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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

Table 3. Features of regional failures

Patient	Stage	Site of neck recurrence	Time to regional failure (mo)	Other sites of failure
1	C	IL RP node	67	None
2	B	IL upper neck	48	LR 2 y after first neck failure
		CL Level II	96	
3	B	IL Level II	74	Bone metastases after 12 y
4	B	IL: Levels I, II, and III	120	Simultaneous LR
		CL: Levels I and III		
5	B	IL Level II	115	Simultaneous brain metastases
6	B	CL Levels IB, IIA, IIB, and IV	40	Simultaneous meningeal metastases
7	B	IL Level II and RP	106	LR at 30 mo

Abbreviations: IL = ipsilateral; RP = retropharyngeal; CL = contralateral; LR = local recurrence.

failures, six occurred in patients with Kadish Stage B and one in a patient with Stage C disease. The overall rate of regional failures was 32% for Kadish Stage B patients and 20% for Stage C. The most common site of nodal failure was Level II (involved in 6 of 7 patients), followed by Levels IB and III (each involved in 2 patients) and Level IV (1 patient). Retropharyngeal nodes were involved at the time of neck recurrence in 2 patients. Two patients had bilateral neck failure, and 1 patient had only contralateral neck failure. One patient had parotidean lymph node involvement at his second regional relapse. The features of all regional failures are summarized in Table 3.

Distant metastases developed in 4 patients: 2 were diagnosed at the time of regional failure; 2 others followed either local or regional failure. The sites of metastases were the brain (in 3 patients) and bone (in 1 patient).

Salvage treatment

Of the 10 patients who recurred locally in the surgery-alone group, 5 were treated with surgery and RT, 2 had surgery alone, 1 was treated with RT alone, 1 was treated with RT and chemotherapy, and 1 patient received supportive care with no attempt of salvage. Of the 2 patients who recurred locally in the RT group, 1 was treated with surgery alone and the other was salvaged by surgery, RT, and chemotherapy. Overall, of the 12 patients who recurred locally, 7 remained free of disease at their last follow-up at a median interval of 19 months (range, 2–48 months) from their salvage treatment; 2 were alive with disease, and 3 patients died of their disease.

Salvage treatment for neck failures included modified radical neck dissection (MRND) followed by adjuvant neck RT in 2 patients, MRND alone in 2 patients, and RT alone in 1 patient. One patient with isolated retropharyngeal lymph node failure was salvaged with excision plus RT. Another patient who had simultaneous brain metastases received MRND followed by palliative neck RT and whole-brain irradiation and subsequently died of his disease. Overall, of the 7 patients with regional failure, 3 remained free of disease 25, 31, and 74 months after salvage therapy. Salvage therapy and outcome are summarized in Table 4.

Survival data

The 5-year actuarial overall survival estimates were 100% for the adjuvant RT group and 80% for the surgery-alone group (p = 0.14; Fig. 1). Five-year DFS was 87.5% in the RT group vs. 31% in the surgery-alone group, and this difference nearly reached statistical significance (p = 0.05; Fig. 2).

Table 4. Outcome of salvage therapy (excluding 2 patients who received palliative or supportive treatment only)

Parameter	Initial therapy	Salvage therapy	n	Outcome
Local recurrence	Surgery alone	Surgery + RT	5	4, NED
				1, AWD (brain)
		Surgery	2	2, NED
		RT	1	DOD
		RT + chemotherapy	1	DOD
	Surgery + RT	Surgery + RT + CT	1	NED
		Surgery	1	AWD
Regional failure		MRND + RT	2	1, NED
				1, AWD (bone)
		MRND	2	1, NED
				2, AWD
		Excision + RT	1	NED
		RT alone	1	DOD

Abbreviations: RT = radiotherapy; NED = no evidence of disease; AWD = alive with disease; DOD = died of disease; CT = chemotherapy; MRND = modified radical neck dissection.

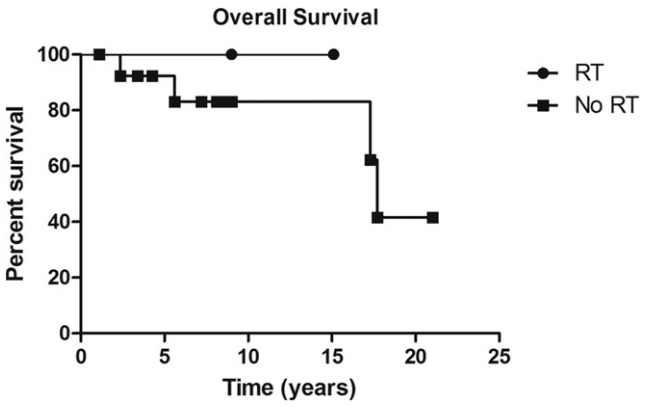

Fig. 1. Overall survival for patients treated with postoperative radiotherapy (RT) and patients treated with surgery alone (No RT). $p = 0.14$.

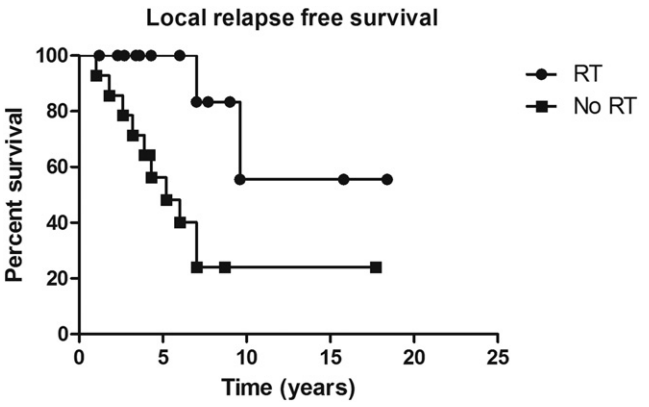

Fig. 3. Local relapse-free survival for patients treated with postoperative radiotherapy (RT) and patients treated with surgery alone (No RT). $p = 0.005$.

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 ($p = 0.005$; Fig. 3). Gender and stage were not significant prognostic factors affecting DFS.

DISCUSSION

The available data on ENB treatment and outcome are limited to small retrospective single-institution series with great variability in patient selection, tumor staging, and treatment approaches. Nevertheless, CFR has been shown to significantly improve local control rates and is widely accepted as the surgical approach of choice (4–6). The role of adjuvant therapies, however, is still controversial. Early studies suggested that CFR alone was sufficient for early-stage tumors (Kadish Stage A or B) if negative margins were obtained (2, 28, 29).

In our series, in which the majority of patients underwent CFR or equivalent surgery with negative margins, the addition of postoperative RT to the tumor bed improved local control significantly, from 30% at 5 years to 100%. Disease-free survival was also improved in patients who

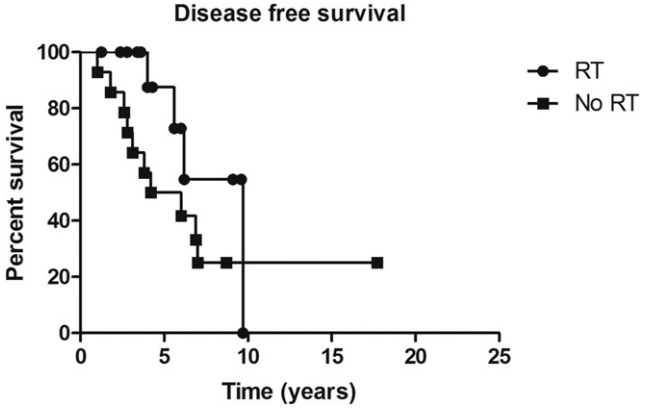

Fig. 2. Disease-free survival for patients treated with postoperative radiotherapy (RT) and patients treated with surgery alone (No RT). $p = 0.05$.

received adjuvant RT compared with those who had surgery alone, but this difference only nearly reached statistical significance. This finding is in agreement with other studies, in which the addition of RT, either before or after surgery, significantly improved local control rates from as low as 0 to 45% for surgery alone to 75–86% with the addition of RT (8–12, 15, 30, 31). Surgery with RT is, therefore, the standard of care for locally advanced ENB.

As local control has improved thanks to improved surgical techniques and the use of adjuvant RT, regional failures become even more important. In our series, in which all patients had clinically N0 disease at presentation and initial treatment did not include neck dissection or neck RT, neck metastases developed in 27% of the patients. Neck metastases were initially thought to be a rare occurrence in ENB (26, 28), but more-recent series suggest otherwise (20–22). Although the rate of clinical neck involvement at presentation is generally low (11–15, 23, 32, 33), the rate of microscopic nodal involvement is unknown because ENB patients with clinically negative necks do not usually undergo neck dissection. However, as was demonstrated in our series, the rate of metachronous neck metastases is quite significant if the neck is not electively treated and varies between 18% and 28% in most studies (8, 11–14, 16–18, 23, 32–34). The time to regional failure is typically long, as was the case in our series (11, 14, 15, 35–38). A summary of data from selected series is given in Table 5.

An important question is whether the risk of nodal metastasis correlates with tumor stage. The risk for nodal metastases did correlate with tumor stage in a few studies, which suggested that patients with Kadish Stage C are most at risk (11, 24, 20). However, our series suggests that patients with Stage B have a similar risk as those with Stage C and therefore should be considered for elective neck RT as well.

Given the high rate of regional failure and because cervical lymph node involvement has been shown to be a significant prognostic factor for distant failure and DFS (9, 23, 31), elective treatment of the neck at the time of initial therapy may improve treatment outcomes. In a review of the literature by Beitler *et al.* (23), neck failures occurred in

Table 5. Reported rates of cervical lymph node metastases in patients with esthesioneuroblastoma

Study (reference)	N	Node positive at presentation (%)	Stages	Delayed nodal involvement (%)	Stages	Overall nodal metastases (%)
Bachar *et al.*, 2008 (8)	39	10.3	NS	20	NS	28
Beitler *et al.*, 1991 (23)	14	0	–	28.6	B: 2 C: 2	28.6
Chao *et al.*, 2001 (13)	25	4	NS	16.7	NS	20
Dias *et al.*, 2003 (9)	35	9	NS	6.3	NS	14.3
Dulguerov *et al.*, 1992 (10)	24	8.3	NS	9.1	B: 1 C: 1	17
Foote *et al.*, 1993 (12)	49	6	NS	17.4	B: 4 C: 4	22.4
Diaz *et al.*, 2005 (11)	30	7	B	18	C	23
Levine *et al.*, 1994 (32)	35	6	NS	21.2	NS	25.7
McLean *et al.*, 2007 (15)	21	0	–	14.3	NS	14.3
Theilgaard *et al.*, 2003 (34)	40	7.5	NS	13.5	NS	20
Zappia *et al.*, 1993 (33)	21	0	–	19	B: 2 C: 2	19
Loy *et al.*, 2006 (14)	50	6	NS	15	NS	20
Monroe *et al.*, 2003 (16)	22	9	NS	44*	C	
Resto *et al.*, 2008 (17)	27	18.5	NS	20*	NS	
Koka *et al.*, 1998 (18)	40	18	A: 1 C: 6	19*	NS	
Zafereo *et al.*, 2008 (19)	18	22.2	NS	0*	–	
Present study	29	0	–	25	B: 6 C: 1	25

Abbreviation: NS = not specified.

* Only patients who did not receive elective nodal irradiation were included. Overall nodal metastases rates were not calculated because elective nodal irradiation was used in some of the patients.

19% of the patients and correlated with worse outcome. Isolated neck failures, without local recurrence, occurred in 9% of the patients, and the authors suggested that elective neck treatment could have cured those patients. Other authors recommend withholding elective neck therapies and avoiding the morbidity associated with them, because neck failures tend to occur late and can be easily detected and salvaged (11, 14). In fact, salvage data are sparse and hard to extract. Successful salvage rates range from 27% to 80% (2, 10, 11, 20, 39–41). In our series, only 3 of 7 patients with neck failures were successfully salvaged and remained free of disease.

Only few cases of elective neck treatment are reported in the literature (Table 6). In a retrospective series from the University of Florida, elective bilateral neck RT was given to 11 patients, whereas 9 other patients did not receive neck RT. None of the patients who received neck RT had neck failure, in contrast to 4 patients (44%) in the group that did not receive neck RT. The authors concluded that "elective neck RT is effective in preventing cervical recurrences" and recommended that it be considered in all patients with Kadish Stages B and C (16). In two other series, the rate of neck failures among patients who had received elective neck irradiation was lower than that of patients who had not received it (17, 18). Our series adds a relatively high number of patients who did not receive elective neck treatment, and their high rate of neck failures lends support for the recommendation of the University of Florida to treat the clinically negative neck (16).

Table 6. Studies comparing regional failure rates with or without elective neck RT

Study (reference)	Neck failures with elective neck RT, % (*n*)	Neck failures without elective neck RT, % (*n*)
Monroe *et al.*, 2003 (16)	0 (0/11)	44 (4/9)
Resto *et al.*, 2008 (17)	15 (1/7)	20 (3/15)
Koka *et al.*, 1998 (18)	0 (0/12)	19 (4/21)
Zafereo *et al.*, 2008 (19)	100 (2/2)	0 (0/7)

Abbreviation as in Table 4.

If elective neck RT is to be given, which neck levels should be targeted? The most common site of nodal failure in our series was Level II, followed by Level IB. Levels III and IV and retropharyngeal nodes were also found to be involved. Parotidean involvement was found in 1 patient at his second neck failure. Levels II, IB, and the lateral retropharyngeal nodes are the first-echelon nodes for most ENBs. The lymphatic vessels of the anterior cribriform plate and anterior nasal cavity pass superficially to join those of the external nasal skin, ending in Level IB nodes. The rest of the nasal cavity and the paranasal sinuses drain to upper Level II, either directly or through the retropharyngeal nodes. However, the anterior and middle ethmoidal cells drain to Level IB nodes, and the posterior nasal floor probably drains to the parotid nodes (42, 43). Only few studies report the sites of nodal failure in ENB. Loy *et al.* (14) reported involvement of Levels I, II and V, as well as the retropharyngeal nodes.

Kim *et al.* (44) reported two cases of retropharyngeal node involvement, together with Levels II and III in one case, and with Levels IB and II in the other. Zollinger *et al.* (45) described four cases of retropharyngeal nodal involvement, one of which also had involvement of Level I and parotidean lymph nodes. Failures in parotidean lymph nodes have also been described by others (2, 3, 12, 14, 21).

Of the 7 patients who had neck failures in our study, 2 had bilateral involvement, and 1 patient had contralateral failure only. Similar rates of bilateral involvement were reported in other series (14, 18). Given the central location of these tumors and the pattern of nodal failure in our series, we would recommend including bilateral Levels II, IB, and retropharyngeal nodes in the target volume. Although parotidean lymph node involvement has been reported, its incidence is likely low, and we would still use bilateral parotid sparing intensity-modulated RT for neck treatment.

In conclusion, our experience with this uncommon malignancy confirms that adjuvant RT to the tumor bed has a beneficial effect on local control, even in the era of CFR and subcranial resection. These surgeries alone, for Kadish Stages B and C, even with negative margins, provided poor local control rates. For regional control, our data provide an affirmation of the Florida data and recommendations for adjuvant neck RT, because our series adds a substantial number of patients whose neck was not electively treated at the time of initial therapy, resulting in a high risk of cervical nodal failure. Elective neck RT can potentially decrease the rate of regional failures. Using intensity-modulated RT, the additional morbidity of neck RT (compared with RT to the primary site only) can be reduced. Given the fact that half of our neck failures were associated with failures at other sites, the impact of elective neck treatment on overall survival is hard to predict.

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