

ESTHESIONEUROBLASTOMA: THE PRINCESS MARGARET HOSPITAL EXPERIENCE

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Abstract: *Background.* Esthesioneuroblastoma is rare. The aim of the study was to review our experience and to evaluate the staging system and treatment that best correlates with the patient outcome.

Methods. Thirty-nine patients were identified between 1972 and 2006.

Results. At presentation 10% had cervical metastases. None had distant metastasis. Five were treated with surgery, 2 with chemotherapy, 1 with radiotherapy, and 30 with surgery and radiation. Local disease control was 82.6% at 5 years. Recurrence was seen in 33% with local and regional disease recurrence at 15% and 18%, respectively. The 5- and 10-year overall survival rates were 87.9% and 69.2%, respectively. Dulguerov classification correlated most closely to survival and recurrence.

Conclusions. Dulguerov classification best correlates with the patient's outcome. A combined approach is the preferred treatment. It makes no difference whether radiotherapy is given pre or postsurgical resection. Recurrence can occur even 15 years after treatment. Therefore, long-term follow-up is essential. ©2008 Wiley Periodicals, Inc. *Head Neck* 30: 1607–1614, 2008

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Esthesioneuroblastoma (ENB), also termed olfactory neuroblastoma, is an uncommon neuroendocrine malignancy arising from the basal layer of the olfactory epithelium.¹ Based on the tissue of origin, these tumors tend to arise in the nasal vault at either the cribriform plate, upper surface of the septum, or superior turbinate. In North America, ENB accounts for approximately 0.3%

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Table 1a. Hyams grading system.

	Lobular preservation	Mitotic index	Nuclear polymorphism	Fibrillary matrix	Rosettes	Necrosis
T1	+	None	None	Prominent	HW rosettes	None
T2	+	Low	Moderate	Present	HW rosettes	None
T3	±	Moderate	Prominent	Low	HW rosettes	Rare
T4	±	High	Marked	Absent	None	Frequent

of all cancers of the upper aerodigestive tract and between 3% and 6% of all intranasal malignancies.¹ A literature review by Broich et al noted approximately 1000 cases reported between 1924 and 1997.¹ Since then there have been additional reports, however, given the rarity of this tumor, the majority of studies comprise retrospective reviews of institutional experiences with series ranging from case reports to approximately 40 patients.²

More cases of ENB are being reported due to the widespread recognition of the condition as well as the improved histopathologic diagnostic techniques, such as immunohistochemistry and electron microscopy. Because of the small number of patients diagnosed annually, uncertainty arises around staging nomenclature and treatment modalities.³ Interpretation of the literature is hindered by the fact that the disease incidence is low, there is no universal staging system, no treatment approach has been consistently used between studies, and institutional reports frequently include other sinonasal neoplasms.

We previously reported on a subset of 12 surgical patients treated between 1981 and 1994.⁴ The objective of this study was to report on our experience in the treatment of all patients with ENB managed at the Princess Margaret Hospital (PMH) over a 23-year period, and secondarily to evaluate the best staging system that correlates with the patient's clinical outcome.

PATIENTS AND METHODS

Between 1972 and 2006, the clinical records of all patients with ENB treated at the Princess Margaret Hospital, Toronto, Canada, were reviewed. Patients were identified through the hospital cancer registry and the radiotherapy record system. Demographic, clinical, pathologic, and outcome data were obtained from chart review. A head and neck pathologist reviewed all the available histopathology slides to confirm the diagnosis and grade of the tumor based on the Hyams grading system (Table 1a). Patients were staged by the authors using both the Kadish⁵ and Dulguerov staging⁶ systems (Table 1b). Staging was performed by reviewing the imaging and descriptions of the extent of disease by the treating physicians. When imaging was not available for the patients treated early in the series, staging was based on the descriptions of the extent of the tumor in the chart. Patients were considered eligible for inclusion if they had a newly diagnosed and previously untreated pathologically confirmed ENB managed at the PMH during the selected time period. Of 40 cases identified, 1 tumor on pathology review was excluded from the study. Thus, there were 39 eligible patients available for the study.

Statistics. Demographic- and treatment-related information was summarized using descriptive statistics. Outcomes of interest were overall sur-

Table 1b. Dulguerov classification Kadish staging system.

Dulguerov classification	Kadish staging
Characteristics	Stage
T1, tumor involving the nasal cavity and/or paranasal sinuses (excluding sphenoid), sparing the most superior ethmoidal cells	A, tumor limited to the nasal cavity
T2, tumor involving the nasal cavity and/or paranasal sinuses (including the sphenoid) with extension to or erosion of the cribriform plate	B, tumor involving the nasal and paranasal cavities
T3, tumor extending into the orbit or protruding into the anterior cranial fossa, without dural invasion	C, tumor extends beyond the nasal and paranasal cavities
T4, tumor involving the brain	
N1, any form of cervical lymph-node metastasis	
M0, no metastases	
M1, distant metastasis	

Table 2. Summary of presenting symptoms and signs.

	No. (39)	%
Side (left:right:bilateral)	15:17:7	39:44:17
Nasal obstruction	29	(74.4)
Epistaxis	13	(33.3)
Anosmia	19	(48.7)
Nasal discharge	15	(38.5)
Headache	9	(23.1)
Nasal mass	36	(92.3)
Neck mass	4	(10.3)
Vision loss	8	(20.5)

vival, local recurrence-free survival, locoregional recurrence-free survival, and recurrence-free survival. These time to event outcomes were defined from the date of biopsy to the outcome of interest, i.e. date of recurrence, death or last known follow-up in which the patient was confirmed to be alive. The Kaplan-Meier method was used to estimate time to event outcome statistics. Cox proportional hazards regression methods were used to explore predictors of time to event outcomes. A stepwise selection process was attempted to create an optimal multivariate model; however, it is noted that there was little statistical power for a multivariate model. Thus, entry and stay criteria were modified to an $\alpha = 0.10$, but appropriate caution is necessary for interpreting the multivariate model.

RESULTS

Demographic Data. Twenty-two patients were men and 17 were women. The mean and median age at presentation was 50 years, with a range from 20 to 79 years. The mean follow-up time in this study group was 82.3 months, with a range of 1.8 months to 32.8 years.

Patients presented with a wide range of symptoms and signs (Table 2). Symptom duration ranged from 1 to 36 months, with a median of 10 months and an average of 12 months. Nasal obstruction was the most common symptom, occurring in approximately 75% of patients ($n = 29$) with a nasal mass being the most common physical finding at initial examination and noted in 92% of patients ($n = 36$).

Staging using the Kadish and Dulguerov staging systems is presented in Table 3. Twenty-one patients presented with early-stage disease (T1 or T2) and 18 presented with advanced disease (T3

Table 3. Kadish and Dulguerov staging system of the patient cohort.

	No.	%
Kadish stage		
1	5	12
2	15	39
3	19	49
Dulguerov staging system		
T category 1:2:3:4	6:15:10:8	15:38:26:21
N category 0:1	35:4	90:10
M category 0	39	100

or T4). At presentation, 4 of the 39 patients (10%) had cervical metastases, whereas none had distant metastases. Hyams grade was obtained in 17 patients; 1 patient was classified as grade 1, 8 were grade 2, 4 were grade 3, and 4 were grade 4.

Treatment. Treatment varied depending upon the extent of disease. The various treatment modalities are summarized in Table 4. A total of 35 patients were managed with surgery: 5 were treated with surgery alone, 30 patients were

Table 4. Treatment characteristics.

Characteristic	Value
Chemotherapy, n (%)	5 (12.8)
Surgery, n (%)	35 (89.7)
Surgery type ($n = 35$)	
Combined approach:	23 (66.7%)
Subcranial + LRMM	6 (17.1%)
Craniotomy + LRMM	17 (48.6%)
Endoscopic	6 (17.1%)
Other surgery	5 (14.2%)
Surgical complications ($n = 35$), n (%)	8 (22.9)
Radiation, n (%)	33 (84.6)
Radiation relative to surgery ($n = 30$)	
Preoperative	16 (53.3)
Postoperative	14 (46.6)
Dose ($n = 33$)	
4000	1
4500	2
5000	14
5500	3
6000	10
Unknown	3
Fraction ($n = 33$)	
0	1
20	4
25	14
30	11
Unknown	3
Radiation complications ($n = 33$), n (%)	6 (15.3)

Abbreviations: LRMM, laeral rhinotomy with medial maxillectomy.

Table 5. Site of recurrence ($n = 39$).

Recurrence	No.	%
Local	6*	15.4
Regional	7	17.9
Distant	3	7.7

*Four patients developed concurrent regional failure.

treated with surgery and radiation with 3 of these patients receiving concurrent chemotherapy. All the patients treated with surgery alone had early stage disease (T1 and T2). Radiation therapy was the sole treatment in 1 patient. Preoperative radiation was given in 16 cases, whereas 14 patients were treated with postoperative radiation. The mean dose of radiation was 5313 cGy (median, 5000 cGy; range, 5000–6000 rads) for the preoperative group and 5457 cGy (median, 5500 cGy; range, 4500–6000 rads) for the postoperative group. Conventional radiotherapy was used in 24/33 and intensity-modulated radiotherapy (IMRT) in 9/33. Chemotherapy was given with radiation in 2 patients and 3 patients were treated with the combination of surgery and chemoradiation.

Of the 35 patients who underwent surgical resection, a combined intracranial and extracranial approach (“craniofacial resection”) was used in 58% ($n = 23$) of the patients. Neck dissections were only performed in the 4 patients presenting with nodal metastases. Surgical reconstruction of the skull base defect utilized a pericranial flap and a fascia lata graft in 15 cases. A pericranial flap alone was used in 3 patients and fascia lata graft alone was used in 5 cases.

Complications. Postoperative complications occurred in 20% ($n = 8$) of the surgical patients. In the immediate postoperative period, there were 2 cases of tension pneumocephalus and 1 case each of subcutaneous emphysema, periorbital cellulitis, sinusitis, rapid atrial fibrillation, and lower extremity deep venous thrombosis. Delayed complications were minor and included epiphoria, diplopia, proptosis, lid ptosis, and recurrent epistaxis.

Within the group who had postoperative complication, 2 received preoperative radiotherapy and 4 received postoperative radiotherapy. The other 2 patients did not receive any radiotherapy. One of the patients who received postoperative radiotherapy was treated with chemotherapy as well. Six patients (15.3%) who underwent radiation therapy experienced late radiation-related complications. There were 4 cases of optic neurop-

athy, 2 of which resulted in blindness and decreased visual acuity in 2. One patient developed cataracts and another patient was diagnosed with osteoradionecrosis of the frontal bone. Minor complications, such as dry eyes and nasal mucosal irritation or crusting, were reported by 33% ($n = 11$) of patients.

Locoregional and Distant Disease Failure. Recurrence was documented in 30.7% (12/39) of the patients. Both the mean and median time from diagnosis to recurrence was 57 months, with a range from 4 months to 15 years. Six of the 39 patients (15%) developed local disease recurrence with a median time to recurrence of 51.5 months. Four of the 6 patients who developed local disease recurrence developed concurrent regional disease failure. Seven of the 39 patients (18%) developed regional disease recurrence with a median time to recurrence of 68 months. Distant disease failure occurred in 3 patients (bone, retroperitoneum, and lung) with a median time to failure of 39 months. The site of recurrence is summarized in Table 5. Surgical salvage with or without postoperative radiation was attempted in 5 patients and radiation or chemoradiation in the remaining patients with local and/or regional failure.

Survival. At last follow-up 22 patients (56.4%) were alive without disease. Ten patients (26%) are known to have died with a median time from diagnosis to death of 6.1 years (range, 0.1 to 11.7 years). Status at last follow-up is summarized in Table 6. The 5- and 10-year overall survival rates were 87.9% and 69.2%, respectively (Figure 1), whereas the 5- and 10-year recurrence-free survival rates were 76% and 44.7%, respectively (Figure 2). Table 7 presents the rates of overall survival, recurrence-free survival, local recurrence-free survival, and locoregional recurrence-free survival at 1, 5, 10, and 15 years. The median overall survival was estimated at 11.7 years (95% CI 10.9-not reached) and median recurrence-free survival was estimated to be 9.0 (6.2–14.3) years.

Table 6. Patients' status at last follow-up.

	No.	%
Alive without disease	22	56.4
Alive with disease	5	12.8
Dead of disease	8	20.5
Dead without disease	2	5.1
Unknown	2	5.1

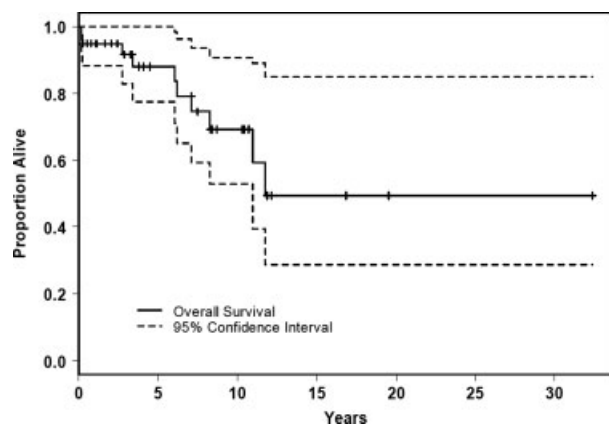


FIGURE 1. Overall survival.

Of the 12 patients who developed a recurrence, at last follow-up 3 were alive without evidence of disease, 4 were alive with disease, and 5 died of their disease.

The overall survival at 5 and 10 years according to Dulguerov T-category was 100% for T1, 100% and 89% for T2, 89% and 53% for T3, and 56% and 28% for T4.

The overall survival at 5 and 10 years according to Kadish stage was 100% for Kadish 1, 100% and 89% for Kadish 2, and 76% and 36% for Kadish 3. The results were statistically significant for both staging category. The overall survival by regional disease at 5 years was 87% for N_0 and 100% for positive neck (N_1). The 10 years overall survival for N_0 was 72% whereas the overall survival for N_1 was not applicable. These results were not statistically significant.

Predictors of Survival. On univariable analysis only Kadish stage ($p = .015$) and Dulguerov T-category ($p = .006$) were statistically significant pre-

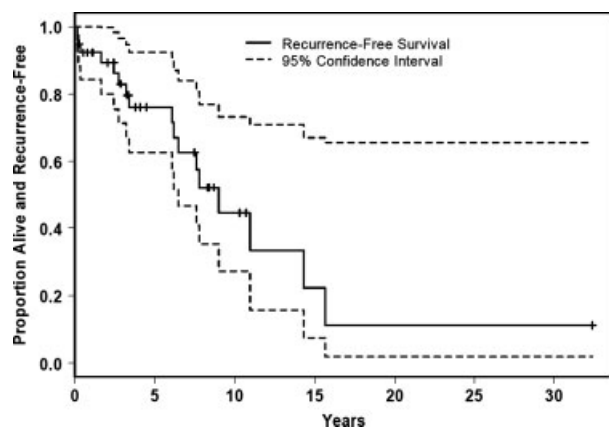


FIGURE 2. Recurrence-free survival.

Table 7. Survival outcome.

Outcome	Y	Survival rate, %	Median survival, y
Overall survival	5-y	87.9	11.7
	10-y	69.2	
	15-y	49.4	
Recurrence-free survival	5-y	76.0	9.0
	10-y	44.7	
	15-y	22.3	
Local recurrence-free survival	5-y	82.0	10.9
	10-y	51.7	
	15-y	38.8	
Locoregional recurrence-free survival	5-y	82.5	9.0
	10-y	46.3	
	15-y	34.7	

dictors of survival, although having surgery approached statistical significance ($p = .071$). Similarly for recurrence-free survival (Table 8) higher Kadish stage (HR = 5.66, 95% CI 1.87–17.10) and T-categories (HR = 2.92, 95% CI = 1.51–5.68) were predictive for shorter survival times. T-category, Kadish stage, the presence of nodal disease, and radiotherapy, all were entered into a multivariate model and found to be statistically significant predictors of recurrence-free survival and local recurrence-free survival. However, the confidence intervals are wide due to our small sample size; therefore, the stability of the estimates is questionable. The only predictors of locoregional recurrence-free survival were Dulguerov T-category and Kadish stage. None of the following parameters (age, sex, chemotherapy, or any type of surgery) were found to correlate with survival or recurrence. Predictors of local and locoregional recurrence-free survival are presented in Tables 8 and 9.

DISCUSSION

The present study reports on the Princess Margaret Hospital's long-term experience with treating ENB. Although the study confirms some of the findings reported by others, we were able to high-

Table 8. Local recurrence-free survival.

Predictor	Hazard ratio (95% CI)	p value
Kadish score	8.72 (1.95–39.05)	.005
T category	4.12 (1.82–9.37)	<.001
Multivariate Analysis		
T category	4.49 (1.30–15.44)	.017
N category	251.19 (6.98–9042.47)	.003
Kadish	32.40 (1.66–634.27)	.022
Radiation	0.02 (0.001–0.49)	.017

Table 9. Locoregional recurrence-free survival.

	Odds ratio (95%CI)	<i>p</i> value
Kadish Score	4.92 (1.61–15.07)	.005
T category	3.42 (1.64–7.13)	.001
Multivariate analysis		
T category	4.63 (1.99–10.77)	<.001
N category	13.34 (2.07–85.77)	.006

light the need for a uniform grading system, the role of multimodal treatment, and the need for a multi-institutional, prospective study to determine long-term outcomes.

The importance of a uniform staging system cannot be overemphasized. There are at present 2 clinical staging systems commonly used in the literature, the Kadish classification and the Dulguerov classification, both of which appear to correlate with clinical outcomes.^{7,8} The Kadish staging system is easy to employ and has been used in numerous studies. Details regarding the extent of local disease are limited; however, this system fails to address regional disease, which is important for assessing and comparing outcomes.^{9,10} Dulguerov and Calcaterra proposed a more detailed classification, which was based on the TNM system. We staged our patients using both staging systems. Most of our patients (48%) were seen with advanced Kadish stage C disease. Only 12% of patients were seen with nasal disease sparing the sinuses and brain (Kadish A). This is in accordance with other studies.^{11,12} Kadish stage C disease, however, encompasses a wide spectrum of disease extent ranging from a T2 to T4 stage utilizing the Dulguerov staging system. Although the majority of our patients were Kadish stage C, T2 tumors were the most common and early stage tumors (T1 and T2) accounted for 53% of the patients when staging with the Dulguerov classification system. Although we noted that both systems are predictors of survival and recurrence, the detail contained within the Dulguerov staging system will allow for better interpretation of outcomes between treatment modalities and individual case series. Specifically, the Dulguerov staging system differentiates between involvement of the nasal cavity, sinuses, and cribriform plate, as well as extension of disease to the anterior fossa, dura, and brain. Moreover, it provides information concerning regional and distant involvement and separates disease extent by the traditional T, N, and M categories. All these anatomical parameters are not addressed in the Kadish system. Therefore, we

recommend that the Dulguerov system should be the main staging system adopted for reporting outcomes in ENB patients.

There is significant variability in treatment approaches to ENB. Our treatment approach has been to offer surgery as the primary treatment modality for resectable disease, with radiation considered in either the preoperative or postoperative setting.

Based on the higher control rates with craniofacial resection reported in the literature, the majority of our patients have undergone a transcranial or subcranial approach with or without associated transnasal or endoscopic access. More recently there has been a shift to endoscopic approaches in selected T1 and T2 patients. Initial reports of the use of transnasal endoscopic resection of Kadish stage A or B ENBs followed by postoperative radiation therapy^{13–15} show short-term results comparable to those of traditional craniofacial surgery.¹⁶ Although it is our belief that there is an evolving and expanding role for the endoscopic approach, transcranial or subcranial approaches still remain the gold standard by which all other treatments need to be judged, in conjunction with an appropriate follow-up.¹²

As with other series, the majority of our patients underwent combined modality treatment with surgery and radiation. Postoperative radiation has been shown to improve local control, especially for ENBs which are either high-grade, advanced-stage, large-volume, or have extensive local invasion.^{17,18} Postoperative radiotherapy should also be considered in early-stage tumors in order to reduce the risk of recurrence.³ Based on the location of these tumors and their close proximity to critical structures, resection with wide surgical margins is often not possible, and occasionally the resection may revert to a piecemeal approach. On the basis of literature review, it appears that most institutions favor postoperative radiation.^{6,17,19} In our series 16 patients were treated with preoperative radiotherapy and 14 with postoperative radiotherapy. In recent years, we have favored a preoperative approach,²⁰ combined with conventional or intensity modulated technology. Preoperative treatment offers the following advantages: more accurate target volume delineation, reduced treated volume with consequent improve sparing of adjacent critical structures and the possibility to utilize lower total dose since postsurgical hypoxia has not yet occurred. No convincing data are available to compare preoperative versus postoperative radiotherapy in

ENB due to disease rarity.³ Although the administration of preoperative radiation may shrink a large tumor to a resectable size with potential clear margins,^{10,21} some authors believe that tumor shrinkage may obscure the actual required extent of resection.^{22,23} Although we were not able to find any significant difference in survival or recurrence when comparing preoperative versus postoperative radiation therapy, interpretation of these results must take into account that this was a retrospective observational case series and limited by small patient numbers. Overall, multimodality therapy with surgery and radiation appears to be of advantage and is recommended for all advanced tumors.^{8,10,11}

The role of chemotherapy remains uncertain and controversial.^{16,23,24} Some authors advocate for the use of chemotherapy, stating that it improves locoregional and distant control.^{24,25} Eden et al treated advanced ENB with cyclophosphamide and vincristine, followed by radiotherapy and surgery.¹⁰ With this regimen, they achieved 5- and 10-year survival rates of 72% and 60%, respectively. Others reported similar results without chemotherapy⁶ and did not find chemotherapy to significantly improve the survival of patients with high-risk tumors. This, however, may represent a selection bias, because only highly advanced tumors were treated with the addition of chemotherapy.²⁶ Five patients (12.8%) in this series were treated with chemotherapy; however, no benefit was found between this treatment and the survival or recurrence rate. Because of the small group of subjects treated with chemotherapy, we cannot draw any conclusions regarding this treatment.

The meta-analysis by Dulguerov et al³ noted an average local recurrence rate of 29%, an average regional recurrence rate of 16% and a distant metastasis rate of 17%. Recurrence rates in the current study were 15% for local recurrence and 18% for regional recurrence. Although we attempted to assess the relationship of recurrence site to radiotherapy fields, insufficient data was available to do so. Distant metastases occurred in 8% of patients. Late relapse of ENB can occur many years after initial diagnosis and definitive therapy^{16,27} with recurrent disease having been reported to occur even after 10 years.^{10,25} One of our patients had recurrence after 15 years, and the earliest recurrence was after 4 months. Therefore, close- and long-term follow-up is necessary.

Our 5- and 10-year survival rates of 87.9% and 69.2%, respectively, compare favorably with the

literature. In a meta-analysis³ of 25 studies of 390 of patients the reported overall survival at 5 years was 45%, with extremes of 86%^{28,29} and 0%.²⁹ However, the authors noted that for the larger studies the survival rates approximated 70%. Of the few studies^{6,10,28} with reported 10-year survival data, the average survival was 52%.³ In the present study, more than half of the patients (56%) were alive at the last date of follow-up and recurrence free. Of the 12 patients who had a recurrence, 5 (42%) have died since then, whereas of the 27 patients who did not have a recurrence, only 5 (19%) of these patients have died. Higher survival rates in the current study may be attributed to the fact that only 20% had T4 disease and the majority of patients were treated with combined modality therapy. The only factors that influenced recurrence and survival were the Dulguerov T-category and the Kadish stage. Unlike other studies, the degree of histopathologic differentiation (Hyams score) was not found to be a significant risk factor for development of a recurrence. However, there were a limited number of patients available to assess the impact of Hyams grade on survival. Other authors have also found that patient age, intraorbital invasion, dural invasion, histologic findings of the primary tumor, surgical margin, prior treatment, and prior chemotherapy had an impact on overall survival.²⁶

In conclusion, we advocate the use of a uniform staging system and recommend the Dulguerov classification, which was found to correlate with survival and recurrence. A combined modality approach is the preferred treatment for most lesions. At the same time, very small tumors located below the cribriform plate can be considered for resection without additional radiotherapy. Chemotherapy did not influence recurrence or survival, and the role it plays in the treatment of this disease is still not clear. We emphasize that recurrence can occur even 15 years after completion of treatment, necessitating long-term follow-up of this patient population.

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