Fibrosarcoma in Pediatric Patients: Results of the Italian Cooperative Group Studies (1979–1995)

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Background and Objectives: Fibrosarcoma is a rare soft tissue sarcoma (STS) that has two peaks of incidence in pediatric patients: one in infants and young children (infantile fibrosarcoma), another in older children (“adult type” fibrosarcoma). The purpose of this study was to describe the clinical features and the treatment results in patients affected by fibrosarcoma enrolled in two consecutive studies run by the STS-Italian Cooperative Group (ICG) between 1979 and 1995.

Patients and Methods: Twenty-five evaluable patients were grouped according the intergroup rhabdomyosarcoma staging (IRS) system: 12 Gr I, 5 Gr II, 8 Gr III. The cut-off point between the two forms was considered the age of 2 years: 14 patients were affected by infantile and 11 by adult type of fibrosarcoma. The therapeutic guidelines were not strict and not different for the two forms: patients with initial macroscopic excision (Gr I–II) were given IV A or V AC; Gr III had V AC or V AIA and subsequent excision, if feasible. Radiation therapy (RT) was delivered in patients >3 years with microscopic (42 Gy) and macroscopic (54 Gy) residuals.

Results: Thirteen patients are alive without evidence of disease: 10 in first complete remission (CR), 7 Gr I, 1 Gr II, 2 Gr III, 3 in second CR after local relapse (LR) (2 Gr I, 1 Gr II). Two Gr I patients are alive with metastatic relapse. Nine patients died: six of progressive disease (PD) (three Gr II, three Gr III), two because of a second tumor (one Gr I, one Gr III) and one because of other causes (Gr III). One Gr III patient was lost at follow up, 2 years from diagnosis. The 10 years overall survival (OS) is 67.4% and the progression-free survival (PFS) is 52.2%. The OS for patients <2 years is 78.6% (11 of 14), versus 51% for patients >2 years (5 of 11).

Conclusions: The complete excision at diagnosis was the treatment of choice and was related to the best outcome. Microscopical residuals were difficult to treat with chemo-radiotherapy in both forms of fibrosarcoma. Neoadjuvant chemotherapy (CT) obtained a partial remission (PR) only in three of eight cases, while no conclusions concerning the efficacy of CT for infantile forms are possible. Patients <2 years had a better outcome than
the older ones: most of them had a tumor on extremities which was excised at diagnosis.


**KEY WORDS: fibrosarcoma; infantile fibrosarcoma; soft tissue sarcoma**

**INTRODUCTION**

Fibrosarcoma represents about 10% of pediatric non-rhabdo soft tissue sarcomas (NRSTS) and is the most common soft tissue sarcoma (STS) in children under 1 year of age. There are two peaks of incidence: one in infants and young children (infantile fibrosarcoma) and another in patients aged between 10 and 15 [1,2].

Both are composed of spindle cells with different growth patterns: solid, hemangiopericitoma like, and herringbone. High mitotic index and high cellularity are present in spite of the low aggressivity of the lesion. An adequate immunohistochemical panel is necessary for a differential diagnosis with other sarcomas (malignant peripheral nerve sheat tumors, rhabdomyosarcomas, and smooth muscle tumors). A differential diagnosis with miøfibromatosis and infantile hemangiopericytoma is sometimes impossible, even if a diffusely infiltrative growth pattern is more indicative for miøfibromatosis [3].

The clinical characteristics of the tumor, the age of the patient, and presently also cytogenetic differences, are considered main factors in distinguishing the infantile or the adult type and deciding on their adequate treatment [4,5]. The age limit between the two forms is a matter of discussion: at present most authors consider as cutoff point the age of 2 years, others the age of 4 or 5 years [3].

Surgery is the mainstay of treatment in both forms; the role of chemotherapy (CT) and radiation therapy (RT) is still debated, even if the infantile fibrosarcoma seems to be more chemosensitive.

This report reviews the clinical characteristics and the treatment results of children and adolescents with fibrosarcoma, registered in the studies of the STS-Italian Cooperative Group (ICG).

**PATIENTS AND METHODS**

Between January 1979 and December 1995, 30 patients under 18 years affected by fibrosarcoma were registered in two consecutive national protocols RMS-79 and RMS-88. All the cases had a localized disease. In this paper, we describe the 25 of 30 patients, 10 of the first study and 15 of the second, for which adequate data were available. They were 10 males and 15 females with a median age of 24 months (range 8 days–187 months) representing 12% of patients with NRSTS (25 of 209) and 4.4% of those with STS (25 of 575) enrolled in the studies. All the histologic specimens were reviewed by a panel of pathologists. For all cases from a minimum of two to a maximum of eight Ematossilin–Eosin stained sections were reviewed and a complete immunohistochemical panel represented by S-100 (DAKO, Clone COW S100 diluition 1:7000), MNF116 (DAKO, Clone MNF116 diluition 1:100), HHF 35 (DBA Clone HHF35 diluition 1:300) was performed on formalin fixed, paraffin embedded specimens for differential diagnosis from other sarcomas. Diagnosis of fibrosarcoma was made when at the E.E. stain a highly cellular mitotically active neoplasia with spindle cells, without signs of neural or rhabdomioblastic differentiation was present and the immunohistochemistry showed diffuse negativity for all markers (Fig. 1A,B). Only in one case a slight positivity for muscle Specific Actin (HHF 35) was evident. The age was the main criterium to differentiate infantile subtypes from adult subtypes: the fibrosarcomas found in patients younger than 2 years were considered infantile.

The group included 14 patients with the infantile form (in 7 of 14 under 3 months of age the tumor was considered congenital) and 11 with the “adult type” form. They were grouped according to the intergroup rhabdomyosarcoma staging (IRS) system: Gr I complete microscopical excision; Gr II excision with microscopical residuals (IIa) or with lymphnodes involvement (IIb) or both (IIc); Gr III biopsy or excision with macroscopical residuals. According to TNM pretreatment classification, tumors confined to the organ or tissue of origin were considered T1; those involving contiguous organs or structures T2.

The therapeutic guidelines of the studies were not strict, in particular there were no sharp differences in treatment between the infantile and adult forms of fibrosarcoma. Wide excisions were always recommended, and a more aggressive multidisciplinary approach was suggested in older patients. However, initial anatomic or funtional demolitive procedures (i.e., extremity amputation, pneumonectomy, large head-neck dissection, pelvic exenteration, procedures with permanent urinary or intestinal diversion) were discouraged. CT with vincristine, dactinomycin, and cyclophosphamide, or vincristine adriamycine and cyclophosphamide (VAC/CAV regimen, RMS-79), or ifosfamide, vincristine, dactinomycine (IVA regimen, RMS-88) was recommended for all the patients in Gr I and Gr II after primary surgery. Neoadjuvant CT with VAC regimen (cyclophosphamide,
dactinomycin, vincristine) in the first study or with VAIA (vincristine, dactinomycin, ifosfamide, adriamycin) in the second study was given to patients in Gr III: a delayed surgery, if feasible, followed CT, and subsequently a maintenance CT with CAV/VAC or IVA was administered. RT was recommended in patients > 3 years of age: 40–45 Gy in cases with microscopical disease after primary surgery, 45–54 Gy when delayed surgery was not radical or not possible. Children younger than 3 years did not receive RT because of the high risk of late sequelae. In the case of failure of CT and/or RT, mutilating surgery was accepted. Response to treatment was defined as follows: complete remission (CR) equals no evidence of disease; partial remission (PR) equals reduction >50% of initial tumor volume; objective remission (OR) equals reduction >25% of initial tumor volume; stable disease (SD) equals reduction <25% of initial tumor volume; progression of disease (PD) equals increase of the initial tumor volume or appearance of new lesions.

RESULTS

The clinical features, the IRS Groups, the treatment and the outcome of the patients are reported in Table I. The extremities were the most frequent localizations (14 of 25), especially in patients under 2 years of age (10 of 14, and 5 of 7 among the congenital cases). The masses in young patients had a fast growth in most instances. No significant differences were evident between patients younger and older than 2 years regarding the initial T status and the tumor size (Table II). Involvement of regional lymphnodes was not detected in any case at clinical and imaging investigations.

After initial surgery 12 patients were classified in Gr I, 5 in Gr II, (4 IIa, 1 IIc), and 8 in Gr III. Eight out of the 14 patients aged < 2 years (4 of 7 patients among those with congenital fibrosarcoma) had initially a radical excision, while only 4 of 11 of the older patients had completely resected tumors at diagnosis. Three patients < 2 years and two > 2 years of age had microscopical residuals after initial surgery; a biopsy was performed initially in three children < 2 years and in five > 2 years.

The treatment and the outcome of the patients are described according to IRS Group:

Gr I: Five patients (aged 1, 3, 6, 27 months) had surgery alone; six (aged 1, 7, 17, 19, 101, 112 months) received surgery (mutilating in the oldest patient), and CT; a 177-month-old boy underwent the complete excision plus CT (IVA) and RT (40 Gy).

Eight cases achieved and maintained the first CR, but one, whose primary was on extremity, died of a second tumor (PNET) that occurred on the thoracic wall 3 years after the diagnosis of fibrosarcoma. The panel of pathologists confirmed two different tumors.

A local relapse (LR) occurred at 6, 8, and 10 months from diagnosis in three children, who had had surgery alone (two) and surgery + CT (one). After LR they received multimodal therapy which included mutilating surgery (amputation) in the first two: at present two are alive in second CR and one is alive with pulmonary metastases.

A 101-month-old girl treated with excision and CT suffered from pulmonary metastases at 58 months from diagnosis and is alive with disease.

Gr II: Four patients had a primary excision with microscopical residuals (Gr IIa). Two of them, aged 3 and
7 months, did not receive postoperative CT: the first is alive in CR, the second had a LR after 1 year and at present he is alive in second CR after a new radical excision. Two other patients, aged 4 and 24 months, who had CT after the excision, presented LR after 5 and 6 months, and died of progressive disease (PD) despite further multimodal therapy.

One patient in Gr IIc, an 87-month-old boy, presented pulmonary metastases after CT (V AC) and RT (50 Gy) and died of disease (DOD).

Gr III: Eight patients (aged 1, 2, 7, 51, 60, 156, 167, 187 months) with inoperable tumor underwent an open biopsy at diagnosis. Among the five patients treated in the RMS-79 study with neoadjuvant CA V regimen, three achieved a PR, while two showed a PD. Of the three patients treated in the second study with V AIA regimen, one obtained a minor response (OR), one had SD and one died during treatment because of cardiac malformation.

After neoadjuvant CT the seven patients were treated with radical surgery (two), incomplete excision + RT (one), RT + CT (three) and with CT alone (one). Four of the seven cases achieved the CR, but one died because of a second tumor (not otherwise specified) that appeared 11 years later. Three patients never achieved the CR and died from PD.

### TABLE I. Features, Treatment, and Outcome of the 25 Patients With Fibrosarcoma

<table>
<thead>
<tr>
<th>Age mo/sex</th>
<th>Primary site</th>
<th>T status</th>
<th>IRS group</th>
<th>Treatment (CT response)</th>
<th>Outcome and further therapy</th>
<th>Present status &amp; follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/M</td>
<td>Calf</td>
<td>T1a</td>
<td>III</td>
<td>CT (NE)</td>
<td>Cardiac malformation</td>
</tr>
<tr>
<td>2</td>
<td>1/M</td>
<td>Foot</td>
<td>T1b</td>
<td>I</td>
<td>S</td>
<td>LR (CT + Mut.S)</td>
</tr>
<tr>
<td>3</td>
<td>1/M</td>
<td>Calf</td>
<td>T1a</td>
<td>I</td>
<td>S</td>
<td>NED 104 mo</td>
</tr>
<tr>
<td>4</td>
<td>1/F</td>
<td>Forearm</td>
<td>T1a</td>
<td>I</td>
<td>S + CT</td>
<td>NED 109 mo</td>
</tr>
<tr>
<td>5</td>
<td>2/F</td>
<td>Paravertebral</td>
<td>T2b</td>
<td>III</td>
<td>CT</td>
<td>PD</td>
</tr>
<tr>
<td>6</td>
<td>3/M</td>
<td>Retropertioneal</td>
<td>T2b</td>
<td>I</td>
<td>S</td>
<td>NED 197 mo</td>
</tr>
<tr>
<td>7</td>
<td>3/F</td>
<td>Arm</td>
<td>T2a</td>
<td>IIa</td>
<td>S</td>
<td>NED 98 mo</td>
</tr>
<tr>
<td>8</td>
<td>6/M</td>
<td>Foot</td>
<td>T1a</td>
<td>I</td>
<td>S</td>
<td>NED 60 mo</td>
</tr>
<tr>
<td>9</td>
<td>7/F</td>
<td>Retropertioneal</td>
<td>T2b</td>
<td>I</td>
<td>S + CT</td>
<td>NED 217 mo</td>
</tr>
<tr>
<td>10</td>
<td>7/F</td>
<td>Arm</td>
<td>T1a</td>
<td>IIa</td>
<td>S</td>
<td>LR (CT + S)</td>
</tr>
<tr>
<td>11</td>
<td>7/F</td>
<td>Thigh</td>
<td>T2b</td>
<td>III</td>
<td>CT (OR) + S</td>
<td>NED 80 mo</td>
</tr>
<tr>
<td>12</td>
<td>17/F</td>
<td>Buttock</td>
<td>T1b</td>
<td>I</td>
<td>S + CT</td>
<td>LR (CT + RT + S)</td>
</tr>
<tr>
<td>13</td>
<td>19/F</td>
<td>Arm</td>
<td>T1b</td>
<td>I</td>
<td>S + CT</td>
<td>NED 186 mo</td>
</tr>
<tr>
<td>14</td>
<td>24/M</td>
<td>Thoracic wall</td>
<td>T2a</td>
<td>IIa</td>
<td>S + CT</td>
<td>LR + Met (CT + S)</td>
</tr>
<tr>
<td>15</td>
<td>27/F</td>
<td>Forearm</td>
<td>T1a</td>
<td>I</td>
<td>S</td>
<td>Multiple LR</td>
</tr>
<tr>
<td>16</td>
<td>51/F</td>
<td>Pericardial</td>
<td>T1b</td>
<td>III</td>
<td>CT (PD) + RT</td>
<td>PD</td>
</tr>
<tr>
<td>17</td>
<td>60/F</td>
<td>Thoracic</td>
<td>T1b</td>
<td>III</td>
<td>CT (SD) + RT + S</td>
<td>NED 175 mo</td>
</tr>
<tr>
<td>18</td>
<td>87/M</td>
<td>HNnPM</td>
<td>T1a</td>
<td>Ilc</td>
<td>S + CT + RT</td>
<td>Lung metastases</td>
</tr>
<tr>
<td>19</td>
<td>101/F</td>
<td>Thigh</td>
<td>T1b</td>
<td>I</td>
<td>S + CT</td>
<td>Lung metastases</td>
</tr>
<tr>
<td>20</td>
<td>112/M</td>
<td>Calf</td>
<td>T1b</td>
<td>I</td>
<td>Mut.S + CT</td>
<td>NED 36 mo, died 2nd tumor</td>
</tr>
<tr>
<td>21</td>
<td>130/F</td>
<td>Pericardial</td>
<td>T2b</td>
<td>IIa</td>
<td>S + CT</td>
<td>LR</td>
</tr>
<tr>
<td>22</td>
<td>156/M</td>
<td>Presacral</td>
<td>T2b</td>
<td>III</td>
<td>CT (PR) + RT</td>
<td>Lung metastases</td>
</tr>
<tr>
<td>23</td>
<td>167/F</td>
<td>Thigh</td>
<td>T2a</td>
<td>III</td>
<td>CT (PR) + Mut.S</td>
<td>NED 132 mo, died 2nd tumor</td>
</tr>
<tr>
<td>24</td>
<td>177/M</td>
<td>Thoracic wall</td>
<td>T1a</td>
<td>I</td>
<td>S + CT + RT</td>
<td>NED 71 mo</td>
</tr>
<tr>
<td>25</td>
<td>187/F</td>
<td>HNPM</td>
<td>T2b</td>
<td>III</td>
<td>CT (PR) + RT</td>
<td>NED 24 mo, lost follow up</td>
</tr>
</tbody>
</table>

AWD, alive with disease; CT, chemotherapy; DOD, died of disease; Mut.S, mutilating surgery; LR, local relapse; NE, not evaluable; NED, no evidence of disease; OR, objective response; PD, progression of disease; PR, partial response; RT, radiotherapy; S, surgery; SD, stable disease; mo, month.

### TABLE II. Clinical Features and Surgical Groups According to Age

<table>
<thead>
<tr>
<th>No.</th>
<th>≤ 2 Years</th>
<th>&gt; 2 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Extremity</td>
<td>Axial</td>
<td></td>
</tr>
<tr>
<td>T status</td>
<td>T1</td>
<td>T2</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>&lt; 5 cm</td>
<td>&gt; 5 cm</td>
<td></td>
</tr>
<tr>
<td>IRS group</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
</tbody>
</table>

7 months, did not receive postoperative CT: the first is alive in CR, the second had a LR after 1 year and at present he is alive in second CR after a new radical excision. Two other patients, aged 4 and 24 months, who had CT after the excision, presented LR after 5 and 6 months, and died of progressive disease (PD) despite further multimodal therapy.

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Fibrosarcoma in Pediatric Age

In pediatric age, the clinical features are slightly different in relation to age. In infancy, fibrosarcomas are found mostly in superficial or deep tissues of distal extremities, while they are axial only in 30% of cases [1]; proximal regions of extremities, deep trunk and cavitary sites are the favorite localizations in older patients [1,4]. This is in agreement with the findings in our series: 10 of 14 children aged < 2 years had the tumor on extremities (5 in distal segments) and 4 on axial sites, while among 11 patients > 2 years the tumor was axial in 7 and on extremities in 4 (2 distal).

A painless, rapidly enlarging, and dome shaped mass with the overlying skin red, tense, and ulcerated, giving the impression of a vascular tumor, is the main symptom in childhood. The mean diameter of the tumor may exceed 10–15 cm. In older patients, the fibrosarcoma grows slowly and pain is present in one third of the cases [6].

Infantile and adult fibrosarcoma are histologically identical. There are no pathological pictures that allow reliable prediction of the clinical course of the disease [3,5]. Histologic grading, a predictor of tumor aggressiveness in adults, has not been proved to be an indicative factor in pediatric age [3,7]. Moreover immunohistochemical and ultrastructural analyses can not identify the two forms. Chromosomal abnormalities have been reported in cases of infantile fibrosarcoma: trisomy 11, deletion of long arm of 17, and a [12,13] translocation; clonal translocations, translocations [2,15] and [7,22], have also been described in adult-type fibrosarcoma. In our study, the cases were observed before cytogenetic investigation to differentiate the infantile fibrosarcoma from the adult one, so as to improve our knowledge on their clinical behavior [6,8,9].

Despite their common histological aspect and slightly different characteristics at presentation, the two types of fibrosarcomas show different clinical behavior. Infantile fibrosarcoma has an initial rapid growth but an indolent evolution in most instances, so that local recurrence is common but metastatic spread is rare and survival is greater than 80%, especially for tumors originating on the extremities [2,6,10,11]. Spontaneous regression of congenital fibrosarcomas has been reported [12] and some authors believe that it should be considered an intermediate form between fibromatosis and adult fibrosarcoma [4,13]. In older children and in adolescents, fibrosarcomas tend to behave more like to their adult counterparts: in these cases LR often precedes dissemination and the survival rate is less than 60% [1,4,5].

The goal of treatment for both infantile and adult fibrosarcoma is the complete nonmutilating excision of the tumor mass [3,6]. An initial radical removal is correlated with the site and the size of the tumor; and is linked to the best prognosis: in our series 11 of 12 Gr I patients are alive (9 in CR and 2 with disease). The

### TABLE III. Overall Survival at 10 Years According to Age, IRS Group, Site, and Protocol

<table>
<thead>
<tr>
<th>Group</th>
<th>Site</th>
<th>Age</th>
<th>Patients</th>
<th>Events</th>
<th>% (CI 95%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRS group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Extremity</td>
<td>&lt; 2</td>
<td>14</td>
<td>3</td>
<td>78.6 (57.0–100)</td>
<td>0.3</td>
</tr>
<tr>
<td>II and III</td>
<td>Axial</td>
<td>&gt; 2</td>
<td>11</td>
<td>6</td>
<td>51.0 (20.0–82.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Site</td>
<td>Protocols</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMS-79</td>
<td></td>
<td></td>
<td>10</td>
<td>6</td>
<td>46.7 (14.2–79.2)</td>
<td>0.059</td>
</tr>
<tr>
<td>RMS-88</td>
<td></td>
<td></td>
<td>15</td>
<td>3</td>
<td>80.0 (60.0–100)</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

Fibrosarcoma is a STS of adult and pediatric age, but in infants and young children it is generally considered a separate entity because of its markedly different behavior.

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radicality of the excision at diagnosis was the only significant prognostic factor in our analysis (Table III).

The resection with microscopic residuals does not assure the achievement of the cure. In cases with infantile fibrosarcoma, CT might be recommended if a re-excision is not feasible, while RT is rarely delivered. Considering the low aggressivity of this form some authors recommend only a strict follow-up. The benefit of CT was not evident in our experience. Those two patients treated with surgery alone are alive without disease (one after LR treated with CT and mutilating surgery) while the other two, treated also with CT, had an unfavorable outcome. In patients with inoperable infantile fibrosarcoma, several reports describe good response to CT, adopting different regimens: vincristin and dactinomycin are the recommended drugs in some cases associated with ifosfamide or cyclofosfamide [14–18]. Our data do not support these experiences: in our group the two Gr III patients aged < 2 years, who received neoadjuvant CT, showed a poor response to VAC as well as to VAIA regimens.

In older patients, an aggressive excision should be the treatment of choice: RT is mandatory when adequate margins can not be obtained and a reoperation is not possible [1,19]. CT is indicated preoperatively in cases of inoperable tumors, even if its efficacy is still debated, and postoperatively because of the frequent occurrence of micrometastases [20,21]. In our experience, 10 of 11 patients had CT: no data are available concerning its efficacy in Gr I–II. Three out of five Gr III cases were treated with VAC achieving a partial response, while two treated with VAIA showed a minor response. Among these five patients those two who underwent radical surgery and one of the three treated with RT achieved the CR.

The use of the term infantile type rather than adult type of fibrosarcoma is highly influenced by the age of the patient. In the absence of other tools, age is a crucial point in planning the treatment and defining the outcome of the disease. Many cases of fibrosarcoma are diagnosed in the first year of life and 50% of them are congenital. Some authors consider as infantile fibrosarcoma those forms diagnosed before 4–5 years of age [5,10,11,13], while others accept only those cases within 2 years [3,22]. In a group of 12 neonatal fibrosarcomas, the outcome was favorable in all the patients: 10 had had a complete surgery and only 1 received postoperative CT [23].

On the other hand, patients of intermediate age (3–6 years) remain a therapeutic challenge for oncologists, surgeons, and radiotherapists.

In our group, the 14 patients under 2 years of age (11 < 1 year and 7 of them congenital) had a better outcome than the older ones. Most of these tumors were not invasive and could be excised completely at diagnosis: 11 of 14 are alive without disease (5 of 7 among the congenital forms), 2 are DOD and 1 died because of cardiac malformation; in particular none of 10 patients with a primary tumor on extremities DOD. LR was the main cause of treatment failure, but 3 of 4 relapsed patients were cured with further multimodal therapy.

Among the 11 patients aged > 2 years, 5 achieved first CR (but 2 died of second tumor), 2 are alive with disease after local and distant relapse, 4 DOD following LR and metastatic spread. We must underline that none of the patients were cured after LR or pulmonary metastases. The outcome of the three patients aged between 2 and 5 years, whose forms could be considered infantile, was similar to that of the older patients. Only one is alive in first CR after multimodal intensive treatment, one is alive with disease after LR and pulmonary metastases, while one patient died of PD.

Nowadays mutilating surgery is recommended only in case of poor response after primary CT or in case of relapse, for infantile as well as for adult fibrosarcoma. In our group, 4 of 25 patients had a mutilating excision. It was performed initially in one case who achieved the CR, at delayed surgery in one adolescent achieving the CR, and after LR in other two patients (only one infant obtained the CR). At present, we would avoid initial mutilating surgery and start with neoadjuvant therapy.

CONCLUSIONS

The results achieved in our series are similar to those reported in the literature [3,5,17]. The significantly better OS registered in the patients of the RMS-88 protocol is probably related to the high number of complete resection at diagnosis (n = 9) and the high rate of patients < 2 years registered in this study (n = 10).

An initial complete excision was the treatment of choice and was related to the best outcome, being the only significant prognostic factor. The presence of microscopical residuals after primary surgery caused a LR in 2 of 4 patients: CT was not effective in these patients. Neoadjuvant CT determined a partial response in two cases, in particular no conclusions are possible in this series concerning the efficacy of CT for infantile fibrosarcomas, as reported in previous experiences.

Patients under 2 years of age had a better prognosis than the older ones; however, this favorable outcome was influenced by the tumor site and the surgical treatment. In fact, most of them had a tumor on extremities that could be excised at diagnosis. Moreover, most of the infantile fibrosarcomas with LR were cured by aggressive therapy (including mutilating surgery). In older patients, a multimodal treatment is required as in adults: in our group all the patients who relapsed had an unfavorable outcome.
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REFERENCES