



Clinical presentation, treatment, and outcome of alveolar soft part sarcoma in children, adolescents, and young adults

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Abstract

Purpose: Alveolar soft part sarcoma is a rare soft tissue neoplasm that can affect children and adolescents. There are few reported series of these patients in the literature. To define the clinical presentation, treatment, and outcome of young people with this rare sarcoma, we reviewed our clinical experience.

Methods: After institutional review board approval, we examined the records of all patients younger than 25 years old who received treatment at our institution for alveolar soft part sarcoma in the past 30 years. Demographics, tumor sizes, sites and extent of disease, treatments used, progression-free survival, and overall follow-up were evaluated.

Results: Each of the 20 patients presented with a mass. Primary disease sites were thigh (n = 8), trunk (n = 6), retroperitoneum (n = 2), and scalp, neck, forearm, and calf (n = 1 each). Metastatic sites included lymph nodes, lung, and brain. Four patients presented to us with incomplete excision of the primary, and 1 had undergone embolization of what was thought to be a vascular malformation. Although wide local excision provided the best chance for a patient to remain free of disease, 14 (70%) of 20 patients exhibited metastases either at presentation or later. Thirty-one metastasectomies were performed. Chemotherapy was used in 11 patients; radiation was used in 8. Median overall follow-up was 36 months; median progression-free follow-up was 12.5 months. Younger patients tended to have Intergroup Rhabdomyosarcoma Study group I disease. Tumors smaller than 5 cm were associated with longer progression-free survival.

Conclusions: Achievement of complete microscopic resection is critical in localized alveolar soft part sarcoma, but incomplete excision and misdiagnosis are often encountered. Despite the occurrence of metastases in 70% of patients, 5-year overall survival was 83%. We found an association between smaller tumor size and longer time to progression. We were not able to demonstrate any benefit from chemotherapy or radiation. Metastasectomies have been performed in multiple long-term survivors.

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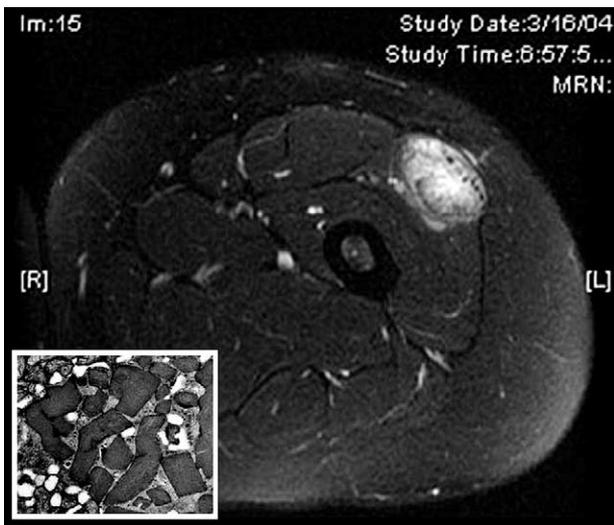


Fig. 1 Magnetic resonance image of an alveolar soft part sarcoma in the vastus lateralis muscle. (inset), Electron micrographic view of the intracellular crystals in the tumor.

Alveolar soft part sarcoma is a rare soft tissue malignant neoplasm that affects young people. It can present in any region of the body, having been described from the tongue [1] to the sacrum [2] and is most commonly seen in the trunk and the extremity [3-5]. Often indolent, the primary tumor may grow for years before medical attention is sought. Widespread metastases are frequent.

The tumor received its name owing to its pseudo-alveolar histological appearance, characterized by cells arranged in clusters with a loss of central cohesion. It is a highly vascularized tumor with small vascular spaces interdigitating between nests of cells. On electron microscopy, the cells of alveolar soft part sarcoma contain characteristic, electron-dense polygonal crystals in the cytoplasm (Fig. 1) [6], which contain complexes of the proteins monocarboxylate transporter 1 and CD147 [7].

This retrospective study of children, adolescents, and young adults sought to define the clinical presentation, methods of diagnosis, treatments used, and results obtained for young people seen at a major cancer center with alveolar soft part sarcoma. We reviewed a 30-year, single-institution experience with young patients with this disease. To recapitulate the modes of presentation likely to be encountered by pediatricians and pediatric surgeons, we looked solely at patients who were younger than 25 years old at the time of diagnosis.

1. Methods

A waiver of authorization (WA0374-04) was obtained from our institutional review board, in compliance with institutional and Health Insurance Portability and Accountability Act standards. We identified patients from all institutional databases treated at The Memorial Sloan-Kettering

Cancer Center for alveolar soft part sarcoma who were younger than 25 years old at the time of diagnosis and who were treated between 1974 and 2004. All patients had pathology reviewed at our institution. Medical records, operative notes, pathology and radiology reports, and correspondence that was part of the medical record were used as primary source data. Follow-up data were obtained from notes and correspondence in the medical record. No patients were contacted for supplemental data.

Extent of disease was classified retrospectively according to the Intergroup Rhabdomyosarcoma Study (IRS) clinicopathologic grouping system (group I–group IV), and TNM grouping was assigned according to standard published criteria [8]. Clinicopathologic assessment of tumor size and invasiveness was made using available data from pathology reports, preoperative radiology, and operative notes. Patient 12 presented after grossly incomplete tumor excision, and we estimated the size of the initial tumor by adding the diameter of tumor excised to the residual disease seen on imaging.

Time to progression was measured from the date of diagnosis to the date of pathological confirmation or, when not resected, to the date of the first radiological indication of progressive disease. For 1 patient (#19), brain metastases were diagnosed at an outside hospital during 1984, but the precise date could not be ascertained, so progression was estimated to occur at the midpoint of that year. Probability estimates of 5-year overall follow-up and progression-free follow-up were obtained by the product limit method [9], and differences between time to progression between groups were evaluated using log-rank statistics [10].

2. Results

2.1. Clinical presentation

Twenty patients (10 male, 10 female) with a median age at diagnosis of 16.5 years (range 6-24) were identified (Table 1). The most common presentation was a mass ($n = 17$), accompanied by pain ($n = 4$), numbness ($n = 1$), and nausea and vomiting ($n = 1$).

The most common site for the primary sarcoma was the thigh ($n = 8$). This was followed by the trunk ($n = 6$), the retroperitoneum ($n = 2$), and the scalp, neck, forearm, and calf ($n = 1$ each). Primary tumor size, known in 13 of 20 patients, averaged 6.5 cm (range 2.4-15). Vascular invasion was specifically noted by the pathologist in 6 of the primary tumors (30%).

At the time of diagnosis, regional spread was present in 2 patients: a thigh lesion had eroded into the femur in one, and a neck primary had spread to a neck node and submandibular gland in the other. Distant metastases were seen in the lungs of 7 of the 20 patients at initial presentation. Among these, 2 had brain metastases at presentation as well.

Reverse transcriptase–polymerase chain reaction, which can detect the ASPL-TFE3 fusion transcripts characteristic

Table 1 Demographics and tumor data

Patient #	Age at diagnosis	Sex	Size of primary (cm)	Sites at presentation	Symptoms	Subsequent sites	TNM
1	6	M	5.1	Calf	Mass	Lung	Txb N0 M0
2	12	F	9	Thigh	Unknown	Lungs, chest wall, brain	T2b N0 M0
3	13	M	2.5	Scalp	Mass	Lungs	T1a N0 M0
4	14	M	9	Thigh, lungs	Mass		T1b N0 M1
5	14	M	Unknown	Chest wall	Mass	Lung	Tx N0 M0
6	15	F	Unknown	Chest wall	Mass, pain		T2x N0 M0
7	15	F	Unknown	Thigh	Unknown	Lungs, acetabulum, chest wall, retroperitoneum	Tx N0 M0
8	15	M	2.4	Forearm	Mass, numbness		T1a N0 M0
9	16	F	4	Breast	Mass		T2a N0 M0
10	16	F	9	Thigh, lung	Mass	Contralateral lung	T1b N0 M1
11	17	F	Unknown	Thigh, lungs, cerebellum	Mass		Tx N0 M1
12	17	M	7.4	Neck, lymph node, submandibular gland	Mass		T2b N1 M0
13	17	M	2.5	Chest wall	Mass		T2a N0 M0
14	17	F	4	Thigh	Mass, pain		T2a N0 M0
15	19	F	7	Thigh, lungs	Mass		T2b N0 M1
16	20	M	3.5	Back	Mass		T1a N0 M0
17	22	F	Unknown	Chest wall, lungs	Mass, pain		T2x N0 M1
18	22	F	Unknown	Retroperitoneum	Unknown	Pelvis, paraaortic nodes, liver	Tx Nx Mx
19	22	M	11	Thigh, femur, lungs	Mass, pain	Brain, liver, spleen, kidney, chest wall	T2a N0 M1
20	24	M	15	Retroperitoneum, lungs, brain	Mass, nausea, vomiting		T2b N0 M1

of the (X;17) translocation of alveolar soft part sarcoma, was positive in 3 of 3 tumors tested.

2.2. Patterns of metachronous spread

Brain metastases developed subsequent to diagnosis in 2 additional patients, but no patient had brain metastases in the absence of lung metastases. Every patient with brain metastases had lesions in the cerebellum, although some had multifocal disease including other parts of the brain as well.

Five patients without pulmonary metastases at diagnosis went on to develop lung metastases. Counting the 7 other patients who had lung metastases at the time of initial presentation, a total of 12 (60%) of 20 patients exhibited lung metastases at some point.

Besides brain and lungs, other sites of late metastatic disease included chest wall (n = 3), retroperitoneum/pelvis/paraaortic nodes (n = 2), liver (n = 2), spleen (n = 1), kidney (n = 1), and acetabulum in a patient with a thigh primary (n = 1).

2.3. Diagnosis and initial surgical therapy

Eight (40%) of 20 patients had no preoperative imaging performed (Table 2). Although 13 (65%) of 20 patients presented with localized or locoregional disease, we could only identify one patient who had a biopsy followed by

wide local excision by the same surgeon. Most patients came to our center after initial excision at an outside institution, and 4 of these patients had undergone attempted excisional biopsies but had positive margins. One patient presented to us after having undergone embolization of what was thought to be a vascular malformation; this was recognized at embolization to be a solid tumor and core biopsy was immediately obtained.

Those who presented to our institution with locoregional disease underwent definitive wide local reexcision to render them IRS group I, with the exception of patient 12, who was found on lymph node dissection to have tumor in a regional node, classifying him as IRS group IIb. Lymph node biopsy was performed concurrently in 3 cases, lymph node dissection in 3, and sentinel node biopsy in 2. Two patients with locoregional disease (patients 7 and 18) underwent initial definitive surgery at outside institutions in 1967 and 1975, respectively; operative notes and original pathology reports were not available, so their IRS grouping could not be determined. Both ultimately had regional recurrence and metastases, with pathological confirmation of the diagnosis of alveolar soft part sarcoma at our center.

Those rendered free of disease (IRS group I) at the time of definitive surgery tended to have good outcomes. Of the 10 patients in this group, 2 are alive with small lung nodules

Table 2 Treatments, outcomes, and follow-up

Patient #	Preoperative imaging	Primary operation	Definitive operation	IRS Group	Operations for metastases	Chemo- or biologic therapy	Radiation to primary	Radiation to metastases	Follow-up since diagnosis (mo)	Progression-free survival (mo)	Status
1	Y	Excisional biopsy	WLE/LNBx	I	2	(+)		1500 cGy to lungs	135	13	NED
2	?	Incisional biopsy	WLE/LND	I	3	(+)		Brachytherapy I-192 4500 cGy	148	7	NED
3	Y	Excision, (+) margins	WLE/SNBx	I	1				22	18	AWD
4	?	Incisional biopsy		IV		(+)			16	16	AWD
5	?	Excisional biopsy	WLE/LNBx	I		(+)			290	284	AWD
6	N	Excisional biopsy	WLE/LND	I					11	11	NED
7	N	Unknown		Unknown	4	(+)	XRT	XRT to acetabulum	207	21	DOD
8	N	Excision, (+) margins	WLE/LNBx	I					6	6	NED
9	N	Excisional biopsy	WLE (mastectomy)	I					175	175	NED
10	N	Excisional biopsy		IV	8	(+)			239	8	NED
11	Y	Excisional biopsy		IV	1	(+)			21	21	AWD
12	N	Excision, (+) margins	WLE/LND	IIb			5580 cGy XRT		15	15	NED
13	N	Excision, (+) margins	WLE	I					4	4	NED
14	Y	Embolization, core biopsy	WLE/SNBx	I					10	10	NED
15	Y	Core biopsy	WLE	IV	2				50	44	AWD
16	N	Excisional biopsy	WLE	I					51	51	NED
17	?	Incisional biopsy		IV		(+)	XRT		16	10	DOD
18	?	Unknown		Unknown	5	(+)	4000 cGy XRT	50 Gy pelvic XRT; 129 mCi I-125 implants; Ir-192 implants	354	8	AWD
19	Y	Incisional biopsy	WLE/intramedullary rod	IV	5	(+)	XRT		59	12	DOD
20	Y	Incisional biopsy		IV		(+)		3000 cGy whole brain	6	1	AWD

WLE, wide local excision; LND, lymph node dissection; LNBx, excisional lymph node biopsy; SNBx, sentinel node biopsy; XRT, external-beam radiation therapy; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease.

and 8 have no evidence of disease (NED), with a median follow-up since initial diagnosis of 37 months (range 4-290). There have been no local recurrences among the IRS group I or group II patients but 4 developed distant metastases.

Of the patients with recognized metastatic disease at diagnosis (IRS group IV), 5 of 7 initially underwent incisional or core biopsy, but 2 had excisional biopsy. In this group of 7 patients, 2 are dead of disease (DOD), 4 are alive with disease (AWD), and one has NED after multiple metastasectomies, with a median follow-up since diagnosis for these 7 patients of 21 months (range 6-239).

2.4. Surgery for metastases

Thirty-one operations for metastases were carried out, distributed among almost half (9/20 or 45%) of the patients. The median number of metastasectomies performed for this group was 3, with a range of 1 to 8. Operations included thoracoscopy (n = 2), thoracotomy (n = 17), laparotomy (n = 5), craniotomy (n = 6), and curettage of the acetabulum (n = 1). Four patients (#1, #7, #10, and #18) had metastasectomies 10 years or later after their initial diagnosis. Of the 9 patients who had metastasectomies, 2 are DOD, 4 are alive with disease, and 3 have NED, with a median follow-up since diagnosis of 135 months (range 21-354).

2.5. Use of chemotherapy and biologic therapy

Chemotherapy and/or biologic therapy was given to 11 (55%) of 20 patients. Of these 11, 6 were treated owing to the presence of IRS group IV disease at diagnosis, and 4 were given chemotherapy after the onset of metastases later in their course. However, 1 patient (#5), who was IRS group I, received multiagent chemotherapy after a wide local excision despite there being no residual local or distant disease.

Of the 11 receiving chemotherapy, 3 are DOD, 5 are alive with disease, and 3 have NED, with a median follow-up from diagnosis of 135 months (range 6-354). As there is no standard regimen of chemotherapy for alveolar soft part sarcoma, a vast assortment of chemotherapeutic and biologic agents were administered to patients in this series, including antimetabolites, alkylating agents, mitotic inhibitors, anthracyclines, antimicrotubule agents, antineoplastics, antifolates, COX-2 inhibitors, interleukin-2, interferon- α , and TNP-470. No complete or partial responses were seen with any agent.

2.6. Use of radiation therapy

External beam radiation (XRT) was used on the primary tumor site in 5 (25%) of 20 patients and to metastatic sites in 4 (20%) of 20 patients. Of the 5 receiving primary site XRT, 3 have died of disease, 1 is alive with metastatic disease, and 1 has NED. One patient, who received whole-brain radiation, had XRT without resection. External beam radiation was combined with surgical metastasectomy in 2 patients (1 now NED, 1 DOD) and with metastasectomy plus brachytherapy in another patient (now AWD 354 months after diagnosis). Brachytherapy, without XRT, was used after

resection in 1 patient now NED 148 months after diagnosis. Although the results particularly with brachytherapy are intriguing, given the small numbers, no conclusion can be drawn regarding the role of XRT, brachytherapy, or chemotherapy for alveolar soft part sarcoma.

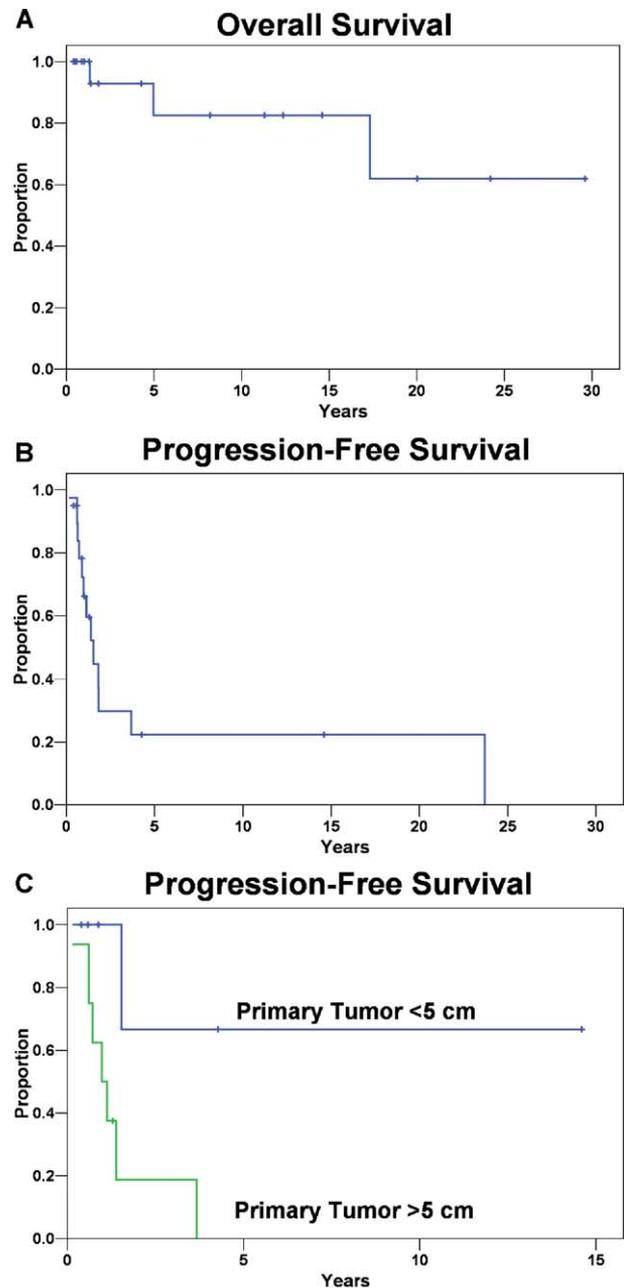


Fig. 2 A, Kaplan-Meier curve showing overall follow-up for patients with alveolar soft part sarcoma. B, Kaplan-Meier curve showing progression-free survival in patients with alveolar soft part sarcoma. The relatively long overall follow-up compared with the short time to progression indicates that patients are living long despite the progression of disease. C, Kaplan-Meier curve showing progression-free survival for those with primary tumors of 5 cm or smaller (upper line) vs those larger than 5 cm (lower line) ($P = .03$).

2.7. Survival and follow-up

Median overall follow-up since diagnosis is 36 months (range 4-354). Median progression-free survival is 12.5 months (range 1-284). Five-year overall survival is 83% (95% confidence interval, 60-100), and 5-year progression-free survival is 22% (95% confidence interval, 0-44) (Fig. 2A and B).

There were trends in disease differences, and hence in outcomes, between the 10 patients aged 16 years and younger and the 10 patients aged 17 years and older. The majority of the younger cohort (7/10 or 70%) had IRS group I disease. In contrast, the majority of the older cohort (6/10 or 60%) had IRS group II to IV disease. Age did not significantly impact time to progression.

Tumor size appeared to impact upon time to progression. There was significantly longer progression-free survival for those with primary tumors 5 cm or smaller, versus those with tumors bigger than 5 cm ($P = .03$) (Fig. 2C).

2.8. Deaths

Three patients are known to have died of disease. Patients 7 and 19 both had thigh primaries that progressed to widely metastatic disease and both received multiple metastasectomies, chemotherapy, and XRT. These 2 each had an identifiable period when their disease was neglected: patient 7 presented to our hospital 7 years after diagnosis of unilateral lung metastases, with no interim therapy, and had progressed by then to bilateral metastases; patient 19 had a diagnostic delay for 16 months and then had lung metastases at presentation. Patient 17, though, already had an unresectable chest wall mass at presentation, along with pulmonary metastases. She died in hospice 16 months after diagnosis.

3. Discussion

Achievement of complete microscopic resection of localized alveolar soft part sarcoma is of paramount importance. Eighty percent of our IRS group I patients remain NED, and 100% are free of local recurrence at last follow-up. The few existing pediatric series of this disease in the literature show similar results. A study of alveolar soft part sarcoma in 19 pediatric patients from the Italian Soft-Tissue Sarcoma Cooperative Group found that 9 of 9 IRS group I patients remained NED, with follow-up ranging from 11 to 243 months, with many having received no adjuvant therapy [5]. In another report on 11 pediatric patients, 4 of 5 IRS group I patients were NED with follow-up of 0.6 to 17.3 years [4]. Together, these are a compelling argument for complete excision of the primary tumor with negative margins. We could not show a benefit from chemotherapy or radiation.

Initial management pitfalls were encountered commonly. Four patients came to our center with positive margins after attempted excisional biopsies. Another presented after

embolization, undertaken without prior biopsy. Eight (40%) of 20 patients had no preoperative imaging performed. Preoperative imaging, usually with magnetic resonance imaging, is mandatory and fine-needle aspiration or core needle biopsy should be considered before definitive surgery. Because of the presence of intracellular crystals, fine-needle cytology can be diagnostic [11-15].

Larger tumor size (>5 cm) was associated with diminished progression-free survival in this series. In the 1989 report from our institution, Lieberman et al [3] also reported that larger tumor size adversely impacted survival, as did the presence of metastases at diagnosis and higher age at diagnosis.

Fourteen (70%) of 20 patients in this series had regional nodal or distant parenchymal metastases. Although this tumor may spread to a remarkable variety of tissues, the lung remains the principal site requiring surveillance. No patient in our series had brain metastases without also having lung lesions, as previously seen in a study of 70 patients of all ages from Portera et al [16], but all 4 of our patients with brain metastases had lesions in the cerebellum, an association not noted before. Finally, the presence of lymph node metastases in 2 (10%) of 20 patients should prompt clinical consideration of the draining nodal basins for these tumors.

The very short progression-free survival (median 12.5 months) but much longer time of overall follow-up (median 36 months) suggests that long-term survival is possible even with metastatic disease. Resection of metastases may play a role, although it cannot be proven that metastasectomy—as opposed to the indolent nature of the disease—is the cause of long survival. Patient 10 had a thigh primary at age 16, has undergone 8 thoracotomies, and is now NED almost 20 years after initial diagnosis. Patient 18 was 22 years old when a retroperitoneal alveolar soft part sarcoma was resected; after 5 more laparotomies in 10 years, she was rendered cancer-free for 20 years until, 30 years after initial diagnosis, a CT scan showed liver lesions. Patient 1, at age 6 the youngest in this series, had a calf primary excised, then had 2 pulmonary resections, and is NED 11 years after diagnosis.

Our approach allows for expectant observation when metastatic disease is low volume, imageable, and dormant over several time points. For example, patient 3 is being followed with stable pulmonary nodules proven at thoracoscopy to be alveolar soft part sarcoma. Patient 15 has a stable lung density that has been followed for 4 years, and through a pregnancy.

In the past 10 years, molecular analyses have shown that alveolar soft part sarcoma is associated with a chromosomal translocation from band p11.2 on the X chromosome to 17q25 [17,18]. Ladanyi et al [19] reported in 2001 that a unique fusion gene transcript, ASPL-*TFE3*, was present in 12 of 12 cases evaluated. The emerging understanding that there is a specific molecular defect associated with alveolar soft part sarcoma makes this a potentially fruitful time for the study of this rare tumor. By practicing appropriate

diagnostic techniques, aggressive surgical control of the primary site, and assiduous, long-term surveillance for metastases, physicians have enabled patients to survive for very long periods with this disease.

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