A Clinicopathologic Study of Head and Neck Malignant Peripheral Nerve Sheath Tumors

Adepitan A. Owosho^{1,2} · Cherry L. Estilo² · Joseph M. Huryn² · Ping Chi^{3,4} · Cristina R. Antonescu⁵

Received: 20 June 2017 / Accepted: 21 July 2017 / Published online: 31 July 2017
© Springer Science+Business Media, LLC 2017

Abstract Head and neck high grade malignant peripheral nerve sheath tumors (HN-MPNSTs) are rare highly aggressive soft tissue sarcomas that show overlapping morphologic and immunophenotypic features with melanoma and other high grade sarcomas, resulting in diagnostic challenges, particularly in sporadic settings. Recent discoveries have implicated loss of function mutations in the polycomb repressive complex 2 (PRC2) components, including *EED* or *SUZ12* genes, as one of the leading pathogenetic mechanisms in high grade MPNST. MPNSTs with PRC2 loss are associated with complete loss of trimethylation at lysine 27 of histone H3 (H3K27me3), which emerged as a reliable immunohistochemical marker in the diagnosis of sporadic and radiation induced MPNST. As the diagnosis of MPNST in the HN is particularly challenging to distinguish from melanoma and other sarcoma types, we carried out a clinicopathologic analysis on HN-MPNST patients managed at our institution over a 20-year period (1997–2016), using the latest diagnostic criteria including H3K27me3 staining and other molecular investigations. The overall survival of HN-MPNST was compared with other HN soft tissue

sarcomas. The diagnosis of HN-MPNST was confirmed in 13 patients (seven males and six females), with a mean age of 31 years; with 3 (23%) patients being of pediatric age. The most common site was the neck soft tissue (77%). Two-thirds of patients (n=9) had stigmata of NF1, three had prior radiotherapy and only one developed a de novo MPNST. All except one tumor (86%) tested showed loss of H3K27me3 expression, including all non-NF1 patients. The 2 and 5-year DSS rates were 50 and 30%. The 2-year DFS rate was 21%. Adverse predictors on DSS included adult age (p=0.011), prior-history of RT (p=0.003) and recurrence (p=0.003). Compared to other molecularly confirmed subsets of HN sarcomas (Ewing and Ewing-like sarcoma, rhabdomyosarcoma and synovial sarcoma), HN-MPNST had the worst overall survival (p<0.0001). We conclude that HN-MPNSTs are highly aggressive sarcomas associated with an unfavorable outcome and the utility of H3K27me3 IHC stains in the evaluation of MPNST is a reliable ancillary diagnostic adjunct.

Keywords Malignant peripheral nerve sheath tumor · NF1 · H3K27me3 · Polycomb repressor complex 2

✉ Cristina R. Antonescu
antonesc@mskcc.org

¹ College of Dental Medicine, University of New England, Portland, ME 04103, USA

² Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA

³ Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, USA

⁴ Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, USA

⁵ Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA

Introduction

Malignant peripheral nerve sheath tumors (MPNST) are rare soft tissue sarcomas accounting for approximately 5–10% of soft tissue sarcomas [1]. The most common anatomic sites are the limbs and trunk, with the head and neck accounting for 12–19% of cases [2–4]. Head and neck MPNST (HN-MPNST) comprise approximately 4% of all HN sarcomas [5].

About half of MPNST occur in the setting of hereditary syndrome neurofibromatosis type 1 (NF1) [1, 6, 7], while

10% of MPNST are associated with prior history of radiation. In the remaining cases MPNST develop sporadically, without prior history of radiation or known genetic predisposition [1]. High grade MPNSTs have a highly aggressive clinical behavior, with a high rate of local recurrence (28–57%) [2, 8–11] and distant metastasis (28–34%) [2, 8]. Some studies have suggested that patients with NF1-associated MPNSTs are diagnosed at an earlier age and follow a more aggressive clinical course compared to sporadic MPNST [2, 3, 12], while others were not able to confirm this association [13, 14]. One study correcting for other known prognostic factors, such as anatomic site and size, showed no significant difference with the NF1 association [15]. Prior studies have found that the 5-year overall survival of HN-MPNST ranged from 20 to 51% [10, 16–18] with the overall survival related to age, tumor size, stage at presentation, early recurrence, surgical intervention, surgical margin and post-operative radiation [16–18].

Histopathologic diagnosis of high grade MPNST has been quite challenging outside the NF1 setting or clinical history of prior radiation, due to its non-specific morphologic features, shared with other entities such as spindle/neurotropic melanoma, monophasic synovial sarcoma, adult-type fibrosarcoma, spindle squamous cell carcinoma, among others [19, 20]. In addition, most MPNST lack a specific immunohistochemical profile, with the traditional markers for neural differentiation S100 protein and SOX10 having a suboptimal sensitivity and specificity [21–25]. Recently, our group and others demonstrated inactivation of the different components of polycomb repressive complex 2 (PRC2) through mutations of *EED* or *SUZ12* in the majority of MPNST [26–28]. Homozygous inactivation of PRC2 leads to loss of trimethylation at lysine 27 of histone 3 (H3K27me3) on immunohistochemical analysis, which has become a reliable diagnostic marker in distinguishing MPNST from histologic mimics. Loss of H3K27me3 expression in MPNST was found to be specifically sensitive for sporadic and radiation-induced cases, while showing lower sensitivity in NF1-related MPNST and low to intermediate histologic grades [29]. One study has shown that loss of H3K27me3 expression is an indicator for inferior survival [30]. In this study we reclassified a cohort of HN-MPNST by applying the latest diagnostic criteria and carried out a clinicopathologic analysis of patients managed at our institution over a 20-year period.

Patients and Methods

The study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center (MSKCC), New York. The electronic records of the Department of Pathology at MSKCC were searched for MPNST diagnosed

in the head and neck region from 1997 to 2016. The following clinical data was retrieved: age at diagnosis, gender, anatomic site, history of neurofibromatosis type 1 (NF1) syndrome, prior radiation to the anatomic site, modality of therapy (surgical resection, radiotherapy and/or chemotherapy), history of initial metastasis before therapy, local recurrence, distant recurrence, vital status (alive or died of disease) and survival time. Follow-up was calculated up until December 31, 2016. Cases with tissue available were evaluated for loss of H3K27me3 by immunohistochemistry (IHC). A rabbit monoclonal antibody, clone C36B11 of H3K27me3 (1:200 dilution; Cell Signaling Technology, Danvers, MA) was used. Staining was performed on whole tissue section slides as previously described [26, 29]. A nuclear signal was evaluated and recorded as positive or negative, compared to the internal positive controls (stromal, endothelial and/or inflammatory cells). The diagnosis of MPNST was re-evaluated based on the following constellation of the findings: clinical history of NF1 or prior radiation, typical morphologic patterns, focal/patchy S100 protein reactivity (defined as <20% of tumor cells) or non-specific immunoprofile and the presence of a pre-existing benign peripheral nerve sheath tumor. A diagnosis of sporadic high grade MPNST was confirmed only if it demonstrated loss of H3K27me3 by IHC, showed a typical morphologic pattern of intersecting fascicles of monomorphic spindle cells, with or without focal/patchy S100 protein reactivity. In our institution, patients with HN-MPNST are usually treated mainly with surgery. Adjuvant radiotherapy is employed in tumors larger than 5 cm and for anatomic sites where local control may be difficult by surgery alone, such as head and neck. Patients with unresectable tumors will be initiated with chemotherapy, radiotherapy or a combination of both and subsequently evaluated for possible resection.

Statistical Analysis

Statistical analysis was performed on an SPSS platform (version 24.0; IBM corp., Armonk, NY). The endpoints of the study were disease specific survival (DSS), defined as the time from the date of diagnosis to the date of death as a result of disease or complication and disease free survival (DFS), defined as the time from date of diagnosis to the first event after local treatment i.e. local or metastatic relapse, or death as a result of disease. Kaplan–Meier estimate was used to calculate the DSS, DFS, and the statistical significance of different clinicopathologic variables age group [adult/pediatric], etiology [RT-induced/NF1-associated] and recurrence [no recurrence/local recurrence/distant recurrence] in relation to DSS of MPNST patients was assessed by log-rank analysis. The overall survival (OS) of the HN MPNST study group was compared by log-rank

analysis with other HN soft tissue sarcomas with previously confirmed molecular diagnosis from our database, i.e. Ewing sarcoma, Ewing sarcoma-like with alternative *CIC* gene rearrangements, rhabdomyosarcoma and synovial sarcoma. A $p < 0.05$ was considered to be significant for all statistical analyses.

Results

Clinicopathologic Features

A total of 24 HN-MPNST cases were retrieved from our institutional (MSKCC) database spanning over two decades, between 1997 and 2016, including NF1 associated MPNST ($n=9$), RT-induced MPNST ($n=3$) and sporadic MPNST ($n=12$). Upon re-evaluation, 11 cases of sporadic MPNST were excluded: 8 due to lack of tissue for evaluation of loss of H3K27me3; 2 with retained H3K27me3 and one considered as low grade MPNST. The final cohort consisted of 13 HN-MPNST patients. A summary of the clinical characteristics are presented in Table 1. There were 7 (54%) males and 6 (46%) females, with ages ranging from 12 to 66 years old, with a mean of 31 years. There were three children (23%) and the remaining ten (77%) patients were of adult age (>18

years). The neck soft tissue was the most common anatomic site, accounting for 77% of all head and neck sites. Other locations were scalp, parotid/pre-auricular area and soft tissue of the mandible. Nine (70%) patients had a history of NF1 syndrome and were diagnosed with HN-MPNST at a mean age of 26 years (range 12–59 years). Three (23%) patients, with a mean age of 46 years (range 26–66 years) at diagnosis, had a history of prior radiation to the neck (6, 38 and 43 years prior, respectively), for a diagnosis of lymphomas. The only sporadic HN MPNST that could be confirmed occurred in a 27 year-old in the neck. The tumor size could be assessed in 12 patients ranging from 4.7 to 21 cm, mean of 7.9 cm; with 10 (83%) patients presenting with tumor sizes >5 cm. The review of radiographic images (mostly MRI) showed large sized lesions causing a mass-effect on nearby structures (Figs. 1, 2). Only one patient presented at diagnosis with metastasis to the lung. All except one patient (11, 92%) who presented with localized disease underwent surgical resection for their primary tumor; the only patient whose tumor was not resected was considered inseparable from the brachial plexus and internal jugular vein and was treated with chemoradiation. All patients who had surgical resection received adjuvant radiotherapy except one patient who was medically deemed not fit for additional therapy. Five patients received adjuvant

Table 1 Clinical features, H3K27me3 results and follow-up data of MPNST arising in the head and neck

Case #	Age/sex	Site	Etiology	Size (cm)	H3K27me3	Therapy ^a	Recurrence (site)	Follow-up duration	Vital status
1	27/M	Neck	S	6.0	Loss	Surgery and RT	LR	25 mos	DOD
2	36/M	Neck	NF1	9.0	Retained	Surgery , RT and CT	DR (lung)	15 mos	DOD
3	20/M	Parotid	NF1	5.2	ND	Surgery , RT and CT	LR	29 mos	DOD
4	12/F	Neck	NF1	6.6	ND	Surgery , RT and CT	NR	141 mos	Alive (NED)
5	26/M	Neck	RTI	4.7	Loss	Surgery , RT and CT	LR, DR (brain)	7 mos	DOD
6	59/F	Neck	NF1	21	ND	Surgery	DR (lung)	9 mos	DOD
7	45/M	Neck	RTI	4.7	ND	CT		10 mos	DOD
8	15/F	Scalp	NF1	10	ND	Surgery and RT	LR	116 mos	Alive (NED)
9	31/F	Neck	NF1	5.3	Loss	RT and CT	LR, DR (lung, pelvis)	24 mos	DOD
10	66/M	Neck	RTI	6.7	Loss	Surgery and RT	LR, DR (lung)	13 mos	DOD
11	17/F	Soft tissue mandible	NF1	NA	ND	Surgery , RT and CT	LR	57 mos	Alive (NED)
12	27/F	Neck	NF1	7.3	Loss	Surgery and RT	NR	13 mos	Alive (NED)
13	20/M	Neck	NF1	8.3	Loss	Surgery and RT	LR	13 mos	Alive (NED)

CT chemotherapy; RT radiotherapy; LR local recurrence; DR distant recurrence; NR no recurrence; DOD died of disease; NED no evidence of disease; NA not available; ND not done; S sporadic; RTI radiotherapy induced

^aTherapy in bold was the first modality administered

Fig. 1 MRI findings of HN-MPNST. **a** NF1-associated MPNST of the pharynx (neck) in a 27-year old female, alive at 7 months; **b** NF1-associated MPNST of the scalp in a 15-year old female who developed LR and is alive at 110 months; **c** Sporadic-associated MPNST of the neck in a 27-year old male who developed a LR and died of disease at 25 months

oped LR and is alive at 110 months; **c** Sporadic-associated MPNST of the neck in a 27-year old male who developed a LR and died of disease at 25 months

Fig. 2 RT-associated MPNST in a 66-year old male with prior history of radiation for lymphoma. **a** CT scan of a parapharyngeal mass displacing major vessels around periphery; **b** Gross specimen showing a white-tan fleshy mass with areas of hemorrhage and necrosis; **c** Morphology shows long intersecting fascicles of monomorphic undifferentiated spindle cells; **d** Immunohistochemically, the tumor showed focal SOX10 nuclear reactivity. The patient followed an aggressive clinical course, developing LR and DR, and succumbing of disease 13 months after diagnosis

chemotherapy. The patient who presented with metastasis at diagnosis received neoadjuvant chemotherapy alone.

The morphologic appearance was composed predominantly of relatively monomorphic spindle cells arranged in intersecting long fascicles (Fig. 2). The lesional cells showed hyperchromatic ovoid nuclei, with inconspicuous nucleoli and scant cytoplasm. All tumors showed a high mitotic activity of >16 MF/10 HPFs and geographic necrosis. One tumor showed evidence of divergent differentiation with rhabdomyoblastic and cartilaginous components (Triton tumor) (Fig. 3). All tumors included

in this study were classified as high-grade lesions. No significant peritumoral lymphoid infiltrate was noted in these tumors.

S100 or SOX10 immunohistochemical stains were available for re-review in 10 MPNST cases, showing reactivity in 7/10 cases with focal staining (Figs. 2, 3). The remaining three cases were associated with NF1. All cases evaluated with melanotic markers such as HMB-45, Melan-A, Tyrosinase, A103 and MITF were negative. H3K27me3 staining was evaluated by immunohistochemistry in seven cases (1 sporadic, 2 RT-induced and 4 NF1 associated MPNST),

Fig. 3 Histopathology of HN-MPNST (Triton tumor). Tumor composed intersecting fascicles with areas of areas of geographic necrosis (**a**), composed of monomorphic spindle cells with high mitotic activity (**b**), and foci of rhabdomyoblastic (**c**) and cartilaginous differentiation (**d**); immunohistochemically; the tumor showed focal S100 protein positivity (**e**) and loss of H3K27me3 expression (**f**)

showing loss of expression in all except one NF1-related MPNST (Fig. 3).

Follow-up Data

Follow-up information (Table 1) was available for all patients, ranging from 13 to 141 months, median of 24 months. One patient presented with distant metastasis at initial diagnosis. Among the remaining patients presenting with localized disease, 10 (83%) patients developed recurrence following treatment: five patients developed local recurrence (LR) alone, two patients developed distant recurrence (DR) (lungs) and three patients developed both LR and DR (lungs, pelvis and brain). Overall, the metastatic rate was 46% (6/13) in the entire group and 42% (5/12) in the localized group. Lungs were the most common site for distant recurrence (4/5 patients). Eight out of 13 patients (62%) died of disease (DOD) with a median survival of 14 months (range 7–29 months), including all

six patients with metastatic disease and two patients with localized disease. Two patients who remained free of disease are alive; 3/5 (60%) patients who recurred locally are still alive; while no (0/5) patient who recurred distantly is alive. 44% (4/9) of NF1-associated MPNST patients DOD at a mean survival time of 19 months (range 9–29 months). However, all RT-induced MPNST patients DOD at a mean survival time of 10 months (range 7–13 months).

Survival Analysis

On survival analysis, the HN-MPNST patients showed a 50% 2-year DSS and a 30% 5-year DSS rates (Fig. 4a). The median DFS of HN-MPNST patients was 9 months. The 2-year DFS was 21%. Adult patients had a poorer outcome compared to pediatric patients ($p=0.011$) (Fig. 4b). RT-induced MPNST patients had an unfavorable outcome compared to NF1-associated MPNST patients (DSS: $p=0.003$) (Fig. 4c). Also, presence of recurrence (NR vs. LR vs. DR)

Fig. 4 Kaplan–Meier curve of disease specific survival of HN-MPNST patients based on age, etiology, recurrence and therapy modality. **a** 2 and 5-year DSS: 50 and 30%, **b** DSS in relationship to age ($p=0.011$), **c** etiology ($p=0.003$), and **d** recurrence ($p=0.003$)

was statistically significant on DSS ($p=0.003$) (Fig. 4d). On comparing the OS between the HN MPNST study group ($n=13$) to other head and neck soft tissue sarcomas (OHNSTS) from our database with confirmed molecular diagnosis (Ewing sarcoma $n=8$, Ewing-like sarcoma with CIC-rearrangements $n=11$, rhabdomyosarcoma $n=97$ and synovial sarcoma $n=34$) [31–35], MPNST patients had the worst outcome ($p<0.0001$) (Fig. 5).

Discussion

Head and neck MPNST (HN-MPNST) are rare, highly aggressive tumors associated with high rates of loco-regional recurrences, distant metastases and mortality. There are limited clinicopathologic studies focusing on

single institution experience of HN-MPNST, due to the rarity of this disease [10, 16, 18, 25]. The diagnosis of HN-MPNST can be quite challenging outside a clinical history of NF1 or prior radiation to the site due to the lack of distinct histologic criteria or specific immunoprofile. Various other tumors share morphologic overlap with MPNST, particularly in the HN location, such as spindle cell carcinoma, neurotropic melanoma, or other spindle cell sarcomas, such as monophasic synovial sarcoma, adult-type fibrosarcoma, etc. Furthermore, both immunostains typically used to demonstrate a neural line of differentiation, S100 protein and SOX10, have suboptimal sensitivity and specificity [21–25]. Recently, our group and others demonstrated that loss of trimethylation at lysine 27 of histone H3 (H3K27me3) by IHC is a reliable diagnostic marker in MPNST [29, 30, 36–38]. Our study specifically showed

Fig. 5 Kaplan–Meier curve of overall survival of HN-soft tissue sarcoma patients based on pathologic diagnosis. **a** Ewing and Ewing-like sarcomas, MPNSTs, rhabdomyosarcomas and synovial sarcomas

that loss of H3K27me3 expression was highly sensitive (>90% of cases) in both sporadic and RT-induced MPNST, two clinical settings in which the diagnosis of MPNST is most challenging [29]. Similarly, all RT-induced MPNST tested by Röhrich et al. and Schaefer et al. demonstrated loss of H3K27me3 [36, 38]. Although not yet confirmed by others, a multi-institutional study by Cleven et al. suggested that loss of H3K27me3 is not specific to MPNST, which can also be seen in 60% of synovial sarcoma and 38% of dermatofibrosarcoma protuberans (DFSP) [30]. In contrast, other studies showed no loss of H3K27me3 in synovial sarcomas [29, 37–39], while Asano et al. also demonstrated partial loss of H3K27me3 in 60% of DFSP [37]. Although most studies are in agreement with the practical utility of loss of H3K27me3 in high grade MPNST, one study has emphasized the lower sensitivity of this marker at the low and intermediate grade end of MPNST spectrum, in keeping with the concept that PRC2 losses represent late genetic events in the MPNST tumor progression [26, 38]. Furthermore, PRC2 complex alterations have not been detected in epithelioid MPNST, which retain H3K27me3 expression, suggesting a distinct pathogenesis [29, 30, 36–38]. In our study, loss of H3K27me3 expression was seen in all except one case tested (6/7, 86%), while focal reactivity for S100 protein was seen in 70% (7/10) of cases.

Similar to other reported series, our cohort of HN-MPNST had a predilection for adults and neck soft tissue location [10, 16, 17]. Based on the National Cancer Institute's (NCI) SEER database, the 5-year DSS rate for high grade HN-MPNST was reported as 49.7% [4]. Similar studies from single institutions have placed the 5-year overall survival (OS) rates of HN-MPNST as 46.5, 33

($p=0.001$), **b** MPNST patients had a worst outcome compared to OHNSTs ($p<0.0001$)

and 20% and a 5-year DFS rate was 15% [10, 16, 18]. In our cohort, the 2 and 5-year DSS rates were 50 and 30%, while the 2-year DFS rate was 21%. Interestingly, the three children with HN MPNST (all NF1-associated, involving the following sites: neck soft tissue, scalp and soft tissue mandible) from our study are alive with no evidence of disease at a median survival time of 116 months, showing a statistically significant DSS by Kaplan–Meier curve compared to adult patients. In keeping with this observation, the NCI SEER database also showed that age at diagnosis was a significant factor in HN-MPNST [17]. Furthermore, there was also a statistical significance of DSS by Kaplan–Meier curve when comparing the various etiologies in our cohort: patients with RT-induced MPNST had a significantly poorer outcome compared to NF1 associated MPNST. However, the role of various etiologies of MPNST remain controversial in the literature; some studies suggesting that NF1 associated MPNST have a poorer outcome compared to other etiologies [2, 3, 12], while Wong et al. showed on multivariate analysis that RT-induced MPNST were associated with a significant poorer outcome in OS [13]. Furthermore, Gladdy et al. showed that RT-induced MPNST was an adverse independent predictor of DSS and with no 5-year survival among 10 patients with high-grade, RT-induced MPNST being observed [40]. Moreover, LaFemina et al. showed a trend towards statistical significance between RT-induced MPNST and DSS [8].

Our analysis also showed that the presence of recurrence was a statistical significant factor on DSS. Patients without recurrence events are all alive, while all patients who developed DR died of disease. Other prior studies have shown that large tumor size (>5 cm), stage at

presentation, surgical resection and the application of post-operative radiotherapy are statistically significant factors on survival of HN-MPNST patients [16, 17]. In our study, 62% (8/13) of patients developed local recurrence and 46% developed distant metastasis. The management of MPNST is mainly surgical resection for small size and early stage tumors to achieve local control with negative margins, while palliative RT is recommended in the setting of metastatic disease, large size and late stage tumors [17, 41]. The role of adjuvant chemotherapy in the management of MPNST is limited, given its rarity and relative lack of activity in the metastatic setting. In our experience, the RECIST response rate of MPNST to common chemotherapeutic regimen (doxorubicin–ifosfamide) is below 10%. However, the study by Kroep et al. showed that doxorubicin–ifosfamide combination regimen had the best response rate compared to standard first-line doxorubicin alone, ifosfamide alone or anthracyclines alone [42]. It has been suggested that HN-MPNST has a poorer prognosis among HN-sarcomas [17]. In our analysis, comparing the OS of HN PMNST with other HN soft tissue sarcomas (i.e. Ewing and Ewing-like sarcoma, rhabdomyosarcoma and synovial sarcoma), MPNST patients had a significantly worst outcome. A recent study using the NCI SEER database showed that HN-MPNST had a significantly higher DSS compared to MPNST of other sites [4].

In summary, we present a well-characterized series of HN MPNST managed at a single, tertiary cancer center institution, over a 20-year period of time. Our findings confirmed the highly aggressive behavior of this subset, particularly in the HN location, with 30% 5-year DSS rate and a 21% 2-year DFS rate. Age, RT-induced etiology and recurrence were statistical significant factors affecting disease specific survival. The utility of H3K27me3 IHC stains in the evaluation of MPNST is an effective ancillary diagnostic adjunct, however, further studies are needed to resolve the on-going discrepancy on the sensitivity of H3K27me3 as a marker for MPNST [30, 37]. Among soft tissue sarcomas of the head and neck, MPNST are associated with a poorer overall survival. As our study encompassed a relatively limited number of cases, larger series might be beneficial to validate our results.

Acknowledgements Supported in part by NIH/NCI Cancer Center Support Grant P50-CA140146-01 (CRA), Cycle for Survival (CRA); P30-CA008748, Kristen Ann Carr Foundation (CRA).

Compliance with Ethical Standards

Conflicts of interest All authors have contributed to this work and we declare that there are no financial conflicts associated with this study and that the funding source has no role in conceiving and performing the study.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Not applicable.

References

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. WHO classification of tumours of soft tissue and bone. Lyon: IARC Press; 2013. pp. 134–5.
2. Ducatman BS, Scheithauer BW, Piepgras DG, Reiman HM, Ilstrup DM. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. *Cancer*. 1986;57:2006–21.
3. Valentin T, Le Cesne A, Ray-Coquard I, Italiano A, Decanter G, Bompas E, et al. Management and prognosis of malignant peripheral nerve sheath tumors: the experience of the French Sarcoma Group (GSF-GETO). *Eur J Cancer*. 2016;56:77–84.
4. Patel TD, Shaigany K, Fang CH, Park RC, Baredes S, Eloy JA. Comparative analysis of head and neck and non-head and neck malignant peripheral nerve sheath tumors. *Otolaryngology-head and neck surgery: official journal of American Academy of Otolaryngology-head and neck. Surgery*. 2016;154:113–20.
5. Peng KA, Grogan T, Wang MB. Head and neck sarcomas: analysis of the SEER database. *Otolaryngol–Head Neck Surg*. 2014;151:627–33.
6. Anghileri M, Miceli R, Fiore M, Mariani L, Ferrari A, Mussi C, et al. Malignant peripheral nerve sheath tumors: prognostic factors and survival in a series of patients treated at a single institution. *Cancer*. 2006;107:1065–74.
7. Hrehorovich PA, Franke HR, Maximin S, Caracta P. Malignant peripheral nerve sheath tumor. *Radiogr*. 2003;23:790–4.
8. LaFemina J, Qin LX, Moraco NH, Antonescu CR, Fields RC, Crago AM, et al. Oncologic outcomes of sporadic, neurofibromatosis-associated, and radiation-induced malignant peripheral nerve sheath tumors. *Ann Surg Oncol*. 2013;20:66–72.
9. Das Gupta TK, Brasfield RD. Solitary malignant schwannoma. *Ann Surg*. 1970;171:419–28.
10. Vege DS, Chinoy RF, Ganesh B, Parikh DM. Malignant peripheral nerve sheath tumors of the head and neck: a clinicopathological study. *J Surg Oncol*. 1994;55:100–3.
11. D'Agostino AN, Soule EH, Miller RH. Primary malignant neoplasms of nerves (malignant neurilemmomas) in patients without manifestations of multiple neurofibromatosis (Von Recklinghausen's disease). *Cancer*. 1963;16:1003–14.
12. Porter DE, Prasad V, Foster L, Dall GF, Birch R, Grimer RJ. Survival in malignant peripheral nerve sheath tumours: a comparison between sporadic and neurofibromatosis type 1-associated tumours. *Sarcoma*. 2009;2009:756395.
13. Wong WW, Hirose T, Scheithauer BW, Schild SE, Gunderson LL. Malignant peripheral nerve sheath tumor: analysis of treatment outcome. *Int J Radiat Oncol Biol Phys*. 1998;42:351–60.
14. deCou JM, Rao BN, Parham DM, Lobe TE, Bowman L, Pappo AS, et al. Malignant peripheral nerve sheath tumors: the St. Jude Children's Research Hospital experience. *Ann Surg Oncol*. 1995;2:524–9.
15. Zou C, Smith KD, Liu J, Lahat G, Myers S, Wang WL, et al. Clinical, pathological, and molecular variables predictive of malignant peripheral nerve sheath tumor outcome. *Ann Surg*. 2009;249:1014–22.
16. Ma C, Ow A, Shan OH, Wu Y, Zhang C, Sun J, et al. Malignant peripheral nerve sheath tumours in the head and neck region: retrospective analysis of clinicopathological features and treatment outcomes. *Int J Oral Maxillofac Surg*. 2014;43:924–32.

17. Arshi A, Tajudeen BA, St John M. Malignant peripheral nerve sheath tumors of the head and neck: demographics, clinicopathologic features, management, and treatment outcomes. *Oral Oncol.* 2015;51:1088–94.
18. Minovi A, Basten O, Hunter B, Draf W, Bockmuhl U. Malignant peripheral nerve sheath tumors of the head and neck: management of 10 cases and literature review. *Head Neck.* 2007;29:439–45.
19. Bahrami A, Folpe AL. Adult-type fibrosarcoma: a reevaluation of 163 putative cases diagnosed at a single institution over a 48-year period. *Am J Surg Pathol.* 2010;34:1504–13.
20. Rodriguez FJ, Folpe AL, Giannini C, Perry A. Pathology of peripheral nerve sheath tumors: diagnostic overview and update on selected diagnostic problems. *Acta Neuropathol.* 2012;123:295–319.
21. Nonaka D, Chiriboga L, Rubin BP. Differential expression of S100 protein subtypes in malignant melanoma, and benign and malignant peripheral nerve sheath tumors. *J Cutan Pathol.* 2008;35:1014–9.
22. Nonaka D, Chiriboga L, Rubin BP. Sox10: a pan-schwannian and melanocytic marker. *Am J Surg Pathol.* 2008;32:1291–8.
23. Karamchandani JR, Nielsen TO, van de Rijn M, West RB. Sox10 and S100 in the diagnosis of soft-tissue neoplasms. *Appl Immunohistochem Mol Morphol.* 2012;20:445–50.
24. Miettinen M, McCue PA, Sarlomo-Rikala M, Biernat W, Czapiewski P, Kocczynski J, et al. Sox10—a marker for not only schwannian and melanocytic neoplasms but also myoepithelial cell tumors of soft tissue: a systematic analysis of 5134 tumors. *Am J Surg Pathol.* 2015;39:826–35.
25. Scheithauer BW, Erdogan S, Rodriguez FJ, Burger PC, Woodruff JM, Kros JM, et al. Malignant peripheral nerve sheath tumors of cranial nerves and intracranial contents: a clinicopathologic study of 17 cases. *Am J Surg Pathol.* 2009;33:325–38.
26. Lee W, Teckie S, Wiesner T, Ran L, Prieto Granada CN, Lin M, et al. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. *Nat Genet.* 2014;46:1227–32.
27. Zhang M, Wang Y, Jones S, Sausen M, McMahon K, Sharma R, et al. Somatic mutations of SUZ12 in malignant peripheral nerve sheath tumors. *Nat Genet.* 2014;46:1170–2.
28. De Raedt T, Beert E, Pasmant E, Luscan A, Brems H, Ortonne N, et al. PRC2 loss amplifies Ras-driven transcription and confers sensitivity to BRD4-based therapies. *Nature.* 2014;514:247–51.
29. Prieto-Granada CN, Wiesner T, Messina JL, Jungbluth AA, Chi P, Antonescu CR. Loss of H3K27me3 expression is a highly sensitive marker for sporadic and radiation-induced MPNST. *Am J Surg Pathol.* 2016;40:479–89.
30. Clevon AH, Sannaa GA, Briaire-de Bruijn I, Ingram DR, van de Rijn M, Rubin BP, et al. Loss of H3K27 tri-methylation is a diagnostic marker for malignant peripheral nerve sheath tumors and an indicator for an inferior survival. *Mod Pathol.* 2016;29:582–90.
31. Owosho AA, Estilo CL, Huryn JM, Zhang L, Fletcher CD, Antonescu CR. Head and neck round cell sarcomas: a comparative clinicopathologic analysis of 2 molecular subsets: ewing and CIC-rearranged sarcomas. *Head Neck Pathol.* 2017. doi:[10.1007/s12105-017-0808-2](https://doi.org/10.1007/s12105-017-0808-2).
32. Antonescu CR, Owosho AA, Zhang L, Chen S, Deniz K, Huryn JM, et al. Sarcomas with CIC-rearrangements are a distinct pathologic entity with aggressive outcome: a clinicopathologic and molecular study of 115 cases. *Am J Surg Pathol.* 2017;41:941–49.
33. Owosho AA, Huang SC, Chen S, Kashikar S, Estilo CL, Wolden SL, et al. A clinicopathologic study of head and neck rhabdomyosarcomas showing FOXO1 fusion-positive alveolar and MYOD1-mutant sclerosing are associated with unfavorable outcome. *Oral Oncol.* 2016;61:89–97.
34. Owosho AA, Chen S, Kashikar S, Zhang L, Chen CL, Wexler LH, et al. Clinical and molecular heterogeneity of head and neck spindle cell and sclerosing rhabdomyosarcoma. *Oral Oncol.* 2016;58:e6–11.
35. Owosho AA, Estilo CL, Rosen EB, Yom SK, Huryn JM, Antonescu CR. A clinicopathologic study on SS18 fusion positive head and neck synovial sarcomas. *Oral Oncol.* 2017;66:46–51.
36. Rohrich M, Koelsche C, Schrimpf D, Capper D, Sahm F, Kratz A, et al. Methylation-based classification of benign and malignant peripheral nerve sheath tumors. *Acta Neuropathol.* 2016;131:877–87.
37. Asano N, Yoshida A, Ichikawa H, Mori T, Nakamura M, Kawai A, et al. Immunohistochemistry for trimethylated H3K27 in the diagnosis of malignant peripheral nerve sheath tumours. *Histopathology.* 2017;70:385–93.
38. Schaefer IM, Fletcher CD, Hornick JL. Loss of H3K27 trimethylation distinguishes malignant peripheral nerve sheath tumors from histologic mimics. *Mod Pathol.* 2016;29:4–13.
39. Pasmant E, Sohier P, Larousserie F. Synovial sarcomas do not show H3K27 trimethylation loss using immunohistochemistry. *Am J Surg Pathol.* 2017;41:283–5.
40. Gladdy RA, Qin LX, Moraco N, Edgar MA, Antonescu CR, Alektiar KM, et al. Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas? *J Clin Oncol.* 2010;28:2064–9.
41. Bishop AJ, Zagars GK, Torres KE, Bird JE, Feig BW, Guadagnolo BA. Malignant peripheral nerve sheath tumors: a single institution's experience using combined surgery and radiation therapy. *Am J Clin Oncol.* 2016. doi:[10.1097/COC.000000000000303](https://doi.org/10.1097/COC.000000000000303).
42. Kroep JR, Ouali M, Gelderblom H, Le Cesne A, Dekker TJ, Van Glabbeke M, et al. First-line chemotherapy for malignant peripheral nerve sheath tumor (MPNST) versus other histological soft tissue sarcoma subtypes and as a prognostic factor for MPNST: an EORTC soft tissue and bone sarcoma group study. *Ann Oncol.* 2011;22:207–14.