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Original article

Alveolar soft part sarcoma in children and adolescents: A report from the Soft-Tissue Sarcoma Italian Cooperative Group

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Summary

Background: Alveolar soft part sarcoma (ASPS) is a rare malignant tumor and little is known about its clinical features and management. We report on a series of 19 pediatric patients managed over 20 years.

Patients and methods: Primary conservative surgery was performed in all patients and was radical in nine, non-radical in three; seven patients underwent biopsy alone (3 unresectable tumors, 4 metastatic disease). In two cases radical surgery was performed after primary chemotherapy. Radiotherapy was delivered to 8 patients, chemotherapy to 15.

Results: After a median follow-up of 74 months, the five-year survival was 80% for the whole series, 91% for patients with localized disease, 100% for patients with tumor ≤ 5 cm, and 31% for those > 5 cm; 16 of 19 patients were alive (12 of 12 with grossly-resected tumor in first continuous remission). Chemotherapy achieved two partial remission among seven evaluable patients.

Conclusions: Pediatric ASPS has a more favorable prognosis than its adult counterpart. In this series, tumor size correlates with metastatic disease at onset and is the major factor influencing survival. Surgery is the mainstay of therapy. The effectiveness of adjuvant therapy remains to be established, though radiotherapy may be advisable in cases of inadequate surgery.

Key words: alveolar soft part sarcoma, pediatric tumors, soft tissue sarcoma

Introduction

Alveolar soft part sarcoma (ASPS) is one of the most unusual malignant soft tissue sarcomas. It accounts for 5% of pediatric non-rhabdomyosarcoma soft tissue sarcomas [1]. Though some immunohistochemical studies have recently indicated that ASPS may originate from striated muscles, there is still considerable uncertainty as to the exact nature of this tumor [2–5]. ASPS occurs principally in individuals between 15 and 35 years of age. Female patients outnumber males, especially during the first two decades of life [6]. The tumor usually arises in the skeletal muscle of the extremities; the head and neck region, including the orbit and tongue, is a common site in children, however. Approximately 20% of patients have metastatic disease at the time of initial diagnosis. The lung, bone and central nervous system are the favored metastatic sites. The clinical course is often indolent and the occurrence of metastases after prolonged disease-free intervals (sometimes exceeding 10 years) has been reported [3]. According to the POG grading criteria, all ASPSs are conventionally defined as grade 3 tumors [1]. Complete surgical excision is the mainstay of therapy and the principal predictor of outcome: the prognosis is usually only good for patients submitted to radical resection. The utility of adjuvant treatment with chemotherapy or radiotherapy remains to be seen. Few data are available on the clinical features and management of childhood ASPS [7]. Even for adult ASPS, large series have been reported only rarely [6, 8, 9], the majority of papers being case reports.

This report describes the clinical characteristics, treatment and outcome of a series of consecutive children with ASPS managed over a 20-year period by the Soft Tissue Sarcoma-Italian Cooperative Group (STS-ICG), affiliated to AIEOP (Italian Association of Pediatric Hematology/Oncology).

Patients and methods

Between January 1979 and December 1999, 19 consecutive pediatric patients with a diagnosis of ASPS were treated at AIEOP centers. Their clinical data, histopathological findings and treatment modalities were reviewed. In each case, the histopathological diagnosis was confirmed by the STS-ICG board of pathologists, according to previously-defined histopathological criteria [3].

Median age at diagnosis was 12 years (range 4–18 years). The group included 13 girls and 6 boys. The sites or organs affected by the primary tumor were the extremities in 10 patients (upper and lower, 5 each), the head and neck region in 4 (the tongue in 2) and the trunk in 5 (abdominal wall in 2, pelvis, retroperitoneum and chest wall in 1 each). There was no lateral predominance. Four patients (21%) had metastatic disease at onset, their primary tumor being located in the buttocks in

Table 1. Alveolar soft part sarcoma – clinical features, treatment and outcome.

Patient	Sex	Age (years)	Site	TNM	IRS	Surgery	CT	RT (Gy)	Outcome
1	Female	15	Chest wall	$T_{2A}N_0M_0$	1	Radical S	–	–	Alive in first CR at 11 months
2	Female	18	Tongue	$T_{1A}N_0M_0$	1	Radical S	–	–	Alive in first CR at 13 months
3	Female	17	Lower extremity	$T_{1A}N_0M_0$	1	Radical S (primary re-excision)	–	–	Alive in first CR at 21 months
4	Male	16	Abdominal wall	$T_{1A}N_0M_0$	1	Radical S	–	–	Alive in first CR at 30 months
5	Female	14	Abdominal wall	$T_{1A}N_0M_0$	1	Radical S (primary re-excision)	VACA	–	Alive in first CR at 45 months
6	Female	13	Upper extremity	$T_{1A}N_0M_0$	1	Radical S (primary re-excision)	VACA	–	Alive in first CR at 136 months
7	Male	7	Lower extremity	$T_{1A}N_0M_0$	1	Radical S (primary re-excision + lymphadenectomy)	VACA	–	Alive in first CR at 173 months
8	Male	9	Lower extremity	$T_{1A}N_0M_0$	1	Radical S (primary re-excision)	VACA	–	Alive in first CR at 234 months
9	Female	12	Upper extremity	$T_{1A}N_0M_0$	1	Radical S (primary re-excision)	VACA	50	Alive in first CR at 243 months
10	Female	12	Head–neck	$T_{1A}N_0M_0$	2	Non-radical S	IVA	40	Alive in first CR at 64 months
11	Male	13	Upper extremity	$T_{1A}N_0M_0$	2	Non-radical S	IVA	40	Alive in first CR at 124 months
12	Female	4	Upper extremity	$T_{1A}N_0M_0$	2	Non-radical S + lymphadenectomy	VACA	44	Alive in first CR at 180 months
13	Male	9	Upper extremity	$T_{2B}N_0M_0$	3	Biopsy Delayed radical S after CT	VAIA	–	PR after CT, pathological CR at delayed surgery; alive in first CR at 86 months
14	Female	5	Tongue	$T_{1A}N_0M_0$	3	Biopsy Delayed radical S after CT	VAIA	–	No response to CT; alive in first CR after partial glossectomy at 139 months
15	Male	13	Head neck	$T_{2B}N_0M_0$	3	Biopsy	VACA	60	PR to CT, CR after RT; local relapse at 20 months; DOD at 42 months
16	Female	12	Lower extremity	$T_{2B}N_1M_1$	4	Biopsy	CEVAIE	Palliative	No response; alive with ED at 33 months
17	Female	7	Lower extremity	$T_{1B}N_0M_1$	4	Biopsy	CEVAIE	–	No response; alive with ED at 43 months
18	Female	16	Pelvis	$T_{2B}N_1M_1$	4	Biopsy	VACA + CDDP/DTIC	Palliative	No response; DOD at 16 months
19	Female	12	Retroperitoneum	$T_{2B}N_0M_1$	4	Biopsy	VACA + CDDP/DTIC	Palliative	No response; DOD at 30 months

Abbreviations: S – surgery; CR – complete remission; PR – partial remission; ED – evident disease; DOD – dead of disease; CT – chemotherapy; RT – radiotherapy; VAVA, IVA, VAIA, CEVAIE – see text; CDDP – cisplatin, DTIC – dacarbazine.

two cases, in the retroperitoneum in one, and in the pelvis in one. The sites of metastases were the lung and skeleton in case one each, while two patients had disseminated metastatic disease (lung, skeleton, lymph nodes and liver). All these features are summarized in Table 1.

The time elapsing between the onset of symptoms and diagnosis ranged from six weeks to two years (median 6 months). In all cases, the sign leading to diagnosis was an enlarging mass, with or without pain.

On clinical and radiological assessment, the maximum diameter of the tumors ranged between 1.5 and 30 cm; it was ≤ 5 cm in 13 patients, > 5 cm and < 10 cm in 1, and ≥ 10 cm in 5. All four patients with

metastatic disease had a primary tumor with a maximum diameter ≥ 10 cm.

Tumor extent was assessed according to both the clinical tumor-node-metastasis (TNM) pretreatment staging system and the Intergroup Rhabdomyosarcoma Study (IRS) post-surgical grouping system. According to the TNM, lesions confined to the organ or tissue of origin were defined as T_1 and lesions with extension to contiguous structures as T_2; T_1 and T_2 groups were further divided into subsets A or B according to tumor diameter, $\leq$ or >5 cm, respectively. Regional node involvement was designated as N1 (no node involvement, N_0) and distant metastases at the time of diagnosis as M_1 (no distant metastases, M_0) [10]. The IRS group 1 referred to completely-resected tumors; group 2 included grossly-resected tumors with microscopic residual disease; group 3 contained patients with gross residual disease after incomplete resection or biopsy; and group 4 indicated those with metastatic disease at onset [11].

Patients were managed with a multi-modality therapeutic approach including surgery, radiotherapy, and chemotherapy, according to the treatment protocols in use at the time. Attempted conservative surgery was the mainstay of treatment: primary excision was planned when complete and non-mutilating resection was considered feasible, otherwise a biopsy was performed. Primary re-excision was recommended prior to any other therapy in the case of suspected microscopic residual tumor, in an attempt to achieve radical surgery. If conservative complete excision was considered unfeasible at the time of diagnosis, surgery was delayed until after chemotherapy to induce tumor shrinkage and improve resectability.

Thereafter, in compliance with the therapeutic guidelines, radiotherapy was administered to all patients considered at high risk of local relapse due to incomplete resection, and to metastatic children for palliative purposes. External beam irradiation on the primary tumor was administered with conventional fractionation (200 cGy/day) for a total dose ranging from 40 to 50 Gy. The radiation target volume included the initial mass plus 2–3 cm margins and the surgical scars as well.

Chemotherapy was recommended in the presence of microscopic or macroscopic residual disease after surgery. In patients who underwent initial complete resection, any use of adjuvant chemotherapy depended on the physician's decision. Different chemotherapeutic regimens were adopted over the years. The VACA regimen consisted of vincristine 1.5 mg/m^2, weeks 1, 4, and 7, Adriamycin 30 mg/m^2/day × 2, weeks 1 and 7, cyclophosphamide 1200 mg/m^2, weeks 1, 4, and 7, and actinomycin-D 0.5 mg/m^2/day × 3, week 4, for a total of 37 weeks. Ifosfamide was adopted in the IVA (ifosfamide 3 g/m^2/day × 2, vincristine 1.5 mg/m^2, actinomycin-D 1.5 mg/m^2, every 3 weeks for a total of 27 weeks) and VAIA regimens (vincristine 1.5 mg/m^2, weeks 1–7, actinomycin-D 1.5 mg/m^2/day, weeks 1 and 7, ifosfamide 3 g/m^2/day × 2 weeks, 1, 4, and 7, adriamycin 40 mg/m^2/day × 2, week 4; for a total of 27 weeks). In metastatic patients a more intensive regimen, including ifosfamide at higher doses (9 g in 3 days) in combination with carboplatin and etoposide was administered; the CEVAIE schedule consisted of carboplatin 500 mg/m^2, week 1, epiadriamycin 150 mg/m^2, week 1, vincristine 1.5 mg/m^2, weeks 1–7, actinomycin-D 1.5 mg/m^2, week 4, ifosfamide 3 g/m^2/day × 3, weeks 4 and 7, etoposide 200 mg/m^2/day × 3, week 7; for a total of 27 weeks). In all regimens, the maximum dose of vincristine and actinomycin-D administered was 2 mg.

Survival rates were computed using the Kaplan–Meier method [12]. Overall survival (S) was calculated from diagnosis to death or last follow-up evaluation, while event-free survival (EFS) was evaluated from diagnosis to disease progression, relapse, death from any cause or last follow-up visit. Patients were followed up at three-monthly intervals for the first two years, six-monthly for the next two years, and yearly thereafter. Follow-up was updated at April 2000, and ranged from 11 to 243 months (median 75 months).

Response to therapy, evaluated using radiographic criteria, was defined as follows: complete response (CR) was consistent with the complete disappearance of disease; response was partial (PR) in the case of a tumor reduction $>50\%$ in the sum of the products of the maximum perpendicular diameters of all measurable lesions; stable disease (SD) indicated a reduction $< 50\%$ of the tumor (considered as no response); progressive disease (PD) defined any increase in the size of the lesions or the appearance of new lesions.

Results

According to the TNM staging system, 12 children were classified as T_{1A}, 1 as T_{1B}, 1 as T_{2A}, and 5 as T_{2B}. All children with T_{1A} or T_{2A} tumors were N_0M_0; four patients (1 T_{1B} and 3 T_{2B}) revealed distant metastases at diagnosis (M_1), with node involvement in two cases (N_1).

The first approach was conservative surgery in all patients. Nine patients were classified as IRS group 1 because of a microscopically complete resection of the tumor. In six of these, radical surgery was obtained by a primary re-excision performed at an AIEOP center no more than two months after initial surgery with suspected microscopic residual disease performed elsewhere. Residual tumor was confirmed at histopathological evaluation in only one of these six patients. Three patients underwent marginal resection with microscopic residual disease and were classified as IRS group 2. Regional lymphadenectomy was performed in two children, during the first surgical approach in one and together with primary re-excision in the other; in both cases, the lymph nodes proved normal. In three cases with localized tumor, the primary surgical approach consisted of biopsy alone (IRS group 3) due to tumor site and extent: in two, conservative radical surgery was considered unfeasible because of the head-neck tumor location; the third had a large tumor on the arm for which radical surgery would have required amputation. After preoperative chemotherapy, two of these IRS group 3 patients underwent conservative radical surgery and one of them achieved a pathologically-confirmed CR. The four patients with metastatic disease at onset underwent no surgery, except for the diagnostic biopsy taken from the primary tumor in each case.

Radiation therapy was administered to eight patients. The three patients classified as IRS group 2 received irradiation within one month of surgery for a total dose of 40–44 Gy. Radiotherapy (50 Gy) was also delivered to the only IRS group 1 patient showing pathological evidence of disease at radical re-excision, and to one of the three IRS group 3 patients with unresectable oropharyngeal tumor, who experienced PR after primary chemotherapy. This boy received external beam irradiation at a dose of 60 Gy and achieved CR. Unfortunately, he developed a local relapse a few months later and died of disease 42 months after diagnosis. Palliative radiotherapy was given to three other patients with metastatic disease: 15 Gy on lung metastases in one patient; 36 Gy on the primary retroperitoneal tumor in the second; on both primary pelvic tumor (30 Gy) and bone metastases (rachis 40 Gy, skull 30 Gy) in the third.

Chemotherapy was given to all patients except for four belonging to IRS group 1 (15 of 19). The other five

IRS group 1 cases and one IRS group 2 patient received adjuvant chemotherapy according to the VACA schedule. The other two IRS group 2 patients were treated by the IVA regimen. Primary chemotherapy in IRS group 3 patients consisted of the VACA regimen in one and the VAIA in two. Two metastatic children treated before 1988 received chemotherapy including the drugs in the VACA regimen plus dacarbazine and cisplatin. CEVAIE was administered as front-line therapy in the two IRS group 4 patients treated more recently.

Response to chemotherapy was evaluable in the seven cases with measurable disease (3 IRS group 3 and 4 IRS group 4). A clinical PR was observed in two of the three non-metastatic patients (1 VACA, 1 VAIA): one of them underwent subsequent surgery and achieved a pathologically-confirmed CR. No clinical response was observed in metastatic patients; 2 experienced rapidly progressive disease and died 16 and 30 months after diagnosis, respectively. Two others remained alive with slowly progressing disease at 33 and 43 months from diagnosis; they had no response to intensive chemotherapy (CEVAIE regimen) and retrieval treatment including topotecan, and were out of treatment at the time of the report.

The estimated five-year overall S in this series was 80%, with a median follow-up of 74 months. At 5 and 10 years, S for the 15 patients with localized disease was 91% and EFS 93%, with a median follow-up of 105 months.

At the cut-off date, 16 out of 19 patients were still alive. All 12 IRS group 1 and 2 patients were alive in first continuous remission with a median follow-up of 94 months. Two of the three IRS group 3 patients were alive, following chemotherapy and delayed surgery, at eighty-six and one hundred thirty-nine months from diagnosis. Two of the four metastatic patients were alive at thirty-three and forty-three months from diagnosis, with evidence of disease.

Based on tumor size, the five-year S was 100% for patients with tumor diameter ≤ 5 cm, and 31% for those > 5 cm. Tumor size was closely associated with metastatic spread: four of the six patients with tumor > 5 cm had distant metastases at onset.

No difference in outcome was evident in relation to age, sex, site of primary tumor, or type of treatment.

The treatment was devoid of severe acute toxicity, and at the cut-off date no patient had developed severe iatrogenic sequelae.

Discussion

The rarity of ASPS accounts for the paucity of published reports and explains why little information is available on clinical features and management. Conversely, the literature pertaining to ASPS histogenesis and immunohistochemical studies is remarkably large; despite extensive investigations, however, the histogenesis of ASPS continues to be an unsettled issue half a century after its first description.

In the Memorial Sloan-Kettering Cancer Center's series described by Lieberman et al. (the largest reported, with patients of all ages collected over a 63-year period), the survival of patients who were not metastatic at diagnosis decreased dramatically from 77% at 2 years, to 60% at 5 years, 38% at 10 years, and 15% at 20 years [6]. This suggested that a long-term follow-up was mandatory, though our own and other reported series [9] did not confirm the tendency for very late metastatic spread and death reported by Lieberman et al. In our group, the most belated failure occurred 20 months after diagnosis; follow-up only exceeded 10 years in 7 patients, however, and some of the currently tumor-free patients may relapse later on.

The only reported series on ASPS of pediatric age is the one from the St. Jude Children's Research Hospital by Pappo et al. [7]. They described 11 children and adolescents treated at their institution over a 32-year period, 9 of them still alive and disease-free, with a 12-year overall S rate of 74%. The authors emphasized that the main predictor of survival was tumor resectability and that none of their patients with gross residual or metastatic disease responded to combination chemotherapy. These observations were consistent with ours (in our series, the five-year overall S was 80% for the whole group and 91% for the non-metastatic group). This favorable outcome for patients with localized disease was possibly related to the decision to perform a wide tumor resection in most cases. Our data support the suggestion that ASPS in pediatric age has a more favorable prognosis than its adult counterpart. Childhood ASPS might behave better, depending either on a different tumor biology or on a different pattern of clinical presentation, e.g., completely resectable tumors, as found in the majority of our cases. In adult ASPS the main cause of treatment failure is represented by metastatic disease, not by local relapse; in our series, distant relapses never occurred in patients with localized tumor at diagnosis. The lower rate of metastatic spread in children than in adults suggests a less aggressive behavior and different biological features in pediatric ASPS. In our series, it is hard to say whether the large proportion of patients submitted to adjuvant chemotherapy (66%) may have influenced the low incidence of metastatic recurrence.

Complete resection represented a strong predictor of outcome in our series, too: all 12 patients without macroscopic residual disease after surgery were alive in first CR.

In addition, our data are consistent with the series of 14 patients reported by Evans et al. [9], where the major factor related to survival and the likelihood of metastatic disease was tumor size: in our experience, all patients with a maximum tumor diameter > 10 cm presented with metastatic disease at onset. The five-year S for patients with tumor > 5 cm was only 31%, the prognosis for metastatic patients remaining very poor.

As in other soft tissue sarcomas, the role of radiotherapy and chemotherapy in the treatment of ASPS remains to be established.

Sherman et al. reported prolonged local control in six of six patients with localized disease treated with radiotherapy and recommended adjuvant radiation therapy in all adult patients [13]. In agreement with Pappo et al. [7], we would not recommend the use of radiotherapy in all children, in an effort to prevent delayed morbidity, since local control would not seem to be a real problem if the primitive lesion is adequately excised. Radiotherapy could improve local control in the case of incompletely resected tumors, particularly in the event of microscopic residual disease, so we suggest the use of radiation therapy in patients with inadequate surgical margins. In our series, 3 of 3 IRS group 2 patients submitted to adjuvant radiotherapy were alive in first CR at 64–180 months from diagnosis.

Some data on responses to chemotherapy – primarily anthracycline-based regimens – have been reported, but there is no consensus as to the actual effectiveness of chemotherapy. In the pediatric series reported by Pappo et al. [7], none of the patients with unresected or disseminated disease responded to chemotherapy. In our group, none of the metastatic children benefited clinically from chemotherapy, but we observed two objective responses among the three patients with unresected tumor. Though the small number of patients prevents any clear evidence from emerging, chemotherapy might have a role in enhancing resectability and preventing demolition surgery. Since its role is undefined, the use of chemotherapy in T_{1A} – IRS group I patients (such as the 5 cases in our series) would probably be considered as overtreatment. In such cases, complete surgery should represent the only treatment.

In conclusion, our experience confirms that conservative complete excision remains the treatment of choice for patients with ASPS. Every effort should be made to perform adequate initial surgery, and primary re-excision is recommended – if feasible – in the event of inadequate surgical margins at the first operation. An aggressive surgical approach could also be considered for each resectable metastasis, given the poor prognosis of metastatic patients. We suggest the use of radiotherapy in the case of inadequate surgery, but not in patients submitted to complete resection with free histopathological margins. The effectiveness of chemotherapy remains uncertain and cooperative studies with follow-up evaluation are needed to elucidate the value of adjuvant treatment.

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