Clinical Study

The prognostic implications of Hyam's subtype for patients with Kadish stage C esthesioneuroblastoma

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ABSTRACT

Esthesioneuroblastoma (EN) is a rare sinonasal tumor with varied aggressiveness and potential for intracranial invasion. EN is staged anatomically with radiographic evaluation using the Kadish staging system (stages A, B, and C) and histologically by using Hyam's criteria (grades 1–4). Here we show that despite radiographic evidence of aggressive features, the prognosis of patients with Kadish stage C EN is best predicted by tumor histology using Hyam's criteria. We retrospectively analyzed patients with EN with Kadish stage C who were evaluated and treated at our institution between 1995 and 2009. Clinical information was collected using patient medical records, imaging, and review of pathological specimens. Twenty patients with Kadish stage C EN were identified with mean age of 51 years (31–70 years) with a median follow-up of 41.4 months (1.3–175 months). Upon pathological review, 44.4% of patients had low-grade (1/2) and 55.6% had high-grade (3/4) histology. About 37.5% of patients with low-grade EN had undergone gross total resection (GTR) and the remaining 62.5% had GTR and adjuvant radiation, whereas 50% of patients with high-grade ER had undergone GTR, 20% had undergone GTR and adjuvant radiation, and 30% had been treated with a subtotal resection (STR) and adjuvant radiation. The 5-year and 10-year survival in patients with low-grade EN was 86% in comparison to 56% and 28% with high-grade EN, respectively. In patients with low-grade EN, the 2-year progression free survival (PFS) was 86% and the 5-year PFS was 65% in comparison to 73% and 49% in patients with high-grade EN, respectively. The patient's tumor histology (Hyam's criteria) appeared to be the best way of predicting the prognosis and for selecting patients for adjuvant radiotherapy.

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1. Introduction

Esthesioneuroblastoma (EN) is a rare sinonasal malignancy with varied aggressiveness, including the possibility for intracranial invasion. EN is typically staged anatomically with radiographic evaluation using the Kadish staging system,[1] and histologically with Hyam's criteria.[2,3] The Kadish staging includes grades A, B, and C representing radiographic findings of tumor in the sinus, paranasal sinuses, and extending beyond the cribriform plate, respectively (Table 1). Hyam's criteria categorize tumors into four grades, representing a spectrum of relatively benign to malignant histologic features (Table 2). Patients with Kadish stage C typically require neurosurgical involvement.

Both Kadish staging and Hyam's histologic classification have been used to provide a prognosis and to help guide treatment decisions, including the appropriate use of neoadjuvant or adjuvant therapies.[1–7] We reviewed 956 patients reported in the published literature.[5] Our analysis demonstrated that histologic tumor grade independently predicted patient survival, and that the biologic behavior of EN could be summarized as representing two patterns: low and high grade. Furthermore, this analysis found that the prognosis was excellent when Kadish stage C tumors were associated with low-grade histology, despite radiographic evidence of aggressive tumor behavior, including intracranial invasion.

Here we validate the findings from our systematic review with a more detailed dataset collected retrospectively from our institutional experience. We show that despite radiographic and anatomic features of aggressive behavior, the prognosis of patients with Kadish stage C tumors is best predicted when based on the biology of the tumor, as reflected by Hyam's grade. Our findings have implications for post-operative management, particularly regarding the utility of adjuvant therapy after gross total resection (GTR) in patients with Kadish stage C, low-grade tumors.

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Table 1
Kadish staging for esthesioneuroblastoma

Group A	Tumor is limited to nasal cavity
Group B	Tumor is localized to the nasal cavity and paranasal sinuses
Group C	Tumor extends beyond the nasal cavity and paranasal sinuses

Table 2
Hyam's grading criteria

	Low-grade		High-grade	
	1	2	3	4
Lobular architecture	+	+	±	±
Mitotic activity	−	+	++	+++
Nuclear pleomorphism	−	±	+	++
Rosettes	HW±	HW±	FW±	−
Necrosis	−	−		++

HW = Homer Wright rosette, FW = Flexner–Wintersteiner rosette.
(Reproduced from Morita et al.[3] with the kind permission of Wolters Kluwer Health).

2. Methods

2.1. Patient population

We retrospectively identified all patients between 1995 and 2009 who underwent evaluation and initial treatment for EN at our institution, and who had a confirmed pathology with central review. We excluded all patients with any other intracranial tumor history and those patients with Kadish stages A or B. From this cohort of patients with Kadish stage C, we evaluated all patients undergoing primary craniotomy for resection of a histologically proven EN with operative and radiographic data (n = 20 patients). This study was approved by the University of California San Francisco Committee on Human Research under the approval CHR# H41995-34889-01.

2.2. Data collection

Clinical information was collected retrospectively using patient medical records, radiographic data, and pathologic specimens. All clinical assessments were reviewed by the senior author (A.T.P.).
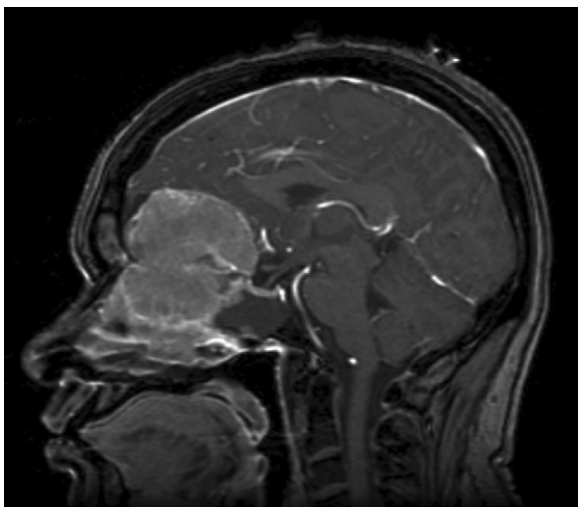

Fig. 1. Sagittal, T1-weighted MRI with contrast of Patient 9 demonstrating the typical radiographic appearance of Kadish stage C esthesioneuroblastoma.

Patient age was defined as age at the time of surgery. Both the pre-operative, post-gadolinium T1-weighted MRI and/or the surgeon's operative note were reviewed to confirm tumor location and Kadish stage. Tumors were classified using MRI as Kadish stage: A, confined to sinuses; B, extension into the paranasal sinus; or C, extension through the cribriform plate (Fig. 1a). Radiographic patterns of recurrence are demonstrated for a patient with intracranial recurrence (Fig. 2a) and a patient with nodal recurrence (Fig. 2b).

Histological features were extracted from pathology reports associated with tumor resection, with confirmation by central review. The tumors were first categorized by Hyam's classification into grades 1 to 4 and then divided into two groups: low-grade (grades 1 or 2) and high-grade (grades 3 or 4). Extent of resection was assessed based on the surgeon's operative note in conjunction with the post-operative MRI. Post-operative assessments and imaging were examined for evidence of recurrence, treatment of recurrence, and overall survival (OS).

2.3. Statistical analysis

Kaplan–Meier estimates were used to generate survival curves. Differences in time to recurrence or death from disease after initial treatment were analyzed by the log-rank test. Statistical tests were considered significant for $p < 0.05$. Continuous variables are presented as mean ± standard error (SE). All descriptive and statistical analyses were performed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Patient demographics and clinical characteristics

Between 1995 and 2009, 20 patients with Kadish stage C EN were available for review (Table 3a), and their demographic information is summarized in Table 3b. The mean age of these patients was 51 ± 2.5 years, and 86% of the patients were male. A positive smoking history, a known risk factor for EN,[8] was found in 25% of our patients, and 27% of our patients had a history of occupations that would predispose them to EN such as working in the logging industry.[8] Orbital involvement was seen in 38% of patients and brain involvement in 43%. Frequently encountered radiologic findings included dural thickening (36%), cystic components (41%), shift/mass effect (29%), and hydrocephalus (12%). The mean tumor volume was 91.9 ± 15.9 mL, and the mean largest diameter was 6.0 ± 0.4 cm. Median post-operative follow-up was 41.4 months and ranged from 1.3 months to 175 months.

Upon presentation to our specialty clinics, symptoms were largely referable to the sinonasal tract; presenting symptoms for all patients are described in Table 4. Some of the most common presentations included epistaxis (53%), congestion/nasal obstruction (53%), palpable or disfiguring mass (53%), anosmia (40%), headache (26.7%), and proptosis (20%).

3.2. Pathologic features of the tumors

By light microscopy, the tumors demonstrated typical histologic features of EN, including uniform small tumor cells with round nuclear contours and scant cytoplasm, in a prominent neurofibrillary background. Homer Wright rosettes (with central neurofibrillary-like material) were present in some tumors. Mitotic activity varied, as did other cytologic features of malignancy, such as tumor necrosis. Immunohistochemistry demonstrated typical patterns of reactivity for the neuronal markers synaptophysin (100%), neuron specific enolase (91%), chromogranin (72%), and S-100 (72%). EN