A Population-Based Analysis of Nodal Metastases in Esthesioneuroblastomas of the Sinonasal Tract

Edward C. Kuan, MD, MBA; Hassan B. Nasser, MD; Ryan M. Carey, MD; Alan D. Workman, MTR; Jose E. Alonso, MD; Marilene B. Wang, MD; Maie A. St. John, MD, PhD; James N. Palmer, MD; Nithin D. Adappa, MD; Bobby A. Tajudeen, MD

INTRODUCTION

Esthesioneuroblastoma (ENB) is a rare malignant tumor widely believed to arise from olfactory neuroepithelium that accounts for approximately 3% to 6% of neoplasms of the sinonasal vault and paranasal sinuses.1–3 Although there are no specific symptoms pointing to a diagnosis of ENB, patients most commonly present with unilateral nasal obstruction and epistaxis.1 As a rare primary malignancy of the head and neck, considerable debate exists regarding definitive management guidelines owing to its variable biological activity and wide variety of staging systems. These issues are compounded by the fact that few individual clinicians or academic institutions will routinely encounter these patients, unless at a specialized skull base referral center.

Various staging classifications have been proposed to describe the clinical behavior of ENBs. The Kadish system, followed later by the modified Kadish system (with the addition of accounting for nodal and distant metastases), was first developed based on the extent of tumor in the sinonasal cavity, orbits, and brain.4 Dulguerov and Calcaterra later proposed staging utilizing extent of invasion based on radiographic imaging.5 The generally accepted treatment approach for these tumors involves a combination of surgery and radiation therapy, with surgical resection accomplished typically by way of transnasal transfacial craniofacial resection with craniotomy, transnasal transfacial craniofacial resection without craniotomy, or expanded endoscopic endonasal craniofacial resection, depending on tumor location and date of presentation.

OBJECTIVE: Esthesioneuroblastoma is an uncommon malignancy of the sinonasal tract arising from the olfactory epithelium. Surgical management of the primary site, often via an endoscopic approach, with or without adjuvant radiation, is often curative. There is growing but ultimately limited data regarding management of the neck and the risk of nodal metastases. In this study, we examine the incidence and patterns of esthesioneuroblastoma-related cervical nodal metastases using the Surveillance, Epidemiology, and End Results (SEER) database.

METHODS: The SEER registry was queried for all patients with esthesioneuroblastomas diagnosed between 1973 and 2012. Patient data was then analyzed with respect to age, sex, race, modified Kadish stage, grade, survival functions, and nodal disease including specific nodal basins.

RESULTS: Three hundred and eighty-one cases of esthesioneuroblastoma with information on nodal metastases were identified. The overall cervical nodal metastasis rate was 8.7%. Level II metastases were most common (6.6%). A total of 4.5% of cases presented with multiple positive nodal basins. Male sex (P = 0.009) and higher tumor grade (P = 0.009) correlated with the presence of level II metastases. There was no association of primary tumor site to the presence of nodal metastases (P > 0.05). The presence of nodal disease significantly predicted poorer overall (P = 0.001) and disease-specific survival (P = 0.017).

CONCLUSION: The incidence of nodal metastases in esthesioneuroblastoma at diagnosis is rare, and elective management of the neck remains controversial. Primary tumor site does not appear to predict metastases at specific nodal basins. Higher tumor grade may be a harbinger of eventual nodal metastases.

KEY WORDS: Esthesioneuroblastoma, olfactory neuroblastoma, nodal disease, metastasis, head and neck oncology.

LEVEL OF EVIDENCE: NA

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Addition of adjuvant radiotherapy has been shown to improve both local control rates as well as statistically significant differences in overall survival. In fact, a number of studies have demonstrated that patients treated with surgery and radiation have significantly improved locoregional control compared with patients treated with surgery alone, even in patients with a more locally advanced primary tumor. Adjuvant chemotherapy is sometimes added for high-grade, recurrent, or locoregionally advanced tumors.

Despite advances in surgical approaches and radiotherapy, the presence of regional and distant metastatic disease has been identified as one of the main challenges affecting long-term survival. Dulguerov et al. demonstrated that in patients with cervical lymph node metastases there is a significant difference in treatment success when compared to node-negative (N0) patients (29% vs. 64%). Although the importance of cervical lymph node metastases as a negative predictor of survival has been well established, knowledge concerning the lymphatic spread patterns of ENB is lacking. Furthermore, our understanding and treatment of ENB is currently limited to data generated by retrospective studies with limited numbers of patients. As such, there is no clear consensus regarding optimal elective management of the clinically and radiographically N0 neck. In this analysis, we intend to further characterize the lymphatic nodal metastatic patterns of ENB using a validated, large-sample, population-based database, and thus help provide evidence-based recommendations for treatment of the clinically negative neck.

**MATERIALS AND METHODS**

We retrospectively reviewed the incidence and patterns of cervical lymph node metastases in a cohort of patients with primary ENB of the sinonasal tract using the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (Rockville, MD). The SEER 18 database was queried to identify all patients with a diagnosis of olfactory neuroblastoma or ENB (histologic code 9522) between January 1, 1973, and January 1, 2012. Institutional review board approval is exempt for SEER studies due to the database being deidentified and publicly available.

Patient data including age, sex, race, tumor grade, overall survival, and disease-specific survival, as well as incidence and precise location of cervical lymph node disease, were reviewed. Overall survival (OS) was defined as beginning from the time of initial treatment to death from any cause. Disease-specific survival (DSS) was defined as the time from initial treatment to death from a cause unrelated to malignancy. Overall survival and DSS were estimated using the Kaplan-Meier method. Associations between categorical variables were determined using Spearman correlation testing. The log rank test was used to determine statistically significant predictors of survival on univariate analysis. Following univariate analysis, the multivariate Cox proportional hazards model was used to estimate the independent impact of nodal metastases on OS and DSS. Covariates with \( P < 0.20 \) on univariate analysis were included in the multivariate model. A \( P \) value of less than 0.05 was considered statistically significant for all tests. Statistical analyses were performed using SPSS 21 (IBM Corporation, Armonk, NY).

**RESULTS**

**Patient Demographics**

Three hundred and eighty-one total patients with diagnosis of ENB and information on presence of cervical lymph node metastases were identified. Of these, 225 (59%) were male and 156 (41%) were female. The average patient age was 52.8 ± 17.2 years. Two hundred and ninety-seven (78%) were Caucasian; 31 (8%) were African American; and 53 (14%) were of other unspecified ethnicity.

**Primary Site**

The primary tumor site was identified as being in the nasal cavity in 315 (83%) patients, in the maxillary sinus in 11 patients, in the ethmoid sinus in 33 patients, in the frontal sinus in three patients, in the sphenoid sinus in six patients, involving multiple sinuses in six patients, and was not otherwise specified in seven patients. Tumor grade was not available for all patients included in this cohort, but in patients with this information available, 26 patients had well-differentiated tumors; 86 patients had moderately differentiated tumors; 57 had poorly differentiated tumors; and 28 had undifferentiated tumors.

**Cervical Lymphatic Drainage**

Table I summarizes the nodal metastatic patterns of cases included in the current study. The overall incidence of cervical lymph node metastases was 8.7%. Metastases to the level II neck were found to be most common (6.7%), followed by level III (2.7%), and level I (2.1%). A total of 4.5% of cases presented with metastases to multiple lymph node basins, whereas 4.2% of patients had metastases in a single lymph node basin. No patients in the study cohort developed distant metastases.

| Table I. Patterns of Nodal Metastases in Esthesioneuroblastoma |
|------------------|------------------|
| Nodal Metastatic Patterns | Number (%) |
| Any cervical metastases | 33 (8.7%) |
| One nodal basin | 16 (4.2) |
| Multiple nodal basins | 17 (4.5) |
| Nodal basins (levels) | |
| I | 8 (2.1) |
| II | 25 (6.6) |
| III | 10 (2.7) |
| IV | 6 (1.6) |
| V | 3 (0.8) |
| VI | 0 |
| VII | 1 (0.3) |
| Facial | 0 |
| Parapharyngeal | 1 (0.3) |
| Parotid | 4 (1.1) |
| Suboccipital | 1 (0.3) |
Factors Predicting Cervical Lymph Node Metastases

Bivariate correlation revealed that both male sex \((P = 0.009)\) and high tumor grade \((P = 0.009)\) were statistically correlated with presence of level II metastases. There was no association between primary tumor site and the presence of nodal metastases.

Nodal Disease as a Predictor of Overall Survival and Disease-Free Recurrence

Table II illustrates the results of both univariate and multivariate regression analysis. On univariate analysis, the presence of nodal disease was a significant predictor of worse OS and DSS (Fig. 1). Interestingly, when factoring in other covariates, the presence of nodal metastases was no longer an independent predictor of either OS or DSS, although age and tumor grade were confirmed to be independent prognosticators. On post-hoc analysis, although higher tumor grade trended toward predicting cervical nodal metastases, this relationship was not statistically significant \((P = 0.058)\).

DISCUSSION

ENB is a rare primary malignancy of the sinonasal cavity, with an estimated overall 5-year survival being reported between 62\% to 86\%.\(^{11-13}\) Although advances in endoscopic endonasal approaches and radiotherapy have improved treatment options for patients, risk of locoregional or distant treatment failure remains high for some years following initial treatment. Prior studies have suggested that the presence of cervical lymph node metastases negatively impacts overall survival.\(^{1,14,15}\) However, a thorough understanding of the lymphatic spread patterns of ENB is currently lacking, and many studies have advocated different approaches to elective treatment of the N0 neck.\(^{6,14}\) Studies on the incidence of lymph node metastases have varied in the literature, with earlier work reporting rates of 5\% to 17\%.\(^{2,15,16}\) Delayed cervical metastases have been discovered for up to 12 years after initial treatment of the primary site in

### Table II

<table>
<thead>
<tr>
<th>Covariates Included</th>
<th>Overall Survival</th>
<th>Disease-Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of nodal disease</td>
<td>2.73 (1.48–5.04)</td>
<td>2.50 (1.18–5.31)</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.02–1.05)</td>
<td>1.02 (1.00–1.04)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.326</td>
<td>0.189</td>
</tr>
<tr>
<td>Grade</td>
<td>2.18 (1.55–3.05)</td>
<td>3.15 (2.01–4.92)</td>
</tr>
<tr>
<td>Presence of nodal disease</td>
<td>0.196</td>
<td>0.983</td>
</tr>
</tbody>
</table>

Hazard ratios and 95\% CIs are only included for those covariates that were statistically significant at the 0.05 level.

CI = confidence interval.

Fig. 1. Overall (left) and disease-specific (right) survival of patients with esthesioneuroblastoma based on presence of nodal metastasis \((n = 381)\). N+, presence of nodal metastases; N0 = no nodal metastases. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
up to 16% of patients.\textsuperscript{1,6} In one retrospective review, over 40% of patients developed delayed cervical metastases after initially only undergoing local treatment.\textsuperscript{9} One systematic review reported a 60% mortality rate in patients with recurrence in the neck.\textsuperscript{2}

However, robust data demonstrating the efficacy of elective radiotherapy or neck dissection in patients with ENB is lacking, and studies are generally limited by relatively short follow-up periods or small sample sizes. The SEER database, as a population-based database, affords the advantage of providing adequate statistical power in studying rare diseases such as ENB. Indeed, the SEER database has been previously utilized in attempting to better understand determinants of survival and the tumor behavior exhibited by ENB, as well as to examine nodal metastatic patterns in sinonasal malignancies. Jethanam et al. first reported that the presence of nodal metastases was a predictor of poor survival in a cohort of patients with ENB who were included in the SEER registry prior to 2002.\textsuperscript{11} Ahn et al., in two separate studies, aimed to determine patterns of nodal metastasis in squamous cell carcinoma of the nasal cavity and maxillary sinus, sinonasal small cell carcinoma, and sinonasal undifferentiated carcinoma, in order to elucidate the role of elective treatment of the neck in these cases.\textsuperscript{17,18} No other studies have since explored the topic of nodal status in ENB, and the current study is the first to provide an in-depth analysis on this controversial question through a population-based approach.

Based on the results, the current study suggests that the overall incidence of cervical lymph node metastases at the time of diagnosis of ENB is quite rare (less than 10%). This data is also consistent with other work demonstrating that the level II lymph node basin is the most common site of metastasis.\textsuperscript{14,15,19} Furthermore, more than half of patients with nodal disease had multi-level involvement, which is also consistent with the findings reported by Banuchi et al.\textsuperscript{15} Given this low incidence of nodal disease, it is not surprising to understand the difficulty in developing standardized guidelines for management of the N0 neck in ENB. At this point, no recommendation can be made about elective neck dissection or radiation therapy for the N0 neck, although continued surveillance for future development of metastatic disease would be crucial in gaining long-term disease control.

On univariate analysis, consistent with Jethanam et al.’s findings, the presence of cervical lymph node metastasis was associated with poorer OS and DSS in our cohort as well.\textsuperscript{11} However, this relationship did not hold on multivariate analysis when considering two other important independent prognosticators—age and tumor grade—both found to be associated with the presence of cervical metastases. For most head and neck malignancies, advanced age is a powerful negative prognosticator, likely due to associations with medical comorbidities and overall health status not captured by the SEER data. However, the current study found that tumor grade was an even more impactful confounder of survival as a function of nodal disease. Tajdeen et al. previously reported on the significance of advanced tumor grade as a predictor of survival in ENB using the SEER database.\textsuperscript{20} Another multi-institutional study by Nalavenkata et al. found a similar trend between neck metastasis and tumor grade, with those patients presenting with neck disease initially having higher tumor grade overall.\textsuperscript{21} Taken together, these findings suggest that there may be a potential role in stratifying long-term surveillance of ENB patients by initial tumor grade on biopsy or resection because these patients may be at more risk to develop regional recurrence. An example model for implementing this would be to have patients with higher grade tumors receiving more frequent follow-up endoscopies and neck exams and consideration of neck imaging as well as routine radiographic evaluation of the resection bed.

There are several limitations to the current study. First, lymph node status in the SEER registry is determined through pathologic analysis, and thus all estimates of patterns of nodal metastases are based on absolute pathologic data and may underestimate the actual incidence of metastatic disease (i.e., occult and radiographic metastases). Second, SEER does not include data on timing of development of nodal disease (i.e., initial versus delayed), limiting Kaplan-Meier analysis, especially for diseases with delayed recurrences such as ENB. Third, analysis of the association between tumor grade and nodal metastases is limited by incomplete data in which the number of cases with adequate information on tumor grade was relatively low, thus decreasing statistical power. The SEER database also does not include specific tumor variables, such as the Hyams grading system, in reporting for ENB cases. Thus, it is possible that the four-tiered tumor grading system as listed does not necessarily correlate with the four-tiered Hyams grading system, although a previous SEER study established a robust relationship between tumor grade and survival in ENB. Fourth, though uncommon, ENBs may metastasize to the contralateral neck, and this information is not included in the SEER database.\textsuperscript{19,22} Fifth, SEER does not specify laterality for malignancies, especially in consideration of differing strategies between treatment of unilateral and bilateral ENB.\textsuperscript{23} Ultimately, prospective multi-institutional studies evaluating various surgical and radiotherapy approaches should be considered to determine the optimal strategy to treatment of the N0 neck.

**CONCLUSION**

In this population-based analysis, the incidence of nodal metastasis in ENB is relatively low, and no recommendation can be made about elective treatment of the N0 neck. The most common nodal basin involved is the level II neck. As suggested by some prior studies, higher tumor grade may suggest more aggressive behavior and manifest in the form of nodal metastases.

**BIBLIOGRAPHY**