Patterns of recurrence and survival in sporadic, neurofibromatosis Type 1–associated, and radiation-associated malignant peripheral nerve sheath tumors

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OBJECTIVE Malignant peripheral nerve sheath tumors (MPNSTs) are an aggressive group of soft tissue sarcomas that can arise sporadically, in the context of neurofibromatosis Type 1 (NF1) or at a site of prior irradiation. Large series profiling the features and outcomes of sporadic, NF1-associated, and radiation-associated MPNSTs are limited. The goal of this study was to elucidate differences between MPNST etiologies in a large single-institution retrospective study.

METHODS Patients (n = 317) were identified through the tumor registry of The University of Texas MD Anderson Cancer Center. Clinicopathological features were retrospectively collected. Features were compared among MPNST subtypes for patients who had sufficient clinical history (n = 289), and clinicopathological features were used to identify adverse predictors of recurrence and survival outcomes.

RESULTS Five-year local recurrence-free survival (LRFS), distant recurrence-free survival (DRFS), and disease-specific survival (DSS) estimates were 56.6%, 49.6%, and 53.6%, respectively, for the high-grade MPNST cohort. Five-year DSS was lower in NF1-associated and radiation-associated MPNST than in sporadic MPNST (52%, 47%, and 67%, respectively, p = 0.140). Patients with radiation-associated MPNST had worse 5-year LRFS than those with the sporadic and NF1-associated subtypes (RT-associated vs sporadic, p = 0.010; RT-associated vs NF1-associated, p = 0.232). Truncally located tumors, positive surgical margins, local recurrence, and metastasis were predictors of adverse DSS in multivariate analysis.

CONCLUSIONS Radiation-associated MPNSTs are associated with poorer local recurrence-free and disease-specific survival than sporadic and NF1-associated tumors. NF1-associated MPNSTs may have worse survival outcomes owing to large tumor size, compromising truncal location, and lower rate of negative resection margins compared with sporadic tumors.

<http://thejns.org/doi/abs/10.3171/2015.12.JNS152443>

KEY WORDS malignant peripheral nerve sheath tumor; MPNST; neurofibromatosis Type 1; radiation-induced sarcoma

ACCOUNTING for 2%–5% of soft tissue sarcomas, malignant peripheral nerve sheath tumors (MPNSTs) are a complex group of tumors that arise from the peripheral nerve sheath.^{4,9} Approximately 40%–50% of MPNSTs arise within the setting of neurofibromatosis Type 1 (NF1), a highly penetrant autosomal dominant ge-

netic disorder caused by a loss-of-function mutation in the *NF1* gene. The lifetime incidence of malignant transformation of existing neurofibromas in NF1 patients is approximately 10%.^{8,24} An additional 40%–47% of MPNSTs develop sporadically, and 10%–13% arise in a prior field of therapeutic radiation.^{8,15} Management of these tumors is

ABBREVIATIONS DRFS = distant recurrence-free survival; DSS = disease-specific survival; HR = hazard ratio; LRFS = local recurrence-free survival; MPNST = malignant peripheral nerve sheath tumor; NF1 = neurofibromatosis Type 1.

SUBMITTED October 21, 2015. **ACCEPTED** December 11, 2015.

INCLUDE WHEN CITING Published online April 1, 2016; DOI: 10.3171/2015.12.JNS152443.

challenging, as the benefit of chemotherapy has not been widely demonstrated, and the success of radiotherapy for local control has not consistently been reported.^{1,7,19,23,25} Negative margin resection—often impeded by large tumor size and extensive nerve involvement—remains the mainstay of curative treatment.^{3,11} MPNSTs have a high propensity for local relapse without complete resection and a high risk for metastatic spread. Prognosis in patients with MPNST remains poor, with reported 5-year disease-specific survival (DSS) rates ranging from 39% to 60% in multiple single-institution series over the last 15 years.^{1,7,19,23,25} However, some small studies have demonstrated superior survival in patients with low-grade variants of MPNST, suggesting a benign natural history in these rare lesions compared with their high-grade counterparts.^{2,22} Whether NF1 is adversely associated with survival remains controversial.^{14,19,23} Additionally, studies comparing outcomes of radiation-associated MPNST to other subtypes are sparse as a consequence of their rarity.¹⁵ The objective of this study was to identify adverse predictors of recurrence and survival in patients with sporadic, NF1-associated, and radiation-associated MPNSTs. As a secondary goal, low-grade MPNSTs were interrogated separately from high-grade MPNSTs to determine their natural history and optimal clinical management.

Methods

With approval of The University of Texas MD Anderson Cancer Center Institutional Review Board, a retrospective database containing 317 patients with a pathologically confirmed MPNST diagnosis between 1990 and 2014 was constructed. Data were collected under a Waiver of Consent/Authorization approved by the institutional review board. Patients who had adequate clinical history ($n = 289$) were included for statistical analysis (Fig. 1). Clinicopathological characteristics were collected in a comprehensive medical record review. A diagnosis of sporadic MPNST was made as previously described and in the absence of NF1 or prior local radiotherapy for a different malignancy.²⁵ A tumor was classified as NF1-associated if documented genetic testing confirmed a germline *NF1* mutation or by clinical evaluation based on the 1987 National Institutes of Health consensus criteria for diagnosis of NF1.¹⁸ Patients with a history of therapeutic radiotherapy at least 6 months prior for an unrelated malignancy within the local field containing the newly arising MPNST were considered to have a radiation-associated MPNST.¹⁰

Resection margins were obtained from pathology notes. A resection margin was considered microscopically negative (R0) if the closest margin was > 1 mm from the inked surface, microscopically positive (R1) if the closest margin was ≤ 1 mm from the inked surface, or macroscopically positive (R2) for any subtotal resection where gross disease was present at inked margins. Tumors were graded as high or low on the basis of nuclear atypia, presence of hyperchromasia, mitotic activity, cellularity, and growth pattern.^{6,21} Select studies have demonstrated more favorable outcomes in low-grade MPNSTs compared with high-grade MPNSTs; therefore, we reviewed patients with low-grade MPNSTs independently ($n = 12$).^{2,22} Patients in

the high-grade cohort who did not receive surgical intervention as part of their primary treatment ($n = 22$) or who underwent subtotal R2 resection ($n = 23$) were evaluated independently, owing to their anticipated poor prognosis. Only patients who had primary tumors in the absence of synchronous metastasis at diagnosis were included in the outcomes analysis (Fig. 1).

Characteristics between MPNST subtypes were compared using chi-square or Fisher's exact test for categorical variables and the nonparametric Mann-Whitney U-test or Kruskal-Wallis test for continuous variables, as appropriate. Log-rank methods were employed to estimate local recurrence-free survival (LRFS), distant recurrence-free survival (DRFS), and DSS outcomes. A disease-specific event was recorded if the patient experienced MPNST-specific death. Multivariate Cox regression models were constructed by including any variables with statistical significance below a p value cutoff of 0.05 at the univariate level. All 2-sided p values < 0.05 were considered statistically significant. All computations were performed using SPSS version 22.0 (IBM Corp.).

Results

Patient Characteristics and Presentation

A total of 289 patients with MPNST treated at our institution between 1990 and 2014 were included. Tumor and demographic characteristics of these patients are summarized in Table 1. The median duration of follow-up was 2.13 years (range 0.05–36.0 years), 2.18 years (range 0.03–29.8 years), and 1.74 years (range 0.25–13.7 years) for sporadic, NF1-associated, and radiation-associated MPNSTs, respectively. One hundred fifteen patients (40%) presented with sporadic disease, 148 (51%) with MPNST in association with NF1, and 26 (9%) with MPNST subsequent to previous local radiation therapy for a different malignancy. The median latency period for the development of radiation-associated MPNST from prior irradiation was 16 years (range 0.86–37 years); the most common indications for prior radiotherapy were breast carcinoma (33%) and Hodgkin's lymphoma (22%).

The diagnosis of MPNST was established histologically in all cases (MPNST 89%, epithelioid MPNST 7%, triton tumor 4%). Primary disease was most commonly located in the trunk (54%), followed by the extremities (31%), but location varied between MPNST subtypes ($p = 0.008$). The most commonly affected nerve in the 157 cases of truncally located disease was within the lumbosacral nerve roots ($n = 37$ [24%]), followed by the brachial plexus ($n = 30$ [19%]) and the thoracic nerve roots ($n = 17$ [11%]). The sciatic nerve was affected in 12 (8%) of 157 truncally located cases and 25 (40%) of 63 lower extremity cases; 19 (50%) of 38 cases of NF1-associated MPNSTs located within the lower extremity arose from the sciatic nerve. Symptoms at primary diagnosis were available for 245 patients (85%); 38 patients (16%) were asymptomatic but with a palpable mass effect, and 4 patients (2%) were asymptomatic with incidental discovery of their disease. Two hundred and three (83%) of 245 patients were symptomatic, and 120 (49%) of these 245 patients reported more than 1 symptom. The most common symptom was

FIG. 1. Flowchart showing patient selection and study analysis.

pain in 173 (71%) patients, followed by extremity weakness in 32 (13%), extremity numbness in 22 (9%), paresthesia in 14 (6%), and gait instability or foot drop in 13 (5%). There were no statistically significant differences between symptoms at presentation and MPNST subtype; however, patients with NF1-associated tumors were more likely to be symptomatic at presentation than patients with sporadic or radiation-associated tumors (90% vs 75% and 73%, respectively, $p = 0.006$).

Twelve tumors (4%) were determined to be low grade. Low-grade MPNSTs were more likely to be superficially located compared with high-grade MPNSTs (31% vs 5% for low-grade and high-grade MPNSTs, respectively, $p = 0.004$). All NF1-associated low-grade MPNSTs arose within a neurofibroma.

Treatment Characteristics

Two hundred sixty-seven patients (92%) underwent resection of the primary disease. One hundred fifty-nine of these patients (59%) underwent definitive resection of their primary tumor at outside institutions, and 108 (41%) had their tumor excised at our institution. The margin status was reviewed by a sarcoma pathologist at our institution. Resection was not performed in the remaining cases due to advanced disease ($n = 17$) or medical comorbidities ($n = 5$).

Nine patients (3%) with localized primary tumors required amputation, and an additional 6 patients (2%) required amputation after local recurrence. Twenty-three patients (8%) underwent R2 resections (Table 2). Of these procedures, 17 were carried out with curative intent; however, additional resection to obtain negative margins was not pursued owing to rapidly progressive disease ($n = 9$) or prohibitive location ($n = 8$). Median time to disease-specific death following incomplete (R2) resection was 0.8 years. Six patients underwent palliative R2 resection. Indications for palliative resection were pain ($n = 3$), spinal cord compression ($n = 2$), and bowel obstruction ($n = 1$). Five of 6 patients reported temporary alleviation of symptoms; however, all patients had progressive disease, resulting in death following palliative procedures. Median time to disease-specific death following palliative (R2) resection was 1.19 years.

Two hundred seventy-four patients (95%) presented with localized disease; 75 (27%) of these 274 patients underwent resection alone (Table 2). In addition to resection, 45 patients (16%) received chemotherapy, 75 (27%) received radiation therapy, 64 (24%) received combination chemotherapy and radiation therapy, and 15 (5%) underwent palliative chemotherapy or radiotherapy without resection. Chemotherapy regimens varied but most often included doxorubicin $\pm$ ifosfamide as a first-line therapy;

TABLE 1. Demographic and tumor characteristics of 289 patients with MPNSTs*

Characteristic	MPNST				p Values†
	Overall, n = 289 (100)	Sporadic, n = 115 (39.8)	NF1-Assoc, n = 148 (51.2)	Radiation-Assoc, n = 26 (8.9)	
Age in years					<0.001 (<0.001)
Median	37	43	33	52	
Range	1–81	5–81	1–75	20–77	
Tumor size in cm					<0.001 (<0.001)
Median	8.0	6.0	10	6.0	
Range	1.0–35.0	1.0–32.0	2.5–35.0	1.5–15.0	
Sex					0.720 (0.906)
F	134 (46.4)	52 (45.2)	68 (45.9)	14 (53.8)	
M	155 (53.6)	63 (54.8)	80 (54.1)	12 (46.2)	
Disease at primary Dx					
Localized	274 (94.8)	105 (91.3)	143 (96.6)	26 (100.0)	0.071 (0.065)
Metastatic	15 (5.2)	10 (8.7)	5 (3.4)	0 (0.0)	
Location					
Head/neck	43 (14.9)	23 (20.0)	13 (8.8)	7 (26.9)	0.008 (0.211)‡
Cervical nerve root	15 (5.2)	4 (3.5)	5 (3.4)	6 (23.0)	
Cranial nerve	13 (4.5)	8 (6.9)	4 (2.7)	1 (3.8)	
Other nerve	9 (3.1)	8 (6.9)	1 (0.7)	0 (0.0)	
Nerve unknown	6 (2.1)	3 (2.6)	3 (2.0)	0 (0.0)	
Trunk	157 (54.3)	54 (47.0)	85 (57.4)	18 (69.2)	
Brachial plexus trunks/divisions	21 (7.3)	5 (4.3)	9 (6.1)	9 (34.6)	
Brachial plexus cords	9 (3.1)	4 (3.5)	2 (1.3)	3 (11.5)	
Lumbosacral nerve root	37 (12.8)	19 (16.5)	18 (12.2)	0 (0.0)	
Thoracic nerve root	17 (5.9)	3 (2.6)	12 (8.1)	2 (7.6)	
Sciatic nerve	12 (4.2)	1 (0.8)	10 (6.8)	1 (3.8)	
Phrenic nerve	4 (1.4)	1 (0.8)	3 (2.0)	0 (0.0)	
Obturator nerve	4 (1.4)	0 (0.0)	4 (2.7)	0 (0.0)	
Femoral nerve	6 (2.7)	2 (1.7)	3 (2.0)	1 (5.9)	
Other nerve	25 (8.7)	7 (6.1)	16 (10.8)	2 (11.8)	
Nerve unknown	20 (6.9)	12 (10.4)	8 (5.4)	0 (0.0)	
Upper-extremity nerve	26 (8.9)	13 (11.3)	12 (8.1)	1 (3.8)	
Radial	4 (1.4)	2 (1.7)	2 (1.3)	0 (0.0)	
Median	7 (2.4)	3 (2.6)	3 (2.0)	1 (3.8)	
Ulnar	7 (2.4)	3 (2.6)	4 (2.7)	0 (0.0)	
Other	4 (1.4)	3 (2.6)	1 (0.6)	0 (0.0)	
Nerve unknown	4 (1.4)	2 (1.7)	2 (1.3)	0 (0.0)	
Lower-extremity nerve	63 (21.8)	25 (21.7)	38 (25.7)	0 (0.0)	
Sciatic	25 (8.7)	6 (5.2)	19 (12.8)	0 (0.0)	
Femoral	7 (2.4)	3 (2.6)	4 (1.4)	0 (0.0)	
Obturator	2 (0.7)	0 (0.0)	2 (1.3)	0 (0.0)	
Tibial	9 (3.1)	5 (4.3)	4 (2.7)	0 (0.0)	
Other	10 (3.5)	3 (2.6)	6 (4.1)	0 (0.0)	
Nerve unknown	10 (3.5)	8 (6.9)	2 (1.3)	0 (0.0)	
Depth§					
D	272 (94.1)	104 (90.4)	143 (96.6)	25 (96.2)	0.096 (0.037)
S	17 (5.9)	11 (9.6)	5 (3.4)	1 (3.8)	

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TABLE 1. Demographic and tumor characteristics of 289 patients with MPNSTs*

Characteristic	MPNST				p Values†
	Overall, n = 289 (100)	Sporadic, n = 115 (39.8)	NF1-Assoc, n = 148 (51.2)	Radiation-Assoc, n = 26 (8.9)	
Histologic subclassification					
MPNST, not further classified	258 (89.3)	94 (81.7)	140 (94.6)	24 (92.3)	0.001 (<0.001)
Epithelioid	20 (6.9)	17 (14.8)	2 (1.4)	1 (3.8)	
Triton tumor	11 (3.8)	4 (3.5)	6 (4.1)	1 (3.8)	
Grade					
Low–intermediate	12 (4.2)	6 (5.2)	5 (3.4)	1 (3.8)	0.791 (0.480)
High (or not evaluated)	277 (95.8)	109 (94.8)	143 (96.6)	25 (96.2)	

Assoc = associated; chemo = chemotherapy; D = deep; Dx = diagnosis; S = superficial.

* Values are number (%) unless otherwise indicated. The sum of percentages may not equal 100 due to rounding.

† In each cell, the first value is for comparison of sporadic, NF1-associated, and radiation-associated characteristics; the second value is for comparison of sporadic and NF1-associated characteristics. Boldface type indicates statistical significance of $p < 0.05$.

‡ Additionally, comparisons were made between 4 major anatomical locations: head/neck, trunk, upper extremity, lower extremity.

§ Tumors with extension through or seated below the superficial fascia were considered deep.

others included gemcitabine ± docetaxel, cisplatin, dacarbazine, cyclophosphamide, epirubicin, vincristine, etoposide, and pazopanib.

Of 15 patients (5%) with metastasis at initial presentation, 7 (2%) received systemic therapy, 4 (1%) underwent chemotherapy in addition to resection, and 4 (1%) underwent combination chemoradiotherapy in addition to resection. Review of the patients with metastatic disease who underwent surgery revealed that 2 patients required surgical intervention to provide palliation. One patient presented with intense neck pain and the second patient had urinary and bowel obstruction. Six patients underwent resection at outside hospitals; 5 of whom had staging imaging at the time of surgery and were known to have metastatic disease. The median survival of patients with metastatic disease who underwent surgery was 0.78 years versus 1.73 years for those who were treated with systemic therapy.

Low-Grade MPNST Outcomes

Only 3 (25%) of 12 patients with low-grade MPNST developed local recurrence after resection (Table 3). R0 resection was achieved in 1 of 3 recurring cases and 7 of 9 nonrecurring cases. No patients with low-grade lesions developed metastasis, and 5-year DSS outcomes were superior to all high-grade cohort outcomes, with 100% of patients surviving at the end of the study period (Fig. 2).

High-Grade MPNST Local and Distant Recurrence-Free Survival

Local and distant recurrence outcomes were assessed for 225 patients (sporadic, $n = 89$; NF1-associated, $n = 119$; radiation-associated, $n = 17$) who presented with high-grade localized disease and had undergone R0 or R1 resection. After a median follow-up of 2.7 years (range 0.03–36.0 years), 84 patients (37%) developed local recurrence (34%, 38%, and 53% for sporadic, NF1-associated, and radiation-associated subtypes, respectively) after resection. Median time to local recurrence was 0.95 years. Nine patients un-

derwent amputation; 3 patients experienced recurrence at the stump. Of the 84 patients (37%) who experienced local recurrence, 18 (21%) underwent resection alone for recurrent disease, 45 (42%) received chemotherapy or radiotherapy in addition to resection, and 21 (9.3%) did not receive salvage intervention. A comparison of patients who underwent resection at our institution versus outside institutions did not reveal any statistically significant difference in LRFS (3-year LRFS following R0 resection 84% vs 77%, respectively, $p = 0.286$; 3-year LRFS following R1 resection 48% vs 38%, respectively, $p = 0.425$).

One hundred and five patients (47%) developed distant recurrence (47%, 47%, and 41% for sporadic, NF1-associated, and radiation-associated subtypes, respectively). Median time to distant recurrence was 1.4 years. Thirty-three (31%) of 105 patients had metastases to multiple organs; the most common locations included the lungs ($n = 85$), paraspinal region ($n = 12$), bone ($n = 10$), lymph nodes ($n = 8$), brain ($n = 7$), liver ($n = 5$), pelvis ($n = 5$), and leptomeningeal ($n = 4$). Less common sites of metastases involved the mediastinum, retroperitoneum, musculature of the extremities, bladder, vagina, and spleen.

Univariate analyses for LRFS and DRFS revealed no significant differences in outcomes between neoadjuvant and adjuvant radiation therapy or chemotherapy. Therefore, neoadjuvant and adjuvant therapy variables were combined to strengthen statistical power (Table 4). The 5-year LRFS was 59%. Univariate analysis revealed that patients with sporadic tumors had better LRFS compared with patients with radiation-associated tumors ($p = 0.010$, hazard ratio [HR] 0.42; Table 4, Fig. 3). Patients who received radiation therapy in addition to resection had a better LRFS compared with patients who did not receive radiation therapy ($p = 0.040$, HR 0.64; Table 4). In multivariate analysis, tumors ≥ 10 cm and with positive margins remained significant prognosticators of adverse LRFS ($p = 0.056$, HR 2.09; $p < 0.001$ HR 3.13, respectively; Table 4).

At our institution, radiotherapy is typically not offered to patients who present with radiation-associated MPNST,

TABLE 2. Treatment characteristics of 274 patients with localized disease at presentation*

Characteristic	MPNST				p Value (p Value)†
	Overall, n = 274 (100)	Sporadic, n = 105 (38.3)	NF1-Assoc, n = 143 (52.2)	Radiation-Assoc, n = 26 (9.5)	
Surgery					
Y	259 (94.5)	102 (97.1)	133 (93.0)	24 (92.3)	0.321 (0.248)
N	15 (5.5)	3 (2.9)	10 (7.0)	2 (9.5)	
Resection Margins (n = 259)					
R0	145 (60.0)	66 (64.7)	70 (52.6)	9 (37.5)	<0.001‡ (<0.001)
R1	54 (20.8)	13 (12.7)	36 (27.1)	5 (20.8)	
R2	23 (8.9)	7 (6.9)	9 (6.8)	7 (29.2)	
Unknown	37 (14.3)	16 (15.7)	18 (13.5)	3 (12.5)	
Therapy, resected (n = 259)					0.312§ (0.590)
Surgery alone	75 (27.3)	31 (29.5)	36 (25.2)	8 (30.8)	
Chemotherapy alone + surgery	45 (16.4)	19 (18.1)	19 (13.3)	7 (26.9)	
Neoadjuvant	18 (6.6)	5 (4.7)	10 (6.9)	3 (11.5)	
Adjuvant	26 (9.5)	14 (13.3)	9 (6.3)	3 (11.5)	
Both neo-/adjuvant	1 (0.3)	0 (0.0)	0 (0.0)	1 (3.8)	
Radiation alone + surgery	75 (27.4)	29 (27.6)	39 (27.3)	7 (26.9)	
Neoadjuvant	11 (4.0)	3 (2.8)	8 (5.9)	0 (0.0)	
Adjuvant	63 (22.9)	26 (24.8)	31 (21.7)	6 (23.1)	
Other (IORT)	1 (0.3)	0 (0.0)	0 (0.0)	1 (3.8)	
Chemoradiotherapy + surgery	64 (24.4)	23 (21.9)	39 (27.3)	2 (7.7)	
Neoadjuvant	22 (8.0)	8 (7.6)	14 (9.8)	0 (0.0)	
Adjuvant	29 (10.6)	14 (13.3)	14 (9.8)	1 (3.8)	
Other combination	13 (4.7)	1 (1.0)	11 (7.7)	1 (3.8)	
Palliative therapy, no resection (n = 15)					0.240 (0.296)
Chemo	9 (3.3)	3 (2.9)	5 (3.5)	1 (3.8)	
Radiotherapy	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	
Chemoradiotherapy	5 (1.8)	0 (0.0)	4 (2.7)	1 (3.8)	
LR	98 (35.7)	33 (31.4)	51 (35.7)	14 (53.8)	0.102 (0.486)
DR	120 (43.8)	47 (44.8)	65 (45.5)	8 (30.8)	0.369 (0.914)

Chemo = chemotherapy; DR = distant recurrence; IORT = intraoperative radiotherapy; LR = local recurrence; N = no; Y = yes.

* Values are number (%). The sum of percentages may not equal 100 due to rounding. Boldface type indicates statistical significance of $p < 0.05$.

† Comparison between sporadic, NF1-associated, and radiation-associated characteristics (comparison between sporadic and NF1-associated characteristics).

‡ Comparisons exclude unknown resection margins.

§ Overall comparison between resection alone, chemotherapy + surgery, radiotherapy + surgery, or chemoradiotherapy + surgery.

as, in the vast majority of cases, they cannot be meaningfully irradiated without unacceptable toxicity. Therefore, an alternative local relapse outcome analysis including patients who were treated at our institution for their primary sporadic or NF1-associated disease was constructed to evaluate the utility of radiation therapy in this group (Table 5). In univariate analysis we observed a local recurrence risk reduction in patients who received radiation therapy and resection ($p = 0.058$, HR 0.49). The 5- and 10-year LRFS for patients who received radiation therapy was 82% and 71%, respectively, versus 67% and 59%, respectively, for those who did not. Adjusted multivariate analyses for this cohort revealed positive margins and males to be associated with worse LRFS.

Five-year DRFS was 50%. Adverse predictors of DRFS in univariate analysis included male sex, nonepithelioid or

triton MPNSTs, tumors ≥ 10 cm, deep location, and treatment with chemotherapeutics (Table 4). Only tumor size (≥ 10 cm) remained a significant predictor of poor DRFS in multivariate analysis ($p = 0.034$, HR 1.76; Table 4).

High-Grade MPNST Disease-Specific Survival

Of the entire cohort ($n = 289$), 131 patients died of disease, 17 died of unrelated causes, 86 had no evidence of active malignancy, and 55 were alive with disease at the end of the follow-up period. Median DSS time was 5.5 years, and 5-year DSS was 51% (Fig. 2). Patients with high-grade MPNST who had incomplete (R2) resection ($n = 23$), did not receive surgical intervention ($n = 22$), or had metastasis at presentation ($n = 15$) had similar outcomes with significantly worse prognosis than patients who presented with localized disease and received R0 or R1 resection; there-

TABLE 3. Characteristics and survival in 12 patients with low-grade MPNSTs

Case No.	Subtype	Age (yrs)	Location	Neurofibroma Component	Depth	Therapy	Surgical Margins	LR	DR	DOD
1	NF1-assoc	26	Thoracic spine	Spinal	D	None	R0	N	N	N
2	NF1-assoc	39	Intercostal nerve	Plexiform	D	None	R0	N	N	N
3	NF1-assoc	47	Sciatic nerve, thigh	Diffuse	D	None	R0	N	N	N
4	NF1-assoc	43	Brachial plexus	Plexiform	D	None	R1	N	N	N
5	NF1-assoc	69	Back	Plexiform	S	Radiotherapy	R1	N	N	N
6	Radiation-assoc	60	Brachial plexus	None	D	None	R2	Y	N	N
7	Sporadic	68	Chest	None	S	Radiotherapy	R0	N	N	N
8	Sporadic	13	Forehead	None	S	None	R1	Y	N	N
9	Sporadic	60	Lumbosacral	None	D	Chemo	R0	Y	N	N
10	Sporadic	40	Peritoneum	None	D	None	R0	N	N	N
11	Sporadic	64	Shoulder	None	S	None	R0	N	N	N
12	Sporadic	79	Retroperitoneum	None	D	Chemo	R0	N	N	N

DOD = MPNST-specific death.

Survival Estimates	2-year	5-year	10-year
Overall	68%	52%	42%
Low-grade	100%	100%	100%
High-grade R0 or R1 resection	75%	59%	49%
High-grade R2 resection	37%	0%	0%
High-grade not resected	22%	-	-
Metastasis at primary diagnosis	27%	13%	0%

FIG. 2. Kaplan-Meier curves showing DSS for the MPNST populations.

TABLE 4. Univariate and multivariate analysis of local recurrence-free and distant recurrence-free survival*

Variable	LRFS			DRFS		
	Univariate		Multivariate	Univariate		Multivariate
	HR (95% CI)	p Value		HR (95% CI)	p Value	
Age in years, ≥ 45 vs < 45	1.03 (0.65–1.63)	0.888		1.36 (0.91–2.01)	0.132	
Sex, F vs M	0.59 (0.38–0.91)	0.018	0.65 (0.30–1.39)	0.63 (0.42–0.93)	0.022	0.83 (0.50–1.35)
Subtype						
Sporadic vs NF1-associated	0.85 (0.54–1.33)	0.463		0.85 (0.58–1.25)	0.413	
Sporadic vs radiotherapy-associated	0.42 (0.23–0.82)	0.010	0.36 (0.12–1.79)	1.17 (0.54–2.51)	0.686	
Histology, other† vs MPNST	0.86 (0.43–1.71)	0.658		0.46 (0.21–1.00)	0.050	0.62 (0.26–1.44)
Size in cm, ≥ 10 vs < 10	2.26 (1.23–4.16)	0.008	2.09 (0.98–4.49)	2.06 (1.26–3.36)	0.004	1.76 (1.04–2.97)
Location, trunk vs other‡	2.01 (1.29–3.14)	0.002	1.43 (0.67–3.04)	1.06 (0.72–1.57)	0.749	
Depth, D vs S	3.25 (0.79–13.2)	0.100		9.39 (1.31–67.5)	0.026	1.79 (0.93–15.3)
Chemo, Y vs N	0.90 (0.57–1.38)	0.599		1.51 (1.02–2.22)	0.037	1.15 (0.68–1.94)
Radiotherapy, Y vs N	0.64 (0.41–0.98)	0.040	0.84 (0.41–1.68)	0.84 (0.56–1.24)	0.365	
Margins, pos vs neg	3.62 (2.18–6.04)	<0.001	3.13 (1.56–6.25)	0.97 (0.58–1.62)	0.631	

Neg = negative; pos = positive.

* Boldface type indicates statistical significance of $p < 0.05$.

† Epithelioid type or triton tumor.

‡ Extremity or head/neck.

fore, these patients were excluded from subsequent univariate and multivariate survival analyses. Survival was worse for patients who underwent amputation compared with those who underwent R0 limb-sparing surgery ($p = 0.003$, HR 4.5, 5-year DSS 25% and 78%, respectively).

Individual interrogation between MPNST subtypes revealed superior DSS in sporadic compared with NF1-associated and radiation-associated patients ($p = 0.016$, HR 0.59; $p = 0.058$, HR 0.52; Table 6, Fig. 3). Truncal location, positive resection margins, local recurrence, and metastasis were adverse predictors of DSS in multivariate analysis ($p = 0.039$, HR 1.92; $p = 0.014$, HR 2.41; $p = 0.059$, HR 1.95; $p < 0.001$, HR 10.7, respectively).

Discussion

In the present study, we aimed to identify and contrast features predictive of recurrence and survival in patients with sporadic, NF1-associated, and radiation-associated MPNST. First, we found that low-grade MPNSTs have a benign natural history, with a low risk of recurrence with negative margin resection and better survival outcomes compared with their high-grade counterparts. In our investigation of high-grade MPNST, the importance of negative margin resection was confirmed to be a key determinant of local control and disease-specific outcomes. We found that local recurrence patterns are more aggressive in radiation-associated MPNST compared with sporadic or NF1-associated MPNST, which may in part be attributed to the propensity for these tumors to be deeply located in the trunk, where negative margins were less likely to be achieved. Lower survival estimates in NF1- and radiation-associated MPNST may in part be explained by their differences in location, size, and positive margin rate compared with sporadic MPNST.

A review of 6 recent similar single-institution retrospective series that had at minimum 100 patients in their cohort is summarized in Table 7. Including our series, the most common adverse prognostic factor associated with survival was large tumor size (6 of 7 studies), followed by positive resection margins (3 of 7 studies) and truncal location (2 of 7). Only Porter et al.¹⁹ identified NF1 as an adverse prognostic factor associated with survival while Stucky et al.²³ and our study identified a trend. In our cohort, a shorter disease-specific survival trend for radiation-associated MPNST was noted when compared with sporadic and NF1-associated MPNST, which supports findings by LaFemina et al.¹⁵ in which radiation-associated MPNST patients were found to have a poorer prognosis. Six of the 7 series investigated the impact of chemotherapy and radiotherapy on survival outcomes, and only Anghileri et al.¹ reported radiation therapy to be associated with a significant survival benefit.

MPNSTs pose a challenging management dilemma. Patients often present with large tumors that infiltrate multiple segments of nerve, which makes obtaining negative margins and maintaining acceptable neural functionality with surgical intervention problematic. Similar to others, we found that patients who underwent resection with negative margins and tumors < 10 cm had better LRFS outcomes.^{6,8,10} Additionally, our study demonstrates that

FIG. 3. Kaplan-Meier curves showing LRFS stratified by MPNST subtype (RT-associated vs sporadic, $p = 0.010$; RT-associated vs NF1-associated, $p = 0.232$) (left), and DSS stratified by MPNST subtype (RT-associated vs sporadic, $p = 0.272$; RT-associated vs NF1-associated, $p = 0.714$) (right). RT-associated = radiotherapy-associated.

radiotherapy in combination with an R0/R1 resection is associated with better local control (5-year LRFS 82% vs 67% for those who were not treated with radiation therapy). Despite this finding, the use of radiation therapy failed to definitively show benefits associated with disease-specific outcomes (similar to previous reports).^{1,7,19,23,25}

Current chemotherapeutics have not been consistently shown to provide a significant survival benefit.^{1,7,19,23,25} We found that patients treated with chemotherapy had worse outcomes than those who did not receive chemotherapy. However, in our cohort, chemotherapy was administered more often to patients with truncally located or large tumors and to patients with advanced disease. The therapeutic benefits of chemotherapy, therefore, remain unclear. Three patients had complete response to therapy, which illustrates that chemotherapy can be of significant benefit in select patients. Additional research is needed to identify predictive biomarkers for therapeutic response to improve outcomes for patients with MPNST.

Cytogenetic analysis and DNA sequencing of MPNSTs has identified several recurring genetic aberrations (involving genes such as *NF1*, *TP53*, *CDKN1B*, *PDGFRA*, and *HGF*) and irregular receptor tyrosine kinase activity that could be exploited for treatment or to highlight other targetable molecular dysregulations.^{12,17,20} However, several clinical trials using the targeted inhibitors erlotinib, sorafenib, and imatinib, among others, have been conducted in sarcoma patients, including those with MPNST, with minimal observed responses.^{3,8} Combination therapy to achieve a more complete signaling blockade, such as coinhibition of signaling pathways and upstream activators; the conversion of promising preclinical targets into clinical trials, such as histone deacetylase inhibitors and PI3K/mTOR inhibitors; or further identification of targetable nodes, may improve outcomes for MPNST patients.^{13,16,26}

Our study is limited by its retrospective nature, the inherent heterogeneity of primary management, and the

TABLE 5. Univariate and multivariate predictors of adverse LRFS in patients with sporadic or NF1-associated MPNST who presented to our institution with primary disease ($n = 128$)*

Variable	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age in years, ≥ 45 vs < 45	0.85 (0.38–1.91)	0.691		
Sex, F vs M	0.37 (0.17–0.82)	0.014	0.34 (0.12–0.94)	0.039
Subtype, sporadic vs NF1-associated	0.40 (0.17–0.84)	0.036	0.38 (0.13–1.15)	0.385
Histology, other† vs MPNST	0.67 (0.34–2.32)	0.805		
Size in cm, ≥ 10 vs < 10	2.35 (0.92–5.99)	0.074		
Location, trunk vs other‡	2.06 (0.99–4.27)	0.051	1.17 (0.48–2.84)	0.721
Chemo, Y ($n = 59$) vs N ($n = 69$)	1.06 (0.52–2.19)	0.862		
Radiotherapy, Y ($n = 69$) vs N ($n = 59$)	0.49 (0.24–1.02)	0.058	0.49 (0.20–1.23)	0.130
Margins, pos vs neg	5.08 (2.27–11.4)	< 0.001	3.90 (1.69–8.97)	0.001

* Patients with localized primary sporadic or NF1-associated MPNST who underwent R0 or R1 resection. Boldface type indicates statistical significance of $p < 0.05$.

† Epithelioid type or triton tumor.

‡ Extremity or head/neck.

TABLE 6. Univariate and multivariate predictors of adverse disease-specific survival*

Variables	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age in years, ≥ 45 vs < 45	1.18 (0.77–1.81)	0.438		
Sex, F vs M	0.66 (0.43–0.99)	0.047	1.53 (0.81–2.91)	0.194
Subtype				
Sporadic vs NF1-associated	0.59 (0.39–0.91)	0.016	1.00 (0.48–2.06)	0.997
Sporadic vs radiotherapy-associated	0.52 (0.26–1.08)	0.058	1.35 (0.48–3.75)	0.568
Histology, other† vs MPNST	0.59 (0.27–1.29)	0.192		
Size in cm, ≥ 10 vs < 10	3.14 (1.88–5.23)	<0.001	1.78 (0.91–3.84)	0.092
Location, trunk vs other‡	1.56 (1.07–2.27)	0.021	1.92 (1.03–3.58)	0.039
Depth, D vs S	2.37 (0.75–7.52)	0.141		
Chemo, Y vs N	1.68 (1.12–2.53)	0.012	1.46 (0.76–2.08)	0.261
Radiotherapy, Y vs N	0.64 (0.43–0.97)	0.035	0.81 (0.46–1.47)	0.501
Margins, pos vs neg	2.14 (1.32–3.45)	0.002	2.41 (1.19–4.84)	0.014
LR, Y vs N	2.46 (1.63–3.72)	<0.001	1.95 (0.96–3.89)	0.059
DR, Y vs N	4.61 (2.83–7.52)	<0.001	10.7 (4.89–23.5)	<0.001

* Boldface types indicates statistical significance of $p < 0.05$.

† Epithelioid type or triton tumor.

‡ Extremity or head/neck.

small number of radiation-associated MPNSTs meeting study eligibility criteria. Furthermore, as a high-volume tertiary center, we were able to obtain, to our knowledge, the largest single-institution MPNST cohort to date, but follow-up data are variable between survivors. However, our cohort was subjected to thorough subset analysis and offers insights on the management of a rare disease that is understudied as a result of limited cohort sizes. Few studies reporting the natural history of MPNST have described the features and outcomes of these aggressive tumors with specific attention to MPNST etiology as exhaustively as the present series. In addition to reporting the treatment and outcomes for our cohort, we profile the nerves of involvement and accompanying symptoms with respect to the MPNST subtype, profile the sites of metastasis, and describe the behavior of low-grade MPNSTs separately from high-grade MPNSTs.

Conclusions

The goal of curative management for all MPNSTs should be negative margin resection whenever possible. Additionally, supplemental radiation therapy for local control should be considered. Large index tumor size was implicated as a major adverse prognostic factor, which recapitulates the importance of early diagnosis and intervention in these aggressive tumors, particularly in the NF1 population where fluorine-18–labeled fluorodeoxyglucose PET/CT has been shown to be a useful adjunct imaging tool to MRI when malignant change needs to be excluded.^{5,27} Finally, differences in clinicopathological features and patterns of local recurrence and survival do exist between sporadic, NF1-associated, and radiation-associated MPNSTs; therefore, the etiology of these tumors should be considered in the management of patients and in future studies evaluating tumor biology.

TABLE 7. A review of MPNST in select recent single-institution retrospective studies

Authors & Year	No. of Pts	% 5-Year Survival	Adverse Prognostic Features				Pos Margins	Therapy Benefit	
			NF1-Assoc	Radiation-Assoc	Location	Size		Radiotherapy	Chemo
Present series	289	52†	T	NS	T (trunk)	SS (≥ 10 cm)	SS	NS	NS
LaFemina et al., 2013	105	—	NS	SS	NS	SS (larger)	SS	—	—
Fan et al., 2014	146	57‡	NS	—	NS	NS	NS	NS	NS
Stucky et al., 2012§	175	60†	T	—	SS (trunk)	SS (≥ 5 cm)	NS	NS	NS
Zou et al., 2009	140	39†	NS	NS	NS	SS (≥ 10 cm)	NS	NS	NS
Porter et al., 2009	123	51‡	SS	—	NS	SS (> 200 ml)	NS	NS	NS
Anghileri et al., 2006	205	40†	NS	—	SS (trunk, HN)	SS (larger)	SS	SS	NS

HN = head/neck; NS = not statistically significant; pts = patients; SS = statistically significant; T = trend.

† Disease-specific survival.

‡ Overall survival.

§ Series was a single-institution study but patients were treated at 3 different locations.

Acknowledgments

Funding for this research was provided in part by NIH/NCI K08CA160443 (K.E.T.), The Sally M. Kingsbury Sarcoma Research Foundation (K.E.T.), and Amschwand Sarcoma Cancer Foundation (supporting C.M.K.). We thank Jill Designe for review and editing the manuscript. We also thank Geoffrey Giacco for identification of the study cohort.

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Disclosures

Dr. Hunt reports being a consultant with Armada Health.

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Conception and design: Torres, Watson, Al Sannaa, Lazar. Acquisition of data: Torres, Watson. Analysis and interpretation of data: all authors. Drafting the article: Torres, Watson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Torres. Statistical analysis: Watson. Administrative/technical/material support: Torres. Study supervision: Torres.

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