Long-Term Outcome of Esthesioneuroblastoma: Hyams Grade Predicts Patient Survival

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Abstract

Object Esthesioneuroblastoma (ENB) is a rare malignant neuroendocrine tumor originating from the olfactory neuroepithelium in the cribriform plate. Controversy still exists regarding the role of pathologic grading (Hyams grade) in prognostication. This study was undertaken to describe our experience with ENB and assess the role of pathologic grading in patient outcome.

Methods This was a retrospective, single-institution experience, including 109 patients with ENB treated at our institution from 1962 to 2009. Multivariate analysis was performed utilizing Cox regression analysis models utilizing age, gender, modified Kadish stage, and Hyams grade.

Results Mean age was 49 ± 16 (median 50) years at presentation (range 12 to 90 years). Median follow up was 5.1 years. All-cause mortality was significantly influenced by Hyams grading in univariate ($p = 0.04$) and multivariate ($p = 0.02$) analysis, in addition to proven prognostic factors, Kadish staging, lymph node metastasis, and age. Median survival was 9.8 years compared with 6.9 years with low (grade 1 to 2) versus high (grade 3 to 4) Hyams grade. Median overall survival was 7.2 ± 0.7 years.

Conclusion ENB has a variable outcome, which is primarily prognosticated by the extent of involvement at presentation (Kadish stage and lymph node metastasis) and higher Hyams pathologic grade.

Keywords

- ▶ esthesioneuroblastoma
- ▶ olfactory neuroblastoma
- ▶ outcome
- ▶ Hyams grade
- ▶ surgical treatment

Introduction

Esthesioneuroblastoma (ENB)—also known by a variety of names such as *olfactory neuroblastoma*, *olfactory esthesioneuroblastoma*, *esthesioneurocytoma*, and *olfactory placode*

tumor, to name a few—is a rare nasal neoplasm with an incidence 0.4 per 1,000,000 people.¹ ENB typically presents with unilateral nasal obstruction or epistaxis.^{2–4} Treatment paradigms vary considerably from institution to institution and country to country. Few institutions see an adequate

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number of ENB cases to establish proven treatment regimens or to allow clinical trials. An attempt by the North American Skull Base Society to enroll patients with anterior skull base malignancies in a multi-institutional trial to establish a treatment protocol failed to accrue enough patients to proceed.⁵

Population-based analysis of the Surveillance Epidemiology and End Results (SEER) database confirm that Kadish staging, lymph node involvement, and age at diagnosis have significant prognostic value.⁶ These findings have been confirmed in a large meta-analysis published in 2010 by Kane et al.⁴ Further, Kane et al found, as previously published by our institution, that higher grade pathology (by Hyams criteria) may predict poorer prognosis.^{4,7} This finding, however, has not been confirmed by a direct retrospective or prospectively conducted trial in a similar manner. Further, some institutions as recently as 2006 advocated no pathologic interpretation beyond confirming ENB and therefore do not report a Hyams grade, since it is believed ENB grade is of no prognostic significance.⁸ This study was performed to detail our experience with these tumors and to assess the prognostic value of Hyams grading in a large single-institution series.

Methods

Inclusion Criteria

This study is a retrospective single-institution study. Approval was obtained from the Institutional Review Board. Inclusion criteria for further analyses were the following:

(1) Pathologically confirmed ENB at our institution. Notably, all pathology slides were reviewed to exclude sinonasal undifferentiated carcinoma, lymphoma, rhabdomyosarcoma, mucosal malignant melanoma, and neuroendocrine carcinoma, either at the time of resection or re-reviewed by our expert neuropathologist for confirmation.

(2) Treatment at Mayo Clinic Rochester, either primary resective surgery, revision surgery, or adjuvant therapy. Patients seen for consultation only, without treatment at our institution, were excluded. Between 1962 and 2009, 109 patients were identified utilizing these criteria from the neurosurgical, pathological, and clinical database based on the keyword search “esthesioneuroblastoma or olfactory neuroblastoma.” The majority of lesions were treated between 1980 and 2009 as shown in ►Fig. 1 (88%).

Staging

Modified Kadish staging⁹ (with modification from Chao et al in 2001) was used based on best information as follows: Stage A: ENB confined to nasal cavity; Stage B: ENB confined to paranasal sinuses; Stage C: tumor extends beyond confines of nose locally to include the skull base, intracranial compartment, or orbit; Stage D: distant disease, either to regional lymph nodes or distant metastasis.

Surgical Resection

Standard surgical therapy for Kadish C and D lesions has been up-front craniofacial resection with the goal of negative surgical margins. Kadish A and B lesions were most common-

Figure 1 Distribution of esthesioneuroblastoma cases at date of earliest pathologic confirmation. Breakdown of number of cases (y-axis) by year in decades (x-axis). There appears to be relative stability in our esthesioneuroblastoma population from 1990 to 2010. Eighty-eight percent of cases occurred after 1980.

ly treated with transnasal endoscopic resection or lateral rhinotomy, also with the goal of negative surgical margins.

Pathology

Pathologic examination of ENB often reveals a lobular architecture that is frequently lost with higher-grade lesions. Cells have round or oval nuclei and a scant cytoplasm. Some tumors show advanced neuronal differentiation with rosette formation or abundant neuropil formation resembling neuroblastoma. Tumors typically express neuronal markers such as synaptophysin and cytokeratin staining is negative. Low-grade tumors (Hyams 1 to 2) show absent or low mitotic activity (<5 mitosis per 10 high-power fields), whereas in high-grade tumors (Hyams 3 to 4), the mitotic index is high (≥5 mitosis per 10 high-power fields). Grade 4 tumors commonly show severe anaplasia or necrosis. Eighty-seven (of 109) cases had slides available for re-review, and a Hyams grade was assigned by a neuropathologist blinded (CG) to outcomes. See ►Table 1 for summary characteristics.

Statistical Analysis

JMP 8.02 (JMP®, Version 8. SAS Institute Inc., Cary, NC, USA) was used to process the data, applying nonparametric statistical tests (FET) or Pearson's chi-squared analysis as appropriate to assess significance. Multivariate models were performed in SAS (SAS Institute Inc., Cary, NC) with Cox proportional hazards regression method to build models accounting for age (continuous), sex (discrete), and staging/grading through our biostatistics department. Kaplan-Meier survival analysis was used to estimate survival distributions, and log-rank test was utilized to test significance between groups.

Results

Demographics

There were 109 patients in this series. Seventy-nine underwent primary resection at Mayo Clinic Rochester, an additional 30 underwent primary resection elsewhere; however, these patients received subsequent evaluation and treatment at our institution. Forty-four percent of patients were women (48 women, 61 men). The mean age at presentation was 49 ± 16 years (95% confidence interval 46 to 52 years) and

Table 1 Hyams Histologic Grading System for Esthesioneuroblastoma

Microscopic Features	Hyams			
	1	2	3	4
Pleomorphism	—	+	++	+++
Lobular architecture	+	+	+/-	+/-
Neurofibrillary matrix	+++	+	+/-	—
Rosettes	+	+	+/-	+/-
Mitoses	—	—	+	+++
Necrosis	—	—	+	+++

there was no evidence of a bimodal distribution (►Fig. 2). The median age was 50, with a range of 12 to 90 years, implying that the distribution was normal.

Staging and Grading

Distribution of cases with respect to modified Kadish staging can be seen in ►Fig. 3. Overall, the majority were Kadish C (61%) with only one patient (1%) consistent with a Kadish A. Pathologic material was available for re-review in 87 cases of histologically confirmed ENB for review. Hyams grades were as follows: grade 1 in five patients (6%), grade 2 in 42 (48%), grade 3 in 32 (37%) and grade 4 in eight (9%). Due to the few cases of grade 1 and grade 4 tumors, these were included with grade 2 and 3 patients, respectively, for multivariate analysis, thus allowing us to compare low-grade (grade 1 to 2) to high-grade (grade 3 to 4) tumors. Surgical circumferential margins were definitively available in 65 cases, and in 46 patients (71%), the margins were negative. Eighteen patients (17%) presented with cervical lymph node metastases and 44 (40%) patients in this series developed lymph node involvement in the course of their disease.

Adjuvant Treatment

Due to the prolonged period for this study, there was no uniform radiation treatment prescribed; however, 84% ($n = 87$) received radiation as part of their treatment, this was most commonly after surgical resection. Mean treatment dose was 5460 Gray (Gy), median dose was 5580 Gy delivered in 30 to 33 fractions. Fifty-four percent ($n = 56$) underwent

chemotherapy as part of their treatment. Once again there was no standard chemotherapeutic regimen, but most patients were treated with a platin-based approach.

Outcome

Median overall survival regardless of stage or grade was 7.2 ± 0.7 years (87 ± 7.9 months). Mean progression free survival was 4.8 ± 0.7 years (58.5 ± 8.2 months) and median was 3.5 years (42.0 months) (range 1–229 months). The 5 and 10 year survivals were 63% and 40%. Median follow up for the cohort is 62.4 months (>5 years). Mean survival from time of lymph node positive diagnosis was 41 ± 7.2 months (median 22.4 months) (range 1 to 184 months). Outcome with respect to Kadish stage is shown in ►Fig. 4 and, as previously reported, Kadish stage significantly impacts outcome. Kaplan-Meier survival curves with respect to low- and high-grade Hyams pathology is shown in ►Fig. 4. There is a statistically significant difference when Hyams grade is considered (univariate [$p = 0.04$] and multivariate [$p = 0.02$]). We assessed the impact of age at presentation of 65 or greater on overall survival, which was significant ($p = 0.02$) (►Fig. 4C). Moreover, surgically negative margins at the time of surgery, as well as postoperative radiation therapy (conventional), also improved survival (►Fig. 5). Interestingly, there is a high correlation between Hyams grade and Kadish stage (►Fig. 6).

Discussion

ENB is an uncommon tumor, accounting for only 3% of intranasal neoplasms; however, we are beginning to make

Figure 2 Age distribution of cases. There appears to be a unimodal distribution of cases among these 109 cases at age of presentation. The mean age is 49 ± 16 years (95% confidence interval 46 to 52 years). The median age was 50, with a range of 12 to 91 years.

Figure 3 Distribution of (A) Kadish staging and (B) Hyams grading for cases in which this information is available.

Figure 4 Impact of staging (Kadish), age (<65), and pathologic grade (Hyams) on survival. Kaplan-Meier survival curves for (A) modified Kadish staging ($p < 0.001$). (B) Age >65 ($p = 0.02$). (C) Hyams low and high grade ($p = 0.04$). (D) Hyams further separated to Hyams 1/2, 3, and 4, note Hyams grade 4 has a particularly poor outcome ($p < 0.001$).

strides in understanding the tumor's complexity.³ Despite first being described in the literature in 1924 by Berger et al, there is still a limited collective experience with these tumors.¹⁰ This report represents the largest single-institution experience in the literature.^{1,2,4,6,8-23} Due to the relatively large sample size ($n = 109$), it is possible in this group to distinguish more subtle prognostic factors and to confirm previously reported meta-analyses findings.^{2,4,12} The mean age of this cohort was 49 ± 1.5 years, which is within mean for published studies available. The mean age in 956 patients reported in the literature was 45 ± 0.7 years.⁴ There was no evidence of a bimodal distribution, as has been described in the literature. A slight male predominance is frequently reported and is the case in this series (56% male).⁴ Interestingly, as suggested by meta-analysis, in our series age >65 years old negatively impacts survival after the diagnosis of ENB.

Although there are several staging systems available in addition to modified Kadish staging, such as those proposed by Biller or Dulguerov, our institution has utilized the former system.¹² This series is unique in that over 75% of the ENB presented as Kadish C or D, which is substantially higher than most reported series, which typically report 50% or less.^{4,9,12,15} We agree with Dulguerov et al that the current staging systems lack distinction specifically within the Kadish C cohort, such as distinguishing dural transgression; however, due to low numbers, even within this series it is difficult to firmly differentiate this subset of tumors.^{2,12} However, it may be useful to divide Kadish C lesion postoperatively by whether or not negative margins could be achieved, or whether it is simply unresectable. We report a median

survival of 7.2 ± 0.7 years regardless of stage or pathology. The 5- and 10-year survivals were 63% and 40%, respectively. These 5- and 10-year survivals were within reported ranges.^{1,2,6,9,11-16} For instance the SEER database reports 62% and 41%, and Dulguerov et al reported 74% and 60% 5- and 10-year survivals, respectively.^{2,6,12} The overall survival did appear to be on the lower end of reported ranges; however, we suspect the survival is related to the percentage of Kadish C and D lesions, which was over 75% in our study. For instance, Dulguerov and Calcaterra reported 5- and 10-year survival rates of 74% and 60% respectively, but in their series of 26 patients, only 27% ($n = 6$) were stage C or higher.^{2,12} Moreover, the SEER database reports 33% of their 261 patients to have Kadish C or higher lesions, considerably less than in our series; however, they report almost identical 5- and 10-year survival of 62.1% and 40.6%, which mirror our results and suggest that these outcomes are less biased due to the large study population numbers.⁶ Finally, in a large population-based study in which surgical bias could be excluded, 48% were Kadish C or higher, and median survival was 3.1 years with a 5-year survival rate of 60%.^{1,15}

The impact of Hyams grade is yet to be fully understood. Meta-analysis of the data suggests that Hyams grade does influence recurrence and survival, but this is less clear in institutional studies.^{4,7} The prognostic significance of pathologic grading is perhaps confounded often by the influence of clinical staging. Hyams has proposed straightforward pathologic criteria that should predict aggressiveness of ENB; however, Kadish staging appears to do the same. Consequently, in the small series that appear throughout the literature, it appears to be difficult to separate the relative influence of

Figure 5 Survival, surgical margins, and adjuvant treatment. Ten-year survival based on (A) surgical margins and (B) radiation therapy. There is significant influence of surgical margins ($p = 0.04$) and radiation, limited only to Kadish (C, D) patients ($n = 81$) ($p < 0.001$).

these two variables to overall outcome, and they may in fact confound one another.^{2,4,12} However, our previous institutional studies would support Hyams grading as the most significant prognostic indicator in ENB.^{7,24} Therefore, it re-

Figure 6 Modified Kadish staging and Hyams grading correlate highly. Modified Kadish stage (x-axis) is shown in proportion to each stage's Hyams grading (gray is low grade [1/2], black is high grade [3/4]). There is a strong correlation with higher-grade tumors and higher stage at presentation, gamma correlation of association 95% confidence interval (0.34 to 0.81).

quires a larger series to demonstrate the effect of both, and the meta-analysis of Kane et al further supports this.⁴ They report that, within their study, Hyams was so predictive of outcome that Kadish staging lost prognostic significance when controlling for grade.⁴ As seen in **Fig. 6**, there is an extremely high correlation of low-grade pathology and low stage, as well as high-grade pathology and high stage. Further, lymph node metastasis is a significant prognostic indicator of poorer survival, denotes Kadish stage D disease, and correlates with higher-grade Hyams pathology. We now recommend positron emission tomography preoperatively for prognostic purposes, to assess for lymph node metastasis since this has such a profound effect on all-cause mortality. Age in all studies continues to have a prognostic significance, and this finding is no different here.^{2,4,12} In multivariate analysis, or univariate analysis using 65 as the cutoff age (based on Kane et al), age has a profound effect on patient outcome.^{2,4,12} Notably, sex did not impact survival as would be expected.

One additional interesting aspect of this study supports the staging system of Biller et al, which determines their highest stage tumor by the inability to get negative margins at the time of surgery.²⁵ Negative surgical margins at the time of surgery impacts survival in this study, as well. This clearly has significance concurrently as we attempt to integrate endoscopic endonasal surgery into the treatment paradigm of ENB.²³ Clearly there is a role for endoscopic surgery in Kadish A and B disease. Further, in our own series we continue to utilize craniofacial resection for suspected Kadish C and D disease, though we have more recently utilized an endoscopic transnasal approach to avoid the cosmetic deformity and wound issues associated with the lateral rhinotomy incision. However, as endoscopic approaches have proliferated, surgeons have questioned the necessity of an oncologic resection. For instance, Unger et al have reported on an intriguing series of patients managed with purely endoscopic resection and postoperative stereotactic radiosurgery to the residual tumor and margins with thus far seemingly good results.^{26,27} Despite this, it is our recommendation that surgeons advocate the approach for the patient that will have the highest likelihood of negative margins.

Conclusion

ENB has a variable outcome that is primarily prognosticated by the extent of involvement at presentation (Kadish stage and lymph nodes metastasis). However, it appears that higher Hyams grade pathology at diagnosis influences patient all-cause mortality and outcome the most. The extent of disease at presentation may be a surrogate for higher-grade pathology.

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