Radiosurgery is an Effective Treatment for Recurrent Esthesioneuroblastoma: A Multicenter Study

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Abstract

Objective Esthesioneuroblastoma (ENB) is a rare malignant neuroendocrine neoplasm that is prone to both local and metastatic recurrence. Local recurrence may often be treated with repeat resection. However, stereotactic radiosurgery (SRS) offers a noninvasive option.

Design Prospective database review.

Participants Gamma knife prospective databases were queried at all institutions within the North American Gamma Knife Consortium, 16 at the time of this report. All patients who had undergone SRS for ENB were included.

Main Outcome Measure Response of recurrent ENB to SRS.

Results A total of 31 locally recurrent tumors in 13 patients were treated with SRS. The median age was 49 years (range: 19–79 years). At a median follow-up of 36 months (range: 1–100 months), 13 (48%) treated tumors were smaller, 11 (41%) were stable, and 3 (11%) showed continued growth following SRS. Univariate analysis did not find any significant factor relating to failure of treatment. Notably, no treatment-related complications (0%) were observed in this cohort.

Conclusion SRS appears to provide a safe and effective option for treatment of recurrent intracranial ENB. Overall, 89% of treated tumors were controlled in this multi-institutional study.

Keywords

- ▶ esthesioneuroblastoma
- ▶ olfactory neuroblastoma
- ▶ stereotactic radiosurgery
- ▶ gamma knife

Introduction

Esthesioneuroblastoma (ENB) is a rare sinonasal cancer, occurring with an incidence of 0.4 per 1 million.¹ Most patients present with anosmia, nasal congestion, and epistaxis.² The initial pathologic diagnosis can usually be made via transnasal biopsy in the office or operating room. Craniofacial resection is the most common treatment for primary disease, either in conjunction with preoperative radiation and che-

motherapy, or selective postoperative radiation and adjuvant chemotherapy depending on Kadish stage, Hyams grade, and the presence of nodal metastasis.^{1–11} Purely endoscopic transnasal resection is gaining popularity as an initial surgical strategy for ENB to avoid any potential complications of a craniotomy.^{12–14} The vast majority of literature regarding ENB is centered around the controversies regarding the treatment of primary disease.^{2,3,6,10,15–18} Much less attention has been given to the treatment of recurrence, with only a few

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reports available regarding the role of chemotherapy in treating advanced metastatic disease and even fewer concerning local intracranial recurrence.^{19–21}

ENB recurrence has two patterns, that of local recurrence with possible central nervous system dissemination, or metastatic disease to cervical lymph nodes and/or the lungs or skeleton.^{19–22} Local ENB recurrence has typically been managed with revision craniotomy and progressive adjuvant therapies.² With the advent of stereotactic radiosurgery (SRS), noninvasive tumor control is a potential option that may reduce the morbidity associated with revision craniotomy for a malignant tumor.²³ We previously presented a single-institution experience detailing eight patients treated with SRS for ENB; seven had locally recurrent disease.²⁴ This report represents an expansion of that data to include this multi-institutional study and confirms SRS treatment is safe and effective for locally recurrent ENB.

Methods

Patient Selection

Institutional review board approval was obtained at all institutions involved with this study. Inclusion criteria for further analyses included (1) pathologically confirmed ENB previously resected at one of the participating institutions or review of pathologic specimens by one of the participating institution's departments of pathology if operated elsewhere, and (2) recurrent cranial disease treated with SRS. Enrollment included SRS procedures between 1990 and 2011.

North American Gamma Knife Consortium

The North American Gamma Knife Consortium (NAGKC) represents a multi-institutional clinical cooperative group of centers of excellence in North America that perform a high volume of SRS using the Leksell Gamma Knife (Elekta AB, Stockholm, Sweden). At the time of this data acquisition, 16 centers were members of NAGKC (Appendix A). All 16 centers queried their databases for treatment of ENB; only 4 reported treating ENB with SRS.

Stereotactic Radiosurgery

Depending on the center, models U, B, C, 4C, or Perfexion Gamma Knife units were used. All patients were treated as outpatients. All procedures began with the application of the Leksell Model G stereotactic head frame (Elekta AB) using a local anesthetic. After frame placement, postgadolinium high-resolution, thin-slice stereotactic T1-weighted or spoiled gradient recalled magnetic resonance imaging (MRI) was performed for treatment planning. T2-weighted studies were performed at most centers as well. Stereotactic computed tomography (CT) was also used in selective cases at the discretion of the treating physicians. SRS dose planning was then performed in consultation with a neurosurgeon, radiation oncologist, and medical physicist using the latest available version of Gamma Plan (Elekta AB). An example plan can be seen in ► **Fig. 1**. Dose prescription was based on tumor size and proximity to critical structures, most commonly the optic nerves. The dose and timing of any prior radiation

Fig. 1 Example of gamma knife radiosurgery treatment plan. Axial magnetic resonance imaging (MRI) (spoiled gradient recalled with gadolinium contrast) showing a focal recurrence in the left superior ethmoid/anterior skull base region treated with stereotactic radiosurgery following prior craniofacial resection. Note the yellow line around the lesion that represents the 50% prescription isodose line.

therapy was also considered. For tumors located in sellar or parasellar regions, the dose delivered to the optic nerves or chiasm was limited to ≤ 10 Gy in most cases, to reduce the risk of radiation-induced optic neuropathy. Radiologic tumor response was determined by the following scheme: regression (> 2 -mm tumor regression using the greatest axial tumor dimension), stable (≤ 2 -mm regression or growth in greatest axial dimension), and failure (> 2 -mm tumor growth within the SRS targeted field). Notably, there are no recognized response criteria for ENB to radiation; therefore we have used these criteria that recognize formal radiographic response since initially treating these with SRS.

Follow-Up

Patients were typically followed clinically and radiographically at 3- to 6-month intervals after gamma knife radiosurgery; the last known MRI was used for follow-up. MRIs were used as the neuroimaging study of choice unless there was a contraindication for an MRI, in which case CT was utilized.

Statistical Analysis

Data were typically expressed in median, mean plus standard deviation, and range. Univariate analysis (JMP v.9.0, SAS, Carry, North Carolina, United States) was performed to assess for prognostic factors related to tumor progression; a p value < 0.05 was deemed statistically significant.

Results

All 16 institutions queried their databases for treatment of locally recurrent ENB. Thirteen patients were identified, with only 4 of 16 institutions in the consortium reporting treating ENB with SRS during the study period.

Demographics

A total of 54% ($n = 7$) of the patients treated in this series were women. Median age was 49 years (mean age: 50 ± 4 years; range: 19–79 years).

Table 1 Surgical staging, margins, grades, and adjuvant therapy

Patient no.	Age, y	Sex	Surgical margins*	Kadish stage	Biller stage	Dulguerov stage	Hyams grade	Prior radiation	Prior chemotherapy
1	43	M	NA	C	T4	T4	NA	+	+
2	67	M	–	B	T2	T2	NA	+	–
3	68	F	+	D	T4	T4	NA	+	–
4	40	F	+	C	T3	T4	NA	+	–
5	19	F	+	B	T1	T2	NA	+	–
6	79	M	+	A	T1	T1	3	–	–
7	52	M	+	C	T4	T4	3	+	+
8	55	F	+	C	T2	T3	2	+	+
9	36	M	+	C	T4	T4	2	–	+
10	44	F	–	C	NA	NA	3	+	+
11	40	F	+	C	T4	T4	3	+	+
12	49	M	+	C	T4	T4	3	+	+
13	61	F	NA	C	NA	NA	3	–	–

All patients had an operation. Plus and minus signs indicate if surgical margins were positive or negative at the conclusion of surgery. Abbreviation: NA, not available.

Primary Treatment and Adjuvant Therapy

All 13 patients had initially undergone gross total resection of primary disease. At initial presentation nine patients (69%) presented with Kadish stage C lesions, two (16%) had stage B, one (8%) had stage A, and an additional one patient (8%) had Kadish stage D disease prior to initial resection. Biller et al⁴ and Dulguerov/Calcaterra⁶ staging are reported in ►Table 1. Fractionated radiation had been delivered in 10 patients (77%) before recurrence and treatment with SRS. The median fractionated radiation dose was 52.2 Gy (range: 27–69 Gy). Seven patients (54%) had received chemotherapy prior to SRS, usually with a platinum-based regimen.

Gamma Knife Radiosurgery

Within the 13 patients in this study, 31 procedures were performed during 22 separate treatment sessions, each time for a separate local recurrence. The median treatment volume was 5.4 cm³ (range: 1.4–76.3 cm³), whereas the median marginal and maximum dose were 15 Gy (range: 7–18 Gy) and 30 Gy (range: 16–45 Gy), respectively (►Table 2). Details of the 31 procedures can be seen in ►Table 3.

Table 2 Gamma knife surgery parameters

Characteristic	Mean ± SD	Median (range)
Margin dose, Gy	14.3 ± 2.9	15 (7–18)
Maximum dose, Gy	30.5 ± 6.8	30 (16–45)
No. of isocenters	6.5 ± 4.4	5 (1–22)
Treatment volume, cm ³	14.5 ± 18.3	5.4 (1.4–76.3)
Length of follow-up since SRS, mo	28.1 ± 25.0	23 (1–100)

Abbreviations: SD, standard deviation; SRS, stereotactic radiosurgery.

Notably, of 31 separate tumors, 27 (87%) had imaging follow-up available for review. Three tumors (11%) showed definite radiographic failure defined as documented growth > 2 mm in any plane. Thirteen tumors (48%) had a positive treatment response with documented reduction in tumor volume, and an additional 11 (41%) had tumors that remained stable during a median radiographic follow-up of 36 months (range: 1–100 months). Univariate analysis did not find any significant factor ($p < 0.05$) relating to treatment failure including margin dose, maximum dose, tumor volume, presenting stage or grade of ENB, or patient age. Notably, there were no radiation-related symptomatic complications.

Discussion

This report represents the combined efforts of 4 institutions (of 16 queried) to determine the efficacy of SRS to treat focal intracranial recurrence of ENB, a very rare lesion. Reports of case series available in the literature of patients with ENB reveal that for patients treated with aggressive initial management, > 50% of patients develop recurrent disease.²⁴ Most recurrences are local within the anterior skull base or upper nasal cavity.² The great majority of articles dedicated to the treatment of ENB focus only on primary disease with very few reports that address salvage management for recurrent or residual disease.¹⁰ As a group, we favor surgical removal if intracranial recurrence is accessible; however, it may be true that salvage SRS may be equivalent in local disease control. Therefore, we consider SRS in patients of advanced age, the medically infirm, situations where transcranial resection may incur unacceptable morbidity, or the patient refuses open or endoscopic resection of the recurrent tumor. In this study, we report the outcomes of 13 patients who underwent 31 SRS

Table 3 Patient-specific Stereotactic Radiosurgery treatments

Patient no.	Treatment no.	Age, y	Kadish	No. of isocenters	Margin dose, Gy	Maximum dose, Gy	Treatment volume, cc	Duration of follow-up, mo	SRS response
1	1	43	C	22	10	20	10.7	100	Smaller
2	1	67	B	3	16	32	4.7	84	Stable
3	1	68	D	5	14	28	13.3	23	Smaller
	2			2	15	30	4.8	23	Smaller
	3			2	15	30	2.7	23	Smaller
	4			11	7	17	49.5	23	Smaller
	5			7	8	16	13.1	23	Smaller
	6			1	15	18	4.1	2	Stable
	7			12	15	30	4.6	2	Failure
	8			4	15	30	3.8	2	Failure
4	1	40	C	4	18	32.7	5.9	14	Stable
	2			1	18	30	2.7	14	Stable
	3			4	18	30	4.6	14	Stable
5	1	19	B	9	14	28	33.7	3	Smaller
	2			6	14	28	14.9	1	NA
6	1	79	A	4	16	40	11.3	40	Smaller
7	1	52	C	11	12	40	76.3	10	Stable
	2	52		3	12	30	13.5	10	Stable
	3	52		6	12	40	56.3	10	Stable
8	1	55	C	12	16	40	8.4	67	Stable
	2			5	16	32	2.1	67	Stable
9	1	36	C	14	12	24	NR	36	NA
	2			9	12	30	23	26	NA
10	1	44	C	5	14	35	13.6	36	Smaller
11	1	40	C	7	10	25	38.4	22	Failure
12	1	49	C	6	18	45	4.9	43	Smaller
13	1	61	C	4	16	32	4.2	64	Stable
	2			5	16	32	4.5	37	Smaller
	3			4	16	32	1.4	24	Smaller
	4			8	17	34	3.7	17	Smaller
	5			4	17	34	1.4	12	NA

Abbreviations: NA, not available; NR, no report.

salvage procedures for focally recurrent tumor. A total of 89% of tumors (24/27) with radiographic follow-up demonstrated local control at a median of 36 months, with up to 100 months of follow-up in one patient. The data support the concept that SRS for locally recurrent ENB is a sound strategy associated with a low risk of short-term morbidity.

In a previous report of seven patients treated with SRS for ENB, it was suggested that the lone failure was due to a low marginal dose of 10 Gy.²⁴ In this study, however, several tumors were treated at lower doses, namely 7, 8, and 10 Gy without failure. Alternatively, one patient with Kadish D disease in this multi-institutional series with relatively small

tumor volumes (4.6 and 3.8 cc) did not respond to a marginal dose of 15 Gy in two separate treatments and continued to have local progression. It is likely (given the initial presentation) that the histology of this patient's tumor was very aggressive. Unfortunately, some institutions continue to treat all ENB as the same, although it has been shown that Hyams grading is extremely important in predicting the tumor's behavior and patient outcome; in this case, it may have predicted this patient's tumor as a poor responder.² Unfortunately, Hyams grade was not available on 5 of 13 initial resections, and 6 of 8 remaining tumors were all grade 3, so meaningful statistical analysis of tumor grade and

marginal dose was not possible. Regardless, in this small study, there were no failures of treatment when > 15 Gy was used, although in univariate analysis this did not reach statistical significance. Therefore, based on this initial experience, a marginal dose > 15 Gy appears to be desirable. Because tumor recurrences most often develop at cranial sites without adjacent critical brain or cranial nerve structures, higher tumor margin doses (as reported by Unger et al) are indicated, as long as the dose to the optic nerve is limited to < 10 Gy.^{13,14,24}

Since our previous report of seven patients, there was an additional case report of successful SRS treatment of a Kadish C lesion.¹⁹ A tumor volume of 7.5 cm³ was treated with a marginal dose of 20 Gy and a maximum dose of 40 Gy.¹⁹ Of particular interest, the patient had a lesion extending into the cavernous sinus that was deemed inoperable; this was not the case in this series because most lesions could have been addressed with repeat craniotomy. This lesion was resistant to both prior chemotherapy trials and conventional radiotherapy.¹⁹ There was a reported dramatic reduction in tumor size and symptomatic improvement at 2 years. The patient also had an out-of-field recurrence, which was also treated with a marginal dose of 20 Gy and is now stable.¹⁹ Nearly 50% of the tumors treated in this present study had a similar reduction in tumor volume after treatment. At present, a marginal dose between 15 and 20 Gy appears effective for the treatment of recurrent ENB.

What is further interesting is that ~ 77% of the patients in this series had prior fractionated radiation therapy and developed in-field recurrence. Fortunately, despite repeat, and in some cases high-dose SRS, there was no observed toxicity or complications after a median follow-up of 36 months. One potential explanation for this is that typically recurrences occur on the dura near the frontal lobes; although no induced radiation toxicity was observed, it is possible that retreatment in this area of low critical brain function is better tolerated.

Although little data are available regarding the risks of revision craniotomy in patients with ENB, there is evidence from other primary brain tumor series that repeat surgery increases the risk of perioperative complications to > 20%, or over double the complication rate seen with primary surgery.²³ Given this high potential for complications and associated hospitalization, SRS may be a more efficient option in terms of complication avoidance (here 0%), and potentially more cost effective avoiding a prolonged hospital recovery from a repeat craniotomy.

Conclusion

SRS appears to provide a safe and effective option for treatment of recurrent intracranial ENB, controlling disease in 89% of patients, as demonstrated in this multi-institutional study. Revision transcranial resection and/or repeat fractionated external-beam radiation may carry substantial morbidity and may be avoided by using noninvasive treatment options such as SRS for locally recurrent ENB.

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Conflicts of Interest

L. Dade Lunsford is a consultant and shareholder in Elekta, the maker of Gamma Knife. There was no grant funding for this article. The remaining authors report no conflicts of interest, personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

References

- 1 Theilgaard SA, Buchwald C, Ingeholm P, Kornum Larsen S, Eriksen JG, Sand Hansen H. Esthesioneuroblastoma: a Danish demographic study of 40 patients registered between 1978 and 2000. *Acta Otolaryngol* 2003;123(3):433–439
- 2 Van Gompel JJ, Giannini C, Olsen KD, et al. Long-term outcome of esthesioneuroblastoma: Hyams grade predicts patient survival. *J Neurol Surg B Skull Base* 2012;73(5):331–336
- 3 Bäck L, Oinas M, Pietarinen-Runtti P, et al. The developing management of esthesioneuroblastoma: a single institution experience. *Eur Arch Otorhinolaryngol* 2012;269(1):213–221
- 4 Biller HF, Lawson W, Sachdev VP, Som P. Esthesioneuroblastoma: surgical treatment without radiation. *Laryngoscope* 1990; 100(11):1199–1201
- 5 Chao KS, Kaplan C, Simpson JR, et al. Esthesioneuroblastoma: the impact of treatment modality. *Head Neck* 2001;23(9): 749–757
- 6 Dulguerov P, Calcaterra T. Esthesioneuroblastoma: the UCLA experience 1970–1990. *Laryngoscope* 1992;102(8):843–849
- 7 Foote RL, Morita A, Ebersold MJ, et al. Esthesioneuroblastoma: the role of adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys* 1993;27(4):835–842
- 8 Hyams V. Tumors of the Upper Respiratory Tract and Ear. Washington, DC: Armed Forces Institute of Pathology; 1988
- 9 Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. *Cancer* 1976;37(3):1571–1576
- 10 Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. Esthesioneuroblastoma: prognosis and management. *Neurosurgery* 1993;32(5):706–714; discussion 714–715
- 11 Ozsahin M, Gruber G, Olszyk O, et al. Outcome and prognostic factors in olfactory neuroblastoma: a rare cancer network study. *Int J Radiat Oncol Biol Phys* 2010;78(4):992–997
- 12 Ong YK, Solares CA, Carrau RL, Snyderman CH. New developments in transnasal endoscopic surgery for malignancies of the sinonasal tract and adjacent skull base. *Curr Opin Otolaryngol Head Neck Surg* 2010;18(2):107–113
- 13 Unger F, Haselsberger K, Walch C, Stammberger H, Papaefthymiou G. Combined endoscopic surgery and radiosurgery as treatment modality for olfactory neuroblastoma (esthesioneuroblastoma). *Acta Neurochir (Wien)* 2005;147(6):595–601; discussion 601–602
- 14 Unger F, Walch C, Stammberger H, Papaefthymiou G, Haselsberger K, Pendl G. Olfactory neuroblastoma (esthesioneuroblastoma): report of six cases treated by a novel combination of endoscopic surgery and radiosurgery. *Minim Invasive Neurosurg* 2001;44(2): 79–84
- 15 Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. *Lancet Oncol* 2001;2(11):683–690

- 16 Elkon D, Hightower SI, Lim ML, Cantrell RW, Constable WC. Esthesioneuroblastoma. *Cancer* 1979;44(3):1087–1094
- 17 Ingeholm P, Theilgaard SA, Buchwald C, Hansen HS, Francis D. Esthesioneuroblastoma: a Danish clinicopathological study of 40 consecutive cases. *APMIS* 2002;110(9):639–645
- 18 Loy AH, Reibel JF, Read PW, et al. Esthesioneuroblastoma: continued follow-up of a single institution's experience. *Arch Otolaryngol Head Neck Surg* 2006;132(2):134–138
- 19 Dinca EB, Radatz MW, Rowe J, Kemeny AA. Gamma Knife® radiosurgery for recurrent intracranial olfactory neuroblastoma (esthesioneuroblastoma): a case report. *J Med Case Reports* 2012;6(1):240
- 20 Gore MR, Zanation AM. Salvage treatment of local recurrence in esthesioneuroblastoma: a meta-analysis. *Skull Base* 2011;21(1):1–6
- 21 Kim HJ, Cho HJ, Kim KS, et al. Results of salvage therapy after failure of initial treatment for advanced olfactory neuroblastoma. *J Craniomaxillofac Surg* 2008;36(1):47–52
- 22 Dias FL, Sa GM, Lima RA, et al. Patterns of failure and outcome in esthesioneuroblastoma. *Arch Otolaryngol Head Neck Surg* 2003;129(11):1186–1192
- 23 Hoover JM, Nwojo M, Puffer R, Mandrekar J, Meyer FB, Parney IF. Surgical outcomes in recurrent glioma: clinical article. *J Neurosurg* 2013;118(6):1224–1231
- 24 Van Gompel JJ, Carlson ML, Pollock BE, Moore EJ, Foote RL, Link MJ. Stereotactic radiosurgical salvage treatment for locally recurrent esthesioneuroblastoma. *Neurosurgery* 2013;72(3):332–339; discussion 339–340