Posttreatment prognosis of patients with esthesioneuroblastoma

Clinical article

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Object. There is no Class I evidence to guide the appropriate management of esthesioneuroblastoma (EN). Most data currently guiding treatment come from small- or modest-sized series gathered at individual centers that have concluded that surgery with radiotherapy is the preferred treatment. In this study, the authors summarize the published literature on treatment outcomes in patients with EN. The objective was to ascertain what variables predict prognosis in these patients and to determine the relative effect of different therapies.

Methods. The authors identified 205 published studies containing treatment outcomes for surgery, radiotherapy, chemotherapy, or multimodal treatment. Using Kaplan-Meier analysis, the survival of patients who received surgery was compared with that in those who received surgery and radiotherapy. Additionally, Kadish staging was compared with low- and high-grade Hyams criteria to assess for subgroup prognostic significance in survival differences.

Results. Nine hundred fifty-six patients met the inclusion criteria, with a median follow-up time of 3 years. Kaplan-Meier analysis demonstrated no difference in survival between patients who underwent surgery alone and those who underwent surgery plus radiotherapy at 5 years (78 vs 75%) or 10 years (67 vs 61%, respectively) (p = 0.3). Univariate analysis demonstrated worse survival in cases involving Kadish Grade C tumors, Hyams Grade 3 and 4 tumors, and in patients older than 65 years of age. Multivariate analysis demonstrated that Hyams Grade 3 and 4 lesions carried significant risk (proportional hazard = 4.83, p < 0.001) with 5- and 10-year survival of 47 and 31%.

Conclusions. A biopsy should always be obtained in cases suspected of EN because histology is a strong prognostic indicator and will help guide appropriate treatment. Unimodal surgery and combined surgery/radiotherapy appear to be of equivalent efficacy with respect to survival in patients with EN. Chemotherapy should be considered in high-grade EN. (DOI: 10.3171/2010.2.JNS091897)

Key Words • esthesioneuroblastoma • olfactory neuroblastoma • surgery • radiation therapy • prognosis

This analysis was unable to find a statistically significant difference between surgery alone and surgery with adjuvant radiotherapy. However, based on a trend, they concluded by recommending excision followed by postoperative radiotherapy as the preferred treatment approach. Additional smaller series from single institutions have also concluded that surgery with adjuvant radiotherapy is the ideal treatment for EN.14

In this study, we have performed a comprehensive review of the published literature on patients treated for EN with subsequent follow-up. We have synthesized the data to determine optimal staging, grading, and treatment approaches.

Methods

Article Selection

Unique articles were identified via a Boolean PubMed search using the key words “esthesioneuroblastoma,” “olfactory neuroblastoma,” “surgery,” “Kadish,” “Hyams,” “radiation therapy,” “prognosis,” and “esthesioneurobstoma,” also known as olfactory neuroblastoma, is a primitive neuroectodermal tumor that is thought to arise from the olfactory epithelium of the upper nasal cavity. It exhibits a wide variety of clinical behavior, including a propensity for intracranial invasion. Until now, the literature on EN has consisted of mostly case reports and case series.

Because of both the rarity and varied behavior of EN, it has been difficult to definitively establish the appropriate management for this tumor. Multiple systems have been proposed to help guide physicians in prognostic counseling as well as directing patients toward the appropriate treatment regimen.50,83,94,134 The lack of authoritative evidence has resulted in heterogeneous treatment selections including unimodal approaches composed of surgery, radiotherapy, or chemotherapy, as well as multimodal therapies. A meta-analysis published in 2001 attempted to review and determine appropriate treatment.49

Abbreviations used in this paper: EN = esthesioneuroblastoma; NS = not significant.
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blastoma” alone and in combination. We then searched all references in these papers.

Inclusion criteria for this set of articles were as follows: 1) individual patient data were reported in a dis-aggregated fashion; 2) primary treatment modality was clearly reported and limited to surgery, radiotherapy, conventional chemotherapy, or any combination thereof; and 3) outcome data including follow-up duration and/or time until death were reported. Only 2 published series, both from the same academic group, reported the use of radiosurgery as primary treatment for EN.46,107 Given the small total number of these cases (20) and given that radiosurgery is a distinct treatment modality from radiotherapy, they were excluded from our analysis.

Data Extraction

Data from individual reports and case series were extracted. Papers that reported only sum-aggregate results were not used in our analysis, as these data did not permit meaningful analysis. Primary treatment strategy was coded separately for surgery, radiotherapy, chemotherapy, surgery with radiotherapy, surgery with chemotherapy, and surgery with chemotherapy and radiotherapy. Follow-up duration was tabulated in months. Disease status, mortality, and cause of death were extracted and coded for at the termination of follow-up. Kadish stages and Hyams grades were both extracted when possible. The Kadish scheme is a radiographic grading scale, and lesions were categorized into Stages A (tumor limited to nasal fossa), B (tumor extends into paranasal sinuses), and C (tumor extends beyond paranasal sinuses).94 The Hyams grade is a histology grading scale, and lesions were categorized into Grades 1, 2, 3, and 4 according to Hyams criteria.83,134 Additionally, we binarized Hyams grades into low-grade (Hyams Grade 1 and 2) and high-grade (Hyams Grade 3 and 4) pathology to perform a more powerful analysis because we found that Hyams Grade 1 and 2 lesions clustered separately from Grade 3 and 4 lesions in a survival analysis (Fig. 1C). High-grade Hyams histology is characterized by necrosis, mitoses, nuclear pleomorphism, and lack of rosettes.47

Statistical Analysis

The Pearson chi-square test was used to analyze for differences in preoperative categorical factors. Kaplan-Meier estimates were used to generate survival curves. Differences in time to death from disease were analyzed by the log-rank test. Cox proportional hazard modeling was used to assess for differences in survival adjusting for differences in preoperative variables. Statistical tests were considered significant at p < 0.05. Continuous variables are presented with the SE. Differences in age were tested for significance using the independent sample t-test after demonstrating normality of the data. All descriptive and statistical analysis was performed using SPSS version 16.0.

Results

Results of the Systematic Review

Our search methods identified 205 articles1–5,7–13,16–38,40–46,48,50,51,53–79,81,82,84–118,120–133,135–142,144,146–148,184–195,198–212,214–222 reporting on 956 patients who met our inclusion criteria. Our analyses focused mainly on patients receiving surgery or surgery with radiotherapy. The relevant demographics and characteristics of these 2 treatment groups are summarized in Table 1. The median follow-up duration for all patients was 3 years.

Is Posttreatment Prognosis Improved by the Addition of Radiotherapy to Resection?

Outcome data were available for 266 patients who underwent surgery and 398 patients who received adjuvant radiotherapy in addition to surgery as primary treatment. The median follow-up duration for all patients from treatment initiation to death or discontinuation of follow-up was 3 years (range 1–360 months). The follow-up duration did not differ significantly between the treatment groups. The mean age for both groups was 45 years. The proportion of patients older than 65 years (15 vs 14%, p = NS, chi-square test) and of male sex (52 vs 50%, p = NS, chi-square test) was not significantly different between the treatment groups. Additionally, the proportion of high-grade tumors (40%) was the same in each treatment group (Table 1).

We found that there was no survival benefit for those patients who received radiotherapy in addition to surgery compared with surgery alone (Fig. 2). Patients who received surgery as monotherapy compared with surgery and radiotherapy had statistically equivalent prognosis at 5 years (78 vs 73%) and 10 years (67 vs 61%, respectively) (p = 0.3, log-rank test). Given that neurosurgeons typically become involved in cases of intracranial invasion, we also performed a survival analysis on 2 select groups of higher-grade tumors. Removing all Hyams Grade 1 tumors from our analysis or performing our analysis on solely Stage C tumors still resulted in statistical equivalence between the 2 treatment conditions at 5 and 10 years of follow-up (p = 0.61, log-rank test [Hyams Grade 1 removed]; p = 0.82, log-rank test [Kadish Stage C only]; data not shown).

Posttreatment Prognosis After Radiotherapy as Sole Treatment for EN

Eighty-eight patients who received monotherapy radiotherapy for EN were available for survival analysis. The median follow-up duration was 20 months (range 2–408 months). Survival at 2, 5, and 10 years was 58, 52, and 46%, respectively (Fig. 3).

Factors Impacting Prognosis of Patients With EN

Univariate analysis showed that cases of patients older than 65 years had poorer survival than their younger counterparts. These patients had worse survival than younger patients at 2 years (76 vs 90%) and 5 years (53 vs 78%, respectively) (p < 0.01, log-rank test). However, age did not remain significant on multivariate analysis and dropped out of the regression model. There was no significant difference in survival between males and females.

In univariate analysis, Kadish stage predicted overall survival in all patients receiving unimodal surgical treat-
ment (225 cases) (Fig. 4 upper). Five-year survival for Kadish Stages A (36 cases), B (74), and C (115) was 88, 79, and 68%, respectively, and 10-year survival was 79, 74, and 50% (p < 0.01, log-rank test).

Univariate analysis of 63 patients receiving mono-therapy surgery in whom Hyams grading was determined revealed that the Hyams grade was a strong predictor of overall survival (Fig. 1A). Patients with Hyams high-grade tumors (26 cases) had significantly worse prognosis than those with Hyams low-grade tumors (37 cases) at 2 years (89 vs 68%), 5 years (89 vs 47%), and 10 years (89 vs 31%, respectively) (p < 0.01, log-rank test). Of note, in all of these patients who underwent resection alone, and in those who had low-grade Hyams, there were no deaths during the 9 months of total follow-up.

Because we found that radiotherapy provided no survival benefit or disadvantage, and to include all patients who had received surgery as part of their management, we performed Kaplan-Meier analysis on patients who underwent surgery or surgery plus radiotherapy. Similar results were obtained for this group of patients as well. In univariate analysis, Kadish stage continued to predict prognosis in 574 patients receiving surgery or surgery and radiotherapy (Fig. 4 lower). Kadish Stage A (79 cases), B (201), and C (294) had 5-year survival of 86, 80, and 64%, and 10-year survival of 81, 73, and 48%, respectively (p < 0.001, log-rank test).

Hyams grade also maintained significant prognostic value in predicting prognosis in 133 patients who had received either surgery or surgery and radiotherapy (Fig. 1B). Hyams high-grade histology (52 cases) compared with low-grade histology (81 cases) was associated with
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**TABLE 1: Summary of demographic and tumor-related data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>Op</th>
<th>Op &amp; Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>664</td>
<td>266</td>
<td>398</td>
</tr>
<tr>
<td>mean age ± SE (yrs)</td>
<td>45 ± 0.7</td>
<td>45 ± 1.1</td>
<td>45 ± 1.0</td>
</tr>
<tr>
<td>age &gt;65 yrs</td>
<td>14%</td>
<td>15%</td>
<td>14%</td>
</tr>
<tr>
<td>male</td>
<td>51%</td>
<td>52%</td>
<td>50%</td>
</tr>
<tr>
<td>Kadish Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>14%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>B</td>
<td>35%</td>
<td>33%</td>
<td>36%</td>
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<tr>
<td>C</td>
<td>51%</td>
<td>51%</td>
<td>51%</td>
</tr>
<tr>
<td>Hyams Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15%</td>
<td>21%</td>
<td>10%</td>
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<tr>
<td>2</td>
<td>46%</td>
<td>39%</td>
<td>50%</td>
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<td>27%</td>
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<td>60%</td>
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</tr>
<tr>
<td>3+4</td>
<td>40%</td>
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</tbody>
</table>

significantly worse survival at 2 (67 vs 94%), 5 (49 vs 89%), and 10 years (35 vs 86%, respectively) (p < 0.001, log-rank test).

Multivariate Cox regression of Kadish stages and Hyams grades (Table 2) demonstrated that Hyams Grades 3 and 4 (high grade) independently predicted poor survival and a more rapid decline to death (HR 4.83, 95% CI 2.0–11.6, p < 0.001). When accounting for Hyams grade, Kadish Stages B (HR 2.1, 95% CI 0.75–5.79, p = NS) and C (HR 4.81, 95% CI 0.64–36, p = 0.13) were no longer significant independent risk factors for patient survival, although there was a trend for Kadish Stage C to predict a more rapid progression to death. To further evaluate the usefulness of Kadish or Hyams grading, we tabulated the proportion of low- and high-grade Hyams histology found in each subgroup of Kadish stage (Fig. 1D). Of note, of those patients with Kadish Stage A tumors, 14% had high-grade Hyams lesions.

**Posttreatment Prognosis for Patients With High-Grade Tumors Receiving Adjuvant Chemotherapy**

As our results demonstrated that Hyams Grade 3 and 4 tumors had particularly poor prognosis, we wished to determine if adjuvant chemotherapy in this group provided any survival benefit. Thirty-four patients had Hyams Grade 3 or 4 EN and underwent surgery only (23 cases) or surgery with adjuvant chemotherapy (11 cases). In patients who received chemotherapy in addition to surgery, we observed a nonsignificant improvement in survival at 2 years (91 vs 68%) and 5 years (78 vs 47%, respectively) (p = NS, log-rank test) (Fig. 5 upper).

Fifty-four patients were available for a similar analysis including patients who received either surgery or surgery with radiotherapy compared with surgery with chemotherapy or surgery, radiotherapy, and chemotherapy. In patients receiving chemotherapy in addition to surgery or surgery and radiotherapy, compared with surgery or surgery and radiotherapy, we also demonstrated a nonsignificant improvement in survival at 2 years (89 vs 68%) and 5 years (75 vs 47%, respectively) (p = NS, log-rank test) (Fig. 5 lower).

**Discussion**

Due to the overall rarity of EN, the selection of appropriate prognostic guides and treatment methodologies has not been based on Class I or II data. Esthesioneu-
roblastoma has typically been managed first using staging to provide prognostic information preoperatively and then by surgery with adjuvant radiotherapy as the choice for definitive treatment.\textsuperscript{11,14,15,40,49,134} To address these outstanding issues, we collected a large pool of patient data and demonstrated several key elements that should help guide appropriate management of EN.

Clinical data that provide meaningful prognostic information help guide both the physician as well as the patient toward optimal disease management. For EN, multiple systems have been devised to determine a patient’s prognosis and appropriate therapeutic pursuit including Kadish stage, Hyams grade, Dulguerov/UCLA grade,\textsuperscript{49} and typical tumor staging strategy.\textsuperscript{47,50,83,94,134} The Kadish stage has been most uniformly used. The Hyams grade has been frequently binarized into low and high grades, consisting of Grade 1/2 and Grade 3/4. We found the Dulguerov/UCLA system has been infrequently used.

Our study demonstrated the prognostic importance of Hyams grades in EN. The Hyams grading scheme is composed of 4 grades based on a variety of histological features including architecture, mitotic activity, nuclear pleomorphism, rosettes, and necrosis.\textsuperscript{47,83} Grades 3 and 4 are defined by histological features that would be expected of aggressive tumors, such as nuclear pleomorphism, high mitotic activity, and necrosis, whereas low-grade tumors do not exhibit these features, having more preserved architecture as well as Homer-Wright pseudorosettes. Our data suggest that to convey maximum clinically relevant information, Hyams grade may be simplified to combine Grades 1 and 2 to a low-grade category and Grades 3 and 4 into a high-grade category, because these grades naturally cluster together in a survival analysis (Fig. 1C). Low-grade tumors appear to be essentially cured by resection (Fig. 1A) with no deaths occurring past 9 months postoperatively, and a survival of 89\% at all reasonable points of follow-up. High-grade tumors appear to be a distinct entity clinically, as the survival is only 47 and 31\% at 5 and 10 years, respectively.

There are several possible explanations underlying the dichotomous behavior of EN. It is possible that EN may have 2 distinct variants: one a low-grade variant cured by resection and the other an anaplastic variant associated with poor outcomes and a propensity to progress despite treatment. Another possibility is that these high-grade tumors are in fact not ENs, but rather misdiagnoses. Other malignant tumors of the sinonasal tract and nearby anatomical regions can be confused with EN including neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, pituitary adenoma, melanoma, and lymphoma.\textsuperscript{47} Cohen and colleagues\textsuperscript{39} demonstrated that, in a series of 12 consecutive patients referred to their center with the presumptive diagnosis of EN, only 2 patients were confirmed to actually have an EN. The diagnosis and differentiation of EN from other tumors includes judicious use of histological examination, immunohistochemical markers, and electron microscopy when necessary. Sinonasal undifferentiated carcinoma is an aggressive neoplasm arising from the same region as EN, and it carries a tendency for invasion, extremely poor prognosis, and treatment resistance.\textsuperscript{80,183} Thus, it is possible that the high-grade tumors seen in our review may represent other aggressive malignancies misdiagnosed as EN.

We also examined the more frequently used prognos-
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Our study showed that staging on its own contains useful prognostic information. Namely, Kadish Stage C tumors have significantly worse prognosis then Stage A tumors. However, when taken into consideration in conjunction with Hyams grading criteria, staging no longer significantly predicts survival of patients because Kadish Stage C largely reflects a subset of higher Hyams grade tumors. On the other hand, Hyams grading criteria independently predict survival, with high-grade tumors portending very poor prognosis. Kadish stage appears to have the advantage of being determined noninvasively by MR imaging, whereas Hyams grade requires surgical biopsy. However, because of the dramatic decrease in survival observed in high- versus low-grade tumors according to the Hyams system, it is advisable to obtain a biopsy whenever possible to determine a more powerful and accurate prognostic indicator to better guide treatment decisions. Furthermore, Fig. 1D demonstrates that 14% of tumors found to be Kadish Stage A will be of high Hyams grade on examination of biopsy specimen. Thus, relying solely on Kadish stage may miss some of the more aggressive tumors.

In this study, given the unsettled issue of radiotherapy’s role as either adjuvant or monotherapy, we also examined the role of radiotherapy as primary treatment and, importantly, as an adjunct to surgery. Our data suggests that radiotherapy alone provides suboptimal treatment when compared with surgery: 5-year survival for radiotherapy alone and resection alone is 52 and 78%, respectively (Figs. 2 and 3). We further demonstrated in a sample of nearly 700 patients that radiotherapy added no additional benefit to patients’ survival through 10 years of follow-up. This is in contrast to recommendations put forth by reports from smaller series and a meta-analysis, which were not able to achieve statistical significance. We further found that adjuvant radiotherapy did not confer any survival benefit to surgery in patients with Hyams Grade 2–4 tumors or to patients with Kadish Stage C disease. The use of adjuvant radiotherapy is thus not clearly supported by the literature but may have a role in specific cases. This is important because radiotherapy, if not indicated, in addition to its monetary cost carries with it clear associated morbidities including risk for radiation necrosis, radiation vascular and demyelinating injury, and neurological dysfunction. Larger prospective studies are needed to more definitively determine the utility of adjuvant radiotherapy for EN. In this regard, we performed a power calculation on our results to determine the number of patients needed to achieve a power of 0.8 in a prospective randomized control trial comparing treatment modalities. The minimum sample size needed was determined from the time of follow-up with maximal survival discrepancy (96 months) and at the outer limits of the 95% CIs for the 2 treatment groups. At these most extreme points, 100 patients would be needed in each treatment arm to achieve a power of 0.8. Alternatively, if the average survival statistic (the midpoint of the 95% CIs) at the same time point was used, then 425 patients would be required in each treatment arm to achieve a power of 0.8. Given the rarity of this tumor we believe these numbers would be prohibitively large to successfully complete such a trial. However, we hope that systematic reviews, such as this one, provide the impetus for the formation of consortia, such as the RTOG (Radiation Therapy Oncology Group), to consider trials designed to answer these important questions.

Based on our results demonstrating long-term durable tumor control in low-grade EN, as well as progression despite treatment in high-grade EN, we pursued further treatment-based analysis in this subgroup of patients with poor prognosis. We examined whether chemotherapy, in addition to surgery or surgery and radiotherapy, could play a beneficial role in patients with high-grade tumors and a poor prognosis (Fig. 5 upper). Although we did not have adequate numbers to effectively pursue this anal-

![Fig. 5. Kaplan-Meier curve depicting survival in patients who received chemotherapy in addition to surgery (upper) or surgery alone or surgery with radiotherapy (XRT) (lower). All patients in these analyses had high-grade Hyams pathology. The difference was not statistically significant.](image-url)
ysis, our data suggested promise for chemotherapy as adjuvant treatment for high-grade ENs. We found at least a 15–20% survival difference added by chemotherapy. This would require a trial with 100 patients in each treatment arm to achieve a power of 0.8. Our findings are in line with other published data indicating that this subgroup of patients may benefit from the addition of chemotherapy to resection. The University of Virginia and the Mayo Clinic have particularly convincing data, from large patient series, demonstrating significant benefit from the use of either preoperative or adjuvant chemotherapy in Stage C disease.

Although our results are a useful synopsis of the published literature, there are limitations to our study approach. First, our analysis can only reflect the quality of the composite studies utilized and may contain some source study bias. Second, because of the varied format of data presentation across studies we were not able to analyze or control for all variables of interest. Third, since not all data were reported for every patient, the analysis may have unintentionally introduced a degree of selection bias. Fourth, some of the variables reported and entered into our analysis may have interrater variability, such as histological grade, radiological grade, and the adequacy of radiation therapy or resection. Fifth, our method of disaggregated data compilation and Kaplan-Meier calculations do not allow for a formal meta-analysis.

Conclusions

We report the results of a summary of the published literature on the prognosis of EN after treatment with various modalities. Given the relative rarity of this tumor, this study aimed to accurately describe outcome characteristics using a data set that would be difficult to accumulate at a single center treating this tumor. Future research on the treatment of EN should focus on the relationship between extent of resection and outcomes, as well as investigating novel or improved treatment algorithms for anaplastic variants of EN.

Disclosure

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