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When, how and why to treat the neck in patients with esthesioneuroblastoma: a review

Adam M. Zanation,
Department of Otolaryngology-Head and Neck Surgery, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Alfio Ferlito,
Department of Surgical Sciences, ENT Clinic, University of Udine, Udine, Italy. Department of Surgical Sciences, ENT Clinic, Azienda Ospedaliero-Universitaria, Piazzale S. Maria della Misericordia, 33100 Udine, Italy

Alessandra Rinaldo,
Department of Surgical Sciences, ENT Clinic, University of Udine, Udine, Italy

Mitchell R. Gore,
Department of Otolaryngology-Head and Neck Surgery, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Valerie J. Lund,
Professorial Unit, Royal National Throat, Nose and Ear Hospital, University College, London, UK

Kibwei A. McKinney,
Department of Otolaryngology-Head and Neck Surgery, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Carlos Suárez,
Department of Otolaryngology, Hospital Universitario Central de Asturias, Instituto Universitario de Oncología, del Principado de Asturias, Oviedo, Spain

Robert P. Takes, and
Department of Otolaryngology-Head and Neck Surgery, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Anand K. Devaiah
Department of Otolaryngology-Head and Neck Surgery, Boston University School of Medicine, Boston, MA, USA

Alfio Ferlito: a.ferlito@uniud.it

Abstract

Esthesioneuroblastoma is an uncommon tumor that presents in the sinonasal cavity and anterior skull base. Cervical metastases are not frequently found on initial presentation but eventually occur in 20–25% of these patients. This presents the treating physician with the difficult decision as to how and when to treat the neck in this disease. The aims of this study were to provide a comprehensive review of the incidence of N+ disease at presentation, make recommendations about the optimal treatment strategy of patients with N+ disease, explain the role of elective neck treatment in patients with N0 disease, and comment on treatment of patients with late cervical

Correspondence to: Alfio Ferlito, a.ferlito@uniud.it.

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metastases that require salvage therapy, using the literature review of the incidence and treatment of neck disease in patients with esthesioneuroblastoma. This review revealed an approximately 5–8% incidence of cervical nodal metastasis at the time of presentation. Combined modality therapy with surgery and radiotherapy is recommended to treat the N+ neck at the time of diagnosis and later. Chemotherapy may have a role combined with radiation treatment, but there are little data to support this. There is limited evidence to substantiate the use of elective neck dissection or elective radiotherapy in the clinically and radiologically N0 neck. Patients who have late cervical metastases have a clear survival advantage (59 vs. 14%) when treated with combined surgery and radiotherapy relative to single modality methods alone. The results indicate that the management of the neck in esthesioneuroblastoma continues to be a significant challenge in the treatment algorithm of these complex patients.

Keywords

Esthesioneuroblastoma; Olfactory neuroblastoma; Lymph node metastasis; Treatment; Sinonasal cancer

Introduction

Esthesioneuroblastoma (ENB) is an uncommon malignant neuroendocrine tumor of the sinonasal region, sometimes referred to as olfactory neuroblastoma, and was first described by Berger et al. [1] in 1924. This tumor, in the past, was erroneously considered benign or low-grade malignant [2]. There remains some controversy as to the cell of origin of ENB, although the most widely accepted opinion is that ENB arises from the olfactory epithelium [3], which would account for the intimate relationship of most ENBs with the cribriform plate, the midline superior nasal structures, and the anterior skull base. ENB has a relatively low incidence, making the assembly of large case series or randomized trials difficult, and the determination of standard of care for management more complex. The literature that establishes combination surgery and radiation (plus or minus chemotherapy) as the standard of care for primary site (skull base and sinonasal) disease is based upon small, single-institution series and meta-analyses of combinations of treatment data. In a treatment review (which included 26 studies with 390 patients), the authors found a survival advantage using surgery with radiation compared with surgery or radiation alone [4]. In 42 patients undergoing craniofacial resection for this disease, local recurrence was significantly higher if radiotherapy was not given (28 vs. 4%) even though these patients had less extensive disease [5]. In 2009, Devaiah and Andreoli [6], analyzing 361 cases of ENB in 23 journal articles, found that surgery yielded more disease-free outcomes and better survival rates than nonsurgical treatment modalities, but it should be kept in mind that most data do not derive from prospective studies but retrospective series. In addition, they observed that endoscopic surgery produced better survival rates than open surgery, even when stratifying for publication year. Nevertheless, most of the open surgery tumors belonged to the Kadish C and D stages, whereas the endoscopic techniques were more commonly used for Kadish A and B tumors, contributing, at least partially, to the better survival found for the endoscopic approach. Oncologic principles with clearance of margins and intradural dissection (if needed) should be maintained in the setting of endoscopic resections [7,8].

Given the treatment advantage for multimodality therapy in primary site disease, what is the current recommended management of the neck in these patients? The difficulty in establishing the optimal approach to the neck in the ENB patient stems from several factors, including the low incidence of this disease, which makes it difficult to perform randomized trials or assemble retrospective cohorts with large numbers of patients, and the high

proportion of late neck metastases, which can present several years after treatment of the primary tumor.

In this review, we outline 4 main points. First, what is the incidence of N+ disease at presentation and delayed N+ disease? Second, what is treatment of the neck in patients with N+ disease at presentation? Third, is there a role for elective neck treatment for the clinically and radiologically N0 patient at initial presentation? And last, what is the recommended treatment strategy for salvage therapy for late cervical metastases?

Cervical lymph node metastases

ENB is a malignant tumor with a likelihood for cervical lymph node metastasis [9]. Many authors have examined the rate of neck metastasis in patients with ENB, with larger series typically reporting a rate of neck metastasis between 20 and 25% [10–12]. In 2002, Rinaldo et al. [10] evaluated the incidence of lymph node metastases in patients with ENB, collecting data from only the largest and most recent series reported in the literature, in which the diagnosis was often supported by histochemical, immunocytochemical and/or ultrastructural investigations. They found an incidence of 23.4% of synchronous and metachronous lymph node metastasis from 15 institutions worldwide though the range was wide. In 2003, Ferlito et al. [11] calculated a cumulative metastatic rate of 23% of cervical lymph nodes in 494 cases of ENB from 26 institutions worldwide. In a meta-analysis published in 2009 by Gore and Zanation [12], the overall rate of neck metastases was 20.2% for 678 ENB patients (137 of 678). These numbers come very close to the somewhat arbitrary rate of 20% that is still utilized for elective N0 neck treatment in head and neck aerodigestive tract cancers. What makes ENB more difficult to analyze and make recommendations is the presence of “late neck metastasis.” While approximately 20–25% of patients with ENB may eventually present with neck disease, only 5–8% have N+ disease at presentation [4,10,12]. Gore and Zanation [12] noted that 62% of ENB cervical metastases occurred 6 or more months after primary treatment.

However, high incidence of metastasis in follow-up may be explained by a slow growth rate of a tumor, with micrometastasis initially undetected at presentation, becoming manifest after primary site treatment. But this is also influenced by the thoroughness of the initial diagnostic work-up at presentation and the intensity of follow-up. The incidence of occult metastasis (or the rate of late metastasis) and the need for elective neck treatment depend on the means used to evaluate the neck.

Patients suffering from advanced primary site stage appear to be at higher risk for the development of cervical metastases. In a survey of 207 ENB cases identified out of 8 published series, Davis and Weissler [13] found a cumulative cervical metastatic rate of 27% (55 of 207 patients). This metastatic rate was stratified according to Kadish stage. Cervical metastasis occurred in 14% of Kadish group A patients, 11% of Kadish group B patients, and 44% of Kadish group C patients. The differences were statistically significant. Although most of metastatic nodes are located in the lateral region of the neck, retropharyngeal nodes can occur [14]. In 2008, Zollinger et al. [15] published 4 cases of retropharyngeal lymph node metastasis in a series of 17 ENB patients, but they did not report data on the impact of retropharyngeal nodes on survival.

Management of the N+ neck at primary presentation

Dulgerov et al. [4] performed a stratified meta-analysis of treatment outcomes including 26 studies and 390 patients between 1990 and 2000. Overall and disease-free survival at 5 years averaged 45% (SD 22) and 41% (SD 21) in this meta-analysis. When sub-divided by treatment modality, survival was 65% for surgery plus radiotherapy, 51% for radiotherapy

and chemotherapy, 48% for surgery, 47% for surgery plus radiotherapy and chemotherapy, and 37% for radiotherapy alone. The histopathological grading according to Hyams and the presence of cervical lymph-node metastases were significant prognostic factors. The authors' conclusions were that a combination of surgery and radiotherapy is the optimal approach to primary ENB treatment. However, it should be kept in mind that in this analysis of retrospective series there may have been selection in the choice of treatment based on factors that may also have prognostic significance. The fact that surgery followed by combined chemoradiotherapy seems to result in worse outcomes compared with surgery followed by radiotherapy alone may be explained by the choice for combined post-operative chemoradiation in higher stage tumors or unfavorable histopathological features.

This meta-analysis [4] found a rate of 5% of cervical metastasis at the time of initial diagnosis. Survival data demonstrated that only 29% of initially N+ patients were treated successfully, compared with 64% of N0 patients (odds ratio 5.1; 95% CI 1.6–17.0). Given the significant decrease in survival for node-positive disease in ENB, the authors advocated aggressive treatment by neck dissection and radiotherapy at the time of treatment of the primary site for clinically or radiologically evident nodal disease in patients with ENB. This seems to be the consensus of most authors [16], and most centers advocate the treatment of N+ disease with neck dissection and post-operative radiation. What is interesting about Dulgerov's recommendation regarding N+ treatment is that the authors did not sub-stratify those N+ patients by treatment type. The recommendation of surgery and radiotherapy is based on the generalization that it is beneficial to the entire series and not just to the N+ patients.

The role of chemotherapy combined with radiation is unknown and unproven in ENB. Some centers make the assumption that the concurrent chemotherapy plus radiotherapy advantage seen in the randomized controlled trials of squamous cell carcinoma may apply to other head and neck/skull base malignancies [2,17]. There is no comparative data to support additional chemotherapy in ENB; however, the University of Virginia reports excellent long-term ENB outcomes with trimodality (chemotherapy, radiation and surgery) treatment [18]. Recently, Zhang et al. [19] reported a series of 21 patients treated with preoperative radiotherapy (Kadish A and Kadish B) and preoperative chemoradiotherapy (Kadish C). The 5-year crude overall survival rate was 76.2%, and they speculated that preoperative radiotherapy or chemoradiotherapy can give surgeons the chance to choose less invasive surgical approaches, especially the endoscopic surgical techniques [19].

There are no data to support the type or extent of neck dissection for N+ patients. Most centers would advocate a selective neck dissection [10]. The presence of extra-capsular neck disease would warrant a more aggressive approach. However, this information is known only after histopathological examination and therefore cannot be used for pre-operative assessment, but can be considered an indication for post-operative radiotherapy. Usually, the contralateral N0 neck is not dissected unless there are suspicious nodes or unilateral nodes that approach midline.

Management of the N0 neck

Given the high percentage of patients who develop cervical nodal disease, treatment of the clinically negative neck may be warranted [20]. However, even though the overall incidence of neck node metastasis is greater than 20% in ENB, the majority of surgeons currently do not consider elective neck dissection to be part of the initial treatment. This is because most cervical node metastases occur over a long period of time. It is quite likely that one may be able to treat them at a later date when they are clinically apparent [10,12].

In their study of elective nodal irradiation (ENI) for ENB, in 2010, Noh et al. [21] examined treatment outcomes of patients with ENB and the need for ENI. Fourteen patients were analyzable with a median follow-up of 27 months over a 10-year period. The overall 3-year survival rate was 73.4%. Local failure occurred in 3 patients (21.4%), regional cervical failure in 3 (21.4%), and distant failure in 2 (14.3%). Three cervical failures occurred in the 4 patients treated with ENI or neck dissection (75%), none of whom received systemic chemotherapy. No cervical nodal failure occurred in patients treated with combined systemic chemotherapy regardless of previous ENI. Neither ENI nor neck dissection was observed to prevent regional failure ($P = 0.099$). However, the results of this paper are statistically under-powered and the follow-up very short. Combined systemic chemotherapy seemed to influence the regional failure rate as no patient who received systemic chemotherapy had nodal failure. The authors thus concluded that ENI during skull base radiotherapy for ENB seemed to play a limited role in preventing cervical nodal failure.

In 2003, the University of Florida published a series of 22 patients (1972–1998) who received radiation therapy for ENB [22]. Their protocol was to irradiate bilateral necks in most patients regardless of nodal status. The overall incidence of cervical lymph node metastases was 27% (6 of 22 patients). Eleven patients received elective radiation therapy to the cervical and supraclavicular lymph nodes. The neck was irradiated bilaterally in all cases except one, with a median dose of 50 Gy (range 40–50 Gy). Treatment fields included the lower cervical nodal regions and the supraclavicular fossa and were typically delivered using an anterior field with a midline larynx block. There were no nodal failures in the 11 patients treated with elective neck irradiation. By contrast, 4 of 9 patients (44%) experienced neck node recurrence when elective neck fields were omitted ($P = 0.02$). Locoregional failures occurred in 6 of 9 patients (67%) without elective neck irradiation compared with 3 of 11 patients (27%) with ENI ($P = 0.17$). All 4 patients with neck recurrences had modified Kadish C staging at diagnosis. None of the 4 patients received neoadjuvant or concurrent chemotherapy. The primary limitation of this study are the short follow-up time (mean of 36 months), the long range of pathologic diagnoses with potential for inclusion of non-ENB small round blue cell tumors, and the sparse description of additional neck treatment modalities within the series (e.g. usage of therapeutic or staged neck dissections).

The authors of this review could not find a series of N0 ENB patients that were treated with elective staging neck dissections.

Thus, it has not been established that the N0 neck in ENB should be treated prophylactically with radiotherapy or elective neck dissection. The University of Florida data shows promise and it is likely that there are other institutions performing ENI at the time of primary ENB treatment. These centers should pool their data so the potential benefits ENI are more clearly measurable.

Management of late neck metastases

In 2009, Gore and Zanation [12] examined a total of 678 patients with ENB. The overall rate of cervical metastases was 20.2%, with a 12.4% rate of late neck metastases. The overall successful 1-year salvage rate for late neck metastases with surgery, radiation, or combined therapy was 31.2% (Table 1). An odds ratio analysis revealed that surgery plus radiation provided a statistically significant increase salvage success compared with surgery or radiation alone. A salvage odds ratio of 8.6 was calculated comparing surgery and radiation to single modality treatment ($P = 0.003$), with a number-needed-to-treat of 3. The odds ratio of combined surgery + radiotherapy versus surgery alone (7.6) and radiotherapy alone (11.4) was also statistically significant. There was no significant difference in the rate of successful salvage between surgery alone or radiotherapy alone (odds ratio = 1.5).

Given the high rate of late neck metastases, the authors determined that it is reasonable to screen patients whose neck is clinically or radiologically N0 at the time of diagnosis of their primary ENB, for recurrence 6 months and 1 year after diagnosis with computed tomography scans of the neck, and yearly thereafter. The authors also recommend serial examinations of the neck for clinical signs of metastasis when patients are seen in follow-up for their primary site. In addition, salvage treatment of neck metastases occurring 6 months or more after treatment of the primary site with combined surgery and radiotherapy is recommended, as a clear disease free survival advantage (59 vs. 14%) has been shown in these patients with combined versus single modality therapy [12]. Magnetic resonance imaging and/or ultrasound and fine needle aspiration is also used as a screening tool in some centers.

Conclusion

Although large trials have been difficult to organize, several useful studies address the complex issues of treatment of the N0 and N+ necks in ENB, as well as metastases to the neck occurring more than 6 months after diagnosis of the primary site. The consensus seems to be that treatment with neck dissection followed by radiotherapy should be used only when and if clinical or radiographic and preferably cytological evidence of neck disease is apparent, as elective treatment of the neck at the time of primary site therapy does not have significant data to outweigh the additional disadvantages. Additionally, it is not known whether elective treatment of the neck would improve prognosis. Additional chemotherapy may be beneficial to maximize aggressive treatment in advanced staged and N+ ENB. Last, we recommend salvage of neck metastases occurring 6 months or more after treatment of the primary site be treated with combined surgery and radiotherapy, as we have shown a clear disease free survival advantage (59 vs. 14%) in these patients with combined modality therapy versus single modality (Table 1).

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Table 1

Late neck metastases salvage data from Gore and Zanation [12]

	N	Successful salvage
Total	45	14 (31%)
Surgery	19	3 (16%)
Radiotherapy	9	1 (11%)
Single modality*	28	4 (14%)
Surgery + Radiotherapy	17	10 (59%)**

*Single modality treatment combines the groups treated with surgery only or radiation only

**Odds ratio compared with single modality treatment for successful 1-year disease free survival was 8.6 ($P = 0.003$)