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CLINICAL INVESTIGATION **Head and Neck**

ESTHESIONEUROBLASTOMA: IS THERE A NEED FOR ELECTIVE NECK TREATMENT?

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Purpose: To assess the risk of cervical lymph node metastases after definitive treatment for esthesioneuroblastoma (ENB) that did not include elective neck therapy.
Methods and Materials: This was a retrospective analysis of 26 ENB patients treated at the University of Michigan between 1995 and 2007. Tumor stage was Kadish A in 1 patient, B in 19, C in 5, and unknown in 1. Craniofacial or subcranial resection was performed in 24 patients (92%), with negative margins in 22 (92%). Postoperative radiotherapy (RT) to the primary site was given in 12 patients (46%), and 14 patients (54%) had surgery alone. All patients had clinically N0 disease, and no patient underwent elective neck dissection or radiation. Median follow-up was 72 months.
Results: Local relapse-free survival was significantly better for patients who received postoperative RT compared with those who had surgery alone: 100% vs. 29% at 5 years, respectively ($p = 0.005$). Five-year disease-free survival was 87.5% in the RT group vs. 31% in the surgery-alone group ($p = 0.05$). Regional failure was observed in 7 patients (27%), 6 with Kadish Stage B and 1 with Stage C disease. The most common site of nodal failure was Level II, and 3 patients failed in the contralateral neck. Only 3 patients with regional failure were successfully salvaged.
Conclusion: The high rate of regional failures when the neck is not electively treated justifies elective nodal RT in patients with both Kadish Stages B and C. In addition, our experience confirms the beneficial effect on local control of adjuvant RT to the tumor bed. © 2011 Elsevier Inc.

Esthesioneuroblastoma, Olfactory neuroblastoma, Craniofacial resection, Subcranial resection, Elective neck irradiation.

INTRODUCTION

Patients with esthesioneuroblastoma (ENB) typically present with advanced disease, owing to early local spread through the cribriform plate to the base of skull. Tumor growth can vary widely, from indolent growth with late local recurrences to highly aggressive, locally advanced tumors with rapid regional and metastatic spread (1–4). The advent of craniofacial resection (CFR) in the 1970s has lead to a significant improvement in surgical outcomes (5–7). Adjuvant radiotherapy (RT) targeting the tumor bed seems to confer a benefit in terms of local control and is the standard of care for patients with locally advanced tumors (8–15).

Few studies have directly addressed the approach to the clinically negative neck; however, the results are mostly conflicting (16–23). The small number of patients and the variability in treatments make it even harder to draw firm conclusions. The lack of standardized approach is reflected in a popular radiation oncology textbook, which states that "the available data do not justify routine elective nodal treatment" (24) but recommends in another section of the book that "with advanced-stage disease, cervical lymph nodes should be initially managed by irradiation, radical neck dissection, or a combination of both" (25).

One of the very few studies that directly addressed the issue of prophylactic neck irradiation for ENB was published by the University of Florida group (16). In this study, patients who had received elective neck therapy had a significantly lower rate of neck recurrences compared with patients who had not been treated electively. At our institution, the policy for ENB has been an avoidance of elective neck RT in all patients. This uniform policy provides us now with a unique opportunity to assess the results of avoiding neck treatment, affirming or refuting the University of Florida recommendations.

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METHODS AND MATERIALS

Patient data

Between 1995 and 2007, 27 patients were seen and treated at the University of Michigan Comprehensive Cancer Center with the diagnosis of ENB and without evidence of regional lymph node metastasis according to staging neck CT scans. One patient received elective neck irradiation and was excluded from the analysis. Eighteen of the patients had their surgery at the University of Michigan, whereas 8 others were referred to our institution for further treatment, either adjuvant therapy of primary disease or salvage treatment of recurrent disease, after having surgery elsewhere dating back to as early as 1987. The patients were retrospectively identified through the Cancer Center tumor database, and the patients' charts, imaging studies, and computerized notes were reviewed after receipt of approval from the institutional review board. Table 1 outlines the baseline characteristics of the 26 patients who underwent definitive treatment. The median age was 46.5 years (range, 11–75 years). Nineteen men and 7 women were treated. The symptoms at presentation included: nasal obstruction ($n = 11$), epistaxis ($n = 10$), headache ($n = 3$), facial swelling ($n = 1$), and proptosis ($n = 1$). The median interval from the onset of symptoms to diagnosis was 6 months (range, 0–24 months).

Patients were retrospectively staged on the basis of surgical notes or imaging findings, according to the Kadish classification system (26). Nineteen patients had Stage B disease (paranasal sinus involved), 5 patients had Stage C disease (extension beyond the paranasal sinusus), and 1 patient had Stage A disease (nasal cavity involvement only). The extent of tumor in 1 patient was not documented accurately enough to allow for accurate staging. None of the patients had clinical neck involvement at presentation.

There is a partial overlap between our cohort and a recently published series of 15 patients, all surgically treated at the University of Michigan. This series, which concentrates on surgical aspects, comprised patients with either involved or uninvolved cervical lymph nodes (27).

Treatment

Craniofacial resection or transglabellar–subcranial resection was performed in 24 of 26 patients (92%), and negative margins were obtained in 22 of these patients (92%). Two patients underwent other surgeries: endoscopic resection without cranial approach in 1 and maxillectomy in the other, and both had negative surgical margins. No patient underwent elective neck dissection as a part of their initial surgical treatment.

Table 1. Patient baseline characteristics by treatment group

Characteristic	Radiotherapy ($n = 12$)	No radiotherapy ($n = 14$)
Sex		
Male	11	8
Female	1	6
Stage (Kadish)		
A	0	1 (7)
B	9 (75)	10 (72)
C	3 (25)	2 (14)
Unknown	0	1 (7)
Margin status		
Positive	1 (8.5)	0
Negative	10 (83)	14 (100)
Unknown	1 (8.5)	0
Surgical procedure		
CFR or subcranial resection	12	12 (87)
Other	0	2 (13)

Abbreviation: CFR = craniofacial resection.
Values are number (percentage).

Table 2. Patterns of failure

Parameter	RT ($n = 12$) n (%)	RT ($n = 12$) Kadish stage	No RT ($n = 14$) n (%)	No RT ($n = 14$) Kadish stage
Local recurrence	2 (17)	B: 2	10 (71)	B: 8 C: 1 Unknown: 1
Regional failure	5 (42)	B: 4 C: 1	2 (14)	B: 2
Local and regional failure	2	B: 2	1	B: 1
Regional and distant failure	2	B: 2	1	B: 1

Postoperative RT to the primary site was part of the initial treatment in 12 patients (46%), whereas 14 patients (54%) had surgery alone without adjuvant RT (Table 1). The decision on whether to refer the patient to RT was at the discretion of the surgeon. Radiotherapy in all patients was delivered to the tumor bed alone and did not include elective neck irradiation. There were no statistically significant differences in tumor stage, type of surgery, or surgical margin status between the two groups. The median RT dose delivered was 58 Gy (range, 50–60 Gy), in 1.8–2 Gy per fraction, 5 days per week. Two of the 12 patients were treated with chemotherapy combined with RT.

Statistical analysis

The endpoints analyzed were actuarial survival, disease-free survival (DFS), and local relapse-free survival, defined from the date of surgery. Survival estimates were calculated using the Kaplan-Meier method, and survival differences were analyzed by the log–rank test.

RESULTS

Patterns of failure

The median follow up was 72 months (range, 8–251 months). Patterns of failure are summarized in Table 2. Of the 14 patients who did not receive postoperative RT, 10 (71%) developed local recurrences, compared with 2 of the 12 patients (17%) who did receive adjuvant RT ($p = 0.006$). The median time to first local recurrence was 34.5 months in the surgery-alone group (range, 6–83 months). The 2 patients in the RT group who relapsed locally had their recurrences at 72 and 115 months.

Regional failures in cervical lymph nodes were observed in 7 (27%) of the 26 patients and were all biopsy proven. In 6 of these patients the neck was the first site of failure. The neck was the only site of failure in 3 patients, whereas in 3 others there was simultaneous primary site failure or metastatic disease. The median time to neck failure was 74 months (range, 40–120 months). Of the seven regional