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Malignant peripheral nerve sheath tumors of the head and neck: Demographics, clinicopathologic features, management, and treatment outcomes

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SUMMARY

Objectives: To determine the epidemiology and prognostic indicators in patients with malignant peripheral nerve sheath tumors (MPNST) of the head and neck.

Materials and methods: The surveillance, epidemiology, and end results registry was reviewed for patients with head and neck MPNST from 1973 to 2011. Study variables included age, sex, race, tumor size, stage at presentation, and treatment modality.

Results: There were 374 cases of head and neck MPNST identified. Mean age at diagnosis was 50.7 years; 60.2% of patients were male and 82.6% were white. After diagnosis, 38.8% of patients underwent surgery and radiation therapy and 48.1% underwent surgery alone. Kaplan–Meier analysis demonstrated overall (OS) and disease-specific survival (DSS) of 51% and 67% at 5 years. Multivariate Cox regression analysis showed that age ($p = 0.030$), stage ($p = 0.002$), surgery ($p = 0.037$), and size ($p < 0.001$) were predictors of OS, while stage ($p < 0.001$) and size ($p < 0.001$) were predictors of DSS. For stage I/II cancers, surgery ($p = 0.011$) and size ($p = 0.010$) were predictors of OS, and size ($p = 0.001$) predicted DSS. For stage III/IV cancers, both radiotherapy ($p = 0.024$, $p = 0.009$) and size ($p = 0.001$, $p = 0.001$) predicted OS and DSS. For tumors $\leqslant$5 cm, stage ($p = 0.031$) predicted DSS. For tumors >5 cm, male gender ($p = 0.005$), stage ($p = 0.001$), surgery ($p = 0.003$), and radiotherapy ($p = 0.050$) were determinants of OS, and male gender ($p = 0.022$), stage ($p < 0.001$), and radiotherapy ($p = 0.002$) were determinants of DSS.

Conclusion: Surgical resection confers survival benefit in patients with early stage MPNST, while radiotherapy improves survival in cases with metastatic disease. Surgery and radiotherapy are prognostically important in patients with tumors >5 cm.

Introduction

Malignant peripheral nerve sheath tumors (MPNST) are an uncommon malignancy of peripheral nerves. The most common anatomical sites involved are the extremities, trunk, and retroperitoneum, with the head and neck accounting for only 2–9% of cases [1–3]. These tumors can arise either sporadically or in association with neurofibromatosis (NF). Neurofibromatosis type I (NF1), also known as von Recklinghausen's disease, accounts for 40–50% of MPNST cases, with an average age of onset 10–15 years younger than in sporadic cases and a predilection for central anatomical locations [4–6]. While the development of MPNST in this population has been related to genetic insults involving p53 and p16, NF1 gene activity is believed to predispose patients to spontaneous development or transformation of Schwann cells from a preexisting benign neurofibroma [7–9]. MPNST are one of the serious clinical consequences of NF and have a prevalence of 1–10% among NF1 patients [10,11]. In sporadic MPNST, there appears to be an association with a history of radiation and the development of a particularly aggressive and treatment-resistant phenotype [12–14]. Clinical presentation of this disease in the head and neck is heterogeneous but may involve a rapidly enlarging mass, coughing or hoarseness, radicular pain or paresthesias, and neurological deficits, depending on the anatomy involved.

MPNST are considered high-grade malignant tumors and involve a high rate of metastasis with infrequent but possible lymphatic spread [15]. Furthermore, there is a historically high rate of

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recurrence, with up to 50% local recurrence and up to 33% metastases to lung and bone [5,16,17]. According to several published studies, the five-year survival of head and neck MPNST ranges from 16% to 52%, with better prognosis associated with complete resection, size <5 cm, histological differentiation, and decreased expression of Ki-67 antigen [18–23]. As with most soft tissue sarcomas, wide en bloc resection is the mainstay of treatment for MPNST. Adjuvant radiation therapy, usually in the postoperative setting, plays an integral role in local disease control. However, its role in either reduction of rates or improvement in survival in cases with distant metastases remains controversial [24–29]. At present, chemotherapy is reserved for inoperable or exceedingly large (greater than 5–8 cm) tumors, cases with incomplete resection, or in patients with metastatic or recurrent disease [17,30].

While there are several published small case series and reports on MPNST of the head and neck, there is a dearth of population data, and no studies have examined prognostic indicators of survival in cohorts larger than 120 cases. Because of limited studies and data on these relatively rare tumors, prognostic indicators of survival and treatment outcomes continue to be poorly understood and controversial, with much of the current knowledge and clinical approach being limited to generalizations from MPNST of other anatomical regions or other soft tissue sarcomas. The purpose of this study was to determine the demographics, clinicopathologic features, management, and treatment outcomes of MPNST of the head and neck in a larger population. We used data from the population-based US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) cancer database to analyze the patient and disease characteristics that determine overall (OS) and disease-specific survival (DSS) after diagnosis.

Materials and methods

A population-based search for patients diagnosed with MPNST of the head and neck was performed using the case-listing session protocol of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) 18 database (www.seer.cancer.gov); the database is a widely-used cancer registry that covers an estimated 28% of the US population, including 23% of African Americans and 40% of Hispanics. Geographic regions covered include San Francisco-Oakland, Connecticut, metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, metropolitan Atlanta, San Jose-Monterey, Los Angeles, Alaska, rural Georgia, California, Kentucky, Louisiana, New Jersey, and greater Georgia. No internal review board approval was required in this study because the database uses publicly available information with no personal identifiers. The SEER database has been validated independently for analysis of both head and neck malignancies and MPNST [31–35].

Patients diagnosed with MPNST from 1973 to 2011, the widest date ranges available in the latest version of the SEER software, were reviewed. Histologic ICD-0-3 codes were used to include malignant peripheral nerve sheath tumor (9540/3) and malignant neurilemmoma (9560/3) in the query. Site specific codes were used to confirm that the tumor originated in the head and neck [36]. The following primary data were extracted from the database for analysis: age at diagnosis, sex, race, histologic subtype (ICD), tumor extent and tumor size from both extent of disease (EOD) and collaborative stage (CS) coding methods, tumor grade and stage, treatment with surgery and/or radiation therapy, cause of death, and survival months. Where available, TNM staging was recorded as explicitly listed in the SEER registries for all patients diagnosed from 2003 to 2011. For cases diagnosed prior to 2003, TNM stage was retroactively determined, where possible without ambiguity, using CS and EOD staging codes for tumor size, extent, lymph node involvement, and evidence of distant metastasis using classification criteria determined by the American Joint Committee on Cancer (AJCC). TNM staging and grade classification were then used to determine stage at presentation (I–IV).

Primary outcome was defined as time in months from diagnosis to death from any cause for OS, and time from diagnosis to death specific to the cancer-related diagnosis for DSS. Descriptive statistics were calculated for all variables. OS and DSS curves were calculated using the Kaplan–Meier method. Differences in survival were formally tested for using the log-rank test. Covariates were assessed for predictive performance with univariate and multivariate Cox proportional hazards regression models, using hazard ratios with corresponding 95% confidence interval, with regard to OS and DSS. Comparisons between groups were deemed statistically significant at the $p < 0.05$ threshold. Statistical analyses were performed using SPSS 21 software (IBM Corp., Armonk, NY).

Results

The SEER database search revealed 374 patients with primary MPNST of the head and neck from 1973 to 2011. 60.2% were males and 82.6% were white (Table 1). The mean and median age of diagnosis was 50.7 and 52 years, respectively, with ages ranging from 0 to 93. Definitive staging was possible in 48.7% of cases with the majority of cases presenting as Stage I (20.9%) or Stage II (12.8%) tumors. The mean and median tumor size at the time of diagnosis was 4.5 and 3.9 cm, respectively, with sizes ranging from 0.3 to 20 cm. After diagnosis, 38.8% of patients underwent surgery and radiation therapy, 48.1% underwent surgery alone, and 3.7% underwent radiation alone, while 5.9% received neither.

Survival analysis from Kaplan–Meier curves (Fig. 1A and B) revealed that the 5-year OS and DSS for all patients with MPNST was 51% and 67%, respectively (Table 2); the median OS was

Table 1
Demographics.

Age	Years
Mean	50.7 ± 22.4
Median	52
Min	0
Max	93
Characteristic	Percentage (%)
Sex	
Female	39.8
Male	60.2
Race	
White	82.6
Black	8.8
Asian	4.8
Pacific Islander	3.2
Native American/Alaskan Native	0.5
Stage at presentation	
Stage I	20.9
Stage II	12.8
Stage III	7.5
Stage IV	7.5
Unknown	51.3
Treatment modality	
Surgery + radiation	38.8
Surgery only	48.1
Radiation only	3.7
No therapy	5.9
Unknown	3.5
Size (cm)	
Mean	4.5 ± 3.2
Median	3.9