Risk of Delayed Lymph Node Metastasis in Clinically N0 Esthesioneuroblastoma

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J Neurol Surg B 2017;78:68–74.

Abstract

Objective To determine both the rate of delayed cervical lymph node metastasis in patients with esthesioneuroblastoma (ENB) and a clinically N0 untreated neck and the effectiveness of salvage treatment.

Design Retrospective review.

Setting Tertiary academic medical center.

Participants All patients from January 1, 1965, to December 31, 2010, who received definitive treatment for ENB.

Main Outcome Measures The study involved 52 patients: 27 (52%) patients underwent surgery and adjuvant radiotherapy (SART) to the primary site only and 25 (48%) underwent surgery alone (SA) as treatment of the primary site, without elective neck dissection.

Results Median follow-up for the SART group was 10 years versus 15.7 years for the SA group. The 10-year delayed cervical lymph node metastasis estimate is 41%. With median follow-up of 47 months after salvage treatment, the 4-year cervical lymph node recurrence-free survival estimate is 70%; the 5-year overall survival estimate is 39%.

Conclusions Delayed cervical lymph node metastases are common, indolent, and salvaged effectively in most patients. We propose that patients with ENB and clinically N0 cervical lymph nodes may choose to forego elective neck dissection or elective neck radiotherapy in favor of neck observation within their initial treatment.

Keywords

- ▶ cervical lymph node metastasis
- ▶ esthesioneuroblastoma
- ▶ radiotherapy
- ▶ surgery

received

February 16, 2016

accepted after revision

May 27, 2016

published online

July 6, 2016

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Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0036-1584904>.
ISSN 2193-6331.

Background

Esthesioneuroblastoma (ENB) is a rare, anterior skull base tumor that can extend intracranially.^{1–5} Definitive management has been difficult to establish, primarily given the rarity of ENB.⁶ Further complicating the clinical situation, many different tumors mimic ENB and add to the challenges of its diagnosis and treatment.⁵ Finally, ENB often changes morphologic characteristics, grade, and presentation throughout its natural history.⁵

The generally accepted treatment regimen for ENB combines surgery and radiotherapy treatment, with possible chemotherapy for high-grade tumors, locally or regionally advanced, or both.^{6–10} Cervical lymph node metastasis is reported to occur in 19 to 28% of ENB cases.^{6,11–14} The prevalence of cervical nodal metastasis has led to recommendations that patients without clinical evidence of cervical nodal metastasis should receive elective treatment of the cervical nodes during the original tumor presentation and treatment.^{6,11,12,14,15} Patients who undergo elective neck irradiation or dissection have a 0 to 75% risk of subsequent delayed cervical lymph node metastases.⁶

We hypothesized that ENB patients without clinical evidence of cervical nodal metastasis may not benefit from elective cervical lymph node treatment because of ENB's indolent natural history, relatively low incidence of lymph node metastasis, high rate of successful salvage treatment, and the acute and late adverse effects of elective cervical lymph node dissection or radiotherapy. In this study, we examined the cases of ENB treated at our institution to determine the risk of delayed cervical lymph node metastasis after treatment of the primary tumor only, without elective cervical lymph node treatment. We also determined the cervical lymph node recurrence rates and overall survival following salvage treatment in patients who had delayed cervical lymph node metastasis.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. In accordance with Minnesota state statutes, living patients consented to the review of their health records. We electronically searched the health records and cancer registry databases for all instances of ENB reported in the medical record from January 1, 1965, to December 31, 2010. We obtained the health records of 190 unique patients. Among these patients, 122 had confirmed ENB. We limited our study to patients who (1) received definitive treatment at our institution, (2) had not received prior surgery or radiotherapy for the tumor, (3) had not received elective cervical lymph node dissection or irradiation, and (4) did not have cervical lymph node metastasis on presentation. In total, 52 patients were eligible for study inclusion.

Descriptive statistics are reported as number for discrete variables and as mean (standard deviation) or median (range) as appropriate for continuous variables. For specific recurrence-free survival (local, cervical lymph node, or distant), any recurrence-free survival and overall survival estimates

were calculated with the Kaplan–Meier method, reporting the estimate and 95% confidence interval (CI). The association of treatment type (surgery and adjuvant radiotherapy [SART] vs. surgery alone [SA]) with each outcome was assessed with Cox proportional hazards regression model. Results are reported as hazard ratio (HR) and 95% CI. Similarly, among the subset of 14 patients who had cervical lymph node recurrence and underwent salvage treatment, the outcomes of subsequent cervical lymph node recurrence and overall survival were assessed. In these analyses, survival began at the date of the salvage treatment for the first cervical lymph node recurrence.

The α level was set at 0.05 for statistical significance. All analyses were done with statistical software (SAS version 9.3; SAS Institute Inc, Cary, NC.). Hyams tumor grade was not included in the models because the grade is missing in 10 patients; therefore, the univariate and multiple variable models would include only 42 patients. In addition, the number of events of each type was not great enough to warrant three variables in the models.

Results

In total, 27 (52%) patients underwent SART to the primary site only and 25 (48%) underwent SA as treatment of the primary site. No patient in either treatment group received elective neck dissection or radiotherapy. When evaluating baseline characteristics for the two groups, we did not find significant differences between the SA and SART groups for age at diagnosis, sex, or Hyams grade (**►Table 1**). The Kadish stage was significantly higher for the SART group than the SA group. Craniofacial resection was performed for 42 (81%) patients as the definitive surgical treatment. SA patients were treated between January 1, 1966, and December 31, 2008; SART patients were treated between January 1, 1985, and December 31, 2011. Of the 52 patients, 40 were treated between January 1, 1985, and December 31, 2008.

For patients receiving adjuvant radiotherapy to the primary site, the median (range) overall treatment time was 42 (38–50) days, the number of fractions was 31 (28–36), the dose per fraction was 180 (178–202) cGy, and the total dose was 5,580 (5,400–6,480) cGy. Ten patients were treated with intensity-modulated radiotherapy. The overall median (range) follow-up was 13.8 years (1 day to 31.3 years); median follow-up was 10.0 years for the SART group and 15.7 years for the SA group.

Local recurrence-free survival was significantly greater for the SART group at 10 years (80%) than the SA group (35%) ($p = 0.01$; HR [95% CI]: 3.7 [1.3–10.4]) (**►Fig. 1** and **►Table 2**). This advantage for the SART group persisted in a multiple variable model that also included the Kadish stage ($p = 0.001$; HR [95% CI]: 6.7 [2.1–21.4]) (**►Table 3**). In total, 14 SA patients had local recurrence; 10 had undergone craniofacial resection, of which 5 recurrences were Hyams grade 2, 3 were grade 3, 1 was grade 4, and 1 had the grade missing. Five SART patients had local recurrence, and of these, 4 had undergone craniofacial resection—2 recurrences were Hyams grade 2, 2 were grade 3, and 1 had the grade missing.

Table 1 Patient demographic characteristics, Kadish stage, and Hyams tumor grade

Characteristic	SART (n = 27)	SA (n = 25)	Total (n = 52)	p-Value
Sex				0.17 ^a
Female	7	11	18	
Male	20	14	34	
Kadish stage				<0.001 ^b
Missing	1	0	1	
A	0	10	10	
B	3	9	12	
C	23	6	29	
Age at diagnosis, y				0.39 ^b
Mean (SD)	47.7 (13.9)	51.5 (17.3)	49.5 (15.6)	
Median (IQR) Range	52.0 (37.0, 58.0) (10.0–67.0)	51.0 (42.0, 64.0) (15.0–78.0)	51.0 (39.5, 60.5) (10.0–78.0)	
Hyams tumor grade				0.28 ^c
Missing	7	3	10	
1	2	1	3	
2	9	16	25	
3	7	4	11	
4	2	1	3	

Abbreviations: IQR, interquartile range; SA, surgery alone; SART, surgery and adjuvant radiotherapy; SD, standard deviation.

^a χ^2 test.

^bEqual variance t-test.

^cWilcoxon rank sum test.

No difference was found in delayed cervical lymph node metastasis-free survival at 10 years between the treatment groups (55% for SART vs. 64% for SA; $p = 0.92$; HR [95% CI]: 1.051 [0.403–2.741]) (►Fig. 2 and ►Table 2). No difference was detected in a multiple variable model that also included the Kadish stage ($p = 0.30$; HR [95% CI]: 1.775 [0.596–5.283]) (►Table 3). The number of patients with a delayed cervical lymph node metastasis was similar between treatment groups (SART: 8/27; SA: 9/25).

Fig. 1 Local recurrence-free survival over 10 years. RT indicates radiotherapy.

Seventeen patients had delayed cervical lymph node metastases (►Table 4). The median time to delayed cervical lymph node metastasis was 58 months, with the longest development at 146 months. Six patients had local recurrence before the delayed cervical lymph node metastasis (median [range]: 36 [0 {simultaneous} to 70 months]). Four patients had delayed cervical lymph node metastasis before a local recurrence by 1, 2.5, 3, and 47 months, respectively. Two patients had dura-based distant metastases at 27 and 77 months, respectively, before the delayed cervical lymph node metastasis. The delayed cervical lymph node metastases were unilateral in 11 patients, in whom it involved levels I ($n = 4$), II ($n = 8$), III ($n = 4$), IV ($n = 2$), V ($n = 1$), VIII ($n = 1$), and IX ($n = 1$). Delayed cervical lymph node metastases were bilateral in five patients, involving levels I ($n = 4$), II ($n = 4$), III ($n = 2$), IV ($n = 1$), V ($n = 1$), VII ($n = 1$), VIII ($n = 1$), and IX ($n = 1$). One patient's involved lymph node levels were not known.

Nine patients underwent salvage neck dissection and adjuvant radiotherapy. The median (range) overall treatment time was 41 (24–64) days, number of fractions was 32 (15–50), dose per fraction was 190 (120–200) cGy, and total dose was 6,000 (3,000–6,300) cGy. Two patients were treated with intensity-modulated radiotherapy. Five patients underwent salvage neck dissection only. Three patients did not undergo salvage therapy because simultaneous distant metastases or comorbid illnesses developed that were more life threatening

Table 2 Univariate Cox model of survival at 10-year end point

Model	Group, %		p-Value	HR (95% CI)
	SA	SART		
Local recurrence-free survival	35	80	0.01	3.732 (1.335–10.433)
Cervical lymph node recurrence-free survival	64	55	0.92	1.051 (0.403–2.741)
Distant metastasis-free survival	83	53	0.23	0.534 (0.190–1.500)
Any recurrence-free survival	32	45	0.99	0.994 (0.478–2.067)
Overall survival	62	77	0.99	0.996 (0.455–2.176)

Abbreviations: CI, confidence interval; HR, hazard ratio; SA, surgery alone; SART, surgery and adjuvant radiotherapy.

Table 3 Multiple variable Cox model for survival end points

End point	p-Value	HR (95% CI)
Local recurrence-free survival	0.001	6.726 (2.112–21.419)
Cervical lymph node recurrence-free survival	0.30	1.775 (0.596–5.283)
Distant metastasis-free survival	0.75	0.806 (0.208–3.125)
Any recurrence-free survival	0.48	1.417 (0.540–3.713)
Overall survival	0.19	1.858 (0.728–4.741)

Abbreviations: CI, confidence interval; HR, hazard ratio.

than the delayed cervical lymph node metastases. These patients survived 3, 3, and 20 months, respectively, following the diagnosis of delayed cervical lymph node metastasis. The median (range) follow-up for the 14 patients undergoing salvage treatment was 47 (2–130) months. In four patients, cervical lymph node recurrence developed following salvage treatment at 10, 18, 36, and 65 months, respectively. After salvage treatment, the 4-year cervical lymph node recurrence-free survival was 70% (►Fig. 3). The 5-year overall survival following salvage treatment for the delayed cervical lymph node metastases was 39% (►Fig. 3).

We found no difference in distant metastasis-free survival, recurrence-free survival, or overall survival between the two treatment groups at 10 years (SART 53% vs. SA 83%; $p = 0.23$; HR [95% CI]: 0.534 [0.190–1.500]; SART 45% vs. SA 32%;

$p = 0.99$; HR [95% CI]: 0.994 [0.478–2.067]; and SART 77% vs. SA 62%; $p = 0.99$; HR [95% CI]: 0.996 [0.455–2.176], respectively (►Figs. 4–6 and ►Table 2). No difference occurred in these end points for the two treatment groups in a multiple variable model that included the Kadish stage (►Table 3).

Discussion

In this study, we confirmed that patients treated with SART have a significantly lower rate of local recurrence than patients treated with SA despite having more locally advanced disease.^{4,8,16–18} We recommend adjuvant radiotherapy following surgical resection to optimize local tumor control and avoid the morbidity and death associated with uncontrolled local disease. However, additional information is needed regarding the acute and late toxicity associated with adjuvant radiotherapy and the success of salvage treatment in SA patients with a local recurrence. Adjuvant radiotherapy to the primary tumor site does not appear to lower the risk of subsequent cervical lymph node metastases.

Several studies have come to conflicting conclusions on the need for elective cervical lymph node radiotherapy in ENB patients with a clinically N0 neck.^{6,7,11,12,14,15,19–21} In 1976, Kadish et al¹⁶ found that only 3 of 17 cases had cervical lymph node metastasis, and the investigators recommended against elective neck radiotherapy. Beitler et al¹¹ recommended elective cervical radiotherapy after conducting their own study and a review of all English language literature on ENB, in which they found that 21 (19%) of 110 patients had cervical lymph node metastases. Monroe et al¹⁵ recommended elective cervical lymph node radiotherapy because

Fig. 2 Delayed cervical lymph node metastasis-free survival over 10 years. RT indicates radiotherapy.

Table 4 Characteristics of the 17 patients with delayed cervical lymph node metastasis

Patient no.	Time to delayed cervical lymph node metastasis, mo	Hyams grade	Local recurrence	Treatment of nodal metastasis	Nodal disease controlled
2	56	2	No	S + RT	Yes
3	99	3	No	S + RT + CT	No
5	95	2	No	S + RT	Yes
7	58	1	No	S + RT	Yes
8	34	3	No	S	Yes
10	30	3	No	S + RT	Yes
12	51	2	Yes	None	NA
18	60	2	Yes	S	No
30	10	3	Yes	S + RT + CT	No
32	8	3	Yes	S + RT	Yes
33	144	2	Yes	S	Yes
35	2	4	Yes	None	NA
37	146	3	Yes	None	NA
40	97	2	Yes	S + RT	Yes
45	117	Missing	Yes	S + RT	No
48	1	3	Yes	S	Yes
53	74	2	No	S	Yes

Abbreviations: CT, chemotherapy; NA, not applicable; RT, radiotherapy; S, surgery.

they reported that 4 (44%) out of 9 patients developed cervical lymph node metastasis when not electively treated. Noh et al¹⁴ reported a negligible role for elective cervical lymph node radiotherapy, pointing to a greater role for systemic chemotherapy. Demiroz et al¹² supported elective cervical lymph node radiotherapy given that 7 (27%) of 26 patients presented with cervical lymph node metastasis. The findings of these studies are limited by their small number of patients and relatively short follow-up.

In contrast, our study was conducted on a larger number of patients who were monitored for a longer period. We found that the 10-year estimate is 41% for development of delayed

cervical lymph node metastasis in patients with ENB and a clinically N0 neck undergoing local treatment only, with no elective cervical lymph node treatment. This event can occur as late as 12 years after the initial treatment. For the majority of patients (70% at 4 years), delayed cervical lymph node metastases were effectively salvaged. Therefore, long-term monitoring is important for ENB patients.

We propose that patients with ENB and a clinically N0 neck may choose to forego elective neck dissection or elective neck radiotherapy in favor of observation with salvage treatment as needed because most patients who received salvage treatment died of other causes. It appears that at most, 4 of

Fig. 3 Cervical lymph node recurrence-free survival and overall survival during 5 years since salvage treatment. Data are after salvage treatment of delayed cervical lymph node metastasis.

Fig. 4 Distant metastasis-free survival over 10 years. RT indicates radiotherapy.

Fig. 5 Any recurrence-free survival over 10 years. RT indicates radiotherapy.

the 52 patients in this study potentially could have benefited from elective cervical lymph node treatment had it been administered. This number contains the four patients without comorbid illnesses or distant metastases who underwent unsuccessful salvage treatment for the delayed cervical lymph node metastases. However, three of the four patients also had a local recurrence that may not have been salvaged or could have metastasized to an electively treated neck. This approach has the added benefits of reducing treatment cost and avoiding the acute and late toxicity associated with elective neck dissection (e.g., wound infection; bleeding; head, neck, shoulder, and limb dysfunction; pain; marginal mandibular nerve injury; thoracic duct injury; aesthetics; fibrosis; and lymphedema) and elective neck radiotherapy (e.g., painful mucositis, thickened secretions, altered taste, dehydration, weight loss, dermatitis, dry mouth, dental caries, osteoradionecrosis, fibrosis, lymph edema, hypothyroidism, dysphagia, laryngeal edema, chondronecrosis, and myelopathy). Our study is limited by the lack of a cohort undergoing elective treatment of the cervical lymph nodes.

Conclusion

Radiotherapy to the primary tumor site significantly reduces the risk of local recurrence and is recommended.⁸ Such

Fig. 6 Overall survival over 10 years. RT indicates radiotherapy.

radiotherapy does not reduce the risk of cervical lymph node metastases. The risk of delayed cervical lymph node metastasis is prolonged and modest; therefore, long-term follow-up is crucial. Successful salvage treatment options are available. We propose that patients with ENB and clinically N0 cervical lymph nodes may decide to forego elective neck dissection when being treated primarily with surgery. In addition, they may forego elective neck radiotherapy when being treated primarily with radiotherapy or when indications exist for postoperative adjuvant radiotherapy to the primary tumor site. On the basis of our experience, we recommend observation of the clinically negative neck and salvage treatment, as needed. If initial clinical examination or imaging, or both, show lymph nodes considered to be involved with disease, then treatment of the nodal disease is indicated.

Conflict of interest

Authors report no conflicts of interest.

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