Clear Cell Sarcoma of Tendons and Aponeuroses in Pediatric Patients

A Report from the Italian and German Soft Tissue Sarcoma Cooperative Group

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BACKGROUND. Clear cell sarcoma (CCS) of tendons and aponeuroses is extremely rare in childhood and little information is available on its clinical management. Originally believed to be a type of melanoma of soft tissue origin, CCS is now considered a distinct clinicopathologic entity that behaves like a high-grade soft tissue sarcoma. We report on a series of 28 pediatric patients treated from 1980 to 2000 by the Soft Tissue Sarcoma Italian Cooperative Group and the German Cooperative Group.

METHODS. Patients were treated with a multimodality therapeutic approach. Surgical resection was complete in 17 patients (mutilating in 3), radiotherapy was administered to 8 patients, and 20 patients received chemotherapy.

RESULTS. After a median follow-up of 102 months (range, 19–238 months), the 5-year and event-free survival rates were 66.4% and 63.3%, respectively. Seventeen patients were alive in first remission, two were alive in second remission, and nine had died of disease. The response to chemotherapy in the 7 evaluable patients included one partial remission, one minor response, and five no responses. Radiotherapy contributed to achieving local control in four of six Intergroup Rhabdomyosarcoma Study (IRS) Group II patients. Statistically significant differences in outcome were evident according to IRS group, tumor size, and site.

CONCLUSIONS. Our study confirms the aggressive behavior of CCS. Complete surgical resection represents the mainstay of treatment, and even the only treatment for patients with small tumors. Radiotherapy may control microscopic residual disease after surgery. Chemotherapy is ineffective and the prognosis is unfavorable for patients with unresectable and large tumors. ***Cancer* 2002;94: 3269–76.** *© 2002 American Cancer Society.*
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KEYWORDS: clear cell sarcoma, malignant melanoma of soft part, pediatric tumors, soft tissue sarcomas.

Clear cell sarcoma (CCS) of tendons and aponeuroses is a rare malignant tumor that occurs mainly in the extremities of young adults, accounting for 1% of all soft tissue sarcomas. It is particularly uncommon in children. CCS was first described as a distinct clinicopathologic entity by Enzinger in 1965.[1] Due to the histologic features overlapping with malignant melanoma (its proposed neural crest origin, melanin synthesis, expression of S-100 protein, and melanocyte-associated antigen HMB-45, as well as ultrastructural evidence of melanosomes), CCS was originally considered to be a melanoma of soft tissue origin and was called "malignant melanoma of soft parts."[2] More recently, the specific chromosomal translocation t(12;22) (q13; q12) involving DNA transcription factors ATF-1 on chromosome 12

and the EWS gene on chromosome 22 has been detected in 60–75% of CCS cases.[3,4] This translocation is absent in patients with malignant melanoma, leading to the conclusion that these tumors deserve two separate nosologic positions, despite their immunohistochemical similarity and common histogenic origin.[5–7] A normal precursor cell corresponding to the neoplastic elements of CCS has yet to be identified.

Although the literature pertaining to histopathologic studies on CCS seems extensive, few published reports and little information are available on its clinical features and management. In particular, the tumor's clinical behavior, optimal treatment strategy, and outcome in children have not been well characterized.

To contribute more information on the clinical management of childhood CCS of tendons and aponeuroses, we report on a series of pediatric patients treated by the Soft Tissue Sarcoma Italian Cooperative Group (STS-ICG) and the German Cooperative Group (CWS).

MATERIALS AND METHODS

Between January 1980 and January 2000, 28 consecutive cases of previously untreated children with a diagnosis of CCS were registered at ICG (11 patients) and CWS (17 patients) centers. These patients represented 0.8% of all pediatric soft tissue sarcomas registered during the study period. Complete information on clinical data, treatment modalities, and outcome was available for all patients and was reviewed. The histopathologic evaluation was confirmed at the time of diagnosis by the ICG and CWS boards of pathologists. Histologic criteria for the diagnosis of CCS are the intimate association of small solid aggregates of round to fusiform, pale-staining cells within the dense connective tissue of tendons and aponeuroses, the fine reticular stroma surrounding the cells, the relative uniformity of cells showing abundant clear cytoplasm, the prominence of the nucleoli, and the presence of scattered multinucleated giant cells.[1,2,8,9] Mitotic figures are generally infrequent. A confirmation of diagnosis is obtained by immunohistochemistry with a diffuse or focal positivity for S-100 protein and melanocyte-associated antigen HMB-45, positivity for neuron-specific enolase (NSE), and, occasionally, for Leu-7 (CD57), and synaptophysin has also been recognized.[1,2,8]

Tumor extent was assessed according to both the clinical Tumor-Nodes-Metastases (TNM) pretreatment staging system[10] and the Intergroup Rhabdomyosarcoma Study (IRS) postsurgical grouping system.[11] The TNM definition T1 refers to tumors confined to the organ or tissue of origin, whereas T2 lesions invade contiguous structures; T1 and T2 groups are further classified as A or B according to tumor diameter ($\leq$ or $>$ 5 cm, respectively). Regional lymph node involvement was designated as N1 (no node involvement is designated N0) and distant metastases at onset as M1 (no metastases — M0).[10] After initial surgery, patients were classified according to the IRS system: Group I includes patients with completely excised tumors, Group II indicates patients with grossly resected tumors with microscopic residual disease and/or regional lymph node spread, Group III includes patients with gross residual disease after incomplete resection or biopsy, and Group IV comprises patients with metastases at onset.[11]

Patients were treated using multimodality therapeutic approaches including surgery, chemotherapy, and radiotherapy, based on current protocols. Treatment strategies did not change substantially over the years. Primary excision was attempted when complete and nonmutilating resection was considered feasible, otherwise a biopsy was required and chemotherapy was administered to shrink the tumor and make it more manageable at subsequent surgery. In some cases, repeat surgery (primary re-excision) was recommended before any other treatment when microscopic residual disease was suspected.

Radiotherapy was administered to patients at risk of local recurrence due to microscopically or macroscopically incomplete resection. External beam irradiation was administered with conventional fractionation (200 cGy per day) for a total dose ranging from 35 to 58 Gy, median 45 Gy. The radiation target volume included the initial mass plus 2–3 cm margins and the surgical scars.

Different chemotherapeutic regimens, in use for rhabdomyosarcoma protocols, were adopted over the years. The VACA regimen consisted of vincristine 1.5 mg/m^2, Weeks 1, 4, and 7, doxorubicin 30 mg/m^2 per day, for 2 days, Weeks 1 and 7, cyclophosphamide 1200 mg/m^2, Weeks 1, 4, and 7, and actinomycin-D 0.5 mg/m^2 per day, for 3 days, Week 4, for a total of 37–46 weeks. Ifosfamide replaced cyclophosphamide in the VAIA regimen (vincristine 1.5 mg/m^2, Weeks 1–7, actinomycin-D 1.5 mg/m^2, Weeks 1 and 7, ifosfamide 3 g/m^2 per day, for 2 days, Weeks 1, 4, and 7, doxorubicin 40 mg/m^2 per day, for 2 days, Week 4, for a total of 27 weeks). In two patients with metastatic spread, a more intensive regimen including carboplatin and etoposide was used: the CEVAIE schedule consisted of carboplatin 500 mg/m^2, Week 1, epirubicin 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 per day, for 3 days, Weeks 4 and 7, etoposide 150 mg/m^2 per day, for 3 days, Week 7, for a total of 27 weeks (in

all regimens, the maximum dose of vincristine and actinomycin-D administered was 2 mg). Two patients were treated with ifosfamide 2.5 g/m^2 per day and doxorubicin 20 mg/m^2 per day, for 3 days, every 3 weeks, for five courses.

Response to treatment was evaluated after 9 weeks of therapy and was based on the reduction in the sum of the products of the perpendicular diameters of all measurable lesions, defined as follows: complete response (CR), complete disappearance of disease; partial response (PR), tumor reduction greater than 50%; minor response (MR), a reduction of greater than 25%. Stable disease or a reduction less than 25% was recorded as no response, whereas an increase in tumor size or the detection of new lesions was evidence of disease progression.

Event-free survival (EFS) and overall survival (OS) rates were estimated using the Kaplan–Meier method.[12] Patients were evaluated from the date of diagnosis to disease progression, relapse, or death from any cause (whichever occurred first) for EFS, and up to death for OS. The time scale extended to the latest follow-up if none of these events were observed. The log rank test was used to compare the survival curves for the different subgroups of patients to establish the potential value of prognostic factors.[13] Patient follow-up, as of September 2001, ranged from 19 to 238 months (median, 102 months).

TABLE 1
Clinical Features

No.	28
Period	1980–2000
Gender	19 boys, 9 girls
Age	2–21 yrs (median, 14 yrs)
≤ 10 yrs	7
> 10 yrs	21
Primary site	
Extremities	20 (lower 14)
Trunk	4
Pelvis	2
Abdomen	1
Kidney	1
Tumor size (cm)	1–18 cm (median, 4 cm)
< 5	15
5–10	8
> 10	5
TNM stage	
T1A	8
T1B	4
T2A	7
T2B	9
N1M0	3
N1M1	2
IRS grouping	
Group I	13
Group II	8
Group III	5
Group IV	2

TNM: Tumors-Nodes-Metastases; IRS: Intergroup Rhabdomyosarcoma Study.

RESULTS

Twenty-eight patients were treated during the study period. The group included 19 boys and 9 girls, 2–21 years of age. The time elapsing between the onset of symptoms, generally a painless enlarging soft tissue mass, and diagnosis was available for most patients and ranged from 2 to 60 months (median, 10 months). In 20 patients, the primary tumor occurred in the extremities. Table 1 shows the baseline clinical features of the 28 patients. Five had regional lymph node involvement at presentation (N1) and two had lung metastases (N1M1). According to the IRS system, 13 patients were classified as Group I (complete resection at diagnosis), 8 as Group II (6 with microscopically incomplete resection and 2 with complete resections, N1), 5 as Group III (1 with macroscopically incomplete resection and 4 underwent biopsies), and 2 as Group IV (distant metastases).

Seventeen patients received a complete tumor resection at first surgical attempt in 13 cases, at primary re-excision in 2 (performed after the first inadequate surgery but before any other treatment), and at delayed surgery in 2 (after primary chemotherapy). Two N1 patients underwent complete primary tumor resection associated with lymphadenectomy (one at first surgery and one at primary re-excision) and 1 N1M1 patient underwent complete excision of both primary tumor and involved lymph nodes at first surgery, as well as complete lung metastasectomy after chemotherapy. Three patients underwent mutilating surgery: a 13-year-old boy with a tumor of the thigh larger than 20 cm and infiltration of the femoral vessels underwent coxofemoral dysarticulation; a 16-year-old boy with a tumor of the second finger of the left hand underwent finger dysarticulation; and radical nephrectomy was performed on a 14-year-old girl on the assumption of a primary malignant renal neoplasm. Her postsurgical diagnosis was CCS of soft parts localized in the kidney.

Postoperative radiotherapy was administered at a dose of 35–58 Gy (median, 45 Gy) to eight patients whose tumor resection had been incomplete (six IRS Group II, one Group III, one Group IV). Irradiation was delivered to the primary tumor site in seven cases and to both the primary site and the involved lymph nodes in one case. All six IRS Group II patients without complete resection of the primary lesion received radiotherapy; local control was achieved in four of these patients. Radiotherapy was not performed as the

front-line treatment for four Group III patients. It was unnecessary in one patient who had complete resection after chemotherapy and three patients did not receive radiotherapy because their disease progressed within a few months of surgery. The two irradiated patients with gross residual disease after surgery did not respond significantly to radiotherapy.

Chemotherapy was administered to 20 patients: 10 received the VAIA regimen, 6 VACA, 2 ifosfamide and doxorubicin; the 2 patients with metastic spread received CEVAIE. Chemotherapy was not delivered to six patients in Group I, one patient in Group II treated with radiotherapy, nor was it delivered to a 16-year-old patient who refused the treatment (N1, complete resection).

Response to chemotherapy was evaluable in seven patients with measurable disease: one PR, one MR, and five patients with no response.

With a median follow-up of 102 months (range, 19–238 months), OS and EFS rates were 66.4% (standard error [SE] 9.2%) and 63.3% (SE 9.3) at 5 years and 66.4% (SE 9.2) and 58.8 % (SE 9.7) at 10 years, respectively. Seventeen patients were alive at first CR (i.e., 12 of 13 IRS Group I patients, 3 of 8 Group II, 1 of 5 Group III, and 1 of 2 Group IV). The patient with metastatic spread still in CR received radical resection of the primary tumor, chemotherapy with PR of lung metastases, and a metastasectomy.

Eleven patients had tumor progression or recurrence 2–64 months (median, 8 months) after diagnosis: site of progression/recurrence was local in four, local with distant metastases in one, lymph node involvement and distant metasis in one, with distant metastases in five. Metastases were located in the lung in six cases and in the bones in one case. Among the patients with recurrence, 9 of 11 had a primary tumor size larger than 5 cm. Nine patients died of disease despite further treatment 4–43 months (median, 9 months) after diagnosis. Two patients were alive in second CR 50 and 61 months after relapse: both of them had a local recurrence after microscopically incomplete resection and subsequent radiotherapy, and achieved a second CR with additional surgery and chemotherapy. Clinical features, treatment modalities, and outcome of each patient are reported in Table 2.

Table 3 shows the univariate analysis comparing the estimated EFS of the different subsets of patients stratified according to various characteristics. Statistically significant differences in outcome were evident in relation to the extent of surgery (IRS groups, Fig. 1), tumor size (Fig. 2), and site of primary lesion. The *P* value was not significant for sex, age, N status, and T status.

DISCUSSION

Our study represents the largest reported series of CCS of tendons and aponeuroses in pediatric patients. The rarity of CCS in childhood is demonstrated by the presence of only one published report, from the St. Jude Children's Research Hospital, with only five patients treated over 35 years.[14] Experience in adults is also limited,[9,15–19] accounting for the few data available on the clinical management of this rare soft tissue tumor.

CCS typically affects adults in their third and fourth decades, although it can occur at any time of life. In the extensive review by Chung and Enzinger,[2] the age of patients ranged from 7 to 83 years, with a median age of 27 years. Only 2% of reported cases were younger than 10 years old. The tumor usually arises in the lower extremities (about 70% of cases), the foot and ankle in particular, and is deep seated and intimately bound to tendons, aponeuroses, and fasciae. Clinically, it often presents as a painless slowly enlarging mass that has been present for several months or even years.[20] At presentation, most of the tumors are smaller than 5 cm in greatest diameter. Radiologically, CCS can be mistaken for a benign process.[21] Our findings confirm these known features, as well as the aggressive behavior and tendency to metastasize to regional lymph nodes and, more frequently, to the lung. In our series, a very uncommon non-soft tissue location was described, documenting the second reported case of CCS arising in the kidney.[22]

Chung and Enzinger[2] described CCS as a fully malignant neoplasm with a poor prognosis even in patients who received adequate treatment. Results from adult series are unsatisfactory, generally with a 5-year survival rate of less than 50%.[9,15–19] The outcome in our series is better, with OS and EFS rates of 68.9% and 62.7%, respectively, at 5 years, although the likelihood of local and distant recurrences after a prolonged disease-free interval must be taken into account. Chung and Enzinger reported a median time to recurrence of 4.2 years, with a range of 1–10 years. In the Mayo Clinic experience reported by Eckardt et al.,[17]the survival rate was 67% at 5 years, but decreased to 33% at 10 years and to 10% at 20 years. These data suggested the need of long-term follow-up for all patients. We are fully aware that some of our currently tumor-free patients may develop recurrences (three of them had a follow-up of less than 36 months). However, in our cohort, the 10-year EFS rate was 58.8%, the median time to recurrence was 8 months, and all but two patients developed a recurrence within 18 months of diagnosis.

TABLE 2
Clinical Features, Treatment, and Outcome of the 28 Patients with Clear Cell Sarcoma

Patient no.	Gender	Age (yrs)	Site	TNM	Size (cm)	IRS	Surgery	Chemotherapy (CT)	Radiotherapy	Outcome
1	M	9	Extremity	T1AN0M0	3–5	I	Complete resection (primary re-excision)	No	No	Alive in 1st CR at 238 mos from diagnosis
2	M	13	Extremity	T2BN0M0	> 10	I	Complete resection (coxofemoral dysarticulation)	VACA Response to CT: N.E.	No	Metastatic recurrence (bone) at 2 mos DOD at 6 mos
3	F	10	Extremity	T1AN0M0	3–5	I	Complete resection	VACA N.E.	No	Alive in 1st CR at 215 mos
4	M	15	Extremity	T1AN0M0	< 3	I	Complete resection	No	No	Alive in 1st CR at 176 mos
5	F	12	Extremity	T2AN0M0	< 3	I	Complete resection	VAIA N.E.	No	Alive in 1st CR at 160 mos
6	M	11	Extremity	T2AN0M0	< 3	I	Complete resection	VAIA N.E.	No	Alive in 1st CR at 159 mos
7	M	3	Abdomen	T2BN0M0	5–10	I	Complete resection	VAIA N.E.	No	Alive in 1st CR at 30 mos Lost at follow-up
8	F	14	Extremity	T2AN0M0	3–5	I	Complete resection	VAIA N.E.	No	Alive in 1st CR at 111 mos
9	M	21	Extremity	T1AN0M0	< 3	I	Complete resection	No	No	Alive in 1st CR at 80 mos
10	F	11	Extremity	T1AN0M0	< 3	I	Complete resection	VAIA N.E.	No	Alive in 1st CR at 69 mos
11	F	7	Extremity	T1AN0M0	< 3	I	Complete resection	No	No	Alive in 1st CR at 66 mos
12	F	14	Kidney	T1AN0M0	3–5	I	Complete resection (radical nephrectomy)	No	No	Alive in 1st CR at 24 mos
13	F	15	Extremity	T1BN0M0	5–10	I	Complete resection	No	No	Alive in 1st CR at 19 mos
14	F	7	Trunk	T2AN0M0	3–5	II	Incomplete resection	VAIA N.E.	35 Gy	Alive in 1st CR at 147 mos
15	M	15	Extremity	T1AN0M0	< 3	II	Incomplete resection	VACA N.E.	58 Gy	Local recurrence at 64 mos Alive in 2nd CR at 125 mos
16	M	15	Extremity	T1BN0M0	5–10	II	Incomplete resection	VACA N.E.	48 Gy	Metastatic recurrence (lung) at 10 mos DOD at 16 mos
17	M	8	Trunk	T1BN0M0	5–10	II	Incomplete resection	No	45 Gy	Local recurrence at 14 mos Alive in 2nd CR at 64 mos
18	M	16	Extremity	T2AN1M0	< 3	II	Complete resection (Finger dysarticulation and lymphadenectomy)	Refused	No	Alive in 1st CR at 93 mos
19	M	11	Extremity	T2BN1M0	5–10	II	Complete resection (Primary re-excision and lymphadenectomy)	VACA N.E.	No	Metastatic recurrence (lung) at 18 mos DOD at 30 mos
20	M	15	Extremity	T2AN0M0	3–5	II	Incomplete resection	VACA N.E.	46 Gy	Metastatic recurrence (lung) at 36 mos; DOD at 43 mos
21	M	15	Extremity	T2AN1M0	< 3	II	Incomplete resection	VAIA N.E.	45 Gy On T and N	Alive in 1st CR at 64 mos
22	M	15	Extremity	T2BN0M0	> 10	III	Biopsy Delayed complete surgery	IFO-ADM No response	No	Alive in 1st CR at 236 mos
23	F	14	Trunk	T2BN0M0	> 10	III	incomplete resection	VAIA No response	45 Gy	Local progression at 2 mos DOD at 5 mos
24	M	17	Pelvis	T2BN0M0	> 10	III	Biopsy	VAIA MR to CT	No	Local progression at 6 mos DOD at 13 mos
25	M	15	Pelvis	T2BN0M0	> 10	III	Biopsy, delayed incomplete surgery	IFO-ADM No response	No	Metastatic recurrence (lung) at 6 mos DOD at 9 mos
26	M	11	Trunk	T2BN0M0	5–10	III	Biopsy	VAIA No response	No	Local and distant (lung) progression At 2 mos, DOD at 10 mos
27	M	2	Extremity	T2BN1M1	5–10	IV	Complete resection on T/N Delayed metastasectomy	CEVAIE RP to CT	No	Alive in 1st CR at 29 mos
28	M	18	Extremity	T1BN1M1	5–10	IV	Incomplete resection	CEVAIE No response	45 Gy	Metastatic progression (lung) at 2 mos DOD at 4 mos

TNM: Tumor-Nodes-Metastases; IRS: Intergroup Rhabdomyosarcoma Study; CR: complete remission; PRO: progression; DOD: dead of disease; Response to CT N.E.: not evaluable (no measurable disease); PR: partial remission; MR: minor response; VAIA: vincristine, actinomycin-D, ifosfamide, doxorubicin; VACA: vincristine, actinomycin-D, cyclophosphamide, doxorubicin; ADM: Doxorubicin; IFO: ifosfamide; CEVAIE: carboplatin, epiadriamycin, vincristine, actinomycin-D, ifosfamide, etoposide.

TABLE 3
Univariate Analysis

	5-yr EFS (%)	*P* value
Overall	63.3	
IRS Group I (n = 13) vs. Group II (n = 8) vs. Group III (n = 5)	92.3 vs. 50.0 vs. 20.0	0.0016
Size < 3 cm (n = 9) vs. 3–5 cm (n = 6) vs. 5–10 cm (n = 8) vs. > 10 cm (n = 5)	100.0 vs. 80.0 vs. 37.5 vs. 20.0	0.0017
Extremities (n = 20) vs. other sites (n = 8)	74.3 vs. 37.5	0.0354
Females (n = 9) vs. males (n = 19)	88.9 vs. 51.5	0.0586
≤ 10 yrs (n = 7) vs. > 10 yrs (n = 21)	85.7 vs. 56.3	0.1508
N0 (n = 23) vs. N1 (n = 5)	64.2 vs. 60.0	0.9321
T1 (n = 12) vs. T2 (n = 16)	75.0 vs. 54.7	0.5248

EFS: event-free survival; IRS: Intergroup Rhabdomyosarcoma Study.

Our study shows that tumor size is the most important predictor of survival, together with the quality of surgical resection (IRS groups). Prognosis is also significantly better for patients whose tumors arose in the extremities rather than at other sites, where complete tumor excision is more difficult. The differences in outcome regarding these variables are statistically significant despite the relatively few cases. However, age does not represent a statistically significant prognostic factor, even if patients older than 10 years of age show a tendency for a worse prognosis.

The prognostic role of tumor size has been reported by others.[8,15–17,20] In the series from the M. D. Anderson Cancer Center, survival depended on the onset of distant metastases and correlated directly with tumor size, whereas local recurrence was primarily a consequence of inadequate surgery.[17]

In our series, pathologic re-evaluation of histologic specimens or slides to assess degree of cellularity, mitotic activity, and the amount of necrosis was not possible in the majority of cases, due to the number of centers from different countries involved in the study. In most cases of CCS, histologic features show modest cellular pleomorphism, a low mitotic index, and little or no necrosis. Lucas et al.[16] suggested that, except for tumor necrosis, the histopathologic features and grading of CCS are of little use in predicting its clinical behavior, which resembles that of a high-grade soft tissue sarcoma.

Complete surgical resection remains the mainstay of treatment for CCS patients. In our subset, complete surgical resction represents an important predictor of outcome. In patients with complete excision, adjuvant treatment seems unnecessary: all seven patients treated with complete resection alone were alive in first CR without any further therapy, and 12 of 13 children classified as IRS Group I were alive in first CR (the only patient with recurrence in Group I had a tumor larger than 10 cm). Like other reports, our data support the need for aggressive surgical resection in all patients with CCS. When conservative complete excision is not feasible, mutilating surgery should be considered.

Because regional lymph node spread is almost as common as lung metastases, some authors recommend prophylactic elective regional lymph node dissection as part of the therapy.[15,19] In our series, five children presented with lymph node involvement at diagnosis and only one had lymph node spread at recurrence. Our data would therefore suggest using lymphadenectomy only in case of clinical lymphadenopathy. The opportunity to perform sentinel lymph node biopsy is an issue that deserves further investigation.

The role of adjuvant radiotherapy after incomplete tumor resection is not clear as yet. In the series from the Netherlands Cancer Institute, adjuvant radiotherapy to the primary tumor site seemed to have a significant beneficial effect on survival. Because all seven irradiated patients were alive with no evidence of disease, the authors advocated the use of radiotherapy.[19] Various findings suggest that radiotherapy could be effective in controlling microscopic residual disease after surgery.[17] In our series, radiotherapy failed to produce any significant response in the two patients with gross residual disease, whereas it probably played a decisive part in achieving local control in four of six IRS Group II patients.

The problem of local control is important in the management of CCS patients. However, our series, like others, showed that distant metastases are the major cause of treatment failure. In the series from the Mayo Clinic reported by Lucas et al.,[16] metastases developed in 63% of patients (and in all patients with tumors larger than 5 cm). The high risk of distant metastases, particularly in patients with large tumors, and the poor outcome in patients with unresected disease support the use of chemotherapy in such cases

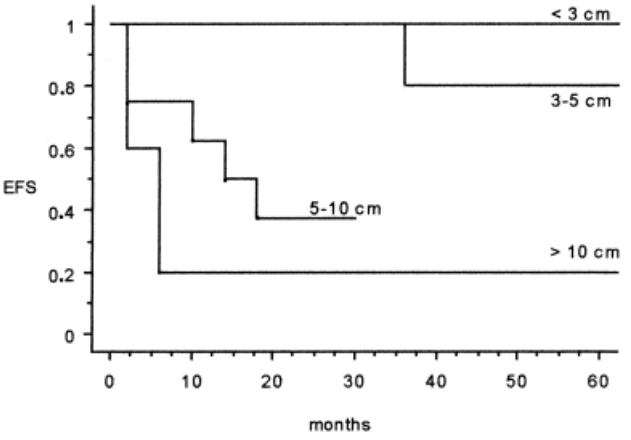

FIGURE 1. Kaplan–Meier estimation of event-free survival rates according to tumor size.

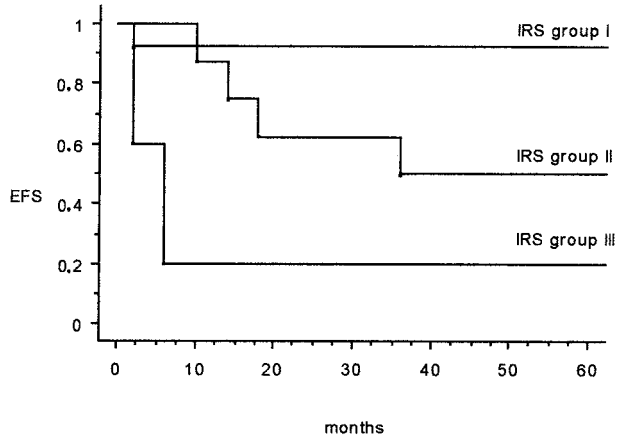

FIGURE 2. Kaplan–Meier estimation of event-free survival rates according to Intergroup Rhabdomyosarcoma Study grouping.

and the evaluation of new chemotherapeutic regimens.[23] Our results (seven patients with evaluable disease: one PR, one MR, and five patients with no response) and those of other reports on the effectiveness of chemotherapy, adopting the drugs and schedules in use for rhabdomyosarcoma or other soft tissue sarcomas, are not encouraging.[19]

There are few, but interesting data on immunotherapy, which has been proposed for the treatment of CCS patients due to the sensitivity of malignant melanoma to biological response modifiers. A remarkable response to interferon α-2b was reported by Steger et al. [24] and was partially confirmed by Lauro et al., [25] who treated a patient with metastatic CCS with subcutaneous interferon and concomitant chemotherapy. Further investigations are needed to define the role of immunotherapy in CCS patients.

In conclusion, our study confirms the aggressive behavior of CCS of tendons and aponeuroses. As shown in recent biological studies, CCS behaves more like a high-grade soft tissue sarcoma than a malignant melanoma, from which it should be distinguished as a clinicopathologic entity. Complete tumor resection represents the mainstay of treatment and is the sole treatment for patients with small tumors. The prognosis for patients with unresected and large tumors is poor, also in relation to the scarce efficacy of adjuvant treatments. Prospective cooperative studies are needed to define the best treatment strategies and to explore new active agents.

REFERENCES

1. Enzinger FM. Clear-cell sarcoma of tendons and aponeuroses. An analysis of 21 cases. *Cancer.* 1965;18:1163–1174.
2. Chung EB, Enzinger FM. Malignant melanoma of soft parts. A reassessment of clear cell sarcoma. *Am J Surg Pathol.* 1983;7:405–413.
3. Langezaal SM, Graadt van Roggen JF, Cleton-Jansen AM, Baelde JJ, Hogendoorn PCW. Malignant melanoma is genetically distinct from clear cell sarcoma of tendons and aponeurosis (malignant melanoma of soft parts). *Br J Cancer.* 2001;84:535–538.
4. Zucman J, Delattre O, Desmaze C, et al. EWS and ATF-1 gene fusion induced by t(12;22) translocation in malignant melanoma of soft parts. *Nature Genet.* 1993;4:341–345.
5. Bridge JA, Borek DA, Neff JR, Huntrakoon M. Chromosomal abnormalities in clear cell sarcoma. Implications for histogenesis. *Am J Clin Pathol.* 1990;93:26–31.
6. Stenman G, Kindblom LG, Angervall L. Reciprocal translocation t(12;22)(q13;q13) in clear-cell sarcoma of tendons and aponeuroses. *Genes Chrom Cancer.* 1992;4:122–127.
7. Graadt van Roggen JF, Mooi WJ, Hogendoorn PC. Clear cell sarcoma of tendons and aponeuroses (malignant melanoma of soft parts) and cutaneous melanoma: exploring the histogenic relationship between these two clinicopathological entities. *J Pathol.* 1998;186:3–7.
8. Harmer MH. TNM classification of pediatric tumors. Geneva: UICC International Union Against Cancer, 1982:23–28.
9. Maurer HM, Beltangady M, Gehan EA, et al. The Intergroup Rhabdomyosarcoma Study I: a final report. *Cancer.* 1988;61:209–220.
10. Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc.* 1958;53:457–481.
11. Conover WJ. Practical nonparametric statistics. New York: Wiley, 1980:153–169.
12. Parasuraman S, Rao BN, Bodner S, et al. Clear cell sarcoma of soft tissues in children and young adults: the St. Jude Children's Research Hospital Experience. *Pediatr Hematol Oncol.* 1999;16:539–544.
13. Pinkerton CR, Philip T. Clear cell sarcoma. *Pediatr Hematol Oncol.* 1999;16:495–497.
14. d'Amore ESG, Ninfo V. Clear cell tumors of the somatic soft tissues. *Semin Diagn Pathol.* 1997;14:270–280.
15. De Beuckeleer LH, De Schepper AM, Vandevenne JE, et al. MR imaging of clear cell sarcoma (malignant melanoma of soft parts): a multicenter correlative MR-pathology study of 21 cases and literature review. *Skeletal Radiol.* 2000;29:187–195.

16. Lucas DR, Nascimento AG, Sim FH. Clear cell sarcoma of soft tissues: Mayo Clinic experience with 35 cases. *Am J Surg Pathol.* 1992;16:1197–1204.
17. Eckardt JJ, Pritchard DJ, Soule EH. Clear cell sarcoma: a clinicopathologic study of 27 cases. *Cancer.* 1983;52:1482–1488.
18. Sara AS, Evans HL, Benjamin RS. Malignant melanoma of soft parts (clear cell sarcoma): a study of 17 cases, with emphasis on prognostic factors. *Cancer.* 1990;65:367–374.
19. Montgomery EA, Meis JM, Ramos AG, Frisman DM, Martz KL. Clear cell sarcoma of tendons and aponeuroses: a clinicopathologic study of 58 cases with analysis of prognostic factors. *Int J Surg Pathol.* 1993;1:89–99.
20. Deenik W, Mooi WJ, Rutgers EJ, Peterse JL, Hart AA, Kroon BB. Clear cell sarcoma (malignant melanoma) of soft part. A clinicopathologic study of 30 cases. *Cancer.* 1999;86:969–975.
21. Finley JW, Hanypsiak B, McGrath B, Kraybill W, Gibbs JF. Clear cell sarcoma: the Roswell Park Experience. *J Surg Oncol.* 2001;77:16–20.
22. Rubin BP, Fletcher JA, Renshaw AA. Clear cell sarcoma of soft parts. Report of a case primary in the kidney with cytogenetic confirmation. *Am J Surg Pathol.* 1999;23:589–594.
23. Radstone DJ, Revell PA, Mantell BS. Clear cell sarcoma of tendons and aponeuroses treated with bleomycin and vincristine. *Br J Radiol.* 1975;52:238–241.
24. Steger GG, Wrba F, Mader R, Schlappack O, Dittrich C, Rainer H. Complete remission of metastasized clear cell sarcoma of tendons and aponeuroses. *Eur J Cancer.* 1991; 27:254–256.
25. Lauro S, Bordin F, Trasatti L, Lanzetta G, Della Rocca C, Frati L. Concurrent chemoimmunotherapy in metastatic clear cell sarcoma: a case report. *Tumori.* 1999;85: 512–514.