Soft tissue sarcomas in adolescents and young adults: a comparison with their paediatric and adult counterparts

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Summary

Survival outcomes for adolescent and young adult patients with soft tissue sarcomas lag behind those of children diagnosed with histologically similar tumours. To help understand these differences in outcomes, we discuss the following issues with regard to the management of these patients with soft tissue sarcomas: delays in diagnosis, trial availability and participation, aspects of the organisation of care (with an emphasis on age-specific needs), national centralisation of sarcoma care, international consortia, and factors related to tumour biology. Improved understanding of the causes of the survival gap between adolescents and young adults with sarcomas will help drive new initiatives to improve final health outcomes in these populations. In this Review, we specifically focus on embryonal and alveolar rhabdomyosarcoma, synovial sarcoma, and adult soft tissue sarcomas diagnosed in adolescents and young adults, and discuss the age-specific needs of these patients.

Introduction

Sarcomas are rare tumours of connective tissue characterised by marked heterogeneity and including more than 70 histological subtypes.[1] Sarcomas are rare, representing 6–15% of paediatric cancers (<15 years), 11% of adolescent and young adult cancers (15–29 years), and 1–2% of adult cancers worldwide.[2–4] In children aged 0–15 years, the largest group of soft tissue sarcomas consists of rhabdomyosarcoma, where osteosarcoma or Ewing's sarcoma are the most prevalent bone tumours.[4] Rhabdomyosarcoma occurs mainly in children younger than 7 years, with another incidence peak during adolescence (16–19 years). The peak incidence of osteosarcoma in children coincides with the growth spurt during adolescence, with a second peak in older adults (>80 years), in whom the disease is much less common. Osteosarcoma in elderly people is most often localised to the head and neck region, or it can be associated with irradiation or Paget's disease of the bone. Ewing's sarcoma, which can occur in bones and soft tissue, also occurs predominantly in children and young adults, and similarly has a peak age of incidence in adolescents, but with no second peak in older adults. Synovial sarcoma, a soft tissue sarcoma, has a peak incidence in individuals in their early to mid 30s, but can occur in children (aged 1–18 years). For patients younger than 18 years with soft tissue sarcoma other than rhabdomyosarcoma or synovial sarcoma, the fact that there is little connection with the adult sarcoma community and inadequate access to novel drugs hampers progress in improving survival for this population.

Paediatric sarcomas, including embryonal and alveolar rhabdomyosarcoma, Ewing's sarcoma, and osteosarcoma, are characterised by their chemosensitivity and the fact that chemotherapy is an integral part of the treatment programme for patients of all ages, which has largely been responsible for the improvements in survival seen over the past 30 years. However, this development has been less pronounced for other soft tissue sarcomas occurring at a young age, such as synovial sarcoma, and it is certainly not true for malignant peripheral nerve sheath tumours and alveolar soft part sarcoma.

It has been known for many years that the prognosis of sarcomas varies with age, being substantially superior in children compared with young adults; although the reasons for this discrepancy are not fully clear, they are multifactorial.[5] Because the centralisation of care occurred much earlier for children with cancer than for adults, most children with sarcoma are treated according to standard protocols or within clinical studies. By contrast, the care of young

adults with soft tissue sarcomas is still considerably disparate in many countries. Adherence to treatment protocols (as exemplified in patients with acute lymphoblastic leukaemia), treatment dose intensity, and treatment in expert paediatric centres could explain both the improvement in outcome for childhood sarcomas in recent decades and the differences in outcome between children and young adults with histologically similar sarcomas.[6–10] To understand the differences between outcomes in adolescents and young adults and those in children and adults, various other factors need to be taken into consideration.

A higher stage at diagnosis is often reported to contribute to worse outcomes. Adolescents and young adults tend to present with symptoms at a more advanced stage than do children, and this delay in diagnosis could influence outcomes, at least in certain tumours.[11,12] This relation between delay in diagnosis and survival is, however, complex, and is partly due to patient-related factors and partly due to physician-related or health-system-related factors. Moreover, in some diseases, the biology of the tumour is so dominant that it overrules any effect that delay in diagnosis from these above-mentioned factors could have on survival.

The shortage of available trials and poor accrual to existing trials have also been identified as important factors contributing to the worse survival of adolescents and young adults with sarcomas compared with children. Accrual of adolescent and young adult patients with soft tissue sarcomas has been reported to be about 5–34% of the expected accrual based on incidence, compared with more than 70–80% for paediatric patients.[13] This issue was exemplified in an analysis by the European paediatric Soft Tissue Sarcoma Study Group (EpSSG) that allowed patients aged up to 21 years to be included in the study. The study showed an observed accrual rate for EpSSG trials of 64% for patients aged 0–14 years compared with 30% for patients aged 15–19 years.[14] The so-called five As model (availability, accessibility, awareness, appropriateness, and acceptability) has been proposed in a bid to improve participation of adolescents and young adults in clinical trials.[15]

Although the impact of treatment on outcomes is often mentioned, we must not ignore the contribution of patient-related factors. Adolescents and young adults with cancer face specific problems. Care for, and treatment of, adolescents and young adults in general is a largely new discipline in oncology.[16–18] At a global level, organisation of this care is very sparse and many initiatives are still in early stages. These patients are in a developmental phase of their life when they are suddenly confronted with a life-threatening disease. While their siblings and friends learn how to live independently, young people with cancer often face stagnation or even

regression in their own personal development. These factors have a role—albeit not necessarily a well defined one—in adherence to treatment, and thus in final outcomes. Although these aspects have not yet been studied in detail for adolescents and young adults with sarcoma, there is no reason to assume that they will not be applicable to these patients.

When considering differences in outcome between children and adolescents and young adults with soft tissue sarcomas, differences in the biology of the tumour should also be taken into account. Many aspects of sarcoma biology are not fully clear at this stage, but the best known example of the correlation between age-related biological factors and worse outcomes can be found in synovial sarcoma.[19] Increased genomic complexity with increasing age might at least partly explain good survival outcomes for children.[20]

In this Review, we focus on soft tissue sarcomas of adolescence and young adulthood, and exemplify the different features of the most prevalent soft tissue sarcomas that are either typical paediatric ones and occur at childhood, adolescence, and young adulthood, or that typically occur predominantly during adolescence and young adulthood; we also focus on adult-type soft tissue sarcomas that are present in paediatric, adolescent, and young adult patients. By doing so, we aim to explore the different factors that might explain why adolescent and young adult patients with soft tissue sarcomas have worse outcomes than do children. We focus on soft tissue sarcomas, with the exception of gastrointestinal stromal tumours, which are very rare in children and adolescents and are distinct from gastrointestinal stromal tumours in adults with regards to sex (occurring more frequently in women than in men), presentation (mainly gastric and multifocal), mutation status (mostly caused by an absence of activating mutations: 85% in paediatric gastrointestinal stromal tumours *vs* 15% in adult gastrointestinal stromal tumours), and response to imatinib.[21]

Rhabdomyosarcoma

Management of rhabdomyosarcoma in adolescents and young adults can be challenging. Among the different soft tissue sarcoma histotypes, rhabdomyosarcomas represent a distinct entity that clearly differs from other soft tissue sarcomas with regard to its natural history and sensitivity to chemotherapy. Rhabdomyosarcomas are always characterised by a high grade of malignancy and a marked propensity to metastasise, such that all patients with

rhabdomyosarcoma are assumed to have micrometastatic disease at diagnosis and therefore need to be treated with systemic therapy. Conversely, rhabdomyosarcomas are generally characterised as having a good response to chemotherapy, with responses of roughly 80–90%,[22–26] as well as good responses to radiotherapy in general.

Embryonal and alveolar rhabdomyosarcomas typically occur in children (accounting for more than 50% of soft tissue sarcomas in paediatric patients) but they can also occur in adults, albeit rarely. In contrast to the classical histological classification, a biological characterisation might be more accurate for predicting prognosis, and this form of classification is currently being incorporated in risk stratification. Patients are classified as having either fusion-negative rhabdomyosarcomas (corresponding to embryonal rhabdomyosarcoma) or *PAX3–FOXO1* or *PAX7–FOXO1* fusion-positive rhabdomyosarcomas (ie, alveolar rhabdomyosarcoma). Fusion-negative rhabdomyosarcomas with an alveolar histological appearance have a genomic profile and a clinical course more similar to embryonal rhabdomyosarcomas than to fusion-positive alveolar cases.[27,28] In adults, the predominant rhabdomyosarcoma subtype is pleomorphic, which should be considered as a separate type of rhabdomyosarcoma because it behaves like other high-grade soft tissue sarcomas of adulthood and does not have the same chemosensitivity associated with embryonal and alveolar rhabdomyosarcomas. In this Review, we focus on paediatric types of rhabdomyosarcomas—namely, the embryonal and alveolar subtypes.

The gain in survival achieved in children with rhabdomyosarcomas in the past few decades (approximately 70% of patients with localised disease can now be cured[24,25]) has been ascribed to the centralisation of care in specialised centres and the high rate of inclusion in cooperative multi-institutional clinical trials that are able to enrol a large number of patients on the basis of a risk-adapted, intensive multimodal treatment strategy.[8,10,22–25,29]

Although optimal local treatment remains an essential part of the treatment programme of rhabdomyosarcomas, multi-agent chemotherapy can be considered the mainstay of therapy. This is an important distinction between paediatric and adult soft tissue sarcomas. The chemosensitivity of rhabdomyosarcoma has altered the role of local therapies, leading to an increased use of conservative organ-sparing surgery and a reduction in the proportion of patients for whom radiotherapy is indicated (or the doses used), to minimise, when possible, the risk of long-term radiation-related sequelae.[30] The backbone of treatment for paediatric patients with localised rhabdomyosarcoma is an intensive alkylation-based multidrug

chemotherapy regimen given for 6–9 months: ie, the IVA (ifosfamide, vincristine, dactinomycin) regimen or the VAC (vincristine, dactinomycin, cyclophosphamide) regimen.[24,31] Doxorubicin has been investigated as being an effective drug, but results from an EpSSG study[32] show that addition of doxorubicin to the standard IVA regimen did not improve outcomes in the localised high-risk population. The addition of irinotecan-vincristine to VAC in the ARST0531 study[33] did not improve outcomes compared with the standard arm, but since irinotecan-vincristine plus VAC showed less toxicity (due to less alkylating agents) than the standard VAC regimen it has become the current standard for the Children's Oncology Group.

Additional treatment options for rhabdomyosarcoma include low-dose metronomic chemotherapy maintenance (under investigation in Europe),[26,34] the dose-compression approach (full-dose chemotherapy administered with a shorter interval between doses; eg, 1–2 weeks instead of the usual 3 weeks) that proved to be effective in patients with metastatic disease whose outcomes are generally poor (ClinicalTrials.gov number: NCT00354744),[35] and potentially effective targeted agents (eg, temsirolimus, such as in NCT02567435).[26]

The prognosis of rhabdomyosarcoma depends on multiple factors, including histological subtype, primary tumour site and size, lymph node involvement, and distant metastasis. Complex risk stratification based on these variables is used in paediatric cancer trial protocols to determine the appropriate intensity of treatment.[36,37] Among these variables, the patient's age has also emerged as a factor that substantially influences survival: in various series,[38,39] patients over 10 years of age have been reported to have a worse prognosis than children younger than 10 years of age. In an Italian study that compared clinical features of adolescents (aged 15–19 years) with those of children (<15 years) treated with the same therapeutic strategies,[40] the adolescent subgroup was shown to have a significantly higher prevalence of unfavourable features (including the alveolar subtype, nodal infiltration, and metastases at diagnosis) than those prevalent in children, a significant delay in diagnosis (confirmed by other studies), a reduced likelihood of being enrolled in the national cooperative paediatric treatment protocol (27% for adolescents *vs* 90% for children), and worse survival (5-year overall survival of 57·2% in patients aged 15–19 years *vs* 68·9% in patients <15 years; p<0·006).

The clinical characteristics and outcomes appeared to be even more unfavourable in adults with rhabdomyosarcomas than in adolescents. The few published series on adult patients described poor outcomes, with overall survival in the range of 20–50%.[41–43] An epidemiological analysis[44] from the North American Surveillance, Epidemiology and End Results (SEER)

database, comparing 1071 adults (>19 years) with 1529 children (≤19 years), confirmed that adults were more likely than children to have adverse prognostic variables. However, the final outcome (a 5-year survival rate of 26·6% in adults *vs* 60·5% in children) appeared to be independent of these variables, because adults had significantly worse treatment outcomes when a subset of patients with similar tumours was compared (ie, with the same histotype, same stage, and same sites).[44] The EUROCARE-5 study[5] reported 5-year survival rates of 66·6% among patients aged 0–14 years with rhabdomyosarcomas diagnosed between 2000 and 2007, compared with 39·6% among patients aged 15–19 years during the same period.

No explanation is available for the fact that outcomes worsen with increasing age. Inadequate experience among adult oncologists for the treatment of non-pleomorphic rhabdomyosarcomas is likely to have a role. Management of embryonal and alveolar rhabdomyosarcomas in adults is compromised by inadequate care in specialised centres in some countries, resulting in patients being treated at several sites by non-specialists who only occasionally encounter patients with these tumours. Likewise, there is a scarcity of dedicated treatment protocols for adolescents and young adults. The delivery of treatment might therefore have an important role.[29] A large, retrospective, single-institution study[43] stratified adult patients with embryonal and alveolar rhabdomyosarcoma according to the degree to which they had been treated appropriately, on the basis of existing treatment guidelines for childhood rhabdomyosarcoma. The study confirmed poor overall results in adults (a 5-year survival of 40%), with only 43 (39%) of 110 patients treated in line with paediatric treatment protocols. For this 39%, the outcome was similar to that of paediatric patients (ie, 5-year survival in this subgroup was 61% and increased to 72% for patients with embryonal rhabdomyosarcomas), and overall rate of response to chemotherapy was 85%.[43] These findings suggest that adult patients would fare better if they were treated with properly administered paediatric regimens.[44]

The factors that prevent adult patients from receiving proper treatment need to be clarified. Various studies[45–48] have described differences in pharmacokinetics—for example, in the metabolism of vincristine, dactinomycin, and alkylating agents—in relation to age that might be responsible for different responses and toxicity. In other words, treatment protocols designed for children might be less effective or too toxic for adult patients. However, an extensive discussion of age-related pharmacological aspects to explain the differences in toxicity related to different chemotherapeutic drugs is beyond the scope of this Review. New strategies of cooperation and collaboration between paediatric and adult oncologists are clearly

needed for adult patients with rhabdomyosarcomas. Paediatric cooperative groups have raised the upper age limits for their protocols (up to 25 years in Europe[32] and up to 50 years in the USA[33]), but adult oncologists need to be involved in the development of these studies from the outset. The Italian Sarcoma Group, which is mainly concerned with adult oncology, has developed a prospective registry for adult patients with rhabdomyosarcoma, with some treatment suggestions based on paediatric strategies in cooperation with paediatric experts. An assessment of the results of this initiative is ongoing.

Little information is available on the biology of paediatric-type rhabdomyosarcoma in adults; a more pronounced expression of multidrug-resistant proteins in these tumours has been described in adults than in paediatric counterparts,[49] but further collaborative efforts are needed to increase our knowledge of rhabdomyosarcoma biology in adults and, if differences are found, to adjust the treatment strategy accordingly.

Synovial sarcoma

Few studies have directly compared overall outcomes of adults and adolescents with synovial sarcoma in the same setting, but those that have compared these groups showed that younger patients with synovial sarcoma have a better outcome than do older patients (table),[19,50–53] with the exception of a retrospective series[51] of 250 patients. In a large analysis[50] of 213 children and adolescents (<18 years) and 1055 adults (≥19 years), based on data from the SEER database, survival was improved in young patients, with a 5-year cancer-specific survival of 83% (SD 79·9–86·1) for children and adolescents compared with 62% (SD 60·2–63·8) for adults (p<0·001). This difference was particularly important for patients older than 30 years compared with patients younger than 18 years (hazard ratio [HR] 3·36; 95% CI 2·05–5·39; p<0·001). In this study, children and adults had a similar stage at presentation, but different outcomes. A nationwide study[19] based on data from the Netherlands Cancer Registry included 613 patients, of whom 461 had localised disease. The 5-year overall survival (calculated on the basis of Kaplan-Meier curves) of patients with localised disease decreased with age: 89·3% (SD 84·7–93·9) in children younger than 18 years, 73·0% (SD 69·2–76·8) in patients aged 18–34 years; 54·7% (SD 51·1–58·3) in patients aged 35–65 years, and 43·0% (SD 36·0–50·0) in patients over 65 years of age.[19] Relative survival rates, used as a proxy for disease-specific

survival, were not largely different from estimated overall survival rates, except for patients over 65 years for whom relative survival was 52% at 5 years and 46% at 10 years. Treatment effects were not observed in this localised group. Apart from age, the site and size of the tumour had a significant impact on survival. In a retrospective study[52] of 237 patients aged 15–35 years with localised synovial sarcoma, age was strongly associated with outcome, with worse outcomes for patients older than 35 years in univariate and multivariate analyses, both for overall survival (HR 2·16; p=0·004) and for distant recurrence-free survival (HR 1·56; p=0·028). Finally, the results of Ferrari and colleagues,[53] based on a single-centre retrospective analysis, show a decrease in metastasis-free survival with increasing age (table). The precise reasons for these differences were, until recently, not well understood. For synovial sarcoma, there are no conclusive data to show that early tumour detection has age-related aspects, or to prove that early detection is associated with favourable outcomes.

New data on molecular profiling in synovial sarcoma have revealed interesting insights. To analyse the intrinsic molecular behaviour of synovial sarcoma, a 67-gene signature related to chromosome integrity and genomic complexity named CINSARC (a complexity index in sarcoma) has been developed, along with a genomic index that uses comparative genomic hybridisation on tumour cells (figure). These indices have shown high prognostic value in adult soft tissue sarcomas.[20,54] A subsequent analysis[20] comparing 100 adult and paediatric synovial sarcoma specimens confirmed that a somatic genomic complexity analysis can predict tumour outcomes for this disease. Even if tumours in the two groups shared the same histological features, translocations, and types of fusion transcripts, they had completely different metastatic outcomes. No specific gene patterns were found to discriminate between paediatric and adult tumours, but a strong link was observed between the degree of genomic complexity and the metastatic outcome in children.[20] Specifically, paediatric patients with tumours that had no detectable quantitative rearrangements did not develop metastases. However, for adults, 37 (64%) of 58 patients harboured rearrangement profiles, of whom 28 (76%) developed metastases, compared with 4 (19%) of 21 paediatric patients. This study offers a biological explanation for the widely differing outcomes of paediatric and adult patients with synovial sarcomas, showing that metastatic outcomes are strongly associated with chromosomal complexity in both age groups and that this instability is frequent in adult synovial sarcomas but not in paediatric synovial sarcomas.[20] This prospective clinical validation of the genomic index in synovial sarcomas confirms that this index is an important molecular prognostic marker that is easy to use and has the potential to guide therapeutic management. An open

study in synovial sarcoma, called Synobio, on paediatric patients (aged 0–25 years) from the EpSSG, aims to confirm the prognostic value of the genomic index.

In addition to the stage at diagnosis and molecular profile, age-related differences between children and young adults might exist in the application of chemotherapeutic regimens for patients with synovial sarcomas. Lagarde and colleagues[20] have suggested that greater use of chemotherapy in paediatric patients (≤18 years) than in adults (>19 years) might explain the differences in survival (81·8% of children receiving chemotherapy *vs* 41·7% of adults). However, such a treatment effect was not seen in the study[19] from the Netherlands Cancer Registry, in which adjuvant chemotherapy had no effect on survival. To date, neoadjuvant chemotherapy in adult patients (aged >18 years) with synovial sarcoma has not shown a survival benefit in published studies.[52,55] The question of whether response to chemotherapy might be related to genomic complexity may arise. However, a study by Chabika and colleagues[56] showed no association between these two variables. Therefore, the mechanism leading to metastatic relapse of synovial sarcoma is likely to be an intrinsic biological characteristic of the tumour rather than one related to its specific sensitivity to chemotherapy. Nevertheless, disparities in access to specialised care and enrolment in clinical trials might also explain some of the differences in survival, as the adolescent and young adult populations are not commonly included in treatment protocols.[17]

Adult soft tissue sarcomas in paediatric and adolescent patients

The majority of soft tissue sarcoma histologies collectively termed non-rhabdomyosarcoma soft tissue sarcomas by paediatric oncologists are those that occur in adulthood.[57–61] The term non-rhabdomyosarcoma soft tissue sarcomas, still used by paediatric oncologists, reflects the historical approach to treatment according to the principles derived from the management of rhabdomyosarcoma, which is clearly a distinct entity. However, during the past few decades, both the European and the North American paediatric cooperative groups have developed clinical protocols specifically tailored to these tumours, with an effort to adapt their treatment approach so that it resembles that used for adults.[62] Current paediatric treatment programmes use the same variables for risk stratification known to influence survival in adults and adopt

the full-dose ifosfamide-doxorubicin regimen as standard chemotherapy when systemic treatment is required.[63–67] However, the distribution of soft tissue sarcoma subtypes differs considerably between adults and children, and various data suggest that the clinical behaviour of a given histology might be different in different age groups, with the clinical course of paediatric tumours generally being more favourable than that of adult tumours, but head-to-head comparisons in similar patients groups with soft tissue sarcomas are scarce. Although the decline in age-related outcomes occurs gradually, synovial sarcoma is an exception: children have a notably better outcome than do adults.[67,68] Therefore, caution should be taken in extrapolating data from adult series and in applying adult treatment protocols to children (eg, the indication for radiotherapy could vary according to the age of the patient, because of the different degrees of risk and the potential impact of radiation-induced sequelae).

Clinical management of adolescents and young adults with soft tissue sarcomas is a challenge, requiring an experienced multidisciplinary team with specific skills. Referral to high-volume centres and adherence to treatment guidelines have been reported to be important factors associated with improved survival for this patient population.[69–71]

The complexity of the treatment of soft tissue sarcomas is also related to their biological heterogeneity according to tumour grade and histological subtype. Although surgery is the keystone of treatment, the responsiveness of adult soft tissue sarcomas to chemotherapy is generally uncertain. However, the heterogeneity of soft tissue sarcomas also affects the predictability of response to chemotherapy; for example, synovial sarcoma is more sensitive to standard chemotherapy than are other soft tissue sarcomas such as alveolar soft-part sarcoma or clear cell sarcoma.

Neoadjuvant chemotherapy in patients with unresectable advanced disease might achieve tumour shrinkage and convert unresectable cancers into conservative complete resections, as well as helping to treat any micrometastases promptly, because these patients are at a high risk of distant dissemination regardless of the local control measures adopted. Reported responses to chemotherapy were slightly higher in a paediatric series than in adults, with a variability related to tumour grade and histotype.[61,62,72,73] Anthracyclines with or without ifosfamide remain the frontline systemic therapy for most histotypes in both paediatric and adult patients, with some evidence of a dose response for both agents and better activity for the combination therapy versus single-agent doxorubicin.[72,73] Phase 3 results are awaited to confirm the remarkable gain in overall survival of almost 1 year with the combination of doxorubicin and

the PDGFRα antibody olaratumab versus single-agent doxorubicin.[74] However, various drugs other than the ifosfamide–doxorubicin combination are also effective against particular histotypes in adults: for example, the gemcitabine–docetaxel regimen is considered second-line chemotherapy in the USA, with better activity in angiosarcomas and leiomyosarcomas (particularly those of gynaecological origin).[75] Trabectedin has been approved in Europe for relapsed or refractory adult soft tissue sarcomas, with specific activity against liposarcomas and leiomyosarcomas, and has been approved in the USA for second-line treatment of liposarcomas and leiomyosarcomas.[76–78] Eribulin has shown an overall survival benefit in unresectable and metastatic liposarcoma.[79] Ongoing research is focusing on new histology-driven therapeutic approaches, and future clinical trials are likely to concentrate on specific histology-based accrual rather than accrual of patients with heterogeneous soft tissue sarcoma histologies.

In patients with localised disease, the possible role of adjuvant chemotherapy in the prevention of distant recurrences after initial surgery is still a matter of controversy and, despite initially promising results in high-risk extremity soft tissue sarcomas, final results showing improved survival in the long term have not been published.[55,80–82] Pooled data from adjuvant studies by the European Organisation for Research and Treatment of Cancer (EORTC) suggest a potential benefit of adjuvant treatment in R2 resected extremity tumours, but a prospective clinical trial is required before this observation can be used to influence clinical practice.[55] Thus, the choice of whether or not to administer adjuvant chemotherapy can only be based on shared and personalised decision making, for those patients who are at high risk of metastatic disease and for those patients whose tumours have histological characteristics that make them more likely than others to respond to chemotherapy.

Hopefully, identification of more druggable targets and development of more active small molecules and antibodies will increase options for effective treatment in the metastatic and adjuvant (and neoadjuvant) settings. Several tyrosine kinase inhibitors have shown activity in various histotypes of soft tissue sarcoma, including imatinib in dermatofibrosarcoma protuberans, sunitinib and cediranib in alveolar soft-part sarcoma, VEGF receptor inhibitors in solitary fibrous tumours and desmoplastic small round cell tumours, the mTOR inhibitor sirolimus in perivascular epithelioid cell tumours, and the anaplastic lymphoma kinase (ALK) inhibitor crizotinib in inflammatory myofibroblastic tumours.[83] Pazopanib—a multitargeted receptor tyrosine kinase inhibitor—has been approved for the treatment of refractory soft tissue

sarcomas after a phase 3 randomised trial of pazopanib versus placebo in advanced or metastatic soft tissue sarcomas (excluding liposarcomas) showed an improvement in median progression-free survival (4·6 months *vs* 1·6 months; HR 0·31; 95% CI 0·24–0·40; p<0·0001).[84]

Clinical trials of new agents are often restricted in paediatric and adolescent populations. Therapeutic results seen in adult patients need to be confirmed in paediatric patients, but confirmatory studies are not yet done sufficiently. Physicians dealing with adolescents should determine whether the results observed in adults can be translated to paediatric patients, and whether a given soft tissue subtype has the same biological and clinical characteristics in different age groups. Effective progress in the treatment of adolescents can only be achieved through new forms of collaboration, including close cooperation between adult and paediatric oncologists to share experiences and skills, collaboration with biologists to identify relevant targets and pathways relevant to tumour growth and, where possible, to adjust the therapy on the basis of tumour biology, and broad networking with pharmaceutical industries and regulatory authorities to speed up the whole process.

Models of care and organisation of paediatric and adult oncology trials in Europe

For bone sarcoma, many examples exist of good collaboration between countries and between different groups of oncologists. The European Osteosarcoma Intergroup has existed for decades, and the globally executed EURAMOS study (NCT00134030) is a great example of collaboration between paediatric and adult oncologists.[85,86] Similarly, the Euro-Ewing99, Euro-Ewing2012 (ISRCTN 92192408), and rEECurr (ISRCTN 36453794) studies are also being done by representatives of both professional specialties.[87] However, collaborative efforts and international networks between paediatric and adult oncologists for soft tissue sarcomas are not as well developed as those for bone sarcomas.

For example, the EpSSG has only done studies in children. Even the most recently developed rhabdomyosarcoma study, the FaR-RMS study, has been created by paediatricians only, albeit with the inclusion of patients without upper age limits. Meanwhile, the EORTC Soft Tissue

and Bone Sarcoma Group has always developed protocols for adults only. The EORTC's CREATE trial, which uses crizotinib (ClinicalTrials.gov number: NCT01524926), has now included subgroups of soft tissue sarcomas also occurring in paediatric patients, and has thus included paediatricians in its investigations. To allow the progress of new trials in the era of targeted therapies and novel immunological strategies, a collaborative effort between paediatric oncologists and adult oncologists is clearly needed from the outset. These collaborations should also include pathologists, molecular biologists, and professionals with expertise in psychosocial issues that could interfere with active treatment and have an impact on late effects in adolescent and young adult patients with sarcomas.[88]

Paediatric and adult oncologists have launched the EuroJOSS initiative for the development of joint studies in synovial sarcoma. This collaboration is new and still faces many challenges, but benefits from a strong pan-European support network. Such collaborations should not, however, be limited to the most common adolescent and young adult sarcomas but should also address rare histotypes, such as epithelioid sarcomas, desmoplastic small round cell tumours, clear cell sarcomas, and alveolar soft part sarcomas.

A global multicentre study[89] focusing on hereditary genetic factors has revealed that patients with sarcoma might have specific genetic aberrations that could affect screening and eventually affect their response to novel therapeutic strategies. These genetic factors are likely to have a greater role for younger patients. International, collaborative research is needed to address the many unanswered questions on this important topic.

Apart from treatment protocols, it is important to create an environment for young adults and adolescents with sarcoma that is tailored to their own personal lives. Therefore, dedicated multidisciplinary teams for these young, but not paediatric, patients are considered to be increasingly important, as these patients encounter their own age-specific issues such as changed body image (due to major surgical procedures, radiotherapy, or chemotherapy), fertility, sexual and other relationships, education, employment (often first jobs), housing, independent living, psychosocial age-related issues, and so on.[88] The importance of addressing these aspects is now recognised, since these efforts could contribute to an improved adherence to treatment and improved patient experience. As the treatment strategies for sarcomas often entail intensive treatment schedules and lasting late effects, adolescents and young adults with soft tissue sarcomas would clearly benefit from programmes tailored to their age-specific

needs, especially when integrated with sarcoma expert teams and incorporated into national and even international networks.[90]

Conclusion

Soft tissue sarcomas are rare in adolescents and young adults, and improving survival has been challenging in the past few decades because of treatment-related and age-related factors. Sarcomas in this age group encompass the tail end of predominantly paediatric sarcomas (such as embryonal and alveolar rhabdomyosarcomas), sarcomas specifically related to young patients with cancer (such as Ewing's sarcoma, osteosarcoma, and synovial sarcoma), and the first adult sarcomas occurring at an unusually young age. Hereditary genetic factors might be involved in certain sarcomas to a greater extent than previously thought, which could have consequences for family counselling and might lead to new treatment paradigms.

Differences in outcomes between children and young adults with the same histological sarcoma diagnoses are partly due to tumour-associated factors, as best exemplified in synovial sarcoma, and partly due to differences in treatment. Inadequate access to centres of expertise and to new clinical trials have contributed substantially to the slow progress in improving outcomes. To address this problem, increased collaboration at both the national and international level is needed between experts from solid paediatric oncology and the adult sarcoma specialties. Given the rarity of these tumours and the effort involved in initiating and running clinical trials in these indications, centralisation of care and research in each country is needed for this age group. Ideally, care should be delivered by teams that include experts on adolescent and young adult oncology to address the age-specific needs of these patients.

Moreover, at an international level, medical specialists from paediatric and adult oncology disciplines should take responsibility for the development and initiation of new clinical trials. Funding of such trials remains challenging, which can delay new initiatives. A new approach towards global funding, with support from different sources, including the pharmaceutical industry, charities, and funding organisations, is needed to start and grow these initiatives. Digital methods of communication should be further explored to develop a more interconnected international community, with the aim of improving outcomes of adolescent and young adult patients with sarcoma.

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Table 1: Age-related studies of patients with synovial sarcoma with localised disease at diagnosis

	Stage	Outcome	p value
Sultan et al (2009);[50] n=1268			
Age ≤18 years (n=213)	Localised and metastatic disease	5-year cancer-specific survival 83% 10-year cancer-specific survival 75%	<0·001
Age >19 years (n=1055)	Localised and metastatic disease	5-year cancer-specific survival 62%10-year cancer-specific survival 52%	..
Vlenterie et al (2015);[19] n=461			
Age <18 years (n=54)	Localised disease	5-year overall survival 89%;10-year overall survival 77%	<0·001*
Age 18–34 years (n=148)	Localised disease	5-year overall survival 73%;10-year overall survival 64%	<0·001*
Age 35–64 years (n=204)	Localised disease	5-year overall survival 55%;10-year overall survival 48%	<0·001*
Age ≥65 years (n=55)	Localised disease	5-year overall survival 43%;10-year overall survival 28%	<0·001*
Palmerini et al (2009);[51] n=204 (localised only)			
Age <18 years (n=21)	Localised disease	5-year overall survival 89%	0·09*
Age 18–65 years (n=170)	Localised disease	5-year overall survival 71%	0·09*
Age >65 years (n=13)	Localised disease	5-year overall survival 73%	0·09*
Italiano et al (2009);[52] n=237			
Age 0–35 years (n=119)	Localised disease	Overall survival, multivariate test HR 2·16 (95% CI 1·28–3·64)	0·004
Age >35 years (n=118)	Localised disease	..	..
Ferrari et al (2004);[53] n=215			
Age ≤16 years (n=41)	Localised disease, with macroscopic resection	5-year metastasis-free survival 69%	NR
Age 17–30 years (n=66)	Localised disease, with macroscopic resection	5-year metastasis-free survival 53%	NR
Age >30 years (n=108)	Localised disease, with macroscopic resection	5-year metastasis-free survival 43%	NR

HR=hazard ratio. NR=not reported. * p value based on the multivariate analysis.

Figure 1. Distribution of the CINSARC, genomic index, and metastasis-free survival in paediatric and adult patients with synovial sarcoma. An example of two CGH profiles in children and adults with synovial sarcoma. In this analysis, paediatric patients with synovial sarcoma have more favourable biological tumour features than do adults, a lower somatic tumour complexity index, lower genomic index signatures, and less metastatic tumour evolution. Data adapted from Lagarde and colleagues.20 CGH=comparative genomic hybridisation. CINSARC=a somatic tumour complexity index in sarcoma signatures. C+=high CINSARC. C–=low CINSARC. GI+=high genomic index. GI–=low genomic index. M+=metastatic event. M–=absence of metastatic event.