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RESEARCH ARTICLE

Outcome and prognostic factors in pediatric malignant peripheral nerve sheath tumors: An analysis of the European Pediatric Soft Tissue Sarcoma Group (EpSSG) NRSTS-2005 prospective study

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Abstract

Background: Malignant peripheral nerve sheath tumors (MPNST) are rare tumors of childhood. The role of standard chemotherapy in unresectable MPNST is still unclear. We report the outcome and prognostic factors in the EpSSG risk-adapted prospective study for localized pediatric MPNST.

Methods: Patients were stratified into four treatment groups defined by surgical resection, tumor size, and tumor grade (G): (a) surgery-only group—resected tumors G1; (b) adjuvant radiotherapy group—R0/R1, G2 tumors; (c) adjuvant chemotherapy group—R0/R1, G3 tumors; and (d) neoadjuvant chemotherapy group—R2 resected tumors and/or nodal involvement. Chemotherapy consisted of four courses of ifosfamide-doxorubicin and two courses of ifosfamide concomitant with radiotherapy (50.4-54 Gy).

Abbreviations: CI, confidence intervals; CT, computed tomography; EFS, event-free survival; EpSSG, European Paediatric Soft Tissue Sarcoma Group; G, grade; IRS, Intergroup Rhabdomyosarcoma Study; MPNST, malignant peripheral nerve sheath tumor; NF1, neurofibromatosis type 1; NRSTS, nonrhabdomyosarcoma soft tissue sarcoma; OS, overall survival; PFS, progression-free survival.

Results: Overall, the study included 51 patients. The 5-year event-free survival (EFS) and overall survival (OS) were 52.9% (95% confidence interval, 38.1-65.8) and 62.1% (46.7-74.3), respectively. The 5-year EFS was 92% (56.6-98.9) for treatment group 1 ($N = 13$), 33% (0.9-77.4) for treatment group 2 ($N = 4$), 29% (4.1-61.2) for treatment group 3 ($N = 7$), and 42% (23.1-60.1) for treatment group 4 ($N = 27$). Response rate to chemotherapy (partial response + complete response) in patients with measurable disease was 46%. The presence of neurofibromatosis type 1 (NF1; 51% of patients) was an independent poor prognostic factor for OS and EFS.

Conclusion: The outcome for patients with resectable MPNST was excellent. Standard ifosfamide-doxorubicin for unresectable MPNST rendered the best reported outcome. Children with NF1 disease seem to have worse prognosis.

KEYWORDS

adjuvant chemothexrapy, EpSSG study, MPNST outcome study, NF1, NRSTS, outcomes research, Phase 3 study, sarcoma, soft tissue

1 | INTRODUCTION

Malignant peripheral nerve sheath tumors (MPNST) are malignant tumors arising from the nerve sheath, possibly from Schwann cells and perineural cells. In an analysis of the American Survival, Epidemiology, and End Results (SEER) database, only 14% of 1182 MPNST cases were in children, with an incidence of 0.56 per million person-years.[1,2] MPNST however represent the third most common nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) in children.[3] Half of the children have underlying neurofibromatosis type 1 (NF1), a genetic condition with germ line disruption of the *NF1* gene with a predisposition to develop malignant tumors, mostly MPNST. The lifetime risk of patients with NF1 to develop MPNST is 10%.[4,5] The other half of MPNST arise in individuals without NF1 in peripheral nerves. The prognostic role of NF1 disease in MPNST is still unclear.[6] NF1 was generally considered a poor prognostic factor, but the higher incidence of deep-seated tumors and higher prevalence of incomplete resection in patients with NF1 may be more prognostic than the biological behavior of NF1-related MPNST.[7,8]

The cornerstone of MPNST treatment remains surgical resection, but is often not possible due to expected damage to adjacent nerves and neurovascular bundles and deep tumors extending to adjacent structures (T2 tumors). The role of adjuvant therapies in unresectable disease is limited and has not been fully established.[9–13] Pediatric MPNST have an overall survival (OS) of 51% at 5 years, and a 5-year progression-free survival (PFS) of 37%.[2]

In 2005, the European Pediatric Soft Tissue Sarcoma Group (EpSSG) developed a protocol specifically dedicated to NRSTS, including patients with MPNST, and stratified according to tumor grade, size, and surgical resectability to receive local treatment and ifosfamide and doxorubicin chemotherapy. We present the results of this prospective European study for children with localized MPNST.

2 | METHODS

2.1 | Patients and study design

The EpSSG-NRSTS-2005 study was a prospective European observational study for localized NRSTS for patients <21 years of age, including patients with MPNST. The study was performed in accordance with the Declaration of Helsinki. Ethical Committee approval was obtained in all participating countries, and written informed consent was received from all patients and/or parents. A web-based database system provided by CINECA (Inter-University Computing Consortium; Casalecchio, Italy) was implemented for management of the study. Clinical data, compliance to the study treatment, toxicity, and outcome of all patients were analyzed.

2.2 | Diagnosis and pathology

The histological diagnosis was reviewed by the EpSSG pathology panel, or an expert sarcoma pathologist. Material was available for (inter-)national review in all cases. The criteria for the diagnosis of MPNST were a malignant tumor with Schwannian differentiation arising in a peripheral nerve, or in a patient with NF1, or in a preexisting neurofibroma. Diagnosis was based on Schwann cell differentiation and the exclusion of other spindle cell sarcomas. Tumors were graded according to the FNCLCC (Fédération Nationale des Centres de Lutte Contre Le Cancer) grading system.[14,15]

2.3 | Staging and surgery

Staging was based on computed tomography (CT) scan or magnetic resonance imaging of the primary site, and chest CT scan and Tc^{99}m Bone Scan or 18-fludeoxyglucose-positron emission tomography CT scan for distant disease. The Intergroup Rhabdomyosarcoma Study (IRS) group and tumor node metastases postsurgical staging were used.

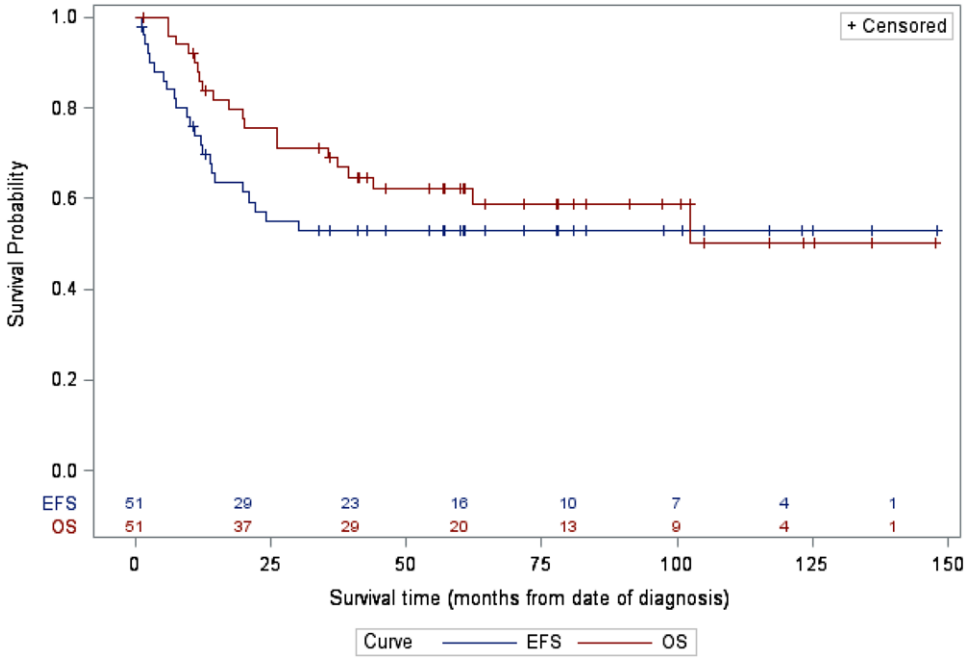

FIGURE 1 Event-free survival and overall survival estimates

Classification of surgical resection R0 (complete resection) corresponds to IRS group I, R1 (microscopic residual disease) corresponds to IRS group II, and R2 (residual macroscopic disease or biopsy only) corresponds to IRS group III.[16,17] Patients with distant metastases at presentation were excluded from this study.

2.4 | Treatment

Primary surgery after biopsy was recommended if considered achievable, without damage to neurovascular structures. In others, biopsy was advised.

Patients were stratified into four clinical groups (Figure 1):

1. "surgery-only group" (IRS group I ≤5 cm, tumors IRS group I with >5 cm, and FNCLCC grade (G) 1, and IRS group II/N0 and G1);
2. "adjuvant radiotherapy group" (IRS group I, >5 cm and G2 or G3; IRS group II/N0, G2-G3, ≤5 cm and G2, >5 cm);
3. "adjuvant chemotherapy group" (group I, >5 cm, G3; IRS group II/N0, G3, >5 cm);
4. "neoadjuvant chemotherapy group" (IRS III and/or N1).

Adjuvant and neoadjuvant chemotherapy consisted of three courses (courses 1-3) of combination chemotherapy followed by delayed surgery, when feasible, and radiotherapy. During radiotherapy, ifosfamide alone was administered (courses 4 and 5) and after radiotherapy the final chemotherapy (course 6) was again combination chemotherapy.

The combination chemotherapy consisted of ifosfamide 3 g/m^2/day for 3 days plus doxorubicin 37.5 mg/m^2/day for 2 days (doxorubicin cumulative dose 300 mg/m^2; IFO-DOXO regimen). The ifosfamide alone consisted of 3 g/m^2/day for 2 days. Adjuvant radiotherapy patients received 50.4-59.4 Gy radiation therapy after surgery (week 9). The 50.4 GY was for IRS I patients, >5 cm, and for IRS III preoperative radiotherapy or postoperative in R0 resection. The 54 Gy was for IRS II, G2, G3, and IRS III, R1 patients. In IRS III patients, N1 tumors received 59.4 GY. Treatment was applied in conventional fractionation with 1.8 Gy per day, 5 days per week. The target volume was based on initial tumor volume.

Response to chemotherapy was assessed after three IFO-DOX: complete response (CR) = complete disappearance of visible tumor with no residual disease; partial response (PR ≥ 2/3) = volume response 66-99%; minor partial response (PR < 2/3) = volume response 34-65%; stable disease (SD) < 33% reduction in tumor volume; progressive disease (PD) = a more than 40% increase in tumor volume, or the appearance of new lesions.

Volume (V) was calculated based on the formula: $V = \pi/6 \times a \times b \times c = 0.52 \times a \times b \times c$ in cubic centimeter, in which a = length (in centimeter), b = width (in centimeter), and c = thickness (in centimeter).[18] Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

2.5 | Statistical analysis

Data were collected and updated until April 2018. Survival time was calculated from diagnosis to the time of event or last follow-up. Tumor progression, relapse, occurrence of second malignancy, or death due to any causes were considered for event-free survival (EFS). OS was measured from the date of diagnosis to death for any reason. The survival probability was computed according to the Kaplan-Meier method and the log-rank test. The 5-year EFS and OS were reported with their 95% confidence intervals (CIs). Uni- and multivariate analyses were

performed using the Cox proportional hazard regression method for the variables: age (<10 years; ≥10 years), size (≤5 cm; >5 cm), IRS group (I-II; III), tumor grading (G1-G2; G3) and NF1 (absent; present) on EFS and OS. A stepwise variable selection procedure was applied to the covariates with a *P*-value of at least .25 at univariate analysis. Hazard ratios (HRs) with their 95% CI calculated according to the Wald method were reported for significant variables. All data analyses were performed using the SAS statistical package (SAS, release 9.4; SAS Institute, Inc., Cary, NC).

3 | RESULTS

3.1 | Patient characteristics

Between August 2005 and March 2016, 59 patients with MPNST were diagnosed from 32 centers in five European countries. Eight patients were excluded based on discordance with central pathological review. The remaining cohort of 51 patients represents 4.4% of the total of 1161 patients with NRSTS registered in the study. NF1 disease was diagnosed in 51% of all patients. NF1 disease was diagnosed clinically in half of the patients, and for the rest genetically confirmed by somatic alterations of the *NF1* gene.

The cohort consisted mainly of teenagers with a median age of 13.7 (range 0.02-21.3) years and more than 70% of patients >10 years of age at the time of diagnosis. Tumors were mostly unresectable (52.9% IRS group III). Most tumors (59%) were >5 cm in diameter and a large group of tumors extending into adjacent structures (T2; 41%). High pathological tumor grade (G3) was diagnosed in 61% of tumors. Regional lymph node involvement was limited to only one patient (Table 1).

TABLE 1 Clinical characteristics

	No. of patients *n* = 51	%
Age (y) at diagnosis		
Median (min-max)	13.7 (0.02-21.3)	
<10	15	29
10-17	32	63
≥18	4	8
Gender		
Female	26	51
Male	25	49
Postsurgical tumor staging (IRS)		
Group I	13	25
Group II	11	22
Group III	27	53
Primary tumor invasiveness (T)		
T1—localized to the organ or tissue of origin	29	59
T2—extending beyond the tissue or organ of origin	21	41
Tx—insufficient information about the primary tumor	1	-
Tumor size		
a: ≤5 cm	19	37
b: >5 cm	30	59
x: not evaluable	2	4
Regional lymph node involvement		
N0—no evidence of lymph node involvement	50	98
N1—evidence of regional lymph node involvement	1	2
Grading		
1	8	16
2	12	23
3	31	61

3.2 | Treatment groups and compliance

The overall compliance with the chemotherapy treatment protocol was 88%. Deviation from the protocol was reported for toxicity, administration of additional chemotherapy, and missing data on drug delivery.

i. Surgery-only group (*n* = 13)
In 11 patients, primary resection was performed according to protocol guidelines. Noncompliance occurred in two patients: one patient received chemotherapy and radiotherapy treatment (6 IFO/DOXO + 54.4 Gy) and one patient received additional radiotherapy treatment (50.4 Gy).

ii. Adjuvant radiotherapy (*n* = 4)
In this group, two patients received RT according to protocol and two did not receive radiotherapy (physician decision).

iii. Adjuvant chemotherapy group (*n* = 7)
Five patients received chemotherapy and radiotherapy, according to the protocol, while two patients received chemotherapy treatment only.

iv. Neoadjuvant chemotherapy group (*n* = 27).
Chemotherapy treatment data are available for all patients.

Twenty of 27 IRS III patients underwent delayed secondary surgical resection. Data regarding the entity of surgery were available for all patients: 12 R0, 6 R1, and 2 R2. Secondary surgery was followed by adjuvant radiotherapy treatment in 15 of 20 patients, and 1 patient received preoperative radiotherapy. Three patients in this group received only RT treatment. In the total cohort, radiotherapy was applied in 28 patients versus 23 receiving no radiotherapy. Radiotherapy was given in 2 patients in the surgery-only group (50.4 and 54.4 Gy), 2 patients in the adjuvant RT group (54.0 and 64.8 Gy), 5 patients in the adjuvant CT group (median 50.4; range 50.0-54.0 Gy), 19 patients in the neoadjuvant CT group of which 16 underwent additional delayed surgery (15 RT after surgery, 1 preoperative RT), and 3 received only radiotherapy (median 50.4; range 35.2-64.8 Gy). The rate of local and nodal relapse and/or tumor progression was equal for irradiated patients (32%) and nonirradiated patients (35%). These relapse

TABLE 2 Overall and event-free survival by patient characteristics (univariate analysis)

	Overall survival				Event-free survival		
Characteristic	***N***	**No. of events**	**5-y OS (95% CI)**	***P*-value**	**No. of events**	**5-y EFS (95% CI)**	***P*-value**
All patients	51	20	62.1 (46.7-74.3)		23	52.9 (38.1-65.8)	
Age (years)							
<10	15	4	79.4 (48.8-92.9)	0.147	4	73.3 (43.6-89.1)	0.106
≥10	36	16	54.4 (36.0-69.6)		19	43.6 (26.6-59.4)	
Size (cm)							
≤5	19	5	77.0 (49.7-90.7)	0.080	7	61.3 (35.5-79.3)	0.314
>5	30	15	50.1 (30.4-66.9)		16	44.4 (25.9-61.4)	
IRS group							
I-II	24	8	68.5 (45.0-83.6)	0.277	8	65.2 (42.3-80.8)	0.050
III	27	12	56.9 (35.6-73.5)		15	42.2 (23.1-60.1)	
Resection							
R0/R1	42	17	69.3 (52.2-81.3)	0.0005	14	57.9 (41.3-71.4)	0.0095
R2	9	6	26.7 (4.1-57.9)		6	33.3 (7.8-62.3)	
Grading							
I-II	20	7	69.3 (44.0-84.9)	0.387	7	65.0 (40.3-81.5)	0.195
III	31	13	56.9 (36.5-73.0)		16	44.2 (25.7-61.2)	
Therapy group							
Surgery-only	13	1	91.7 (53.9-98.8)		1	92.3 (56.6-98.9)	
Surgery + Radiotherapy	4	2	66.7 (5.4-94.5)	0.054	2	33.3 (0.9-77.4)	0.022
Adjuvant CT	7	5	28.6 (4.1-61.2)		5	28.6 (4.1-61.2)	
Neoadjuvant CT	27	12	56.9 (35.6-73.5)		15	42.2 (23.1-60.1)	
NF1							
No	25	7	80.0 (58.4-91.1)	0.014	8	68.0 (46.1-82.5)	0.040
Yes	26	13	42.6 (21.7-62.1)		15	36.3 (17.7-55.3)	
Risk group							
Low	34	17	86.7 (56.4-96.5)	0.024	20	81.3 (52.5-93.5)	0.006
High	17	3	49.9 (31.5-65.8)		3	38.9 (22.4-55.1)	

95% CI: 95% confidence interval

rates were not different between patients with NF1 versus patients without NF1 or for patients of different treatment groups.

3.3 | Toxicity

Toxicity of chemotherapy was as expected. In the adjuvant chemotherapy group, grade 3 toxicity occurred in 14% of patients for infection, mucositis, and myelosuppression and grade 4 myelosuppression occurred in 14%. In the neoadjuvant group, grade 3 toxicity was registered in 35% of patients for infection, 5% for neuropathy, 25% for mucositis, and 15% for myelosuppression. There was no treatment-related mortality. "Other" grade 3 and 4 toxicities were in four patients with seizure, encephalopathy, cardiomyopathy, and pulmonary failure.

3.4 | Outcome

The median follow-up for surviving patients was 64.6 months (range 1.3-147.7). In total, there were 23 events: six patients developed locally progressive disease and two combined locally progressive and metastatic disease during treatment. After the completion of treatment, 12 tumors relapsed (median time to relapse 10.2 months, range 1.2-30.2): five local relapse, one combined local and nodal relapse, three local and metastatic relapse, and three metastatic relapse. In addition, three patients with NF1 developed secondary tumors (one acute myeloid leukemia, one triton tumor in abdomen outside the radiation field, and one spinal gangliocytoma outside the radiation field) and had all received radiotherapy as part of their treatment for MPNST. All tumor progressions and relapses developed in the neoadjuvant treatment group, except for one local relapse in the adjuvant radiotherapy treatment group and one local relapse in the surgery-only group.

At the time of analysis, 29 patients were alive in the first CR off therapy, 1 patient was alive in the third CR off therapy, 3 patients were alive with suspected residual disease off therapy, 2 patients were lost to follow-up, and 20 patients died (19 due to MPNST progression and one after a second tumor).

The 5-year OS is 62.1% (95% CI, 46.7-74.3; Table 2, Figure 1). The 5-year EFS is 52.9% (95% CI, 38.1-65.8; Table 2). In a univariate

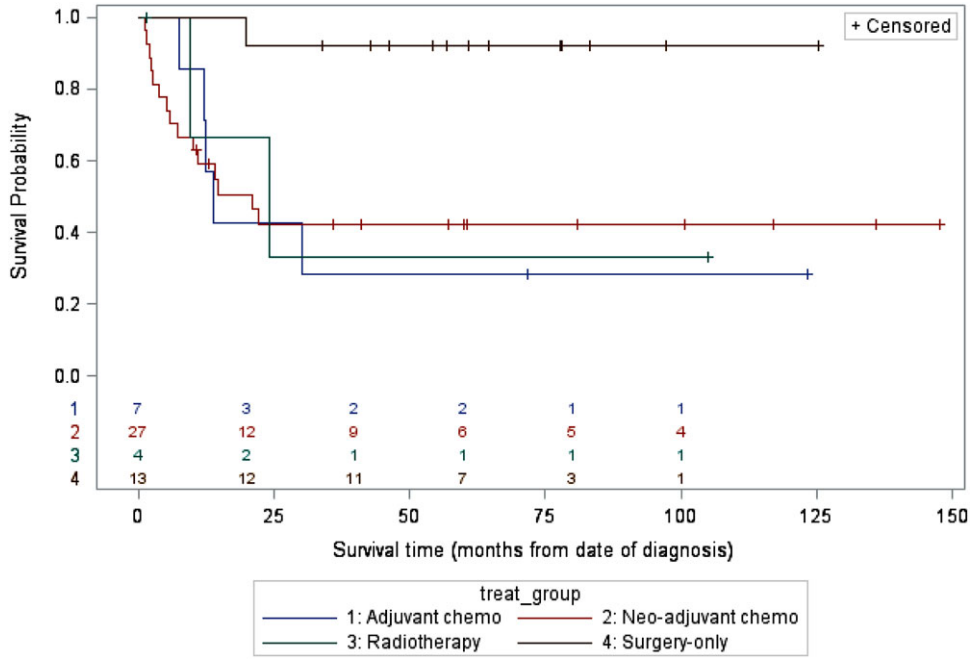

FIGURE 2 EFS according to treatment group

analysis, negative prognostic association for OS and EFS was found for IRS group III, treatment group (adjuvant and neoadjuvant group), and the presence of NF1 disease (Table 2, Figure 2, and Figure S1). Prognosis was not associated with age at diagnosis, tumor size, or tumor grading.

In a multivariable analysis, NF1 was associated with an inferior OS (*P*-value .008; HR 3.54 [95% CI, 1.4-9.0]) and EFS (*P*-value .031; HR 2.8 [95% CI, 1.1-7.1]). Additionally, IRS group III was associated with worse EFS (*P*-value .041; HR 2.47 [95% CI, 1.04-5.90]; Figure S1).

3.5 | Chemotherapy response

The tumor response to chemotherapy was evaluable in 26 of 27 patients in the neoadjuvant chemotherapy group. The overall response rate is 46.2%: CR in 3.9%, PR in 15.4%, minor partial response (20-50% reduction in tumor volume) in 26.9%. SD was observed in 34.6% and progressive disease in 19.2%. There was no difference in chemotherapy response between NF1 (40%) and patients without NF1 (50%).

4 | DISCUSSION

This is the first prospective study of the treatment of pediatric patients with localized MPNST. It reached a 5-year OS and EFS of 62.1% and 52.9%, respectively. The outcome was excellent for patients with small resectable tumors, while in unresectable disease the outcome was at least comparable or better than historic, retrospective studies. In addition, our study showed that NF1 disease was a poor prognostic factor for outcome.

For resectable tumors, the outcome was excellent (5-year OS and EFS of 92%). Resection of small tumors was effective for both patients with NF1 and patients without NF1. Only one patient developed a local relapse and died of disease. Carli et al showed an OS and PFS of 82% and 61% for group I tumors, and 62% and 37% for group II tumors.[2] The excellent outcome for small resectable tumors was also observed in other NRSTS tumors of the prospective EpSSG-NRSTS-2005 study, that is, synovial sarcoma,[19,20] infantile fibrosarcoma,[21] and alveolar soft part sarcoma.[22,23]

Radiotherapy is important for local control of soft tissue sarcoma in general and was established for patients with adult MPNST with or without NF1 disease.[8,24] Here, we could not confirm an additive role of radiotherapy in pediatric MPNST. However, considering the importance of local control and of radiotherapy in adult MPNST, it is advisable to apply radiotherapy in pediatric MPNST similar to other pediatric NRSTS. The radiotherapy doses used in this protocol were relatively low because of the young age of the subjects compared to standard doses in adults (>55 Gy). In the future, proton beam radiotherapy may offer safe dose escalation by diminishing the nontarget high-dose volumes in children.

We compared the outcome, role of NF1 disease, and response to chemotherapy between our study, and two other studies: the largest retrospective pediatric MPMST study[2] and a first-line chemotherapy in adult MPNST EORTC study[24] (Table 3). First, the outcome for group III patients is superior in the pediatric studies compared to the adult study. Between the pediatric studies, the survival in our prospective EpSSG-NRSTS-2005 study was higher for IRS III patients (5-year EFS 44.2% vs 27.1%, respectively). However, this should be interpreted with caution since the study methods were very different, as well as the chemotherapy used. Perhaps the outcome for patients in this EpSSG study is explained by standardization of treatment and high compliance to the uniform protocol guidelines. Superiority of the IFO-DOXO regimen compared to other regimens cannot be substantiated from these results. Second, the chemotherapy response seems

TABLE 3 Outcome comparison between MPNST studies

	EpSSG study, *N* = 51	Carli et al,[2] *N* = 167	Kroep et al,[24] *N* = 175
All patients	5-y EFS, 52.9% 5-y OS, 62.1%	5-y PFS, 39% 5-y OS, 51%	4.1-y PFS, 17 wk 4.1-y OS, 48 wk
IRS group	IRS I and II, 5-y EFS, 65.2%	IRS I, 5-y PFS 60.7%	N.A.
		IRS II, 5-y PFS 36.6%	N.A.
	IRS III, 5 y, 42.2%	IRS III, 5-y PFS, 27.1%	4.1-y PFS, 17 wk 4.1-y OS, 48 wk
NF1 disease	Yes, 5-y OS, 42.6% No, 5-y OS, 80.0%	Yes, 5-y OS, 32.1% No, 5-y OS, 55.1%	N.A. N.A.
Chemotherapy Response rate	46.2%	45%	21%

Abbreviations: EFS, event-free survival; N.A.: not applicable; OS: overall survival; PFS, progression-free survival.

better in children compared to adult patients with MPNST: in the EORTC study, the overall chemotherapy response was only 21% with a median survival of 48 weeks. This EpSSG study observed a chemotherapy response of 46.2% with no difference between patients with NF1 and patients without NF1. The chemotherapy response was similar (45%) in the pediatric study by Carli et al[2] however they did observed a lower chemo response (17%) in patients with NF1 versus patients without NF1 (55%).

In multivariate analysis, NF1 disease and IRS group III were independent predictors of inferior EFS and NF1 disease additionally prognostic for reduced OS. It is unclear what aspects of NF1-related MPNST are responsible for the generally worse outcome compared to patients without NF1. We did not observe a higher incidence of IRS III disease or differences in relapse pattern in NF1 subjects, although the NF1 group included three secondary tumors. Recent reports from adult MPNST studies suggest that NF1 seems to lose its prognostic significance when corrected for the higher incidence of deep-seated tumors in NF-1 patients and incomplete resections of NF1-related MPNST.[7,8] Considering the equal response to radiotherapy and chemotherapy in our study for NF1 and patients without NF1, it may be suggested that in pediatric patients the role of NF1 disease is also more associated with higher incidence of organ invasion (T2) and higher IRS grouping and not related to a more aggressive biological behavior for NF1 tumors.

The EpSSG-NRSTS-2005 study used tumor grading in the treatment stratification. Most MPNST are of high grade in this and other studies.[8] We observed no difference in outcome between grade I-II versus III, although the intensification of treatment in grade III tumors may play a role. To the best of our knowledge, no study has been conducted on the prognostic significance of grading in MPNST. The value of grading in the treatment stratification is therefore still unclear.

The overall conclusion of this and other studies is that localized pediatric MPNST can be well managed by surgery and additional radiotherapy for large, or not completely resected or grade 2/3 tumors. For initially unresectable tumors, the standard addition of chemotherapy is favorable and recommended. IFO-DOX can be considered as a "backbone" chemotherapy treatment for future study of novel compounds in unresectable MPNST.

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CONFLICT OF INTEREST

All authors declare not having any actual or potential conflict of interest including any financial, personal, or other relationships with other people or organizations within that could inappropriately influence (bias) their work.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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