Dear Colleagues,

The AHNS Skull Base Surgery Section is very pleased to present its first AHNS Journal Club Issue. Our ultimate goal for the Skull Base Surgery Section issues will be to provide insight into contemporary management of skull base tumors through themed issues. This particular issue will address controversies in the recently published literature on nodal metastases in olfactory neuroblastoma (ONB) by reviewing the recently published literature.

Traditionally, elective treatment of cervical nodal metastases for head and neck primaries is advocated when the risk of occult metastases reaches > 20%. However, sinonasal malignancy (as a group) has been shown to have a lower incidence of cervical metastases on presentation making elective treatment of the neck in sinonasal malignancy controversial and somewhat rare. With respect to ONB, the incidence of nodal metastases at the time of diagnosis (modified Kadish stage D) is low, approximately 8%.\textsuperscript{1,2} In spite of this rare incidence at diagnosis, up to 20.2% of patients with ONB will develop nodal disease within 5 years of diagnosis.\textsuperscript{3}

Single institution studies have tried to identify risk factors for nodal recurrence (positive margins, modified Kadish C Staging, Hyam’s grade, the presence of dural invasion) and identify patients who might benefit from elective treatment of the neck.\textsuperscript{4-6} This has led to more recent studies examining elective treatment of high-risk nodal basins including retropharyngeal, level IB and level II lymph nodes.\textsuperscript{7} Elective neck irradiation provides 100% locoregional control in small, single-institution series, but was associated with worse overall survival in patients over 50. Salvage treatment of the delayed nodal recurrence has 5-year LRC rates of 30-80% and is
highest when both surgery and radiation are used.\textsuperscript{3,6} It remains unclear whether or not elective treatment of the neck reduces distant metastasis or has meaningful impact on survival as metastases are largely found in the brain, leptomeningeal spine, or the spinal skeleton.\textsuperscript{6,7}

In this issue, we present recent evidence regarding nodal metastases in ONB. It is suggested you read them in the order presented. We believe this evidence may impact future trends in the treatment of ENB and hope you enjoy this issue. Comments are welcome and can be sent to meghan.turner@hsc.wvu.edu.

Sincerely,

Meghan T. Turner, MD
Assistant Professor of Head and Neck Surgery
West Virginia University Health Sciences Center

Harishanker Jeyarajan, MD
Assistant Professor of Head and Neck Surgery
University of Alabama Birmingham School of Medicine

Marilene Wang, MD
Professor of Head and Neck Surgery
Ronald Reagan UCLA Medical Center

Shirley Y. Su, MBBS
Associate Professor of Head and Neck Surgery
The University of Texas M.D. Anderson Cancer Center

Patterns of Regional and Distant Metastasis in Esthesioneuroblastoma

Victoria E Banuchi, MD Laura Dooley, MD, Nancy Y Lee, MD, David G. Pfister, Sean McBride, MD MPH, Nadeem Riaz, MD, Mark H Bilsky, MD, Ian Ganly, MD, Jatin P Shah, MD, Dennis H Kraus, MD, and Luc GT Morris, MD MSc

From The Laryngoscope, July 2016

Objectives/hypothesis
To define the incidence and risk factors of metastatic disease and the effectiveness of salvage therapy in esthesioneuroblastoma (ENB).

Study design
Retrospective analysis of 57 patients presenting from 1979 through 2009.

Methods: Cumulative incidence of neck failure, distant failure, and survival were assessed using the Kaplan-Meier method.

Results: Overall survival for all patients was 85% at 5 years and 75% at 10 years. Overall survival was negatively impacted by intracranial tumor extension (P < 0.001), positive resection margins (P = 0.05), and neck metastases (P = 0.017). Neck lymph nodes were not routinely electively irradiated during this time period. Nodal metastases developed in 17% of patients at a median time of 60 months. Kadish stage was not associated with a risk of nodal metastasis (P = 0.78). After treatment for nodal recurrence, locoregional control was achieved in 78% of patients. Of patients developing nodal recurrence, more than half developed distant metastases. The cumulative incidence of distant metastasis was 39% at a median time of 40 months. Patients who presented with Kadish stage C or D had a significantly increased risk of distant failure (P < 0.001). In patients developing nodal (P = 0.017) or distant metastasis (P = 0.001), the probability of survival was significantly decreased.

Conclusion: Regional and distant metastases in patients with esthesioneuroblastoma occur in a delayed fashion and negatively impact survival. Neck nodal recurrence may be a harbinger of distant metastases. At the Memorial Sloan Kettering Cancer Center, New York, New York, we now treat the majority of ENB patients with elective nodal irradiation. However, the chief obstacle to long-term cure is distant metastases.


Keywords: Esthesioneuroblastoma; metastasis; neck dissection; olfactory neuroblastoma.

Summary Statements:
- The incidence of nodal disease at diagnosis was 11%. The incidence of delayed nodal metastases in 17% at median time to recurrence of five years. The cumulative incidence of nodal metastases (both presenting with metastases and developing metastases) over 10 years in olfactory neuroblastoma was 40%.
Salvage treatment of delayed metastases result in regional control rates of 78% and 50% longterm survival due to the development of distant metastases.

Delayed distant metastases develop in 39% of patients of patients with delayed neck disease within 40 months.

**Strengths**

- This study on studies on olfactory neuroblastoma that provides long-term survival data of 85% OS at 5 years. And 75% OS at 10-years.
- 10-year disease free survival was significantly related to Kadish Stage at presentation (p=0.001). Specifically, 10-year DFS was 69% for Kadish Stage A, 56% for Kadish Stage B, 46% for Kadish Stage C and 0% for Kadish Stage D.
- This is the first study to exam the effect of regional recurrence on long-term survival and suggests that 38% of patients with regional recurrence will go on to development distant metastases in spite of treatment and regional control.

**Weaknesses**

- While this is one of the largest series on olfactory neuroblastoma outcomes (51 patients), there are still few patients from which to draw conclusions (51).
- This is a single-institution’s tertiary referral center’s results over a long period of time during which the surgical approach and radiation techniques and use of adjuvant therapies was not homogeneous.
- The results of this study are not necessarily translatable to other centers.

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

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

*From The Laryngoscope, May 2019*

**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.

**Summary statements:**
- In the SEER database, which covers 34.6% of the US cancer registries, the overall incidence of nodal metastases in the 381 patients with olfactory neuroblastoma was 8.7%.
- Level II neck metastases were the most common site of metastases (6.6%).
- High tumor grade was related to the presence of level II neck metastases.

**Strengths**
- Population based study that draws from multiple centers (both academic and community) and provides accurate survival in the population, when single institution studies may have skewed survival based on advanced disease or more aggressive management strategies.
- This study includes a larger number of patients than any single or multi-institutional study can accrue and therefore a more accurate assessment of the pathologic incidence of presence of nodal metastases at diagnosis.
- This study demonstrates the adverse effect of nodal metastases on survival and disease-free survival in a large population but was not an independent predictor as this both age and grade were associated worse survival.

**Weaknesses**
- This study may underestimate the rate of nodal metastases because the SEER registry only provides information on pathologically positive nodes. It does not provide information about clinically or radiographically positive nodes.
- This study may not provide accurate information on the development of delayed metastases (after initial staging) and this is of interest as up to 20% of patients may develop delayed onset metastases from clinically or radiographically occult nodal metastases at the time of diagnosis.
- While grade was associated with the presence of level II metastases, the SEER database does not provide information on Hyam’s grade, which is most often used to assess risk of nodal metastases and distant spread in olfactory neuroblastoma.
There are patients in this series who had primary tumors of the maxillary sinus, sphenoid sinus, and frontal sinus. This is not typical of olfactory neuroblastoma which originates in the nasal cavity and spreads to these other sites. It brings into questions whether or not other high-grade sinonasal malignancies have been included.

**The Role of Elective Nodal Irradiation for Esthesioneuroblastoma Patients with Clinically Negative Neck**


*From the Practical Radiation Oncology, July-August 2016*

**Abstract:**

**Purpose:** Although adjuvant radiation to the tumor bed has been reported to improve the clinic outcomes of esthesioneuroblastoma (ENB) patients, the role of elective neck irradiation (ENI) in clinically node-negative (N0) patients remains controversial. Here, we evaluated the effects of ENI on neck nodal relapse risk in ENB patients treated with radiation therapy as a component of multimodality treatment.

**Methods and materials:** Seventy-one N0 ENB patients irradiated at the University of Texas MD Anderson Cancer Center between 1970 and 2013 were identified. ENI was performed on 22 of these patients (31%). Survival analysis was performed with focus on comparative outcomes of those patients who did and did not receive ENI.

**Results:** The median follow-up time for our cohort is 80.8 months (range, 6-350 months). Among N0 patients, 13 (18.3%) developed neck nodal relapses, with a median time to progression of 62.5 months. None of these 13 patients received prophylactic neck irradiation. ENI was associated with significantly improved regional nodal control at 5 years (regional control rate of 100% for ENI vs 82%, P < .001), but not overall survival or disease-free survival. Eleven patients without ENI developed isolated neck recurrences. All had further treatment for their neck disease, including neck dissection (n = 10), radiation (n = 10), or chemotherapy (n = 5). Six of these 11 patients (54.5%) demonstrated no evidence of further recurrence with a median follow-up of 55.5 months.

**Conclusion:** ENI significantly reduces the risk of cervical nodal recurrence in ENB patients with clinically N0 neck, but this did not translate to a survival benefit. Multimodality treatment for isolated neck recurrence provides a reasonable salvage rate. The greatest benefit for ENI appeared to be among younger patients who presented with Kadish C disease. Further studies are needed to confirm these findings.
**Summary:**
- Single institution retrospective review of patients with esthesioneuroblastoma, to determine whether elective nodal radiation (ENI) of N0 patients resulted in any change in outcomes.
- No patients who underwent ENI developed nodal disease in the neck; however ENI did not confer a survival benefit.
- Patients who did not receive ENI who developed neck recurrence were able to be salvaged, and over 50% had no further recurrence, with a median follow-up of 55 months.

**Strengths:**
This is one of the largest single institutional studies of treatment of the N0 neck in patients with esthesioneuroblastoma. Patients were followed for a relatively long follow-up period of 6-350 months. As a single institution study, the clinical and pathologic records were able to be examined for detailed information about staging, surgery, pathology, radiation dose and technique, patterns of failure, and salvage treatments, unlike in database studies or systematic reviews.

**Weaknesses:**
Because of the rarity of this tumor type, single institution series are of limited size. In this study, there were 22 patients out of 71 who underwent ENI. Information is not provided as to how the decision was made to irradiate this cohort of patients, although it appeared to be more commonly given for Kadish C patients. The time period of the review (1970-2013) encompassed a variety of changes in surgical and radiation techniques, as well as chemotherapy agents, which increases the heterogeneity of the population and potentially impacts outcomes. Patients with esthesioneuroblastoma may develop recurrence at the primary site or in the neck more than 10 years out; therefore, long follow-up is necessary to determine true survival outcomes.
Results:
Thirteen studies met inclusion criteria with information regarding the association of neck recurrence and mortality, and 15 studies had data associating neck recurrence and Kadish stage. The neck recurrence rate was 14.1% in studies analyzing mortality. Among those patients who developed regional metastases, mortality was 60%. Of patients without regional recurrence, the mortality rate from disease was 26% (P < 0.0001) and overall mortality was 32% (P < 0.0001). The rate of neck recurrence within each Kadish stage was 0%, 11%, 21%, and 18% for Kadish stages A, B, C, and D, respectively. The trend toward an increased incidence of neck recurrence from stage A to stage D is statistically significant, with P value 0.003.

Conclusion:
The rate of neck recurrence in esthesioneuroblastoma is close to 15%. There is a strong association of recurrence with Kadish stage B and C. Mortality from disease in patients with recurrence in cervical lymph nodes is significant when compared to those who never develop neck disease. Prospective studies are needed to evaluate a potential role for elective neck dissection versus elective neck radiation for patients with esthesioneuroblastoma.

Summary:
- A systematic review was performed to look for the incidence of neck recurrence after treatment for esthesioneuroblastoma, association with Kadish stage, and outcomes for patients who develop neck recurrence.
- The neck recurrence rate was 14.1%, with strong association with Kadish stage B and C.
- Mortality rate in patients who develop regional metastases was 60%, while the mortality rate in patients without regional disease was 26%.

Strengths:
As esthesioneuroblastoma is a rare malignancy, single institution series are small, and systematic reviews allow analysis of data from multiple institutions. Treatment of the N0 neck remains controversial, and this analysis helps to give perspective on the incidence of neck recurrence, and the outcomes for patients who do develop recurrence in the neck.

Weaknesses:
Cause of mortality and details about the treatment of the neck recurrences were not available, to determine whether patients died from their disease, or whether salvage treatment of neck recurrence was effective. The role for elective treatment of the N0 neck remains unclear, as only a few patients in this review underwent elective nodal irradiation. The role for elective neck dissection for an N0 neck is likewise unclear. Further prospective studies would be ideal, but challenging in light of the rarity of this malignancy.
Dural Invasion Predicts the Laterality and Development of Neck Metastases in Esthesioneuroblastoma

John P Marinelli, Jeffrey R Janus, Jamie J Van Gompel, Michael J Link, Eric J Moore, Kathryn M Van Abe, Brandon W Peck, Christine M Lohse, Daniel L Price


Objectives: Neck metastases in patients with esthesioneuroblastoma (ENB) constitute the most significant predictor of poor long-term survival. Recently, researchers discovered the existence of dural lymphatic channels that drain to the cervical lymph nodes. From this physiologic basis, we hypothesized that patients with ENB who develop dural invasion (DI) would exhibit a proclivity for neck metastases.

Design Retrospective review.

Setting Tertiary referral center.

Participants All patients treated for ENB from January 1, 1994 to December 31, 2015.

Main Outcome Measures Incidence, laterality, and recurrence rate of neck metastases by DI status.

Results: Sixty-one patients were identified (38% female; median age 49, range, 10-80), 34 (56%) of whom had DI and 27 (44%) did not. Of patients with DI, 50% presented with or developed neck disease following treatment compared with just 22% of those without DI (p = 0.026). Bilateral neck disease was more common in patients with DI (11/34, 32%) compared with those without (2/27, 7%) (p = 0.018). Five-year regional recurrence-free survival rates were 88% for those without and 64% for those with DI (p = 0.022). Kadish C patients with DI were more likely to develop regional recurrence when compared with Kadish C without DI and Kadish A/B (p = 0.083). Further, Kadish C patients with DI displayed worse overall survival than Kadish C without DI and Kadish A/B. Kadish D patients displayed the worst overall survival. The difference in overall survival among these four groups was significant (p < 0.001).

Conclusion: DI by ENB is associated with increased incidence of cervical nodal metastases, bilateral neck disease, worse regional recurrence-free survival, and poorer overall survival. These data support the division of Kadish C by DI status.

Summary statements

- Patients with DI exhibited over a twofold elevation in the incidence of neck metastases and significantly worse regional recurrence-free survival rates when compared with patients without DI.

- Bilateral neck disease was almost five times as common in patients with dural invasion.

- Dural invasion may predict neck metastases independent of Hyams’ grade.
**Strengths**

- Novel Study that provides evidence of dural invasion as an independent risk factor for nodal metastasis.
- Study that provides evidence of dural invasion as a risk factor for decreased recurrence free survival.
- Study addresses the controversy of unilateral versus bilateral neck metastasis.

**Weaknesses**

- Small retrospective analysis of 63 patient with variable follow-up durations. The small number of patients in this study prohibits analysis by margin status.
- This study is based on intraoperative pathologic sampling of dural margins which may be incomplete.

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**Olfactory Neuroblastoma: Fate of the Neck--A Long-term Multicenter Retrospective Study**


*From the Otolaryngology and head and neck surgery, February 2016*

**Abstract**

**Objective:** Olfactory neuroblastoma and the management of neck disease has posed considerable challenges to the treating physician. The aims of the study were to determine the incidence and factors influencing neck disease and to identify at-risk patients with cervical node-negative disease at presentation.

**Study design:** Multicenter case series with retrospective chart review.

**Setting and subjects:** In sum, 113 patients with a histopathologic diagnosis of olfactory neuroblastoma across 6 tertiary hospitals in Australia and the United States.

**Methods:** Treatment modalities for the primary site and neck included surgery, radiotherapy, and combined therapy. Treatment outcomes were measured in relation to date of primary treatment, and long-term follow-up was recorded. Disease-free survival was calculated as time for patients to develop delayed neck disease following primary treatment.

**Results:** A total of 113 patients (46 females, 49.7 ± 13.2 years) were identified with a median follow-up of 41.5 months (interquartile range, 58.2); 7.1% of patients presented with primary neck disease, while 8.8% of patients presented with delayed neck disease. Neck disease was present in patients with Hyams grade II (22.2%), III (55.6%), and IV (22.2%) lesions ($\chi^2(2) = 5.66, P = .13$). Histologic grade was higher in patients with primary neck disease ($\chi^2(2) = 16.22, P$
Positive surgical margins were associated with a higher risk of delayed neck disease compared with clear surgical margin (17.9% vs 5%, P = .034).

**Conclusion:** Neck metastasis is an important clinical consideration for olfactory neuroblastoma at presentation and in surveillance. Primary treatment of the neck could be considered in select patients. Long-term surveillance of the neck and primary site is essential.

**Summary Statements:**
- 15.9% of patients developed nodal disease with 8.8% presenting as delayed
- Hyam’s grade was comparatively higher in those that presented with primary neck disease vs delayed
- A positive surgical margin significantly increased the risk of delayed nodal disease (17.9% Vs 5%)

**Strengths:**
- Relatively large retrospective cohort of 113 patients across 6 international centres
- Correlating clear margin status with statistically significant reduction in delayed nodal recurrence
- Correlating primary nodal disease with more aggressive biologic behaviour
- Satisfactory median follow up of 41.5 months

**Weaknesses:**
- No clear, uniform method of determining nodal status
- Inconsistent use of adjuvant radiation across centres