Salvage Treatment of Local Recurrence in Esthesioneuroblastoma: A Meta-analysis

Mitchell R. Gore, M.D., Ph.D.,¹ and Adam M. Zanation, M.D.¹

ABSTRACT

Esthesioneuroblastoma has a local recurrence rate of ~30%, but no standard regimen for salvage of local recurrence has been established. We report data from 678 patients from series published since 1990, with a risk reduction analysis of salvage with surgery, radiation, or combined surgery and radiation therapy. We found a 28.5% rate of local recurrence after treatment, and a 42.6% rate of successful salvage with surgery, radiation, or combined treatment. The odds ratio for successful salvage, defined as disease-free survival for at least 1 year, was not significantly different for combined surgery and radiation versus surgery alone or radiation alone or for surgery alone versus radiation alone. The salvage odds ratio for combined surgery and radiation therapy versus radiation therapy alone, 3.5, approached, but did not reach statistical significance. This study reveals a reasonable rate of successful salvage of local esthesioneuroblastoma recurrence using surgery, radiation, or combined surgery and radiation.

KEYWORDS: Esthesioneuroblastoma, salvage, sinus, nasal cavity, olfactory neuroblastoma

Esthesioneuroblastoma (ENB) is an uncommon tumor of the sinonasal region that accounts for ~3 to 6%^{1,2} of all primary malignant sinus tumors, and less than 1% of all head and neck cancers.² ENB, sometimes referred to as olfactory neuroblastoma,³ was first described by Berger et al in 1924.⁴ There is debate regarding the cell of origin of ENB, with the most widely accepted theory being that ENB arises from the olfactory epithelium,⁵ which would account for the intimate relationship of most in situ ENBs with the cribriform plate, the midline superior nasal structures, and the anterior skull base. ENB tends to have an indolent course, as early tumors tend to be asymptomatic. As a result, most patients present with advanced disease. Given the uncommon nature of ENB, a standard treatment regime has been difficult to agree on. Adding to the difficulty of

treatment is the relatively high recurrence rate of ENB. Most authors report a local recurrence rate of 20 to 30%. To our knowledge, the literature has not examined the cumulative rate of local recurrence from the larger series published during the craniofacial resection era. Additionally, there is little comment in the literature regarding the rate of successful salvage of local recurrence in ENB. An examination of the success rate of salvage treatment, as well as the treatment modality most effective for successful salvage, would provide valuable insight into the optimal treatment for local recurrence.

STUDY DESIGN

We examine the rates of local recurrence from several of the larger case series published since 1990.^{1,2,5-37} We

¹Department of Otolaryngology, Head, and Neck Surgery, University of North Carolina Hospitals, North Carolina.

Address for correspondence and reprint requests: Adam M. Zanation, M.D., Department of Otolaryngology, Head, and Neck Surgery, CB#7070, UNC-Chapel Hill School of Medicine, Chapel Hill, NC 27599-7070 (e-mail: azanatio@med.unc.edu).

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included studies in which the diagnosis of ENB was supported by immunohistochemical, histochemical, or histological analysis. Our inclusion criteria were patients with confirmed ENB with local tumor recurrence from

studies since 1990 from which data was available on the rate of local tumor recurrence. We examined the rate of salvage of local failure with surgery, radiotherapy (RT), or combined surgery and radiotherapy (SRT). Successful

Table 1 Meta-analysis Data Series

Study	Total <i>n</i>	<i>n</i> Local Recurrence	<i>n</i> Local Recurrence Salvage	<i>N</i> Local Salvage Failed	<i>n</i> Treated with S, RT, or SRT	Local Salvage Failure/Success Pattern
Dias et al ¹	35	4	N/A	N/A	19	N/A
Schmidt et al ¹⁸	4	3	2	1	3	Failure: 1-RT-DOD locoregional, 2-SRT; success: 0
Beitler et al ¹²	14	4	4	2	14	Failure: 2-RT one AWD at prim, one DOD distant(lung); success: 1-S
Davis and Weissler ¹³	4	0	0	0	4	Failures: 0
Dulguerov and Calcaterra ¹⁹	24	9	7	5	19	Failure: 1-S, 2-RT, 3-SRT; success: 1-S
Morita et al ⁷	49	19	16	7	45	N/A
Sakata et al ²⁰	7	4	N/A	N/A	7	N/A
Zappia et al ²¹	21	6	6	5	21	Failure:1-RT-local, 3-S-local, 1-SRT local, AWD; success: 1-SRT
Slevin et al ²³	9	1	0	0	8	0 S/SRT failures, 1 chemotherapy failure
Guedea et al ²²	7	0	0	0	2	0 local recurrence
Irish et al ²⁴	12	N/A	N/A	N/A	36	N/A
Theilgaard et al ⁹	40	7	N/A	N/A	N/A	N/A
Koka et al ⁸	40	23	15	9	28	Failure: 10 SRT; success-5-SRT
Levine et al ²⁵	35	5	N/A	N/A	N/A	N/A
Pickuth et al ²⁶	22	14	N/A	4	N/A	N/A
Resto et al ²⁷	27	4	4	3	17	Failure: 2-SRT-?, 1-RT-primary disease; success: 1-SRT
Martel et al ²⁸	18	2	N/A	N/A	N/A	N/A
Miyamoto et al ²⁹	12	4	4	3	12	Failure: 2-SRT-DOD/local, 1-RT local/ distal-DOD; success: 1-S
Chao et al ³⁸	25	8	N/A	N/A	25	N/A
Simon et al ³⁰	13	4	4	1	13	Failure: 1-S/DOD; success: 1-S, 2-SRT
Hwang et al ³¹	21	6	4	4	14	Failure: 2-S, 2-RT all DOD; success: 0
Iliades et al ³²	3	N/A	N/A	N/A	N/A	N/A
Kumar et al ³⁹	5	1	0	0	2	0 primary salvage
Argiris et al ¹⁵	16	12	8	5	16	Failure: 2-S local and local, 2-SRTCNS/bone/ scalp & brain, 1-RT-meninges/brain; success: 1-RT, 1-S, 1-SRT
Lund et al ⁶	42	7	7	4	42	Failure:4-S
Monroe et al ¹⁶	22	9	3	1	22	Failure: 1-RT-DOD/local; success: 1-RT-NED, 1-S/RT-NED
McLean et al ³³	21	8	3	N/A	N/A	N/A
Loy et al ³⁴	50	4	2	1	50	Failure: 1-SCT DOD orbit/cavernous sinus; success: 1-SCT NED
Eich et al ³⁵	19	7	2	1	17	Failure: 5 CT DOD 1 chemotherapy-related, rest local; success: 2-SRT/CT-NED, NED
Unger et al ⁵	14	3	3	0	14	0 primary failures
Devaiah et al ³⁶	7	1	0	0	7	0 SRT salvage, 1 chemotherapy salvage AWD
Eden et al ³⁷	40	10	10	6	37	Failures: 6-S or SRT-locoregional; success: S or SRT +/- chemotherapy
Total	678	189	101	62	513	

AWD, alive with disease; CNS, central nervous system; CT, computed tomography; DOD, died of disease; NED, no evidence of disease; RT, radiotherapy; RT-NED; S, surgery alone; SCT, skull computed tomography; SRT, combined surgery with radiotherapy.

salvage therapy was defined as disease-free survival at 1 year postsalvage, as follow-up data was available for patients with neck failure from at least 12 months postsalvage therapy. Primary recurrences treated exclusively with chemotherapy were not included in the salvage data, and patients treated with chemotherapy in addition to another modality were included with that modality. The rate of failure among patients treated with surgery, RT, and SRT among patients in which salvage of local recurrence failed versus successful salvage of local recurrence was examined. We also examined the location of failure for patients for which this data was reported. Odds ratios (OR) and confidence intervals (CI) were calculated using $OR = ad/bc$, standard error (SE) of $(\log_e OR) = \text{square root}(1/a + 1/b + 1/c + 1/d)$, $Y = \log_e OR - (N_{1-\alpha/2} \times SE(\log_e OR))$, $Z = \log_e OR + (N_{1-\alpha/2} \times SE(\log_e OR))$ (where $\alpha = 0.05$ to give the 95% CI), and $CI = e^Y$ to e^Z .⁴⁰ Fisher's exact test was then used to calculate the p -value for the association between groups and outcomes, with $p \leq 0.05$ considered statistically significant.

RESULTS

A total of 678 patients (Table 1) were included in the available studies.^{1,2,5-37} Of these patients, data on initial treatment of the primary tumor was available for 560. Of these 560, 513 (91.6%) were treated with either surgery, RT, or a SRT. Of the 678 total patients, data on local recurrence was available for 663 patients. Of these patients, 189 experienced local tumor recurrence (28.5%, 189/663). Of the 189 patients who had local recurrence, data on whether salvage was attempted was available for 137. Of these 137 patients, 101 (73.7%) underwent attempted local salvage with surgery, RT, or SRT. Of the 101 patients who underwent attempted local salvage, 58 of 101 (57.4%) failed, while the remaining 43 of 101 (42.6%) experienced disease-free survival for at least 1 year.

The treatment modality used in salvage therapy used was available for 69 of the 137 patients who underwent attempted salvage therapy for local recurrence (Table 2). Patients who underwent chemotherapy in addition to another modality were included with that

Table 2 Number of Patients with Failure of Salvage Treatment by Modality

Failed	n	%	Salvaged	n	%
Total S	14	28.2%	total S	6	28.6%
Total RT	12	25.0%	total RT	2	9.5%
Total SRT	22	45.8%	total SRT	13	61.9%
Total	48			21	

RT, radiotherapy; S, surgery alone; SRT, combined surgery with radiotherapy.

modality (e.g., patients who were salvaged with chemoradiation were included in the RT group). Patients who underwent chemotherapy alone were not included in the attempted salvage group. Patients with local recurrence who underwent attempted salvage and failed, 22 of 48 (45.8%), had been salvaged with SRT. The remaining patients were evenly divided between attempted salvage with RT alone (25.0%, 12 of 48) and surgery alone (29.2%, 14 of 48). For patients who underwent successful salvage of local recurrence (i.e., disease-free survival for at least 1 year), the majority were salvaged with SRT (61.9%, 13 of 21). Six of 21 patients (28.6%) had been successfully salvaged using surgery alone, and 2 of 21 patients were successfully salvaged with RT alone (9.5%).

Table 3 shows the results of an OR analysis for SRT versus surgery alone, RT alone, and surgery alone plus RT alone. The outcome was successful salvage therapy of local recurrence, with successful salvage defined as disease-free survival for at least 1 year. The data showed no clear difference in the rate of successful salvage between the different modalities. The OR for successful local salvage for SRT versus surgery alone was 1.4 (95% CI 0.43 to 4.5, Fisher's exact test two-tailed p -value = 0.77, number needed to treat [NNT] = 14). For SRT versus RT alone, the OR for successful salvage was 3.6 (95% CI = 0.7 to 18.4, Fisher's exact test two-tailed p -value = 0.17, NNT = 5). For SRT versus surgery alone plus RT alone, the OR for successful salvage was 1.9 (95% CI 0.7 to 5.5, Fisher's exact test two-tailed p -value = 0.3, NNT = 8). For surgery alone versus RT alone, the OR was 2.6 (95% CI 0.4 to 15.2, Fisher's exact test two-tailed p -value = 0.42, NNT = 7).

Table 3 Odds Ratio Analysis of Combined Surgery and Radiotherapy versus Surgery Alone, Radiotherapy Alone, Surgery Alone plus Radiotherapy Alone, and Surgery Alone versus Radiotherapy Alone

Salvage Modality	OR for Salvage	95% CI of Odds Ratio	NNT	95% CI of NNT	Fisher's Exact Test Two-Tailed p -Value
SRT versus S alone	1.4	0.4 to 4.5	14	N/A	0.77
SRT versus RT alone	3.5	0.7 to 18.4	5	N/A	0.17
SRT versus S alone + RT alone	1.9	0.7 to 5.5	8	N/A	0.3
S alone versus RT alone	2.6	0.4 to 15.2	7	N/A	0.42

CI, confidence interval; NNT, number needed to treat for one patient to benefit from treatment; OR, odds ratio; RT, radiotherapy; S, surgery alone; SRT, combined surgery with radiotherapy.

DISCUSSION

ENB, also referred to as olfactory neuroblastoma, is a relatively uncommon tumor of the paranasal sinuses and skull base. Given the low frequency with which this tumor occurs, it has been difficult to assemble large case series or prospective trials. Additionally, the management of ENB has evolved greatly over the years since Berger and Luc described the first cases in 1924.⁴ While surgery with RT, with or without chemotherapy if there is distant disease, has become the most widely accepted treatment regimen for initial disease,⁴¹ there is still no consensus on the best modality for salvage of local recurrence after initial treatment. In this study, we examined the combined data from the largest studies published since 1990. Overall, 91.6% (513/560) of patients for whom data on treatment modality was available were treated with surgery, RT, or SRT. The overall rate of local recurrence was 28.5%, which is similar to the rate reported by Diaz et al.⁴² Salvage of local recurrence was attempted in the majority of patients, with 73.7% of the 137 patients for whom salvage data was available undergoing attempted salvage with either surgery, RT, or a combination of the two. There was an encouraging rate of successful salvage, defined as disease-free survival for at least 1 year. Of the patients who underwent attempted salvage, 42.6% (43/101) were salvaged successfully. The largest number of patients in both the failed and successful salvage groups was treated with SRT, with 45.8% (22/48) of patients in the failed salvage group and 61.9% (13/21) of patients in the successful salvage group. In the failed salvage group, approximately equal numbers of patients were treated with surgery alone (28.2%, 14/48) and RT alone (25%, 12/48). In the successful salvage group, a greater number of successfully salvaged patients were treated with surgery alone (28.6%, 6/21) than RT alone (9.5%, 2/21). These numbers seemed to point to SRT as the superior salvage modality, so we performed an OR analysis (Table 3) to determine whether there was indeed an increase in the rate of successful salvage for combined modality therapy versus single modality therapy for local recurrence. We did not find a statistically significant increase in the rate of successful local salvage therapy for SRT versus surgery alone (OR SRT versus surgery alone = 1.4, 95% CI 0.4 to 4.5, $p=0.77$, NNT=14), SRT versus RT alone (OR SRT versus RT = 3.5, 95% CI = 0.7 to 18.4, $p=0.17$, NNT=5), or SRT versus the combined data for surgery alone and RT alone (OR SRT versus surgery plus RT = 1.9, 95% CI 0.7 to 5.5, $p=0.3$, NNT=8). We also found no significant difference in the rate of successful salvage for surgery alone versus RT alone (OR = 2.6, 95% CI = 0.4 to 15.2, $p=0.42$, NNT=7). These data are in contrast to the data regarding salvage of late neck metastases, in which there was a clear advantage in

disease-free survival for at least 1 year for SRT versus surgery alone, RT alone, or the combined data for surgery alone and RT alone.

Our study shows no clear advantage for combined modality therapy versus surgery alone or RT alone in salvage of local recurrence. Additionally, we found no difference in the rate of successful salvage for surgery alone versus RT alone. The majority of patients who failed attempted salvage, and for whom data was available, recurred locoregionally (23/28), while 5 of 28 recurred at distant sites. Our data indicates that close follow-up of patients treated for ENB for local recurrence with imaging and physical exam is important, as the rate of local recurrence is in the area of 30%. Additionally, our data indicates that attempted salvage is worthwhile in patients who are healthy enough to undergo repeat surgery and are able to receive RT, as the 1-year salvage rate for local failure approaches 50% (42.6% or 43/101).

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