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ORIGINAL REPORT

Pediatric Malignant Peripheral Nerve Sheath Tumor: The Italian and German Soft Tissue Sarcoma Cooperative Group

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ABSTRACT

Purpose
To assess the value of chemotherapy and radiotherapy in children with malignant peripheral nerve sheath tumors (MPNSTs) and to identify risk factors associated with outcome.

Patients and Methods
A total of 167 untreated eligible patients enrolled onto the Italian and German studies between 1975 and 1998 entered this analysis. Seventeen percent of patients had neurofibromatosis type 1 (NF1). Chemotherapy was administered to 74% of patients; radiotherapy was administered to 38% of patients.

Results
With a median follow-up of 7 years, 5-year overall survival (OS) and progression-free survival (PFS) were 51% and 37%, respectively. The 5-year OS and PFS by Intergroup Rhabdomyosarcoma Study (IRS) groupings were as follows: group I, 82% and 61%; group II, 62% and 37%; group III, 32% and 27%; group IV, 26% and 21%, respectively. Univariate analysis identified IRS groups, size, invasiveness, primary site, age, and presence of NF1 as prognostic factors; multivariate analysis identified absence of NF1, tumor invasiveness T1, IRS groups I to II and extremity of primary site as independent favorable factors for OS. A trend was observed toward a benefit from radiotherapy after initial gross resection. The overall response rate to primary chemotherapy, including minor responses, in group III patients was 45%.

Conclusion
MPNST is an aggressive tumor for which complete surgical resection is the mainstay of successful treatment. Postoperative radiotherapy may have a role in improving local control in patients with minimal residual tumor. The reported responses to primary chemotherapy suggest that it may be effective in patients with tumor considered unresectable at diagnosis.

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INTRODUCTION

A malignant peripheral-nerve sheath tumor (MPNST) is a spindle cell sarcoma that often arises in proximity to peripheral nerves or shows nerve sheath differentiation. It occurs mainly in adults and only 10% to 20% of MPNSTs are diagnosed in the first two decades of life.[1-4] They nonetheless represent one of the most frequent nonrhabdomyosarcomatous soft tissue sarcomas in pediatric age.[1-4] The term MPNST is preferred to malignant schwannoma or neurofibrosarcoma because these tumors can have the appearance of any nerve sheath cell, including Schwann cells, perineural fibroblasts, or fibroblasts.[1-4] Usually, the clinical presentation is an enlarging soft tissue mass arising in the trunk, extremities, or head and neck region, with or without pain and dysesthesia; most of the lesions are deep seated. A nerve of origin can be identified in more than 70%

of patients.[1-4] MPNST may develop in a pre-existing neurofibroma in approximately 40% of patients, and particularly in patients with neurofibromatosis type 1 (NF1).[2,5-7] Patients with NF1 have a greater risk of multiple neural crest-derived tumors and other malignancies. The onset of MPNST in these patients is well known; in different reported series of MPNSTs, 21% to 67% of tumors occurred in patients with NF1.[7,8] A lifetime MPNST risk of 8% to 13% was reported in a recent study, however.[9]

Because of the rarity of this tumor, there are few published reports and little information is available on its clinical management, particularly in pediatric patients.[1,3,4,10-18] MPNST is reported to behave aggressively, with a high rate of local recurrence and a propensity to metastasize. The outcome seems favorable only when a small and localized tumor can be excised completely.[1] Surgical resection represents the mainstay of treatment, whereas the role of adjuvant treatment is unclear as yet; the effectiveness of chemotherapy and radiotherapy in this tumor is a relevant issue awaiting some answers.

To contribute additional information on the clinical management of childhood MPNST, we report on a large series of pediatric patients recruited over a 25-year period according to the protocols of the German Cooperative Soft Tissue Sarcoma Group (CWS), the Italian Cooperative Group (ICG) on childhood soft tissue sarcoma, and the Istituto Nazionale Tumori (INT) of Milan, Italy.

PATIENTS AND METHODS

A total of 167 consecutive previously untreated children and adolescents with a diagnosis of MPNST were enrolled onto different protocols between December 1975 and December 1998. The German studies (CWS-81, CWS-86, CWS-91, and CWS-96) included 91 patients, whereas 76 patients were enrolled at Italian centers (51 in the ICG protocols RMS-79, RMS-88, and RMS-96; 25 in the INT protocols up until 1996, after which INT patients were included in the ICG studies). This set of patients represented 5% of all pediatric soft tissue sarcomas registered by the two Cooperative Study Groups during the study period (N = 3,265).

All patients, or their guardians, provided their informed consent to the studies, according to the established rules. Clinical data, treatment modalities, and outcomes were reviewed. The histopathologic diagnoses were reviewed centrally by the pathology panel of each cooperative group at the time of diagnosis. All pathology forms were reviewed for the purpose of this analysis. Unfortunately, tumor grade was available only in a minority of patients because the data were not reported in early patients, or when only a biopsy specimen was available.

Clinical Grouping

Investigations at diagnosis included physical examination, evaluation of local extent with computed tomography (CT) and/or nuclear magnetic resonance scan, staging evaluation with conventional chest x-ray or chest CT scan, abdominal ultrasound, and whole body bone scan.

Disease was staged according to both the clinical TNM pretreatment staging system[19] and the Intergroup Rhabdomyosarcoma Study (IRS) postsurgical grouping system.[20] The TNM definition of 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 more than 5 cm, respectively. Regional node involvement was designated as N1 (no node involvement, N0); distant metastases at onset was designated as M1 (no metastases, M0).[19] After initial surgery, patients were classified according to the IRS system: group I includes completely excised tumors, group II indicates grossly resected tumors with microscopic residual disease and/or resected regional lymph node involvement, group III includes patients with gross residual disease after incomplete resection or biopsy, and group IV comprises patients with metastases at onset.[20]

Treatment

Patients were treated mainly using multimodality therapeutic approaches, including surgery, chemotherapy, and radiotherapy, based on protocols adopted over the years. Overall treatment strategies did not change substantially during the study period, although in some instances decisions about any adjuvant chemotherapy and postoperative radiotherapy for patients who had had complete primary resection were customized and depended on the physician's attitude, resulting in some differences in the choices of treatment.

Primary excision was attempted when complete and nonmutilating resection was considered feasible; otherwise, a biopsy was taken, and chemotherapy was administered to reduce the tumor and make it resectable at subsequent surgery. In some patients, primary re-excision (defined as a second operation performed within 2 months of the first surgery) was recommended before any other treatment if microscopic residual disease was suspected and considered removable. In patients considered unresectable at diagnosis, delayed surgery was considered after three cycles of primary chemotherapy and (in some patients) preoperative radiotherapy.

Different chemotherapeutic regimens (used for rhabdomyosarcoma protocols) were adopted over the years. Table 1 lists the various chemotherapy schedules used. The first Italian[12] and German[13] protocols and the INT[14] protocol used VACA or VAC/CAV regimens including vincristine, doxorubicin, cyclophosphamide, and dactinomycin. Ifosfamide replaced cyclophosphamide in VAIA and IVA regimens. Carboplatin and etoposide were used in the CEVAIE schedule or as two-drug therapy. In addition, a combination of cisplatinum (CDDP) and etoposide or other regimens (without ifosfamide or cyclophosphamide) were used in 10 patients. Primary chemotherapy was given to patients considered unresectable at diagnosis. Adjuvant chemotherapy was suggested after initial gross resection in the presence of large tumors ($>$ 5 in diameter).

Radiotherapy was administered, concomitantly with chemotherapy, to patients considered at risk of local relapse due to micro- or macroscopically incomplete resection, or tumor size. The indication for postoperative radiotherapy (ie, radiotherapy after complete resection or after delayed surgery, and the doses) was not standardized, however. Radiotherapy was delivered using megavoltage photon or electron beam energies, with conventional fractionation (1.8 to 2.0 Gy daily for 5 days a week) or with hyperfractionated accelerated radiotherapy (two daily fractions of 1.6 Gy, with a 6- to 8-hour interval). The recommended dose

Table 1. Chemotherapy Regimens

Regimen	Components
VAC/CAV (ICG-RMS 1979)	VAC: vincristine 1.5 mg/m^2 on day 8 IV (max 2 mg); actinomycin 1.5 mg/m^2 on day 8 IV (max 2 mg); cyclophosphamide 150 mg/m^2 IM or orally days 1–7 CAV: cyclophosphamide 150 mg/m^2 IM or orally on days 1–7; doxorubicin 35 mg/m^2 IV on day 8; vincristine 1.5 mg/m^2 IV on day 8 (max 2 mg); for 52 weeks
VAIA (ICG-RMS 1988)	Vincristine 1.5 mg/m^2 IV (max 2 mg) weeks 1, 2, 3, 4, 7; actinomycin 1.5 mg/m^2 IV (max 2 mg) on day 1 of weeks 1, 7; ifosfamide 2 g/m^2 IV on days 1–5 of weeks 1, 4, 7; doxorubicin 40 mg/m^2 IV on days 1, 2 of week 4; for 27 weeks
IVA (ICG-RMS 1988)	Ifosfamide 3 g/m^2 IV on days 1–3 of weeks 1, 4, 7; vincristine 1.5 mg/m^2 IV (max 2 mg) weeks 1, 2, 3, 4, 7; actinomycin 1.5 mg/m^2 IV (max 2 mg) on day 1 of week 7; for 27 weeks
VACA (CWS 1981-INT Milano)	Vincristine 1.5 mg/m^2 IV (max 2 mg) weeks 1, 2, 3, 4, 7; actinomycin 0.5 mg/m^2 IV (max 2 mg) on days 1–3 of week 4; cyclophosphamide 1,200 mg/m^2 IV on day 1 of weeks 1, 4, 7; doxorubicin 30 mg/m^2 IV on days 1, 2 of weeks 1, 7; for 52, 37, or 26 weeks
VAIA (CWS 1986-CWS 1991 and ICG-RMS 1996)	Vincristine 1.5 mg/m^2 IV (max 2 mg) weeks 1, 2, 3, 4, 7; actinomycin 0.5 mg/m^2 IV (max 2 mg) on days 1–3 of weeks 1, 7; ifosfamide 3 g/m^2 IV on days 1, 2 of weeks 1, 4, 7; doxorubicin 40 mg/m^2 IV on days 1, 2 of week 4; for 27 weeks
CEVAIE (CWS 1996-ICG-RMS 1996)	Carboplatin 500 mg/m^2, week 1; epirubicin 150 mg/m^2, week 1; vincristine 1.5 mg/m^2, weeks 1, 7; actinomycin 1.5 mg/m^2, week 4; ifosfamide 3 g/m^2/d for 3 days, weeks 4, 7; etoposide 200 mg/m^2/d for 3 days, week 7; for 27 weeks

Abbreviations: ICG, Italian Cooperative Group; RMS, rhabdomyosarcoma; IV, intravenously; max, maximum; IM, intramuscularly; CWS, German Cooperative Soft Tissue Sarcoma Group; INT, Istituto Nazionale Tumori.

changed over the years and also varied, according to the presence of microscopic residual disease or gross tumor, from 65 to 70 Gy (recommended dose for unresectable gross tumor in the earlier studies) to 45 Gy (recommended dose using a hyperfractionated accelerated modality for microscopic residues). The radiation target volume included the initial mass plus 2- to 3-cm margins and the surgical scars as well. For unresectable tumor, radiotherapy was given both preoperatively (starting at weeks 7 to 10) and postoperatively (weeks 11 to 13), on the strength of customized decisions based on a multidisciplinary discussion.

Response to primary chemotherapy was evaluated after 9 weeks of treatment (three cycles), and was based on the reduction in volume of all measurable lesions, defined as follows: complete response (CR), complete disappearance of disease; partial response (PR), tumor volume reduction more than two thirds of the initial tumor volume; and minor response (MR), a reduction more than one third to less than two thirds of the initial tumor volume. Stable disease or a reduction less than one third was recorded as no response, although an increase in tumor size or the detection of new lesions was considered as progression of disease.

Statistical Methods

Progression-free survival (PFS) and overall survival (OS) were estimated according to the Kaplan-Meier method.[21] Patients were evaluated from the date of diagnosis up to disease progression or relapse for PFS, and up to death for OS. The time scale extended up to the latest follow-up if none of these events was observed. The log-rank test was used to compare the survival curves for the different subgroups of patients.[22] The statistical significance of each variable was then tested by multivariate analysis using the stepwise model and Cox regression analysis to establish the potential value of the prognostic factors.[23] The χ^2 test was used to compare different radiotherapy modalities between subsets of patients.

Patient follow-up, as of January 2004, ranged from 28.5 months to 28.9 years (median, 7.3 years).

RESULTS

Clinical Characteristics

In all, 167 patients with MPNST were treated during the study period. In two patients, MPNST occurred as a second tumor, 2 and 12 years after the diagnosis of acute lymphoblastic leukemia and acute myeloid leukemia, respectively. Table 2 lists the clinical features of all patients as a whole, and in the groups with and without NF1. Age at diagnosis ranged from 1 week to 20 years. The most common primary sites were the extremities (40%). Most patients had large, invasive tumors ($>$ 5 cm, 64%; T2, 54%). Regional lymph node involvement at onset was recorded in 6% of patients, distant metastases was recorded in 9% of patients (the sites of metastases were the lung in 10 patients, the brain in two patients, the liver and bone in one patient each, and not specified in one patient). The two patients with brain metastases were symptomatic, and brain CT scan was prompted by the symptoms (pain in one patient, seizure in the other patient); the primary tumor site was the trunk in one patient and the head/neck region (parameningeal site) in the other patient. Seventeen percent of patients had NF1. The treatment given to patients according to the IRS grouping system is summarized in Table 3.

Surgery

At diagnosis, 78 patients had a grossly complete tumor resection: 48 patients were classified as IRS group I because they had histologically free margins. Thirty were classified as IRS group II because they had microscopic residual disease (marginal resection). It is worth noting that, of the 44 patients with initial marginal resection, 14 (32%) were reclassified to a lower group (to group I) after primary

Table 2. Clinical Characteristics

Characteristic	No.	%	NF1 No		NF1 Yes		*P*
			No.	%	No.	%	
All patients	167	100	138	83	29	17	
Sex							
Male	83	49.7	73	52.9	10	34.5	.07
Female	84	50.3	65	47.1	19	65.5	
Age, years							
< 1	14	8.4	14	10.1	—	—	.002
1–9	56	33.5	52	37.7	4	13.8	
≥ 10	97	58.1	72	52.2	25	86.2	
Median	11		10		13		
Site							
HN	35	21.0	30	21.7	5	17.2	.9
GU no BP	1	0.6	1	0.8	—	—	
Extremities	67	40.1	56	40.6	11	37.9	
Trunk wall	38	22.8	30	21.7	8	27.7	
Retroperitoneal/visceral	26	15.5	21	15.2	5	17.2	
Tumor size, cm							
≤ 5	51	30.5	47	34.1	4	13.8	.03
> 5	108	64.7	84	60.9	24	82.8	
Unknown	8	4.8	7	5	1	3.4	
Tumor invasiveness							
T1	69	41.3	60	43.5	9	31.0	.2
T2	91	54.5	72	52.2	19	65.5	
Tx	7	4.2	6	4.3	1	3.5	
Regional lymph nodes							
N0	142	85.0	119	86.2	23	79.3	.9
N1	11	6.6	9	6.5	2	6.9	
Nx	14	8.4	10	7.3	4	13.8	
IRS grouping							
I	48	28.7	41	29.7	7	24.1	.08
II	30	18.0	29	21.0	1	3.4	
III	74	44.3	57	41.3	17	58.6	
IV	15	9.0	11	8.0	4	13.9	

Abbreviations: NF1, neurofibromatosis type 1; HN, head and neck; GU, genitourinary; BP, bladder or prostate; IRS, Intergroup Rhabdomyosarcoma Study.

resurgery. Overall, 35 patients were treated with surgery alone (ie, 27 of the 48 classified as group I and eight of the 30 in group II).

Among the 74 patients in group III, 37 had incomplete tumor resection and 37 had only biopsy; 24 of 74 subsequently had delayed surgery, 20 after chemotherapy (three cycles), three after chemotherapy and radiotherapy, and one after radiotherapy alone. Delayed surgery involved amputation in four patients and conservative resection in 20 patients (which was complete in 11 patients, with suspected microscopic disease in six patients, and with macroscopic residual tumor in three patients).

Chemotherapy

Chemotherapy was administered to 124 patients (74%; ie, 15 of 15 children with metastatic disease, 70 of 74 patients in group III, 20 of 30 in group II, and 19 of 48 in group I). Response to chemotherapy (at week 9) was assessable in 64 patients with measurable disease (57 in group III and seven in group IV). Responses included two CRs (3%), 16 PRs (25%), and 11 MRs (17%); 35 patients had no response. The overall response rate was 45%.

Considering the different chemotherapy regimens, the response rate was 65% (24 of 37) to regimens including ifosfamide (VAIA, IVA, CEVAIE), 17% (three of 17) to those including cyclophosphamide (VACA, VAC/CAV), and 20% (two of 10) to the other regimens (including cisplatin and etoposide; $P = .002$).

A significantly lower response rate was obtained in patients with NF1 than in those without NF1; 17.6% (three of 17) and 55.3% (26 of 47), respectively ($P = .007$).

Radiotherapy

Radiation therapy was given to 63 patients: 12 of 48 patients in group I, 11 of 30 in group II, 35 of 74 in group III, and five of 15 in group IV. In most patients, radiation therapy was administered concomitantly with chemotherapy, starting between the 10th and 14th week of treatment. The total dose ranged from 45 to 70 Gy (median, 50 Gy).

Table 3. Treatment by IRS Group

Treatment	IRS Group I	II	III	IV
S	27	8	2	—
S + RT	2	2	—	—
S + RT + CT	10	9	—	—
S + CT	9	11	—	8
CT	—	—	24	1
CT + S	—	—	13	1
CT + S + RT	—	—	6	—
CT + RT	—		23	—
CT + RT + S	—		3	1
CT + S/RT	—		1	4
RT + S	—		1	—
RT	—	—	1	—

Abbreviations: IRS, Intergroup Rhabdomyosarcoma Study; S, surgery; RT, radiotherapy; CT, chemotherapy; S/RT, surgery and radiotherapy but the sequence is not known.

Table 4 lists the local treatment failures by IRS grouping in patients with and without radiotherapy. Among all of the patients with localized disease, local progression or relapse occurred in 51% of patients (77 of 152). Radiotherapy failed to maintain or achieve local tumor control in 26 of 58 patients (45%). A better local control rate was obtained in irradiated patients (and particularly in cases with minimal residual disease), but the difference was not statistically significant. Not enough data were available to analyze the effect of different radiotherapy doses and fractionation.

Outcome

After a median follow-up of 7.3 years, PFS was 37.2% at 5 years (95% CI, 29.6% to 44.7%) and 34.5% at 10 years (95% CI, 26.6% to 42.5%), and OS was 51.1% (95% CI, 43.2% to 59.0%) and 43.4% (95% CI, 34.7% to 52.0%) at 5 and 10 years, respectively (Fig 1).

Survival rates were analyzed chronologically, arbitrarily defining two periods (from 1975 to 1985 and from 1986 to 1998), which differed in terms of radiologic assessment (with the introduction of magnetic resonance imaging) and chemotherapy regimens (with the introduction of ifosfamide): 5-year OS and PFS was 41% and 29% in the first period (39 patients) and 54% and 41%, respectively, in the second period (128 patients), with $P = .2$ for OS and $P = .04$ for PFS.

At the time of this analysis, 58 patients were alive in first CR, 13 patients were alive in second CR, and three patients were alive with disease (another four patients were lost to follow-up with disease). The 5-year local failure-free survival rate was 47.4% (95% CI, 39.5% to 55.3%), whereas the 5-year metastasis-free survival rate was 80.7% (95% CI, 73.8% to 87.7%), indicating that local failure represented the major cause of death.

Treatment failure was observed in 102 patients (61%), usually involving local progression or relapse (83%): local progression occurred in 32 patients, local and metastatic progression occurred in four patients, local relapse occurred in 42 patients, local relapse with the development of new metastases occurred in seven patients, and metastases occurred in 17 patients (10 with pulmonary spread). Time to relapse was 2 to 119 months for local treatment failures (median, 11 months from diagnosis), and 5 to 152 months for distant treatment failures (median, 16 months). Considering the patients with local relapse alone, 11 (26%) of 42 were alive in second CR, whereas only one of 24 (4%) was alive without evidence of disease in the subset of patients with distant relapse (with or without local relapse).

Overall, 89 patients died, 84 as a result of their disease, four as a result of treatment-related toxicity, and one as a result of a second tumor (cerebral glioma in a patient with NF1 treated with surgery alone).

IRS Group I Patients

Patients with complete surgical resection at diagnosis (48 patients) represented the subset with the best outcome (OS, 79.1% at 10 years): 27 of them were treated with surgery alone, 11 of whom experienced relapse and had a 5-year PFS of 61%. Adjuvant treatment was given to 21 group I patients (10 chemotherapy and radiotherapy, nine chemotherapy, and two radiotherapy): nine of 21 experienced relapse and had a 5-year PFS of 60%.

Given that no fully standardized approach to the treatment of these patients was used over the years (the decision to administer adjuvant therapies was sometimes individualized),

Table 4. Radiotherapy and Local Failure

IRS Group	RT Yes LR	RT Yes No. of Patients	RT Yes %	RT No LR	RT No No. of Patients	RT No %	Total LR	Total No. of Patients	Total %	*P*
I	2	12	17	13	36	36	15	48	31	NS
II	5	11	45	13	19	68	18	30	60	NS
III	19	35	54	25	39	64	44	74	60	NS
Total	26	58	45	51	94	54	77	152	51	NS

Abbreviations: RT, radiotherapy; IRS, Intergroup Rhabdomyosarcoma Study; LR, local relapse; NS, not significant.

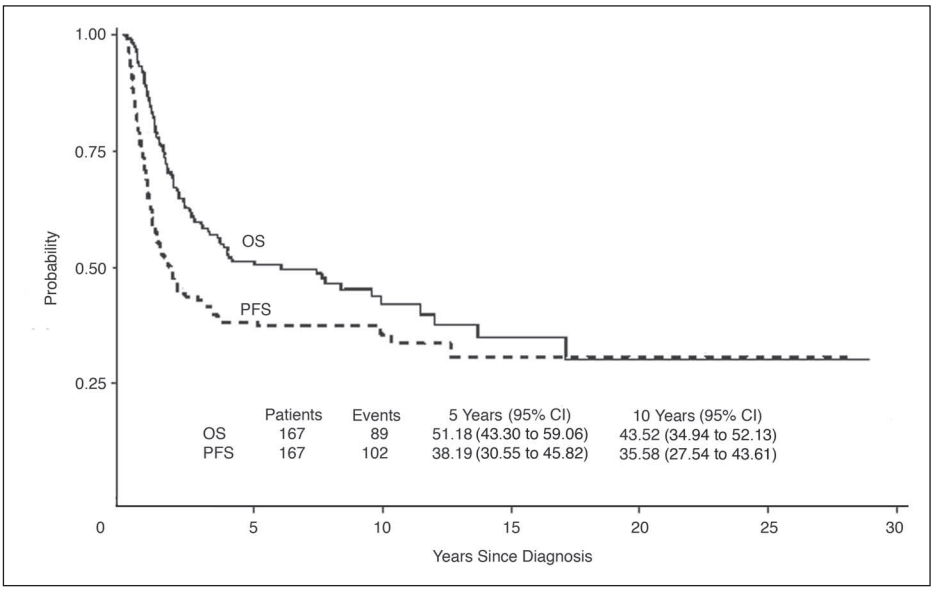

Fig 1. Overall survival (OS) and progression-free survival (PFS) for the entire series of patients (Pts).

a comparison of the incidence of the main prognostic factors was performed between the two groups (patients treated with surgery only *v* those also treated with postoperative therapies), which showed a higher (but not statistically significant) incidence of unfavorable characteristics in the latter group (T2, 18% *v* 28%; size > 5 cm, 33% *v* 52%; age > 10 years, 40% *v* 62%; NF1, 11% *v* 19%). This finding may influence our results. In particular, if we only consider local failure in IRS group I patients, the use of radiotherapy would seem to improve local control, as indicated by a lower local relapse rate in irradiated patients (17% *v* 36%; Table 4). The difference was not statistically significant, however, probably because of the small number of patients involved. Irradiated patients had better local control despite a higher incidence of large tumors (58% *v* 36%) and older age (75% *v* 41%). IRS group I patients with tumors more than 5 cm had more local and metastatic relapses (11 of 18) than those with tumors less than 5 cm (seven of 28; $P = .01$).

IRS Group II Patients

Among the 30 patients classified as IRS group II after initial surgery, eight were treated with surgery alone and 22 were treated with chemotherapy (11 patients), radiotherapy (two patients), or both (nine patients). PFS at 5 years was higher in patients given adjuvant treatment (41% *v* 25% for those treated with surgery alone), despite most of the patients having tumors more than 5 cm (72% *v* 37% in the group treated with surgery alone). As in the group I patients, the local failure rate was higher in nonirradiated patients, but not significantly so (Table 4).

To analyze the role of chemotherapy, we compared patients treated with surgery alone (eight children) versus patients treated with surgery plus chemotherapy,[11] excluding patients who also received radiotherapy. The 5-year PFS rates were similar in the two groups (25% *v* 27.2%). Here again, patients receiving chemotherapy had larger tumors at diagnosis (70% *v* 45%).

IRS Group III to IV Patients

In group III, chemotherapy was administered to 70 of 74 patients, thus preventing any comparison between subsets of patients who had or had not received systemic treatment. Tumor response to neoadjuvant chemotherapy was nonetheless observed in the 57 assessable group III patients and had a favorable impact on OS: the 5-year OS was 50% (95% CI, 30% to 70%) and 5.4% (95% CI, 0% to 15%) in responders (including minor responses) and nonresponders, respectively ($P = .004$). Eleven patients with tumors considered unresectable at diagnosis had delayed complete resection after the tumor size was reduced with chemotherapy (six PR and five MR) and seven of 11 patients were alive with no evidence of disease at the time of this report.

In group IV, the three long-term survivors achieved CR with chemotherapy and surgery.

Prognostic Factors

Table 5 lists the univariate analysis comparing the estimated PFS and OS of the different patient subsets stratified by clinical characteristics at diagnosis. Statistically significant differences in outcome emerged in relation to extent of surgery (IRS group), tumor size, local invasiveness, site of primary lesion, presence of NF1, and age at diagnosis. Survival was particularly poor in patients with NF1.

In multivariate analysis, the factors correlated independently and significantly with favorable OS were absence of NF1, noninvasive local tumor status (T1), small tumor size (< 5 cm), IRS groups I to II, and the extremities as the

Table 5. Univariate Analysis

Variable	No. of Patients	Overall Survival: Treatment Failed	Overall Survival: 5-Year OS	Overall Survival: 95% CI	Overall Survival: *P*	Progression-Free Survival: Treatment Failed	Progression-Free Survival: 5-Year PFS	Progression-Free Survival: 95% CI	Progression-Free Survival: *P*
All patients	167	89	51.18	43.30 to 59.06	—	102	38.19	30.55 to 45.82	—
IRS grouping									
I	48	12	82.09	70.82 to 93.36	< .0001	20	60.73	46.50 to 74.97	.0009
II	30	13	62.33	43.66 to 81.00		21	36.67	19.42 to 53.91	
III	74	52	31.92	20.85 to 42.99		50	27.13	16.40 to 37.85	
IV	15	12	26.67	4.29 to 49.05		11	21.43	0 to 42.92	
Age, years									
< 1	15	5	64.20	38.78 to 89.62	.0086	6	51.28	23.10 to 79.47	.0241
1–9	55	21	62.83	49.52 to 76.14		27	52.17	38.49 to 65.86	
≥ 10	97	63	42.59	32.37 to 52.81		69	28.76	19.54 to 37.97	
Tumor invasiveness									
T1	69	21	76.54	66.11 to 86.98	< .0001	32	58.44	46.62 to 70.27	< .0001
T2	91	68	28.46	18.80 to 38.12		68	19.78	11.14 to 28.41	
Tumor size, cm									
≤ 5	51	14	82.30	71.13 to 93.47	< .0001	21	62.73	49.01 to 76.44	< .0001
> 5	108	73	35.32	25.93 to 44.70		77	25.57	17.00 to 34.15	
Site									
HN	35	21	46.98	30.03 to 63.93	.0007	23	33.37	17.15 to 49.58	.0182
GU no BP	1	0	100			0	100		
Extremities	67	23	72.14	60.81 to 83.47		33	54.00	41.84 to 66.16	
Trunk wall	38	26	33.51	18.08 to 48.95		30	19.39	6.56 to 32.21	
Retroperitoneum/visceral	26	19	30.77	13.03 to 48.51		16	28.16	9.19 to 47.13	
NF1									
Yes	29	22	32.14	14.84 to 49.44	.0038	22	19.00	4.08 to 33.92	.0045
No	138	67	55.12	46.44 to 63.79		80	42.09	33.57 to 50.62	

Abbreviations: OS, overall survival; PFS, progression-free survival; IRS, Intergroup Rhabdomyosarcoma Study; HN, head and neck; GU, genitourinary; BP, bladder or prostate; NF1, neurofibromatosis type 1.

primary site. The same factors (except for IRS group) were significant for PFS.

NF1 Patients

The 29 patients with NF1 form a particular subset. Table 2 compares the clinical findings for these patients with patients without NF1. Most NF1 patients were older than 10 years old and had large, invasive, unresectable tumors.

The rate of response to chemotherapy was significantly lower in NF1 patients: 17.6% *v* 55.3% in patients without NF1 ($P = .007$). NF1 was one of the most significant prognostic factors, as listed in Tables 5 and 6: the outcome was extremely poor in NF1 patients, with a 5-year OS of 32% and PFS of 19%.

DISCUSSION

Our study deals with the largest reported series of MPNST in children and adolescents, drawing data from different countries and different protocols performed over the years. The primary aim of this analysis was to attempt to define the optimal treatment strategy. MPNST is a rare malignancy, so a prospective randomized trial on the role of adjuvant treatment has not been feasible to date.

The results of our study indicate that complete surgical removal is the mainstay of treatment and a strong predictor of survival; thus, every effort should be made to perform adequate initial surgery with free histologic margins. Unfortunately, MPNST is locally aggressive: failure to achieve local control remains the major cause of treatment failure, but complete surgical excision at diagnosis is rarely feasible (it was achieved in < one third of the patients in this series). Primary re-excision has to be recommended (where feasible) for inadequate surgical margins at the first operation: in our series, 14 of 44 patients (32%) who initially had marginal resection achieved microscopically free margins after primary re-excision and were therefore reclassified lower to group I. The need to obtain free histologic margins is also suggested by the poor PFS in our subset of IRS group II patients (36.7% at 5 years). However, we can not exclude that the inferior outcome in group II patients compared with those in group I may have been due to other factors such as the preponderance of invasive (T2, 47% *v* 24%) and large (size > 5 cm, 60% *v* 39%) tumors.

This is even more evident in patients considered unresectable at diagnosis (group III), whose unfavorable outcome (5-year PFS, 27%) is consistent with other published pediatric series (see the experiences of the

Table 6. Multivariate Analyses of OS and PFS

Prognostic Variables	OS			PFS		
	Relative Risk	95% CI	*P*	Relative Risk	95% CI	*P*
IRS grouping						
I, II	1					
III, IV	2.39	1.4 to 4.1	.002			NS
Tumor size, cm						
≤ 5	1			1		
> 5	2.0	1.0 to 3.9	.04	1.96	1.1 to 3.4	.02
Tumor invasiveness						
T1	1			1		
T2	2.01	1.2 to 3.6	.01	1.95	1.2 to 3.2	.007
Neurofibromatosis						
No	1			1		
Yes	1.88	1.4 to 3.1	.01	2.19	1.3 to 3.6	.002
Site						
Extremities	1			1		
HN	1.98	1.0 to 3.8	.02	1.53	0.9 to 2.7	.02
Trunk wall/retroperitoneum/visceral	1.90	1.1 to 3.2		1.70	1.1 to 2.7	

Abbreviations: OS, overall survival; PFS, progression-free survival; IRS, Intergroup Rhabdomyosarcoma Study; HN, head and neck.

Children's Hospital of Philadelphia[17] and St Jude Children's Research Hospital[18]).

Complete surgery would seem insufficient, however, in quite a large proportion of cases: 5-year PFS was only 61% in IRS group I patients (*v* figures reportedly approximately 80% for other nonrhabdomyosarcoma soft tissue sarcomas [NRSTS]),[24] and local relapse was the major cause of failure in this group too.

Our data can throw little light on the role of adjuvant treatments. The lack of a fully standardized therapeutic approach, the limited number of patients in each subset, and the imbalance in the prognostic factors are the shortcomings of our analysis. Regarding patients in IRS group I, we were unable to demonstrate a survival advantage in the group given adjuvant treatment, but they also had a higher incidence of unfavorable features (large and invasive tumors, age older than 10 years), so it may be that adjuvant treatment succeeded in counteracting their negative effect.

After microscopically incomplete surgery, the local relapse rate seems better in patients who received radiotherapy—a finding partially consistent with other reports,[14,15] suggesting possible benefits of irradiation in controlling microscopic residual tumor, whereas the effect of radiotherapy in patients with gross disease remains uncertain. Wanebo et al[15] suggested that adjuvant radiotherapy also be used in completely resected patients when tumors are large (> 5 cm) and invasive, or at unfavorable sites.

Although the lack of local control is the major cause of treatment failure, distant metastases can occur. The role of systemic chemotherapy is not entirely clear. Favorable responses to chemotherapy have only been reported occasionally, so MPNST is regarded as a scarcely responsive tumor.[12] In published series,[13,17,18] patients treated with adjuvant chemotherapy showed no significantly better outcome. But 74% of patients received chemotherapy in the current series and the overall response rate in patients with measurable disease after primary chemotherapy (45% response rate with 28% of major responses) is remarkable, particularly using regimens containing ifosfamide (65%). Moreover, in some patients the limited tumor shrinkage achieved by chemotherapy enabled a delayed conservative surgery that had been considered unfeasible at diagnosis. For the time being, primary chemotherapy should be attempted, in our opinion, in all patients when a macroscopically complete conservative surgery is initially unfeasible.

The potential benefit of adjuvant chemotherapy is even more uncertain. Our data are unable to demonstrate the merits of adjuvant chemotherapy, but we know that a large subset of surgically resected patients have a poor outcome, partly due to the onset of distant metastases.

Aggressive therapeutic approaches are mandatory in patients at high risk (ie, with large, invasive, unresectable tumors on the trunk or in the head and neck). In such patients, even mutilating surgery must be considered if primary chemotherapy fails to shrink the tumor.

OS was particularly discouraging in children with NF1, whatever the treatment used. This may be due to various factors such as the unfavorable clinical presentation and the poor response to chemotherapy. Moreover, every effort should be made to plan a careful follow-up in patients with NF1 to enable the early diagnosis of MPNST (as well as other malignancies, such as glioma and leukemia, for which these patients are at risk).

The number of patients in our study permitted a statistical analysis capable of defining the most important prognostic factors. In addition to the presence of NF1, the extent of surgery, tumor size, local invasiveness, and primary site were statistically significant for prognosis.

In our series, histologic grades were unfortunately unavailable for most patients, so we could offer no information on their role as a predictor of outcome. Histologic grade is now considered one of the most important prognostic factors for pediatric NRSTS and adult soft tissue sarcomas.[24] High-grade tumors have a greater propensity to metastasize and may, in principle, have a greater chance of benefiting from chemotherapy, so grading should be considered essential in deciding whether chemotherapy is indicated. The fact that most of the tumors in our patients had not been graded is clearly a weakness of our analysis, but it is worth noting that recently published data indicate that grading may not have a prognostic value for MPNST.[8,25]

In summary, MPNST is a rare tumor that behaves aggressively, with a particularly high rate of local recurrence, although distant metastases can also occur. Overall outcome is not as satisfactory as in other pediatric soft tissue sarcomas. Aggressive treatments are required in all cases with adverse prognostic factors. The new European protocol for NRSTS (developed by the new European Pediatric Soft Tissue Sarcoma Study Group) includes MPNST patients in the group with adult-type soft tissue sarcomas, and recommends adjuvant therapies according to the risk of local and distant relapse, based on residual disease after initial surgery, tumor size, and grade. Although our data are inconclusive in this direction, adjuvant chemotherapy with an ifosfamide/doxorubicin regimen will be recommended to patients with grade 3 tumors larger than 5 cm.[26,27] Meanwhile, biologic studies are opening new prospects for the treatment of these tumors, identifying new potential therapeutic targets, such as the epidermal growth factor receptor, which is overexpressed in NF1 patients with high-grade MPNST and may play a part in their tumorigenesis.[28]

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