Esthesioneuroblastoma: The Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital Experience with Craniofacial Resection, Proton Beam Radiation, and Chemotherapy

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ABSTRACT

Objectives: To determine the efficacy of craniofacial resection and proton radiation for the management of esthesioneuroblastoma (ENB). **Design:** A retrospective chart review was performed of all patients presenting with ENB and completely managed at the Massachusetts General Hospital (MGH) and the Massachusetts Eye and Ear Infirmary (MEEI) from 1997 to 2006. **Setting:** A tertiary referral center. **Main Outcome Measures:** Disease-free and overall survival. **Participants:** All patients presenting with ENB and completely managed at the MGH and the MEEI from 1997 to 2006. **Results:** Ten patients were identified with a median follow-up time of 52.8 months. Average age at presentation was 45 years. Nasal obstruction was the most common presenting symptom. Three patients presented with Kadish stage B disease and seven with stage C. No patient had evidence of cervical or metastatic disease at presentation. Seven patients were treated with craniofacial resections (CFR) followed by proton beam radiation with or without chemotherapy. Three patients were treated with initial chemotherapy with no response. They subsequently underwent CFR followed by proton beam radiation. The 5-year disease-free and overall survival rates were 90% and 85.7%, respectively, by Kaplan-Meier analysis. No patient suffered any severe radiation toxicity. **Conclusion:** ENB can be safely and effectively treated with CFR followed by proton beam irradiation. Proton

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irradiation may be associated with less toxicity than photon irradiation. The role of chemotherapy remains unclear.

KEYWORDS: Esthesioneuroblastoma, proton radiation, craniofacial resection

Esthesioneuroblastoma (ENB) is a rare malignant tumor of the nasal vault, believed to arise from the olfactory epithelium. It was first described by Berger and colleagues in 1924,¹ and given the name *esthésioneuroépithéliome olfactif*. Since its first description, the histologic origin of these tumors has been debated, but they are now thought to arise from olfactory stem cells of neural crest origin.^{2,3} In the present literature, these tumors are referred to as olfactory neuroblastomas or ENBs.

Treatments strategies for ENB have included every combination of surgery, radiation, and chemotherapy.²⁻⁶ Although transfacial surgical approaches have been used in the past, studies have demonstrated that craniofacial resection (CFR) offers superior local control and improved overall survival.^{4,7,8} This is believed to be due to an improved ability to resect tumors en bloc with negative margins. While most institutions offer postoperative radiotherapy to patients with advanced-stage disease,⁸⁻¹⁰ the University of Virginia has achieved excellent results with preoperative radiotherapy with or without chemotherapy. A meta-analysis by Dulguerov and colleagues³ demonstrated that surgery with radiation is the most frequently used approach, and the one achieving the highest cure rates.

Standard photon radiotherapy can result in marked morbidity when treating paranasal sinus malignancies because of radiosensitive adjacent structures including the globe, optic nerves, chiasm, brain, and brainstem. Photons deliver their highest dose at the skin, followed by a continuously decreasing dose with increasing depth of penetration. This means that any structure between the tumor and the skin receives an even greater dose than the tumor itself. Protons have a physical advantage over photons as they deposit nearly all of their energy at their point of greatest penetration. This phenomenon is

known as the Bragg peak. The exact depth of penetration is dependent on the energy of the proton beam, which can be very precisely controlled to place the Bragg peak within the tissues targeted to receive the radiation dose. As the protons are absorbed in a very specific distribution, adjacent healthy tissues receive a greatly reduced dose. This superior physical property of protons could potentially lead to improved local control and decreased acute and late toxic effects.¹¹ Preliminary studies have shown that proton radiotherapy following surgery is effective for treating other neoplasms of the skull base, including adenoid cystic carcinoma, chordoma, and chondrosarcoma, with decreased treatment toxicity.¹²⁻¹⁴ This suggests that proton therapy may also serve as an effective adjuvant therapy for ENB.

The Massachusetts General Hospital (MGH) Cancer Center and the Massachusetts Eye and Ear Infirmary (MEEI) current protocol for the treatment of ENB involves CFR followed by proton radiation. Postoperative chemotherapy is reserved for patients with positive margins. This article reviews patients who were diagnosed and completely managed at the MGH and the MEEI between 1997 and 2006.

MATERIALS AND METHODS

Study Cohort

From January 1997 to December 2006, 10 patients with newly diagnosed ENBs received all aspects of their treatment at the MGH and the MEEI. Each patient was seen by a multidisciplinary team that included a radiation oncologist, medical oncologist, otolaryngologist, and neurosurgeon. A treatment

Table 1 Patient Demographics, Stage, and Presenting Symptoms

Patient No.	Age at Diagnosis (y)	Sex	Kadish Stage	TNM Stage	Presenting Symptom
1	77	M	C	T3N0M0	Chronic rhinorrhea, epistaxis
2	44	M	B	T2N0M0	Nasal obstruction, rhinorrhea
3	62	M	C	T3N0M0	Epistaxis
4	58	F	C	T4N0M0	Nasal obstruction
5	51	F	B	T1N0M0	Nasal obstruction
6	21	F	C	T4N0M0	Nasal obstruction
7	11	M	C	T3N0M0	Headaches, nasal obstruction
8	44	M	C	T4N0M0	Nasal obstruction
9	42	F	B	T3N0M0	Nasal obstruction
10	35	F	C	T4N0M0	Nasal obstruction, nasal dryness

plan was formulated for each patient that involved one of two possible treatment strategies: (1) induction chemotherapy followed by proton radiation with CFR reserved for chemotherapy nonresponders, or (2) CFR resection followed by proton radiation with or without chemotherapy. During CFR, every effort was made to remove the tumor en bloc with negative margins. Patients were seen by a neuro-ophthalmologist postoperatively as needed.

All medical records including imaging reports, chemotherapy, and radiation records were reviewed retrospectively. Extracted information included patient demographics, symptoms at diagnosis, tumor stage and grade (if available), treatment received, treatment complications, tumor recurrence, and patient survival. The primary end points for the study were progression-free and overall survival rates. Survival was calculated in months from the time of diagnostic biopsy. All end points were determined using the Kaplan-Meier method.¹⁵ This study was approved by the institutional review board of the MEEI and the MGH.

with a range of 11 to 77 years. The most common presenting symptom was nasal obstruction which was present in eight patients (80%). Other symptoms including rhinorrhea (20%), epistaxis (10%), and headaches (10%) were less common.

All relevant pathology was reviewed by the Department of Pathology at the MGH. The diagnosis of ENB was based on light microscopy findings, as well as immunohistochemical staining for synaptophysin, chromogranin, and S100. The Hyams grade was documented for only three patients. All patients were evaluated prior to CFR with magnetic resonance imaging (MRI) of the brain and skull base as well as a fine-cut computed tomography (CT) scan of the skull base.

Tumors were retrospectively staged using the Kadish classification,¹⁶ as well as the TNM schema proposed by Dulguerov and Calcaterra⁸ on the basis of physical examination, MRI, and CT scan at the time of initial presentation. Three patients (30%) presented with Kadish stage B disease, while the remaining seven (70%) had stage C disease. No patients had cervical or metastatic disease at presentation. Patient demographics and initial signs and symptoms of disease are summarized in Table 1.

RESULTS

Patient and Tumor Characteristics

Our series included five women (50%) and five men (50%). The median age at diagnosis was 45 years

Treatment

Treatment protocols fell into one of two groups. Three of the 10 patients were initially managed

Table 2 Treatment and Outcome

Patient No.	Treatment	Surgical Margins	Total (Gy)	Chemo	Recurrence (mo)	Final Status	Total Follow-Up Time (mo)
1	CFR + proton/photon RT	Negative	66	None	No	NED	34
2	CFR + proton/photon RT	Negative	59	None	No	NED	61
3	CFR + proton/photon RT	Positive	59	None	Yes (72)	NED	77
4	CFR, proton RT	Negative	54	None	No	NED	60
5	CFR + proton RT	Negative	70	None	No	NED	18
6	CFR + proton/photon RT + CT	Positive	70	4 cycles cisplatin, etoposide	No	NED	20
7	Endoscopic resection (partial) → CFR + proton RT	Negative	54	None	No	NED	23
8	CT (no response) → CFR + proton/photon RT	Positive	67	2 cycles cisplatin, etoposide	Yes (82)	AWD	118
9	CT (no response) → CFR + proton RT	Positive	60	2 cycles cisplatin, etoposide	Yes (61)	NED	87
10	CT (no response) → CFR + proton/photon RT	Positive	67	2 cycles cisplatin, etoposide → no response → 2 cycles carboplatin, etoposide	Yes (16)	DOD	31

CFR, craniofacial resection; RT, radiotherapy; CT, chemotherapy; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease.

nonsurgically with induction chemotherapy followed by proton beam radiation, as described by Bhattacharyya and colleagues.² Induction chemotherapy was not associated with disease response; therefore, each patient was subsequently managed with CFR followed by either proton radiation (1 patient) or a combination of protons and photons (2 patients). The remaining 7 patients were managed with initial CFR followed either proton radiation (3 patients) or a combination of proton and photon radiation (4 patients). One patient was also treated with postoperative chemotherapy because of positive intracranial margins. Treatment parameters are summarized in Table 2.

Surgery

All patients underwent endoscopic intranasal biopsies as a diagnostic step. Patient 7 underwent an attempted endoscopic excision, but was found to be unresectable via a strictly endoscopic technique, and the procedure was aborted. This patient then underwent CFR. In all cases, CFR was performed

by a multidisciplinary team composed of members from the departments of Neurosurgery and Otolaryngology–Head and Neck Surgery. The details of CFR have been previously described elsewhere.¹⁷ No patient underwent only transfacial surgery. Five patients had positive microscopic margins.

Radiotherapy Planning and Delivery

Patients were immobilized by means of a custom-made dental fixation technique and an integrated thermoplastic head mask.¹⁸ This immobilization device limited the mean net three-dimensional patient motion during the treatment to less than 1 mm. A thin-cut high-resolution CT scan with contrast was obtained in the treatment position. MRI was obtained to assist in target delineation. The gross tumor volume, clinical target volume, and surrounding critical structures were outlined. Dose volume histograms were generated for the gross tumor volume, clinical target volume, and surrounding critical structures. For proton treatment planning, a patch combination (split-target volume)

technique was used to optimize the proton dose distribution within an irregular volume in close proximity to critical healthy structures.¹⁹ The target volume was divided into multiple segments with each treated by a separate radiation field. Using the sharp dose fall-off of the Bragg peak, each field was designed to stop in the penumbra of the other fields. Each treatment field was shaped by an individually designed brass aperture and a Lucite range compensator. An appropriate modulator wheel was selected to spread out the Bragg peak. Daily pretreatment alignment radiographs were obtained and compared with CT-generated, digitally reconstructed radiographs to ensure precise positioning of the treatment fields. Proton beam radiation therapy was delivered at the Harvard Cyclotron Laboratory, Cambridge, MA, or the Francis H. Burr Proton Therapy Center at the MGH using 160-MeV and 230-MeV beams, respectively. For photon radiotherapy, a five-field graduated block technique, consisting of an anterior and two sets of right and left lateral beams targeting the clinical target volume, was used to design the treatment plan. Photon beam radiation therapy was delivered mostly with either 4 or 6 MV.²⁰ All patients tolerated radiotherapy without treatment break.

Radiation Dose and Fractionation

All patients were treated with definitive radiotherapy with curative intent. The total median dose delivered to the gross tumor volume was 62.7

cobalt-gray equivalent (CGE) (range, 54 to 70). The radiation protocol to the primary site combining proton radiotherapy with or without photon radiotherapy evolved over a period of time, so varying fractionation schedules were used (Table 2). On average, patients received 1.82 Gy per fraction over 35.0 fractions.

Chemotherapy

As mentioned above, three patients were treated with induction chemotherapy with no response. All three patients received two cycles of etoposide and cisplatin every 3 weeks. One of these patients received an additional two cycles of carboplatin and etoposide. Patient 6 received four cycles of postoperative cisplatin and etoposide every 3 weeks as adjuvant treatment of a lesion with significant intracranial extension and positive surgical margins along the olfactory nerve tract (Table 2).

OUTCOMES

Local, Regional, and Distant Control

Four patients suffered recurrences an average of 57.8 months after diagnosis (Tables 2 and 3). Patient 3, who had a gross total resection with positive microscopic margins at CFR recurred locally at the edge of his frontal craniotomy bone flap

Table 3 Management and Outcome of Recurrent Tumors

Patient No.	Location	Time to Recurrence (mo)	Management of Recurrence	Final Status
3	Edge of craniotomy bone flap	72	Surgical excision, RT	NED
8	1. Cervical spine 2. Leptomeninges 3. Left neck	82	1. Resection of cervical spine metastases 2. CT + RT 3. Left ND	AWD
9	Left parotid	61	Parotidectomy, ND	NED
10	1. Right frontal lobe 2. Thoracic spine	16	Palliative chemotherapy	DOD

RT, radiotherapy; CT, chemotherapy; ND, neck dissection; NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease.

72 months after diagnosis. Recurrent tumor was managed with surgical excision and reirradiation. He currently is alive without disease 6 months later. Patient 9, treated with initial chemotherapy and then with CFR and proton irradiation, recurred regionally 61 months after diagnosis and was managed with a parotidectomy and neck dissection and is alive without disease at 81 months. Patient 8 was also treated with initial chemotherapy, followed by CFR and mixed photon/proton irradiation. He recurred both regionally and distantly and was managed with surgical resection, chemotherapy, and reirradiation and is alive with disease 28 months later. Patient 10 developed distant metastases to the brain and spine, which was managed with palliative chemotherapy. This patient eventually succumbed to disease 31 months after diagnosis. Overall, five patients in our series had positive surgical margins, including all four patients that recurred. In addition, all three patients that were initially managed with the chemotherapy and radiation protocol recurred.

Survival Rates

Kaplan-Meier survival curves were constructed for 5-year disease-free survival (DFS) and overall survival (OS) rates (Fig. 1). The calculated 5-year DFS and OS rates were 90% and 85.7%, respectively.

Figure 1 Overall (OS) and disease-free survival (DFS) rates over time.

Figure 2 Overall survival rates: initial craniofacial resection (CFR) followed by radiation versus induction chemotherapy followed by CFR and radiation.

There was a trend toward better DFS and OS in patients who underwent initial CFR versus those who underwent initial chemotherapy (Figs. 2 and 3); however this was not significant ($p=0.4$ and $p=0.25$, respectively, by the log rank test). The 5-year OS and DFS for patients undergoing initial CFS followed by radiation were both 100% with the only recurrence in this subset occurring at 72 months after diagnosis. There was also a trend toward improved OS and DFS in patients with negative surgical margins (Figs. 4 and 5); however, this difference was not significant ($p=0.39$ and $p=0.26$, respectively).

Figure 3 Disease-free survival rates: initial craniofacial resection (CFR) followed by radiation versus induction chemotherapy followed by CFR and radiation.

Figure 4 Overall survival rates: positive versus negative surgical margins.

Figure 5 Disease-free survival rates: positive versus negative surgical margins.

COMPLICATIONS

Treatment toxicity was scored using the Common Terminology Criteria for Adverse Events (version 3.0) of the National Cancer Institute.²⁰ Our 10 patients experienced a total of 18 complications from all modalities of therapy (Table 4).

Ocular and Visual Outcome

Although 70% of patients suffered an ocular complication, all of these were mild or moderate (grade 1 or 2) in severity. There were no grade 3 to 5 injuries. The most common toxic effects were diplopia (3 patients) and epiphora (2 patients). One case of abducens palsy spontaneously resolved.

Central Nervous System Outcome

Radiographic brain change was defined as any enhancement seen in delayed hyperintensity on T1-weighted MRI at any follow-up. Two patients experienced asymptomatic (grade 2) radiation brain injury. One patient experienced a postoperative cerebrospinal fluid (CSF) leak and symptomatic pneumocephalus requiring intubation for airway diversion and an endoscopic CSF leak repair, which was successful. Another patient developed asymptomatic postoperative pneumocephalus that resolved after the patient's lumbar drain was clamped.

Wound Healing and Infectious Outcomes

Two patients developed chronic sinocutaneous fistulae in the medial canthal area on the side of their

Table 4 Treatment Complications: Complications Are Categorized by Organ System and National Cancer Institute Grade from Mild (1) to Severe (4)

Grade	Ocular	Central Nervous System	Wound
1	Mild dryness (1)		
2	Epiphora (2), diplopia (3), globe ptosis (1), abducens palsys (1)	Radiation brain injury (2), pneumocephalus (1)	Wound infection (1)
3		Cerebrospinal fluid leak (1), pneumocephalus (1)	Wound infection (1), infected bone flap (1), sinocutaneous fistulae (2)
4			
Total (%)	70	20	50

lateral rhinotomy incision. One patient underwent successful repair with a paramedian forehead flap and prosthesis placement. Repair was planned on the second patient, but was not completed as she developed progressive recurrent disease. Two patients suffered surgical wound infections. One resolved with antibiotics alone, while the other required surgical débridement in addition to antibiotics. One patient developed an infected frontal bone flap 2 years postoperatively that resolved with intravenous antibiotics.

DISCUSSION

The optimal management for ENB has not been clearly defined due to the rarity of the disease. The vast majority of the literature on this subject is presented in the form of small case series similar to this study. The meta-analysis conducted by Dulguerov and colleagues³ provides the most complete data. Dulguerov determined that surgery followed by radiation achieved the highest cure rates, calculated to be 65% at 5 years. Patients treated with surgery, radiation, and chemotherapy fared poorer, with 5-year survival rates of 47%. However, comparison of surgery and radiation versus surgery, radiation, and chemotherapy in a retrospective fashion is biased as patients with advanced disease are more likely to receive adjuvant chemotherapy.^{4,21}

The role of chemotherapy in the treatment of ENB is unclear as some institutions have achieved excellent results with^{4,22,23} or without it.^{10,24} Chemotherapy has been used as primary treatment,^{2,22,25} but in most centers it is used as adjuvant therapy, especially for high-grade tumors.^{4,23,26–29} At the University of Virginia, patients with Kadish stage C disease are first treated with preoperative sequential chemotherapy and radiotherapy (50 Gy) followed by CFR. Their regimen includes two cycles of cyclophosphamide (300 to 650 mg/m²) and vincristine (1 to 2 mg) with or without doxorubicin. With this protocol they have achieved 5-year DFS rates of 86.5%.³⁰ At our institution,

Bhattacharyya and colleagues have described a protocol for treating patients nonsurgically, using induction chemotherapy followed by proton radiation. The regimen utilized was cisplatin (33 mg/m² daily) and etoposide (100 mg/m² daily) for 3 days every 2 weeks for two to four cycles depending on the response. An excellent response rate—defined by at least 50% reduction in tumor volume—was observed in 89% of patients.² However, the long-term outcomes for these patients have not been published. In the present study, the three patients treated with upfront chemotherapy all progressed, ultimately requiring CFR and radiation. Another patient received four cycles of cisplatin and etoposide postoperatively for T4 disease with positive surgical margins. This patient remains alive without disease 13 months after diagnosis. As upfront CFR has provided superior results, induction chemotherapy has been discontinued at our center. Prospective trials are needed to clearly define the role of chemotherapy in the management of this disease.

Most institutions favor surgery as the first treatment modality, followed by radiotherapy.^{8,9,31} Standard radiotherapy for these lesions involves external megavoltage beam and a three-field technique, with dose ranges from 55 to 65 Gy.^{6,8,10,30,32} Expected complications of irradiation of the anterior skull base include radiation retinopathy, orbital inflammation, frontal lobe radionecrosis, delayed wound infections, and bone flap osteomyelitis. Unfortunately, radiation toxicities are frequently not reported in most surgical series. However, the data available suggest that orbital complications are a significant problem. An 8 to 24% rate of severe ocular injury has been reported following photon radiation, resulting in a poor to nonfunctioning eye after administration of doses of 55 to 65 Gy.^{6,8,33}

Over the last two decades there has been increasing evidence that proton beam radiation may offer superior results to standard external beam radiation for lesion of the skull base.^{5,14} As mentioned above, protons have a physical advantage over x-rays as they deposit most of their radiation energy at their point of greatest penetration in the tissue. This physical property is known as the Bragg

peak, which allows precise control of the deposition of radiation in the target field. This allows a maximum dose to be delivered to the target tissue, with minimal doses delivered to adjacent radio-sensitive structures, particularly the optical axis. Previous reports have demonstrated the safety and efficacy of proton radiation in the management of ENB. The aforementioned study by Bhattacharyya demonstrated an excellent response to chemotherapy and proton radiation.² Only one of nine patients suffered an ocular complication, which completely resolved. Nishimura and colleagues treated 14 patients with ENB solely with definitive proton beam radiation with outstanding 5-year DFS and OS rates of 71% and 93%, respectively, with no toxic effects greater than grade 2.⁵ In our present study, 70% of patients suffered ocular complications; however, all of these were grade 1 or 2 in severity and the majority resolved themselves. The three cases of diplopia, one case of globe ptosis, and one case of epiphora (secondary to nasolacrimal duct excision) were attributed to surgical intervention. The remaining three (30%) complications were attributed to radiotherapy and included cases of mild xerophthalmia (grade 1), epiphora, and a transient abducens palsy (grade 2). Two patients (20%) suffered asymptomatic frontal lobe radionecrosis noted on imaging that self-resolved. These frequent but less severe sequelae appear to be a significant improvement compared with results from standard radiotherapy.

The average time to recurrence was 57.8 months, which is consistent with the late recurrences noted in the literature,^{3,6,10,30,32} reinforcing the need for continued long-term follow-up. Of note, all three of the patients who underwent initial chemotherapy instead of initial resection recurred, while only one of seven patients who underwent initial CFR recurred. Conceivably, the delay in definitive management (surgery and radiation) necessitated by induction chemotherapy may have allowed progression of disease, impairing the ability to achieve negative surgical margins and adversely affecting outcome. There was a trend toward improved DFS and OS rates in patients

with negative surgical margins, although these differences were not significant, likely due to a small sample size. Patient 7 had a positive intracranial surgical margin but currently remains free of disease 20 months after diagnosis. This may reflect the ability of proton radiation to control partially resected disease, which has been demonstrated in other studies.¹⁴

The meta-analysis by Dulguerov reported a 5-year OS of 45%.³ Most large studies report 5-year survival rates between 60% and 86%.^{6,8,10,26,30} Although our series is limited in size and follow-up, our calculated 5-year DFS and OS rates of 100% for patients undergoing initial CFR followed by radiation certainly compare extremely favorably. This, in combination with the low rate of serious complications, suggests that CFR followed by proton beam radiation may be the management of choice for ENB.

CONCLUSION

Our series, although constrained by small numbers and limited follow-up, would suggest that CFR followed by proton beam radiation can offer excellent control of ENB with significantly diminished toxic effects, particularly to the orbit.

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Commentary

The authors are to be commended for their work. Although their series is small, the analysis should prompt interesting debate on the optimal treatment for esthesioneuroblastoma. The overall survival and disease-free survival rates compare with the best reported series. A craniofacial resection and negative margins were strong positive predictors for better outcomes. The results also argue against induction chemotherapy in favor of a more aggressive, upfront craniofacial resection. The authors strongly advocate postoperative proton beam radiotherapy because of its unique beam characteristics and relatively low toxicity.

In our experience the morbidity associated with a craniofacial resection can be lessened by combining a transbasal approach with an endoscopic paranasal resection. In this manner, a lateral rhinotomy incision can be avoided entirely. Although some authors even propose performing the entire resection through an endoscope, we believe that skull base and dural margins are best assessed through an open approach. My otolaryngological colleagues are comfortable that they can achieve a margin-free resection with endoscopic access, given that the exposure of the deeper sphenoid and cribriform regions is well

assessed through the cranial approach. Because robotic radiosurgery systems can now easily target the paranasal skull base, we also believe that there is a growing role for radiosurgery in the treatment of discrete residual or recurrent tumors.

Overall, the series provides data to the increasing body of evidence that surgery should play a critical role in the care of esthesioneuroblastoma. Long-term follow-up of this cohort will likely strengthen this opinion.

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