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Malignant peripheral nerve sheath tumours in the head and neck region: retrospective analysis of clinicopathological features and treatment outcomes

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Abstract. Malignant peripheral nerve sheath tumours (MPNST) are rare soft tissue sarcomas. The aim of this study was to assess clinicopathological characteristics and prognostic factors in order to improve the treatment of such tumours in the head and neck region. We performed a retrospective analysis of head and neck MPNST patients in our hospital between 1996 and 2012. Clinical features and pathological findings of these cases ($n = 43$) were summarized. In addition, prognostic variables were evaluated by univariate and multivariate analyses. The median age of the patients at presentation was 41 years. Surgery was the main treatment approach. Pertinent information regarding the presence of neurofibromatosis type 1 was found in 13 patients (30.2%). Two-thirds of these patients were admitted for a primary tumour ($n = 27$, 62.8%), while one-third ($n = 16$, 37.2%) were treated for recurrent neoplasms. The overall survival rate was 46.5%. Multivariable analysis identified tumour size, surgical margins, and postoperative radiotherapy to be independent prognostic factors. MPNST of the head and neck is extremely difficult to manage. Surgery with postoperative radiation may be the optimum choice of treatment for primary head and neck MPNST.

Key words: malignant peripheral nerve sheath tumour; head and neck tumour; surgery; radiotherapy; chemotherapy.

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Introduction

Malignant peripheral nerve sheath tumours (MPNST) constitute a rare group of malignant mesenchymal neoplasms that are commonly believed to arise from peripheral nerves, or to show differentiation of nerve sheath elements, including Schwann cells, fibroblasts, and perineural cells.[1] They account for 3–10% of all soft tissue sarcomas. The estimated incidence of MPNST is claimed to be 0.001%.[2]

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A certain correlation has recently been revealed between MPNST patients and those with neurofibromatosis type 1 (NF-1), which is also known as von Recklinghausen's neurofibromatosis.[3] Approximately 50% of MPNST of the extremities and trunk are derived from the malignant transformation of pre-existing neurofibromas, particularly in NF-1 patients with the distinctive features of café-au-lait spots, intertriginous freckling, Lisch nodules, or dermal and plexiform neurofibromas.[3] Patients with hereditary NF-1 have an 8–13% lifetime risk of developing MPNST, and such diagnoses have usually been given at a relatively young age.[4] Apart from this predilection, MPNST may also occur de novo, or as an uncommon and subsequent event to radiation therapy. Recent studies have suggested that the development of MPNST is a multistage process that may involve a number of altered cell cycle regulators.[5] However, despite all the relevant research to date, the mechanism responsible for the malignant transformation remains poorly understood because of its rarity and aggressiveness.

MPNSTs tend to behave aggressively, with a high rate of recurrence and a propensity to metastasize hematogenously.[6] Like other soft tissue sarcomas, wide surgical resection represents the mainstay of treatment; the role of adjuvant treatment is as yet unclear.[7,8] Despite multimodality approaches, the prognosis of MPNST patients is generally dismal. The reported 5-year survival rate for patients with sporadic MPNST is around 50%, while this drops to as low as 10% for patients with NF-1.[2]

MPNSTs are more likely to occur in the extremities than in the head and neck area.[2] According to some, head and neck MPNST comprise only about 15% of all MPNSTs reported to date.[4] Although a few reports of MPNST in the head and neck region have been published recently, including MPNST involving the tongue,[9] cheek,[10] mandible,[11] parapharyngeal space,[12] infratemporal fossa,[13] and neck,[14] studies with large series of cases are currently rare for this specific anatomical location and little information is available on the clinicopathological features, management options, and treatment outcomes of such disease. To contribute additional knowledge, we reviewed the cases of 43 patients seen in two departments of a single institution.

Materials and methods

After obtaining written approval from the Institutional Clinical Research Supervision Committee (ICRSC), we reviewed the clinical and pathological records of soft tissue sarcoma patients who had been treated surgically and followed up from May 1996 to November 2012. Our selection criteria for MPNST in the present study always conformed to the description given by Ferner and Gutmann[15] and Kar et al.[16] The primary criteria for a diagnosis of this spindle-cell sarcoma include demonstration of origin from a nerve, presence of Schwann cells or neurofibroma components, a nerve-like whorling growth pattern under microscopic inspection, varying degrees of mitosis, nuclear atypia and palisading, and immunohistochemical staining of S-100 or neuron-specific enolase (NSE) protein.[2] Tumours situated largely or entirely at an extracranial site were contained, while lesions within the brain parenchyma were excluded from this study. A total of 49 patients with a diagnosis of MPNST, malignant neurofibroma, or malignant schwannoma in the head and neck area were identified and reviewed thoroughly, using both paraffin sections and clinical features. Six of these cases were then excluded for unconfirmed pathological diagnoses, incomplete treatment records, or insufficient follow-up information.

The presence of NF-1 syndrome was determined on the basis of established National Institutes of Health (NIH) clinical criteria[1] and histological evidence. The tumour location was determined not only on the basis of the centre of the lesion, but also on the adjacent (within 2 cm) or invaded crucial structures, such as the orbital floor, skull base, carotid artery, and parapharyngeal space, where surgery remained complicated or postoperative morbidity was unavoidable once sacrificed. Bone erosion or absorption was determined by radiographic or pathological evidence, whereas vascular invasion was confirmed only pathologically.

All histopathological specimen sections were reevaluated and scored by two pathologists. For the relatively larger tumour volumes in this series, tumour size of the MPNST, as a separate factor, was further classified as $\leq$5, 5–10, or $>$10 cm. Tumour necrosis and the mitotic rate were also recorded. The mitotic count was scored as 0, 1, or 2 using high-power magnification (high-power field (HPF) surface, 0.174 mm^2) of 10 successive fields. Tumour necrosis was assessed likewise: 0, no necrosis on any examined slides; 1, $<$50% necrosis for all examined tumour surface; and 2, $>$50% necrosis. Since grading is not recommended for MPNST under the French National Federation of Cancer Centers (FNCLCC) system, grading is not routinely provided.

All of the patients received surgery as the main treatment approach. External beam radiation therapy (EBRT) at a dose of 54–68 Gy was given to 23 patients after surgery. Adjuvant chemotherapy was only given in seven cases. Three adjuvant chemotherapy regimens were given to primary cases at the discretion of different chemotherapists. Cyclophosphamide and doxorubicin, ifosfamide and cisplatin, and doxorubicin and ifosfamide were the three regimens used for these patients.

All cases were analyzed retrospectively, and treatment outcomes during the follow-up were also compared. The primary endpoint of this study was recurrence, metastasis, and tumour-related death. Since none of the MPNST patients included in this study died from causes other than recurrence or metastasis, the overall survival reported herein is equivalent to tumour-related survival. Finally, the influence of prognostic factors was examined.

SAS 9.2 (SAS Institute, Cary, NC, USA) was used for the statistical analysis. Variables for recurrence and metastasis were compared between groups using the two-tailed Fisher's exact test, with the cut-off *P*-value being 0.05. Survival distributions were estimated using Kaplan–Meier curves and Cox proportional hazards regression models.

Results

Clinical features

The main characteristics of the 43 patients with MPNST are summarized in Table 1. The male to female ratio was 1:0.7. The median age at presentation for the whole series was 41 years (range 19–71 years). A previous history of radiation therapy for other types of tumours including dosimetry details was confirmed in three cases (7.0%); prior radiochemotherapy or radiation alone at a total dose of 62–74 Gy was provided for nasopharyngeal carcinoma or lymphoepithelial carcinoma. The regions involved in the MPNST were close to the first malignancy or within the field of prior radiation, and these cases were classified as radiation-induced MPNST cases (Table 1). Of all the patients under study, pertinent information regarding the presence of NF-1 was available in 13 (30.2%). For these patients, the median age at onset of MPNST was 36 years. Two patients (4.7%) in our series were diagnosed as ex-schwannoma MPNST for the malignant histological change.