



Malignant peripheral nerve sheath tumors: Analysis of the national cancer database

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ABSTRACT

Objectives: Malignant peripheral nerve sheath tumor (MPNST) is a rare type of soft tissue sarcoma (STS) that carries significant mortality. Given the rarity of MPNST, current knowledge on the disease is limited. We aim to characterize patient, tumor, and treatment factors, and determine variables associated with 5-year overall survival (OS) in individuals with MPNST.

Materials and Methods: We utilized the National Cancer Database (NCDB) to identify adult patients diagnosed with MPNST from 2004 to 2015, and analyze patient, tumor, treatment, and survival data. American Joint Committee on Cancer (AJCC 8) staging criteria for STS was utilized.

Results: In our cohort of 2,858 patients with MPNST, median age at diagnosis was 47. The 5-year OS rate was 52%. Age, race, tumor size, and treatment regimen significantly predicted 5-year OS on univariate analysis. AJCC 8 stage appeared to predict 5-year OS in head and neck tumors (though not significantly), but not trunk and extremity tumors.

Conclusion: While our cohort of patients with MPNST are typically relatively young and healthy, 5-year OS is only 52%. Notably, age extremes, large tumor size, and certain treatment regimens are associated with worse outcomes. While AJCC 8 staging guidelines may have some value in predicting OS in head and neck tumors, they do not reliably risk stratify patients with trunk and extremity MPNST. Ultimately, MPNST is associated with high mortality with few modifiable risk factors, and survival may not be adequately predicted by current staging systems.

Introduction

Malignant peripheral nerve sheath tumor (MPNST) is a subtype of soft tissue sarcoma (STS), arising from the peripheral nervous system and showing nerve sheath differentiation [1]. These neoplasms account for 5–10% of all STS, but are quite rare, with an estimated incidence of 0.001% [2,3]. Up to 50–60% of all cases of MPNST are associated with neurofibromatosis type 1 (NF1), 10% are associated with prior radiation exposure, and the rest occur sporadically [4]. MPNST is most commonly diagnosed in patients 20–60 years old, and patients with sporadic tumors develop MPNST around age 40 [3,5–7]. It is a highly aggressive disease, with 5-year overall survival estimated to be only 35–65% [3,5,6,8–12]. MPNST which develop in conjunction with NF1 have historically been thought to carry a worse prognosis, though some recent research has shown no mortality difference between NF1-related

and other MPNST [4–7,9–13]. Poorer prognosis has also been associated with tumor specific factors such as higher grade, larger size, and location in the trunk [3–7,9–13]. Though there is no standardized treatment, the mainstay of management is surgical resection, with possible addition of radiation or chemotherapy [6,8]. Previous studies have demonstrated that extent of resection may be linked to improved survival, but have shown minimal mortality benefit with supplemental radiation or chemotherapy [3–6,8–12].

Given the rarity of the disease, information on disease risk factors, treatment, and survival is very limited. Most research undertaken has been in the form of case reports, small case series, and a few meta-analyses or larger single-institute studies. Problematically, most previous research encompasses patients treated many decades ago, and a recent meta-analysis suggests treatment and mortality characteristics of MPNST have shifted considerably in the past few decades [6].

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Additionally, the American Joint Committee on Cancer (AJCC) released updated cancer staging in 2017 – known as AJCC 8 – which included new criteria for STS, but their value in predicting survival in MPNST has not yet been assessed. Overall, there has never been a study of MPNST using a robust national database. We aim to address this gap in the literature using the National Cancer Data Base (NCDB), which includes data on approximately 70% of new cancer diagnoses in the United States [14]. The scale of the NCDB presents a unique opportunity to study a large number of MPNST cases. We intend to characterize patient, tumor, and treatment factors, and determine variables associated with patient survival.

Methods

Data acquisition and patient selection

The NCDB is a national, prospectively maintained, clinical oncology database begun in 1989 and sponsored jointly by the American College of Surgeons (ACoS) and American Cancer Society (ACS). It contains de-identified clinical patient data submitted by over 1500 hospitals accredited by the ACoS Commission on Cancer (CoC) program [14]. The NCDB includes patient demographic information, treatment regimens, and long-term overall survival.

The NCDB was queried for adult patients (age ≥ 18) diagnosed with MPNST (International Classification of Diseases for Oncology, or ICD-O, 3rd Edition histology codes 9540, 9561, and 9571) from 2004 to 2015 [15]. Patients with diagnosis of a prior neoplasm were excluded in order to capture only patients with a MPNST as a primary neoplasm, and to remove the confounding variable of other cancers.

Pre-operative variables and outcomes

Pre-operative variables including age, sex, race, and Deyo-Charlson Comorbidity Index (DCCI) [16] were considered, as well as tumor and treatment-specific data such as primary site of tumor (using ICD-O topography codes), tumor grade, tumor stage (pathological if available; otherwise clinical), presence of distant metastases, positive regional lymph nodes, tumor size, treatment regimen, and surgical margin status. Tumor stage was divided into low stage (stage I and II) and high stage (stage III and IV) for analysis of the relationship between stage and treatment regimen. For AJCC 8 analysis, we evaluated AJCC 8 stage for each tumor in our dataset using tumor grade, tumor size, nodal status, and presence of distant metastases. The AJCC 8 includes staging guidelines for STS trunk and extremity tumors. For STS of the head and neck, the AJCC 8 provides definitions of tumor size (T), regional lymph nodes (N), and distant metastasis (M) staging, as well as tumor grade assessment (G), but no overall staging groups are presented due to lack of data to define groups [17]. So, for head and neck tumors we utilized the AJCC 8 TNM stages, and applied an overall staging group algorithm proposed by Cates [18]. AJCC 8 guidelines define T4a/b by local invasion, but we did not have this data available, so we categorized tumor T stage by size alone. For Kaplan-Meier survival analysis, we grouped AJCC 8 stages into low (I and II) and high (III and IV) stages. The outcome variable used for analysis was 5-year overall survival (OS), which was determined from time since diagnosis (in months) and vital status at last follow-up.

Statistical analysis

All variables were made categorical prior to analysis. Statistical analysis was performed using SPSS version 24 (IBM SPSS, Armonk, NY, USA). Stage as defined in the NCDB dataset was utilized, and the relationship of demographic, tumor, and treatment variables to 5-year OS was evaluated using Chi-square tests for univariate analysis. Variables with $p < 0.2$ on univariate analysis were included in a multivariate analysis using a binary logistic model with backwards stepwise

selection – variable entry level was set at 0.05 and removal level was 0.10. Univariate analysis of treatment regimen by stage category – low stage and high stage – was conducted. A separate univariate analysis was performed to assess the relationship between treatment regimen and 5-year OS when controlling for stage category. Calculated AJCC 8 stage – official AJCC 8 stage for trunk and extremity, and Cates' staging algorithm using AJCC 8 TNM staging for head and neck tumors – was utilized to conduct a univariate and multivariate analysis of 5-year OS using only pre-operative variables such as demographic factors and tumor characteristics. Kaplan-Meier survival curves were generated for all MPNST, as well as head and neck tumors and trunk and extremity tumors stratified by AJCC 8 stage category, and a log rank test was used to examine the relationship between 5-year OS and AJCC 8 stage for head and neck tumors and trunk and extremity tumors. All comparisons were two-tailed with statistical significance set at $p < 0.05$. Effect size was calculated as odds ratios with corresponding 95% confidence intervals.

Results

Patient characteristics

A total of 2858 patients with a diagnosis of MPNST were identified (Table 1). Patient age at diagnosis ranged from 18 to 90, with a mean of 47. Just over half of patients were male, and the majority were white. Patients largely did not have many significant comorbid conditions, with 88% scoring a 0 on the DCCI.

Tumor characteristics

Tumor topographical categorization varied, with broad categories shown in Table 1. Most tumors were located in extremities or the trunk, with relatively few in the head and neck region or elsewhere. Tumor size also varied widely, though over half of tumors were less than 10 cm. As assessed by the NCDB, nearly a quarter of tumors did not have a known stage, but the remainder were fairly equally divided between low stage (39%) and high stage (37%). At time of diagnosis, 13% had distant metastases, and only 2% had positive regional lymph nodes.

Treatment data

As shown in Table 1, only 5% of patients received no treatment. Most patients underwent surgical resection, with close to a third of all patients receiving surgery alone. A small subset of patients had only radiation or chemotherapy, and the rest received some combination of therapies. However, treatment regimen varied significantly by stage category (Table 2). Patients with low stage tumors were more than twice as likely to have surgery only than high stage patients. Conversely, patients with high stage tumors were much more likely to not undergo a surgical intervention, with 30% of high stage patients receiving only chemotherapy and/or radiation therapy compared to 7% of low stage patients.

Follow-up and 5-year overall survival

Patients were followed for up to 12 years, with median time to last contact of 30.5 months. Just over half had either died before 5 years or had follow-up data past the 5-year mark, and so were included in analysis of 5-year OS. Of patients with 5-year OS data, 52% were alive at the 5-year mark (Fig. 1).

Predictors of 5-year overall survival

On univariate analysis of predictors of 5-year OS using stage as reported in the NCDB dataset, age, race, and tumor size were

Table 1
Patient Characteristics and Univariate Analysis of Predictors of 5-Year Overall Survival (OS).

	All N = 2858 N (%)	5-Year Overall Survival				
		All With 5-Year Follow-Up ^a N = 1442 N	Survival N = 742 N (%)	P Value (χ^2)	Odds Ratio	95% CI
Demographics						
Age						
Mean (SD)	47 (18)					
Range						
< 40	1119 (39.2)	566	271 (47.9)	0.010	1 (REF)	
40–60	1049 (36.7)	565	322 (57)		1.442	1.141 to 1.823
60–80	566 (19.8)	280	134 (47.9)		0.999	0.750 to 1.331
> 80	124 (4.3)	31	15 (48.4)		1.021	0.495 to 2.104
Sex						
Male	1554 (54.4)	752	379 (50.4)	0.402	1 (REF)	
Female	1304 (45.6)	690	363 (52.6)		1.093	0.888 to 1.344
Race						
White	2143 (75.0)	1091	575 (52.7)	0.002	1 (REF)	
Black	547 (19.1)	257	133 (51.8)		0.963	0.733 to 1.263
Asian/Pacific Islander	84 (2.9)	44	21 (47.7)		0.819	0.448 to 1.498
Other	48 (1.7)	29	5 (17.2)		0.187	0.071 to 0.494
Unknown	36 (1.3)					
Charlson Comorbidity Score						
0	2519 (88.1)	1287	666 (51.7)	0.071	1 (REF)	
1	267 (9.3)	134	61 (45.5)		0.779	0.545 to 1.114
2+	61 (2.1)	21	15 (71.4)		2.331	0.899 to 6.046
Tumor Characteristics						
Primary site						
Trunk and Extremity	2124 (74.0)	1071	560 (52.3)	0.170	1 (REF)	
Head and Neck	351 (12.3)	211	111 (52.6)		1.013	0.754 to 1.361
Central Nervous System, Cranial Nerves, and Meninges	126 (4.4)	53	20 (37.7)		0.553	0.313 to 0.976
Overlapping or NOS	257 (9.0)	107	51 (47.7)		0.831	0.558 to 1.237
Grade						
1	546 (19.0)	289	224 (57.6)	0.306	1 (REF)	
2	772 (26.9)	326	169 (51.8)		0.793	0.590 to 1.066
3	419 (14.6)	192	105 (54.7)		0.889	0.628 to 1.259
Not determined	1133 (39.5)					
NCDB Analytic Stage Group						
I	622 (21.8)	420	212 (50.5)	0.350	1 (REF)	
II	481 (16.8)	300	156 (52)		1.063	0.790 to 1.430
III	697 (24.4)	310	140 (45.2)		0.808	0.602 to 1.084
IV	355 (12.4)	51	26 (51)		1.020	0.571 to 1.825
Unknown	703 (24.6)					
Distant Mets at Dx						
Yes	376 (13.1)	46	19 (41.3)	0.161	0.655	0.361–1.189
No or Unknown	2482 (86.5)	1396	723 (51.8)		1 (REF)	
Positive Regional Lymph Nodes						
Yes	55 (1.9)	18	9 (50.0)	0.901	0.943	(0.372–2.389)
No or Unknown	2803 (97.7)	1424	733 (51.5)		1 (REF)	
Size of Tumor (cm)						
Median (SD)	7.5 (14)					
< 5cm	702 (24.6)	473	255 (53.9)	0.035	1 (REF)	
5–10 cm	868 (30.4)	449	233 (51.9)		0.922	0.712 to 1.15
10–15 cm	480 (16.7)	196	89 (45.4)		0.711	0.509 to 0.993
> 15 cm	344 (12.0)	110	45 (40.9)		0.592	0.389 to 0.902
Unknown	476 (16.6)					
Treatment						
Treatment						
Surgery only	918 (32.0)	540	287 (53.2)	0.089	1 (REF)	
Surgery with Chemotherapy and/or Radiation	988 (34.4)	549	284 (51.7)		0.945	0.745 to 1.198
Chemotherapy and/or Radiation only	472 (16.5)	121	51 (42.2)		0.642	0.431–0.957
None performed	144 (5.0)	50	21 (42.0)		0.638	0.355–1.148
Other or Unknown	348 (12.1)					
Surgical Margins						
Negative	1495 (52.3)	918	494 (53.8)	0.920	1 (REF)	
Positive	512 (17.9)	227	123 (54.2)		1.015	0.758–1.359
Unknown	851 (29.8)					

^a Total with 5-year OS data; includes patients who had died before the 5-year mark and patients with follow-up data past the 5-year mark.

Table 2
Treatment Regimen by Stage.

		Low Stage	High Stage	P Value (χ^2)
		N = 1037	N = 988	
		N (%)	N (%)	
Treatment	Surgery only	437 (42.1)	200 (20.2)	< 0.0001
	Surgery with Chemotherapy and/or Radiation	438 (42.2)	360 (36.4)	
	Chemotherapy and/or Radiation only	75 (7.2)	297 (30.1)	
	None performed	35 (3.4)	50 (5.1)	
	Other or Unknown	118 (11.4)	145 (14.7)	

statistically significant predictors (Table 1). Patients whose age at diagnosis was between 40 and 60 years-old had the highest survival at 5-years, at 57%, with both younger and older patients having lower OS. Patients of white, black, and Asian or Pacific Islander race had similar 5-year OS around 50%, but the 2% of patients who fell into the ‘Other’ category had considerably worse OS at 17.2%. Larger tumors were associated with lower OS, with tumors greater than 10 cm in diameter having a 5-year OS of 44% compared to 54% for tumors less than 5 cm in diameter. Though not significant, there were also some differences in 5-year OS between treatment regimens. Surgery alone had the highest rate of survival at 53%, with surgery with chemotherapy and/or radiation (52%) close behind. Patients who underwent chemotherapy and/or radiation alone or had no treatment had non-significantly lower 5-year OS rates, at 42% each.

Multivariate analysis found age, race, and tumor size were statistically significant predictors of 5-year OS (Table 3). Though not shown in tables, the relationship between treatment regimen and 5-year OS when controlling for low stage versus high stage tumors was not found to be a significant predictor of 5-year OS.

AJCC 8 stage and 5-year overall survival

Separate univariate and multivariate analysis of 5-year OS for head and neck tumors, and trunk and extremity tumors, using AJCC 8 staging (official for trunk and extremity, or Cates’ proposal for head and neck) and other preoperative variables was conducted (univariate analysis shown in Table 4 for trunk and extremity tumors and Table 5 for head and neck tumors). For head and neck tumors, no pre-operative predictors were significantly associated with 5-year OS on univariate analysis. Staging groups proposed by Cates based on AJCC 8 TNM staging showed some non-significant differences in 5-year OS – 63% of stage I and 43% of stage II patients were alive at 5 years, compared to 36% of stage III and 50% of stage IV [18]. On multivariate analysis in head and neck tumors, Cates’ AJCC 8 stage was the only significant predictor of 5-year OS. For trunk and extremity tumors, race and tumor size were significantly associated with 5-year OS on univariate analysis, and tumor size alone was significant on multivariate analysis. On Kaplan-Meier survival analysis using a log rank test, Cates’ AJCC 8 staging algorithm did not significantly predict 5-year OS for head and neck tumors, and AJCC 8 stage did not significantly predict 5-year OS in trunk and extremity tumors (Fig. 1).

Discussion

MPNST, though rare, is associated with significant mortality. At this time, it has been inadequately studied, with most research consisting of single institution analyses or case series utilizing patient records from decades ago; thus, the current perspective on MPNST may be significantly outdated. Given the lack of research on this tumor, there is considerable uncertainty surrounding prognostic factors and treatment approaches. The present study addresses this deficit in the literature by

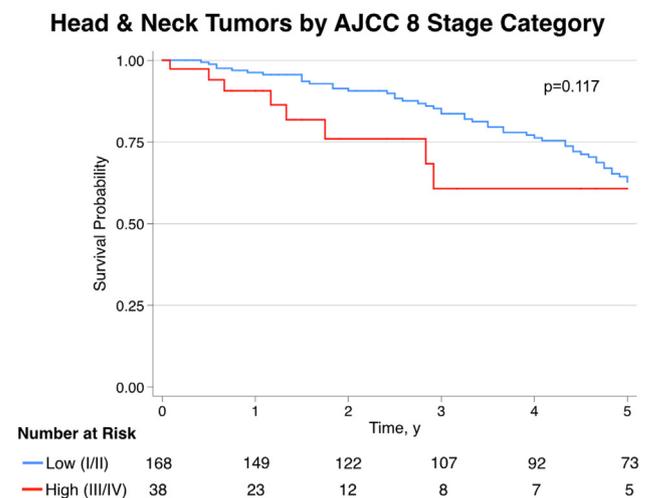
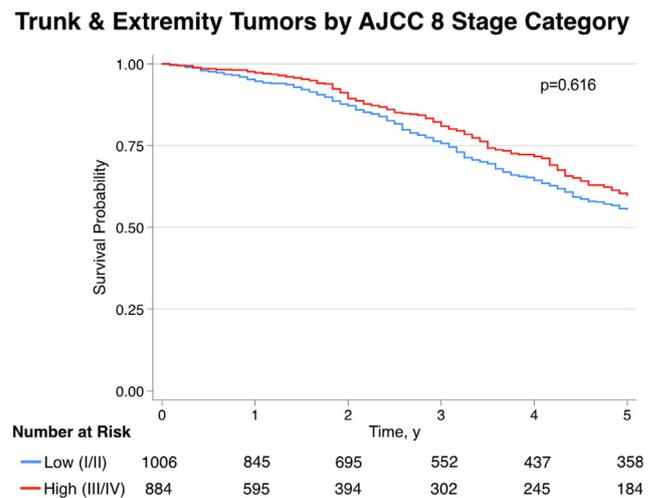
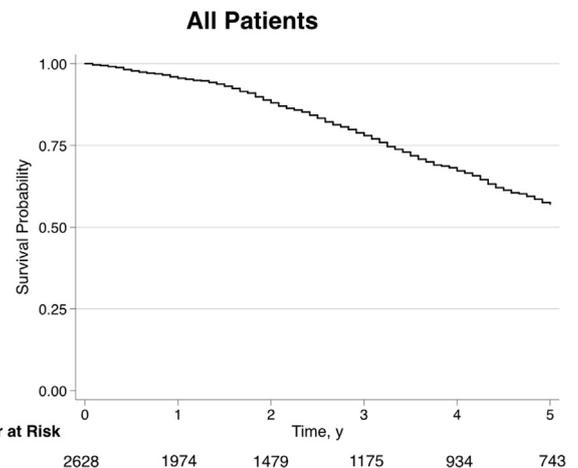


Figure 1. Survival Curve Showing 5-Year Overall Survival for All Patients, Trunk & Extremity Tumors, and Head & Neck Tumors.

utilizing the robust NCDB to analyze MPNST occurring nationwide from 2004 to 2015.

Patient, tumor, and treatment characteristics

Similar to previous research, we found no significant difference in incidence between males and females in our cohort of 2,858 patients [3,6,11]. Our sample was 75% white and 19% black, relatively similar

Table 3
Multivariate Analysis of Predictors of 5-Year Overall Survival (OS).

	Total ^a N	5-Year OS N (%)	P Value (χ^2)	Odds Ratio	95% CI
Age					
< 40	566	271 (47.9)	0.014	1 (REF)	
40–60	565	322 (57)		1.446	1.093–1.912
60–80	280	134 (47.9)		0.885	0.631–1.243
> 80	31	15 (48.4)		1.185	0.536–2.620
Race					
White	1091	575 (52.7)	0.132	1 (REF)	
Black	257	133 (51.8)		0.992	0.721–1.365
Asian / Pacific Islander	44	21 (47.7)		0.948	0.458–1.964
Other	29	5 (17.2)		0.293	0.106–0.811
Size of Tumor (cm)					
< 5cm	473	255 (53.9)	0.037	1 (REF)	
5–10 cm	449	233 (51.9)		0.840	0.636–1.111
10–15 cm	196	89 (45.4)		0.715	0.491–1.040
> 15 cm	110	45 (40.9)		0.520	0.319–0.846

^a Total with 5-year OS data; includes patients who had died before the 5-year mark and patients with follow-up data past the 5-year mark.

to the racial makeup of the population of the United States and similar to previous studies [4]. The average age in our sample was 47, which is slightly older than previously reported age at diagnosis – this is likely in part because many previous studies have included children [3,4,6,7,11,13]. Most patients did not have significant medical comorbidities, with 88.1% having a DCCI score of zero; few other studies have reported patient comorbidities. Taken as a whole, the present study is indicative of a patient population that is primarily middle-aged and healthy.

At time of diagnosis, 13% of patients had distant metastases; similarly, previous studies have found rates from 11 to 16% [6,11]. The present study found 39% of tumors occurred in extremities, followed by 35% in the trunk and 12% in the head and neck. Most previous studies have found a high rate of extremity MPNST, ranging from 35 to 60% of all tumors, with significantly fewer in the trunk [3,6,7,9–11,13]. Median tumor size in the present study was 7.5 cm, very close to previous studies in which tumor size tends to cluster in the 5–10 cm range [6,7].

Previous studies have reported > 90% of patients undergo surgery, higher than the 80% found in the present study [10,11]. Notably, those prior studies were only analyzing patients at single academic centers, which may be more likely to resect MPNST than other sites, such as community centers included in the present study. As in prior research, exact treatment strategies varied between patients, which likely reflects the limited data available to guide treatment selection. Radiation and chemotherapy utilization were very similar to prior reports, which show 44–64% of patients receive radiation and 10–35% receive chemotherapy [3,4,6,7,10,11].

Treatment regimen varied significantly based on stage. Low stage patients were treated by surgery alone over twice as often as high stage patients, and high stage tumors were much more likely to be treated by only chemotherapy and/or radiation and have no surgical intervention at all.

5-Year overall survival and predictive variables

The present study found that for patients with 5-year follow-up data, the 5-year OS was 52%. Most previous research found similar 5-year OS, ranging from 34 to 64% [4,6–10]. Interestingly, a meta-analysis of more than 1800 MPNST patients from 2013 found that prior to

Table 4
Univariate Analysis of AJCC 8 Stage and Preoperative Variables as Predictors of 5-Year Overall Survival (OS) in Trunk and Extremity MPNST.

	All With 5 Year Follow-Up ^a N = 1072	Survival N = 560 N (%)	P Value (Chi- Square)	Odds Ratio	95% CI	
Demographics						
Age						
< 40	440	215 (48.9)	0.056	1 (REF)		
40–60	415	238 (57.3)		1.407	1.074–1.843	
60–80	197	96 (48.7)		0.995	0.711–1.392	
> 80	19	11 (57.9)		1.439	0.568–3.646	
Sex						
Male						
	560	287 (51.2)	0.477	1 (REF)		
Female						
	511	273 (53.4)		1.091	0.858–1.387	
Race						
White						
	814	439 (53.9)	0.010	1 (REF)		
Black						
	189	96 (50.8)		0.882	0.642–1.210	
Asian/Pacific Islander						
	30	15 (50.0)		0.854	0.412–1.770	
Other						
	22	4 (18.2)		0.190	0.064–0.566	
Tumor Characteristics						
Grade						
1						
	276	151 (54.7)	0.604	1 (REF)		
2						
	280	147 (52.5)		0.915	0.656–1.277	
3						
	162	93 (57.4)		1.116	0.754–1.650	
Distant Mets at Dx						
Yes						
	40	17 (42.5)	0.207	0.664	0.351–1.258	
No or Unknown						
	1031	543 (52.7)			1 (REF)	
Positive Regional Lymph Nodes						
Yes						
	12	7 (58.3)	0.673	1.281	0.404–4.062	
No or Unknown						
	1059	553 (52.2)			1 (REF)	
Size of Tumor (cm)						
< 5cm						
	311	170 (54.7)	0.010	1 (REF)		
5–10 cm						
	366	202 (55.2)		1.022	0.754–1.384	
10–15 cm						
	171	76 (44.4)	0.664	0.456–0.966		
> 15 cm						
	107	44 (41.1)	0.579	0.371–0.904		
Stage						
AJCC 8 Stage						
I						
	603	307 (50.9)	0.647	1 (REF)		
II						
	95	51 (53.7)		1.118	0.724–1.724	
III						
	300	161 (53.7)	1.117	0.846–1.474		
IV						
	51	23 (45.1)	0.792	0.446–1.406		

^a Total with 5-year OS data; includes patients who had died before the 5-year mark and patients with follow-up data past the 5-year mark.

2001, patients with NF-1 related MPNST had worse survival outcomes than unrelated MPNST, but that since 2001 this trend has shifted and there is no difference in 5-year OS between the two groups; in the present study, we were not able to distinguish NF-1 related and unrelated MPNST [6].

On univariate analysis, 5-year OS was significantly associated with patient age – both younger than 40 and older than 60 had worse survival – as well as race; tumor size greater than 10 cm; and treatment regimen. One clinicopathologic case series noted that patients older than 30 had better survival, which may be related to our finding that patients younger than 40 have poor outcomes [4]. Large tumor size, typically reported as greater than 10 cm, has consistently been linked to worse OS in prior studies, in keeping with our findings [3,4,6–13].

Table 5
Univariate Analysis of Cates’ AJCC 8 Stage and Preoperative Variables as Predictors of 5-Year Overall Survival (OS) in Head and Neck MPNST.

	All With 5 Year Follow-Up ^a	Survival N (%)	P Value (Chi-Square)	Odds Ratio	95% CI
Demographics					
Age					
	N = 211	N = 111			
< 40	67	30 (44.8)	0.196	1 (REF)	
40–60	93	54 (58.1)		1.708	0.906–3.218
60–80	44	25 (56.8)		1.623	0.754–3.493
> 80	7	2 (28.6)		0.493	0.089–2.725
Sex					
Male	112	56 (50.0)	0.420	1 (REF)	
Female	99	55 (55.6)		1.250	0.727–2.150
Race					
White	168	88 (52.4)	0.566	1 (REF)	
Black	36	31 (58.3)		1.273	0.614–2.637
Asian/Pacific Islander	3	1 (33.3)		0.455	0.040–5.109
Other	1	0 (0.0)		–	
Tumor Characteristics					
Grade					
1	79	51 (64.6)	0.118	1 (REF)	
2	28	13 (46.4)		0.476	0.199–1.140
3	18	8 (44.4)		0.439	0.156–1.240
Distant Mets at Dx					
Yes	2	1 (50.0)	0.941	0.900	0.056–14.581
No or Unknown	209	110 (52.6)		1 (REF)	
Positive Regional Lymph Nodes					
Yes	6	2 (33.3)	0.337	0.440	0.079–2.458
No or Unknown	205	109 (53.2)		1 (REF)	
Size of Tumor (cm)					
< 2 cm	29	18 (62.1)	0.169	1 (REF)	
2–4 cm	53	26 (49.1)		0.588	0.234–1.482
> 4 cm	79	33 (41.8)		0.438	0.183–1.050
Stage					
Cates’ AJCC 8 Stage					
I	101	64 (63.4)	0.149	1 (REF)	
II	21	9 (42.9)		0.434	0.167–1.126
III	11	4 (36.4)		0.330	0.091–1.204
IV	2	1 (50.0)		0.578	0.035–9.519

^a Total with 5-year OS data; includes patients who had died before the 5-year mark and patients with follow-up data past the 5-year mark.

While head and neck tumors and trunk and extremity tumors had similar OS (53% and 52% respectively), relative stage distribution across tumor sites may influence survival analysis.

Past research on treatment regimen’s impact on survival is unclear, with most studies finding no significant effect of adding chemotherapy or radiation to surgical resection. Indeed, Kolberg et al. found that patients undergoing chemotherapy may have worse outcomes, and radiotherapy has no significant effect [6]. However, in the present study, the group with surgery and chemotherapy and/or radiation had similar 5-year OS when compared with surgical resection alone (52% vs. 53%, respectively).

Importantly, when controlling for high versus low stage, treatment regimen was not predictive of 5-year OS. This provides some evidence

that adjuvant therapy such as chemotherapy or radiation therapy do not improve survival, and are likely unnecessary in lower stage tumors, where the most common treatment is surgical resection alone. For high stage tumors there is no clear benefit to adjuvant therapy; however, there was a much higher rate of chemotherapy and radiation therapy used, with no significant negative impact on survival in high stage patients who underwent chemotherapy or radiation therapy compared to patients who had a surgical resection. At this point, the best evidence for treatment regimen to improve OS in MPNST is aggressive surgical resection with the possible addition of systemic therapy, particularly in advanced disease.

Prognostic value of AJCC 8 staging criteria

Tumor stage, as evaluated in the NCDB (likely largely utilizing AJCC 7 criteria), was not significantly correlated with 5-year OS. As the AJCC 8th edition staging guidelines for STS were recently released, we calculated AJCC 8 stage for tumors in our data set to assess whether this newer staging system is a better predictor of 5-year OS in our sample.

The AJCC 8th edition presents staging guidelines designed for trunk and extremity tumors, so we evaluated those cancers as a group. However, for head and neck tumors, the guidelines note that because head and neck STS represent a new neoplasm classification in the 8th edition, there is inadequate data collection to define overall stage grouping [17]. The AJCC 8 does present new staging criteria for STS of the head and neck with definitions of TNM staging, though. Prior to the 8th edition, tumor size was categorized in increments of 5 cm, regardless of location - in the 8th edition, T staging was changed for head and neck tumors, due to the relatively smaller size at presentation of such tumors, to less than 2 cm for T1, 2 to 4 cm for T2, and greater than 4 cm for T3 [17,19]. Given the lack of defined overall staging criteria in the AJCC 8, for our assessment of stage grouping in head and neck tumors we turned to Cates’ algorithm utilizing the AJCC 8 TNM staging - this algorithm was validated in 2756 head and neck STS patients and found to predict survival more effectively than AJCC 7th edition criteria [18]. As mentioned previously, we were not able to perfectly capture AJCC 8 TNM staging guidelines, as T4 tumors are defined by local invasion, which we lacked data on. However, in Cates’ assessment, only 3% of head and neck STS tumors met T4 criteria, so the vast majority of our tumors should be categorized correctly [18].

In our sample, AJCC 8 stage was not significantly predictive of 5-year OS in trunk and extremity cancer on univariate, multivariate, or log rank analysis. However, in head and neck tumors, Cates’ proposed AJCC 8 staging was the only significantly predictive variable on multivariate analysis (though not on univariate or log rank analysis). So, while AJCC 8 stages may have some prognostic utility in MPNST patients with head and neck tumors in this study they did not predict 5-year OS in patients with trunk and extremity tumors. These data indicate that Cates’ proposed AJCC 8th edition staging criteria for head and neck STS may have some applicability, given that it was significant in predicting 5-year OS on multivariate analysis. Ultimately, more study is needed to assess how effective Cates’ criteria it is in stratifying head and neck MPNST. Our analysis may not have reached statistical significance due to a lack of power, so further studies in larger cohorts of head and neck MPNST patients may be useful in assessing AJCC 8 staging guidelines in such tumors. Additionally, no other variables - such as age - appear to be meaningful additions to AJCC 8 staging for head and neck tumors, as Cates’ AJCC 8 stage groups were the only statistically significant predictor of 5-year OS on multivariate analysis.

The present study was not without limitations. Any retrospective study is prone to missing data, treatment bias, and other factors that may influence the results. Follow-up data was incomplete, and only about half of patients had 5-year follow-up data, limiting survival analysis. Additionally, not all relevant variables were available in the NCDB database, most notably NF-1 status. We also did not have data on head and neck tumor local invasion, somewhat limiting our ability to

apply AJCC 8 TNM staging guidelines.

Conclusions

This study provides an enhanced understanding of MPNST patient demographics, tumor characteristics, and predictors of survival. Patients with MPNST are typically relatively young and healthy, yet 5-year OS is only 52%. Age younger than 40 or older than 60, large tumor size, and certain treatment regimens are associated with worse outcomes. AJCC 8th edition staging criteria do not appear to reliably risk stratify patient with MPNST of the trunk and extremities, but Cates' proposed staging algorithm using AJCC 8th edition TNM guidelines might be effective for MPNST of the head and neck, though that was not well-established in the present study. Surgical resection of MPNST is the typical first-line treatment, and the survival benefit of adjuvant therapy is unclear. Contrary to past research, tumor grade, surgical margin status, and tumor location had no significant association with OS. Ultimately, this rare tumor is associated with high mortality, with few modifiable risk factors to improve survival, and current attempts at prognostication via staging systems is likely inadequate. Future research is needed to further elucidate the best staging criteria and treatment regimen for patients with MPNST.

Author contributions

Alia Mowery and Dr. Clayburgh had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: All authors.

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Declaration of Competing Interest

The authors report no relevant financial or personal conflict of interest.

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