Soft-tissue sarcomas of the extremities in patients of pediatric age

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Abstract

Purpose The extremity site is a peculiar location for soft-tissue sarcomas (STS) of children and adolescents. Here we report the experience of the Pediatric Oncology Unit of the Istituto Nazionale Tumori of Milan, Italy, concerning 204 patients with STS of the limbs treated between 1977 and 2006.

Methods The study series included 52 patients with rhabdomyosarcoma (RMS) (65% of which were of the alveolar subtype), nine with extraosseous Ewing sarcoma and 143 with non-rhabdomyosarcoma soft-tissue sarcomas (NRSTS), 38% of which were synovial sarcoma. Patients were treated with a multimodality approach including surgery, chemotherapy, and radiotherapy.

Results For the RMS patients, the 5-year event-free survival (EFS) rate was 37.1%, with distant metastases being the main cause of treatment failure. The outcome was particularly poor for patients with large invasive tumors, hand/foot involvement and/or nodal or distant metastases,

and for patients who were not given radiotherapy. For the extraosseous Ewing sarcoma cases, 5-year EFS was 74%. For the NRSTS cases, the 5-year EFS was 72.6%: tumor size and local invasiveness, tumor grade, malignant peripheral nerve sheath tumor (MPNST) histology, and distant metastases were the main prognostic factors.

Discussion While the limbs are the most common sites of NRSTS and are often characterized by a more favorable prognosis than for axial tumors, the clinical features of extremity RMS often differ from those of RMS of other sites, with a higher incidence of unfavorable prognostic factors (e.g., alveolar subtype) and consequently unsatisfactory treatment results. The treatment of these patients is complex and necessarily multidisciplinary, and it demands not only adequate experience of treating children and adolescents in clinical trials, but also particular skills in the field of orthopedic surgery.

Keywords Extremity site ·
Rhabdomyosarcoma of extremities ·
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Extraosseous Ewing sarcomas

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Introduction

Soft-tissue sarcomas (STS) form a heterogeneous group of mesenchymal extraskeletal malignancies that account for <1% of all malignant tumors in the general population. In childhood and adolescence, however, they represent about 8% of all neoplasms, 50–60% of them being rhabdomyosarcomas (RMS), while the remainder form the varied group of so-called non-rhabdomyosarcoma soft-tissue sarcomas (NRSTS) [1, 2]. RMS is a highly malignant

neoplasm with peculiar features (generally including a good response to chemotherapy) and it is one of the most typical tumors of childhood [1]. Most NRSTS histotypes are typical of adult age, and their aggressiveness—and their propensity to metastasize in particular—usually correlates with the grade of malignancy [2]. Extraosseous Ewing sarcomas/peripheral primitive neuroectodermal tumors (EW/pPNET) are tumors that, by definition, have a high grade of malignancy: they are generally skeletal tumors, but a few cases occur in soft tissues.

Soft-tissue sarcomas can develop virtually anywhere in the body, generally as a progressively expanding soft-tissue mass, sometimes associated with pain, functional impairment, and other specific symptoms correlating with the anatomical location involved. STS sometimes develops in the extremities: the limbs are the most common site for NRSTS, and are generally characterized by a more favorable prognosis than axial tumors, while involvement of the extremities in RMS is usually associated with the unfavorable alveolar subtype and older age, and is considered an adverse prognostic factor [1, 2].

In this study, we review our single institutional experience of extremity STS treated at the Pediatric Oncology Unit of the Istituto Nazionale Tumori of Milan, Italy, over a 30-year period.

Patients and methods

In a database of 717 STS patients under 18 years old diagnosed between 1977 and 2006, we identified the hitherto-untreated patients with tumors occurring in the extremities for whom full details on clinical features, treatment, and outcome were available. The histological diagnosis was established by pathologists at our institution before starting any treatment. NRSTS tumor grading was based on the French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system (a three-grade classification defining a score in relation to tumor differentiation, mitotic index, and tumoral necrosis) [3].

The present study thus considered 204 patients with extremity STS, i.e., 52 cases of RMS, nine of extraosseous EW/pPNET and 143 of NRSTS.

Clinical grouping

Local tumor extent was assessed by computerized tomography (CT) and/or magnetic resonance imaging (MRI) in most of the cases (a few NRSTS patients had been operated prior to admission to our center, after a preoperative evaluation based on ultrasound alone). Staging was based on chest X-ray and/or chest CT scan, abdominal ultrasound

and whole-body bone scan (bone marrow aspirates and/or biopsies were also collected from RMS and EW/pPNET cases). Regional lymph nodes were evaluated by physical examination and/or ultrasound; five RMS patients had inguinal biopsies (in spite of clinically negative nodes), and in all cases nodes were confirmed as being uninvolved by the pathologist.

Disease was staged according to the clinical tumor-node-metastases (TNM) classification [4] and the Inter-group Rhabdomyosarcoma Study (IRS) post-surgical grouping system [5]. According to the former, T1 are tumors confined to the organ or tissue of origin, while T2 lesions invade contiguous structures; T1 and T2 groups are further classified as A or B depending on whether the tumor's diameter is $\leq$ or >5 cm respectively. Regional node involvement is indicated as N0 or N1, and distant metastases at onset as M0 or M1, based on histological or clinical/radiological assessments [4]. The IRS system categorizes patients in four groups based on the amount and extent of residual tumor after initial surgery: group I includes completely excised tumors with negative microscopic margins, group II indicates grossly resected tumors with microscopic residual disease and/or regional lymph nodal spread, group-III patients have macroscopic residual disease after incomplete resection or biopsy, and group-IV patients have metastases at onset [5].

For the purpose of this study, tumor sites of origin were classified as follows: upper proximal sites (shoulder girdle, axilla, arm), upper distal sites (elbow, forearm, hand—including fingers), lower proximal sites (buttock, thigh), lower distal sites (knee, popliteal space, leg, foot).

Treatment

Patients were treated using a multimodality therapeutic approach including surgery, chemotherapy, and radiotherapy, based on the ongoing protocols at the time of their diagnosis. The overall treatment strategy did not change substantially over the years. Primary excision was attempted only if complete, non-mutilating resection was considered feasible; otherwise a biopsy was taken, and chemotherapy (and/or radiotherapy) was administered to shrink the tumor and make it more amenable to subsequent surgery. Surgery was defined as complete (IRS group I) when the histological margins were free, thus including ablative surgeries, compartmental resections (en bloc resection of the tumor and of the entire compartment in which the tumor was anatomically confined), and wide excisions (en bloc excisions through normal tissue, beyond the reactive zone but within the muscular compartment, removing the tumor with its pseudocapsule). Marginal resections (IRS group II) were defined as those coming just

outside the pseudocapsule, with suspected microscopic residual disease (marginal resections according to Enneking's criteria), and cases with microscopically infiltrated margins (what Enneking defined as intralesional) [6]. The term *primary re-excision* is used to mean any re-surgery performed up to 2 months after an initially inadequate resection and before any other treatment, while *delayed surgery* means operations performed after primary chemotherapy or radiotherapy.

Radiotherapy was required for patients considered at risk of local failure (after marginal resection or in the case of large tumors). External beam irradiation was delivered using megavoltage photon or electron beam energies, with conventional fractionation (1.8–2.0 Gy daily for 5 days a week, with total doses ranging from 45 to 64 Gy) or hyperfractionated accelerated schedules (two daily fractions of 1.6 Gy, at 6 to 8-h intervals, for a total dose of 44.8 Gy, or three daily fractions of 1.5 Gy, at 5-h intervals, for a total dose of 48–54 Gy). The radiation fields included the initial tumor volume plus 2–3 cm margins.

Chemotherapy was part of the treatment program since 1977 for most patients, i.e., all RMS and EW/pPNET cases, unresectable and/or high-grade or large NRSTS. Different chemotherapeutic regimens were used over the years, according to protocols adopted at the time: all regimens included cyclophosphamide or ifosfamide, together with anthracyclines (doxorubicin or epirubicin), actinomycin-D, and/or vincristine. In patients with measurable disease, response to chemotherapy was recorded after three courses, based on the radiological evidence of a reduction in the sum of the products of the perpendicular diameters of all measurable lesions, and defined as follows: complete response (CR) = complete disappearance of disease; partial response (PR) = maximal tumor reduction >50%; minor response (MR) = maximal reduction >25%. Stable disease, or a reduction <25% was classified as no response, while an increase in tumor size or the detection of new lesions was considered as progression of disease.

Statistical methods

Event-free survival (EFS) and overall survival (OS) were estimated using the Kaplan–Meier method [7]. Patients were evaluated from the time of their histological diagnosis up to their latest uneventful follow-up visit or disease progression, recurrence or death of any cause for EFS, and up until their death for OS. Local relapse-free survival (LRFS) rates were calculated from diagnosis to local progression or relapse. Metastases-free survival (MFS) rates were calculated from diagnosis to the onset of distant metastases. The log rank test was used to compare the survival curves of patient subgroups in a univariate analysis to ascertain the potential value of

various prognostic factors [8]. Patient follow-up, as at January 2007, ranged from 6 to 320 months (median 120 months).

Results

For the overall series of 204 patients, 5-year EFS and OS were 63.5% (standard error 3.5) and 75.7% (3.1) respectively. Figure 1 shows the EFS curves for the different histotypes.

Rhabdomyosarcoma

Fifty-two patients with limb RMS were included in the study (27 males, 25 females; age 1–21 years, median 11 years).

The interval between the first tumor-related symptoms (swelling in all cases, associated with pain in nine) and the diagnosis of RMS was from 2 weeks to 9 months (median 3 months). Thirty tumors occurred in the lower extremities, 22 in the upper. Thirty-four patients (65%) had the alveolar subtype, 26 (50%) were more than 10 years old, 15 (29%) had regional node involvement, and 15 (29%) had distant metastases at onset (mainly involving the lung, but there was bone and bone-marrow dissemination in 46% of M1 cases). Tumor size was 2–18 cm, median 11 cm.

Complete tumor resection was achieved in 19 patients, five at the first surgical attempt, two at primary re-excision, and 12 at delayed surgery (one amputation). Radiotherapy was given in 38 cases. All patients received chemotherapy, and the response in evaluable cases was: four CR, 26 PR, two MR, three no response. With a median follow-up of 130 months (range 12–320 months) for the whole group, the 5-year EFS was 37.1%, LRFS 78.6%, MFS 41.1%, OS 48.9%. Survival rates did not improve over the years.

Fig. 1 Event-free survival by histotype

Recurrence (after a median 10 months, range 4–61 months) was local in ten cases and distant in 31. Two patients developed second malignancies: one was a case of anaplastic astrocytoma developing 88 months after the RMS was diagnosed (he died of his second tumor), and the other was a case of acute myeloid leukemia 21 months after the RMS was identified (this patient was lost to follow-up).

Table 1 shows the analysis of the risk factors. Alveolar and embryonal subtypes had much the same outcome, nor were there any differences in survival terms between distant locations (31 cases, 5-year OS 49.5%) and proximal sites (21 cases, OS 48.2%), the upper distant site being the most favorable location (OS 63.1%).

Twelve cases of RMS of the foot (eight) and hand (four) were analyzed separately: the histology was alveolar in seven cases and embryonal in five. Both EFS and OS were 33.3% at 5 years (as opposed to EFS 38.3%, OS 54.4% for extremities other than the foot/hand, P = not significant).

As for tumor size and local invasiveness, 60% of the cases were T2B tumors: this subset of patients was characterized by an unfavorable outcome (5-year OS 25.3%). Particularly poor survival rates were observed for N1 (OS 16.7%) and M1 patients (0%). In all 15 N1 cases, the nodal involvement was clinically detectable.

Concerning the treatment, a correlation emerged between radiotherapy and outcome: 5-year EFS and OS

Table 1 Predictors of event-free survival (EFS) and overall survival (OS) for rhabdomyosarcoma patients

Variable	Numbers	5-year EFS	Univariate P	5-year OS	Univariate P
Treatment period					
1977–1989	28	39.3%		50.0%	
1990–2003	24	33.7%	0.5654	45.8%	0.9797
Sex					
Male	27	39.5%		53.3%	
Female	25	34.3%	0.9698	44.5%	0.9898
Age at diagnosis					
≤10 years	26	45.3%		63.1%	
>10 years	26	29.2%	0.1719	33.6%	0.0100
Histology					
Alveolar	34	37.8%		48.6%	
Embryonal	16	36.5%		46.4%	
NOS	2	0%	0.9630	100%	Not feasible
Primary tumor site					
Lower distant	14	28.6%		42.9%	
Lower proximal	16	39.3%		50.5%	
Upper distant	17	41.2%		63.1%	
Upper proximal	5	40.0%	0.8313	40.0%	0.7874
Local invasiveness					
T1	14	57.1%		92.2%	
T2	38	30.1%	0.0478	33.7%	0.0087
Tumor size					
≤5 cm	13	61.5%		84.6%	
>5 cm	39	28.9%	0.0219	37.1%	0.0147
Nodal involvement					
N0	37	47.5%		62.5%	
N1	15	10%	0.0073	16.7%	0.0012
Distant metastases					
M0	37	52.3%		68.0%	
M1	15	0%	<0.0001	0%	<0.0001
IRS group					
Group I	7	42.9%		71.4%	
Group II	8	62.5%		75.0%	
Group III	22	46.7%		63.2%	
Group IV	15	0%	<0.0001	0%	<0.0001

NOS not otherwise specified,
IRS intergroup
rhabdomyosarcoma study

were 42.8 and 57.1% for patients who were given radiotherapy versus 21.4% ($P = 0.0616$) and 28.6% ($P = 0.1744$) for patients who were not.

Extrasosseous Ewing sarcomas/peripheral primitive neuroectodermal tumors

Nine patients (five males and four females aged 1–18 years, median 12 years) were analyzed.

The interval between the onset of symptoms (swelling in eight cases, pain in one) and the final diagnosis was 2 weeks to 9 months (median 3 months). The tumor site was an upper limb in five cases (three proximal) and a lower limb in four (two proximal). Tumor size was 1–10 cm, median 4 cm; 7/9 patients had tumors <5 cm in size; six were classified as T1A, one as T2A, two as T2B. None of the patients had nodal involvement at diagnosis, one had distant metastases (in the lung). According to the IRS staging system, four cases were group I, two were group II, two were group III and one was group IV.

Five patients underwent complete resection, four at diagnosis, one at delayed surgery. None had amputation. Radiotherapy was administered to six cases, while all nine received chemotherapy (one CR and two PR out of three cases evaluable for response). With a follow-up of 23–209 months (median 70 months), 5-year EFS and OS were 74% and 100%, respectively. Three patients had recurrent disease in the regional lymph nodes (15 months after first diagnosis), the central nervous system (after 33 months) and the bone (after 127 months): one patient died of disease (141 months after diagnosis), while two were in second remission at the time of this report (55 and 80 months respectively), after their disease recurred.

Non-rhabdomyosarcoma soft-tissue sarcomas

This group included 143 patients (89 males, 54 females; age 1 month to 19 years, median 13 years).

The first symptom related to the tumor was pain in 11 cases and swelling in all the others; the time to diagnosis ranged from 1 week to 5 years (median 4 months), but was more than 1 year in 20 cases. The different histotypes included in the NRSTS group were: (a) synovial sarcoma, 55 (29 biphasic, 21 monophasic, 5 not-otherwise-specified (NOS)); (b) epithelioid sarcoma, 15; (c) liposarcoma, 14; (d) malignant peripheral nerve sheath tumor (MPNST), 9 (4 associated with neurofibromatosis type 1); (e) clear cell sarcoma, 7; (f) infantile fibrosarcoma, 7; (g) dermatofibrosarcoma protuberans, 6; (h) hemangiopericytoma, 5; (i) leiomyosarcoma, 4; (j) alveolar soft part sarcoma, 4; (k) adult-type fibrosarcoma, 4; (l) malignant fibrous

histiocytoma, 3; (m) angiosarcoma, 2; (n) fibromyxoid sarcoma, 1; (o) extraskeletal myxoid chondrosarcoma, 1; and (p) spindle-cell sarcoma NOS, 6.

Tumor grade was available for 94 cases, and was as follows: 21 G1, 31 G2, 42 G3.

The most frequent site of origin was the thigh (46 cases). In 21 cases, tumor arose in hand and foot: seven of these cases had epithelioid sarcoma (and five of them had tumor of finger) and six had synovial sarcoma. The median tumor size was 5 cm (range 1–20 cm). Only three cases had clinical nodal involvement at onset (two patients with clear cell sarcoma, one with epithelioid sarcoma) and five had distant metastases (all to the lung).

Most patients were classified as IRS group I: complete tumor resection was achieved after primary re-excision in 72/96 cases. Seven patients were amputated. Adjuvant chemotherapy was given to 39 patients, and post-operative radiotherapy to 18. Survival rates did not correlate with either chemotherapy (the 5-year EFS in patients who had chemotherapy was 74.4%, as opposed to 84.9% in those who did not) or irradiation (82.4% vs 80.2%). When only patients with high risk features, i.e., high grade (G3) and large tumor size (>5 cm), were considered, however, the 5-year EFS was 44% in the nine patients who were given adjuvant chemotherapy, and 25% in the four cases who were not (P -value not significant).

Twenty-one patients were classified as IRS group II (microscopic residual disease after surgery); 14 of these received subsequent chemotherapy, and all but two received radiotherapy (one of the two given no radiotherapy relapsed locally).

Twenty-one patients were biopsied as the first surgical attempt (IRS group III): after chemotherapy, 16 underwent delayed surgery (two amputations) and five were irradiated. Response to chemotherapy in evaluable IRS group III/IV cases was: two CR, seven PR, two MR, 11 no response.

With a median follow-up of 118 months (range 6–260 months), 5-year EFS was 72.6%, LRFS 85.7%, MFS 77.5%, and OS 84.2%. The results improved significantly over the years. The median time to recurrence was 13 months (range 1–144 months). One patient developed radiation-induced bone sarcoma 124 months after the diagnosis of MPNST, and died of the second disease. Table 2 shows the univariate analysis by clinical risk factors. Local invasiveness and tumor size were the main prognostic factors: patients with both these adverse variables (T2B patients) had a 5-year EFS of 34.2%. MPNST patients and cases with metastases had poor outcomes. Tumor grade also proved a significant variable. On the contrary, no differences emerged between distal and proximal sites (5-year EFS were 74.9 and 70.4% respectively); patients with tumor of hand and foot had a 5-year EFS of 65.8%.

Table 2 Predictors of event-free survival (EFS) and overall survival (OS) for non-rhabdomyosarcoma soft tissue sarcoma patients

Variable	Numbers	5-year EFS	Univariate <i>P</i>	5-year OS	Univariate <i>P</i>
Treatment period					
1977–1989	67	62.2%		72.9%	
1990–2003	76	82.4%	0.0031	95.3%	0.0007
Sex					
Male	89	76.7%		86.2%	
Female	54	65.9%	0.3688	81.0%	0.3890
Age at diagnosis					
≤10 years	52	79.1%		94.0%	
>10 years	91	68.6%	0.2329	78.6%	0.0317
Histology					
Synovial sarcoma	55	73.3%		84.7%	
MPNST	9	22.2%		44.4%	
All others	79	78.3%	<0.0001	89.2%	<0.0001
Histological grade					
G1	21	95.2%		100%	
G2	31	62.0%		81.0%	
G3	42	54.1%	0.0067	68.55	Not feasible
Primary tumor site					
Lower distant	37	68.2%		85.5%	
Lower proximal	56	71.4%		81.2%	
Upper distant	31	82.8%		93.0%	
Upper proximal	19	68.0%	0.5308	76.0%	0.3338
Local invasiveness					
T1	82	92.3%		94.4%	
T2	61	45.2%	<0.0001	69.5%	<0.0001
Tumor size					
≤5 cm	74	93.0%		97.0%	
>5 cm	69	49.0%	<0.0001	69.3%	<0.0001
Nodal involvement					
N0	140	72.7%		84.6%	
N1	3	66.7%	0.8461	66.7%	0.4582
Distant metastases					
M0	138	74.5%		86.8%	
M1	5	20.0%	<0.0001	20.0%	<i>P</i> < 0.0001
IRS group					
Group I	96	80.5%		87.4%	
Group II	21	71.4%		95.2%	
Group II	21	48.2%		71.9%	
Group IV	5	20.0%	<0.0001	20.0%	<i>P</i> < 0.0001

MPNST malignant peripheral nerve sheath tumor, IRS intergroup rhabdomyosarcoma study

Being the most frequent histotype (55 cases), synovial sarcoma patients were also analyzed separately. EFS and OS at 5 years were 84.7 and 73.3% respectively. No difference in outcome was observed according to histological subtype and tumor site, while tumor size (5-year EFS was 96.4% for tumor ≤5 cm, and 44.8% for size >5 cm), local invasiveness (88.6% for T1 and 58.2% for T2), and IRS group (78.6% for group I, 78.6% for group II, 27.8% for

group III, and 0% for group IV) significantly influence EFS rate.

Discussion

This study describes the experience of a single referral center for pediatric patients with STS of the extremities.

These tumors form a particular, heterogeneous group of malignancies, whose clinical features often differ from those of STS at other sites. Starting with the epidemiological data, a malignant tumor developing at any site other than the limbs is more likely to be an embryonal RMS in pediatric age [1], whereas our series shows that the most frequent extremity STS in this age group is synovial sarcoma (55 cases) followed by alveolar RMS (34 cases), with embryonal RMS in third place (16 cases), with an incidence resembling that of such a rare histotype as epithelioid sarcoma (15 cases).

In fact, the site of origin in a limb is the most common location for NRSTS (63% of our previously published series) [9]. The present subset of extremity cases confirms our main findings in NRSTS of all sites, reported elsewhere [9–11], i.e., quite a satisfactory overall outcome (5-year OS 84%), the prognostic role of IRS grouping, grade of malignancy, tumor size and local invasiveness, the poor prognosis for patients with the MPNST histotype [12] and with metastases at diagnosis. It is worth noting that treatment for extremity NRSTS proved more effective over the years, while this was not the case for RMS.

The clinical—and probably biological—peculiarity of soft part tumors arising in the limbs is especially evident for RMS, where the extremities are involved in around 15–20% of cases [13–17]. Table 3 compares ours with a large series of RMS of all sites, showing that RMS of the extremities are more likely to occur in adolescents, to be of alveolar subtype, to be large in size and locally invasive, and to spread to the lymph nodes. All these clinical variables are known to have a negative influence on the final outcome. Various previous reports have confirmed that the results of treatment for extremity RMS are suboptimal, to say the least, by comparison with RMS cases at other sites

[13–17]. This may be for various reasons, particularly the strict inter-relationships between the site variable and other prognostic factors (histology, tumor size, node involvement, and patient's age). A particular finding of our series, however, is the remarkably poor outcome of embryonal RMS.

Another important factor is the particularly high tendency of extremity RMS to develop distant metastases. In our series, 29% of patients had distant metastases at the time of diagnosis (while the usual rate for RMS of all sites is 10–20%), and bone and bone marrow dissemination were particularly frequent. Our analysis also shows that most recurrences occurred with distant metastases (5-year LRFS was 78.6%, while MFS was 41.1%), unlike the situation in RMS at other sites, where local progression or recurrence is the main cause of treatment failure. Our study also confirms a particularly poor outcome for RMS of the foot or hand (5-year OS 33.3%) [18–20].

To summarize, analyzing the clinical features of this large group of pediatric cases of extremity STS confirms that the treatment of these patients is complex and necessarily multidisciplinary. The clinical approach to these tumors must rely on an adequate experience of treating children and adolescents with RMS and NRSTS in clinical trials, but this particular type of location also demands particular skills in the field of orthopedic surgery. It is important to note that the role of surgery for limb STS has evolved over the years, from primary treatment modality to part of a multidisciplinary approach, and from demolitive operations to more conservative organ-sparing procedures [21–23]. Limb salvage is the surgical treatment of choice, but should be recommended as the first surgical procedure only if the surgeon judges it to be feasible with free histological margins; if not, a biopsy should be taken and surgery reconsidered after chemotherapy (and/or radiotherapy). Primary re-excision has an important role in cases of inadequately planned primary excision (generally performed before admission to a specialized center and without knowing the histotype), when it is best to re-operate on the tumor bed to obtain clear margins [24, 25].

An open issue concerns the need for histological staging of regional lymph nodes: this is generally not recommended for RMS and NRSTS at other sites, but would be more important for extremity STS for proper patient staging and adapting the intensity of treatment [21, 26–28]. For RMS cases in particular, North-American IRS studies have reported that around 40–50% of patients whose lymph nodes were assessed surgically (by biopsy or dissection) revealed nodal involvement [15–17]: the IRS IV study, for instance, showed that 17% of patients with clinically negative nodes had microscopic evidence of nodal spread [16]). Moreover, the final outcome was reportedly better in patients with histologically confirmed negative nodes

Table 3 Comparison of clinical findings in extremity rhabdomyosarcoma (current series) and rhabdomyosarcoma of all sites (large series from the Italian Cooperative Group RMS'96 protocol—courtesy of Prof. M. Carli, Padova)

	Extremity RMS (INT series)	RMS of all sites ^a (Italian series)
Number of patients	52	284
Period	1977–2006	1996–2005
Median age	11 years	5 years
Age >10 years	50%	25%
Alveolar histotype	65%	26%
T2	73%	52%
Size >5 cm	75%	50%
N1	29%	17%
5-year EFS	37.1%	67.3%
5-year OS	48.9%	80.7%

^a About 10% were extremity RMS

(pN0) than in those whose nodes were judged to be negative at clinical or radiological evaluation alone (cN0) [15]. Unfortunately, our series adds no significant information on this issue: in the past, regional lymph nodes were evaluated by physical and/or radiological examination, and few children were biopsied in the event of clinically negative nodes (and none of those who were biopsied revealed microscopic tumor spread). Based on recommendations in the literature and European protocol guidelines, we currently suggest regional nodal biopsy for limb RMS. Studies are underway to evaluate the utility of sentinel lymph node biopsy [28, 29]. The indication for nodal biopsy in cases of NRSTS affecting the extremities is more controversial: some histotypes (i.e., epithelioid sarcoma, clear cell sarcoma, alveolar soft part sarcoma, and angiosarcoma) would appear to have a greater tendency than others to spread to regional lymph nodes, and biopsy may be indicated in such cases [21, 27], though pediatric cases seem to have a weaker propensity for nodal spread than in their adult counterpart (particularly for epithelioid sarcoma [30]) so further studies are needed to clarify this matter.

Of course, good coordination between surgeon, pediatric oncologist, pathologist, and radiotherapist is mandatory to plan a successful multimodality treatment for these patients, and the pediatric oncology team should also consider procedures such as regional arterial perfusion [31, 32] or intraoperative brachytherapy, which are generally used more for adult STS of the extremities but may have a role in some specific pediatric cases.

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