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# Management of sarcomas in children, adolescents and adults: interactions in two different age groups under the umbrellas of GSF-GETO and SFCE, with the support of the NETSARC+ network.

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## Abstract

Sarcomas are a rare heterogeneous group of malignant neoplasms that can arise in almost any anatomic site and any age. Close collaboration among adult and pediatric cancer specialists in the management of these tumors is of foremost importance. In this review, we present the current multidisciplinary organization of care of patients with sarcoma in France and review the main advances made in the last decades in systemic and radiotherapy treatment in the main sarcoma types diagnosed in children, adolescents and young adults (AYA) thanks to the international collaboration.

**Keywords:** Bone sarcoma, soft tissue sarcoma, children, AYA, adults

## Introduction

Sarcomas are a heterogeneous group of malignant neoplasms that arise from cells of a mesenchymal origin. They comprise several histological subtypes and occur in almost any anatomic site and at any age, representing 1-2% and 6% of cancers in adults and children/adolescents, respectively [1]. Because of their rarity and complexity, close collaboration among all cancer specialists (pathologists, molecular biologists, surgeons, radiation oncologists, medical and pediatric oncologists, etc.) is of utmost importance to improve management and outcome.

In France, the current multidisciplinary organization of care of the main two different age groups (children/adolescent <18 years old and adults > 18 years old) is performed under the interconnected umbrellas of the adult French Sarcoma Group (GSF-GETO) and French Society of Pediatric Oncology (SFCE).

In this review, we will present the French current multidisciplinary organization of care of patients with sarcoma. We will then review the key advances in the systemic and radiotherapy treatment made in Europe in the main sarcoma types diagnosed in children, adolescents and young adults (AYA) through the international collaboration of paediatric and adult cancer specialists, to which GSF-GETO/SFCE play an essential role. Main advances in surgical management of sarcomas will be addressed in a separate article.

## Organization of care for children, adolescents and adults with sarcomas in France

In France, management of sarcoma patients in the two different age groups of children/adolescent (<18 years old) and adults ( $\geq$  18 years old) is organized under the

regulation of different overlapping national health authorities texts with various degrees of enforcement, such as CIRCULAIRE n° 161 DHOS/O/2004 (29th March 2004) [2] for pediatric oncology care (<18 years) and instruction N° DGOS/R3/INCA/2016/177 (30th May 2016) for adolescent and young adult oncology care (15-24 years) [3]. In 2009, the French National Cancer Institute (INCa) labelled for a clinical (NETSARC), pathological (RREPS) and bone (RESOS) reference network for the management of adult sarcomas. These 3 reference networks, have merged since 2019 into NETSARC+. Currently, twenty-three centers belong to the NETSARC+ (<http://www.infosarcomes.org/les-reseaux-netsarc-et-resos>). Main criteria for reference centers to fulfill are the number of patients with sarcoma treated, expertise in their multidisciplinary management and involvement in clinical research [4]. In the NETSARC+ centers, surgeons, radiologists, pathologists, radiation oncologists and medical oncologists work together in local sarcoma-specialized multidisciplinary tumor board (MTB), with the purpose to define the best management for patients with sarcoma or suspicion of sarcoma. These MTBs underline the importance of adequate imaging and tumor biopsy prior to any further discussion that is currently performed in 40-45% of adult patients in France [5]. Recent publications underscore the importance of this approach with documented improved outcomes for those patients with sarcoma whose medical file was discussed in MTBs in France before any treatment and those primarily treated within sarcoma reference centers [6,7]. About 5000 new incident cases of sarcomas and aggressive connective tissue tumors are managed by these 23 centers yearly, and their clinical and biological data integrated in the national database (SARCOMABCB; <https://conticabase.sarcomabcb.org>).

Children and adolescents less than 18 years old with sarcomas are treated in one of the 30 centers of the SFCE (<http://sfce.sfpediatricie.com>). These 30 SFCE centers have been selected based on their specific training and expertise in management of children/adolescents with cancer, numbers of patients treated by year and dedicated facilities and access to intensive care and pediatric surgery, neurosurgery and other specialists [2]. Indeed, according to the French Public Health Code (R. 6123-87), the treatment of children and adolescents with cancer must be provided in age-specific facilities [8]. All cases of children and adolescents less than 18 years old have to be presented and discussed, and the care management validated, in one of the interregional MTBs of the current 7 interregional paediatric oncology networks,

founded in 2010 by the INCa with the ultimate aim to guarantee equal quality of access to health care throughout France for all patients less than 18 years old.

Most of the SFCE centers are also NETSARC+ centers, thus facilitating a close collaboration among pediatric and adult cancer specialists for all patients with sarcomas (Figure 1). These links are further strengthened through the bone sarcoma think tank working group GROUPOS (SFCE- GSF-GETO joint bone tumor group), the participation of members of the SFCE sarcoma groups to the administrative board of GSF-GETO and through the INCA-granted intergroup INTERSARC to which GSF-GETO and GO-AJA ("Onco-hematological Group for Adolescents and Young Adults) belong to. The main objective of these intergroups is to improve treatment for sarcoma patients of any age, by fostering age inclusive clinical research and access to innovation and promoting preclinical research.

In addition to the direct benefit for patients, the NETSARC+ network also provides a clinical and biological database which enables clinical research and epidemiological studies. Currently the NETSARC + database gathers almost 61000 patients' cases of all ages (including 5.2% children < 18 years old, and 6% AYA aged 18-25).

This closed collaboration between paediatric and adult cancer specialists has allowed several advances in systemic and radiotherapy treatment through collaborative clinical studies that will be reviewed in the following chapters, including common achievements and variations in current patterns of care.

### Bone sarcomas: a pioneer collaboration from the 80's through first line clinical trials, driven by the AYA epidemiology of this disease

Bone sarcomas (osteosarcoma and Ewing sarcoma) are typical AYA cancers, with most of the cases occurring between 10-25 years old [1]. This epidemiology enabled early collaboration of pediatric and medical oncologists for first line phase III trials since the 80's. Neoadjuvant chemotherapy followed by primary tumor local treatment (and of metastases) and post-operative chemotherapy has become the milestone of bone sarcoma first line treatment [9], although the strategy of osteosarcoma first line trial development have differed in France compared to other countries. Radiotherapy is often used to complete local treatment in Ewing sarcomas, but rarely in osteosarcoma. Pediatric/adult collaboration within the frame of first line clinical trials has successfully improved accrual of AYAs with bone sarcomas in trials in the last decades [10], bringing

important answers for patient management in terms of chemotherapeutic, new drug agents and radiotherapy and tailored the therapeutic strategy.

The recent therapeutic achievements in bone sarcomas in term of chemotherapy and radiotherapy through pediatric/adult and multidisciplinary collaborations are here presented.

## Ewing sarcoma

Ewing sarcoma (ES) first line trials were the first paediatric/adult collaborative joint trials set up in the 90's, which included patients up to 50 years old. Based on previous paediatric experience [11], in term of chemotherapy and risk factor definitions, successive first line ES joint randomized trials were later on set up in Europe and allowed refining the first line chemotherapy strategy.

### [First line treatment of Ewing sarcoma](#)

#### **Systemic treatment**

The EE99/EWING 2008 trial showed tolerability of VIDE (Vincristine, Ifosfamide, Doxorubicin, Etoposide) induction chemotherapy [12] and tailored adjuvant consolidation therapy to risk factors of relapse (metastatic disease status and histologic response to neo-adjuvant treatment). In localised standard risk patients, no difference was seen between VAI (Vincristine, Dactinomycin, Ifosfamide) and VAC (Vincristine, Dactinomycin, Cyclophosphamide) consolidation chemotherapy [13]. The following EE2012 trial compared the compressed VDC-IE (Vincristine/Doxorubicin/Cyclophosphamide, Ifosfamide/ Etoposide; North American standard) to VIDE [14], with first results establishing the compressed VDC-IE as the standard Ewing sarcoma regimen also in Europe.

For localized ES with poor histological response to induction chemotherapy, Busulfan-Melphalan (BuMel) high dose chemotherapy (HDC) has shown improved outcome in terms of EFS compared to conventional adjuvant chemotherapy, notably in patients aged under 25, but with more acute severe toxicity [15]. HDCT can be considered as an option in adult sarcoma guidelines for this group of patients [9].

For lung/pleural metastatic ES, no difference has been shown between conventional adjuvant chemotherapy and whole-lung irradiation (WLI) and BuMel HDC, and the first option is proposed as standard in paediatric patients to avoid late toxicities of BuMel HDC [16]. Nevertheless, no prospective randomized trial has ever been performed

comparing conventional adjuvant chemotherapy with or without WLI. Thus the use of WLI in adult patients is more controversial.

In case of multimetastatic ES, impact on BuMel HDC consolidation is currently assessed by the French (CombinaiR3, NCT03011528) and the Italian Sarcoma Groups (EW-2 trial, NCT02727387) in non-randomised trials, although HDC is currently not recommended by adult guidelines [9]. The role of the addition of Treosulfan-Melphalan (TreoMel) HDC to conventional adjuvant chemotherapy is explored by the German group in a randomised trial (EWING 2008 trial, NCT00987636).

Despite good chemo sensitivity to first-line therapy, most recurrences occur during the first 2 years after initial diagnosis. The impact of maintenance chemotherapy is currently explored in patients with extra-pulmonary metastases in the non-randomized prospective French CombinaiR3 and Italian EW-2 trials. The impact of maintenance chemotherapy in all newly diagnosed patients with ES will be addressed in the next EuroEwing trial. Currently, the EWING 2008 and EE2012 trials are also exploring the question of the addition of zoledronate, a bisphosphonate, as a new drug targeting the microenvironment in addition to adjuvant chemotherapy.

#### **The role of Radiotherapy for the local treatment of Ewing sarcoma**

The previous first line ES trials, although not specifically addressed any radiotherapy question, have also helped to better understand the role and management of radiotherapy in this radiosensitive tumor. Surgery is generally recommended whenever a complete resection with acceptable functional outcome is feasible and will be addressed in depth in a separate article. Definitive radiotherapy is considered only for patients with non-operable tumors. The EE99 trial revealed increased busulfan-related radio-sensitivity that led to current radiotherapy dose constraints for organ at risk when associated to Busulfan (patients expected to receive RT > 30 Gy to the spinal cord or > 45 Gy to large intestinal/lung volumes were no longer eligible for the combination after amendments) [15,17]. The retrospective analysis of local relapse risk factors in the EE99 trial highlighted the important role of the post-operative radiotherapy in localised ES even after complete resection and good histological response [18]. The modality of local treatment depends on the size and location of the tumor, the response to chemotherapy and the balance between enhancing local control while minimizing morbidity [19,20]. Currently, postoperative RT is standard for all patients except for those who have had a wide local excision (negative resection

margins of at least 1 mm) and a good histological response (>90% necrosis) to pre-operative chemotherapy. [18] [9]. Doses are ranging from 45 to 60 Gy according to the indication (exclusive or pre/postoperative, margins, histological response). Noteworthy, a randomized question on radiotherapy dose escalation to poor risk localized disease will be addressed on the next EuroEwing trial.

However this collaborative multidisciplinary work should be adapted to patient age to minimize late effects in particular in the pediatric population and helped by advances in radiotherapy technics. Intensity modulated radiotherapy (IMRT) is increasingly used due to its benefit in terms of protection of critical organs and/or optimal coverage of target volumes [21]. However, IMRT induces a larger integral dose than 3DCRT in children, thus exposing to a greater theoretical risk of secondary tumors. Proton therapy is particularly recommended for vertebral or pelvic localization, with advantages over photon radiotherapy (3DCRT or IMRT), with better sparing of the normal surrounding tissues [22].

Concerning the use of radiation therapy for the treatment of metastatic sites, WLI is currently recommended for children and adolescents [16] with lung/pleural metastases in the adjuvant setting [9]. The role of radiotherapy in the management of other metastatic sites is unclear and is being explored in the current CombinaiR3 French protocol. The optimal radiotherapy dose is extrapolated from primary site data [23]. Hypo-fractionated radiation therapy schedules and stereotactic body radiotherapy may be proposed in selected cases [24].

Noteworthy, in France the local treatment for patients with Ewing's sarcoma are discussed and validated in a sarcoma-specialized multidisciplinary MTB with pediatric and adult cancer specialists (RCP de recours CIRTAL).

### **Second and further line treatment in refractory/ relapsed ES**

In the relapse setting, no standard treatment exists. Paediatric and adult ES expert community have grouped in the European Ewing consortium (EEC) and developed a trial with the aim to define a standard chemotherapy regimen in relapse ES aged up to 50 years old. The European multi-arm multi-stage randomized phase II/III "rEECur" trial tests 4 different chemotherapy arms: topotecan/cyclophosphamide (TC), irinotecan/temozolomide (IT), gemcitabine/docetaxel (GD) and high-dose ifosfamide (IFOS). First interim assessment presented at ASCO 2019 and 2020 showed that GD and IT were less effective than the other 2 arms [25].



At the same time, several trials in the last two decades have assessed new therapeutic agents in relapsed ES (chemo/targeted/immune therapies or drug combinations), not all adapted to the age range at relapse, and with limited efficacy [26]. TKIs seems to have the most promising early clinical data in relapse/refractory ES, with 11% and 26% ORR, and 3.6 and 4.4 median PFS for regorafenib [27] and cabozantinib [28], respectively. Regorafenib has been tested in two randomized trials versus placebo worldwide: the adult SARC024 trial (NCT02048371) and the joint adult/pediatric French REBOGONE (NCT02389244) trial. Data from the latter study will be presented at ESMO 2020. A combination trial of TKI cabozantinib with immune check point inhibitor pembrolizumab is in preparation in France in relapsed ES (PEMBROSARC trial). Based on these results, the addition of a TKI also under discussion in the design of the next EuroEwing trial.

In contrast with ES, the treatment of osteosarcoma has not progressed in the last 30 years.

#### [First-line treatment of osteosarcoma](#)

##### **Systemic treatment**

Chemotherapy has deeply modified the prognosis of patients with osteosarcoma (OS), with several chemotherapy regimens used worldwide based on 3-5 drug combinations of methotrexate, cisplatin, doxorubicin, ifosfamide and etoposide. There is no formal proof on superiority of neoadjuvant chemotherapy on adjuvant and chemotherapy can also be administered after initial complete surgery, notably in case of patients who undergo upfront primary tumor surgery as initial diagnosis. However trials have been developed on neoadjuvant administration of several regimens, with the assessment of histological response to pre-operative chemotherapy on surgical resection.

Adult/paediatric collaboration to build joint first line trials (age < 40-50 years old) has also been effective in OS but with a different approach in France compared to other international sarcoma groups.

The most used chemotherapy is the MAP regimen (M= high-dose methotrexate, AP= doxorubicin-cisplatin) from the EURAMOS-1 trial, with no modification of post-operative chemotherapy after showing no outcome improvement by intensifying chemotherapy by neither adding IE (I= Ifosfamide, E= Etoposide) in patients with poor

response to pre-operative chemotherapy [29] nor pegylated interferon alfa-2b (IFN- $\alpha$ -2b) in patients with good response [30].

On the other hand, France adopted an age-dependant chemotherapy strategy based on the previous French paediatric randomised OS94 [31] and adult phase II trials [32] with the aim to avoid AP in children (with more at risk of late cardiac and ototoxicity), as well as M in adult patients (with more at risk of renal and neurological toxicities). Therefore, the French OS2006 trial had two different reference chemotherapy regimens depending on age at inclusion: A) M-EI regimen for patients < 18 years [33], B) API-AI for patients > 25 years; patients aged 18-25 received either M-EI or API-AI, according to the centre's choice [34]. In addition, in case of patients < 18 years with high-risk osteosarcoma (metastatic, poor histological response to neoadjuvant chemotherapy), a change of AP in post-operative setting was proposed to allow exposure to all the 5 essential drugs of known efficacy in osteosarcoma. The OS2006 collaboration was built on the addition of zoledronate to the previous selected backbone, although with a trend for an unfavourable impact [35], also suggested by a recent Chinese trial [36]. Noteworthy, although no randomized trial has been done between the EURAMOS and the French approach, reported 5 year-EFS rates seem comparable [33].

The only possible new drug success might be the mifamurtide, an immunomodulator with antitumor effects mediated by the activation of monocytes/macrophages in an adjuvant setting with chemotherapy [37,38]. However, the role of mifamurtide combined with chemotherapy in localized OS is debated even amongst experts [9], leading to marketing authorisation by the European Medicines Agency (EMA) but not by the Food and Drug Administration (FDA), and inconsistent reimbursement across countries. Mifamurtide is currently being explored in the French randomized Sarcome-13/OS2016 trial in combination with post-operative chemotherapy in patients with newly diagnosed high-risk OS (poor response to preoperative chemotherapy, metastatic status) (NCT03643133).

Another major strength of the French bone expert collaboration through trial was the sample collection constituted for biological studies within the OS2006 trial [39,40].

### **Radiotherapy in osteosarcoma management**

OS has classically been considered radio-resistant and surgery remains the recommended local treatment, with the extent of surgical resection and margins

status as main prognostic factors [41]. Surgical management of osteosarcoma will be addressed in depth in a separate article.

In case of microscopically or macroscopically incomplete resection, RT might improve local control, and international guidelines currently recommend it [9]. Similarly, in the presence of a fragmented tumor, endovascular tumor emboli or lymph node involvement, local RT could be also discussed. In the event of an inoperable tumor, exclusive RT may also be offered.

There is no consensus neither on the volumes or nor RT doses in OS. In general, the initial volume is usually treated up to 60 Gy for post-operative RT with only microscopic residual disease, and up to 68-70 Gy for macroscopic residual disease or exclusive RT [42,43]. Photons are the current standard recommendation. Because the tolerance of nearby risk organs that may impose dose limits, hadron therapy (proton or carbon ions) may provide an interesting option in this setting. Shared experience of pediatric and adult radiotherapists is valuable.

Protons, through the obtained dose gradient and the optimized protection of critical organs, might sometimes allow the delivering of large doses in a more conformational manner [43,44]. Especially in young patients, the protection of organs at risk is essential, in order to reduce the risk of long-term functional sequelae and second cancers. Pediatric radiation oncologists have good experience of protons in other tumor types, and sharing this expertise with radiation oncologists more used to treat adult patients is of foremost importance to improve local control/toxicity ratio. Several retrospective reports suggest the benefit in local control of carbon ions, which have, in addition to the ballistic advantage of protons, a high linear energy transfer (LET). This means that, for the same prescribed physical dose, the effective total dose and dose per fraction is increased [45,46]. Radiation oncologists used to treat adult patients have much greater experience of increasing the dose per fraction, unlike pediatric radiation oncologists who use small doses per fraction to minimize long term sequelae. Currently, several trials are exploring the value of carbon ions for the treatment of osteosarcoma (NCT01005043, NCT02838602).

### [Second and further line treatment in refractory/ relapsed OTS](#)

A collaborative SFCE and GSF-GETO review of phase-II trials in refractory/relapsed osteosarcomas has highlighted the lack of pediatric/medical oncologist collaboration

worldwide with low access to phase-II trials in the pediatric population compared to the adult one and a general lack of new drug access [47].

GSF-GETO and SFCE collaboration within the French bone sarcoma working group GROUPOS, helped by the intergroup INTERSARC which aim to favor joint pediatric/adult innovative trials to improve sarcoma outcome, have developed several joint phase-II trials to try to improve this situation. Thanks to this collaboration, pediatric-initiated trials have increased their inclusion upper age limit up to 25 (HOPE lenvatinib [48]) and 50 years old (OSII-TPP randomized trial that tested high-dose thiotepa after standard chemotherapy but failed to improve OS/PFS in resectable relapsed osteosarcoma [49]).

Similarly, adult-initiated trials have decreased their accrual age to 10 (REBOGONE [50]), 12 (CABONE [28]), 13 years (METZOLIMOS, NCT02517918), which allowed French patients with relapsed OS to have access to several joint trials at the same time, including three with TKIs (lenvatinib, regorafenib, cabozantinib). Indeed, TKI's are the most efficient new drugs in OS with 33% (lenvatinib [48]), 46% (sorafenib [51]) and 54% (regorafenib [50]) 4-month progression free survival (PFS) and 33% (cabozantinib [28]) 6-month PFS. The combination of lenvatinib with EI has shown a 4-months PFS of 59% [48], and will be further tested in an international randomized trial (EI ± lenvatinib; NCT04154189). Importantly, the French REGOBONE trial was the only trial evaluating a TKI (regorafenib) vs placebo in patients with relapsing osteosarcoma, showing an improvement in PFS, the primary endpoint. Sadly, no paediatric patient was included in this trial [50]. Several explanations can be hypothesized: paediatric accrual was allowed when trial adult recruitment was advanced, randomization against placebo may have reduce the acceptability by some parents and the existence, at the same time, of a paediatric-initiated trial combining TKI with chemotherapy which might have been favoured by paediatric oncologists. Based on these results, the addition of regorafenib is currently tested in a randomized placebo control clinical trial as maintenance therapy in patients  $\geq 16$  years old after adjuvant chemotherapy (REGOSTA trial, NCT04052220).

**Soft tissue sarcomas, a more challenging but emerging pediatric/adult collaboration to further improve**

Soft tissue sarcoma (STS) epidemiology is more diverse than bone sarcoma, with multiple different pediatric-type STS and adult-type STS with more than 100 different histotypes. Although some of these entities are really age specific, other can be seen in both populations (Table 1). In addition similar entities across age might present different chemo sensitivity and a different biology according to age (e.g. synovial sarcoma, GIST) leading to different initial therapeutic approaches by pediatric and adult oncologists. For these several reasons, collaboration of pediatric and adult teams has historically not been so evident in soft tissue sarcomas, although NETSARC+ and the SFCE are actively working towards it. For example, adult patients of all ages with embryonal/alveolar rhabdomyosarcomas are currently recommended to be treated within pediatric trials [52], and conversely for other STS types. The new landscape of targeted therapies and molecular signatures stimulates pediatric and adult teams to learn together and set up common protocols for a tailored treatment.

### [Rhabdomyosarcoma](#)

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, adolescents and young adults, with a peak incidence between the ages of 2 and 5, although up to 40% occur in adults [53]. There are three main histological RMS variants: embryonal, alveolar and pleomorphic with different management. Another fourth uncommon RMS subtype is the spindle cell/ sclerosing RMS. It was initially grouped under embryonal RMS with predilection for paratesticular and head/neck sites and presents different genetic subtypes with different outcomes: NCOA2 and VGLL rearrangements in a subset of congenital cases with good prognosis [54]; MYOD1 mutations that can at any age but mainly in older children and adults, with poor prognosis [55].

### [Systemic treatment of embryonal and alveolar RMS](#)

Current management of embryonal and alveolar RMS is based on the administration of risk-adapted chemotherapy and local therapy (surgery, radiation therapy, or both). Surgical management will be addressed in depth in a separate article. Risk-stratification is based on age and tumor size, primary tumor site, post-surgical stage, disease extension (N and M status), and biopathology including FOXO1 fusion status [56]. Importantly, AYA and adult patients have a much worse outcome compared to children [57]. Standard backbone chemotherapy consists on prolonged alkylating-

based multi-agent chemotherapy regimens administered over 6-9 months (IVA in Europe, VAC in North America, with demonstrated similar efficacy [58].

Taking the more frequent incidence of embryonal and alveolar RMS in children and adolescents, international trial development has been mostly pediatric-initiated, with the STS group of the SFCE as an active member of the European paediatric Soft tissue Sarcoma Study Group (EpSSG). Until recently, attempts to improve outcome of patients with newly diagnosed RMS based on the addition of new systemic induction treatments had been disappointing in Europe. Neither the addition of doxorubicin (Do) to standard IVA in localized high-risk RMS [59], nor addition of the VEGF-targeted antibody bevacizumab to standard IVADo/IVA in metastatic soft tissue sarcoma showed positive results [60]. However, every cloud has a silver lining as recently demonstrated by the positive results of the addition of maintenance low-dose chemotherapy to patients with newly diagnosed localized high-risk RMS [61], as well as the addition of temozolomide to vincristine/irinotecan in the relapse setting [62]. Further randomized questions on the duration of maintenance chemotherapy in newly diagnosed patients with high and very-high risk RMS, as well as the combination of chemotherapy and TKIs in relapse/refractory patients will be addressed in the future Frontline and Relapsed trans-age RhabdoMyoSarcoma (FaR-RMS, EudraCT number 2018-000515-24) EpSSG trial.

#### [Systemic treatment of pleomorphic RMS](#)

Pleomorphic RMS generally arises in adult patients and is considered as a different entity with worse outcome with different therapeutic approach more similar to other adult soft tissue sarcomas [57]. Adequate surgery and radiotherapy remain the cornerstone to improve survival. In neoadjuvant setting chemotherapy should be discussed with a specialized MTB. In metastatic setting doxorubicin based chemotherapy is still the standard of treatment.

#### **Radiotherapy in the management of rhabdomyosarcoma**

Radiotherapy is a major component of RMS treatment strategy. Based on previous results, the RMS 2005 trial implemented a more systematic use of local radiotherapy with 85% of patients with high-risk RMS receiving it [59] compared to 60% in previous European studies [63], leading to improved global outcomes in some sites. However, there is still room for improvement as local failure still represents the majority of all relapses [59,64]. Thus, the future Far-RMS trial will also address the impact on the

timing of radiotherapy (pre-operative vs standard post-operative) for patients with resectable disease, radiotherapy dose escalation to the post-induction primary tumor for resectable disease for tumor with high risk of local failure (large tumors and/or tumors in adult patients), as well as the question of an additional boost in case of unresectable disease [65].

Another major concern for the pediatric radiation oncologists is to minimize the long term sequelae in the younger patients [66]. One possibility is the use of protons to some specific localizations such as parameningeal [67].

Brachytherapy, currently used in various adult indications (prostate adenocarcinomas, head and neck localizations, breast and gynecological carcinomas), is another option to minimize long term sequelae [68]. However, this technique requires highly specialized teams and should therefore be undertaken only in referent national or international centers. Vaginal and bladder-prostate RMS are among the best indications for this technique with reported low delayed toxicity [66, 69, 70]. Brachytherapy can also be used for head and neck localizations, like in the “Ablative Surgery, Mold technique with afterloading brachytherapy and immediate surgical REconstruction” (AMORE) protocol for locally advanced tumors or re-irradiation, with interesting local control rates and long-term survival [71–73].

The role of radiotherapy to metastatic sites is still debated. Several non-randomized/retrospective studies have shown a potential benefit on outcome [74,75] and this question will be addressed in the FaR-RMS trial.

#### **Treatment of other soft-tissue sarcomas**

In France the network NETSARC demonstrated that adequate surgery in reference centers and specialized MDTB improves survival. Although peri-operative chemotherapy has demonstrated survival benefit in high grade extremity STS in some trials, others have been inconclusive due to different practices and interpretation, and the role of pre-operative chemotherapy is still controversial [76-82]. For example, children’s and adolescents receive more frequently adjuvant chemotherapy for localized synovial sarcomas, which has not shown a survival benefit in adult patients. [83-85]. New tools such as CINSARC (Complexity Index in Sarcoma) and Genomic index signatures, that look at muti-genic factors allow to better tailor patient prognosis [86-87]. Within five years the signature has been validated for both adult and pediatric

synovial sarcomas [88]. The role of the CINSARC signature in patient selection for preoperative chemotherapy is currently assessed in the CHIC-STS01 clinical trial (NCT04307277).

Recent studies have also suggested that implementation of next-generation sequencing can help to identify actionable alterations in up to 50% STS cases in adult patients [89]. Thanks to the strong visibility of the NETSARC network, the first randomized study investigating the role of NGS to personalize patient care in patient with advanced STS has been granted by the French Government. The MULTISARC (NCT03784014) study is a prospective randomized study based on the hypothesis that implementation of NGS for the treatment of patients with advanced STS may improve their outcome. Patients with advanced STS will be randomized between 2 groups: in the experimental group, exome and RNA sequencing will be performed and their results discussed in a molecular tumor board to tailor the treatment of patients; in the control group, no molecular profiling will be done and patients will be treated in a conventional way. Thanks to a public-private partnership, 16 targeted therapies will be included in the program. One of the objectives of the MULTISARC study will be to demonstrate that use of NGS data can improve OS of advanced STS by allowing in at least a proportion of them the identification of 1 or more additional appropriate lines of treatment.

Immunotherapy represents also a potential hope for STS patients. The French Sarcoma Group has recently contributed to an unprecedented effort to investigate the immunological landscape of STS which allowed the identification of a subgroup of inflamed STS more likely to benefit from immune checkpoint inhibitors. The first biomarker-driven clinical studies assessing the efficacy of these agents in STS are currently ongoing across sites of the FSG (NCT04095208, NCT02406781)

In case of metastatic disease, doxorubicin is still the standard of care in adult cancer management. Other drugs or polychemotherapy have failed to demonstrate any advantage on survival [90-93]. Nevertheless children and adolescents have been more often offered polychemotherapy (mainly ifosfamide/doxorubicin). The French Sarcoma Group carries on trials in first line with EREMISS-1801 trial focused on maintenance therapy with regorafenib after doxorubicin as monotherapy.

Strength of NETSARC+ is to come up with an answer to a question quickly and together. GSF-GETO studies and trials for rare soft tissue histotypes are good



examples. New agents have been studied since a long time in retrospective studies [94] and prospective trials [95]. Recent successfully led clinical trials illustrate this ongoing work: REGOSARC, PEMBROSARC and the French national program AcSé Pembrolizumab [96].

In addition to setting up collaborative trials, NETSARC + and SFCE collaboration also allows to mimic the best aspects of previously distinct programs. For example, the use of perhaps more targeted therapies beyond the first line of systemic treatment in the treatment of desmoid tumors by pediatric oncologists [97–99]. Furthermore, NETSARC + and SFCE have strengthened their collaboration to improve biological knowledge in this rare disease that affect children and adults such as in the GSF-GETO national clinical-biological prospective cohort of incident cases of aggressive fibromatosis (ALTITUDES, NCT02867033).

## Conclusion

Sarcomas' rarity and complex management underscore the importance of close multidisciplinary collaboration between pediatric and adult cancer specialists in order to guarantee the best patient's care and good quality clinical and translational research. In this context, GSF-GETO/NETSARC+/ SFCE are key players at the French and European level, and have contributed to many improvements in systemic and local treatment during the last decades. It is of foremost importance to continue favoring joint pediatric/adult innovative trials in order to improve sarcoma outcome through the increasing of the upper age limit of pediatric-initiated trials and decreasing the lower age limit in adult-initiated trials, as very effectively achieved in France.

GSF-GETO/NETSARC+/ SFCE will continue actively working together with other key stakeholders to ensure that children, adolescents and adults with sarcomas have access to the best available trials in Europe.

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Figure 1: SFCE and NETSARC + reference centers. In green when a both are based in the same center, in orange when they are located in different centers and in blue when there is only a SFCE with no NETSARC + reference center.

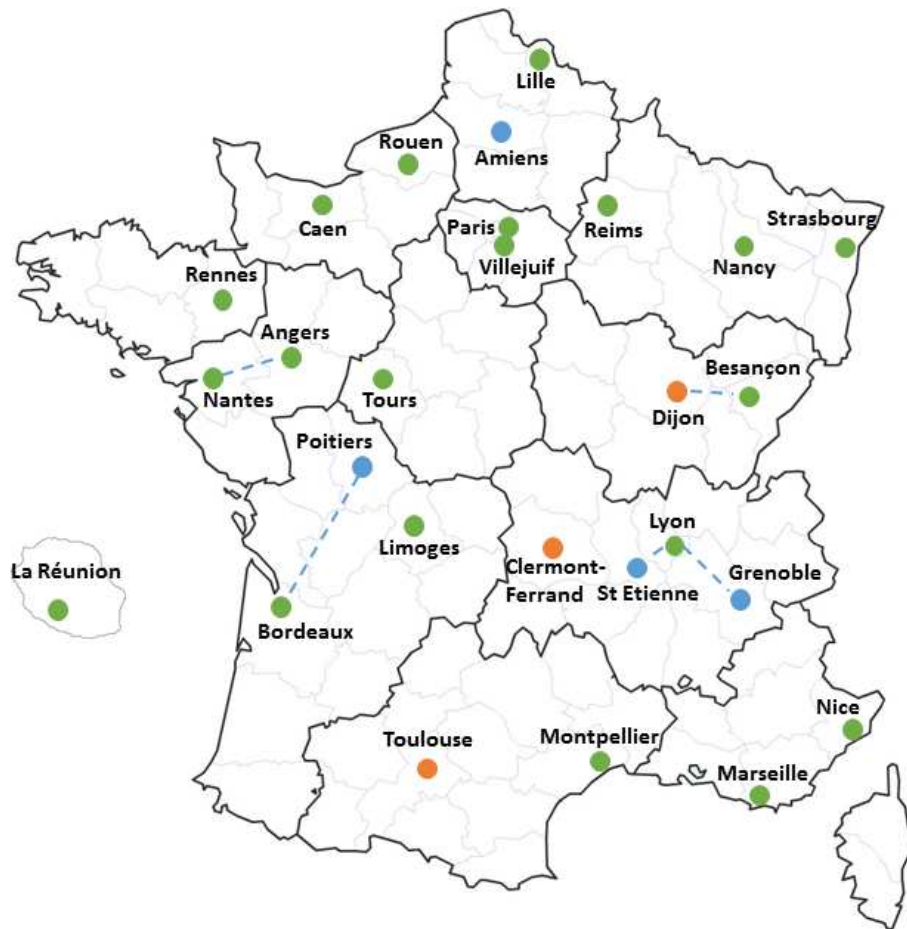


Table 1. Main differences for adult type soft tissue sarcoma (except rhabdomyosarcomas) across ages' group.

<b>Main histotypes</b>	<b>Pediatric characteristics</b>	<b>Adults characteristics</b>	<b>Differences and similarities<sup>100</sup></b>
<b>Malignant peripheral nerve sheath tumor (MPNST)</b>	<sup>101</sup> Median age 13.7years; 51%  NF1	<sup>102, 103</sup> Median age 47 years; 35%  NF1.	For both groups: Poor chemosensitivity;  Main risk factors: NF1 status, tumor margins, metastatic disease.
<b>Desmoid fibromatosis type (DFT)</b>	<sup>104, 105</sup> Median age 11 years;  Male/female 1; Germline APC pathogenic variant <2%.  Previous trauma 7%.	<sup>106</sup> Median age 33 years;  Male/female 4; Germline APC pathogenic variant 4%; previous trauma 9%.	More head and neck primaries (28% vs. 5%) and less truncal tumors (28% vs. 49%) in children vs. adults; worse outcome in children (3 y PFS after chemotherapy: 42% vs. 59%).
<b>Synovial sarcoma (SS)</b>	<sup>107-111</sup> Median age 13 years; risk factors: tumor extend and resectability, tumor size > 5 cm, tumor site (axial worse than limbs primary).	<sup>110</sup> Median age 24-37 years; risk factors: tumor extend, age > 35 years, FNCLCC grade 3, not-R0 margins.	Less metastatic events in pediatric; less tumor rearranged profiles with low genomic index and low CINSARC in children. Better overall outcome in children with localized disease. Same

			poor prognosis for metastatic or relapse tumor.
<b>Dermatofibrosarcoma (DFS)</b>	<sup>112</sup> Median age 6.9 Y, frequent resectable tumors (R0, 76%), few relapses even after R1 margins.	<sup>113</sup> Median age 48 years, MOSH surgery to obtain clear margins	Sensitivity to TKI for locally advanced disease.
<b>Desmoplastic small round cells tumors (DRSCT)</b>	<sup>114-118</sup> median age 13.2 years; 24% localized disease.	<sup>115, 117, 118</sup> Median age 25 years (general population); liver metastases 32%, lung metastases 17%.	Overall same behavior with transient chemosensitivity and unfavorable prognosis.
<b>Alveolar soft part sarcoma (ASPS)</b>	<sup>119-121</sup> Median age 13 years; limbs 63%. Metastatic disease at diagnosis 27%.	<sup>122</sup> Median age 30 years. Metastatic disease at diagnosis 55%.	Best prognosis in children. For both groups: chemoresistant tumor, frequent distant tumor spread (including brain metastases), possible long term survivors with TKI. Indolent nature of the tumor.

<b>Inflammatory myofibroblastic tumor (IMT)</b>	<sup>123</sup> Median age 9.5 years. Localized 98%. Chest primary 30%; 66% ALK +.	<sup>124</sup> Median age 48 years. Chest primary 34%; 63% ALK+.	Overall same behavior; important response to specific tyrosine kinase inhibitors.
<b>Epithelioid sarcoma (ES)</b>	<sup>125</sup> Median age 13.1 years; INI-1 staining loss 87%; 68% extremities; Partial response to neoadjuvant therapy 50%; risk factors: metastatic/nodal spread, resectability, high histologic grade, tumor invasiveness.	<sup>126</sup> Median age 25-37 years; INI-1 staining loss 90%. Risk factors: metastatic/nodal spread, resectability, proximal type. Chemoresistance to conventional chemotherapy agent.	Poor prognosis for metastatic or nodal disease in both groups of age. Possible response after epigenetic agent (EZH2 inhibitors).

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