II, >5 cm, G2	
ADJUVANT CHEMOTHERAPY group (± radiotherapy)	synovial sarcoma	IRS group I, >5 cm	IFO-DOXO IFO-DOXO IFO-DOXO IFO-DOXO
		IRS group II, ≤5 cm	IFO-DOXO IFO-DOXO IFO-DOXO radiotherapy 50.4 Gy
		IRS group II, >5 cm	IFO-DOXO IFO-DOXO IFO-DOXO IFO IFO radiotherapy 54 Gy IFO-DOXO
		axial site or resected N1	
	"adult-type" NRSTS	IRS group I-II, >5 cm, G3 or resected N1	
NEOADJUVANT CHEMOTHERAPY group (± radiotherapy)	synovial sarcoma	IRS group III (unresected disease) or unresected N1	IFO-DOXO IFO-DOXO IFO-DOXO surgery ⇩ IFO IFO radiotherapy 50.4-59.4 Gy IFO-DOXO ± IFO-DOXO*
	"adult-type" NRSTS		

Table 2

EpSSG standard-risk stratification and treatment recommendations for local/locoregional adult-type NRSTS and synovial sarcoma[80]. Adapted from[30].

Surgery

Surgery continues to stand as the cornerstone of treatment. Recent trials [25,24,29] underscored the significance of complete surgical resection as a critical prognostic factor in paediatric Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS). These trials have confirmed that the extent of surgical resection (tumour-resected vs unresectable) strongly influences treatment outcomes in paediatric NRSTS.

Ferrari et al. (2005) analysed a cohort of 40 IRS group III paediatric patients with adult-type NRSTS. The study highlighted the importance of achieving complete surgical resection, as the 5-year overall survival (OS) rate was 80% for patients who underwent complete delayed surgery alone, rising to 86%

for those who received surgery followed by radiotherapy. In contrast, the OS dropped significantly to 36% in patients who did not achieve complete resection, regardless of whether radiotherapy was administered[9]. In comparison, Spunt et al. conducted a larger prospective study under the Children's Oncology Group (ARST0332), involving 529 patients under 30 years of age with NRSTS. This study provided a more comprehensive analysis, stratifying outcomes by risk groups. Patients in the low-risk group had excellent outcomes with a 5-year OS of 98%, while those in the intermediate- and high-risk groups experienced progressively lower survival rates of 75% and 35%, respectively[25]. The findings from this larger cohort underscored the importance of risk-adapted treatment strategies, including surgery and multimodal therapy. Similar results were confirmed by Ferrari et al. in their analysis of the NRSTS2005 study conducted by the E*p*SSG[30], analysing the largest prospectively enrolled cohort of paediatric patients with adult-type NRSTS (569 patients). Furthermore, the study demonstrated that a subset of patients with low-risk tumours, completely resected, were safely managed by surgery alone (5-year OS of 98%). Also, neoadjuvant treatment for IRS III tumours allowed for an increased rate of complete surgical resection, when compared with historical series. Heinz et al. analyzed 483 patients in CWS-96 and 445 patients in CWS-2002P with NRSTS[29]. These studies before and parallel to NRSTS 2005 confirmed the importance of complete resection. In addition, the data showed that radiotherapy was not needed in completely resected tumours. Similar to results of NRSTS 2005, 5-year EFS were 82% in the low-risk group in contrast to 59% in the high-risk groups in both trials. Local radiation seems important in patients after incomplete resection R1.

Preoperative biopsy allows to establishment of adequate surgical planning, based on the tumour´s histology. The extent of surgery should be meticulously deliberated and tailored to the individual patient, considering factors such as anatomical site, relation to important surrounding structures, tumour size, patient's age, and response to initial chemotherapy. The overarching objective is to attain optimal local control, while carefully considering potential treatment sequelae and prioritizing the preservation of function. The surgical management should be entrusted to experienced surgeons specializing in the treatment of soft tissue sarcomas. The surgical approach entails a wide excision aiming for microscopically negative margins (R0), denoting the absence of tumour at the margins. R1 resection refers to an excision where there is evidence of tumour microscopically at the margins, but without visible tumour residue on the resection surface. R2 resection denotes excision where there is visible tumour at the margins or when the tumour is incompletely resected, leading to residual tumour presence on postoperative imaging. Contaminated surgery occurs when there is an unintentional rupture of the tumour pseudocapsule, resulting in the spillage of tumour material into the operative field. In such instances, every effort must be made to control the spillage of material promptly[81,82].

Depending on the time point of surgery, different types of resections can be distinguished. Each type of resection has its unique considerations regarding treatment goals, surgical approach, and potential impact on patient outcomes. The choice of resection type is based on a thorough evaluation of individual patient factors, tumour characteristics, treatment response, and multidisciplinary team consensus:

Primary Resection: This is the initial surgical intervention performed to remove the primary tumour without any prior treatment. It should only be performed if complete resection with negative margins

(R0) is deemed feasible (for definition see above). The surgical specimen must be adequately orientated for pathology examination.

Pre-treatment re-excision: Or "primary re-excision" (PRE), is performed after primary resection, when the pathology margins are positive, with the aim of achieving an R0 resection. A wide, non-mutilating re-excision of the operative site with sufficient margins of normal tissue is performed. The primary goal of PRE is to enhance the quality of the resection by converting an incomplete resection (R1 or R2) to a complete resection. The interval between primary resection and PRE should not be longer than 8 weeks.

Delayed Excision: In this approach, surgery is performed after administering preoperative neoadjuvant therapy, such as chemotherapy or radiation therapy. The goal is to shrink the tumour, making it more amenable to surgical removal and potentially reducing the extent of surgery required. If R0 is not feasible without mutilation or disfigurement, the MDT must consider the possibility of administering other adjuvant treatments.

Palliative Resection: This type of surgery is performed with the primary goal of symptom relief or improvement in quality of life rather than with a curative intent. It may involve debulking or partial resection of tumours to alleviate symptoms such as pain or obstruction, and it is the only scenario in which debulking can be considered as a valid treatment option.

Chemotherapy [83-87]

The standard systemic treatment protocol typically involves the administration of ifosfamide-doxorubicin (Ifo/Doxo) chemotherapy. Historically rooted in adult sarcoma management, this regimen has been widely adopted in the paediatric setting. Pre-operative chemotherapy is commonly employed in cases of local or locoregional disease, serving as a frontline therapy for patients with locally advanced disease, or when surgical resection with clear margins is uncertain. Chemotherapy is preferably administered in the neoadjuvant setting, where it may aid in converting cases into conservative complete resections and promptly addressing any micrometastases.

Debate persists regarding the necessity of adjuvant chemotherapy for adult-type NRSTS to mitigate distant recurrences following initial surgery. Several studies have explored this issue, with varying conclusions. Reports indicate that patients with high tumour grade and large tumour size are at increased risk of metastases post-resection, suggesting potential survival benefits associated with (neo) adjuvant chemotherapy, irrespective of the extent of initial surgery.

In the trials investigating NRSTS within the CWS-96 and CWS-2002P protocols[29], no prognostic benefit was observed with an increased anthracycline dose of 320 mg/m² compared to 240 mg/m². The reported 5-year event-free survival (EFS) and overall survival (OS) rates were 60% [56–64] and 72% [69–76], respectively. These outcomes are comparable to those observed in the "neoadjuvant chemotherapy group" of the E*p*SSG NRSTS 2005 [88] study, which reported 5-year EFS and OS rates of 56% [49–63] and 70% [63–76], respectively. CWS data further validated these findings through a post-hoc analysis, which included synovial sarcoma and "adult-type NRSTS" similar to the NRSTS 2005 cohort, with 5-year EFS and OS rates of 62% and 76%, respectively. Comparable results were also reported by the

Children's Oncology Group (COG) for the "non-metastatic/unresectable" subgroup[89,90]. Given the equivalent outcomes achieved with the Ifo/Doxo regimen[88,89], consideration could be given to reducing the cumulative dose of doxorubicin or/ and reduction of overall cycles in future protocols[89,91,92]. Additionally, the inclusion of vincristine and actinomycin-D, as implemented in earlier CWS protocols, does not appear to provide a justifiable benefit and may not be warranted.

Depending on the treatment group, different regimens should be used (see table 2 above and Appendix):

Six courses are recommended for synovial sarcoma, while seven courses are advised for other adult-type NRSTS. Chemotherapy cycles are scheduled every 21 days.

IFO-DOXO regimen consists of ifosfamide (3 g/m² per day intravenously, for 3 days) in combination with doxorubicin (37.5 mg/m² intravenously per day for 2 days).

IFO regimen comprises ifosfamide alone (3 g/m² intravenously per day for 2 days).

Ifosfamide administration should be accompanied by hyperhydration and uromitexan infusion (4.5 g/m² per day intravenously) according to local practice.

Radiotherapy[49,93-98]:

The role of radiotherapy (RT) may be carefully considered and typically varies depending on several factors including tumour size, location, grade, extent of surgical resection, response to chemotherapy and the patient's age. In general, radiotherapy may be recommended as part of the treatment approach in paediatric NRSTS for several indications.

Adjuvant Therapy: In cases, where complete surgical resection is not achievable or where there is a high risk of local recurrence, adjuvant radiotherapy may be recommended to reduce the risk of recurrence.

Neoadjuvant (preoperative) Therapy: Radiotherapy may be administered preoperatively (neoadjuvant therapy) to shrink the tumour size, facilitate surgical resection, and improve the likelihood of achieving negative surgical margins.

Definitive Therapy: For certain inoperable cases, definitive radical radiotherapy is a feasible option that should be considered. When definitive radiotherapy is given, it is usually as an initial phase of 50.4 or 54 Gray (Gy) depending on the initial tumour size followed by a boost to a total dose 59.4 Gy (in 33 fractions). In the rare event of R2 resection (residual macroscopic disease) the same approach is used for postoperative radiotherapy with a boost dose delivered to this macroscopic residual to a total dose of 59.4 Gy. This treatment could be given simultaneously as an integrated boost.

Palliative Therapy: In cases where the tumour is unresectable or where metastatic disease is present, radiotherapy may be used as palliative therapy to alleviate symptoms, reduce tumour burden, and improve quality of life.

The target volume should include the extend of the disease at the diagnosis, and any current visible disease, as well as a suitable margin (1-2 cm). This volume is usually then modified to account for

specific anatomic barriers to tumour spread and any anatomical changes at time of radiotherapy delineation. The regional lymph nodes are not part of the target volume unless proven positive LN following biopsy, or when the pathology of lymphadenectomy showed positive node involvement.

The standard approach involves conventional fractionation, with a dose of 1.8 Gy administered per day, five days per week. However, in certain cases where patients are undergoing radiotherapy with large field sizes, such as whole abdomino-pelvic or whole lung radiotherapy, or in patients younger than three years old, the dose per fraction may be reduced to 1.5-1.6 Gy to minimize the risk of toxicity. Radiotherapy treatment options encompass a range of modalities tailored to individual patient needs. These may include photon-based techniques such as intensity-modulated radiation therapy (IMRT), electron beam therapy, proton or particle therapy, and brachytherapy, depending on the clinical context and specific requirements of each case. For selected patients with metastatic disease, stereotactic ablative radiotherapy also known as stereotactic body radiation therapy (SBRT or SRT), can also be considered as an effective treatment approach.

Each modality offers distinct advantages and considerations, and the choice of radiotherapy technique and timing is determined through careful evaluation by a multidisciplinary team to optimize treatment outcomes while minimizing potential risks and side effects.

Brachytherapy is an effective radiation therapy modality that delivers high doses of radiation directly to the tumour site with limited exposure to surrounding healthy tissues. Particularly in challenging anatomical locations or recurrent cases, brachytherapy offers a valuable option for achieving local control while minimizing the adverse effects associated with external beam radiation. In certain regions, where precision is crucial due to the proximity of critical organs, brachytherapy, used as part of a multimodal approach, may result in favourable local control and survival outcomes with a manageable toxicity profile, emphasizing the importance of this therapy in complex NRSTS cases where other modalities might be limited[99,100].

Proton Beam Therapy (PBT) presents a promising alternative due to its unique depth-dose characteristics, which allow for more precise tumour targeting while sparing surrounding healthy tissues. Furthermore, similar to conventional irradiation, PBT can effectively target complex tumour shapes and depths, providing high conformity even in anatomically challenging locations. Although the dosimetric advantages of PBT over traditional photon-based RT are acknowledged, clear evidence of its therapeutic superiority is still lacking. Data collection and comparative studies face challenges due to the limited number of proton therapy facilities and the rarity of referred NRSTS cases[101-103].

4.2 Treatment Recommendations for specific histiotypes

Alveolar soft part sarcoma (ASPS), clear cell sarcoma (CCS), and dermatofibrosarcoma protuberans (DFSP) warrant distinct treatment recommendations. In addition, specific treatment recommendations are also essential for other highly malignant tumours characterized by distinct biological features and clinical responses to treatment, which differ from those of adult-type NRSTS. Among these challenging histotypes are rhabdoid tumours and desmoplastic small round cell tumours (DSRCT). Lastly, the extensive spectrum of NRSTS also encompasses three specific entities categorized as soft tissue

tumours of intermediate malignancy (high risk of local recurrence but low tendency to metastasize): desmoid-type fibromatosis, inflammatory myofibroblastic tumour (IMT), and infantile fibrosarcoma (IFS). The approach to the treatment of these three sarcomas has changed over the years and differs from the more aggressive subtypes. For details, please refer to the summaries below (Chapter 5).

In Summary

Comprehensive treatment recommendations and standard-of-care protocols play a crucial role in optimizing outcomes for patients with adult-type NRSTS. These guidelines are informed by a synthesis of evidence-based practices based on clinical trial data, and expert consensus opinions, with the overarching goal of achieving maximal disease control while minimizing treatment-related morbidity and long-term sequelae.

In the present review, we aim to provide an overview of the current landscape of adult-type NRSTS treatment, and treatment for other "more common" NRSTS encompassing epidemiology, histopathological classification, molecular biology, clinical presentation, diagnostic evaluation, prognostic factors, and therapeutic management. Additionally, we will discuss emerging trends in treatment paradigms, ongoing research initiatives, and future directions in the field, with a focus on optimizing outcomes and improving quality of life for patients afflicted with these challenging malignancies.

Concerning treatment recommendations, NRSTS should only be treated in experienced oncology centres with a multidisciplinary team approach, as many different disciplines are needed in the care of these complex patients.

4.3 Low-grade or "intermediate, rarely metastasizing" locally aggressive sarcomas/" sarcoma-likes"[25,68]

These entities include low-grade fibromyxoid sarcoma, angiomatoid fibrous histiocytoma, plexiform fibrohistiocytic sarcoma, solitary fibrous tumour, low-grade myofibroblastic sarcoma, giant cell tumour of soft tissue, pseudomyogenic hemangioendothelioma, retiform hemangioendothelioma, low-grade undifferentiated sarcoma NOS, low-grade undifferentiated spindle cell sarcoma and represent a heterogeneous group of tumours characterized by limited metastatic potential, but with a propensity for local recurrence. Currently there is not a uniform WHO categorization for these heterogeneous entities, rather their clinical behaviour unifies them into one category.

In adults, the main risk associated with low-grade NRSTS (low-grade soft tissue sarcoma; LG-STS) is local recurrence, with an apparently higher risk in the presence of positive margins, with little risk of metastases. The cornerstone strategy for these LG-STS focuses on local therapy consisting of primary surgery with or without radiotherapy. The quality of surgery is the major predictive factor for overall survival (OS), event-free survival (EFS) and Locoregional Relapse-Free Survival (LRRFS) in almost all NRSTS.

Overall survival is estimated at approximately 75%, with a 13% incidence of local relapse (LR) after macroscopically complete tumour resection (R0: microscopically negative; R1: microscopically positive margins). The local relapse rate differs markedly by margin status—about 7% for R0 and 30% for R1 resections.

Paediatric studies on low-grade soft tissue sarcomas, particularly low-grade fibromyxoid sarcoma (LG-FMS) and undifferentiated low-grade sarcomas, have demonstrated similar outcomes, with a 5-year EFS of 90.4% (95% CI, 84.3–97.0) after surgery alone in 85% of patients. The predominant tumour event is local relapse or progression, occurring in roughly 14.8% of cases after R1 resection. These findings support immediate re-excision when feasible. However, given the absence of a significant difference in survival between immediate and delayed re-excision, surgical management at the time of relapse may be a reasonable alternative in selected cases, provided patients are closely monitored.

The role of adjuvant radiotherapy remains unvalidated and is therefore not routinely indicated. However, its use should be discussed on an individualized, multidisciplinary basis, considering factors such as patient age, tumour site, margin status, and follow-up feasibility. Because local recurrences may arise even after long disease-free intervals—up to five years post-treatment, prolonged surveillance is essential.

5. SUBTYPES

5.1 Synovial Sarcoma (SS)

Synovial sarcoma is one of the most common NRSTS in children, adolescents and young adults. It accounts for 42% of paediatric non- rhabdomyosarcoma soft tissue sarcomas and around 8%-10% of all STSs in children with an annual incidence of 0.8 per million in children[104]. The male: female ratio is about 1:1 and the peak incidence is in the third decade of life[40,105].

SS are characterised by a specific translocation t(X;18)(p11.2; q11.2), resulting in the fusion of SS18 gene and one of three closely related genes SSX1, SSX2 and SSX4, which is found in more than 90% of cases. This leads to altered transcription and activation of target genes. The fusion gene SS18::SSX1 is found in two third of the cases [106-108].

Histologically, SS can be subcategorised into three different subtypes: monophasic (spindle cell), biphasic (epithelioid and spindle cells), and poorly differentiated. This latter subtype is rare in children. All histological subtypes are considered high-grade tumours with local invasiveness and the potential to metastasize[80].

Immunohistochemistry shows reactivity for cytokeratin (especially 7 and 19), epithelial membrane antigen, vimentin, and bcl 2 protein, as well as S100 protein and CD99 (MIC2), and stains negative for CD34[39].

It was demonstrated that the SS18-SSX fusion protein competes for assembly with wild-type SS18, forming an altered complex lacking the tumour suppressor BAF47 (hSNF5). The altered complex binds the Sox2 locus and reverses polycomb-mediated repression, resulting in Sox2 activation. Sox2 is uniformly expressed in SS tumours and is essential for proliferation[109].

Most commonly, SS arise in the lower extremities (62%) and upper extremities (21%), followed by the abdomen (7%) and the head and neck (3%) region. Lymph node involvement is uncommon (4%) [23] and only about 10% of the patients show distant metastasis at diagnosis[40,105].

Up until the E*p*SSG NRSTS 2005 study opened, most paediatric patients with SS were treated according to protocols designed for rhabdomyosarcoma with an intensive multidrug chemotherapy and adjuvant chemotherapy for all patients, even if they had completely excised, small tumours[82,110].

Synovial sarcoma (SS) is always considered a high-grade tumour. Treatment approaches for SS are similar to other adult-type NRSTS, but stratification considers factors such as tumour grade, size, and site, with axial tumours typically associated with a worse prognosis."[111,112].

The newer generation of studies from the Children's Oncology Group (COG) and the European *paediatric* Soft tissue sarcoma Study Group (E*p*SSG) has significantly changed the treatment approach for SS. The E*p*SSG data is especially important to highlight, as it shows that low-risk SS patients are now treated without chemotherapy—a major shift from the pre-2005 approach, where the same patients would have received up to nine courses of chemotherapy, as was standard for RMS[113]. The 5-year EFS and OS were 80.7% and 90.7%, respectively[30], achieving better survival rates compared to former published studies[104,112]. Low risk tumours (<5cm) are treated with surgery alone, if microscopically complete resection is achievable (resulting in IRS I). Patients with IRS group II and tumours >5cm are treated with surgery plus adjuvant chemotherapy +/- radiotherapy and IRS group III patients with neoadjuvant chemotherapy, surgery and radiotherapy.

CWS data demonstrated a 5-year EFS and OS of 82.9% ± 5.7% (95% CI) and 92.5% ± 3.9%, respectively[114], which are comparable to the outcomes reported in the E*p*SSG NRSTS 2005 study, where patients with localized synovial sarcoma achieved 5-year EFS and OS rates of 80.7% and 90.7%, respectively[30].

A significant difference between the protocols lies in the chemotherapy regimens used. In the CWS trials, the four-drug VAIA regimen (Vincristine, Actinomycin D, Ifosfamide, and Adriamycin) was employed, while the E*p*SSG study utilized the Ifo/Doxo regimen [88], which included patients with tumours smaller than 5 cm. Given the comparable 5-year EFS and OS rates observed in the CWS and E*p*SSG cohorts, we advocate for a unified European treatment protocol for synovial sarcoma using the Ifo/Doxo regimen[29]. This approach has the added advantage of avoiding vincristine-associated toxicity. The clinical benefit of actinomycin D remains unproven and warrants further investigation. Furthermore, maintenance treatment (MT) with O-TIE demonstrated no survival benefit in the randomized CWS-2007HR study[115].

5.2 Malignant peripheral nerve sheath tumours

Malignant peripheral nerve sheath tumours (MPNST) are aggressive soft tissue sarcomas that arise from the nerve sheath, likely originating from Schwann cells or perineural cells.

In MPNST no specific chromosomal rearrangements have been uncovered by conventional cytogenetics, but a complex karyotype is usually present with loss or rearrangement of 10p, 11q, 17q and 22q[116]. Immunohistochemistry shows reactivity for S100 protein, epithelial membrane antigen,

vimentin, SOXO10 (in 40-60%) and stains negative for CD34, desmin/myogenin/MyoD1 and cytokeratins[117]. Analysis of the American Survival, Epidemiology, and End Results (SEER) database revealed that paediatric cases represent only 14% of 1,182 recorded MPNST cases, with an incidence of 0.56 per million person-years[118,119]. Despite their rarity, MPNST is the third most common subtype of non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) in children[120]. Approximately half of paediatric cases occur in patients with neurofibromatosis type 1 (NF1), a genetic condition characterized by germline pathogenic variants in the *NF1* gene, which predisposes individuals to malignant tumours, primarily MPNST. The lifetime risk of developing MPNST in patients with NF1 is approximately 10%[121,122]. The remaining cases occur sporadically in individuals without NF1, often involving peripheral nerves. While NF1 has traditionally been considered a poor prognostic factor (data from NRSTS 2005 protocol and CWS-details see below), emerging evidence suggests that tumour-specific factors such as deep-seated location and incomplete surgical resection may play a more significant role in outcomes than the underlying biology of NF1-associated MPNST[123,124], making the prognostic role of NF1 disease in MPNST still unclear[125]. Risk of distant metastasis, especially in lungs is important and needs further attention.

Surgical resection is the cornerstone of treatment for MPNST. However, complete resection is often challenging due to the potential for significant neurovascular damage and the presence of large, deep-seated tumours. In definitively unresectable cases, neoadjuvant radiotherapy could be discussed. The role of adjuvant therapies in unresectable cases remains uncertain, with no definitive therapeutic protocols established to date[5,126-129]. Local relapse is common, despite complete resection. Paediatric MPNST carries a poor prognosis, with a 5-year overall survival (OS) of 51% and a 5-year progression-free survival (PFS) of 37%[119].

The NRSTS 2005 protocol from the European paediatric Soft tissue sarcoma Study Group (E*p*SSG) stratified patients by tumour grade, size, and resectability and incorporated local treatment with ifosfamide and doxorubicin chemotherapy[130]. Among 51 patients with localized tumours treated under this protocol, the 5-year event-free survival (EFS) and OS were 52.9% and 62.1%, respectively. Outcomes varied significantly by treatment group, with patients who achieved complete surgical resection demonstrating the best outcomes. The presence of NF1, affecting 51% of patients, emerged as an independent poor prognostic factor for both OS and EFS. However, the use of the standard ifosfamide-doxorubicin regimen was associated with the best-reported outcomes for unresectable MPNST, underscoring its efficacy as a primary treatment approach[130].

Data from the CWS provided further insights into MPNST. In a cohort of 159 patients (all stages), 24% had NF1. Most patients were adolescents with large tumours (>10 cm, 65%), frequently located in the extremities (42%), and a minority presented with nodal or metastatic disease at diagnosis (both 9%). The study reported a 5-year EFS of 40.5% and OS of 54.6%, with similar patterns observed over 10 years (EFS 36.3% and OS 47.1%). Prognostic factors included age, NF1 status, tumour size and site, IRS group, metastatic disease, and achieving first complete remission[131].

Given the comparable outcomes reported in the CWS and E*p*SSG studies, a unified European treatment protocol for MPNST, based on the Ifo/Doxo regimen, is supported. This approach avoids the toxicity

associated with vincristine, while the additional benefit of actinomycin D remains unproven. Maintenance therapy (MT) has not demonstrated a survival benefit. The randomized CWS-2007HR study reported no advantage of MT with O-TIE, and retrospective CWS data on MT with cyclophosphamide/vinblastine similarly showed no benefit[115]. Further research is essential to refine treatment strategies, particularly for patients with NF1 or unresectable disease.

Chemotherapy

The Ifo/Doxo regimen offers a tailored approach, delivering Ifosfamide at 3 g/m² per day for three days and Doxorubicin at 37.5 mg/m² per day for two days. This combination is administered for up to four cycles, with a cumulative doxorubicin dose capped at 300 mg/m². Future trials should focus on lowering the anthracycline doses to 160-240 mg/m^2. Additional cycles of Ifosfamide (3 g/m² per day for two days) are integrated with radiotherapy for patients with larger tumours (>5 cm in IRS Group II) or those in IRS Group III. For intermediate-risk patients, treatment typically involves three to six courses of adjuvant chemotherapy, with radiotherapy as needed. High-risk cases, however, require a more aggressive strategy, comprising six chemotherapy courses, delayed surgery when possible, and radiotherapy. The Ifo/Doxo regimen caps cumulative doses at 48,000 mg/m² for Ifosfamide and 300 mg/m² for Doxorubicin[88].

Local treatment planning in high-risk cases often begins after three cycles of neoadjuvant chemotherapy.

Radiotherapy

Radiotherapy doses are tailored to surgical outcomes for IRS Group III tumours. Without the option for delayed resection, a dose of 59.4 Gy is recommended. Preoperative radiotherapy is set at 50.4 Gy, while postoperative doses vary based on resection margins—50.4 Gy for R0, 54 Gy for R1, and 59.4 Gy for R2 resections. For children under six years of age who achieve secondary complete resections with free margins, additional radiotherapy is generally avoided.

Treatment of metastatic disease

For metastatic disease, the IVADo regimen is recommended as the preferred standard across Europe, given its comparable outcomes to CEVAIE. Maintenance therapy with Cyclophosphamide and Vinorelbine (CYC/VNB) may be considered, though its efficacy remains unproven. Participation in clinical studies, and early-stage trials, is strongly advised to advance treatment knowledge and outcomes.

NF-1 and MPNST

Patients with NF-1 and malignant peripheral nerve sheath tumours (MPNST) require special considerations. The risk of secondary malignancies associated with NF-1 necessitates detailed discussions with families before initiating chemotherapy or radiotherapy (analogous to NRSTS/ adult-type)[130]. However, in most cases therapies are not reduced or modified. Emerging treatments like MEK inhibitors hold promise, particularly for unresectable benign plexiform neurofibromas but only few preclinical data exist on their potential activity in MPNST[131-135], although some early-phase clinical trials are currently recruiting patients (“A Phase 2 Trial of the MEK Inhibitor Selumetinib (AZD6244 Hydrogen

Sulphate) in Combination with the mTOR Inhibitor Sirolimus for Patients with Unresectable or Metastatic Malignant Peripheral Nerve Sheath Tumours. ClinicalTrials.gov ID NCT03433183", and "Early Phase Study Evaluating MEK and MDM2 Inhibition in Patients with NF1 and MPNST (MEKMDM2). ClinicalTrials.gov ID NCT06735820". Decisions regarding the duration and combination of such therapies should remain highly individualized, guided by the treating physician. Families should be thoroughly informed about standard treatments, ongoing research, and potential trial opportunities, with open trials prioritized over individual experimental approaches.

5.3 Alveolar Soft Part Sarcoma

Alveolar soft part sarcomas (ASPS) are very rare sarcomas (< 0.5% of all paediatric sarcomas). In the E*p*SSG NRSTS 2005 trial only 22 patients were registered over 10 years from 15 centres[57,136].

Histologically, ASPS classically appear with large, rounded or polygonal tumour cells with eosinophilic granular or vacuolated cytoplasm and one or more vesicular nuclei forming distinct nests often with central necrosis or loss of cohesion, causing a pseudo-alveolar appearance[137]. Most cases of ASPS express an unbalanced recurrent t(X;17) p(11.2;q25) translocation. This translocation is present as type 1 and 2 variants involving the fusion of the first seven exons of the ASPL (ASPSCR1) gene to exon 6 (type 1) or 5 (type 2) of the *TFE3* transcription factor gene[138].

Immunohistochemically an anti-TFE3 polyclonal antibody staining recognises the carboxy-terminal portion of the TFE3 protein, resulting in strong nuclear staining[137,138].

ASPS shows a peak incidence at 15–35 years. It is more prominent in women with a ratio to 1.5: 1.

In adults, most ASPS can be found is the lower extremities, in children also in the head and neck region, especially the orbit and tongue[139,140]. This tumour is clinically a slowly growing, highly vascularized lesion and should not be confused with an arterio-venous malformation or haemangioma.

ASPS are highly aggressive tumours with a high rate of metastases to the lung and brain. Nevertheless, they often have an indolent course, with long-term survival despite the high rate of metastases[141,142].

In localized ASPS, surgery (possibly combined with radiotherapy) is the treatment of choice, and no adjuvant chemotherapy is recommended [143]

In unresectable/disseminated ASPS, the role of adjuvant/neoadjuvant conventional chemotherapy in ASPS is still under debate. In the E*p*SSG NRSTS 2005 study, the 5-year EFS was 94.7% (95% CI: 68.1–99.2) and the OS is 100%[57]. Here patients received an Ifosfamide/Doxorubicin based treatment with or without radiotherapy[57,143]. Metastatic disease often takes an indolent course. If feasible, multiple focal therapies of distant sites (surgery, stereotaxic irradiation, thermal ablation…) are recommended. The role of chemotherapy in these cases is even more uncertain. However, the indolent character of this disease, even in patients with multiple metastases, lead to first propose a wait and see approach to determine the aggressiveness of the disease. In such situation, only tumours that show progression, may deserve to start therapies. Several studies suggest that targeted agents like Sunitinib, Cediranib, Pazopanib, Tivantinib or Bevacizumab or immune checkpoint inhibitors may be beneficial and prolong survival [143-148]. Further, Azetolizumab seems another promising option[147].

Late metastatic relapse of ASPS after achieving complete remission of localized disease (LD) is a poorly understood phenomenon[11, 16]. Data regarding this scenario are scarce, and the optimal therapeutic approach remains uncertain. To date, few curative treatment options are available for patients with unresectable disease or metastatic disease (MD) [27,57,137,140,149-160]. Further research is needed to identify effective therapeutic strategies for this challenging patient population.

5.4 Clear Cell Sarcoma (CCS) of tendons and aponeuroses

First described by Enzinger in 1965, CCS present a very rare NRSTS, accounting for only 1% of all sarcomas[161].

Histologically, CCS shows melanocytic differentiation, and the tumours are composed of short fascicles of fusiform cells with a clear to granular eosinophilic cytoplasm, vesicular nuclei with prominent nucleoli, and occasional multinucleated giant cells. Melanin and S-100 protein staining are often found positive[162]. Clinico-pathologically and genetically CSS are distinct from conventional malignant melanoma[163]. CCS carries the translocation t(12;22)(q13;q13), which appears to be specific for this sarcoma[163].

CCS usually presents as a slowly growing and frequently painful soft tissue mass, occurring primarily in young adults and rarely in children. It is found at the lower extremities, especially around the ankle and knee, although the overall anatomic distribution is wide. In addition, they show a propensity for lymph node metastases[162,164].

CSS are highly aggressive and classically non-responsive to conventional chemotherapy.[53].

Treatment options and clear recommendations are scarce for patients with CSS. A complete surgical resection represents the treatment of choice, especially for patients with small tumours, with special care to perform lymph node sampling during the procedure. Adjuvant radiotherapy may control microscopic residual disease. Chemotherapy is ineffective and the prognosis is unfavourable for patients with unresectable and large tumours. Unfortunately, there are no paediatric randomized studies, taking into considerations the recent advancements that emphasize the potential of immunotherapy, inspired by promising outcomes in adult studies. However, preliminary data suggest a role of immune checkpoint inhibitors like pembrolizumab, however this needs further evaluation[15,165].

This adult approach reflects a shift away from traditional treatments with limited efficacy, and highlights the growing interest in leveraging immune-based therapies to improve outcomes for CSS patients.

5.5 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma Protuberans (DFSP) are low-grade, small and mainly superficial tumours. They are however, locally aggressive and have relatively high recurrence rates[166,167]. It was first described by Darier and Ferrand in 1924[168].

According to the US “Surveillance, Epidemiology, and End Results (SEER) database”, the overall annual incidence was 0.10 per 100,000 children. The peak incidence is found to be between 15 to 19 years of age. The trunk is the most common site, followed by extremities, while the head and neck region is the least found site. Despite the locally aggressiveness, the tumour rarely metastasizes to lymph nodes or form visceral metastases [167,169].

Histologically, different subtypes can be distinguished: Pigmented DFSP (Bednar tumour), giant cell fibroblastoma (GCF), atrophic DFSP, sclerosing DFSP, granular cell variant, and fibrosarcomatous DFSP. Fibrosarcomatous DFSP is the most aggressive subtype and should be considered as a malignant transformation of a classical DFSP with high recurrence rates and increased risk of distant metastasis. This situation is rare in children and, therefore, deserves to be considered as a high-grade adult-type sarcoma [170]. DFSP is characterized by its ability to invade into the surrounding tissue over a long distance from the main tumour[171].

The main molecular genetic abnormality found in DFSP is the COL1A1-PDGFβ [t (17; 22)] translocation. The chimeric protein *COL1A1::PDGFB* is processed into a functional beta platelet-derived growth factor (PDGFB) ligand that causes the activation of PDGFRB signalling[172]. A rare subset of DFSP has been found to harbour a PDGFD gene rearrangements rather than PDGFB fusions (DFSP with PDGFD rearrangement). A recent study found a further translocation *SLC2A5::BTBD7* [t(1;14)] and several new mutated genes including MUC4/6, KMT2C and BRCA1[173].

DFSP often presents as an asymptomatic, indurated plaque, fixed to the skin of hard consistency. At presentation it mainly measures 1 to 5 cm however would slowly grow if left untreated[174]. Growth is very slow and only a minority of tumours become protuberant[175].

Overall 5-year survival (OS) is very good (100%) with adequate treatment[167]. Main tumour event is local relapse, especially in case of initial incomplete surgery.

A complete surgical resection of DSFP with clear margins is considered the optimal treatment to reduce risk of recurrence[176-178]. The margins should measure 2 to 4 cm and these microscopically negative margins need to be well documented by the pathologist. The Mohs micrographic surgery, a very precise technique designed to treat skin cancers and achieve negative margins, is recommended for these patients[175,179].

The tyrosine kinase inhibitor imatinib has demonstrated good activity in DFSP[180,181]. The clinical efficacy of TKI therapy is due to its action against the aberrant activation of the PDGF/PDGFR pathway in the DFSP[182]. Imatinib may come in place in the case of positive margins after biopsy/ R2 resection or in patients with initially unresectable/metastatic tumours necessitating mutilating surgery. Imatinib may make unresectable tumours resectable. The clinical experience with other tyrosine kinase inhibitors is limited and imatinib remains the gold standard treatment of locally unresectable/metastatic DFSP[176,181]. Metastatic tumours should be considered a malignant transformation in an aggressive sarcoma and treated accordingly. Imatinib should be incorporated in the treatment plan.

5.6 Malignant Rhabdoid Tumour (Extra cranial)

Extra cranial Malignant Rhabdoid Tumours (MRTs) are heterogeneous and rare, aggressive tumours mainly occurring during early infancy, in the first year of life (61%). Male to female ratio is equal[58,183]. MRTs are characterized by a somatic bi-allelic inactivating mutation in the *SMARCB1* gene (95%) or less frequently the *SMARCB4* gene (5%), encoding for INI1 and BRG1, respectively, which are both part of the chromatin remodelling complex SW1/SWF, important in cell cycle control[184]. In infants, MRTs are frequently associated with a *SMARCB1* germline pathogenic variant.

Extra cranial MRTs arise mainly in the kidneys (so-called 'RTK'), soft tissues, and the liver[185]. Malignant extra cranial rhabdoid tumours often show broad but non-specific immunoreactivity. They tend to stain with multiple epithelial, mesenchymal, and occasionally neural or muscle markers, but without a lineage-specific pattern. The most common histopathological profile in all locations is the expression of cytoplasmic vimentin, cytokeratin, EMA. All tumours show negative nuclear INI-1 and BRG1 expression by definition[186]. Somatic molecular analysis will confirm the mutation/deletion of the *SMARCB1* gene.

In a retrospective study of rhabdoid tumours (RT) in children conceived via assisted reproductive technology (ART) across nine countries, 14 cases were identified, including 11 from the EU-RHAB database (2010–2018)[187]. Survival rates, clinical presentation, treatment outcomes, and molecular characteristics in the RT_ART cohort were comparable to those in the EU-RHAB control group, with no significant differences or evidence of imprinting defects.

3-year event-free survival and overall survival is poor and reported to be only 32.3% (95% CI 23.2–41.6%) and 38.4% (95% CI 28.8–47.9%) respectively in the E*p*SSG NRSTS 2005 sub-study analysis. There are no clinical trials on extra cranial rhabdoid tumours; however, the E*p*SSG recommends the treatment strategy with dose-intensive chemotherapy every 2 weeks using vincristine-doxorubicin-cyclophosphamide (VDCy), and ifosfamide-etoposide (IE) according to the amended version of the EpSSG NRSTS 2005 protocol. In a recently published case series of 35 cases, it was shown, that this treatment was feasible without significant short-term toxicity and a comparable (to previous more intensive strategy) 2-year EFS and OS of 47.6% and 42.9%, respectively[188]. The risk of early progression highlights the fact that local therapy, mainly with primary surgery (even considering liver transplant for liver primaries, if necessary) [189,190] ± radiotherapy should happen early in the proposed overall strategy. However, the young age at diagnosis may limit the ability for full dose radiotherapy to be administered in infants. The role of maintenance therapy has not been proven in such disease, even if the EpSSG proposes it in stage IV disease.

Additionally, in a recent analysis, administration of radiotherapy (RT) was identified as an independent prognostic factor for outcomes in children with (brain) atypical teratoid/rhabdoid tumours (AT/RT) in a non-comparative biased way. However, given the young age of patients at the time of RT, careful evaluation of long-term sequelae is essential. These findings emphasize the need for ongoing research and long-term follow-up in this unique patient population[187,191-195].

5.7 Desmoplastic Small Round Cell Tumour

Desmoplastic Small Round Cell tumour (DSRCT) is a very rare tumour entity, which mainly affects adolescent and young adults, with a clear male predominance[196]. DSRCT are mainly found in the abdominal and pelvic cavity and spread on peritoneal surfaces, comparable to carcinomatosis. At presentation, most patients show widespread intra-abdominal metastatic tumours (81%)[197].

DSRCT are characterized by the recurrent t(11;22)(p13;q12) chromosomal translocation that gives rise to the *EWS::WT1* fusion gene[197]. Histologically DSRCT show clustered or nested small, round, undifferentiated cells with hyperchromatic nuclei and little cytoplasm. A further characteristic is the presence of a collagenous stroma and desmoplasia[197].

The prognosis of patients with DSRCT is with a very poor with a median survival between 17 to 25 months only [196,198-204].

Currently there is no uniform treatment approach. In the past 20 years, several studies have been conducted with the attempt to improve outcome. These included aggressive surgery, hyperthermic peritoneal perfusion with cisplatin chemotherapy (HIPEC), high-dose chemotherapy with autologous peripheral stem cell rescue, whole abdominal radiotherapy, and even targeted therapy with monoclonal antibodies and multi-kinase inhibitors have been investigated with mixed success and response[93,94,196,198,201,205-213].

Due to the aggressiveness of the tumour and the poor OS, the E*p*SSG recommends a multimodal approach with aggressive surgery (complete cyto-reductive surgery – CRS-) including the metastatic sites when possible, after neoadjuvant chemotherapy, whole abdominal radiotherapy and chemotherapy like Kushner's P6 regimen, the IVADo regimen as for metastatic rhabdomyosarcoma, or with irinotecan, ifosfamide, vincristine, actinomycin-D (IrIVA)[205,214,215]. The addition of a maintenance therapy at the end with vinorelbine and low-dose oral cyclophosphamide may be considered[211]. The role of HIPEC in paediatric DSRCT is not clear, with reported successful results in selected patients, but these are not consistent though the literature[216-219] .

5.8 Soft Tissue Sarcomas with BCOR and CIC Rearrangement

The *BCOR* family of undifferentiated sarcomas is another rare and aggressive tumour type. They usually present as tumours in bones, the soft tissues, but also in visceral organs like the kidneys. In addition, there is a male predominance [30].

These tumours are characterized by different genetic abnormalities involving the *BCOR* gene: Most common, a paracentric inversion on the short arm of chromosome X, resulting in the fusion of *BCOR* and *CCNB3* and so leading to the overexpression of CCNB3[220, 221] or the *BCOR-ITD* sarcomas with internal. tandem duplications (ITD)[221]. Further *BCOR* gene fusion partners found *are KMT2D, MAML3* and others[221]. Histologically, they are composed of round to spindle shaped cells with variable cellularity. Monomorphic nuclei and fine chromatin pattern can also be found. Furthermore, a delicate capillary network, and varying amounts of myxoid or collagenous stroma are characteristic. Immunohistochemically, most *BCOR*-rearranged sarcomas show positive immunostaining for BCOR, Cyclin D1, SATB2, CD99 and TLE1[221].

The prognosis of a small cohort of patients from several different oncology units was intermediate with a 5-year overall survival of 72%[221].

The *CIC::DUX4* rearranged sarcomas form another group of aggressive tumours. They can also predominantly be found in the soft tissues of children and adolescents[222]. The *CIC::DUX4* fusion results from either a t (4; 19) (q35; q13) or a t (10; 19) (q26; q13) translocation. On histology, the tumour forms sheets or nests of small to medium size round to oval cells. Focally, a myxoid matrix can be observed. Immunohistochemistry stains are positive for membranous CD99, ETV4, WT1 and ERG[223,224,225].

CIC-DUX4 sarcomas show a poor 5-year OS of only 43%, however not many reports are available on the clinical course and behaviour of these tumours[221].

In the absence of dedicated clinical trials, treatment recommendations for sarcomas with BCOR and CIC rearrangements are based on a multimodal approach that includes intensive multi-agent chemotherapy, surgery and potentially radiotherapy[30]. An anthracycline based chemotherapy treatment and R0 resection seem important. If no R0 resection could be achieved, RT seems to improve prognosis[226]. Given the comparable prognosis of BCOR sarcoma to Ewing sarcoma when treated using Ewing protocols, authors recommend the treatment of BCOR sarcoma using the Ewing treatment regimens or its management following similar guidelines.

5.9 Desmoid-Type Fibromatosis

Desmoid-type aggressive fibromatosis (DTF) is a tumour of intermediate malignancy, with a high tendency for a locally aggressive, but slow growth and high recurrence rates. DTF never metastasizes.

The tumours arise from deep-seated, fascial planes and muscular-aponeurotic tissues with two relative peaks in incidence among children between 6 to 15 years and in female adolescents and young adults[227].

The pathogenesis is multifactorial and not completely understood yet, however may involve endocrine factors, trauma (including surgery) and a genetic predisposition either as a sporadic, somatic variant in the beta-catenin gene (*CTNNB1, 90% of cases)*, or in the setting of familial adenomatous polyposis (FAP 10%), both leading to activation of the Wnt/β-catenin pathway [227-229]. Immunohistochemically, DTF demonstrates nuclear β-catenin positivity in most cases and often expresses SMA, S100 (approx.50% of cases) and vimentin, while CD34, and cytokeratin mainly stain negative[230].

Adapted from positive experiences in adult patients, the treatment of DTF has shifted first to an “active surveillance (AS)” if no fast progression or threatening symptom are observed, as proposed in 2005, by the EpSSG. This less aggressive algorithm seems to reduce morbidity due to treatment-related complications and does not interfere with the evolution of the disease [229,231,232]

However, in the case of progressing tumours or threatening symptoms a treatment needs to be implemented. Here a step-wise approach has been proven efficient, with low-dose intravenous weekly methotrexate plus vinblastine over a minimum of 6 month. Another pharmacological treatment option are multi-tyrosine kinase inhibitors as pazopanib or sorafenib, however evidence from clinical trials is sparse[231,233]. Lastly, gamma-secretase inhibitors (AL10, nirogacestat) or β-catenin inhibitors (tegavivint) are now under investigation in adults/adolescents and/or in children and first preliminary results are promising[231,234,235,236].

The role of secondary surgery is controversial and currently a wait-and-see strategy is proposed after maximum tumour reduction, due to the risk of secondary tumour growth stimulation due to the surgery itself and due to the risk of long-term sequelae and morbidity, without enough evidence for a clear benefit. The same is true for local radiotherapy and is currently not recommended due to the benign condition of the disease unless all other options failed[231,232].

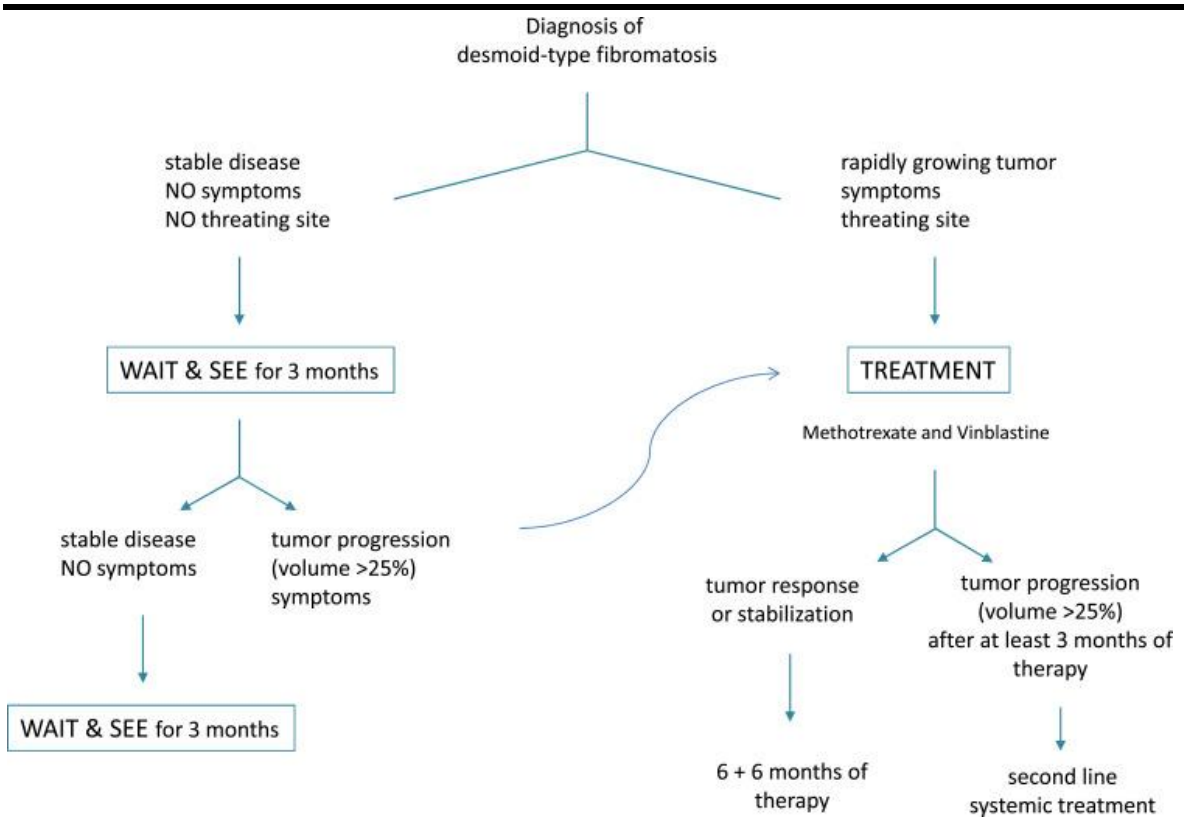

Figure 1 EpSSG flow chart for desmoid-type fibromatosis

5.10 Inflammatory Myofibroblastic Tumours

Inflammatory myofibroblastic tumours (IMT) belong to the group of mesenchymal neoplasms of intermediate malignancy, with a risk of local recurrence but low tendency to metastasize (<5%) [44,237].

They mainly occur in children and young adolescents and are located in the abdomen, thorax, head and neck region, but also the central nervous system, or the limbs[44,238].

Histologically, a myofibroblastic mesenchymal spindle cell proliferation associated with inflammatory infiltration is typically seen[239]. In the majority of cases, the translocation of the “anaplastic lymphoma kinase (*ALK*) gene is present with various gene partners, resulting in a persistently activated protein. Other, less frequent chromosomal fusion transcripts have been found like ROS 1, PDGFRβ, RET and NTRK [44,238,240-242]

Treatment options in well-defined, localized tumours mainly involves surgery with negative margins, leading to a very good prognosis. Here, if a R0/R1 resection is achieved, no further treatment is recommended. However, when surgery is not feasible, as in cases of advanced disease, medical treatment options include low-dose chemotherapy (vinblastine plus low-dose methotrexate) as in desmoid fibromatosis, or corticosteroids[44,243,244]. The recommendations are now becoming outdated, as more clinical evidence and studies are available showing the efficacy of targeted therapies such as ALK inhibitors and also ROS1, RET and NTRK inhibitors, but also here further randomized controlled trials (RCTs) are urgently needed[240,245]. The authors recommend to use these targeted agents in case of

unresectable tumour after failure of steroids, adapted to the somatic molecular alteration as a bridge to a conservative delayed surgery after tumour reduction.

5.11 Infantile Fibrosarcoma

Infantile Fibrosarcoma (IFS) is a tumour of intermediate malignancy and the most common soft tissue sarcoma in infants. IFS mainly occur in deeply located soft tissues of the distal extremities or the trunk, often with a very fast initial growth[246], and can be frequently mistaken as haemangiomas or other vascular anomalies. Characteristic for these tumours is the recurrent t (12; 15) (p13; q25) translocation, leading to the *ETV6::NTRK3* fusion transcript. Less frequently other fusion partners like RAF, RET, or NTRK1 can be found [241,247]

The prognosis for IFS is usually very good with overall survival rates greater than 80%[246].

Treatment options in localized tumours are conservative, non-mutilating excisions[246,248,249]. In patients with unresectable tumours, an upfront, first-line alkylating-, and anthracycline-free VA (vincristine-actinomycin-d) chemotherapy is recommended[248,250]. In the case of unresponsiveness to VA chemotherapy, more intense options might be considered, keeping in mind the young age of the patient.

Moreover, in IFS, NTRK inhibitors have become more and more important, evoking a rapid and sustainable tumour reduction[41,247]. The recent EPI VITRAKVI study by a French group showed that treatment with larotrectinib reduced the need of subsequent therapies compared to a historical control group with chemotherapy in children with locally advanced or metastatic IFS[43].

So overall, the current treatment recommendations propose front-line treatment with either conventional chemotherapy or NTRK inhibitors for patients with advanced localized disease. In patients with metastatic disease or in order to avoid mutilating excision, NTRK inhibitors might be the best upfront option[247,42,43,251-253]. After tumour reduction, surgical resection of a residual mass is recommended.

6. ASSESSMENT OF TUMOUR RESPONSE

Throughout treatment at predefined time-points, a response evaluation should be done, ideally with the same methods as during primary staging.

6.1 Definition of response

Response will be evaluated clinically on the one hand and radiologically according to RECIST 1.1 criteria on the other hand[51]:

The measurement method employed, **must be the same as at diagnosis**. Therefore, consistent size cut-offs should be applied to define both disease progression and response.

Complete Response (CR) is characterized by the complete disappearance of all target lesions, and any pathological lymph nodes must exhibit a reduction in short axis to less than 10 mm.

Partial Response (PR) is indicated by a minimum of a 30% decrease in the sum of diameters of target lesions. To mitigate the risk of prematurely categorizing patients as having progressive disease, the threshold for Progressive disease (PD) was raised to 20% in 1D measurements with the advent of

RECIST 1.0. This adjustment corresponds to a 73% increase in volume and is recommended as the cut-off for assessing response NRSTS. Stable Disease (SD) is described as neither meeting the criteria for sufficient shrinkage to qualify for PR nor exhibiting sufficient increase to qualify for PD. It is crucial to maintain consistency in response categories across protocols[52].

Time points of assessments

As long as no signs of progression are present throughout the course of treatment, assessments should take place at predefined time-points and depend on the specific entity. Often this coincides with the assessments necessary for the planning of local control. In low-risk entities a 1st assessment should be done at the end of treatment and in high-risk entities after 3 cycles of treatment.

If at any time-point a tumour progression is suspected, a full staging (local by MRI and distant) should be performed to determine the extent of progression.

7. RELAPSED DISEASE

For relapsed disease, participation in prospective studies is strongly recommended. Key initiatives include the INFORM registry and the MYKIDS trial (EUDRACT No. 2019-004418-35), both of which provide valuable opportunities for advanced diagnostics, tailored treatment approaches, and further research in this challenging setting. Overall, no standard second line treatment regimen are available for patients with relapse of NRSTS. However, for certain entities, some regimens may be effective , even as palliative treatment: For patients with synovial sarcoma, treatment with high dose ifosfamide might be an option[254-256]. For patients with DSRCT, treatment with trabectedin and irinotecan is a promising option[212].

8. SUMMARY OF KNOWN ADVERSE EVENTS ASSOCIATED WITH TREATMENT RECOMMENDATION

8.1 Dose Modifications and delays

Scheduled administration of chemotherapy is an essential aspect of treatment. However, toxicity monitoring, dose modifications and treatment delays must be considered where clinically appropriate.

All anticancer agents should be modified according to age and weight, in particular for patients <12 months and/or <10 kg.

8.2 Toxicities of chemotherapy agents

Haematological Toxicity

- Anaemia: Transfuse if Hb <7-8 g/dL or symptomatic.

- Thrombocytopenia: Transfuse if platelets <10x10^9/L or in bleeding signs.

- Neutropenia: No primary G-CSF prophylaxis. Use in life-threatening infections or >1-week treatment delays.

Cardiotoxicity

Monitor cardiac function; withhold DOXO if SF <28% or if SF declines >10% and consult a cardiologist. If dysfunction persists, discontinue DOXO.

Bladder Toxicity

Rare with proper uromitexan and hydration. Continue hydration if macroscopic haematuria occurs. Discontinue IFO only for recurrent macroscopic haematuria, substituting CPM: 6g/m2 IFO is replaced by 1.2g/m2 CPM. 9 g/m2 IFO is replaced by 1.5 g/m2 CPM.

Renal Toxicity

Extra GFR tests should be performed if the serum creatinine increases by 100% of the baseline value or exceeds the upper limit of normal for age. Carboplatin dosing should be adjusted according to the most recent GFR.

Monitor nephrotoxicity risk with IFO; discontinue if toxicity > grade 2 and switch to CPM: 6g/m2 IFO is replaced by 1.2g/m2 CPM. 9 g/m2 IFO is replaced by 1.5 g/m2 CPM.

Mild tubular dysfunction is usually transient.

Liver Toxicity & SOS/VOD

Monitor for hepatic dysfunction. If SOS occurs, hold ACT-D until recovery; restart at half-dose and increase progressively if tolerated. Discontinue ACT-D if symptoms persist.

Neurological Toxicity

IFO encephalopathy: Treat seizures with methylene blue (30 mg/m² IV). Omit IFO for grade 3-4 toxicity and replace with CPM (1500 mg/m²).

Vincristine neuropathy: Omit 1-2 doses if grade 3-4 neurotoxicity occurs; restart at 50% dose if tolerated.

Pulmonary abnormalities

The acute onset of tachypnoea following doxorubicin and after whole lung radiotherapy may represent radiation pneumonitis. Unless radiation pneumonitis can be excluded due to infective causes, further doses of doxorubicin should be withheld until the tachypnoea and respiratory symptoms have improved.

8.3 Side Effects of Non-Chemotherapy Agents

For detailed information and side effects of non-chemotherapy agents mentioned in this guideline, please consult the relevant literature and drug information sheets.

9. SUPPORTIVE TREATMENT

The treatment of patients with NRSTS requires a multidisciplinary approach with a high degree of medical competence existing only in institutions familiar with the administration of intensive chemotherapy and adequate infrastructure to provide the necessary supportive care. Supportive treatment is to be given according to international consensus[257-259] and per institutional practise.

10. PATIENT FOLLOW UP

10.1 Imaging follow up

Considering the heterogeneity of the different NRSTs, it is impossible to give a detailed follow up plan. And in most entities, the best strategy for NRSTS patients' follow up has not been established yet. Many of the recommendations here are adapted from the follow up regime of RMS patients and general follow-up recommendations.

However, following completion of treatment, the frequency of follow-up imaging assessments should be every three-four month for the first two years from the end of treatment. In tumour entities, known to metastasise, for the first two years, the frequency of chest radiography/CT scans is similar to local tumour evaluation. After two years, regular chest radiography is performed according to local practice.

Disease related follow-up checks should include:

- Appropriate imaging of primary tumour; for superficial tumours, ultrasound may be used. In all other cases, MRI is the preferred imaging modality.
- Chest radiograph (if an abnormality is found a CT of the chest should be obtained)

10.2 General follow up

For a comprehensive patient follow up, please see the different published follow up guidelines, like the COG survivorship guidelines or the PanCare follow up recommendations [260,261]

Briefly, for those patients, that received ifosfamide/cyclophosphamide (if replaced because of renal toxicity) creatinine and tubular function should be monitored on a yearly base.

For those patients, that received doxorubicin echocardiographs should be done after completion of chemotherapy and at least every 2 years for the first 10 years and then 5 yearly subsequently.

Patients with head and neck malignancies, that received RT, growth and pubertal development should be closely followed, as well as assessment of the pituitary axis on an annually. Further checks of dental status and neuropsychological development regularly, and audiometry where indicated[262].

Follow up may change according to tumour characteristics and in particular tumour site and regional and distant involvement and chemotherapy received and be warranted according to national guidelines.

The schema reported below is a suggestion that can be adapted to national/institutional guidelines and after discussions with parents/patients.

	1st year	**2nd year**	**3rd year**	**4th and 5th year**
Clinical examination	Every 3 months	Every 4 months	Every 4 months	Every 6 month

Primary tumour site Ultrasound ± CT scan or MRI	Every 3 months	Every 4 months	-*	-*
Lung Chest x ray alternating with CT scan	Every 3 months	Every 4 months	Every 4 months	Every 6 months

*If clinically indicated

APPENDIX 1 - TUMOUR STAGING

TNM Staging System	
T1	Definition applies to tumours confined to the organ or tissue of origin
T2	Lesions invade contigus structures
T1 and T2 groups are further classified as A or B according to tumour diameter, or size respectively	
N0	No node involvement
N1	Regional node involvement
M0	No metastases
M1	Distant metastases at onset

IRS System after initial surgery	
group I	Completely-excised localized tumours
group II	Grossly-resected tumours with microscopic residual disease and/or regional lymph nodal spread
group III	Gross residual disease after incomplete resection or biopsy
group IV	Comprises patients with metastases at onset

APPENDIX 2- REGIONAL LYMPH NODES DEFINITION

Localization	**Involved Nodes**
Head & Neck Orbit	ipsilateral jugular, pre-auricular, cervical
Intrathoracic	internal mammary, mediastinal nodes

Thoracic wall	axillary, internal mammary, infraclavicular nodes
Intraabdominal & Pelvic	Sub diaphragmatic, intra-abdominal and iliac lymph nodes according to site.
Abdominal wall	inguinal, femoral nodes
Bladder Prostate	iliac nodes (external, internal and common chains; note that paraaortic nodes are second level nodes).
Cervix and Uterus	iliac nodes (external, internal and common chains)
Paratesticular	external iliac and para-aortic (retroperitoneal) lymph nodes at renal artery or below (inguinal if the scrotum is involved)
Vagina	iliac nodes (external, internal and common chains; note that paraaortic nodes are second level nodes).
Vulva	inguinal nodes
Perineum	inguinal and iliac (may be bilateral)
Upper Limbs	axillary lymph nodes (epitrochlear rarely involved)
Lower Limbs	inguinal lymph nodes (popliteal rarely involved)

APPENDIX 3- DEFINITION OF SITES

To define the site of origin may be difficult in some cases of NRSTS. A correct site assignation is of importance in the choice of treatment. The following definitions are given to facilitate the clinician in the appropriate site classification.
We acknowledge the permission given by the IRSG to modify and use their original document on site definitions:

ORBIT

1. Eyelid

This site is sometimes erroneously designated as “eye”. Although there may occasionally be a case arising from the conjunctiva of the eye, the globe itself is not a primary site. The eyelid is much less frequent than the orbit itself.

2. Orbit

This refers to the bony cavity, which contains the globe, nerve and vessels and the extra-ocular muscles. Tumour in this site will only rarely invade the bony walls and extend into the adjacent sinuses. This is why this tumour which is clearly adjacent to the skull base and its meninges is not by its natural history appropriate to include in the parameningeal sites unless there is invasion of bone at the base of the skull.

PARAMENINGEAL

1. Middle ear

This refers to a primary that begins medial to the tympanic membrane. This tumour is often advanced at presentation and because of extension laterally may present with a mass in front of or under the ear suggesting a parotid origin. It may also extend through the tympanic membrane and appear to be arising in the ear canal. When there is doubt about the site of origin, the “middle ear”

designation should be picked as it implies the more aggressive therapy required of parameningeal sites.

2. Nasal Cavity and Paranasal Sinuses

The three paranasal sinuses are the maxillary sinuses, the ethmoid sinuses, and the sphenoid sinus. These surround the nasal cavity, and a primary in one will frequently extend to another. It can be difficult to determine the exact site of origin, but the choice is academic as the treatment is not affected. The site designation will have a bearing on the design of radiotherapy portals. Tumour arising in the maxillary or the ethmoid sinuses may invade the orbit. This is much more likely than a primary in the orbit invading one of the sinuses. When the distinction between orbit and paranasal sinus is unclear, the site selected should be paranasal sinus as it is the more likely primary site and requires appropriately more aggressive therapy. A primary arising in the sphenoid sinus (rare) may extend inferiorly to involve the nasopharynx.

3. Nasopharynx

This refers to the superior portion of the pharynx which is bounded anteriorly by the back of the nasal septum, superiorly by the sphenoid sinus, inferiorly by a level corresponding to the soft palate, and laterally and posteriorly by the pharyngeal walls.

4. Infratemporal Fossa/Pterygopalative and Parapharyngeal Area

This refers to the tissues bounded laterally by the medial lobe of the parotid gland and medially by the pharynx. Large tumours in this region may extend through the parotid gland and present as a mass of the lateral face, sometimes extending even to the cheek. Where there is doubt as to the primary, the parameningeal designation should be chosen as it confers appropriately more aggressive treatment. The superior boundary of this tissue volume is the base of skull just under the temporal lobe, hence the term “infratemporal”. The distinction between this and the “parapharyngeal” area is academic.

5. Orbital tumours with bone erosion

Tumours arising in the orbit but with intracranial extension or important bone erosion are included in the parameningeal group.

In addition, the following are classified as parameningeal tumours:

Tumours involving vessels or nerves with direct intracranial connection (Arteria carotis interna, vertebralis, N. opticus, trigeminus, facialis etc).

All intracranial and intraspinal tumours (but tumours arising from the paraspinal muscles with intraspinal

extension should be designated as paraspinal, see “Other site” definition) All tumours with cranial nerve paresis, CSF tumour cell positive patients

HEAD AND NECK

1. Scalp

This site includes primaries arising apparently in, or just below, the skin of all the tissues of the face and head that are not otherwise specified below. This usually means the scalp, external ear and pinna, the nose

and the forehead, but not the eyelids or cheek.

2. Parotid

The parotid gland lies just in front of, and under, the ear and may surround both sides of the posterior aspect of the ascending ramus of the mandible. As noted above, large primaries in the infratemporal fossa may erode through the parotid. A true parotid primary should not, on radiographic studies, reveal a mass in the

infratemporal fossa.

3. Oral Cavity

This includes the floor of the mouth, the buccal mucosa, the upper and lower gum, the hard palate, the oral tongue (that portion of the tongue anterior to the circumvallate papillae). A primary arising in the buccal mucosa can be impossible to distinguish from one arising in the cheek, but the distinction is academic. This would also include those lesions arising in or near the lips.

4. Larynx

This refers to primaries arising in the subglottic, glottic, or supraglottic tissues. Tumours of the aryepiglottic folds can be impossible to distinguish from the hypopharynx, but the distinction is academic.

5. Oropharynx

This includes tumours arising from the anterior tonsillar pillars, the soft palate, the base of the tongue, the tonsillar fossa, and oropharyngeal walls. Tumours arising in the parapharyngeal space may indent the oropharyngeal wall. In this circumstance, the primary should be considered parameningeal. If the mucosa of the oropharynx actually contains visible tumour as opposed to being bulged by it, the primary would be oropharynx. Primaries arising in the tongue base, soft palate, or tonsillar region may extend into the oral cavity. The oropharynx designation is preferred.

6. Cheek

This refers to the soft tissues of the face that surround the oral cavity. Tumours arising in the parotid may invade the cheek. As noted above, the distinction between this and the buccal mucosa is academic.

7. Hypopharynx

This refers to the pyriform sinus and may be difficult to distinguish from larynx although the designation is academic.

8. Thyroid and Parathyroid

Primaries arising in these two sites are exceedingly rare, if they exist at all, and should those structures be involved, it would more likely be from a primary arising in an adjacent structure such as the neck or, rarely, the trachea.

9. Neck

This refers to the soft tissues of the lateral neck between the mastoid tip and the clavicle. It does not include those medial structures such as hypopharynx and larynx noted above. Unfortunately, this site overlaps with the designation “paraspinal” included under the site group “trunk”. Primaries arising in the neck can and frequently do behave as a paraspinal primary with direct invasion into the spinal extra dural space, especially if posteriorly placed.

GENITO-URINARY BLADDER AND PROSTATE

1. Bladder

Our criteria for identifying the bladder as a primary site has included the appearance of tumour within the bladder cavity, which can be biopsied under cystoscopy or occasionally at laparotomy. We do not recognize as primary bladder tumours those that simply displace the bladder or distort its shape. The latter are ordinarily primary pelvic tumours, unless otherwise specified.

2. Prostate

It is important to differentiate true prostatic tumours from pelvic tumours.

3. Bladder/Prostate

In approximately 20% of males with bladder or prostatic tumours, the precise site cannot be determined even at autopsy. The histologic features are similar. Although it is desirable to have an indication of the “most probable” site from the institution, and one should to get this, it may not be possible.

GENITO-URINARY NON-BLADDER AND PROSTATE

1. Paratesticular

The tumours arise from mesenchymal elements of the spermatic cord, epididymis, and testicular envelopes, producing a painless scrotal mass.

2. Testis

This designation is usually wrong because the tumours arise from paratesticular structures.

3. Uterus

A tumour in this primary site may be difficult to differentiate from a primary vaginal site, because a tumour originating in the uterus may fill the vagina. After a therapeutic response, the distinction is usually clear. In general, there is a wide separation of age range between these two groups, with the vaginal cases occurring in infancy or early childhood and uterine primaries in adolescents or young adults.

4. Vagina

A patient with a primary vaginal lesion must have evidence of a visible tumour on the vaginal surfaces which can be biopsied through the vagina. Displacement or distortion of the vagina is not sufficient.

5. Vulva

Primary lesions in this site arise in the labia minora or majora.

EXTREMITIES

1. Hand

Refers to the area from the top of the fingers to the wrist

2. Forearm

Refers to the area from the wrist to the elbow joint

3. Arm

Refers to the area from the elbow joint to the shoulder joint. Tumours arising in the axilla are considered as extremity lesions.

4. Shoulder

The posterior aspect of the shoulder, i.e., the scapular area, is an extremity site.

5. Foot

Refers to the area from the top of the toes to the ankle

6. Leg

Refers to the area from the ankle to the knee

7. Thigh

Refers from the area from the knee to the hip joint

8. Buttocks

These are extremity lesions.

OTHER SITES

This term conventionally groups tumours originating from the sites not mentioned above. Prognosis is similar and usually not satisfying.
The following specific sites have been defined:

Thorax

Includes tumours arising in the following sites:

a) Thoracic wall:

includes tumours arising from the thoracic muscles and the parietal pleura

b) Mediastinum

Occasionally a primary rhabdomyosarcoma may arise form trachea, heart or nearby areas.

c) Lung:

includes tumours arising from the lung parenchyma, bronchus and visceral pleura

Diaphragm

Abdominal Wall (including Lumbar or lumbo-sacral wall)

This refers to the anterior abdominal wall from the inferior costal margins superiorly to the inguinal ligaments and symphysis pubis, inferiorly, and extends laterally between the costal margin and posterior iliac crests to the paraspinal region.

Paraspinal

When tumours are described as adjacent to the vertebral column, arising from the paraspinal muscles. This designation is preferable to “abdominal wall” or “trunk” or “neck”. They often show an intraspinal component and this should be specified.

Abdomen - Intraperitoneal

a) Liver

True liver rhabdomyosarcoma is less frequent than bile ducts tumours.

b) Bile duct

Bile Duct is a specific site and can be recognised as such at surgery. This might also be called
“choledochus” or “biliary tract”. There is probably no way one can distinguish an intrahepatic bile duct site from a primary liver site except by examining the excised specimen.

c) Pancreas

d) Bowel

e) Abdomen

The term abdominal refers to tumours arising in the intraperitoneal cavity, when a specific organ of origin such as liver, bile duct, pancreas or intestine cannot be determined.

Abdomen - Retroperitoneal

The term retroperitoneal is reserved for those posteriorly situated abdominal tumours in which there does not seem to be a more specific site. Tumours in a retroperitoneal site are in the posterior aspect of the abdominal and/or pelvis. The term “psoas” as a site is not very specific, as the muscle extends through the posterior
lower abdomen, pelvis and into the leg.

Pelvis

It is difficult to define the site of origin when there is a large tumour in the abdomen. The pelvis designation is reserved for lesions involving the lower part of the abdomen when no more specific site is appropriate.

Perianal

These sites are ordinarily “perirectal” or “perianal”. They are distinguished with difficulty from perineal and vulval sites; but the latter distinction is important.

Perineum

This should include the site which appear the anus posterior to the scrotum in males and posterior to the labia in females. It extends anteriorly to the base of the scrotum in males and to the introitus in females. It must be distinguished from labial and sites.

REFERENCE LIST

1. *Soft Tissue and Bone Tumours WHO Classification of Tumours*, (IARC, France, 2020).
2. Weiss, A.R. & Harrison, D.J. Soft Tissue Sarcomas in Adolescents and Young Adults. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **42**, 675-685 (2024).
3. Ferrari, A.*, et al.* Soft tissue sarcoma across the age spectrum: a population-based study from the Surveillance Epidemiology and End Results database. *Pediatric blood & cancer* **57**, 943-949 (2011).
4. Corey, R.M., Swett, K. & Ward, W.G. Epidemiology and survivorship of soft tissue sarcomas in adults: a national cancer database report. *Cancer Med* **3**, 1404-1415 (2014).
5. Spunt, S.L.*, et al.* Clinical features and outcome of initially unresected nonmetastatic pediatric nonrhabdomyosarcoma soft tissue sarcoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **20**, 3225-3235 (2002).
6. Renzi, S.*, et al.* Non-rhabdomyosarcoma soft tissue sarcomas diagnosed in patients at a young age. An overview of clinical, pathological, and molecular findings. *Pediatr Blood Cancer* **68**, e29022 (2021).
7. Gatta, G.*, et al.* Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet—a population-based study. *The Lancet Oncology* **18**, 1022-1039 (2017).
8. Ferrari, A. & Casanova, M. New concepts for the treatment of pediatric nonrhabdomyosarcoma soft tissue sarcomas. *Expert Rev Anticancer Ther* **5**, 307-318 (2005).
9. Ferrari, A.*, et al.* Adult-type soft tissue sarcomas in pediatric-age patients: experience at the Istituto Nazionale Tumori in Milan. *J Clin Oncol* **23**, 4021-4030 (2005).
10. Ferrari, A.*, et al.* Outcomes of metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) treated within the BERNIE study: a randomised, phase II study evaluating the addition of bevacizumab to chemotherapy. *Eur J Cancer* **130**, 72-80 (2020).
11. Ferrari, A.*, et al.* Adult-type soft tissue sarcomas in paediatric age: a nomogram-based prognostic comparison with adult sarcoma. *European journal of cancer (Oxford, England : 1990)* **43**, 2691-2697 (2007).
12. Spunt, S.L.*, et al.* Clinical Features and Outcome of Initially Unresected Nonmetastatic Pediatric Nonrhabdomyosarcoma Soft Tissue Sarcoma. *Journal of Clinical Oncology* **20**, 3225-3235 (2002).
13. Haimi, M., Peretz Nahum, M. & Ben Arush, M.W. Delay in diagnosis of children with cancer: a retrospective study of 315 children. *Pediatr Hematol Oncol* **21**, 37-48 (2004).
14. Spunt, S.L.*, et al.* Clinical features and outcomes of young patients with epithelioid sarcoma: an analysis from the Children's Oncology Group and the European paediatric soft tissue Sarcoma Study Group prospective clinical trials. *European journal of cancer (Oxford, England : 1990)* **112**, 98-106 (2019).
15. Jones, A.*, et al.* Outcomes of melanoma soft parts/clear cell sarcoma (MSP/CCS) patients (pts) with immune and targeted therapies. *Journal of Clinical Oncology* **37**, e21046-e21046 (2019).
16. (!!! INVALID CITATION !!! 19,20).

17. Gusho, C.A., Fice, M.P., O'Donoghue, C.M., Gitelis, S. & Blank, A.T. A Population-based Analysis of Lymph Node Metastasis in Extremity Soft Tissue Sarcoma: An Update. *J Surg Res* **262**, 121-129 (2021).
18. Andreou, D.*, et al.* Sentinel node biopsy in soft tissue sarcoma subtypes with a high propensity for regional lymphatic spread--results of a large prospective trial. *Ann Oncol* **24**, 1400-1405 (2013).
19. Brady, A.C., Picado, O., Tashiro, J., Sola, J.E. & Perez, E.A. Lymph Node Sampling and Survival in Child and Adolescent Extremity Soft-Tissue Sarcoma. *J Surg Res* **241**, 205-214 (2019).
20. De Corti, F.*, et al.* Sentinel node biopsy in pediatric soft tissue sarcomas of extremities. *Pediatr Blood Cancer* **52**, 51-54 (2009).
21. Weller, J.H.*, et al.* Trends of lymph node sampling and metastasis in pediatric and young adult patients with clear cell, epithelioid, and synovial sarcomas. *Pediatr Blood Cancer* **69**, e29455 (2022).
22. (!!! INVALID CITATION !!! 21-25).
23. Alvarez, E.*, et al.* Lymph node metastases in paediatric and young adult patients with non-rhabdomyosarcoma soft tissue sarcoma (NRSTS): Findings from Children's Oncology Group (COG) study ARST0332. *European journal of cancer (Oxford, England : 1990)* **180**, 89-98 (2023).
24. Ferrari, A.*, et al.* Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG). *The Lancet Child & Adolescent Health* **5**, 546-558 (2021).
25. Spunt, S.L.*, et al.* A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. *Lancet Oncol* **21**, 145-161 (2020).
26. Casanova, M.*, et al.* Epithelioid sarcoma in children and adolescents: a report from the Italian Soft Tissue Sarcoma Committee. *Cancer* **106**, 708-717 (2006).
27. Sparber-Sauer, M.*, et al.* Alveolar soft-part sarcoma: Primary metastatic disease and metastatic relapse occurring during long-term follow-up: Treatment results of four Cooperative Weichteilsarkom Studiengruppe (CWS) trials and one registry. *Pediatric blood & cancer* **65**, e27405 (2018).
28. Schoot, R.A.*, et al.* Imaging recommendations for the management of pediatric non-rhabdomyosarcoma soft tissue sarcoma (NRSTS): Consensus statement of the International Soft Tissue Sarcoma Consortium (INSTRuCT). *EJC Paediatric Oncology* **1**, 100008 (2023).
29. Heinz, A.T.*, et al.* Children and Adolescents With Localised Non-Rhabdomyosarcoma Soft Tissue Sarcoma: Results of the CWS-96 and CWS-2002P Prospective Trials With Reclassification of the Trial Data Incorporating the Recent Soft Tissue Sarcoma Registry. *Pediatr Blood Cancer*, e32159 (2025).
30. Ferrari, A.*, et al.* Pediatric Non-Rhabdomyosarcoma Soft Tissue Sarcomas: Standard of Care and Treatment Recommendations from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). *Cancer Manag Res* **14**, 2885-2902 (2022).
31. Selt, F.*, et al.* Pediatric Targeted Therapy: Clinical Feasibility of Personalized Diagnostics in Children with Relapsed and Progressive Tumors. *Brain Pathology* **26**, 506-516 (2016).
32. Grünewald, T.G.*, et al.* Sarcoma treatment in the era of molecular medicine. *EMBO Mol Med* **12**, e11131 (2020).
33. van Tilburg, C.M.*, et al.* The Pediatric Precision Oncology INFORM Registry: Clinical Outcome and Benefit for Patients with Very High-Evidence Targets. *Cancer Discov* **11**, 2764-2779 (2021).
34. Pfister, S.M.*, et al.* A Summary of the Inaugural WHO Classification of Pediatric Tumors: Transitioning from the Optical into the Molecular Era. *Cancer Discov* **12**, 331-355 (2022).
35. Koelsche, C.*, et al.* Sarcoma classification by DNA methylation profiling. *Nature communications* **12**, 498 (2021).
36. Sbaraglia, M., Bellan, E. & Dei Tos, A.P. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. *Pathologica* **113**, 70-84 (2021).

37. Ferrari, A., *et al.* Controversies and challenges in the management of paediatric non-rhabdomyosarcoma soft tissue sarcomas. *Lancet Child Adolesc Health* **6**, 221-223 (2022).
38. Guillou, L., *et al.* Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **15**, 350-362 (1997).
39. Fisher, C. Synovial sarcoma. *Ann Diagn Pathol* **2**, 401-421 (1998).
40. Kerouanton, A., *et al.* Synovial sarcoma in children and adolescents. *J Pediatr Hematol Oncol* **36**, 257-262 (2014).
41. Laetsch, T.W., *et al.* Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. *Lancet Oncol* **19**, 705-714 (2018).
42. Carton, M., *et al.* Larotrectinib versus historical standard of care in patients with infantile fibrosarcoma: protocol of EPI-VITRAKVI. *Future Oncol* **19**, 1645-1653 (2023).
43. Orbach, D., *et al.* Therapeutic benefit of larotrectinib over the historical standard of care in patients with locally advanced or metastatic infantile fibrosarcoma (EPI VITRAKVI study). *ESMO Open* **9**, 103006 (2024).
44. Pire, A., *et al.* Clinical, pathologic, and molecular features of inflammatory myofibroblastic tumors in children and adolescents. *Pediatric blood & cancer* **69**, e29460 (2022).
45. Ferrari, A., *et al.* The treatment approach to pediatric non-rhabdomyosarcoma soft tissue sarcomas: a critical review from the INternational Soft Tissue SaRcoma ConsorTium. *European journal of cancer (Oxford, England : 1990)* **169**, 10-19 (2022).
46. Schoot, R.A., *et al.* INternational Soft Tissue saRcoma ConsorTium (INSTRuCT) consensus statement: Imaging recommendations for the management of rhabdomyosarcoma. *Eur J Radiol* **166**, 111012 (2023).
47. Gronchi, A., *et al.* Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). *Ann Oncol* **32**, 1348-1365 (2021).
48. van Ewijk, R., *et al.* European guideline for imaging in paediatric and adolescent rhabdomyosarcoma - joint statement by the European Paediatric Soft Tissue Sarcoma Study Group, the Cooperative Weichteilsarkom Studiengruppe and the Oncology Task Force of the European Society of Paediatric Radiology. *Pediatr Radiol* **51**, 1940-1951 (2021).
49. Ferrari, A., *et al.* Synovial sarcoma in children and adolescents: a critical reappraisal of staging investigations in relation to the rate of metastatic involvement at diagnosis. *European journal of cancer (Oxford, England : 1990)* **48**, 1370-1375 (2012).
50. Vali, R., *et al.* SNMMI Procedure Standard/EANM Practice Guideline on Pediatric (18)F-FDG PET/CT for Oncology 1.0. *J Nucl Med* **62**, 99-110 (2021).
51. Eisenhauer, E.A., *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer (Oxford, England : 1990)* **45**, 228-247 (2009).
52. Schoot, R.A., *et al.* Response assessment in pediatric rhabdomyosarcoma: can response evaluation criteria in solid tumors replace three-dimensional volume assessments? *Radiology* **269**, 870-878 (2013).
53. Ferrari, A., *et al.* Clear cell sarcoma of tendons and aponeuroses in pediatric patients: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. *Cancer* **94**, 3269-3276 (2002).
54. Sparber-Sauer, M., *et al.* Epithelioid sarcoma in children, adolescents, and young adults: Localized, primary metastatic and relapsed disease. Treatment results of five Cooperative Weichteilsarkom Studiengruppe (CWS) trials and one registry. *Pediatric blood & cancer* **66**, e27879 (2019).
55. Ayadi, L. & Khabir, A. Pediatric angiosarcoma of soft tissue: a rare clinicopathologic entity. *Arch Pathol Lab Med* **134**, 481-485 (2010).

56. Ferrari, A., *et al.* Malignant vascular tumors in children and adolescents: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. *Med Pediatr Oncol* **39**, 109-114 (2002).
57. Brennan, B., *et al.* Alveolar soft part sarcoma in children and adolescents: The European Paediatric Soft Tissue Sarcoma study group prospective trial (EpSSG NRSTS 2005). *Pediatric blood & cancer* **65**(2018).
58. Brennan, B., *et al.* Outcome of extracranial malignant rhabdoid tumours in children registered in the European Paediatric Soft Tissue Sarcoma Study Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study-EpSSG NRSTS 2005. *European journal of cancer (Oxford, England : 1990)* **60**, 69-82 (2016).
59. Schoot, R.A., *et al.* Imaging recommendations for the management of pediatric non-rhabdomyosarcoma soft tissue sarcoma (NRSTS): Consensus statement of the International Soft Tissue Sarcoma Consortium (INSTRuCT). *EJC Paediatric Oncology* **1**(2023).
60. Terwisscha van Scheltinga, S., *et al.* Lymph Node Staging and Treatment in Pediatric Patients With Soft Tissue Sarcomas: A Consensus Opinion from the Children's Oncology Group, European paediatric Soft tissue sarcoma Study Group, and the Cooperative Weichteilsarkom Studiengruppe. *Pediatric blood & cancer*, e31538 (2025).
61. Grampp, S., *et al.* Spiral CT of the lung in children with malignant extra-thoracic tumors: distribution of benign vs malignant pulmonary nodules. *Eur Radiol* **10**, 1318-1322 (2000).
62. Robertson, P.L., Boldt, D.W. & De Campo, J.F. Paediatric pulmonary nodules: a comparison of computed tomography, thoracotomy findings and histology. *Clin Radiol* **39**, 607-610 (1988).
63. Ferrari, A., *et al.* Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG). *Lancet Child Adolesc Health* **5**, 546-558 (2021).
64. Vaarwerk, B., *et al.* Indeterminate Pulmonary Nodules at Diagnosis in Rhabdomyosarcoma: Are They Clinically Significant? A Report From the European Paediatric Soft Tissue Sarcoma Study Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **37**, 723-730 (2019).
65. Giraudo, C., *et al.* Indeterminate pulmonary nodules in non-rhabdomyosarcoma soft tissue sarcoma: A study of the European paediatric Soft Tissue Sarcoma Study Group. *Cancer* **130**, 597-608 (2024).
66. Burns, K.C., Hoefgen, H., Strine, A. & Dasgupta, R. Fertility preservation options in pediatric and adolescent patients with cancer. *Cancer* **124**, 1867-1876 (2018).
67. Lautz, T.B., Harris, C.J., Laronda, M.M., Erickson, L.L. & Rowell, E.E. A fertility preservation toolkit for pediatric surgeons caring for children with cancer. *Semin Pediatr Surg* **28**, 150861 (2019).
68. Brisset, C., *et al.* Locally aggressive rarely metastazing tumors and low-grade sarcoma in children, adolescents and young adults: The benefits of a national network. *Eur J Surg Oncol* **48**, 508-517 (2022).
69. Collignon, C., *et al.* Stratégie diagnostique des sarcomes des tissus mous de l'enfant et adolescent. *Bulletin du Cancer* **107**, 963-971 (2020).
70. Birgin, E., *et al.* Core needle biopsy versus incisional biopsy for differentiation of soft-tissue sarcomas: A systematic review and meta-analysis. *Cancer* **126**, 1917-1928 (2020).
71. Alcorn, K.M., *et al.* Sentinel lymph node biopsy in pediatric soft tissue sarcoma patients: utility and concordance with imaging. *J Pediatr Surg* **48**, 1903-1906 (2013).
72. Lawrence, W., Jr., Anderson, J.R., Gehan, E.A. & Maurer, H. Pretreatment TNM staging of childhood rhabdomyosarcoma: a report of the Intergroup Rhabdomyosarcoma Study Group. Children's Cancer Study Group. Pediatric Oncology Group. *Cancer* **80**, 1165-1170 (1997).
73. Miettinen, M. *Diagnostic Soft Tissue Pathology*, (Churchill Livingstone 2003).
74. Zürcher, S.J., *et al.* High impact physical activity and bone health of lower extremities in childhood cancer survivors: A cross-sectional study of SURfit. *International journal of cancer* **147**, 1845-1854 (2020).
75. Goldblum J., W.S., Folpe A.L. *Enzinger and Weiss's Soft Tissue Tumors*, (Elsevier, 2019).

76. Martins-Filho, S.N. & Putra, J. Hepatic mesenchymal hamartoma and undifferentiated embryonal sarcoma of the liver: a pathologic review. *Hepat Oncol* **7**, Hep19 (2020).

77. Shehata, B.M.*, et al.* Undifferentiated embryonal sarcoma of the liver is associated with mesenchymal hamartoma and multiple chromosomal abnormalities: a review of eleven cases. *Pediatr Dev Pathol* **14**, 111-116 (2011).

78. Crist, W.*, et al.* The Third Intergroup Rhabdomyosarcoma Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **13**, 610-630 (1995).

79. Ferrari, A.*, et al.* Non-metastatic unresected paediatric non-rhabdomyosarcoma soft tissue sarcomas: results of a pooled analysis from United States and European groups. *Eur J Cancer* **47**, 724-731 (2011).

80. Ferrari, A.*, et al.* Treatment at Relapse for Synovial Sarcoma of Children, Adolescents and Young Adults: From the State of Art to Future Clinical Perspectives. *Cancer Manag Res* **15**, 1183-1196 (2023).

81. Sparber-Sauer, M.*, et al.* The significance of margins in pediatric Non-Rhabdomyosarcoma soft tissue sarcomas: Consensus on surgical margin definition harmonization from the INternational Soft Tissue SaRcoma ConsorTium (INSTRuCT). *Cancer Med* **12**, 11719-11730 (2023).

82. Brecht, I.B.*, et al.* Grossly-resected synovial sarcoma treated by the German and Italian Pediatric Soft Tissue Sarcoma Cooperative Groups: discussion on the role of adjuvant therapies. *Pediatric blood & cancer* **46**, 11-17 (2006).

83. Frustaci, S.*, et al.* Adjuvant treatment of high-risk adult soft tissue sarcomas: a survey by the Italian Sarcoma Group. *Tumori* **92**, 92-97 (2006).

84. Frustaci, S.*, et al.* Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **19**, 1238-1247 (2001).

85. Gronchi, A.*, et al.* Short, full-dose adjuvant chemotherapy in high-risk adult soft tissue sarcomas: a randomized clinical trial from the Italian Sarcoma Group and the Spanish Sarcoma Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **30**, 850-856 (2012).

86. Gronchi, A.*, et al.* Neoadjuvant Chemotherapy in High-Risk Soft Tissue Sarcomas: Final Results of a Randomized Trial From Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) Sarcoma Groups. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **38**, 2178-2186 (2020).

87. Ferrari, A.*, et al.* The role of adjuvant chemotherapy in children and adolescents with surgically resected, high-risk adult-type soft tissue sarcomas. *Pediatric blood & cancer* **45**, 128-134 (2005).

88. Ferrari, A.*, et al.* Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG). *The Lancet Child & Adolescent Health* **5**, 546-558 (2021).

89. Spunt, S.L.*, et al.* A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. *The Lancet Oncology* **21**, 145-161 (2020).

90. Spunt, S.L.*, et al.* A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. *The Lancet Oncology* **21**, 145-161 (2020).

91. Ferrari, A.*, et al.* The role of adjuvant chemotherapy in children and adolescents with surgically resected, high-risk adult-type soft tissue sarcomas. *Pediatric blood & cancer* **45**, 128-134 (2005).

92. Pratt, C.B.*, et al.* Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: A Pediatric Oncology Group Study. *Journal of clinical oncology* **17**, 1219-1219 (1999).

93. Atallah, V.*, et al.* Role of Adjuvant Radiation Therapy After Surgery for Abdominal Desmoplastic Small Round Cell Tumors. *Int J Radiat Oncol Biol Phys* **95**, 1244-1253 (2016).

94. Desai, N.B., *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* **85**, e67-72 (2013).

95. Berlanga, P., *et al.* Intra-abdominal desmoplastic small round cell tumor: The European pediatric Soft tissue sarcoma Study Group (EpSSG) experience. *Pediatric blood & cancer*, e30447 (2023).

96. Ferrari, A., *et al.* Metastatic adult-type non-rhabdomyosarcoma soft tissue sarcomas in children and adolescents: A cohort study from the European paediatric Soft tissue sarcoma Study Group. *Cancer* **129**, 2542-2552 (2023).

97. Ferrari, A., *et al.* Local treatment in initially unresected non-rhabdomyosarcoma soft-tissue sarcomas of children and adolescents: A retrospective single-center experience. *Pediatric blood & cancer* **71**, e30901 (2024).

98. Kelly, S.M., *et al.* Radiotherapy quality assurance in paediatric clinical trials: first report from six QUARTET-affiliated trials. *Radiother Oncol* **182**, 109549 (2023).

99. Fontanesi, J., *et al.* Pediatric brachytherapy. The St. Jude Children's Research Hospital experience. *Cancer* **74**, 733-739 (1994).

100. Merchant, T.E., *et al.* Brachytherapy for pediatric soft-tissue sarcoma. *Int J Radiat Oncol Biol Phys* **46**, 427-432 (2000).

101. measurements, T.I.C.o.R.u.a. ICRU Report 78: Prescribing, Recording, and Reporting Proton-Beam Therapy (2007).

102. Palm, A. & Johansson, K.A. A review of the impact of photon and proton external beam radiotherapy treatment modalities on the dose distribution in field and out-of-field; implications for the long-term morbidity of cancer survivors. *Acta Oncol* **46**, 462-473 (2007).

103. Vennarini, S., *et al.* Proton Therapy in Non-Rhabdomyosarcoma Soft Tissue Sarcomas of Children and Adolescents. *Cancers (Basel)* **16**(2024).

104. Sultan, I., *et al.* Comparing children and adults with synovial sarcoma in the Surveillance, Epidemiology, and End Results program, 1983 to 2005: an analysis of 1268 patients. *Cancer* **115**, 3537-3547 (2009).

105. Venkatramani, R., *et al.* Synovial Sarcoma in Children, Adolescents, and Young Adults: A Report From the Children's Oncology Group ARST0332 Study. *J Clin Oncol* **39**, 3927-3937 (2021).

106. Ladanyi, M., *et al.* Impact of SYT-SSX fusion type on the clinical behavior of synovial sarcoma: a multi-institutional retrospective study of 243 patients. *Cancer Res* **62**, 135-140 (2002).

107. Ladanyi, M. Fusions of the SYT and SSX genes in synovial sarcoma. *Oncogene* **20**, 5755-5762 (2001).

108. Kawai, A., *et al.* SYT-SSX gene fusion as a determinant of morphology and prognosis in synovial sarcoma. *N Engl J Med* **338**, 153-160 (1998).

109. Kadoch, C. & Crabtree, Gerald R. Reversible Disruption of mSWI/SNF (BAF) Complexes by the SS18-SSX Oncogenic Fusion in Synovial Sarcoma. *Cell* **153**, 71-85 (2013).

110. Ferrari, A., *et al.* Synovial sarcoma: a retrospective analysis of 271 patients of all ages treated at a single institution. *Cancer* **101**, 627-634 (2004).

111. Ferrari, A., *et al.* Synovial sarcoma of children and adolescents: the prognostic role of axial sites. *European journal of cancer (Oxford, England : 1990)* **44**, 1202-1209 (2008).

112. Okcu, M.F., *et al.* Synovial sarcoma of childhood and adolescence: a multicenter, multivariate analysis of outcome. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **21**, 1602-1611 (2003).

113. Ferrari, A., *et al.* Surgery alone is sufficient therapy for children and adolescents with low-risk synovial sarcoma: A joint analysis from the European paediatric soft tissue sarcoma Study Group and the Children's Oncology Group. *Eur J Cancer* **78**, 1-6 (2017).

114. Scheer, M., *et al.* The effect of adjuvant therapies on long-term outcome for primary resected synovial sarcoma in a series of mainly children and adolescents. *J Cancer Res Clin Oncol* **147**, 3735-3747 (2021).

115. Koscielniak, E.*, et al.* Maintenance therapy with trofosfamide, idarubicin and etoposide in patients with rhabdomyosarcoma and other high-risk soft tissue sarcomas (CWS-2007-HR): a multicentre, open-label, randomised controlled phase 3 trial. *EClinicalMedicine* **78**, 102957 (2024).

116. Jhanwar, S.C., Chen, Q., Li, F.P., Brennan, M.F. & Woodruff, J.M. Cytogenetic analysis of soft tissue sarcomas. Recurrent chromosome abnormalities in malignant peripheral nerve sheath tumors (MPNST). *Cancer Genet Cytogenet* **78**, 138-144 (1994).

117. Rodriguez, F.J., Folpe, A.L., Giannini, C. & Perry, A. Pathology of peripheral nerve sheath tumors: diagnostic overview and update on selected diagnostic problems. *Acta Neuropathologica* **123**, 295-319 (2012).

118. Bates, J.E., Peterson, C.R., Dhakal, S., Giampoli, E.J. & Constine, L.S. Malignant peripheral nerve sheath tumors (MPNST): a SEER analysis of incidence across the age spectrum and therapeutic interventions in the pediatric population. *Pediatric blood & cancer* **61**, 1955-1960 (2014).

119. Carli, M.*, et al.* Pediatric malignant peripheral nerve sheath tumor: the Italian and German soft tissue sarcoma cooperative group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **23**, 8422-8430 (2005).

120. Ferrari, A.*, et al.* Non-metastatic unresected paediatric non-rhabdomyosarcoma soft tissue sarcomas: Results of a pooled analysis from United States and European groups. *European Journal of Cancer* **47**, 724-731 (2011).

121. Ducatman, B.S., Scheithauer, B.W., Piepgras, D.G., Reiman, H.M. & Ilstrup, D.M. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. *Cancer* **57**, 2006-2021 (1986).

122. Evans, D.G.*, et al.* Malignant peripheral nerve sheath tumours in neurofibromatosis 1. *J Med Genet* **39**, 311-314 (2002).

123. Kolberg, M.*, et al.* Survival meta-analyses for >1800 malignant peripheral nerve sheath tumor patients with and without neurofibromatosis type 1. *Neuro Oncol* **15**, 135-147 (2013).

124. Valentin, T.*, et al.* Management and prognosis of malignant peripheral nerve sheath tumors: The experience of the French Sarcoma Group (GSF-GETO). *European journal of cancer (Oxford, England : 1990)* **56**, 77-84 (2016).

125. Ferrari, A.*, et al.* Soft-tissue sarcomas in children and adolescents with neurofibromatosis type 1. *Cancer* **109**, 1406-1412 (2007).

126. Clark, M.A., Fisher, C., Judson, I. & Thomas, J.M. Soft-tissue sarcomas in adults. *N Engl J Med* **353**, 701-711 (2005).

127. Grobmyer, S.R., Reith, J.D., Shahlaee, A., Bush, C.H. & Hochwald, S.N. Malignant Peripheral Nerve Sheath Tumor: molecular pathogenesis and current management considerations. *J Surg Oncol* **97**, 340-349 (2008).

128. Pratt, C.B.*, et al.* Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: A Pediatric Oncology Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **17**, 1219 (1999).

129. Hawkins, D.S., Spunt, S.L. & Skapek, S.X. Children's Oncology Group's 2013 blueprint for research: Soft tissue sarcomas. *Pediatric blood & cancer* **60**, 1001-1008 (2013).

130. van Noesel, M.M.*, et al.* Outcome and prognostic factors in pediatric malignant peripheral nerve sheath tumors: An analysis of the European Pediatric Soft Tissue Sarcoma Group (EpSSG) NRSTS-2005 prospective study. *Pediatric blood & cancer* **66**, e27833 (2019).

131. Meister, M.T.*, et al.* Malignant peripheral nerve sheath tumors in children, adolescents, and young adults: Treatment results of five Cooperative Weichteilsarkom Studiengruppe (CWS) trials and one registry. *J Surg Oncol* **122**, 1337-1347 (2020).

132. Galvin, R.*, et al.* Neurofibromatosis in the Era of Precision Medicine: Development of MEK Inhibitors and Recent Successes with Selumetinib. *Curr Oncol Rep* **23**, 45 (2021).

133. Landers, S.M.*, et al.* AXL Inhibition Enhances MEK Inhibitor Sensitivity in Malignant Peripheral Nerve Sheath Tumors. *J Cancer Sci Clin Ther* **4**, 511-525 (2020).

134. Nagabushan, S.*, et al.* Efficacy of MEK inhibition in a recurrent malignant peripheral nerve sheath tumor. *NPJ Precis Oncol* **5**, 9 (2021).

135. Wang, J.*, et al.* Combined Inhibition of SHP2 and MEK Is Effective in Models of NF1-Deficient Malignant Peripheral Nerve Sheath Tumors. *Cancer Res* **80**, 5367-5379 (2020).

136. Genevois, A.L.*, et al.* Alveolar soft part sarcomas in young patients: The French national NETSARC+ network experience. *Eur J Surg Oncol* **50**, 108483 (2024).

137. Williams, A.*, et al.* Detection of ASPL/TFE3 fusion transcripts and the TFE3 antigen in formalin-fixed, paraffin-embedded tissue in a series of 18 cases of alveolar soft part sarcoma: useful diagnostic tools in cases with unusual histological features. *Virchows Arch* **458**, 291-300 (2011).

138. Aulmann, S., Longerich, T., Schirmacher, P., Mechtersheimer, G. & Penzel, R. Detection of the ASPSCR1-TFE3 gene fusion in paraffin-embedded alveolar soft part sarcomas. *Histopathology* **50**, 881-886 (2007).

139. Lieberman, P.H.*, et al.* Alveolar soft-part sarcoma. A clinico-pathologic study of half a century. *Cancer* **63**, 1-13 (1989).

140. Casanova, M.*, et al.* Alveolar soft part sarcoma in children and adolescents: A report from the Soft-Tissue Sarcoma Italian Cooperative Group. *Ann Oncol* **11**, 1445-1449 (2000).

141. Wang, H.*, et al.* Prognostic factors in alveolar soft part sarcoma: A SEER analysis. *J Surg Oncol* **113**, 581-586 (2016).

142. Portera, C.A., Jr.*, et al.* Alveolar soft part sarcoma: clinical course and patterns of metastasis in 70 patients treated at a single institution. *Cancer* **91**, 585-591 (2001).

143. Bisogno, G., Ferrari, A., Alaggio, R. & Orbach, D. Treatment options for alveolar soft part sarcoma in pediatric patients. *Expert Opinion on Orphan Drugs* **2**, 579-589 (2014).

144. Stacchiotti, S.*, et al.* Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. *Ann Oncol* **22**, 1682-1690 (2011).

145. Kunisada, T.*, et al.* Soft-tissue sarcoma in adolescents and young adults. *International Journal of Clinical Oncology* **28**, 1-11 (2023).

146. Kerrison, W.G.J., Lee, A.T.J., Thway, K., Jones, R.L. & Huang, P.H. Current Status and Future Directions of Immunotherapies in Soft Tissue Sarcomas. *Biomedicines* **10**, 573 (2022).

147. Chen, A.P.*, et al.* Atezolizumab for Advanced Alveolar Soft Part Sarcoma. *N Engl J Med* **389**, 911-921 (2023).

148. Tan, Z.*, et al.* Anlotinib plus TQB2450, a PD-L1 Antibody, in Patients with Advanced Alveolar Soft Part Sarcoma: A Single-Arm, Phase II Trial. *Clin Cancer Res* **30**, 5577-5583 (2024).

149. Orbach, D.*, et al.* Paediatric and adolescent alveolar soft part sarcoma: A joint series from European cooperative groups. *Pediatr Blood Cancer* **60**, 1826-1832 (2013).

150. Ladanyi, M.*, et al.* The der(17)t(X;17)(p11;q25) of human alveolar soft part sarcoma fuses the TFE3 transcription factor gene to ASPL, a novel gene at 17q25. *Oncogene* **20**, 48-57 (2001).

151. Reichardt, P.*, et al.* Chemotherapy in alveolar soft part sarcomas: What do we know? *European Journal of Cancer* **39**, 1511-1516 (2003).

152. Azizi, A.A.*, et al.* Vascular-endothelial-growth-factor (VEGF) expression and possible response to angiogenesis inhibitor bevacizumab in metastatic alveolar soft part sarcoma. *Lancet Oncol* **7**, 521-523 (2006).

153. Kayton, M.L., Meyers, P., Wexler, L.H., Gerald, W.L. & LaQuaglia, M.P. Clinical presentation, treatment, and outcome of alveolar soft part sarcoma in children, adolescents, and young adults. *J Pediatr Surg* **41**, 187-193 (2006).

154. Stacchiotti, S.*, et al.* Response to sunitinib malate in advanced alveolar soft part sarcoma. *Clin Cancer Res* **15**, 1096-1104 (2009).

155. Ogura, K.*, et al.* Alveolar soft part sarcoma: a single-center 26-patient case series and review of the literature. *Sarcoma* **2012**, 907179 (2012).

156. Falkenstern-Ge, R.F.*, et al.* Lung metastasis of primary alveolar soft-part sarcoma occurring 20 years after initial treatment. *Case Rep Oncol Med* **2013**, 690520 (2013).

157. Kummar, S.*, et al.* Cediranib for metastatic alveolar soft part sarcoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **31**, 2296-2302 (2013).

158. Hodge, J.C.*, et al.* Molecular cytogenetic analysis for TFE3 rearrangement in Xp11.2 renal cell carcinoma and alveolar soft part sarcoma: validation and clinical experience with 75 cases. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* **27**, 113-127 (2014).

159. Kuo, D.J., Menell, J.S. & Glade Bender, J.L. Treatment of Metastatic, Refractory Alveolar Soft Part Sarcoma: Case Reports and Literature Review of Treatment Options in the Era of Targeted Therapy. *J Pediatr Hematol Oncol* **38**, e169-172 (2016).

160. Flores, R.J.*, et al.* Alveolar soft part sarcoma in children and young adults: A report of 69 cases. *Pediatric blood & cancer* **65**, e26953 (2018).

161. Enzinger, F.M. CLEAR-CELL SARCOMA OF TENDONS AND APONEUROSES. AN ANALYSIS OF 21 CASES. *Cancer* **18**, 1163-1174 (1965).

162. Chung, E.B. & Enzinger, F.M. Malignant melanoma of soft parts. A reassessment of clear cell sarcoma. *Am J Surg Pathol* **7**, 405-413 (1983).

163. Langezaal, S.M., Graadt van Roggen, J.F., Cleton-Jansen, A.M., Baelde, J.J. & Hogendoorn, P.C. Malignant melanoma is genetically distinct from clear cell sarcoma of tendons and aponeurosis (malignant melanoma of soft parts). *Br J Cancer* **84**, 535-538 (2001).

164. Kosemehmetoglu, K. & Folpe, A.L. Clear cell sarcoma of tendons and aponeuroses, and osteoclast-rich tumour of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: a review and update. *J Clin Pathol* **63**, 416-423 (2010).

165. Blay, J.Y.*, et al.* Pembrolizumab in patients with rare and ultra-rare sarcomas (AcSé Pembrolizumab): analysis of a subgroup from a non-randomised, open-label, phase 2, basket trial. *Lancet Oncol* **24**, 892-902 (2023).

166. Vandeweyer, E., Somerhausen, N.D.S.A. & Gebhart, M. Dermatofibrosarcoma Protuberans: How Wide is Wide in Surgical Excision ? *Acta Chirurgica Belgica* **102**, 455-458 (2002).

167. Rubio, G.A., Alvarado, A., Gerth, D.J., Tashiro, J. & Thaller, S.R. Incidence and Outcomes of Dermatofibrosarcoma Protuberans in the US Pediatric Population. *J Craniofac Surg* **28**, 182-184 (2017).

168. Darier, J. Dermatofibromes progressifs et recidivants ou fibrosarcomes de la peau. *Ann. Dermatol. Venereol.* **5**, 545-562 (1924).

169. Tsai, Y.J., Lin, P.Y., Chew, K.Y. & Chiang, Y.C. Dermatofibrosarcoma protuberans in children and adolescents: Clinical presentation, histology, treatment, and review of the literature. *J Plast Reconstr Aesthet Surg* **67**, 1222-1229 (2014).

170. Chicaud, M.*, et al.* Dermatofibrosarcoma protuberans, fibrosarcomatous variant: A rare tumor in children. *Pediatr Dermatol* **38**, 217-222 (2021).

171. Tsai, Y.-J., Lin, P.-Y., Chew, K.-Y. & Chiang, Y.-C. Dermatofibrosarcoma protuberans in children and adolescents: Clinical presentation, histology, treatment, and review of the literature. *Journal of Plastic, Reconstructive & Aesthetic Surgery* **67**, 1222-1229 (2014).

172. Simon, M.P., Navarro, M., Roux, D. & Pouysségur, J. Structural and functional analysis of a chimeric protein COL1A1-PDGFB generated by the translocation t(17;22)(q22;q13.1) in Dermatofibrosarcoma protuberans (DP). *Oncogene* **20**, 2965-2975 (2001).

173. Peng, C.*, et al.* Genomic alterations of dermatofibrosarcoma protuberans revealed by whole-genome sequencing. *Br J Dermatol* **186**, 997-1009 (2022).

174. Gloster Jr, H.M. Dermatofibrosarcoma protuberans. *Journal of the American Academy of Dermatology* **35**, 355-374 (1996).

175. Malan, M., Xuejingzi, W. & Quan, S.J. The efficacy of Mohs micrographic surgery over the traditional wide local excision surgery in the cure of dermatofibrosarcoma protuberans. *Pan Afr Med J* **33**, 297 (2019).

176. Rutkowski, P. & Debiec-Rychter, M. Current treatment options for dermatofibrosarcoma protuberans. *Expert Rev Anticancer Ther* **15**, 901-909 (2015).

177. Rust, D.J.*, et al.* Surgical management of dermatofibrosarcoma protuberans. *J Surg Oncol* **128**, 87-96 (2023).

178. Krewer, J.*, et al.* Dermatofibrosarcoma protuberans in children and adolescents: Primary and Relapsed disease-Experience of the Cooperative Weichteilsarkomstudiengruppe (CWS). *J Surg Oncol* **122**, 263-272 (2020).

179. Gross, K.G., Steinman, H.K. & Rapini, R.P. Mohs surgery: fundamentals and techniques. *(No Title)* (1999).

180. Henry, O.S.*, et al.* Tyrosine kinase inhibitors versus radiation therapy in unresectable dermatofibrosarcoma protuberans (DFSP): A narrative systematic review. *Am J Surg* **225**, 268-274 (2023).

181. Gooskens, S.L.*, et al.* Imatinib mesylate for children with dermatofibrosarcoma protuberans (DFSP). *Pediatric blood & cancer* **55**, 369-373 (2010).

182. Stacchiotti, S.*, et al.* Efficacy and biological activity of imatinib in metastatic dermatofibrosarcoma protuberans (DFSP). *Clinical Cancer Research* **22**, 837-846 (2016).

183. Brennan, B., Stiller, C. & Bourdeaut, F. Extracranial rhabdoid tumours: what we have learned so far and future directions. *The Lancet Oncology* **14**, e329-e336 (2013).

184. Lee, R.S.*, et al.* A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. *The Journal of Clinical Investigation* **122**, 2983-2988 (2012).

185. Sultan, I.*, et al.* Age, stage, and radiotherapy, but not primary tumor site, affects the outcome of patients with malignant rhabdoid tumors. *Pediatric blood & cancer* **54**, 35-40 (2010).

186. Morgenstern, D.A., Gibson, S., Brown, T., Sebire, N.J. & Anderson, J. Clinical and pathological features of paediatric malignant rhabdoid tumours. *Pediatr Blood Cancer* **54**, 29-34 (2010).

187. Nemes, K.*, et al.* Current and Emerging Therapeutic Approaches for Extracranial Malignant Rhabdoid Tumors. *Cancer Manag Res* **14**, 479-498 (2022).

188. Enault, M.*, et al.* Extracranial rhabdoid tumours: Results of a SFCE series of patients treated with a dose compression strategy according to European Paediatric Soft tisue sarcoma Study Group recommendations. *Eur J Cancer* **161**, 64-78 (2022).

189. Fuchs, J.*, et al.* A Systematic Review and Meta-Analysis of Malignant Rhabdoid and Small Cell Undifferentiated Liver Tumors: A Rational for a Uniform Classification. *Cancers (Basel)* **14**(2022).

190. Yanagi, Y.*, et al.* The role of living-donor liver transplantation in children with an advanced malignant rhabdoid tumor of the liver in the era of transplant oncology: Case report and literature review. *Pediatr Blood Cancer* **70**, e30582 (2023).

191. Nemes, K.*, et al.* Rhabdoid Tumor Predisposition Syndrome. in *GeneReviews(®)* (eds. Adam, M.P.*, et al.*) (University of Washington, Seattle

192. Nemes, K. & Frühwald, M.C. Emerging therapeutic targets for the treatment of malignant rhabdoid tumors. *Expert Opin Ther Targets* **22**, 365-379 (2018).

193. Theruvath, J.*, et al.* Locoregionally administered B7-H3-targeted CAR T cells for treatment of atypical teratoid/rhabdoid tumors. *Nat Med* **26**, 712-719 (2020).

194. Gastberger, K.*, et al.* Current Molecular and Clinical Landscape of ATRT - The Link to Future Therapies. *Cancer Manag Res* **15**, 1369-1393 (2023).

195. Nemes, K.*, et al.* Rhabdoid tumors in patients conceived following ART: is there an association? *Hum Reprod* **38**, 2028-2038 (2023).

196. Scheer, M.*, et al.* Desmoplastic small round cell tumors: Multimodality treatment and new risk factors. *Cancer Med* **8**, 527-542 (2019).

197. Olivier-Gougenheim, L., Orbach, D., Atallah, V., Marec-Berard, P. & Bertrand, A. Desmoplastic Small Round Cell Tumors With EWS-WT1 Transcript Expression: Should We Consider Children and Adult Patients Differently? *J Pediatr Hematol Oncol* **44**, e637-e642 (2022).

198. Kushner, B.H.*, et al.* Desmoplastic small round-cell tumor: prolonged progression-free survival with aggressive multimodality therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **14**, 1526-1531 (1996).

199. Hayes-Jordan, A.*, et al.* Cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for children, adolescents, and young adults: the first 50 cases. *Ann Surg Oncol* **22**, 1726-1732 (2015).

200. Zmora, O., *et al.* Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for disseminated intra-abdominal malignancies in children-a single-institution experience. *J Pediatr Surg* **53**, 1381-1386 (2018).

201. Hovsepyan, S., *et al.* Desmoplastic small round cell tumor: from state of the art to future clinical prospects. *Expert Rev Anticancer Ther* **23**, 471-484 (2023).

202. Issels, R.D., *et al.* Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma: The EORTC 62961-ESHO 95 Randomized Clinical Trial. *JAMA Oncol* **4**, 483-492 (2018).

203. Issels, R.D., *et al.* Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol* **11**, 561-570 (2010).

204. Wessalowski, R., *et al.* An approach for cure: PEI-chemotherapy and regional deep hyperthermia in children and adolescents with unresectable malignant tumors. *Klin Padiatr* **215**, 303-309 (2003).

205. Bisogno, G., *et al.* Sequential intensified chemotherapy with stem cell rescue for children and adolescents with desmoplastic small round-cell tumor. *Bone Marrow Transplant* **45**, 907-911 (2010).

206. Hayes-Jordan, A., *et al.* Complete cytoreduction and HIPEC improves survival in desmoplastic small round cell tumor. *Ann Surg Oncol* **21**, 220-224 (2014).

207. Italiano, A., Kind, M., Cioffi, A., Maki, R.G. & Bui, B. Clinical activity of sunitinib in patients with advanced desmoplastic round cell tumor: a case series. *Target Oncol* **8**, 211-213 (2013).

208. Stiles, Z.E., *et al.* Desmoplastic Small Round Cell Tumor: Long-Term Complications After Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy. *Ann Surg Oncol* **27**, 171-178 (2020).

209. Gill, H., Shahbazi, N., Yu, Z. & Vanlandingham, W. Yttrium-90 radioembolization in desmoplastic small round cell tumor with recurrent hepatic metastasis following hyperthermic intraperitoneal chemotherapy. *Radiol Case Rep* **16**, 1259-1263 (2021).

210. Siddiqui, A., *et al.* The addition of autologous stem cell transplantation to neoadjuvant chemotherapy, radiation, and HIPEC for patients with unresectable desmoplastic small round cell tumor: a single center case series. *Int J Surg Oncol (N Y)* **5**(2020).

211. Ferrari, A., *et al.* Response to vinorelbine and low-dose cyclophosphamide chemotherapy in two patients with desmoplastic small round cell tumor. *Pediatr Blood Cancer* **49**, 864-866 (2007).

212. Ferrari, A., *et al.* Trabectedin-irinotecan, a potentially promising combination in relapsed desmoplastic small round cell tumor: report of two cases. *J Chemother* **35**, 163-167 (2023).

213. Compostella, A., *et al.* Topotecan/carboplatin regimen for refractory/recurrent rhabdomyosarcoma in children: Report from the AIEOP Soft Tissue Sarcoma Committee. *Tumori* **105**, 138-143 (2019).

214. Ferrari, A., *et al.* Multiagent chemotherapy including IrIVA regimen and maintenance therapy in the treatment of desmoplastic small round cell tumor. *Tumori* **108**, 93-97 (2022).

215. Schoot, R.A., *et al.* Metastatic Rhabdomyosarcoma: Results of the European Paediatric Soft Tissue Sarcoma Study Group MTS 2008 Study and Pooled Analysis With the Concurrent BERNIE Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **40**, 3730-3740 (2022).

216. Hayes-Jordan, A.A., *et al.* Desmoplastic Small Round Cell Tumor Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Results of a Phase 2 Trial. *Ann Surg Oncol* **25**, 872-877 (2018).

217. Königsrainer, I. & Beckert, S. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: where are we? *World J Gastroenterol* **18**, 5317-5320 (2012).

218. Scalabre, A., *et al.* Cytoreductive surgery and hyperthermic intraperitoneal perfusion with chemotherapy in children with peritoneal tumor spread: A French nationwide study over 14 years. *Pediatr Blood Cancer* **65**(2018).

219. Seitz, G., *et al.* [Cytoreductive surgery and HIPEC for peritoneal malignancies in children]. *Zentralbl Chir* **139**, 607-612 (2014).

220. Cohen-Gogo, S., *et al.* Ewing-like sarcomas with BCOR-CCNB3 fusion transcript: a clinical, radiological and pathological retrospective study from the Société Française des Cancers de L'Enfant. *Pediatr Blood Cancer* **61**, 2191-2198 (2014).

221. Kao, Y.C., *et al.* BCOR-CCNB3 Fusion Positive Sarcomas: A Clinicopathologic and Molecular Analysis of 36 Cases With Comparison to Morphologic Spectrum and Clinical Behavior of Other Round Cell Sarcomas. *The American journal of surgical pathology* **42**, 604-615 (2018).

222. Antonescu, C.R., *et al.* Sarcomas With CIC-rearrangements Are a Distinct Pathologic Entity With Aggressive Outcome: A Clinicopathologic and Molecular Study of 115 Cases. *The American journal of surgical pathology* **41**, 941-949 (2017).

223. Yoshimoto, M., *et al.* Detailed cytogenetic and array analysis of pediatric primitive sarcomas reveals a recurrent CIC-DUX4 fusion gene event. *Cancer Genet Cytogenet* **195**, 1-11 (2009).

224. Brčić, I., *et al.* Undifferentiated round cell sarcomas with CIC-DUX4 gene fusion: expanding the clinical spectrum. *Pathology* **52**, 236-242 (2020).

225. Breunis, W., *et al.* Patient-derived tumoroids from CIC::DUX4 rearranged sarcoma identify MCL1 as a therapeutic target. *Nat Commun* **16**, 7688 (2025).

226. Sparber-Sauer, M., *et al.* Clinical characteristics and outcomes for children, adolescents and young adults with "CIC-fused" or "BCOR-rearranged" soft tissue sarcomas: A multi-institutional European retrospective analysis. *Cancer Med* **12**, 14346-14359 (2023).

227. Meazza, C., *et al.* Aggressive fibromatosis in children and adolescents: the Italian experience. *Cancer* **116**, 233-240 (2010).

228. Meazza, C., Alaggio, R. & Ferrari, A. Aggressive fibromatosis in children: a changing approach. *Minerva Pediatr* **63**, 305-318 (2011).

229. Sparber-Sauer, M., *et al.* Systemic therapy of aggressive fibromatosis in children and adolescents: Report of the Cooperative Weichteilsarkom Studiengruppe (CWS). *Pediatr Blood Cancer* **65**, e26943 (2018).

230. Ajabnoor, R. Different Shades of Desmoid-Type Fibromatosis (DTF): Detection of Noval Mutations in the Clinicopathologic Analysis of 32 Cases. *Diagnostics* **14**, 2161 (2024).

231. The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients. *Eur J Cancer* **127**, 96-107 (2020).

232. Bouttefroy, S., *et al.* Desmoid type fibromatosis in pediatric and young adults from French databases: Clinical characteristics and initial outcome according to age. *EJC Paediatric Oncology* **1**, 100012 (2023).

233. Sparber-Sauer, M., *et al.* Rationale for the use of tyrosine kinase inhibitors in the treatment of paediatric desmoid-type fibromatosis. *British journal of cancer* **124**, 1637-1646 (2021).

234. Gounder, M., *et al.* Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors. *N Engl J Med* **388**, 898-912 (2023).

235. Braggio, D.A., *et al.* Preclinical efficacy of the Wnt/β-catenin pathway inhibitor BC2059 for the treatment of desmoid tumors. *PloS one* **17**, e0276047 (2022).

236. Kasper, B., *et al.* Current Management of Desmoid Tumors: A Review. *JAMA Oncol* **10**, 1121-1128 (2024).

237. Jo, V.Y. & Fletcher, C.D. WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. *Pathology* **46**, 95-104 (2014).

238. Telugu, R.B., *et al.* Clinicopathological Study of 18 Cases of Inflammatory Myofibroblastic Tumors with Reference to ALK-1 Expression: 5-Year Experience in a Tertiary Care Center. *J Pathol Transl Med* **51**, 255-263 (2017).

239. Coffin, C.M., Watterson, J., Priest, J.R. & Dehner, L.P. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases. *The American journal of surgical pathology* **19**, 859-872 (1995).

240. Butrynski, J.E., *et al.* Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. *N Engl J Med* **363**, 1727-1733 (2010).

241. Kang, J., *et al.* Clinicopathological findings of pediatric NTRK fusion mesenchymal tumors. *Diagnostic Pathology* **15**, 114 (2020).

242. Antonescu, C.R., *et al.* Molecular characterization of inflammatory myofibroblastic tumors with frequent ALK and ROS1 gene fusions and rare novel RET rearrangement. *The American journal of surgical pathology* **39**, 957-967 (2015).

243. Casanova, M., *et al.* Inflammatory myofibroblastic tumor: The experience of the European pediatric Soft Tissue Sarcoma Study Group (EpSSG). *Eur J Cancer* **127**, 123-129 (2020).

244. Kube, S., *et al.* Inflammatory myofibroblastic tumors-A retrospective analysis of the Cooperative Weichteilsarkom Studiengruppe. *Pediatr Blood Cancer* **65**, e27012 (2018).

245. Mossé, Y.P., *et al.* Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **35**, 3215-3221 (2017).

246. Cecchetto, G., *et al.* Fibrosarcoma in pediatric patients: results of the Italian Cooperative Group studies (1979-1995). *J Surg Oncol* **78**, 225-231 (2001).

247. Orbach, D., *et al.* Spotlight on the treatment of infantile fibrosarcoma in the era of neurotrophic tropomyosin receptor kinase inhibitors: International consensus and remaining controversies. *Eur J Cancer* **137**, 183-192 (2020).

248. Orbach, D., *et al.* Infantile fibrosarcoma: management based on the European experience. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **28**, 318-323 (2010).

249. Sparber-Sauer, M., *et al.* The impact of local control in the treatment of children with advanced infantile and adult-type fibrosarcoma: Experience of the cooperative weichteilsarkom studiengruppe (CWS). *Journal of Pediatric Surgery* **55**, 1740-1747 (2020).

250. Orbach, D., *et al.* Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience. *Eur J Cancer* **57**, 1-9 (2016).

251. Hong, D.S., *et al.* Efficacy and safety of larotrectinib as first-line treatment for patients with TRK fusion cancer. *ESMO Open* **10**, 105110 (2025).

252. Laetsch, T.W., *et al.* Larotrectinib for Newly Diagnosed Infantile Fibrosarcoma and Other Pediatric NTRK Fusion-Positive Solid Tumors (Children's Oncology Group ADVL1823). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **43**, 1188-1197 (2025).

253. Mascarenhas, L., *et al.* Elective Discontinuation of Larotrectinib in Pediatric Patients With TRK Fusion Sarcomas and Related Mesenchymal Tumors. *J Clin Oncol* **43**, 1180-1187 (2025).

254. Lee, S.H., *et al.* High-dose ifosfamide as second- or third-line chemotherapy in refractory bone and soft tissue sarcoma patients. *Oncology* **80**, 257-261 (2011).

255. Meazza, C., *et al.* Prolonged 14-day continuous infusion of high-dose ifosfamide with an external portable pump: feasibility and efficacy in refractory pediatric sarcoma. *Pediatr Blood Cancer* **55**, 617-620 (2010).

256. Ferrari, A., *et al.* Salvage rates and prognostic factors after relapse in children and adolescents with initially localised synovial sarcoma. *Eur J Cancer* **48**, 3448-3455 (2012).

257. Mora, D.C., *et al.* Supportive care for cancer-related symptoms in pediatric oncology: a qualitative study among healthcare providers. *BMC Complement Med Ther* **23**, 104 (2023).

258. Radossi, A.L., *et al.* A systematic review of integrative clinical trials for supportive care in pediatric oncology: a report from the International Society of Pediatric Oncology, T&CM collaborative. *Support Care Cancer* **26**, 375-391 (2018).

259. Groll, A.H. & Ebrahimi-Fakhari, D. Conference Report 33rd European Congress on Clinical Microbiology and Infectious Diseases (ECCMID): New developments in pediatric oncology infectious disease supportive care. *Transpl Infect Dis* **25**, e14146 (2023).

260. Landier, W., *et al.* Development of risk-based guidelines for pediatric cancer survivors: The Children's Oncology Group long-term follow-up guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *Journal of Clinical Oncology* **22**, 4979-4990 (2004).

261. Michel, G., *et al.* Evidence-based recommendations for the organization of long-term follow-up care for childhood and adolescent cancer survivors: a report from the PanCareSurFup Guidelines Working Group. *J Cancer Surviv* **13**, 759-772 (2019).

262. Schoot, R.A., *et al.* Adverse events of local treatment in long-term head and neck rhabdomyosarcoma survivors after external beam radiotherapy or AMORE treatment. *Eur J Cancer* **51**, 1424-1434 (2015).