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Patterns of recurrence and survival in sporadic, neurofibromatosis type 1-associated, and radiation-associated malignant peripheral nerve sheath tumors (MPNSTs)

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Structured Abstract

Objective—MPNSTs are an aggressive group of soft tissue sarcomas that can arise sporadically, in the context of NF1, or at a site of prior irradiation. Large series profiling the features and outcomes of sporadic, neurofibromatosis type 1 (NF1)-associated, and radiation (RT)-associated malignant peripheral nerve sheath tumor (MPNST) 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 our institutional tumor registry. Clinicopathologic features were retrospectively collected. Features were compared among MPNST subtypes for patients who had sufficient clinical history (n = 289), and clinicopathologic features were used to identify adverse predictors of recurrence and survival outcomes.

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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% for the high-grade MPNST cohort, respectively. Five-year DSS was lower in NF1-associated and RT-associated compared to sporadic MPNST (48.7%, 40.9%, and 63.0%, respectively; $p = 0.140$). RT-associated MPNST had worse LRFS than sporadic and NF1-associated subtypes ($p = 0.047$). Truncally located tumors, positive surgical margins, local recurrence, and metastasis were predictors of adverse DSS in multivariate analysis.

Conclusion—RT-associated MPNSTs demonstrate 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 to sporadic tumors.

Keywords

Malignant peripheral nerve sheath tumor; MPNST; neurofibromatosis type 1; radiation-induced sarcoma

Introduction

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 genetic 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 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 surgical resection and a high risk for metastatic spread. Prognosis in patients with MPNST remains poor with reported 5-year disease-specific survival rates ranging from 39–60% 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 to 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 (RT-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 RT-associated MPNST. As a secondary goal, low-grade MPNSTs were interrogated separately from high-grade MPNSTs to determine their natural history and optimal clinical management.

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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. Patients that had adequate clinical history ($n = 289$) were included for statistical analysis (Figure 1). Clinicopathologic 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 NIH consensus criteria for diagnosis of NF1.[18] Patients with a history of therapeutic radiotherapy at least six months prior for an unrelated malignancy within the local field containing the newly arising MPNST were considered to have a RT-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 to 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 received 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 (Figure 1).

Characteristics between MPNST subtypes were compared using χ^2 or Fisher's exact test for categorical variables and the non-parametric 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 disease-specific survival (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 two-sided p values < 0.05 were considered statistically significant. All computations were performed using SPSS version 22.0 (IBM Corp. Armonk, NY).

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. Median follow-up time 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 RT-

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associated MPNSTs, respectively. One-hundred fifteen (40%) patients presented with sporadic disease, 148 (51%) in association with NF1, and 26 (9%) subsequent to previous local radiation therapy for a different malignancy. The median latency period for the development of RT-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 for truncally located disease was within the lumbosacral nerve roots ($n = 37/157$, 24%) followed by the brachial plexus ($n = 30/157$, 19%) and the thoracic nerve roots ($n = 17/157$, 11%). The sciatic nerve was affected in 8% ($n = 12/157$) of truncally located cases and 40% ($n = 25/63$) of lower extremity cases; 50% ($n = 19/38$) of NF1-associated MPNSTs located within the lower extremity arose from the sciatic nerve. Symptoms at primary diagnosis were available for 245 (85%) patients; 16% ($n = 38/245$) of patients were asymptomatic but were able to palpate mass effect and 2% ($n = 4/245$) were asymptomatic with incidental discovery of their disease. Two-hundred and three patients of 245 (83%) patients were symptomatic and 49% ($n = 120/245$) reported more than one symptom. The most common symptom was pain (71%, $n = 173/245$), followed by extremity weakness (13%, $n = 32/245$), extremity numbness (9%, $n = 22/245$), paresthesia (6%, $n = 14/245$), and gait instability or footdrop (5%, $n = 13/245$). 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 RT-associated tumors (90% versus 75% and 73%, respectively; $p = 0.006$).

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

Treatment Characteristics

Two-hundred and sixty-seven (92%) patients had surgical resection of primary disease. One-hundred and fifty-nine (59%) patients underwent definitive resection of their primary tumor at outside institutions and 108 (41%) were excised at our institution. The margin status was reviewed by a sarcoma pathologist at our institution. The remaining patients did not receive surgical resection due to advanced disease ($n = 17$) or medical comorbidities ($n = 5$). Nine (3%) patients with localized primary tumors required amputation and an additional 6 (2%) required amputation after local recurrence (LR). Twenty-three (8%) patients received R2 resections (Table 2). Of these, 17 were resected 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 received palliative R2 resection. Indications for palliative resection were pain ($n = 3$), spinal cord compression ($n = 2$), and

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bowel obstruction (n = 1). Five of 6 patients reported temporary alleviation of symptom; 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 and seventy-four (95%) patients presented with localized disease; of which, 75 (27%) underwent surgical resection alone (Table 2). In addition to surgical resection, 45 (16%) patients received chemotherapy, 75 (27%) patients received radiation, 64 (24%) patients received combination chemo-radiotherapy, and 15 (5%) underwent palliative chemo- or radiotherapy without surgical resection. Chemotherapy regimens varied, but most often included doxorubicin +/− ifosfamide as a first line therapy; others included gemcitabine +/− docetaxel, cisplatin, dacarbazine, cyclophosphamide, epirubicin, vincristine, etoposide, and pazopanib.

Of 15 (5%) patients with metastasis at initial presentation, 7 (2%) received systemic therapy, 4 (1%) received chemotherapy in addition to surgical resection, and 4 (1%) received combination chemo-radiotherapy in addition to resection. Review of the patients with metastatic disease who underwent surgery revealed that two 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; of which, 5 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 of 12 (25%) patients with low-grade MPNST developed LR after surgical resection (Table 3). R0 resection was achieved in 1 of 3 recurring cases and 7 of 9 non-recurring cases. No patients with low-grade lesions developed metastasis. Five-year DSS outcomes were superior to all high-grade cohort outcomes with 100% of patients surviving at the end of the study period (Figure 2).

High-grade MPNST local and distant recurrence-free survival

Local and distant recurrence outcomes were assessed in 225 (sporadic, n = 89; NF1-associated, n = 119; RT-associated, n = 17) patients who presented with high-grade localized disease and received R0 or R1 surgical resection. After a median follow-up of 2.7 years, range 0.03–36.0 years, 84 (37%) patients developed LR (34%, 38%, and 53% for sporadic, NF1-associated, and RT-associated subtypes, respectively) after resection. Median time to LR was 0.95 years. Nine patients had amputation; 3 patients recurred at the stump. Of the 84 (37%) patients that experienced LR, 18 (21%) patients received surgical resection alone for recurrent disease, 45 (42%) received chemotherapy or radiotherapy in addition to surgical resection, and 21 (9.3%) did not receive salvage intervention. Comparison of patients that underwent resection at our institution versus outside institutions did not reveal any statistically significant difference in LRFS (3-yr LRFS following R0 resection 84% v. 77%, p = 0.286; 3-yr LRFS following R1 resection 48% v. 38%, p = 0.425).

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One-hundred and five (47%) patients developed distant recurrence (47%, 47%, and 41% for sporadic, NF1-associated, and RT-associated subtypes, respectively). Median time to distant recurrence was 1.4 years. Thirty-one percent (n = 33/105) of patients had metastases to multiple organs. The most common locations included the lungs (n = 85), paraspinal region (n = 12), bone (n = 10), liver (n = 5), lymph nodes (n = 8), brain (n = 7), pelvis (n = 5) and leptomeningeal metastasis (n = 4). Less common sites 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 or chemotherapy. Therefore, neoadjuvant and adjuvant therapy variables were combined to strengthen statistical power (Table 4). Five-year LRFS was 59%. Univariate analysis revealed sporadic tumors had better LRFS compared to RT-associated tumors (p = 0.010, HR 0.43; Table 4, Figure 3). Patients that received radiation therapy in addition to surgical resection had a better LRFS compared to patients that did not receive radiation (p = 0.040, HR 0.64; Table 4). In multivariate analysis, tumors ≥ 10 cm and positive margins remained significant prognosticators of adverse LRFS (p = 0.056, HR 2.09; p < 0.001 HR 3.13; Table 4).

At our institution, radiation therapy is typically not offered to patients that present with RT-associated MPNST as they cannot be meaningfully irradiated without unacceptable toxicity in the vast majority of cases. Therefore, an alternative local relapse outcome analysis including patients that 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 LR risk reduction in patients who received radiation and surgical resection (p = 0.058, HR 0.49). The 5- and 10-year LRFS for patients that received radiation was 82% and 71%, respectively versus 67% and 59%, respectively for those that were not radiated. 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 distant recurrence-free survival in univariate analysis included males, non-epithelioid 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 of 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 disease-specific survival time was 5.5 years and 5-year DSS was 51% (Figure 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 surgical resection; therefore, these patients were excluded from subsequent univariate and multivariate survival analyses. Survival was worse for patients that had amputation compared to those that had R0 limb sparing surgery (p = 0.003, HR 4.5; 5-year DSS, 25% and 78%, respectively).

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Individual interrogation between MPNST subtypes revealed superior DSS in sporadic compared to NF1-associated and RT-associated patients ($p = 0.016$, HR 0.59; $p = 0.058$, HR 0.52; Table 6, Figure 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).

Discussion

In the present study we aimed to identify and contrast features predictive of recurrence and survival in patients with sporadic, NF1-associated, and RT-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 to 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 RT-associated MPNST compared to sporadic or NF1-associated MPNST, which may in part be attributed to the propensity for these tumors to be located deeply in the trunk where negative margins were less likely to be achieved. Lower survival estimates in NF1- and RT-associated MPNST may in part be explained by their differences in location, size, and positive margin rate compared to 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 (6/7 studies), followed by positive resection margins (3/7 studies), and truncal location (2/7). Only Porter et al[19] identified NF1 as an adverse prognostic factor associated with survival, while Stuckey et al[23] and our study identified a trend. In our cohort, a shorter disease-specific survival trend for RT-associated MPNST was noted when compared to sporadic and NF1-associated MPNST, which supports findings by LaFemina et al[15] in which RT-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 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 that underwent resection with negative margins and tumors < 10 cm had better LRFS outcomes.[6,8,10] Additionally, our study demonstrates that radiation therapy in combination with an R0/R1 resection is associated with better local control (5-year LRFS, 82% versus 67% for those that were not radiated). Despite this finding, the use of radiation failed to definitively show benefits associated to 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

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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.

Sequencing of MPNST has identified several recurring genetic aberrations (such as *NF1, TP53, CDKN1B, PDGFRA*, and *HGF*) and irregular receptor tyrosine kinase activity that could be exploited for treatment or 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 co-inhibition 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 small number of radiation-associated MPNSTs meeting the 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 is variable between survivors. However, our cohort was subjected to thorough subset analysis and offers insights on management of a rare disease that is understudied as a result of the difficulties obtaining reasonably sized cohorts. 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 MPNST subtype, profile the sites of metastasis, and describe the behavior of low-grade MPNSTs separately from high-grade MPNSTs. No predictive measures for malignant transformation in pre-existing neurofibroma of NF1 patients exist; however, our data reveal that 57% of NF1-associated MPNSTs develop in the trunk with 20% arising from the lumbosacral or thoracic nerve roots. In addition to routine follow-up evaluating changes in pain, onset of extremity numbness, weakness, or paresthesia, annual 18F-FDG PET/CT may be considered in patients with spinal or pelvic neurofibromas.

Conclusion

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 18F-FDG PET/CT has been shown to appropriately discriminate between benign peripheral nerve sheath tumors and MPNSTs.[5] Finally, differences in clinicopathologic features and patterns of local recurrence and

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survival do exist between sporadic, NF1-asssociated, and RT-associated MPNST; therefore, the etiology of these tumors should be considered in the management of these patients and in future studies evaluating their biology.

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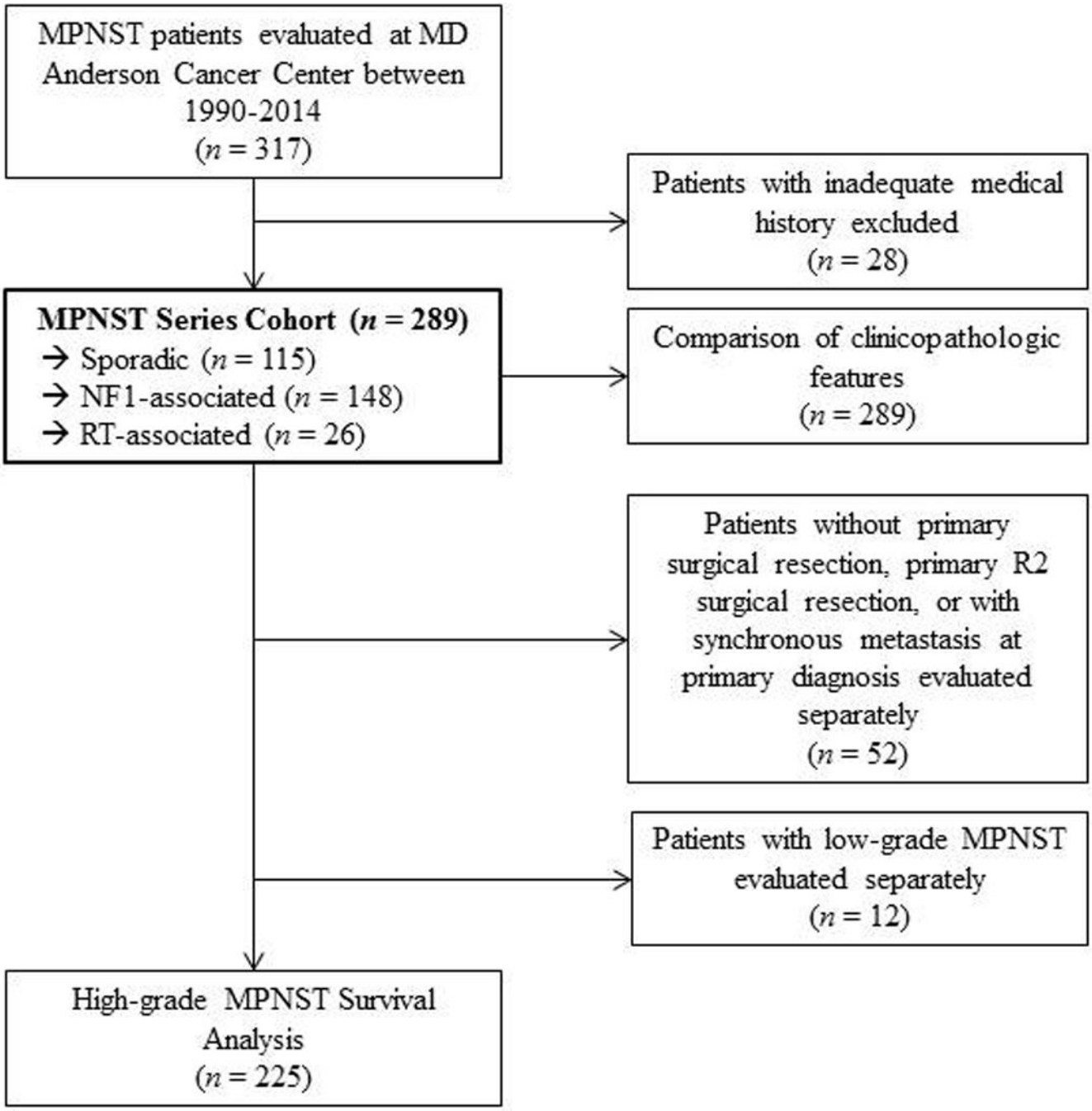

Figure 1.
Patient selection and study analysis flowchart

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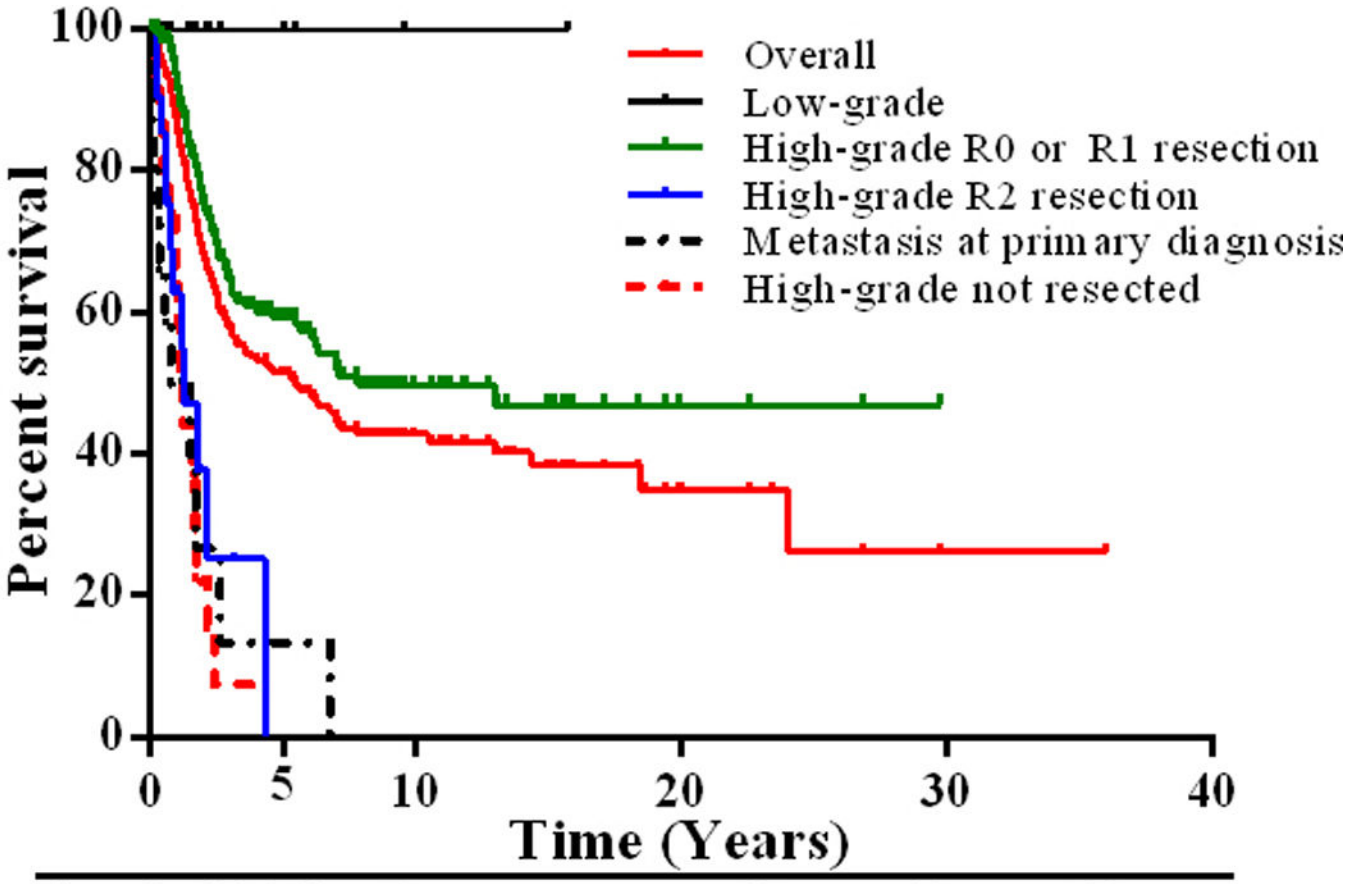

Survival Estimates	2-year	5-year	10-year
Overall	68%	52%	42%
Low-grade	100%	100%	100%
High-grade R0 or R1 resection	75%	59%	49%
High-grade R2 resection	37%	0%	0%
High-grade not resected	22%	-	-
Metastasis at primary diagnosis	27%	13%	0%

Figure 2.
Kaplan-Meier curves of disease-specific survival for MPNST populations

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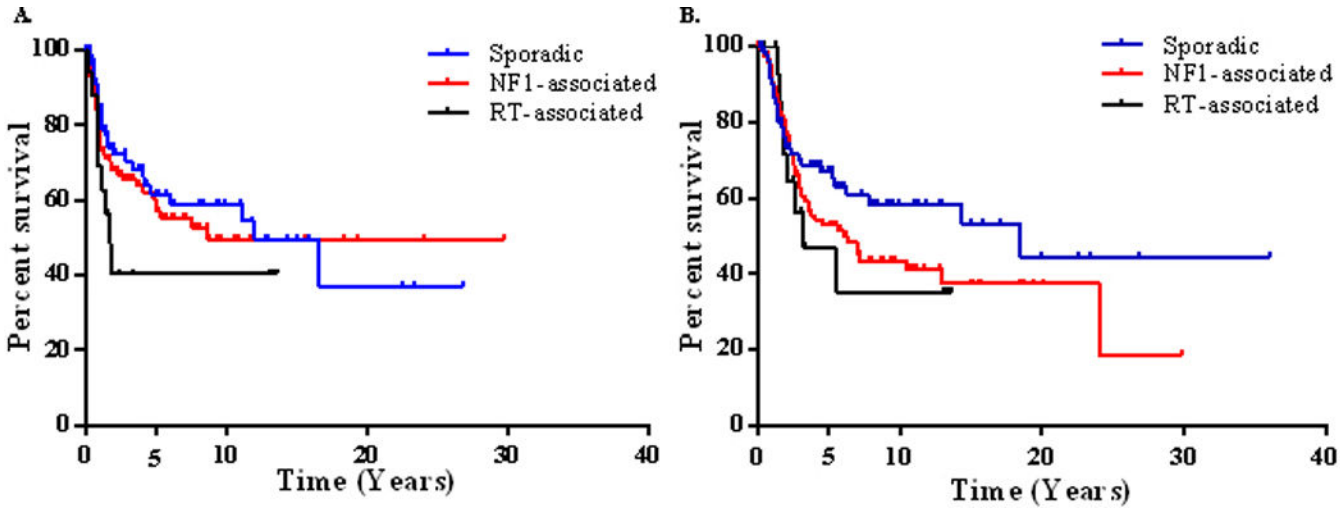

Figure 3.

Kaplan-Meier curves for (*left*) local recurrence-free survival stratified by MPNST subtype (overall comparison, $p = 0.278$), and (*right*) disease-specific survival stratified by MPNST subtype (overall comparison, $p = 0.129$)

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Table 1

Patient and tumor characteristics of 289 patients with MPNST

	Overall	Sporadic	NF1-associated	RT-associated	*P* Value[a] (*P* Value)[b]
N (%) of column total	**289(100)**	**115(39.8)**	**148(51.2)**	**26(8.9)**	
Median age, years (range)	37(1–81)	43(5–81)	33(1–75)	52(20–77)	**<0.001 (<0.001)**
Median tumor size, cm (range)	8.0(1.0–35.0)	6.0(1.0–32.0)	10(2.5–35.0)	6.0(1.5–15.0)	**<0.001 (<0.001)**
Sex					
Female	134(46.4)	52(45.2)	68(45.9)	14(53.8)	0.720 (0.906)
Male	155(53.6)	63(54.8)	80(54.1)	12(46.2)	
Disease at primary diagnosis					
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**[c] (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	4(1.4)	1(0.8)	3(2.0)	0(0.0)	
Obturator	4(1.4)	0(0.0)	4(2.7)	0(0.0)	
Femoral	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	26(8.9)	13(11.3)	12(8.1)	1(3.8)	
Radial nerve	4(1.4)	2(1.7)	2(1.3)	0(0.0)	

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	Overall	Sporadic	NF1-associated	RT-associated	*P* Value[a] (*P* Value)[b]
N (%) of column total	**289(100)**	**115(39.8)**	**148(51.2)**	**26(8.9)**	
Median nerve	7(2.4)	3(2.6)	3(2.0)	1(3.8)	
Ulnar nerve	7(2.4)	3(2.6)	4(2.7)	0(0.0)	
Other nerve	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	63(21.8)	25(21.7)	38(25.7)	0(0.0)	
Sciatic nerve	25(8.7)	6(5.2)	19(12.8)	0(0.0)	
Femoral nerve	7(2.4)	3(2.6)	4(1.4)	0(0.0)	
Obturator nerve	2(0.7)	0(0.0)	2(1.3)	0(0.0)	
Tibial nerve	9(3.1)	5(4.3)	4(2.7)	0(0.0)	
Other nerve	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]					
Deep	272(94.1)	104(90.4)	143(96.6)	25(96.2)	0.096 (0.037)
Superficial	17(5.9)	11(9.6)	5(3.4)	1(3.8)	
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)	

Percentages may not add to 100 due to rounding. Bold indicates statistical significance of $p < 0.05$

[a] Three group comparison between sporadic, NF1-associated, and RT-associated characteristics

[b] Two group comparison between sporadic and NF1-associated characteristics

[c] Comparisons between four major anatomical locations (head/neck, trunk, upper extremity, lower extremity)

[d] Tumors with extension through or seated below the superficial fascia were considered deep.

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Table 2

Treatment characteristics of 274 patients with localized disease at presentation

	Overall	Sporadic	NF1-associated	RT-associated	*P* Value[a] (*P* Value)[b]
N (%) column total	**274 (100)**	**105 (38.3)**	**143 (52.2)**	**26 (9.5)**	
Surgery					
Yes	259 (94.5)	102 (97.1)	133 (93.0)	24 (92.3)	0.321 (0.248)
No	15 (5.5)	3 (2.9)	10 (7.0)	2 (92.3)	
Resection Margins (*n* = 259)					
R0	145 (60.0)	66 (64.7)	70 (52.6)	9 (37.5)	**<0.001[c] (<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-surgically resected (*n* = 259)					0.312[d] (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)	
Therapy-no surgical resection (*n* = 15)					0.240 (0.296)
Palliative chemotherapy	9 (3.3)	3 (2.9)	5 (3.5)	1 (3.8)	
Palliative radiotherapy	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	
Palliative chemoradiotherapy	5 (1.8)	0 (0.0)	4 (2.7)	1 (3.8)	

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	Overall	Sporadic	NF1-associated	RT-associated	*P* Value[a] (*P* Value)[b]
N (%) column total	**274 (100)**	**105 (38.3)**	**143 (52.2)**	**26 (9.5)**	
Local recurrence	98 (35.7)	33 (31.4)	51 (35.7)	14 (53.8)	0.102 (0.486)
Distant metastasis	120 (43.8)	47 (44.8)	65 (45.5)	8 (30.8)	0.369 (0.914)

Abbreviations: IORT, intraoperative radiotherapy. Percentages may not add to 100 due to rounding. Bold indicates statistical significance of $p < 0.05$

[a] Three group comparison between sporadic, NF1-associated, and RT-associated characteristics

[b] Two group comparison between sporadic and NF1-associated characteristics

[c] Comparisons exclude unknown resection margins

[d] Overall comparison between surgery alone, chemotherapy + surgery, radiation + surgery, or chemoradiotherapy + surgery.

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Table 3

Characteristics and survival in 12 low-grade MPNSTs

Subtype	Age	Location	Neurofibroma component	Depth	Therapy	Surgical Margins	LR	DR	DOD
NF1	26	Thoracic spine	Spinal	D	None	R0	−	−	−
NF1	39	Intercostal nerve	Plexiform	D	None	R0	−	−	−
NF1	47	Sciatic nerve, thigh	Diffuse	D	None	R0	−	−	−
NF1	43	Brachial plexus	Plexiform	D	None	R1	−	−	−
NF1	69	Back	Plexiform	S	RT	R1	−	−	−
RAS	60	Brachial plexus	None	D	None	R2	+	−	−
Sporadic	68	Chest	None	S	RT	R0	−	−	−
Sporadic	13	Forehead	None	S	None	R1	+	−	−
Sporadic	60	Lumbosacral	None	D	CT	R0	+	−	−
Sporadic	40	Peritoneum	None	D	None	R0	−	−	−
Sporadic	64	Shoulder	None	S	None	R0	−	−	−
Sporadic	79	Retroperitoneum	None	D	CT	R0	−	−	−

Abbreviations: CT, chemotherapy; D, deep; DOD, MPNST-specific death; DR, distant recurrence; LR, local recurrence; RAS, radiation-associated; RT, radiation therapy; S, superficial

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Table 4

Univariate and multivariate analysis of local recurrence-free and distant recurrence-free survival

	Local recurrence-free survival				Distant recurrence-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, ≥ 45 v. < 45	1.03 (0.65–1.63)	0.888			1.36 (0.91–2.01)	0.132		
Sex, female v. male	0.59 (0.38–0.91)	**0.018**	0.65 (0.30–1.39)	0.269	0.63 (0.42–0.93)	**0.022**	0.83 (0.50–1.35)	0.450
Subtype								
Sporadic v. NF1-associated	0.85 (0.54–1.33)	0.463			0.85 (0.58–1.25)	0.413		
Sporadic v. RT-associated	0.42 (0.23–0.82)	**0.010**	0.36 (0.12–1.79)	0.082	1.17 (0.54–2.51)	0.686		
Histology, other [a] v. MPNST	0.86 (0.43–1.71)	0.658			0.46 (0.21–1.00)	**0.050**	0.62 (0.26–1.44)	0.266
Size, ≥ 10 cm v. < 10 cm	2.26 (1.23–4.16)	**0.008**	2.09 (0.98–4.49)	**0.056**	2.06 (1.26–3.36)	**0.004**	1.76 (1.04–2.97)	**0.034**
Location, trunk v. other [b]	2.01 (1.29–3.14)	**0.002**	1.43 (0.67–3.04)	0.353	1.06 (0.72–1.57)	0.749		
Depth, deep v. superficial	3.25 (0.79–13.2)	0.100			9.39 (1.31–67.5)	**0.026**	1.79 (0.93–15.3)	0.566
Chemotherapy, yes v. no	0.90 (0.57–1.38)	0.599			1.51 (1.02–2.22)	**0.037**	1.15 (0.68–1.94)	0.596
Radiation therapy, yes v. no	0.64 (0.41–0.98)	**0.040**	0.84 (0.41–1.68)	0.619	0.84 (0.56–1.24)	0.365		
Margins, positive v. negative	3.62 (2.18–6.04)	**<0.001**	3.13 (1.56–6.25)	**<0.001**	0.97 (0.58–1.62)	0.631		

Abbreviations: *P, P* Value. Bold indicates statistical significance $p < 0.05$.

[a] Epithelioid type or triton tumor

[b] extremity or head/neck

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Table 5

Univariate and multivariate predictors of adverse local recurrence-free survival in patients with sporadic or NF1-asscociated MPNST that presented to our institution with primary disease ($n = 128$)[a]

	Univariate		Multivariate	
Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age, ≥ 45 v. <45	0.85 (0.38–1.91)	0.691		
Sex, female v. male	0.37 (0.17–0.82)	**0.014**	0.34 (0.12–0.94)	**0.039**
Subtype, sporadic v. NF1-associated	0.40 (0.17–0.84)	**0.036**	0.38 (0.13–1.15)	0.385
Histology, other [b] v. MPNST	0.67 (0.34–2.32)	0.805		
Size, ≥ 10 cm v. <10 cm	2.35 (0.92–5.99)	0.074		
Location, trunk v. other [c]	2.06 (0.99–4.27)	**0.051**	1.17 (0.48–2.84)	0.721
Chemotherapy, yes (n = 59) v. no (n = 69)	1.06 (0.52–2.19)	0.862		
Radiation, yes (n = 69) v. no (n = 59)	0.49 (0.24–1.02)	**0.058**	0.49 (0.20–1.23)	0.130
Margins, positive v. negative	5.08 (2.27–11.4)	**<0.001**	3.90 (1.69–8.97)	**0.001**

Bold indicates statistical significance $p < 0.05$

[a] Patients with localized primary sporadic or NF1-associated MPNST who underwent R0 or R1 resection

[b] Epithelioid type or triton tumor

[c] Extremity or head/neck

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Table 6

Univariate and multivariate predictors of adverse disease-specific survival

	Univariate		Multivariate	
	HR (95% CI)	***P* Value**	**HR (95% CI)**	***P* Value**
Age, ≥ 45 v. < 45	1.18 (0.77–1.81)	0.438		
Sex, female v. male	0.66 (0.43–0.99)	**0.047**	1.53 (0.81–2.91)	0.194
Subtype				
Sporadic v. NF1-associated	0.59 (0.39–0.91)	**0.016**	1.00 (0.48–2.06)	0.997
Sporadic v. RT-associated	0.52 (0.26–1.08)	**0.058**	1.35 (0.48–3.75)	0.568
Histology, epithelioid/Triton v. MPNST	0.59 (0.27–1.29)	0.192		
Size, ≥ 10 cm v. < 10 cm	3.14 (1.88–5.23)	**<0.001**	1.78 (0.91–3.84)	0.092
Location, trunk v. extremity or head/neck	1.56 (1.07–2.27)	**0.021**	1.92 (1.03–3.58)	**0.039**
Depth, deep v. superficial	2.37 (0.75–7.52)	0.141		
Chemotherapy, yes v. no	1.68 (1.12–2.53)	**0.012**	1.46 (0.76–2.08)	0.261
Radiation therapy, yes v. no	0.64 (0.43–0.97)	**0.035**	0.81 (0.46–1.47)	0.501
Margins, positive v. negative	2.14 (1.32–3.45)	**0.002**	2.41 (1.19–4.84)	**0.014**
Local recurrence, yes v. no	2.46 (1.63–3.72)	**<0.001**	1.95 (0.96–3.89)	**0.059**
Distant recurrence, yes v. no	4.61 (2.83–7.52)	**<0.001**	10.7 (4.89–23.5)	**<0.001**

Bold indicates statistical significance $p < 0.05$.

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Table 7

MPNST: a review of select recent single-institution retrospective series

			Adverse prognostic features					Therapy Benefit	
Authors & Year	**No. Patients**	**5 year survival**	**NF1**	**RAS**	**Location**	**Size**	**Positive Margins**	**RT**	**CT**
Present series	289	52%[a]	T	NS	T (trunk)	S (≥ 10 cm)	S	NS	NS
LaFemina et al., 2013	105	-	NS	S	NS	S (larger)	S	-	-
Fan et al., 2013	146	57% [b]	NS	-	NS	NS	NS	NS	NS
Stucky et al., 2011	175	60% [a]	T	-	S (trunk)	S (≥ 5cm)	NS	NS	NS
Zou et al., 2009	140	39% [a]	NS	NS	NS	S (≥ 10 cm)	NS	NS	NS
Porter et al., 2008	123	51% [b]	S	-	NS	S (> 200 ml)	NS	NS	NS
Anghileri et al., 2006	205	40% [a]	NS	-	S (trunk, HN)	S (larger)	S	S	NS

Abbreviations: CT, chemotherapy; HN, head/neck; NF1, neurofibromatosis type1-associated MPNST; NS, not statistically significant; RAS, radiation-associated MPNST; RT, radiation therapy ; S, statistically significant; T, trend

[a] Disease-specific survival

[b] Overall survival

[c] Tri-site series for a single-institution

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Table 1

Clinical parameters of MPNST cohorts.

	MPNST Cohort 1 MDACC (n=80)	MPNST Cohort 2 Stanford (n=66)	MPNST Cohort 3 LUMC (n=16)
Age at diagnosis			
-median (range)	40 (3–73)	n.a.	28 (15–68)
Gender			
-Female	27 (34%)	n.a.	9 (56%)
-Male	37 (46%)	n.a.	7 (44%)
-Not available	16 (20%)		
MPNSTs			
-NF1 associated	34 (43%)	43 (65%)	4 (25%)
-Sporadic	22 (27%)	21 (32%)	12 (75%)
-Radiation associated	5 (6%)	0 (0%)	0 (0%)
-Data n.a.	19 (24%)	2 (3%)	0 (0%)
Treatment			
-Resection	75 (93%)	n.a.	16 (100%)
-Radiotherapy	6 (8%)	n.a.	10 (63%)
-Chemotherapy	16 (20%)	n.a.	4 (25%)
-Not available	48 (60%)		1 (6%)
Mean survival Time *(years)*	4,9	n.a.	5,8
Events	35 (56%)	n.a.	9 (56%)

MPNST=malignant peripheral nerve sheath tumor; MDACC= The University of Texas MD Anderson Cancer Center; SUMC= Stanford University Medical Center; LUMC= Leiden University Medical Center. Events = death due to disease. n.a.=not available.

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Table 2

Distribution of loss or intact H3K27me3 according to tumor subtype.

	Loss of H3K27me3	Intact H3K27me3
MPNSTs	55 (34%)	107 (66%)
-Triton	0 (0%)	5 (100%)
-NF1 associated	33(41%)	47(59%)
-Sporadic	17(32%)	37(68%)
Neurofibroma	0 (0%)	97 (100%)
-Atypical	0 (0%)	8 (100%)
-Plexiform	0 (0%)	24 (100%)
Schwannoma	1 (2%)	43 (98%)
Perineurioma	0 (0%)	4 (100%)
Sarcoma NOS	0 (0%)	26 (100%)
Undifferentiated pleomorphic or spindle cell sarcoma	5 (3%)	172 (97%)
Angiosarcoma	2 (10%)	19 (90%)
Myxofibrosarcoma	0 (0%)	17 (100%)
Synovial sarcoma	9 (60%)	6 (40%)
Melanoma	1 (11%)	8 (89%)
DFSP	3 (38%)	5 (62%)
Clear cell sarcoma	2 (40%)	3 (60%)
Leiomyosarcoma	0 (0%)	5 (100%)
Dedif. Liposarcoma	0 (0%)	1 (100%)
Pleomorphic liposarcoma	0 (0%)	5 (100%)
Rhabdomyosarcoma	0 (0%)	2 (100%)
Osteosarcoma	1 (50%)	1 (50%)

MPNST=malignant peripheral nerve sheath tumor; NOS= not otherwise specified; DFSP=dermatofibrosarcoma protuberans.