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Original Article

Radiation-induced and neurofibromatosis-associated malignant peripheral nerve sheath tumors (MPNST) have worse outcomes than sporadic MPNST

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ABSTRACT

Background: Malignant peripheral nerve sheath tumors (MPNST) may be sporadic or associated with neurofibromatosis or prior radiation. MPNST may behave aggressively with a high rate of local recurrence and distant metastasis.
Methods: In an IRB approved protocol, we reviewed the clinical characteristics, treatment, and outcomes of 280 patients treated for MPNST at Massachusetts General Hospital (MGH) between 1960 and 2016.
Results: There were 138 men and 142 women with a median age of 41 (range: 3–95) years. Tumors were classified as neurofibromatosis-associated (nfMPNST, $n = 77$), radiation-induced (rMPNST, $n = 21$), or sporadic (sMPNST, $n = 182$) MPNST. The median time to development of rMPNST from prior radiation was 15 years. With a median follow-up of 43.1 months, the median overall survival (OS) was 65.3 months. Older age, nfMPNST, rMPNST, increased tumor size, lymph node involvement, metastatic disease, intermediate to high grade, radiotherapy alone, and R2 resection were related to worse OS, whereas surgery with radiotherapy was associated with improved OS. Among the 251 patients without metastasis, nfMPNST, rMPNST, and increased tumor size were correlated with worse metastasis-free survival; nfMPNST, radiotherapy alone, and R1/R2 resection were associated with local recurrence, whereas surgery with adjuvant radiotherapy was related to improved local control in patients with R1/R2 resection.
Conclusions: Both radiation-induced and neurofibromatosis-associated MPNSTs have poorer prognosis than sporadic MPNSTs. Complete resection of the tumor is a significant prognostic factor for MPNST. The addition of radiotherapy after surgery should be considered especially when the surgical margins are positive.

Malignant peripheral nerve sheath tumor (MPNST) is a malignant tumor arising either from a peripheral nerve de novo, a preexisting benign nerve sheath tumor (usually neurofibroma), or in a patient with neurofibromatosis type 1 (NF1). The diagnosis of sporadic MPNST is based on the constellation of light microscopic, immunohistochemical and ultrastructural features suggesting Schwann cell differentiation (WHO 2013 edition page 187) [1]. Approximately 10% of MPNSTs develop as a consequence of prior radiation therapy [2–5]. The cumulative incidence of developing a radiation-induced MPNST reached 0.1% at 30 years from the diagnosis of prior cancer, based on pooled data of 69,460 five-year survivors of childhood cancer from 13 European cohorts [6]. In up to half of the patients [2–5,7,8], MPNSTs occur in association with NF1, which is an autosomal dominant genetic disorder with a birth incidence of approximately 1:3000 [9,10]. MPNST is the leading cause of death in patients with NF1 who have a reported 8%–13% lifetime risk of developing MPNST [11]. Around 65%–88% of

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NF1-associated MPNSTs arise from a pre-existing plexiform (or rarely diffuse) neurofibroma [9,10].

MPNST is a rare disease and one population-based study using the Surveillance, Epidemiology, and End Results (SEER) database demonstrated that the overall incidence in the United States (1973–2009) was 1.46 per million person-years [12]. MPNST behaves aggressively with a high rate of local recurrence and distant metastasis. The 5-year survival ranges from 20% to 50% [7,8,13–16]. It is still unclear whether different etiologies predict prognoses [2]. Additionally, several other factors, such as metastatic disease, grade, surgical margin status, and tumor size, have been indicated as significant prognostic predictors [15–18]. The mainstay of treatment has been surgical excision whenever feasible, however, the roles of radiotherapy and chemotherapy are undetermined.

In this study, we reviewed the clinical characteristics and outcomes of patients treated for MPNST at our institution and sought to characterize the impact of clinicopathologic features and treatment modalities on clinical outcomes.

Patients and methods

Patient selection

Our IRB-approved institutional sarcoma database includes 12,961 patients from the 1960s to 2016. Study data were collected, stored, and managed using Research Electronic Data Capture (REDCap) electronic data capture tools [19]. REDCap is a secure, HIPAA compliant, web-based application designed to support data capture for research studies, providing: (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. The database retrospectively and prospectively collects data from our institution's paper and electronic clinical records on patient demographics, primary and secondary tumor characteristics, treatment, follow up and survival. We queried the database for patients who were diagnosed with MPNST, malignant schwannoma, malignant neurilemmoma, neurogenic sarcoma, or neurofibrosarcoma that was confirmed by pathology, and were treated in our institution.

Variables of interest

Patient demographic variables include age, gender, and race/ethnicity. Tumor characteristics include NF status, prior radiation history, primary tumor site (extremity, head and neck, or trunk), primary tumor size, histology subgroup, extent of disease at diagnosis. Clinical staging was based on the American Joint Committee on Cancer (AJCC) staging system for soft tissue sarcoma. Pathological results include gross margins, closest tumor margins, and French Federation of Cancer Centers Sarcoma Group (FNCLCC) grade. Treatment options include local treatment combinations, e.g. surgery without radiation, surgery plus radiation, and radiation without surgery, and systemic treatment, as whether chemotherapy was given or not. Further radiation information included total radiation dose, modality used, and sequencing relative to surgery. Surgical extent was coded as R0 (no residual tumor), R1 (microscopic residual tumor), or R2 (macroscopic residual tumor) resection. Patient outcome was assessed for survival time (defined as time from the date of diagnosis until one of the following: date of local relapse or distant metastasis, date of death, last-contact date, or study cut-off date), vital status, and cause of death classification.

Statistical analysis

Statistical significance between groups was analyzed using the chi-square tests for categorical variables and the ANOVA or Kruskal–Wallis non-parametric test for continuous variables. The estimated overall survival (OS, defined as time from diagnosis to death from any cause), progression-free survival (PFS, defined as the time from diagnosis to progression, i.e. local or metastatic relapse, or death), local relapse-free survival (LRFS, defined as time from diagnosis to the first local relapse after treatment or death from any cause), and metastasis-free survival (MFS, defined as time from diagnosis to the first metastatic relapse after treatment or death from any cause) were derived using the Kaplan–Meier method and compared by the Mantel–Cox log-rank test. The multivariate Cox proportional hazard model was used to investigate significant prognostic factors. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY). The Kaplan–Meier survival curves were generated in R (version 3.4.1; www.r-project.org), using the 'survminer' package and the 'ggsurvplot' function. All reported p values were two-sided. The level of significance was set at $p < 0.05$.

Results

Patient characteristics

A total number of 299 patients were identified. Nineteen patients were excluded from the final analyses due to the lack of adequate information. There were 138 men and 142 women with a median age of 41 years (range: 3–95 years). Patients were classified as having either neurofibromatosis-associated MPNST (nfMPNST, $n = 77$, 27.5%), radiation-induced MPNST (rMPNST, $n = 21$, 7.5%), or sporadic MPNST (sMPNST, $n = 182$, 65%). Among the 77 patients with nfMPNSTs, only two of them were reported to have mutations detected in NF1 gene, and neurofibromatosis was diagnosed purely based on phenotypic features in the remaining 75 patients; no NF1 genetic test was performed in patients with sMPNST or rMPNST. The extremities were involved in 119 patients (42.5%) followed by the trunk ($n = 104$, 37.1%) and head and neck ($n = 57$, 20.4%). The median size of the tumor at diagnosis was 7.0 cm (range: 0.8–30 cm). Intermediate-grade tumors ($n = 141$, 50.4%) were most common, followed by high- ($n = 97$, 34.6%) and low-grade ($n = 28$, 10.0%) ones. Seven patients (2.5%) presented with regional lymph node involvement, while 29 patients (10.4%) also had distant metastases at the time of diagnosis. Patient demographics and treatment characteristics of the 280 patients are summarized in Table 1.

Among the patients with rMPNST, their prior diseases were diagnosed at a median age of 21 years (range: 1–53 years) and included Hodgkin disease ($n = 8$), testicular cancer ($n = 4$), Wilms disease ($n = 2$), benign disease (frozen shoulder and bone cyst, $n = 2$), lung cancer ($n = 1$), nasopharyngeal cancer ($n = 1$), Ewing sarcoma ($n = 1$), chordoma ($n = 1$), and acute lymphoblastic leukemia ($n = 1$). The median latency between prior radiation to the development of rMPNST was 15 years (range: 6–50 years). Fifteen patients had information on previous radiation dose and the median dose was 40 Gy (range: 16–101 Gy). Compared with sMPNST (extremity/head and neck/trunk: 46.7/21.4%/31.9%) and nfMPNST (39.0%/19.5%/41.6%), rMPNSTs (19.0%/14.3%/66.7%) were more frequently located in the trunk ($p = 0.028$).

Compared with sMPNST, younger patients developed nfMPNST and rMPNST (median: 46.5 years vs. 30 years and 36 years, respectively, $p < 0.001$). nfMPNST and rMPNST were more likely to be intermediate-to-high grade (83.5% vs. 89.7% and 90.5%, $p = 0.056$). sMPNST also presented with a smaller tumor size than nfMPNST or rMPNST (median: 6.5 cm vs. 8.5 cm vs. 7.0 cm,

Table 1
The clinicopathologic characteristics and treatment modalities in patients with MPNST.

	All	sMPNST	rMPNST	nfMPNST	
Characteristics	280	182 (65%)	21 (7.5%)	77 (27.5%)	*P*
Gender					0.492
Female	142 (50.7%)	97 (53.3%)	10 (47.6%)	35 (45.5%)	
Male	138 (49.3%)	85 (46.7%)	11 (52.4%)	42 (54.5%)	
Symptom					
Palpable mass	152 (54.3%)	96 (52.7%)	6 (28.6%)	50 (64.9%)	0.010
Pain	155 (55.4%)	94 (51.6%)	14 (66.7%)	47 (61.0%)	0.212
Neurologic	74 (26.4%)	49 (26.9%)	9 (42.9%)	16 (20.8%)	0.122
Other	39 (13.9%)	28 (15.4%)	1 (4.8%)	10 (13.0%)	0.396
Asymptomatic	4 (1.4%)	2 (1.1%)	1 (4.8%)	1 (1.3%)	0.405
Site					0.028
Extremity	119 (42.5%)	85 (46.7%)	4 (19.0%)	30 (39.0%)	
Head and neck	57 (20.4%)	39 (21.4%)	3 (14.3%)	15 (19.5%)	
Trunk	104 (37.1%)	58 (31.9%)	14 (66.7%)	32 (41.6%)	
Location					0.722
Superficial	22 (7.9%)	15 (8.2%)	1 (4.8%)	6 (7.8%)	
Deep	243 (86.8%)	155 (85.2%)	19 (90.5%)	69 (89.6%)	
NA	15 (5.4%)	12 (6.6%)	1 (4.8%)	2 (2.6%)	
Size					<0.001
≤5 cm	76 (27.1%)	66 (36.3%)	0 (0.0%)	10 (13.0%)	
>5 cm	196 (70.0%)	110 (60.4%)	20 (95.2%)	66 (85.7%)	
NA	8 (2.9%)	6 (3.3%)	1 (4.8%)	1 (1.3%)	
Lymph node involvement	7 (2.5%)	7 (3.8%)	0 (0.0%)	0 (0.0%)	0.145
Distant metastasis	29 (10.4%)	19 (10.4%)	2 (9.5%)	8 (10.4%)	0.991
Grade					0.056
G1	28 (10.0%)	21 (11.5%)	1 (4.8%)	6 (7.8%)	
G2	141 (50.4%)	88 (48.4%)	17 (81.0%)	36 (46.8%)	
G3	97 (34.6%)	62 (34.1%)	2 (9.5%)	33 (42.9%)	
NA	14 (5.0%)	11 (6.0%)	1 (4.8%)	2 (2.6%)	
AJCC stage					0.234
I	37 (13.2%)	28 (15.4%)	2 (9.5%)	7 (9.1%)	
II	147 (52.5%)	95 (52.2%)	15 (71.4%)	37 (48.1%)	
III	67 (23.9%)	40 (22.0%)	2 (9.5%)	25 (32.5%)	
IV	29 (10.4%)	19 (10.4%)	2 (9.5%)	8 (10.4%)	
Heterologous element	22 (7.9%)	10 (5.5%)	1 (4.8%)	11 (14.3%)	0.048
Chemotherapy					0.776
Chemotherapy alone	8 (2.9%)	6 (3.3%)	1 (4.8%)	1 (1.3%)	
Neoadjuvant only	7 (2.5%)	6 (3.3%)	0 (0.0%)	1 (1.3%)	
Adjuvant only	36 (12.9%)	22 (12.1%)	2 (9.5%)	12 (15.6%)	
Neoadjuvant and adjuvant	14 (5.0%)	9 (0.0%)	0 (0.0%)	5 (6.5%)	
No chemotherapy	215 (76.8%)	139 (76.4%)	18 (85.7%)	58 (75.3%)	
Local treatment					0.165
Surgery	87 (31.1%)	64 (35.2%)	9 (42.9%)	14 (18.2%)	
Radiation	20 (7.1%)	14 (7.7%)	0 (0.0%)	6 (7.8%)	
Radiation->surgery	37 (13.2%)	19 (10.4%)	2 (9.5%)	16 (20.8%)	
Radiation->surgery->radiation	25 (8.9%)	17 (9.3%)	2 (9.5%)	6 (7.8%)	
Surgery->radiation	86 (30.7%)	54 (29.7%)	6 (28.6%)	26 (33.8%)	
Surgery->radiation->surgery	21 (7.5%)	13 (7.1%)	1 (4.8%)	7 (9.1%)	
No surgery or radiation	4 (1.4%)	1 (0.5%)	1 (4.8%)	2 (2.6%)	
Surgery type					0.018
R0	129 (46.1%)	75 (41.2%)	7 (33.3%)	47 (61.0%)	
R1	13 (4.6%)	10 (5.5%)	2 (9.5%)	1 (1.3%)	
R2	82 (29.3%)	55 (30.2%)	10 (47.6%)	17 (22.1%)	
Unknown type	32 (11.4%)	27 (14.8%)	1 (4.8%)	4 (5.2%)	
No surgery	24 (8.6%)	15 (8.2%)	1 (4.8%)	8 (10.4%)	

NA, not available. MPNST, malignant peripheral nerve sheath tumor; nfMPNST, neurofibromatosis-associated MPNST; rMPNST, radiation-induced MPNST; sMPNST, sporadic MPNST.

$p = 0.001$). Heterologous elements, e.g. rhabdomyosarcomatous (malignant Triton tumor), osteosarcomatous, and/or chondrosarcomatous differentiation, were reported in 22 patients (7.9%) and were more frequently seen in nfMPNST (14.3% vs. 5.5% in sMPNST and 4.8% in rMPNST, $p = 0.048$). The rate of metastatic disease at presentation was similar (10.4% in sMPNST vs. 10.4% in nfMPNST vs. 9.5% in rMPNST, $p = 0.991$).

Treatment modalities

Among the 280 patients, 256 (91.4%) underwent surgical resection for the primary MPNST. R0 resection was achieved in 129 (46.1%) patients, whereas R1 and R2 resections were documented in 13 (4.6%) and 82 (29.3%) patients, respectively.

A total of 169 patients (60.4%) also received pre- and/or postoperative radiation therapy (RT) to a median RT dose of 59.6 Gy

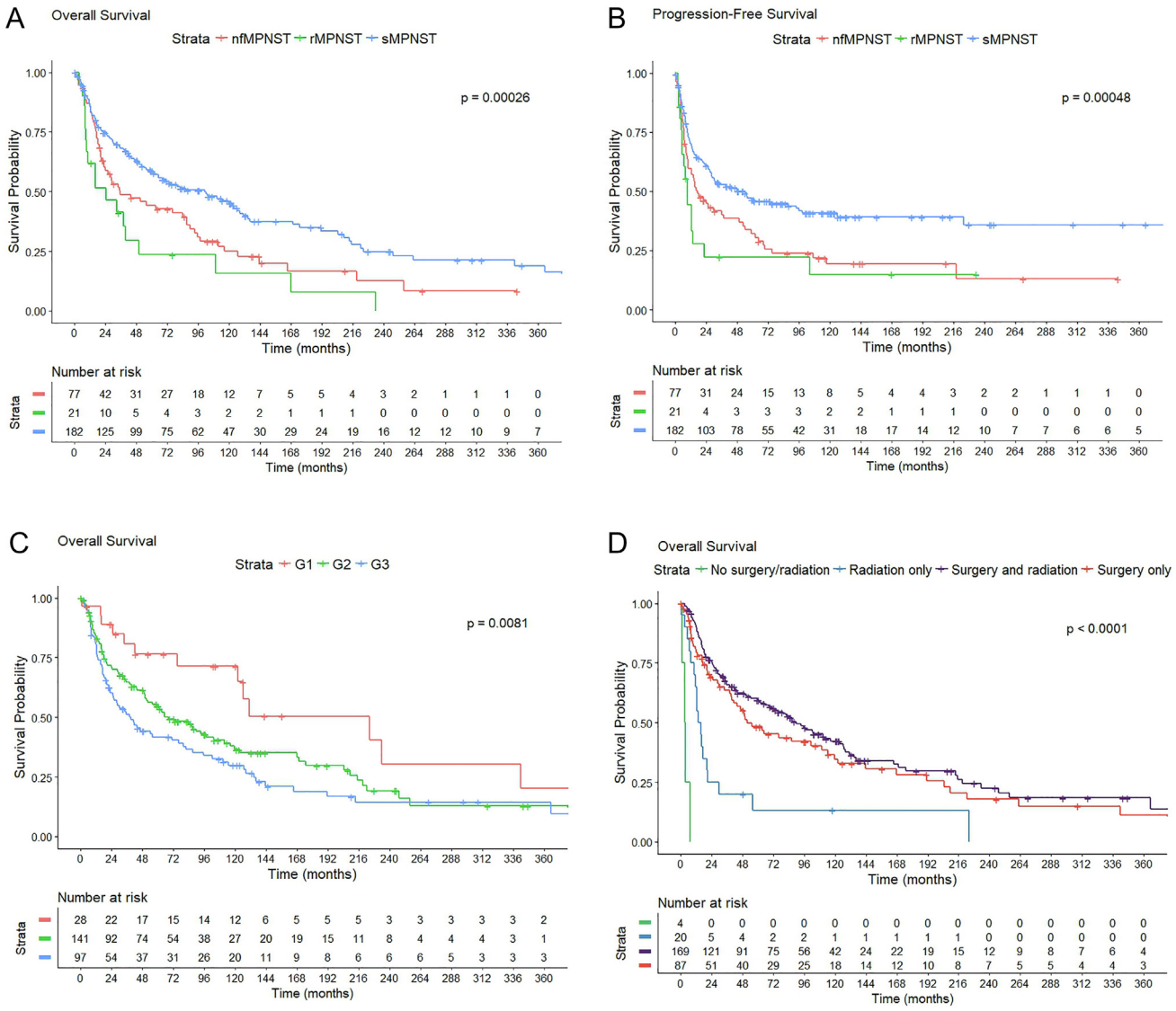

Fig. 1. Kaplan–Meier's curves in all MPNST patients. (A) Overall survival divided by MPNST subgroups. (B) Progression-free survival by MPNST subgroups. (C) Overall survival according to grade. (D) Overall survival according to local treatment. MPNST, malignant peripheral nerve sheath tumor; nfMPNST, neurofibromatosis-associated MPNST; rMPNST, radiation-induced MPNST; sMPNST, sporadic MPNST.

(range: 6–80 Gy). An additional 20 patients (7.1%) had definitive RT alone as local treatment to a median dose of 50.4 Gy (range: 10.8–78 Gy). Information regarding RT modality was available in 178 patients, which included 2D photons in 107 patients (60.1%), 3D photon in 37 patients (20.8%), proton in 37 patients (20.8%), intensity-modulated radiation therapy in 21 patients (11.8%), electron in 10 patients (5.6%), intraoperative electron in 10 patients (5.6%), brachytherapy in 5 patients (2.8%), proton pencil beam scanning in 2 patients (1.1%), and dural plaque in 1 patient (0.6%).

Systemic chemotherapy was administered as neoadjuvant treatment in 7 patients (2.5%), adjuvant in 36 patients (12.9%), or both neoadjuvant and adjuvant in 14 patients (5.0%). Another eight patients (2.9%) received chemotherapy without surgery. Chemotherapy regimen was known in 59 (90.8%) patients. Regimens were standard sarcoma chemotherapeutics alone or in combination. Most patients received doxorubicin and ifosfamide with ($n = 27$) or without ($n = 6$) dacarbazine, or doxorubicin and cyclophosphamide ($n = 5$). Seven patients received the regimen of vincristine, doxorubicin/actinomycin D, and cyclophosphamide, alone ($n = 5$) or with ifosfamide and etoposide ($n = 1$) or cisplatin ($n = 1$). Other regimens included combinations of doxorubicin and dacarbazine ($n = 1$), doxorubicin and bevacizumab on a clinical trial ($n = 1$), gemcitabine and paclitaxel ($n = 1$), gemcitabine and docetaxel ($n = 1$), ifosfamide and etoposide ($n = 1$), vinblastine, dacarbazine, and cisplatin (n = 1), or etoposide, cisplatin, dacarbazine, and actinomycin D ($n = 1$), or single agent doxorubicin ($n = 3$), ifosfamide ($n = 2$), actinomycin D ($n = 1$), or methotrexate ($n = 1$).

No significant difference was found in the percentage of patients who received surgical resection (91.8% in sMPNST, 95.2% in rMPNST, 89.6% in nfMPNST, $p = 0.691$) or chemotherapy (23.6% in sMPNST, 14.3% in rMPNST, 24.7% in nfMPNST, $p = 0.592$). However, among patients who underwent surgery, R0 resection was achieved more often in nfMPNSTs (68.1% vs. 35% in rMPNST and 44.9% in sMPNST, $p = 0.002$). More patients with nfMPNST received RT (79.2% vs. 52.4% in rMPNST and 64.3% in sMPNST, $p = 0.016$).

Table 2
Prognostic factors for overall survival and progression-free survival in all MPNST patients by the univariate analysis.

	Overall survival (months)			Progression-free survival (months)		
Variable	Median	95% CI	Log-rank *P*	Median	95% CI	Log-rank *P*
Overall	65.3	43.2–87.4		28.9	13.7–44.0	
Group			**<0.001**			**<0.001**
sMPNST	101.1	62.0–140.3		54.0	21.9–86.0	
rMPNST	24.3	0.4–48.1		9.2	5.7–12.6	
nfMPNST	35.5	9.0–61.9		17.0	6.5–27.6	
Gender			0.845			0.786
Female	65.0	39.4–90.6		29.7	6.4–52.9	
Male	70.7	30.3–111.1		28.3	8.4–48.1	
Site			**<0.001**			**<0.001**
Extremity	119.6	87.0–152.2		98.8		
Head and neck	56.0	26.5–85.4		21.4	6.9–35.8	
Trunk	28.8	16.9–40.7		13.6	3.7–23.4	
Location			0.058			**0.010**
Superficial	111.5	92.5–130.5		NR		
Deep	51.3	33.0–69.5		24.2	15.6–32.8	
NA	102.4	0.0–240.1		NR		
Size			**<0.001**			**0.001**
≤5 cm	131.1	41.6–220.6		125.9		
>5 cm	39.3	25.5–53.2		21.0	13.1–29.0	
NA	341.7			55.5	11.6–99.4	
Lymph node involvement			0.060			0.319
No	68.2	45.8–90.6		29.7	13.8–45.5	
Yes	16.2	14.1–18.3		11.2	8.2–14.3	
Distant metastasis			**<0.001**			**<0.001**
No	83.9	58.9–108.9		48.0	27.4–68.6	
Yes	12.2	7.6–16.8		6.9	3.5–10.2	
Grade			**0.027**			0.232
G1	224.2	77.3–371.0		125.9	0.0–253.4	
G2	68.2	42.3–94.1		30.0	6.1–54.0	
G3	39.3	23.4–55.2		21.6	9.3–33.9	
NA	29.9	0.0–142.7		21.0	5.2–36.9	
AJCC stage			**<0.001**			**<0.001**
I	131.1	9.7–252.5		125.9	7.0–244.8	
II	86.8	53.1–120.6		52.9	26.6–79.2	
III	35.4	21.7–49.0		25.0	10.8–39.1	
IV	12.2	7.6–16.8		6.9	3.5–10.2	
Heterologous element			0.941			0.563
No	68.2	45.7–90.6		30.0	11.9–48.3	
Yes	39.5	0–100.5		15.2	1.9–28.5	
Chemotherapy			0.379			0.141
No	72.8	47.0–98.5		35.2	15.9–54.5	
Yes	51.3	8.4–94.1		15.3	3.2–27.4	
Local treatment			**<0.001**			**<0.001**
Surgery	51.9	23.1–80.8		21.0	0.0–45.4	
Radiation	13.6	7.0–20.3		5.7	3.6–7.7	
Surgery and radiation	89.6	61.7–117.5		54.1	23.9–84.3	
No surgery or radiation	3.3	0.7–5.9		0.0		
Surgery type			**<0.001**			**<0.001**
R0	97.4	64.0–130.7		125.9	0.0–266.9	
R1	110.8	0.0–298.5		73.7	1.9–145.5	
R2	27.3	14.2–40.3		13.1	6.6–19.6	
Unknown type	101.1	1.9–200.4		28.0	10.1–45.9	
No surgery	12.5	8.7–16.3		5.7	3.0–8.3	

AJCC, American Joint Committee on Cancer. CI, confident interval. NA, not available. NR, not reached. MPNST, malignant peripheral nerve sheath tumor; nfMPNST, neurofibromatosis-associated MPNST; rMPNST, radiation-induced MPNST; sMPNST, sporadic MPNST.

However, among those receiving RT, the dose to patients with nfMPNST was relatively lower (median: 50 Gy vs. 59.5 Gy in rMPNST and 62 Gy in sMPNST, $p < 0.001$).

Survival analysis

With a median follow-up of 43.1 months (range: 0.5–464.3 months), the median OS was 65.3 months (95% confident interval [CI]: 43.2–87.4 months, Fig. 1A). One hundred and twenty-eight patients (45.7%) died from disease, 77 (27.5%) were alive without evidence of disease, 32 (11.4%) died of unknown causes, 24 (8.6%) died of other causes, and 19 (6.8%) were alive with disease at the time of last follow-up. The OS rates for all patients were 51.9% (95% CI: 45.7%-58.1%) at 5 years and 37.2% (95% CI: 30.7%-43.7%) at 10 years. One hundred and seventy-four patients (62.1%) had local/regional recurrences ($n = 117$, 41.8%) and/or further metastases ($n = 95$, 33.9%). The 5- and 10-year rates of PFS were 40.6% (95% CI: 34.5%-46.8%) and 32.5 % (95% CI: 26.2%-38.8%), respectively, with disease progression at a median time of 28.9 months (range: 13.7–44.0 months, Fig. 1B).

On univariate analysis (Table 2, Fig. 1), both nfMPNST and rMPNST showed worse OS (median: 35.5 months and 24.2 months, respectively, vs. 101.1 months, $p < 0.001$, Fig. 1A) and progressed earlier (median: 17.0 months and 9.2 months, respectively, vs.

Table 3
Multivariate analysis of prognostic factors associated with overall survival and progression-free survival in all MPNST patients.

		Overall survival			Progression-free survival		
Variable	*N*	HR	95.0% CI	P	HR	95.0% CI	*P*
Group							
sMPNST	182	1.00		**0.001**	1.00		**<0.001**
rMPNST	21	2.02	1.14–3.57	**0.015**	2.15	1.24–3.72	**0.007**
nfMPNST	77	1.95	1.31–2.90	**0.001**	2.30	1.62–3.26	**<0.001**
Age (per year)		1.01	1.00–1.02	**0.004**			NS
Size							
≤5 cm	76	1.00		**0.003**			NS
>5 cm	196	1.86	1.25–2.77	**0.002**			
NA	8	0.71	0.21–2.40	0.583			
Lymph node involvement							
No	273	1.00			1.00		
Yes	7	2.93	1.14–7.53	**0.026**	2.64	1.04–6.70	**0.040**
Distant metastasis							
No	251	1.00			1.00		
Yes	29	2.19	1.36–3.53	**0.001**	2.47	1.55–3.92	**<0.001**
Grade							
G1	28	1.00		**0.010**			NS
G2	141	2.29	1.24–4.24	**0.008**			
G3	97	2.73	1.45–5.13	**0.002**			
NA	14	2.09	0.89–4.89	0.090			
Local treatment							
Surgery	87	1.00		**<0.001**	1.00		**<0.001**
Radiation	20	2.39	1.25–4.57	**0.008**	2.99	1.62–5.54	**<0.001**
Surgery and radiation	169	0.63	0.44–0.90	**0.011**	0.59	0.41–0.85	**0.004**
No surgery or radiation	4	18.27	5.31–62.89	**<0.001**	3.94	0.91–17.03	0.067
Surgery type							
R0	129	1.00		**0.002**	1.00		**<0.001**
R1	13	0.98	0.40–2.35	0.956	1.66	0.78–3.53	0.192
R2	82	2.05	1.42–2.96	**<0.001**	2.47	1.70–3.58	**<0.001**
Unknown type	32	1.32	0.79–2.20	0.284	2.21	1.33–3.67	**0.002**

CI, confident interval. HR, hazard ratio. NA, not available. NS, not significant. MPNST, malignant peripheral nerve sheath tumor; nfMPNST, neurofibromatosis-associated MPNST; rMPNST, radiation-induced MPNST; sMPNST, sporadic MPNST.

54.0 months, $p < 0.001$, Fig. 1B) than sMPNST, although the difference between nfMPNST and rMPNST was not significant.

On multivariate analysis, older age (Hazard ratio [HR] = 1.01, 95% CI: 1.00–1.02, $p = 0.004$), nfMPNST (HR = 1.95, 95% CI: 1.31–2.90, $p = 0.001$), rMPNST (HR = 2.02, 95% CI: 1.14–3.57, $p = 0.015$), tumor size > 5 cm (HR = 1.86, 95% CI: 1.25–2.77, $p = 0.002$), positive lymph node (HR = 2.93, 95% CI: 1.14–7.53, $p = 0.026$), metastatic disease at diagnosis (HR = 2.19, 95% CI: 1.36–3.53, $p = 0.001$), intermediate (HR = 2.29, 95% CI: 1.24–4.24, $p = 0.008$) or high (HR = 2.73, 95% CI: 1.45–5.13, $p = 0.002$) grade, RT alone (HR = 2.39, 95% CI: 1.25–4.57, $p = 0.008$), and R2 resection (HR = 2.05, 95% CI: 1.42–2.96, $p < 0.001$) correlated with worse OS, whereas surgery with RT (HR = 0.63, 95% CI: 0.44–0.90, $p = 0.011$) was associated with improved OS compared with surgery alone. Similar prognostic factors, except age and tumor size, were also significant for PFS (Table 3).

Among the 251 patients without metastatic disease (M0) at initial presentation, the median OS was 83.9 months (95% CI: 58.9–108.9 months) with 56.5% (95% CI: 50.0%-63.1%) and 40.7% (95% CI: 33.7%-47.7%) alive at 5 and 10 years. One hundred and three patients (41.0%) had at least one local or regional recurrence. The local relapse-free survival rates were 61.4% (95% CI: 54.7%-68.1%) at 5 years and 51.1% (95% CI: 43.5%-58.8%) at 10 years, with local recurrence at a median time of 125.9 months (range: 45.7–206.1 months). Ninety-five patients (37.8%) developed distant metastases, most frequently to lungs ($n = 53$), followed by soft tissue ($n = 31$), spine ($n = 15$) and other bones ($n = 9$), brain ($n = 14$), and liver ($n = 8$), etc. The 5- and 10-year MFS were 60.6% (96% CI: 53.8%-67.3%) and 56.0% (95% CI: 48.7%-63.2%), respectively.

On univariate analyses (Table 4, Fig. 2), nfMPNST and rMPNST had worse OS (median: 51.3 months and 33.0 months, respectively) vs. sMPNST (119.6 months, $p < 0.001$, Fig. 2A). Likewise, MFS is worse for nfMPNST and rMPNST (median: 52.9 months and 17.1 months respectively) compared to sMPNST (not reached, $p < 0.001$, Fig. 2B).

On multivariate analysis, nfMPNST (HR = 2.09, 95% CI: 1.34–3.25, $p = 0.001$), rMPNST (HR = 2.22, 95% CI: 1.10–4.49, $p = 0.026$), and tumor size > 5 cm (HR = 2.36, 95% CI: 1.30–4.26, $p = 0.005$) were correlated with worse MFS. Having nfMPNST (HR = 1.98, 95% CI: 1.23–3.21, $p = 0.005$), RT alone (HR = 2.79, 95% CI: 1.02–7.60, $p = 0.045$), R1 (HR = 2.60, 95% CI: 1.05–6.42, $p = 0.038$) and R2 (HR = 6.32, 95% CI: 3.81–10.49, $p < 0.001$) resection was associated with a higher rate of local recurrence, whereas surgery with RT was related to improved LRFS (HR = 0.31, 95% CI: 0.20–0.49, $p < 0.001$, Table 5). In addition, for patients who received surgical resection, preoperative RT was associated with better LRFS ($p < 0.001$, Fig. 2E), whereas for patients with R1 or R2 resections, the addition of postoperative RT reduced local recurrence ($p < 0.001$, Fig. 2F).

Discussion

Consistent with the literature [2,3,5,7,15–18,20], this study demonstrates that older age, larger tumor size, lymph node involvement, metastatic disease at diagnosis, intermediate to high grade, and R2 resection were significant predictors for poor survival. For patients with non-metastatic MPNST at the time of diagnosis, tumor location in head/neck or trunk was also associated with worse OS.

The association between MPNST and NF1 is well-known. However, outcome difference from the comparisons between NF1-

Table 4
Prognostic factors for overall survival, local relapse-free survival, and metastatic-free survival in the 251 non-metastatic MPNST patients by the univariate analysis.

		Overall survival			Local relapse-free survival			Metastasis-free survival		
Variable	*N*	5-year rate	95% CI	Log-rank *P*	5-year rate	95% CI	Log-rank *P*	5-year rate	95% CI	Log-rank *P*
Overall	251	56.5%	50.0–63.1%		61.4%	54.7–68.1%		60.6%	53.8–67.3%	
Group				**<0.001**			0.066			**<0.001**
sMPNST	163	63.1%	55.2–71.1%		62.5%	54.2–70.7%		70.7%	63.0–78.4%	
rMPNST	19	25.9%	4.3–47.6%		48.2%	23.9–72.5%		39.4%	14.9–63.9%	
nfMPNST	69	49.5%	37.0–62.0%		63.3%	50.9–75.8%		43.0%	29.8–56.2%	
Gender				0.751			0.928			0.555
Female	125	57.3%	47.8–66.7%		62.7%	53.4–72.0%		61.6%	52.1–71.1%	
Male	126	55.9%	46.7–65.0%		60.0%	50.4–69.7%		59.6%	50.1–69.1%	
Site				**<0.001**			**<0.001**			**0.003**
Extremity	109	74.1%	65.3–82.9%		79.0%	70.8–87.2%		69.0%	59.6–78.3%	
Head and neck	54	50.8%	36.2–65.3%		43.7%	28.3–59.1%		66.1%	51.8–80.4%	
Trunk	88	38.5%	27.7–49.3%		48.1%	35.9–60.3%		45.9%	33.6–58.1%	
Location				**<0.001**			**0.012**			**<0.001**
Superficial	22	80.0%	61.9–98.0%		89.6%	75.5–100.0%		75.4%	56.1–94.7%	
Deep	215	52.7%	45.6–59.8%		57.5%	50.2–64.9%		57.8%	50.4–65.2%	
NA	14	82.1%	58.7–100.0%		74.7%	48.9–100.0%		76.9%	53.6–100.0%	
Size				**<0.001**			**0.012**			**<0.001**
≤5 cm	73	77.8%	67.7–88.0%		72.8%	61.7–83.8%		80.9%	71.3–90.5%	
>5 cm	171	47.4%	39.4–55.4%		57.1%	48.8–65.4%		51.1%	42.5–59.6%	
NA	7	55.6%	5.9–100.0%		40.0%	0.0–87.3%		66.7%	28.2–100.0%	
Lymph node involvement				0.321			0.866			0.262
No	246	56.9%	50.3–63.6%		61.6%	54.8–68.3%		61.0%	54.2–67.8%	
Yes	5	40.0%	0.0–83.8%		55.6%	8.7–100.0%		40.0%	0.0–83.8%	
Grade				**0.044**			0.710			0.091
G1	26	78.0%	60.5–95.5%		73.4%	54.4–92.4%		87.7%	74.4–100.0%	
G2	130	58.8%	49.7–67.9%		61.0%	51.7–70.3%		56.3%	46.8–65.8%	
G3	84	45.7%	34.3–57.0%		59.0%	47.1–70.8%		58.5%	46.4–70.5%	
NA	11	63.6%	34.6–92.6%		54.5%	24.5–84.6%		61.9%	31.6–92.1%	
AJCC stage				**0.001**			0.394			**0.041**
I	37	73.7%	58.5–88.8%		68.0%	51.8–84.1%		79.8%	66.2–93.5%	
II	147	60.1%	51.6–68.6%		61.9%	53.3–70.6%		59.3%	50.5–68.1%	
III	67	39.4%	26.8–51.9%		56.2%	42.6–69.9%		51.7%	37.6–65.8%	
Heterologous element				0.858			0.191			0.268
No	230	57.5%	50.6–64.3%		63.0%	56.0–70.0%		61.9%	54.9–68.9%	
Yes	21	47.2%	25.3–69.1%		45.0%	22.6–67.4%		47.2%	23.8–70.6%	
Chemotherapy				0.558			0.950			0.981
No	203	55.9%	48.5–63.2%		59.9%	52.3–67.5%		60.9%	53.4–68.3%	
Yes	48	59.3%	44.9–73.8%		67.0%	52.9–81.1%		59.6%	44.1–75.1%	
Local treatment				**<0.001**			**<0.001**			0.275
Surgery	78	51.6%	39.3–63.9%		41.9%	29.7–54.0%		66.4%	54.4–78.5%	
Radiation	11	18.2%	0.0–41.4%		54.5%	24.5–84.6%		50.0%	18.4–81.6%	
Surgery and radiation	161	61.9%	54.0–69.9%		71.8%	64.1–79.5%		59.1%	50.8–67.3%	
No surgery or radiation	1	–	–		–	–		–	–	
Surgery type				**<0.001**			**<0.001**			**0.041**
R0	122	70.3%	61.7–−78.9%		82.4%	74.9%-89.8%		63.7%	54.5–72.8%	
R1	13	76.2%	52.0–100.0%		64.8%	35.8–93.8%		80.9%	56.2–100.0%	
R2	73	39.3%	27.2–51.3%		40.3%	27.7–52.9%		51.3%	38.1–64.4%	
Unknown type	31	50.0%	30.3–69.7%		29.1%	10.5–47.6%		68.7%	50.3–87.2%	
No surgery	12	16.7%	0.0–38.2%		56.5%	27.3–85.8%		52.4%	21.6–83.2%	

AJCC, American Joint Committee on Cancer. CI, confident interval. NA, not available. NS, not significant. MPNST, malignant peripheral nerve sheath tumor; nfMPNST, neurofibromatosis-associated MPNST; rMPNST, radiation-induced MPNST; sMPNST, sporadic MPNST.

associated and sporadic MPNSTs remains controversial [2,3,5,7,15,16,18]. A recent meta-analysis of over 1800 MPNST patients from the literature demonstrated a significantly worse outcome in NF1-associated MPNSTs but improved prognosis during the last decade [18]. In this study, nfMPNST were more likely to metastasize earlier than sMPNSTs and have worse OS. We observed a 5-year OS rate of 49.5% and a 5-year MFS rate of 43.0% for nfMPNST compared to that of 63.1% and 70.7% for sMPNST among those with non-metastatic disease at diagnosis. The relatively larger tumor size and the slightly more frequent truncal location of nfMPNST in our series may also account for this poor outcome. On the other hand, only two patients with nfMPNST in our series were reported to have mutations in NF1 gene, and for the remaining patients, no genetic test in NF1 was performed or reported. It is possible that NF1 could be underreported over the time due to missing clinical and genetic information.

Even less is known about radiation-induced MPNSTs, largely due to their rarity. The standardized incidence ratio of a secondary MPNST in childhood cancer survivors was the highest among any subtypes of soft tissue sarcoma, with a 40.6-fold increased risk compared with that expected [6]. The reported age distribution of rMPNST varied among different studies. The median age in one study of 14 rMPNSTs was 49 years (range: 37–60 years) [2], while another study of 11 patients showed a median age of 31 years (range: 25–58 years) [21]. The patients with rMPNSTs presented with a median age of 36 (range: 18–65) years in our series. However, the observed median latency of the development of MPNST from prior radiation exposure was 15 (range: 6–50) years, which was only slightly longer than the previously reported median latency of approximately 12–13 years [2,22]. It is possible that rMPNST could occur at any age, which in part depends on when previous radiation was delivered.

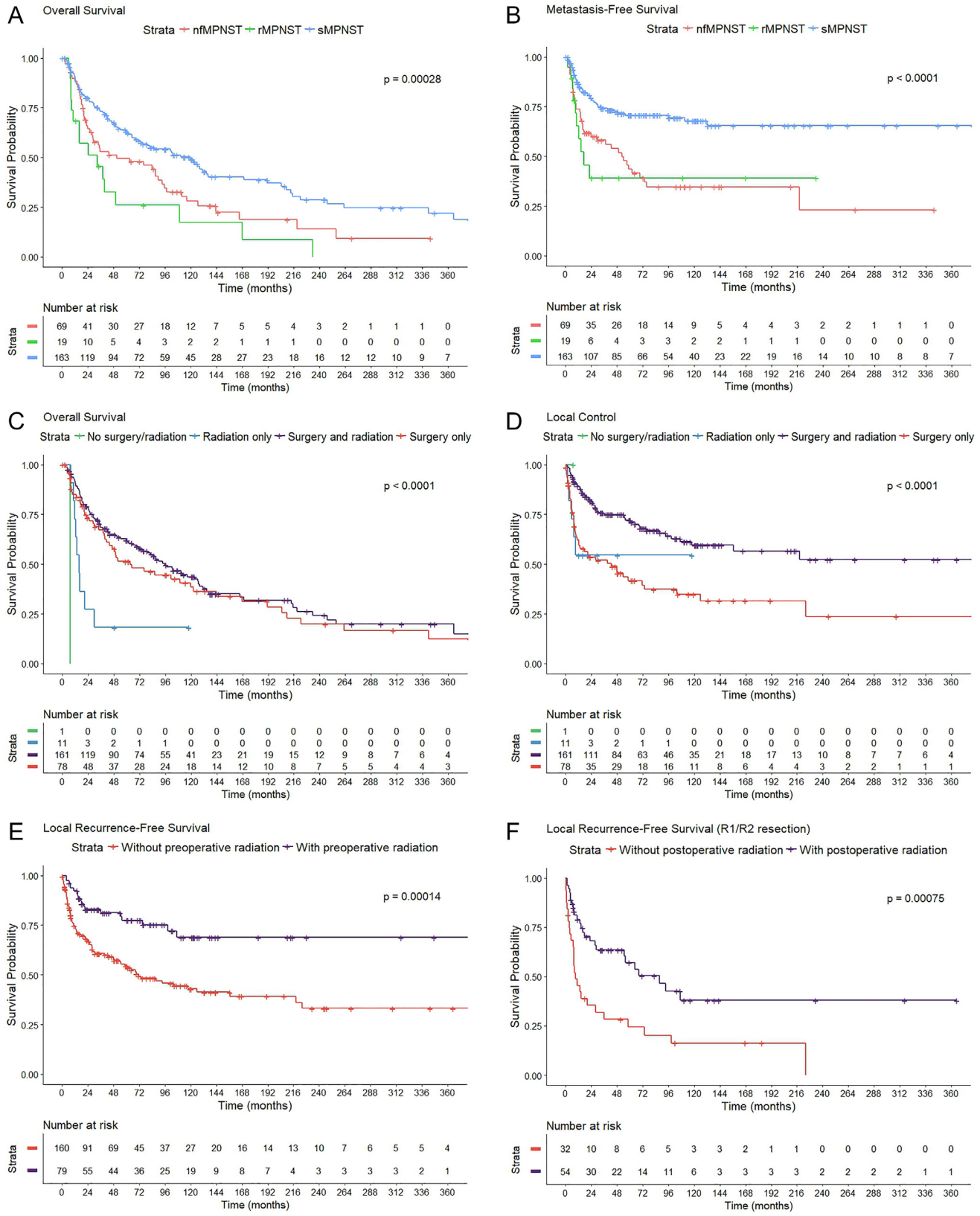

Fig. 2. Kaplan–Meier's curves in non-metastatic MPNST patients. (A) Overall survival divided by MPNST subgroups. (B) Metastasis-free survival divided by MPNST subgroups. (C) Overall survival according to local treatment. (D) Local relapse-free survival according to local treatment. (E) Local relapse-free survival of non-metastatic MPNSTs after surgical resection with or without preoperative radiation therapy. (F) Local relapse-free survival of non-metastatic MPNSTs after R1 or R2 resection with or without postoperative radiation therapy. MPNST, malignant peripheral nerve sheath tumor; nfMPNST, neurofibromatosis-associated MPNST; rMPNST, radiation-induced MPNST; sMPNST, sporadic MPNST.

Table 5
Multivariate analysis of prognostic factors associated with overall survival, local relapse-free survival, and metastatic-free survival in the 251 non-metastatic MPNST patients.

		Overall survival			Local relapse-free survival			Metastasis-free survival		
Variable	*N*	HR	95.0% CI	*P*	HR	95.0% CI	*P*	HR	95.0% CI	*P*
Group										
sMPNST	163	1.00		**0.023**	1.00		**0.001**	1.00		**0.002**
rMPNST	19	1.79	0.97–3.29	0.061	1.41	0.70–2.84	0.336	2.22	1.10–4.49	**0.026**
nfMPNST	69	1.68	1.09–2.59	**0.019**	2.39	1.51–3.79	**<0.001**	2.09	1.34–3.25	**0.001**
Age (per year)		1.02	1.01–1.03	**0.001**			NS			NS
Site										
Extremity	109	1.00		**0.008**			NS			NS
Head and neck	54	1.71	1.05–2.78	**0.030**						
Trunk	88	1.81	1.22–2.70	**0.003**						
Size										
≤5 cm	73	1.00		0.073			NS	1.00		**0.014**
>5 cm	171	1.64	1.06–2.53	**0.026**				2.36	1.30–4.26	**0.005**
NA	7	1.22	0.35–4.20	0.752				3.12	0.89–10.94	0.075
Grade										
G1	26	1.00		**0.009**			NS			NS
G2	130	2.23	1.17–4.28	**0.015**						
G3	84	2.73	1.40–5.31	**0.003**						
NA	11	1.44	0.53–3.87	0.475						
Local treatment										
Surgery	78	1.00		**0.001**	1.00		**<0.001**			NS
Radiation	11	3.28	1.49–7.20	**0.003**	2.38	0.88–6.43	0.088			
Surgery and radiation	161	0.73	0.50–1.08	0.113	0.32	0.21–0.51	**<0.001**			
No surgery or radiation	1	21.79	2.52–188.59	**0.005**	0.00	0.00–6.55E + 255	0.975			
Surgery type										
R0	122	1.00		**0.012**	1.00		**<0.001**			NS
R1	13	0.87	0.35–2.13	0.755	2.78	1.12–6.86	**0.027**			
R2	73	1.91	1.28–2.86	**0.002**	6.02	3.62–9.99	**<0.001**			
Unknown type	31	1.23	0.71–2.11	0.460	4.78	2.58–8.84	**<0.001**			

CI, confident interval. HR, hazard ratio. NA, not available. NS, not significant. MPNST, malignant peripheral nerve sheath tumor; nfMPNST, neurofibromatosis-associated MPNST; rMPNST, radiation-induced MPNST; sMPNST, sporadic MPNST.

Similar to several published reports [2,21,22], the prognosis for patients with rMPNST in our study was poor, with earlier disease progression and distant metastasis resulting in lower OS. We found that rMPNSTs had a 5-year OS of 23.5%, compared to 58.5% for sMPNSTs. However, as also seen in other studies [21,22], rMPNSTs were more commonly located in the trunk (66.7%) and those central tumors may be inherently more aggressive [20]. With more central location and larger tumor size (95.2% larger than 5 cm), it was more difficult to achieve negative surgical margin for rMPNSTs, with R0 resection in only 35% of all rMPNST patients vs. 68.1% of nfMPNSTs and 44.9% of sMPNSTs. Moreover, RT was administered less frequently for rMPNST (52.4%) compared to nfMPNST (79.2%) and sMPNST (64.3%), probably due to the concern of adverse effects from re-irradiation [22]. Therefore, in addition to the potentially more aggressive nature of rMPNSTs themselves, these factors may have contributed to the much poorer outcomes as well.

The role of adjuvant/additive RT remains inconclusive. Some studies failed to demonstrate efficacy for local control [3,22,23], while other reports did not show improved long-term survival [3,5,10,15,22–24]. All studies were based on retrospective settings, as no prospective randomized trials that specifically look at RT in the context of MPNST have yet been conducted. It has been argued that the results might have been biased in a way that patients with more extensive tumors, positive margin status, and unresponsiveness to other therapies were more likely to be selected for RT [23]. Generally, adjuvant/additive RT is recommended for tumors with aggressive features such as intermediate- to high-grade lesions, > 5 cm in size, or with R1 or R2 excision [3,24]. In the current study, in addition to an improved PFS (HR = 0.59, $p = 0.004$) and LRFS (HR = 0.31, $p < 0.001$), additive RT was also correlated with improved OS (HR = 0.63, $p = 0.011$) in all patients. However, due to the retrospective nature of this study, it cannot be ruled out that these favorable outcomes were related to a more indolent biology and a smaller tumor burden. Improved LRFS was also achieved in those who received preoperative RT ($p < 0.001$), which could be attributed to the increased chance of complete resection as indicated by the significantly higher rate of R0 resections after preoperative RT vs. no preoperative RT (77.2% vs. 38.5%, $p < 0.001$). For patients with positive surgical margin, postoperative RT was associated with reduced local recurrence compared to those without adjuvant RT ($p < 0.001$), suggesting that postoperative RT may have a role in improving local disease control in patients with residual disease.

The role of chemotherapy is also uncertain in MPNST. MPNST appears to be of intermediate chemosensitivity to various chemotherapeutic regimens that have been adopted over the years, with response rate ranging from 24% to 45% [13,24–26]. Several studies reported a significantly lower response rate in patients with nfMPNST than in those with sMPNST [13,25,26], even though similar qualitative responses and disease stabilization were achieved in most patients of both groups [25]. We did not observe any significant correlation between treatment with conventional sarcoma chemotherapy and OS ($p = 0.379$) or PFS ($p = 0.141$), even among the 29 patients with metastatic disease at diagnosis ($p = 0.928$ for OS, $p = 0.682$ for PFS) or the 24 patients who did not receive surgical resection ($p = 0.763$ for OS, $p = 0.336$ for PFS). Conventional chemotherapy did not reduce mortality or delay disease progression in this highly aggressive sarcoma cohort. On the other hand, this study is limited by its retrospective nature. Patients were not randomized to receive chemotherapy and some of them might have been treated more aggressively due to those more aggressive factors, e.g. larger size, higher grade, and/or central location.

Of interest is whether novel therapeutics could have a more promising impact. Although several phase II trials of different targeted agents, e.g. erlotinib, sorafenib, imatinib, dasatinib, and alisertib, have failed to demonstrate any benefit for refractory MPNSTs [10,27–30], the completed studies can be compiled to develop a baseline time to progression and referred to as historical comparison for future trials [31]. Some other trials, such as combinations of ganetespib with sirolimus and bevacizumab with RAD001, are ongoing. Moreover, it is hoped that more effective treatments will be available in the future [10,31].

Given the retrospective nature, the long time and heterogeneity in practice of therapy of our cohort due to rarity of the disease, the limitations of this study cannot be ignored. In addition, as our institution has been a specialized center for treatment of sarcoma in the US during the past 50 years, our series consists of a highly selected cohort of patients but is also one of the largest series in the literature. The future of research lies in potentially next generation sequencing data and prognostic, multicenter studies.

In conclusion, both radiation-induced and NF1-associated MPNSTs have poorer prognosis than sporadic MPNSTs, and warrant further studies to determine optimal treatment. Patients who undergo radiation therapy should be monitored for secondary malignancies including MPNST. Complete surgical resection of the tumor is a significant prognostic factor for patients with MPNST. Radiotherapy improved local control after surgery, especially when surgical margins are positive. Multidisciplinary management of MPNST is important to optimize outcome.

Disclosure

The authors report no conflicts of interest.

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