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Patterns of regional and distant metastasis in esthesioneuroblastoma

Victoria E Banuchi, MD^{1,2,*}, Laura Dooley, MD^{1,*}, Nancy Y Lee, MD³, David G. Pfister⁴, Sean McBride, MD MPH³, Nadeem Riaz, MD³, Mark H Bilsky, MD⁴, Ian Ganly, MD¹, Jatin P Shah, MD¹, Dennis H Kraus, MD², and Luc GT Morris, MD MSc¹

¹Head and Neck Service, Department of Surgery; Memorial Sloan Kettering Cancer Center, New York, NY

²North Shore-LIJ Cancer Institute, New York, NY

³Department of Radiation Oncology; Memorial Sloan Kettering Cancer Center, New York, NY

⁴Department of Medicine, Head and Neck Oncology Service; Memorial Sloan Kettering Cancer Center, New York, NY

⁵Neurosurgery; Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Objective—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 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 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.

Corresponding Author: Luc Morris MD MSc FACS, Head and Neck Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Phone: 212-639-3049, Fax: 212-717-3278.

*These authors contributed equally.

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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 MSKCC 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; olfactory neuroblastoma; neck dissection; metastasis

INTRODUCTION

Esthesioneuroblastoma (ENB), or olfactory neuroblastoma, is a rare tumor derived from olfactory neuroepithelium. It is responsible for approximately 6% of cancer cases in the nasal cavity and paranasal sinuses^{1,2,3}.

In most cases, ENB is treated with a combination of surgery and adjuvant radiation. Before the advent of craniofacial resection, a complete oncologic resection of these tumors was rarely achieved, leading to a 5-year survival of 35% or less⁴. Recent advances in both surgical and radiation techniques have led to improved survival and local control. Esthesioneuroblastoma is therefore now considered a potentially curable sinonasal malignancy, even when presenting with locally advanced disease⁵. As patients are now surviving longer, a larger number of patients have been observed to develop metastatic disease, either regional or distant. This observation has led to a growing interest in understanding the patterns and risk factors associated with the development of metastases.

Our current understanding of the metastatic behavior of esthesioneuroblastoma is largely based on small retrospective series, due to the rarity of this tumor. The incidence of neck metastases at presentation has been reported to be low, approximately 5–8%⁶. However, the probability of developing subsequent recurrence in neck nodes has been reported to be 20–25%⁶. Similarly, the incidence of distant metastases at presentation is low, about 7%^{7,8}, but reaches up to as high as 25% during follow up^{7–9}. It is unclear if these data are generalizable to all ENB patients, given that these incidence rates are based on selected patients, some of whom may have been referred to specialized centers for management of recurrent or metastatic disease. These data have generated controversy regarding the optimal management of patients with esthesioneuroblastoma at the time of index treatment, particularly with regard to questions such as management of the nodal basins and the appropriate use of systemic therapy.

Our objective was to analyze a continuously followed cohort of patients treated for esthesioneuroblastoma at Memorial Sloan Kettering Cancer Center (MSKCC) over three decades, in order to comprehensively define the patterns, timing and outcomes of regional and distant metastases. Here, analyzing the outcomes of 57 patients, we identify factors associated with the development of regional or distant metastases, and report the risks of nodal or distant metastasis among patients followed from the time of their initial treatment.

MATERIALS AND METHODS

We obtained IRB approval to retrospectively analyze data from 57 patients presenting to Memorial Sloan Kettering Cancer Center (New York, NY), for treatment of esthesioneuroblastoma between 1979–2009. Five patients with incomplete staging information or pathology not reviewed at MSKCC were excluded. All patients were staged clinically/radiographically according to the Modified Kadish system (Table 1), which we have previously shown to have prognostic value. Kaplan-Meier survival analysis was performed to determine overall (OS) and disease-free survival (DFS), and cumulative incidence of regional/distant metastases. OS was calculated from the day of diagnosis. DFS was defined as the length of time after diagnosis until either disease recurrence or death. Patients without recurrence or death were censored at last followup.

Analysis of treatment and outcomes were based on the 43 patients who presented newly diagnosed and untreated. Metastasis probabilities were based on the cohort of patients who presented de novo to MSKCC for index treatment, without tregional/distant metastases, and remained under continuous followup at MSKCC. The probability of nodal recurrence was based on 42 patients who presented to MSKCC clinically and radiographically node-negative (cN0). Survival and recurrence outcomes were compared using the log-rank test with $\alpha=.05$.

RESULTS

Of 57 patients, 41(72%) were men and 16(28%) women; with median age 53 years (range 14–84). Median follow up time was 68 months. At presentation, 42(74%) of patients had nasal obstruction, 26(46%) had epistaxis, 13(23%) had anosmia, 5(9%) had epiphora, 4(7%) had proptosis and 2(4%) presented with diplopia. In 10 cases (17%), ENB was diagnosed after endonasal surgery. Modified Kadish stage (Table 1) at presentation was A in 13(23%), B in 20(35%), C in 19(33%), and D in 5(9%). At presentation, 21(37%) patients had intracranial tumor extension, and 7 patients had intraorbital extension, of which 5 had concurrent intracranial extension. Five patients presented with clinically apparent nodal metastases and one patient presented with distant metastases (to bone).

Forty-three patients presented untreated to MSKCC: 28 received all subsequent treatment at MSKCC. Of 29 who only received a portion of treatment at MSKCC, 15 underwent surgery, 5 received adjuvant radiation and 9 were treated only for recurrent disease. Most patients (43, 75%) were initially treated with surgery followed by radiation therapy. Nine (17%) patients were treated with surgery alone, for small localized tumors (5 Kadish A and 4 Kadish B). Four (7%) patients were treated without surgery (radiation or chemoradiation) due to unresectable disease. In total, 53 (92%) patients received some form of surgical treatment. Of patients undergoing surgical resection, 41 (77%) had an open operation (anterior craniofacial or subcranial approach), 6 (11%) had a transcranial/endoscopic-assisted approach, 4 (8%) had an entirely endoscopic resection, and 2 (4%) had craniotomy alone.

During this time the general treatment regimen was primary surgery followed by post-operative radiation to the primary site (median dose 5580cGy, range 3420–6600). Elective neck irradiation (ENI) to the node-negative neck was not routinely administered, with only one patient (out of 52 patients presenting cN0) receiving ENI.

Of the patients who presented untreated and received all treatment at MSKCC, OS was 85% at 5 years and 75% at 10 years. DFS was significantly associated with Kadish stage (Figure 1). Factors significantly associated with OS were intracranial tumor extension ($p<0.001$), positive resection margins ($p=0.05$), and presentation with nodal metastases ($p=0.017$), consistent with published analyses from the International Collaborative Study on skull base malignancy¹⁰. Age, sex, stage, type of surgery and use of adjuvant radiation were not significantly associated with OS.

Neck nodal recurrence

Of 43 patients presenting untreated to MSKCC, 5 (11%) had clinical/radiographic evidence of neck metastasis (cN+). Three had neck dissection, and 2 did not have surgery due to unresectable primary tumor, and were treated instead with palliative chemoradiotherapy. They both subsequently died of disease. All 5 patients presenting cN+ developed central nervous system metastases; at last follow up, 4 patients had died of disease and 1 patient was alive with distant metastases.

Of the 52 patients who were cN0 at the time of initial treatment, 1 patient received ENI. Eleven patients subsequently developed nodal metastases (cumulative incidence via Kaplan-Meier, 40% at 10 years). The median time to neck failure was 60 months (range 17–107). Modified Kadish stage at presentation was not associated with the probability of developing neck metastases ($p=0.78$) (Figure 2).

Of the 11 patients who developed neck nodal metastases, 10 had surgically resectable recurrent disease, and 8 ultimately had salvage surgery. Two had a neck dissection and 6 had a neck dissection followed by radiation. Three of the 11 patients with nodal recurrence did not undergo surgical salvage: 2 had synchronous local and distant disease, and one patient developed synchronous unresectable nodal disease and distant recurrence at 36 months after initial presentation. Seven of 8 (87%) patients who underwent attempted surgical salvage were alive 2 years after recurrence. Of these 8 patients, 6 remained free of locoregional disease during this time. One patient experienced a second recurrence in parotid lymph nodes, and one patient experienced bilateral neck recurrence as well as recurrence in retropharyngeal lymph nodes. At time of last followup, 50% (4/8) of the patients undergoing surgical salvage for neck failure remained without evidence of disease with median followup of 57 months, 38% (3/8) died of disease and 12% (1/8) were alive with disease. Of the patients who died of disease after developing neck metastases, the cause of death for all patients was central nervous system metastases; specifically, leptomeningeal disease.

Eight patients undergoing therapeutic neck dissections for isolated neck recurrence had sufficient pathologic data available to delineate nodal level involvement. Seven (88%) of the patients had disease in level II, 4 (50%) level I, 4 (50%) level III, 3 (38%) level IV, 1 (13%)

level V and 2 (25%) retropharyngeal (Figure 5). Half of these patients had disease in 3 or more nodal levels.

To calculate the probability of neck recurrence in patients presenting cN0, we separately analyzed 42 patients who were cN0 at presentation, had no previous treatment, and who received primary therapy at MSKCC with continuous uninterrupted follow up. Among these 42 patients, 7 developed neck recurrence, resulting in an incidence of 17% at 10 years (Figure 3). Median time until recurrence was 60 months (range 1–107 months). Recurrence in the neck was associated with significantly poorer survival compared to patients who did not experience recurrence (17% vs 80% at 15 years, $p=.017$) (Figure 4).

Distant Metastases

The incidence of distant metastases at presentation in our cohort was 1.7% (1/57). Thirteen of 57 patients developed distant metastases after primary treatment. Kadish stage at presentation was significantly associated with the probability of developing distant metastatic disease, $p=0.008$ (Figure 6). In 62% (8/13), these were CNS metastases: 6 patients developed brain metastasis and 4 developed leptomeningeal involvement of the spine. Three patients developed bone metastases (all had disease in the spine with the hip and rib being additionally involved in 2). One patient developed dermal metastases. The median time to distant failure was 40 months (range 9–134 months). The cumulative incidence of distant metastases in patients who presented M0 was 39%. The cumulative incidence of distant metastases was significantly higher in patients presenting with more advanced Kadish stage (early stage A/B, 20% vs. advanced stage C/D, 75%; $p=0.0001$). The survival of patients with distant metastases was significantly decreased when compared to patients not experiencing distant failure (42% vs 92% at 5 years, $p=0.001$).

DISCUSSION

Modern treatment regimens including skull base surgery and advanced radiotherapy techniques have permitted high rates of local control for patients with esthesioneuroblastoma. However, regional and distant metastases, sometimes developing years after index treatment, remain significant obstacles to long term survival. Varying rates of regional and distant recurrence have been reported in a number of small cohort studies. Factors associated with recurrence remain poorly defined. Improved understanding of these factors will be helpful in informing decisionmaking with regard to elective treatment of the neck and adjuvant therapy in patients with esthesioneuroblastoma.

Currently, recommendations for treatment are based on an observed survival advantage with multimodality therapy¹¹. Surgery is favored as first line treatment followed by adjuvant radiation to the primary site¹². However, the optimum treatment of the N0 neck remains unclear. The reported incidence of neck recurrence in ENB patients varies widely in the literature with reports ranging from 15–33%^{13–17}. To some degree, these numbers vary based on patient cohort and analysis methodology. The rate of recurrence is likely to be overestimated in referral center cohorts, which may be enriched for patients referred to a center after the development of recurrence. Studies not using the Kaplan-Meier method to quantify recurrence rate will tend to underestimate the true incidence. In our series, the

incidence of neck metastasis at presentation was low (8%), as anticipated. The incidence of subsequent recurrence in the initially N0 neck was 17%. We did not identify an association between Kadish stage at presentation, and the risk of nodal recurrence.

Our findings are consistent with another contemporary cohort from MD Anderson Cancer Center, in which the neck recurrence rate was 18%¹⁸. The risk of nodal recurrence in both the MSKCC and MD Anderson cohorts approximate the 20% threshold that has traditionally been used to triage patients to elective surgical or radiation treatment of the neck, although these data have been extrapolated from cohorts of mucosal squamous cell carcinoma. Other series have reported higher rates of neck recurrence, ranging from 23%–33%^{13,16}. In our series, the location of cervical metastases at the time of regional failure was usually multilevel, mainly involving the lateral neck (levels I–IV) as well retropharyngeal lymph nodes in 25%. This multi-level disease was also reported by Howell et al¹⁹ who observed that all metastatic nodes were easily seen on CT scan, MRI and PET, including the retropharyngeal nodes which were also at risk of metastasis. Therefore, any elective treatment of the neck such as ENI should ideally encompass multiple nodal basins bilaterally, including retropharyngeal nodes.

Retrospective data support the use of ENI to the neck in order to achieve high rates of regional control⁶. The University of Florida group has reported two series evaluating regional control in cN0 ENB patients receiving ENI. Reviewing 26 patients, Hollen and colleagues reported a 100% rate of regional control at 5 years among patients receiving ENI, compared to 69% for those who did not receive ENI ($p=0.017$)^{16,20}. In contrast, Noh et al²¹ identified nodal recurrence in spite of ENI in 3 of 4 patients. A publication reporting the Massachusetts General Hospital experience with ENB in 22 patients from 1997 to 2013 suggested that due to high incidence of regional metastases (27% in their study) and the negative prognostic value of nodal disease^{11,22,23}, a strong consideration should be given to bilateral ENI²⁴. To date, no series has demonstrated an improvement in OS associated with ENI, for ENB or other head and neck cancer types.

We found that patients developing neck nodal recurrence had significantly poorer survival (17% vs 80% at 15 years, $p=0.017$). Importantly, the cause of death in all patients who died of disease after neck recurrence was distant failure, not uncontrolled locoregional disease. This suggests that, in ENB, the development of nodal metastasis is most likely a biomarker of aggressive tumor biology and a harbinger of distant failure, rather than the cause of death *per se*. Most commonly, these metastases occurred in the central nervous system (brain or spine). It is unknown whether the degree of regional control in nodal basins would be able to substantially diminish the risk of brain/spine metastases from a central nervous system tumor such as ENB. Therefore, we conclude from our data that ENI has the potential to improve regional control, but it remains unknown whether improved locoregional control would translate to improved overall survival, given that the ultimate cause of death in these patients is failure at distant (frequently, CNS) sites.

Surgery and radiation are believed to be the treatment of choice for salvage of neck failure in esthesioneuroblastoma¹⁴. Although no data have been generated to support what type of neck dissection should be done for patients with neck failure, our data indicate that levels 1–

4 are at highest risk of harboring occult nodal disease that ultimately manifests as recurrence. Gore et al demonstrated an odds ratio of 8.6 of successful surgical salvage when neck recurrence was treated with surgery and radiation therapy, as opposed to either surgery or radiation alone¹⁵. In our series, 8 out of 11 patients failing in the neck were treated with attempted surgical salvage. Surgical salvage was usually beneficial, with 7 of 8 (87%) patients treated with salvage neck dissection and radiation alive at least 2 years after treatment. Our data suggest that in most cases, neck metastases can be adequately salvaged, and the risk of unresectable nodal recurrence is low. With neck dissection and radiation, locoregional control can be achieved, but ultimately, these patients face a high risk of developing distant metastases.

In our cohort, the cumulative incidence of distant metastasis, in patients presenting M0, was 39%. The majority of these metastases were in the brain or spine. Leptomeningeal involvement by ENB is known to carry a poor prognosis²⁵.

At our institution, we now employ elective irradiation to neck lymph nodes in the vast majority of esthesioneuroblastoma patients, with a goal of optimizing locoregional control, but with the understanding that available data do not indicate whether this intervention will prolong overall survival. We continue to consider distant metastasis to be the primary obstacle to long term survival in these patients.

CONCLUSION

Both neck and distant metastasis are significant barriers to long-term disease control in patients with esthesioneuroblastoma. These metastases generally present in a delayed fashion. Although distant metastases occur more commonly in patients with more advanced Kadish stage primary tumors, we did not identify any association between Kadish stage and the risk of neck recurrence. In the majority of patients experiencing neck recurrence, the nodal recurrence is salvageable. However, neck recurrence tends to be associated with poorer survival, because neck recurrence often portends subsequent development of distant metastases. Therefore, recurrence in the neck may be a marker of aggressive tumor behavior. It remains unknown whether improved locoregional control would translate to improved overall survival, given that distant metastases are the primary obstacle to long term cure.

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Figure 1. Disease Free Survival Curve based on Kadish Stage

10 year disease free survival is significant based on Kadish Stage at presentation ($p=0.001$).

10y DFS was 69% for Kadish Stage A, 56% for Kadish Stage B, 46% for Kadish Stage C and 0% for Kadish Stage D.

Figure 2. Probability of neck metastasis by Kadish Stage

The probability of neck disease was not significant based on Kadish stage at presentation (0.777). 5 year probability of neck failure for Kadish Stage A, B, and C was 11.1%, 17.3% and 13.9% respectively. 10 year probability of neck failure for Kadish Stage A, B, and C was 40.7%, 41.5% and 28.2% respectively.

Cumulative Incidence of Neck Metastasis

Figure 3. Cumulative Incidence of Neck Metastasis

17% of patients presenting N0 to our institution developed neck metastases during the course of their follow up. Mean follow up was 68 months.

Figure 4. Survival based on neck recurrence vs no neck recurrence

Survival of patients with no neck failure was significantly improved when compared to those who had neck failure at 10 years and 15 years.

Figure 5. Pattern of Neck Failures

Metastatic neck disease mainly occurred in levels 1–3. 3 patients (37.5%) had isolated disease in one level (either one or multiple nodes). 50% of patients (4/8) had disease in 3 or more levels on pathology assessment.

Figure 6. Probability of Distant Metastatic Disease by Kadish Stage

The probability of distant disease was significant based on Kadish stage at presentation, $p=0.008$ when analyzing all patients treated at MSKCC who did not present with distant disease ($n=52$). The 5 year probability of distant failure for Kadish Stage A, B, and C was 0%, 5% and 43.7% respectively. The 10 year probability of distant failure for Kadish Stage A, B, and C was 20%, 18.6% and 57.8% respectively.

Table 1

Modified Kadish Staging System

Stage	Extent of Tumor
A	Tumor is limited to the nasal cavity
B	Tumor in the nasal cavity and extends into the paranasal sinuses
C	Tumor extends beyond the nasal cavity and paranasal sinuses; involving the cribriform lamina, the skull base, the orbit or intracranial cavity
D	Tumor with neck or distant metastases