Published in final edited form as:

Ann Surg Oncol. 2013 January ; 20(1): 66–72. doi:10.1245/s10434-012-2573-2.

Oncologic outcomes of sporadic, neurofibromatosis-associated, and radiation-induced malignant peripheral nerve sheath tumors

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Abstract

Background—Malignant peripheral nerve sheath tumors (MPNSTs) occur sporadically, after prior radiation therapy (RT), or in association with neurofibromatosis type 1 (NF1). It is controversial whether patients with NF1-associated MPNST have worse outcomes. We investigated the prognostic significance of sporadic, NF1-associated, and RT-induced MPNST.

Methods—Patients with primary high-grade MPNST from 1982–2011 were identified from a prospectively-maintained database. Patients with sporadic MPNST were included only if the MPNST was not associated with NF1 or a neurofibroma or if it was immunohistochemically S100-positive.

Results—We studied 105 patients; 42 had NF1-associated tumors, 49 sporadic, and 14 RT-induced. Median age at diagnosis was 38 years. Median follow-up for surviving patients was 4 years. Mean tumor diameter was 5.5 cm for RT-induced tumors and 9.7 cm for NF1-associated and sporadic tumors ($P=0.004$). In multivariate analysis, factors associated with worse disease-specific survival (DSS) were larger size (HR 1.08; 95% CI 1.04–1.13; $P<0.001$) and positive margin (HR 3.30; 95% CI 1.74–6.28; $P<0.001$). Age, gender, site of disease, and S100 staining were not associated with DSS. Three-year and median DSS was similar for NF1 and sporadic cases; combined 3-year DSS was 64% and median DSS was 8.0 years. For RT-induced tumors, 3-year DSS was 49% and median DSS was 2.4 years. The relationship between RT-association and DSS approached statistical significance (HR 2.29; 95% CI 0.93–5.67; $P=0.072$).

Conclusions—Margin status and size remain the most important predictors of DSS in patients with MPNST. NF1-associated and sporadic MPNSTs may be associated with improved DSS compared to RT-induced tumors.

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) arise from a peripheral nerve or demonstrate nerve sheath differentiation. These highly aggressive tumors account for up to 10% of soft tissue sarcoma (STS)^{1–4} and are most commonly diagnosed at ages 20–60.⁵

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The authors have no conflicts of interest to report.

MPNST has three recognized etiologies: tumors may occur in association with neurofibromatosis type 1 (NF1), may be the consequence of previous radiation therapy (RT-induced), or may occur sporadically.

Neurofibromatosis type 1 results from a gain-of-function mutation in the *NF* gene and is inherited in an autosomal dominant fashion. While the natural history is not completely understood, many patients will develop a malignant neurofibroma in their adult life.⁶ While earlier studies estimate that NF1 patients' lifetime risk of developing MPNST is 1–2%, more recent analyses estimate the risk to be 8–13%.^{4, 6} Additionally, NF1 may be underdiagnosed or unrecognized and, ultimately, 20–50% of patients with MPNST are found to have NF1.^{6–9}

MPNSTs are very aggressive, and resection remains the only therapeutic option for cure. Despite current multimodality therapy, the 5-year survival ranges from 35 to 50%.^{4, 10–12} Outcomes for patients with the three etiologic subtypes remain unclear. Some studies have suggested that NF1-associated tumors have a worse disease-specific survival (DSS) compared to sporadic tumors (16–38% compared to 42–57%).^{11, 13} For example, in the largest report on MPNST, Stucky et al. recently reported the Mayo Clinic experience with 175 patients with MPNST. They demonstrated a decrease in 5-year DSS for NF1-associated tumors compared to sporadic tumors that approached statistical significance (54% versus 75%; $P=0.058$).³ In a recent report by Porter and colleagues, evaluation of 123 patients with either sporadic or NF1-associated ($N=33$) tumors demonstrated that NF1 was an independent predictor of poor outcome on multivariate analysis.¹⁴ However, other studies have failed to demonstrate such a reduction in survival, but are limited by patient numbers.^{6, 15–18}

RT-induced soft tissue sarcomas are rare, and only about 5% of these are MPNST.¹⁹ Given the rarity of RT-induced MPNST, very little is known about these tumors. The risk of MPNST after RT is difficult to estimate but has been reported as 0.06%, most commonly following exposure to external beam radiation in the setting of breast cancer or lymphoma.²⁰ Gladdy et al. evaluated outcomes of RT-associated STS compared to sporadic STS and found that size >5 cm, presence of a positive margin, and histologic type (specifically MFH and MPNST) were independent predictors of reduced 5-year DSS. In a matched cohort analysis of RT-induced MFH versus sporadic pleomorphic MFH, RT-induced tumors were associated with a decreased DSS compared to sporadic tumors. Due to sample size limitations, the authors were unable to perform the corresponding analysis for RT-induced MPNST, but they did observe that 5-year DSS for high-grade, RT-induced MPNST was 0%, compared to 54% for non-RT-induced STS. RT-induced MPNSTs were also smaller and more likely to be located in the trunk.²¹ Zou and colleagues reported on 85 patients who underwent complete resection of MPNST and observed that neither NF1 status nor prior radiation exposure was associated with DSS. Once again, however, sample size limited their statistical analysis, as there were only eight patients in the RT group.⁴

In summary, at this time, it is unclear how outcomes in patients with MPNST differ by etiology. The goal of this study was to determine the prognostic significance of sporadic, NF1-associated, and RT-induced MPNST.

Methods

Retrospective review of a prospectively-maintained sarcoma database was performed after institutional review board (IRB) approval. Patients diagnosed between July 1982 and February 2011 with histologically confirmed, primary, high-grade MPNST were included. Patients were excluded if lesions were recurrent or low grade.

MPNSTs were categorized according to etiology: RT-induced, NF1-associated, or sporadic. Tumors were defined as RT-induced if the patients received prior external beam radiotherapy with a field encompassing the location of the MPNST. Some of the patients in this group were described previously.²¹ Tumors were defined as NF1-associated if the patient carried a clinical diagnosis of NF1. This diagnosis was given either in the setting of a confirmed mutation in the *NF1* gene or if the patient met 2 or more of the NIH consensus criteria.²² Other tumors were included and defined as sporadic MPNST if they arose in the absence of a formal NF1 diagnosis or a history of radiation exposure and if they were associated with a neurofibroma and/or positive for S100 immunohistochemical staining. Cases diagnosed solely via electron microscopy were excluded.

A sarcoma surgeon performed all resections at MSKCC. All cases were reviewed by a dedicated sarcoma pathologist.

Clinicopathologic data included age at diagnosis, gender, tumor location, maximum tumor diameter (as both a categorical and a continuous variable), margin status, S100 immunohistochemical status, and use of neoadjuvant or adjuvant chemotherapy and/or radiation. Sites of disease were defined as extremity (upper and lower), trunk (chest wall, proximal extremity or groin, and thoracic), abdomen or retroperitoneum, or head and neck. Margins of resection were defined as R0 (negative), R1 (microscopically positive), and R2 (macroscopically positive). Due to the limited number of R1 (N=17) and R2 (N=13) resections, these groups were combined to improve statistical power.

The primary endpoint of the study was disease-specific survival (DSS), defined as the time from diagnosis to death as a result of disease or complication. The influence of clinicopathologic features on DSS was analyzed using the Kaplan-Meier method and using the log-rank test in the univariate setting and the Cox proportional hazard regression analysis in the multivariate setting. Size comparison was analyzed by Kruskal-Wallis rank sum for comparison of 3 size groups and by a Wilcoxon rank test for comparison of 2 size groups. The competing risk analysis method was used to perform a survival analysis of local (LR) and distant (DR) recurrence, due to the relatively large number of deaths without LR or DR. Three-year, rather than 5-year, DSS was analyzed because, in the RT-induced group, there was only one survivor at 5 years. Therefore, evaluation of 3-year DSS allowed for a more valid statistical analysis.

$P < 0.05$ was considered significant. Sporadic and NF1-associated tumors were combined into a single group for comparison with RT-induced tumors. This comparison was performed because the 3-year DSS between sporadic and NF1-associated cases was not significantly different and because reducing the number of categories improved the statistical power of the analysis of the limited number of DSS events.

Results

Patient and Tumor Characteristics

Of the 148 patients evaluated for MPNST, 105 fulfilled our criteria for primary, high-grade MPNST. The other 43 patients were excluded due to presence of low grade tumor (n=13), alternate pathology (n=8), recurrent rather than primary tumor (n=7), inability to pathologically verify MPNST diagnosis (n=11), and incomplete medical record (n=4). Patient and tumor characteristics are summarized in Table 1. Sporadic tumors were the most common (n=49; 47%), followed by NF1-associated (n=42; 40%) and RT-induced (n=14; 13%; Figure 1).

Females constituted 32% (n=34) of the study cohort. There was no significant difference in gender distribution among the three groups (P=0.13). The median age of diagnosis was 38 yr (range 16–87 yr). Age differed significantly among groups and was consistent with time from RT exposure to tumor development, with the median age at diagnosis 36 yr in sporadic, 39 yr in NF1-associated, and 49 yr in RT-induced (P=0.01). MPNSTs were most commonly located at the extremity (n=42, 40%), followed by the abdomen (including retroperitoneum; n=30; 29%), trunk (n=26; 25%), and, least commonly, head and neck region (n=7; 7%). RT-induced tumors were most common in the trunk (n=8, 57%) and sporadic and NF1-associated were most common in the extremity (41% and 48%, respectively). This difference is not significant (P=0.12; Table 1), but the statistical analysis may be limited by the small sample size. For patients with RT-induced MPNST, the median time from prior RT-exposure to MPNST diagnosis was 12.6 years (interquartile range [IQR] 8.7–26.0 yr).

When tumor diameter was evaluated as a categorical variable (<5 cm, 5–10 cm, >10 cm), tumors were relatively equally distributed among size categories, with 37% of tumors >10 cm, 34% <5 cm, and 29% 5–10 cm. This was also observed in the combined sporadic/NF1-associated subgroup. However, in the RT-induced group, 93% of patients (n=13) had a tumor <10 cm. Only 1 patient (7%) had a tumor >10 cm. Overall, the mean tumor diameter was 9.1 cm (IQR 4–13 cm). Mean tumor diameter, analyzed as a continuous variable, differed significantly among the three groups (P=0.004; Table 1).

Margin status was available in 104 patients. Negative surgical margins were achieved in 74 patients (70%). Resections were R1 in 17 (16%) and R2 in 13 (12%). Of note, three cases were paraspinal (2 truncal and 1 abdominal). Due to known difficulty in resection of paraspinal cases, all three cases underwent an R2 resection. Two of these cases were RT-induced MPNST and received neoadjuvant radiation; one was NF1-associated and did not receive any additional therapy.

Sixteen patients (15%) were treated with neoadjuvant chemotherapy (doxorubicin/ifosfamide [AI]=10, cyclophosphamide, dactinomycin, vincristine, etoposide, ifosfamide [VAC-IE]=2, and one each for gemcitabine, ifosfamide, and dacarbazine/doxorubicin/ifosfamide/mesna [MAID]); 13 were treated with neoadjuvant radiation (12%; intensity-modulated radiation therapy [IMRT]=9, external beam radiation therapy [EBRT]=4). Eighteen (17%) were treated with adjuvant chemotherapy (A=8, AI=4, gemcitabine/docetaxel=2, and one each for MAID, VAC IE, doxorubicin/cyclophosphamide/vinblastine, and unknown); 51 (49%) were treated with adjuvant radiation therapy (EBRT=26, brachytherapy [BT]=15, IMRT=9, neutron beam and gamma knife=1).

Neoadjuvant chemotherapy was given in 19%, 14%, and 7% of NF1-associated, sporadic, and RT-induced cases, respectively. Adjuvant chemotherapy was given in 17%, 18%, and 14%, respectively. Neoadjuvant RT was given in 7%, 12%, and 29%, respectively. Adjuvant RT was given in 57%, 49%, and 21%, respectively.

Survival Analysis

At a median follow-up of 2.6 years for all patients and 4.0 years for surviving patients, 49 of 105 patients were alive. Forty-four patients (42%) had no evidence of disease, 44 (42%) were dead of disease, 7 (7%) died of unknown causes, 5 (4%) died of other causes, and 5 (4%) were alive with disease at the time of last follow-up. Of those who died of disease, 7 (16%) did not have LR or DR at time of death.

The 3-year DSS was 66% for sporadic (CI 0.54–0.82), 60% for NF1-associated (CI 0.46–0.78), and 49% for RT-induced MPNST (CI 0.25–0.96; Figure 2A). As there was no

difference between median and 3-year DSS for NF1 and sporadic cases ($P=0.91$), sporadic and NF1-associated tumors were grouped for the analysis, yielding a combined 3-year DSS of 64% (Figure 2B). The median DSS was 8.0 years for combined sporadic/NF1-associated and 2.4 years for RT-induced MPNST.

Univariate analysis revealed no association with DSS for age, gender, site of disease, and S100 immunohistochemical status (Table 2). However, increasing tumor size ($P<0.001$) and the presence of a positive margin ($P<0.001$) were associated with a worse DSS. The decreased DSS for patients with RT-induced tumors approached statistical significance ($P=0.09$; Table 2).

Multivariate analysis confirmed that larger size (hazard ratio [HR] 1.08; 95% confidence interval [CI] 1.04–1.13; $P<0.001$) and positive margins (HR 3.30; 95% CI 1.74–6.28; $P<0.001$) were associated with a decreased DSS (Table 2). Size was evaluated as both a two-category (< 10 cm versus ≥ 10 cm) and a continuous variable. Multivariate analysis for size as both categorical and continuous variables demonstrated that increasing size was associated with a reduction in DSS ($P=0.001$ and $P<0.001$, respectively). Patients with RT-associated tumors had a 2.29-fold reduction in 3-year DSS (HR 2.29; 95% CI 0.93–5.67; $P=0.072$; Table 2). While this was not statistically significant, the limited number of patients in the RT-induced group limited the analysis.

Recurrence Patterns

Both LR and DR rates were evaluated. LR was present in 29% ($N=12$), 22% ($N=11$), and 43% ($N=6$) of NF1-associated, sporadic, and RT-induced tumors respectively. Of the 29 local recurrences, the majority ($n=19$; 66%) had negative histologic margins at the time of resection. Five (17%) had microscopically-positive margins, and another five had macroscopically-positive margins.

DR was present in 33% ($N=14$), 39% ($N=19$), and 21% ($N=3$) of cases, respectively. Of note, RT-induced tumors demonstrated local failure more commonly than distant failure. In contrast, sporadic and NF1-associated tumors tended to have a higher percentage of patients with DR as compared to LR.

Competing risk analysis demonstrates LR is significantly greater in RT-induced tumors, compared to grouped sporadic and NF1-associated tumors ($p=0.02$; Fig. 3A). However, the association between subgroup and DR does not achieve statistical significance ($p=0.61$; Fig. 3B).

Discussion

This study represents a current report of outcomes based on the etiology of MPNST, inclusive of RT-induced tumors. Previous to this report, there has been conflicting data regarding outcomes associated with sporadic and NF1-associated MPNST. Additionally, due to limited sample size, there have been no formal reports about the survival of RT-induced MPNST, compared to those that are sporadic and NF1-associated. This study attempts to address these outstanding questions in a homogenous cohort of primary, high-grade MPNST.

Here we report a trend towards decreased DSS in patients with RT-induced tumors, compared to those that are sporadic or associated with NF-1. We found that RT-induced MPNSTs have a 3-year DSS of 49%, compared to 66% for sporadic and 60% for NF1-associated. While the small sample size of the RT-induced group limited the power of the

statistical analysis, the hazard ratio suggests that patients with RT-induced MPNST should be considered higher risk compared to those with sporadic or NF1-associated tumors.

The rarity of RT-induced sarcomas has led to conflicting reports in the literature as to their outcomes when compared to sporadic tumors. Zou and colleagues reported on 85 patients with MPNST and found that prior RT was not associated with DSS.⁴ In contrast, Gladdy and colleagues did not observe a single 5-year survivor among 10 patients with high-grade, RT-induced MPNST.²¹ Similarly, Wong and colleagues reported on 134 patients with MPNST, 28 of whom had a history of radiation exposure. On multivariate analysis, RT-induced tumors were associated with a significant reduction in overall survival.¹⁸

Though sporadic and NF1-associated tumors are more frequent than RT-induced tumors, the data remain conflicting about whether outcomes differ for NF1-associated and sporadic MPNST. While some studies have failed to demonstrate significant differences in survival between the tumors associated with the two causes,^{6, 17, 18} others have demonstrated a reduction in survival for patients with NF1-associated tumors.^{11, 13} For example, Hruban and colleagues at MSKCC reported on 43 cases of MPNST of the buttock and lower extremity and failed to demonstrate a significant difference in survival for patients with and without NF1 (65% versus 60%).¹⁷ Wong and colleagues evaluated 134 MPNSTs and similarly failed to demonstrate a significant difference in overall survival. In contrast, early studies by Sordillo and colleagues showed a significant reduction in overall survival in MPNST associated with NF1 compared to other cases (5-year survival of 23% versus 47%).¹³ Carlie and colleagues performed a multivariate analysis of 167 patients with MPNST and reported a 1.88-fold reduction in overall survival in the NF1-associated group.¹¹ In the current analysis of 91 patients with sporadic or NF1-associated MPNST, we found no difference in 3-year DSS between sporadic and NF1-associated tumors (66% versus 60%, respectively).

MPNST is thought to be a sarcoma with complex genomic alterations. Sarcoma types in this class generally are diagnosed at a median of 55–65 years, whereas sarcoma types with a specific translocation but few other genomic alterations are diagnosed at a median of 20–45 years.²³ MPNST represents an exception to this generalization; the median age (38 years in this study) is more like that of a translocation-associated sarcoma than a genomically complex sarcoma. However, the patients with RT-induced MPNST (median age 49 yr) were closer to the age expected for genomically complex sarcomas.

The range of time from RT to MPNST diagnosis was 9–26 years. While some have estimated the minimum latency from time of radiation exposure to MPNST diagnosis to be as short as 1–6 months, our results are consistent with recent reports that estimated a mean latency to be 15–16 years.^{19, 20}

We previously reported that size >5 cm, positive margin status, and histologic type (MFH or MPNST) are independent predictors of worse DSS in patients with RT-induced STS.²¹ Here we show that positive margin status and larger size are the most important independent predictors of reduced DSS in the cohort of patients with MPNST. Similarly, size >5 cm was an independent predictor of reduced DSS in the Mayo Clinic series. They also reported other independent predictors of decreased DSS, including high-grade tumors, truncal location, and locally recurrent tumors.²⁴ Zou and colleagues reported that size >10 cm and negative S100 staining were associated with decreased DSS.⁴

The current study finds that RT-induced MPNSTs may be associated with a reduction in DSS, even though tumors are smaller than sporadic and NF1-associated MPNSTs. While this association has been previously reported,²¹ the cause of this inverse correlation is unknown at this time. However, in the context of this study as well as others that have

demonstrated larger MPNST in the setting of NF1 and sporadic,^{3, 4} these findings possibly reflect a difference in the molecular bases, and therefore biology, of these tumors. Limited sample size has, to date, hindered the elucidation of these biological differences, but future efforts may contribute to our understanding of the differential tumor biology.

Moreover, patterns of failure of RT-induced MPNST demonstrate that RT-induced tumors more commonly recur locally than distantly. This could be related to the difficulty in managing tumors in difficult locations, such as the paraspinal region (14% of the RT-induced MPNSTs, both of which underwent R2 resection) as well as possible compromise of optimal radiation treatment, due to limitations of radiation dose administration in the setting of prior exposure. These findings highlight the need to consider alternative treatment modalities for these difficult-to-treat lesions.

A strength of our study is the use of strict inclusion criteria. Our study population is very homogenous and relied on confirmation of the diagnosis of MPNST with either S100 staining or association with a neurofibroma. We note, however, that we potentially excluded some patients with authentic MPNST that were S100-negative. Others have reported that S100-negative MPNSTs are associated with a significant reduction in 5-year actuarial disease-specific death rates.⁴ Thus, we may have excluded some cases with possibly higher-risk biology from the sporadic MPNST group. Due to the short survival of patients with RT-induced MPNST, we purposely selected 3-year DSS as a more informative endpoint than 5-year DSS. The main limitation of this study, as has been true in all studies on MPNST and other rare tumors, is the small sample size, which limits the power of statistical analyses.

MPNST is an uncommon and heterogeneous subset of STS, comprising RT-induced, sporadic, and NF1-associated tumors. Both the natural history and, more importantly, the biology of these rare tumors are poorly understood. In patients with prior RT, treating physicians should be aware of the possibility of patients developing RT-induced STS in general, including MPNST, and that the latency can be prolonged and variable. RT-induced tumors have characteristically poor tumor biology, a greater incidence of local recurrence, and a trend towards inferior DSS. A deeper understanding of the genetic alterations that drive the more aggressive biologic behavior in RT-induced MPNST may lead to identification of novel treatments approaches. Future studies should focus on elucidating the genetics and genomics of MPNSTs to develop novel treatment paradigms.

Acknowledgments

This work was supported by Soft Tissue Sarcoma Program Project grant P01 CA 047179 and SPORC in Soft Tissue Sarcoma P50 CA 140146.

This work was supported by Soft Tissue Sarcoma Program Project grant P01 CA 047179 (SS), SPORC in Soft Tissue Sarcoma P50 CA 14014 (SS), and the Dr. Murray F. Brennan/Gorin Fellowship Endowment Fund (JL).

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Synopsis

MPNST size and margin status remain the most important predictors for survival for MPNST. While there is no difference in survival between sporadic and NF1-associated MPNSTs, RT-induced tumors may be associated with a reduced survival.

Figure 1.
Study flow chart.

Figure 2.

(a) Disease-specific survival (DSS) for primary, high-grade MPNST according to etiologic subtype. (b) DSS for primary, high-grade MPNST, comparing combined sporadic/NF1-associated versus RT-induced.

Figure 3.

Competing risk analysis for local (LR) and distant (recurrence). In this analysis, LR and DR are treated as the primary variables and death is treated as a competing risk variable. The incidence of LR is significantly different between RT-induced and sporadic/NF-1 associated MPNST ($p=0.02$). However, there is no significant difference in DR incidence between MPNST subtypes ($p=0.61$).

Table 1

Patient characteristics.

Characteristic	Sporadic n=49	NF1-Associated n=42	RT-Induced n=14	P value*
Gender, n (%)				0.13
Female	11 (22)	17 (40)	6 (43)	
Male	38 (78)	25 (60)	8 (57)	
Age at diagnosis, yr, median (IQR)	36 (26–41)	39 (31–44)	49 (37–60)	0.01
Location, n (%)				0.12
Extremity	20 (41)	20 (48)	2 (14)	
Abdomen/RP	15 (31)	12 (29)	3 (21)	
Trunk	11 (22)	7 (17)	8 (57)	
Head and Neck	3 (6)	3 (7)	1 (7)	
Maximum tumor diameter, cm, mean (IQR)	8.4 (3–14)	11.2 (7–13)	5.5 (4–6)	0.004

IQR, interquartile range; NF1, neurofibromatosis type 1; RP, retroperitoneum; RT, radiation therapy

*
P value represents 3 group analysis

Table 2

Univariate and multivariate analysis of predictors of disease-specific survival.

Variable	Univariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P value
Age (> 50 yr vs 50 yr)	0.63 (0.23–2.77)	0.38		
Age (Continuous)	1.00 (0.97–1.02)	0.67		
Gender (Male vs Female)	1.62 (0.82–3.21)	0.17		
Site (Abdominal vs Other)		0.51		
Extremity	0.68 (0.32–1.43)			
Trunk	1.18 (0.55–2.55)			
Head & Neck	0.84 (0.24–2.96)			
S100 IHC (Positive vs Negative)	0.59 (0.25–1.37)	0.22		
Subtype (RT-induced vs Other)	2.01 (0.89–4.52)	0.09	2.29 (0.93–5.67)	0.07
Size (Continuous)	1.08 (1.04–1.12)	<0.001	1.08 (1.04–1.13)	<0.001
Margin (R1/R2 vs R0)	4.04 (2.20–7.39)	<0.001	3.30 (1.74–6.28)	<0.001

CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; RT, radiation therapy