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Alveolar soft part sarcoma in children and adolescents: The European Paediatric Soft Tissue Sarcoma study group prospective trial (EpSSG NRSTS 2005)

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Abstract

Background: As alveolar soft part sarcomas (ASPS) are rare with no prospective series within pediatric sarcoma trials, the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) examined the clinical data and outcomes of ASPS enrolled in a multinational study of nonrhabdomyosarcoma soft tissue sarcomas (NRSTS).

Patients and methods: Twenty-two patients with ASPS were enrolled into the EpSSG NRSTS 2005 study. After surgical resection, subsequent treatment depended on the stratification of patients for completeness of resection and Intergroup Rhabdomyosarcoma Study (IRS) stage, size, and French Federation of Cancer Centres Sarcoma Group (FNCLCC) grade. Chemotherapy using ifosfamide and doxorubicin was performed in IRS group III. Radiotherapy was performed in IRS groups II and III, and FNCLCC grades 2 and 3 tumors.

Results: The median age at diagnosis was 11.5 years (range 2.7–17.5 years). The majority in the series had localized disease (20), with small IRS I tumors (12), and in total 19 had surgical resection upfront. Of the four patients who received conventional chemotherapy, there were no responses. Three of 20 patients with localized tumors and all metastatic patients developed metastases. The median follow up of patients with localized disease is 61.7 months (range 25.7–135.5 months) from diagnosis. The 5-year event-free survival is 94.7% (95% confidence interval: 68.1–99.2), and therefore the overall survival (OS) is 100%.

Conclusion: This report demonstrates the ability to run prospective pediatric studies in NRSTS in multiple European countries, despite the small numbers of ASPS patients. We can conclude that for the majority with small resected tumors, there were few events and no deaths.

KEYWORDS

adolescents, alveolar soft part sarcoma, pediatric

1 | INTRODUCTION

Alveolar soft part sarcomas (ASPS) are rare sarcomas. The most recent population data from the North American population-based Surveillance Epidemiology and End Results (SEER) cancer registry described only 251 patients over a 40-year period.[1] At a molecular level, most cases of ASPS express an unbalanced recurrent t(X;17) p(11.2;q25) translocation, which leads to a chimeric APSCR1-TFE3 transcription factor.[2] ASPS often have an indolent course, with long-term survival despite a high rate of metastases to both lung and brain.[1,3] The rate of metastases, however, differs between pediatric and all age SEER series (27% and 43 %).[1,5] The majority of ASPS occur in the extremities, in particular the lower limb.[1] While epidemiological data in children are lacking, case series from multiple pediatric sarcoma groups have also demonstrated that ASPS occur at other sites such as the head and neck,

Abbreviations: ASPS, alveolar soft part sarcomas; CR, complete response; CT, computed tomography; EFS, event-free survival; EpSSG, European Paediatric Soft Tissue Sarcoma Study Group; FNCLCC, French Federation of Cancer Centres Sarcoma Group; IRS, Intergroup Rhabdomyosarcoma Study; NRSTS, nonrhabdomyosarcoma soft tissue sarcomas; OS, overall survival; PR, partial response; SEER, Surveillance Epidemiology and End Results; STS, soft tissue sarcoma

including the tongue and orbit.[4,5] While most patients require surgery with an R0 resection for local control, the high rate of metastasis would indicate systemic therapy. However, it is thought that these tumors are chemoinsensitive,[4,6,7] but early reports have demonstrated response to antiangiogenic therapies such as cediranib,[8,9] bevacizumab,[10] and sunitinib.[11,12]

In 2005, as part of the EpSSG NRSTS 2005 study on pediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), a prospective non-randomized, international, multiinstitutional, historically controlled trial was started.

Patients with ASPS were included in a large heterogeneous group of adult-type sarcomas. After 10 years, given the rarity of ASPS and the lack of prospective contemporary clinical series within pediatric sarcoma trials, we decided to analyze ASPS separately from the other adult-type sarcomas to assess a standard therapeutic pathway in the pediatric and teenage/young adult age group.

2 | METHODS

2.1 | Patients and study design

Patients diagnosed with ASPS were enrolled for the EpSSG NRSTS 2005 study. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines, and the EU Clinical Directive 2001/20/EC for noncommercial clinical trials (European Union Drug Regulating Authorities Clinical Trials No. 2005-001139-31). Informed written consent was obtained for all patients/parents. The study was managed via a web-based system provided by CINECA, an Inter-University Computing Consortium (Casalecchio, Italy).

The inclusion criteria were as follows: (1) a histological diagnosis of ASPS, (2) age under 21 years, (3) no previous treatment except for surgery, (4) no previous malignancy, and (5) tumor specimens available for pathological review.

National and international review by the pathology panel of the histological diagnosis was advised but not considered mandatory. Patients were included if their local histological diagnosis of ASPS was supported by the presence of ASPSCR1-TFE3 fusion transcript if performed.[13]Tumors were graded according to the French Federation of Cancer Centres Sarcoma Group (FNCLCC).[14] In brief, this grading system from grade 1 (low grade) to grade 3 (high grade) is a scoring-based system taking into account tumor differentiation, number of mitotic figures, and percentage of tumor necrosis.

Following staging investigations, including either computed tomography (CT) or magnetic resonance imaging of the primary site, and CT scan of chest, it was recommended for all patients to undergo surgical resection of primary tumor but if deemed unresectable, biopsy only. The Intergroup Rhabdomyosarcoma Study (IRS) and TNM postsurgical staging was used.[15] According to the definition used in adult sarcomas for the completeness of surgical resection, R0 was complete resection, R1 microscopic residual disease, and R2 macroscopic disease.

Patients with ASPS were treated in the group of "adult-type soft tissue sarcoma," which for the protocol was defined as those sarcomas that are malignant, and typically occur in adulthood, excluding synovial sarcomas. After initial surgical resection with a proposed plan for a R0 resection, subsequent treatment depended on the stratification of patients for surgical and IRS stage, size, and FNCLCC grade. The treatment included neoadjuvant or adjuvant chemotherapy of ifosfamide 3 g/m^2/day over 3 hr with standard mesna hydration as per institutional guidelines for 3 days and doxorubicin 37.5 mg/m^2/day over 4 hr for 2 days or for courses during radiotherapy of ifosfamide 3 g/m^2/day for 3 days alone. Courses were repeated every 3 weeks on full blood count recovery. Radiotherapy was performed using a conventional fractionation (1.8 Gy daily fractions) and indicated in IRS groups II and III patients, with different doses according to the degree of surgery and tumor size, and grades 2 and 3 tumors. The details of the timings and specifics of the courses of chemotherapy and radiotherapy, depending on tumor size, stage, and resection margins, are described in Figure 1. Stage IV tumors were recommended to receive ifosfamide and doxorubicin chemotherapy as per localized disease up to a total of six courses depending on tumor response. Surgery and radiotherapy for primary tumor was recommended as per localized disease, and surgery for lung metastases was encouraged depending on resectability.

In patients with measurable disease and initially inoperable tumors, response to chemotherapy was assessed after three cycles of chemotherapy in terms of radiologically identified tumor volume reduction, that is, complete response (CR) = complete disappearance of visible tumor with no residual disease, major partial response (PR ≥2/3) = volume response in the range of 66–99%, minor PR (<2/3) = volume response in the range of 34–65%, stable disease (SD) = <33% reduction in tumor volume or <39% increase in the volume, progressive disease (PD) = a more than 40% increase in tumor volume, or the appearance of new disease.

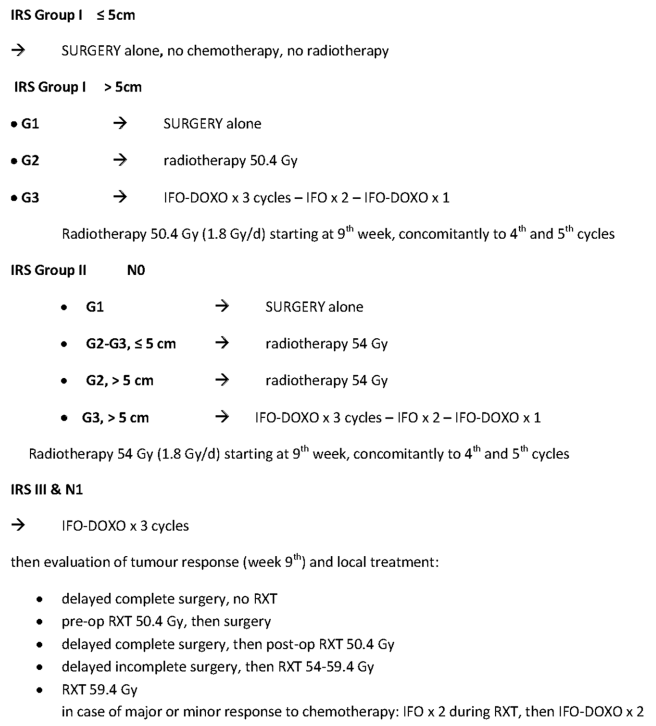

FIGURE 1 Risk-adapted treatment program for adult-type soft tissue sarcomas including ASPS

TABLE 1 Clinical characteristics of the whole series of patients

	Localized n = 20	Metastatic n = 2	Total n = 22	%
Age (years) at diagnosis				
1–9	8	–	8	36.4
10–17	12	2	14	63.6
Median age (range)	11.5 (2.7–17.5)	14 (12.6–15.4)	11.85 (2.7–17.5)	
Female	15	–	15	68.2
Male	5	2	7	31.8
Postoperative tumor staging (IRS)				
Group I	15	–		67.9
Group II	4	–		18.1
Group III	1	–		4.5
Group IV	–	2		9.1
Tumor size				
≤5 cm	17	–	17	77.3
>5 cm	3	2	5	22.7
Site of origin of primary tumor				
Head and neck	6		6	27.3
Extremities	13	2	15	68.2
Trunk	1	–		4.5

2.2 | Statistical analysis

Data were collected via a web-based system and analyzed at Istituto Oncologico Veneto (Padua, Italy) considering information reported till April 4, 2017. Continuous variables were summarized with median, minimum and maximum, and categorical variables were reported as counts and percentages. Survival time was calculated from the date of diagnosis to the time of event or last follow up. Tumor progression, relapse, and death due to any causes were considered for event-free survival (EFS). Overall survival (OS) was measured from the date of diagnosis to death for any reason. All patients were censored at the date of last observation. The survival probability was computed by means of the Kaplan–Meier method and heterogeneity in survival among strata of selected variables was assessed through the log-rank test. The 5-year EFS and OS were reported along with their 95% confidence interval (CI).

3 | RESULTS

Between December 2005 and December 2015, 22 patients were enrolled in the study from 15 centers. No patients were excluded. Over two-thirds of the patients were females (15) and seven were males. The median age at diagnosis was 11.5 years (range 2.7–17.5 years). Patient staging data, site, and size of primary tumor are listed in Table 1. No patients had lymph node metastases. As only two patients had metastases, the majority in the series had localized disease (20 cases), with small IRS I tumors (12 cases), and in total 19 had surgical resection upfront. Fifteen of the 22 cases had either national and/or International pathology review or demonstrated the presence of ASPSCR1-TFE3 fusion transcript. For the latter, this was positive in eight cases. Twelve cases had national and/or international pathology review. The primary site of the tumor was either head and neck or in the majority in the extremities (15 cases). All but one metastatic tumor had T1 non-invasive tumors.

3.1 | IRS I, ≤5 cm (13 cases)

All patients (13 cases) but one underwent a radical surgery at diagnosis according to protocol with only one patient receiving radiotherapy (44.8 Gy) after initial surgery due to a center decision. One patient had two operations to achieve IRS I. The overall median follow-up is 70.7 months (range 12.4–135.5 months). All patients are alive, 11 in the first CR off therapy, one is alive in the second CR off therapy after metastases (10 years from this event), and one is alive with disease after metastases (4 months from this event).

3.2 | IRS I, >5 cm, grade 2 (one case)

This single patient underwent radical surgery at diagnosis followed by 54 Gy radiotherapy .The patient is alive in the first CR off therapy after 65.1 months from diagnosis.

3.3 | IRS I, >5 cm, grade 3 (one case)

This single patient underwent surgery at diagnosis followed by chemotherapy according to protocol and 51.4 Gy radiotherapy. The patient is alive in the first CR off therapy after 32.8 months from diagnosis.

3.4 | IRS II, ≤5 cm, (four cases)

Following surgery, two patients had local radiotherapy (50.4 and 54 Gy), and two had no further treatment. All patients are alive in the

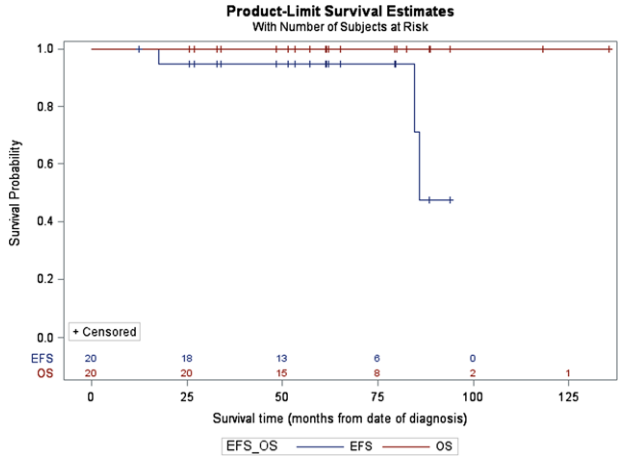

FIGURE 2 Overall survival and event free survival—localized patients

first CR off therapy after a median follow-up of 50.9 months (range 25.7–88.4 months).

3.5 | IRS III (one case)

This single patient received two courses of ifosfamide and doxorubicin chemotherapy as per protocol with stable disease followed by primary surgery and 50.4 Gy radiotherapy. After 85.8 months, the patient had a metastatic relapse but is alive in the second CR off therapy, 118.2 months from diagnosis.

3.6 | Metastatic tumors (two cases)

Both patients had metastases to the lungs, with one patient had bone metastases as well. One patient received four course of doxorubicin/ifosfamide-based chemotherapy resulting in stable disease but remains alive with progressive disease after 22.4 months from diagnosis.

The other patient received five courses of varied chemotherapy including ifosfamide, temozolamide, and irinotecan with stable disease. The patient remains alive with stable disease subsequently receiving sunitinib after chemotherapy, 47.1 months from diagnosis.

3.7 | Outcome data of localized cohort

Three of 20 patients with localized disease developed metastases. All patients are alive with median follow-up of 61.7 months (range 25.7–135.5 months) from diagnosis (Figure 2). The 5-year EFS is 94.7% (95% CI: 68.1–99.2), Figure 2), and therefore the OS is 100%.

4 | DISCUSSION

Our results demonstrate that in this first prospective pediatric study of NRSTS including ASPS, treated in multiple European countries for what is an extremely rare soft tissue sarcoma (STS), patients could be registered, albeit in small numbers. The ASPS cases were enrolled in the study as part of a larger group of "adult-type STS," that is, those sarcomas that typically occur in adulthood. We showed that the long-term outcome of these patients was excellent with no deaths, and the number of events was small with only three of the 20 with localized disease having a metastatic event and one of the two with metastases having a further event, occurred after a long time from diagnosis in some patients. Furthermore, there were no local recurrences, which means that the majority had small tumors.

The study commenced in 2005 and was part of one of "adult-type STS". In this cohort, including ASPS, we considered the role of ifosfamide and doxorubicin chemotherapy in improving response rates in patients with unresectable ASPS-IRS III. We also assessed the response rates to chemotherapy in patients with metastatic or measurable disease. Not surprisingly, no patient had any response to chemotherapy, at least among this small number of three patients, confirming the chemoinsensitivity of this tumor.[4,6] However, the knowledge of chemoinsensitivity perhaps only became clear after the study had commenced, with reports from 2010 onward.[16]

The high proportion of patients with small, resected tumors in this series is also perhaps explained by the failure to enrol large or unresected tumors in what was essentially a conventional chemotherapy protocol. Surgery has been shown to play a critical role in achieving local control, and indeed tumors that are localized and completely excised have an excellent outcome.[1,5] The excellent survival rates observed in our cohort of patients with localized tumors are related to the high resectability rate, due to their initial presentation with a relatively small tumors, and all but one having noninvasive tumors (T1). The previous comparable retrospective pediatric series, combining patients from two previous pediatric STS studies and an institutional cohort, had <55% of patients who were resected at diagnosis, compared with approximately 80% in our series. However, a significant number of patients will develop metastases to both lung and brain; although their outlook is poor, they often have a long and indolent course.[1] Another factor is the data emergence during the study on the role of antiangiogenic drugs such as sunitinib,[5,11,12] bevacizumab,[10] and cediranib.[8,9] While some patients have had stable disease with these agents, others have had PR and rarely CR. Inevitably, these data and competing studies with these agents, especially in the United Kingdom, in ASPS, perhaps prevented patients enrolling in this EPSSG study, in particular patients with unresectable tumors or metastases. However, the distribution of gender (with preponderance for females), though similar to ASPS pediatric series, but higher compared to population-based adult series (SEER), maybe explained by the small numbers in pediatric series compared to the SEER series.[1,4–6] The primary tumor site, however, was very similar to that in previous ASPS series in both children and adults, and the lack of lymph nodes is to be expected as only 6% had positive lymph nodes in previous pediatric series.[1,4–6]

The outcomes in this series, both in the number of events and the lack of deaths, are at least better in comparison with other published pediatric series[5] and confirm the role of complete surgical excision and perhaps radiotherapy for local control in high grade or, indeed, microscopic disease. Again, however, these results must be viewed with caution, given the fact that there were so few patients with large unresectable tumors and/or metastatic disease.

This study confirmed previous outcome data, albeit better due to the large number of small tumors. One might suggest, however,

that there is no role for adjuvant treatment in small resected tumors regardless of their grade, and for a selected few no local radiotherapy. This could be tested in further studies, but as the peak of ASPS is in the range of 15–35 years, and as in the recent SEER publication, 50% of the patients were between 18 and 30 years,[1] which compels us to consider this age range, and hence include the teenage and young adults population, in further studies, rather than the narrow age group of a pediatric or adult series, designing a specific study for this sarcoma type.

The evidence for the role of antiangiogenic agents in phase II studies suggests a benefit of further intervention with these agents, perhaps in patients with unresectable localized disease or patients who present with metastases.[8–12] These antiangiogenic agents have mainly produced stable disease, and are not always well tolerated by patients with thyroid, cardiac, or mainly renal toxicities.[17] Furthermore, many patients with ASPS remain alive with disease for many years.[1] This needs to be considered in the design of future studies, in particular the end points studied. Combined studies of antiangiogenic agents and other drugs are perhaps required in the light of studies in other tumor types such as ovarian cancer, where cediranib has been combined with the PARP inhibitor olaparib in a synergistic way.[18] Another possible agent to consider is tivantinib, a MET inhibitor that has been reported to demonstrate response in two cases of ASPS.[19] The author of this paper suggests that, in view of its low toxicity, this agent could be combined with VEGFR inhibitors such as cediranib.[20] Of course, all these reports underline the need for better knowledge of the biology of this tumor and the need to run parallel biological and biomarker studies with therapeutic interventions.

In conclusion, this report demonstrates the ability to run prospective pediatric studies in NRSTS in multiple European countries; however, despite the small numbers of ASPS patients included, we can conclude that for the majority with small resected tumors, there were few events and no deaths, and hence excellent outcomes. It should also encourage us to develop further interventional, biological, and biomarker studies in this disease across all ages and with novel statistical endpoints.[21]

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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