Article

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Abstract

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Reference

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Esthesioneuroblastoma: The UCLA Experience 1970–1990

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A retrospective review was conducted of all esthesioneuroblastoma cases treated at UCLA Medical Center from 1970 through 1990. Patients were staged according to the staging systems of Kadish, *et al.*,[12] Biller, *et al.*,[5] and a new staging system proposed by the authors.

Of 26 patients treated, 74% were alive at 5 years and 60% were alive at 10 years. Combined treatment with surgery and radiation is advocated since a recurrence-free status was achieved in 92% of the patients, compared with 14% for surgery alone and 40% for radiation alone. A craniofacial resection was performed in 7 patients, all of whom have remained disease free.

Negative prognostic factors included: age over 50 years at presentation, female sex, tumor recurrence, and metastasis. The proposed new staging system predicted disease-free status better than the other staging systems.

INTRODUCTION

Esthesioneuroblastoma is a rare neoplasm of the nasal vault, first described by Berger, *et al.* in 1924.[4] Because of its rarity, this tumor has been difficult to recognize and diagnose pathologically. Furthermore, the cellular origin, histopathological classification, clinical staging, and treatment of esthesioneuroblastoma are all subject to controversy.

Only sporadic cases were reported until 1966 when Skolnik reviewed the world literature.[22] At that time, approximately 100 cases had been described. Local recurrences were frequent (48%); neck lymph node metastasis developed in 11% and distant metastasis in 12%. The 5-year survival was better after surgery (64%) than after radiation therapy (38%); the treatment recommended was surgery, with radiation therapy reserved for recurrences.

Kadish, *et al.*[12] reviewed 17 patients treated over a period of 30 years and proposed a staging classification (Table I). Patients with tumors limited to the nasal cavity (group A) were all disease free at 3 years. Patients in group B had tumors extending to the paranasal sinuses and 4 of 5 group B patients remained free of disease, while only 2 of 5 group C patients (tumor spread beyond the nasal cavity and paranasal sinuses) were disease-free. Kadish, *et al.*[12] also reviewed the results according to treatment modality: 3-year disease-free status was achieved in 8 (100%) of 8 patients treated by surgery alone, 1 (25%) of 4 patients treated by irradiation, and 4 (80%) of 5 patients treated with combined therapy. Despite these numbers, the authors recommended surgery or radiation therapy for group A and B patients and preoperative irradiation followed by surgery, if the patient became operable, for group C disease.

The staging system developed by Kadish, *et al.*[12] seems inadequate for at least four reasons. First, esthesioneuroblastomas either arise in, or spread very rapidly to, the ethmoid sinuses and, if the staging is strictly applied, very few patients will have group A disease. Second, although the inferior extension of the tumor toward the maxillary sinuses increases the disease bulk, it should not hamper the ability to surgically resect the tumor and thus should not necessarily indicate a poorer prognosis. Third, group C disease includes tumors with very different spread and therefore different survival. Finally, the occurrence of metastasis to cervical lymph nodes and distant organs is not properly addressed. Despite these inadequacies, this system was the only staging system used until recently[5] and, as such, has been extremely helpful in comparing the results of treatment of patients with similar tumors.

Elkon, *et al.*[8] and Homzie and Elkon[11] reviewed the English literature from 1966 to 1978 and found

TABLE I.
Staging After Kadish.

Group A: Tumor confined to nasal cavity
Group B: Tumor extending into paranasal sinuses
Group C: Tumor spread beyond nasal cavity and paranasal cavity

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another 97 cases described. No major differences in outcome were found when the three treatment modalities were compared. Three-year survival was good for patients with group A disease (94%, no evidence of disease [NED]), while group B patients had a 83% survival and group C 56% survival. They applied discriminant statistical analysis to their data and concluded that four factors would predict poor prognosis: older age; presence of recurrence; metastasis to lymph nodes or distant organs; and tumor extension to the ethmoids, nasopharynx, orbit, cribriform plate, and/or intracranial extension.

Recognizing the inadequacies of Kadish's classification system, Biller, *et al.*[5] proposed a different staging system (Table II). An advantage of their system is the use of a familiar TNM type of classification. The problem with this staging system is that the classification requires a craniotomy to adequately stage the disease. Also, it assumes that the cribriform plate is involved in all stages of the disease, which, although plausible, is far from certain.

In the hope of remedying some of these problems, we propose another staging system (Table III). The system is based on a TNM type of classification and uses computed tomography (CT) and magnetic resonance imaging (MRI) scans to ascertain the extension of disease. Thus, patients treated by primary or preoperative radiation can be staged as well as surgical candidates. This system recognizes the early involvement of the cribriform plate, but allows for tumors that arise lower in the nasal cavity and which could be treated in a more conservative fashion. Also, a stage is included whereby the tumor is intracranial but remains extradural and, therefore, might have a better prognosis than disease invading the brain.

The UCLA experience with esthesioneuroblastoma was reviewed and the association between disease-free status and treatment or staging variables was analyzed.

METHODS

This study is a retrospective review of patients with esthesioneuroblastoma diagnosed and treated at UCLA Medical Center from 1970 to 1990. Some patients were included in a previous report.[19] The charts, pathology reports, and radiologic studies were reviewed. The age at diagnosis, year of treatment, sex, side of tumor, symptoms, physical examination findings, type of treatment, complications, recurrences, and final outcome were analyzed. Patients were staged according to the classification systems of Kadish, *et al.*,[12] Biller, *et al.*,[5] and the new system proposed by the authors. Staging was accomplished by reviewing the CT and MRI scans, when available, as was the case for the majority of patients treated within the last 10 years. Otherwise patients were staged by reviewing facial series, conventional tomograms, and operative reports.

During the period under study, 26 patients were identified as having esthesioneuroblastoma. Two patients who did not receive treatment at UCLA were lost to follow-up and were excluded. The data for the remaining 24 patients are presented in Table IV. Two patients (K.C., S.L.) were initially treated elsewhere, but recurrences were cared for at UCLA. The remaining patients received surgical and, in the majority of cases, radiation therapy treatment at UCLA. For two patients (K.C., S.A.), insufficient information was available to adequately classify disease according to the different staging systems, but they were included in the treatment analysis. Recurrences and final outcome were obtained from patients' charts and from telephone conversations with the patients or their relatives. In only two patients, both deceased (E.F., M.S.), was information obtained from the referring physician. The average follow-up was 7.2 years.

Surgical procedures most often involved a lateral rhinotomy approach with medial maxillectomy, ethmoidectomy, and tumor excision. Frontal and sphenoid sinusotomies were performed as determined by the extent of the tumor. For the last 6 years, this transfacial approach was combined with a bifrontal craniotomy by the neurosurgical team. The intracranial approach allowed for better exposure of the cribriform plate, olfactory nerves, and the overlaying dura, all of which were resected en bloc with the tumor.

Radiation was administered using standard techniques. Megavoltage external-beam radiation was delivered using a three-field technique: an anterior port was combined with wedged lateral fields to provide a homogeneous dose distribution. The doses varied from 5500 to 6500 cGy and, in most cases, were above 6000 cGy.

Statistical treatment was carried out using contingency-table analysis. Association between variables was examined using chi-squared statistics and probability function distribution.[22]

RESULTS

Epidemiological and Clinical Features

The age distribution of our population is shown in Figure 1. The youngest patient was 4 years and the oldest was 73 years. The mean age was 40 years and

TABLE II.
Staging After Biller.

T1:	Tumor involving the nasal cavity and paranasal sinuses (excluding sphenoid), with or without erosion of the bone of the anterior cranial fossa
T2:	Tumor extending into the orbit or protruding into the anterior cranial fossa
T3:	Tumor involving the brain that is resectable with margins
T4:	Unresectable tumor

TABLE III.
New Staging.

T1:	Tumor involving the nasal cavity and/or paranasal sinuses (excluding sphenoid), sparing the most superior ethmoidal cells
T2:	Tumor involving the nasal cavity and/or paranasal sinuses (including the sphenoid) with extension to or erosion of the cribriform plate
T3:	Tumor extending into the orbit or protruding into the anterior cranial fossa
T4:	Tumor involving the brain

the median was 41 years. There was a significantly worse prognosis associated with tumor diagnosis after the age of 50 years ($\chi^2_1 = 3.82$; $P<.05$).

The delay between the appearance of the first symptom and the beginning of treatment ranged between 0 and 18 months with an average of 6 months. In two thirds of the cases the tumor was on the left side. There was no significant association between delay of diagnosis or side of the tumor with disease recurrence.

There was an equal distribution on the basis of sex. Male patients did better than females: the disease recurred in 50% of women patients, while 75% of the men remained disease-free. This association, however, did not reach statistical significance ($\chi^2_1 = 1.6$; $P>.05$).

The most common symptom was unilateral nasal obstruction (17 patients [71%]) followed by epistaxis (11 patients [46%]). Other symptoms included anosmia (21%), pain (21%), proptosis (21%), diplopia (8%), and syncope (4%).

The most common physical finding was a nasal mass, which was observed in 21 patients (87%). Less common findings were proptosis (21%), neck mass (8%), extraocular paralysis (4%), and nasopharyngeal mass (4%).

Patients were staged according to the classifications of Kadish, *et al.*,[12] Biller, *et al.*,[5] and the new staging proposed by the authors. The distribution of patients according to the various staging systems is shown in Figure 2.

TABLE IV.
UCLA Esthesioneuroblastoma Patients.

Patient	Age	Delay	Sex	Side	Staging			Treatment	Surgical Procedures	Recurrence	Time (Years)	Treatment of Recurrence	Final Outcome	Time (Years)
					Biller (1990)	Dulguerov	Kadish							
G.R.	37	8	M	L	T1	T2	A	Sx + Rxth	CFR + MM + EE	No			NED	0.58
W.K.	53	6	M	L	T1	T1	A	Sx + Rxth	CFR + MM + EE	No			NED	0.67
Z.G.	42	2	M	L	T2	T3	C	Sx + Rxth	CFR + MM + EE + LPR	No			NED	1.67
K.M.	42	0	M	L	T3	T4	C	Sx + Rxth	CFR + MM + EE	No			NED	3.58
H.R.	47	6	M	L	T1	T2	A	Sx + Rxth	CFR + MM + EE	No			NED	3.92
S.P.	26	18	M	L	T1	T1	B	Sx + Rxth	MM + EE + LPR	No			NED	6.83
R.H.	67	12	F	L	T1	T1	A	Sx	MM + EE	Local	3.75	Sx: Endoscopic	DOC with disease	5.08
S.M.	73	8	F	L	T4	T4	C	Rxth	0	Local	0.50	Immunotherapy	DOD	3.33
K.C.	52	0	F	L	NA	NA	NA	Sx	EE	Local	1.00	TFCPR + Rxth	Alive with disease	6.75
V.J.	36	2	F	R	T1	T2	A	Sx + Rxth	TFCPR + EE	Local	3.25	CFR + MM	NED	5.25
D.R.	53	12	M	L	T1	T2	B	Sx	MM + EE	Local	7.00	Interferon	Alive with disease	9.50
D.H.	62	12	F	L	T1	T1	B	Rxth	0	Neck	0.40	RND	DOD	1.67
S.L.	27	0	F	R	T1	T2	B	Sx	CFR + MM + septectomy	Local	10.00	CFR + MM + OE + Rxth	NED	1.25
B.L.	6	2	F	L	T1	T2	A	Sx + Rxth + Chemo	MM + EE + MRND	No			NED	12.83
P.D.	64	12	F	R	T1	T1	A	Sx + Rxth	CPR + MM + EE	No			NED	14.58
M.B.	28	12	F	R	T1	T1	A	Sx + Rxth	MM + EE	No			NED	14.83
M.C.	29	3	M	R	T1	T1	B	Rxth	0	No			NED	16.00
E.F.	45	6	F	L	T1	T2	B	Sx + Rxth	MM + E	Metastasis	0.17	None	DOD	0.17
M.S.	4	6	M	R	T2	T3	C	Chemo + Rxth	0	Local + neck	0.00	Chemo + Rxth	DOD	0.50
C.D.	41	4	M	R	T1	T1	A	Rxth	0	No			NED	16.17
S.J.	48	12	M	L	T2	T3	C	Rxth + Sx	OE + MM + TFCPR	No			NED	17.25
S.R.	17	3	F	R	T2	T3	C	Sx	MM + E	Local	0.25	TN resection + Rxth	DOD	1.42
C.M.	20	6	F	L	T1	T1	B	Sx	MM + E + CPR	No			NED	13.92
S.A.	41	12	M	L	NA	NA	NA	Sx	EE + MM	Local + neck	2.00	Rxth	DOD	16.00

CFR = craniofacial resection; MM = medial maxillectomy; EE = external ethmoidectomy; LPR = lamina papyracea resection; OE = orbital exenteration; TFCPR = transfrontal sinus cribriform plate resection.

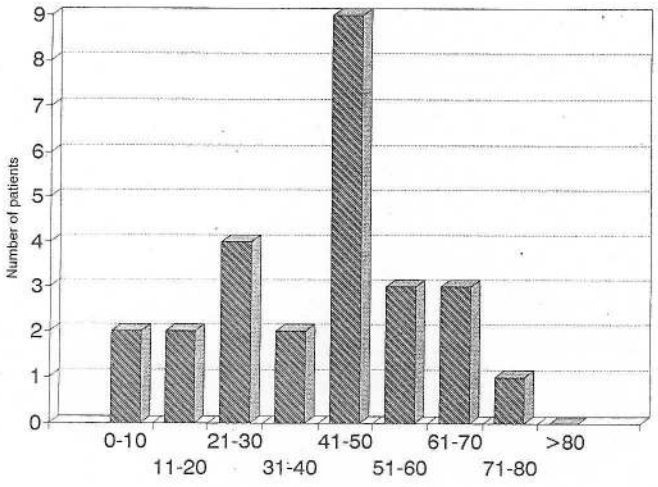

Fig. 1. Age distribution of patients.

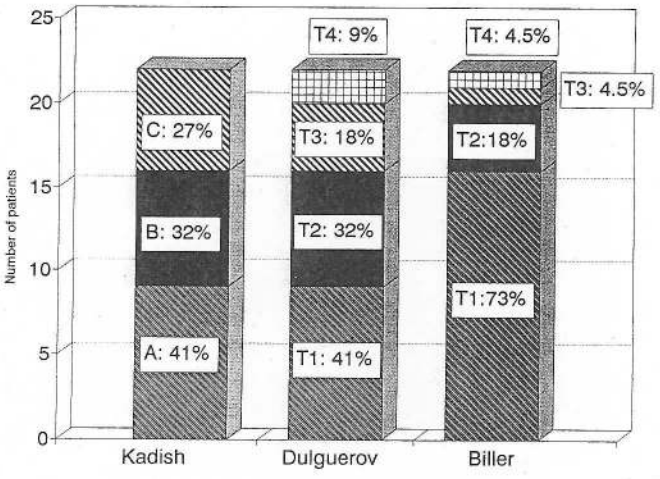

Fig. 2. Patient distribution by stages.

Treatment

Surgery was the only treatment in 7 patients (29%). Radiation therapy was used alone in 5 patients (21%). Twelve patients (50%) were treated with a combination of surgery and radiation. The distribution of patients according to the various treatment modalities is shown in Figure 3.

Of the 7 patients treated with surgery alone, only 1 did not develop a recurrence (C.M., follow-up 14 years). One patient (S.L.) recurred locally 10 years after a craniofacial resection had been performed at an outside facility and was salvaged by a second craniofacial resection and postoperative radiation. Two patients are alive with disease and 3 have died despite numerous surgical treatments and, in three cases, radiation. The overall success of surgery alone was thus low (14%).

Of the 5 patients treated with radiation therapy without surgery, 2 (40%) remained disease-free (C.D. and M.C., follow-up 16 years in both cases). The other 3 patients have died of disease.

Of the 12 patients who had combined therapy, 10 (83%) did not develop a recurrence. One patient (V.J.) had a local recurrence which was treated by craniofacial resection and has remained disease-free (follow-up 5 years). One patient developed distant metastasis and died. Overall, 11 patients (92%) are alive and disease-free.

In the entire population, 20 patients had surgery for local control. Ten patients had a lateral rhinotomy with medial maxillectomy and ethmoidectomy. In this group, only 4 patients (40%) remained disease-free, all of whom had received postoperative radiation. Three patients underwent a resection of the cribriform plate through the frontal sinus, and only 1 patient (33%) did not develop a local recurrence. This patient was also irradiated postoperatively. One patient experienced local recurrence and, after craniofacial resection, has remained disease-free for 5 years.

Craniofacial resection was performed in 7 patients; in 6 cases this was the initial procedure and in 2 cases the procedure was done to salvage a local recurrence. One patient recurred and underwent a second craniofacial resection. All patients who underwent craniofacial resection have remained alive and disease-free. The average follow-up after craniofacial resection was 2.4 years, which was significantly shorter than the follow-up of other treatment groups. The disease-free percentages of the different surgical procedures are summarized in Figure 4.

Survival

The disease-specific survival was 81% (17/21) at 2 years, 74% (14/19) at 5 years, and 60% (9/15) at 10 years. The relapse-free survival was 71% (15/21) at 2 years, 58% (11/19) at 5 years, and 53% (8/15) at 10 years (Figure 5).

Outcome after Recurrence

Local recurrences developed in 8 patients (33%). Two patients were salvaged by craniofacial resection and have remained disease-free for 5 years (V.J.) and 1.25 years (S.L.). Two patients are alive with disease and 4 patients died of disease. The results for salvage local therapy after recurrence were poor (25%). Absence of local recurrence is strongly associated with disease-free status ($\chi^2_1 = 17.02$; $P<.0001$).

Neck metastases were present in 4 patients (17%). In 2 patients, neck metastasis was diagnosed at presentation. One of those (B.L.) underwent a modified neck dissection followed by chemotherapy and has remained disease-free for 13 years. The other patient, as well as the 2 patients who developed neck metastasis after the initial treatment of the primary, are all dead.

Distant metastasis developed in 2 patients (8%)

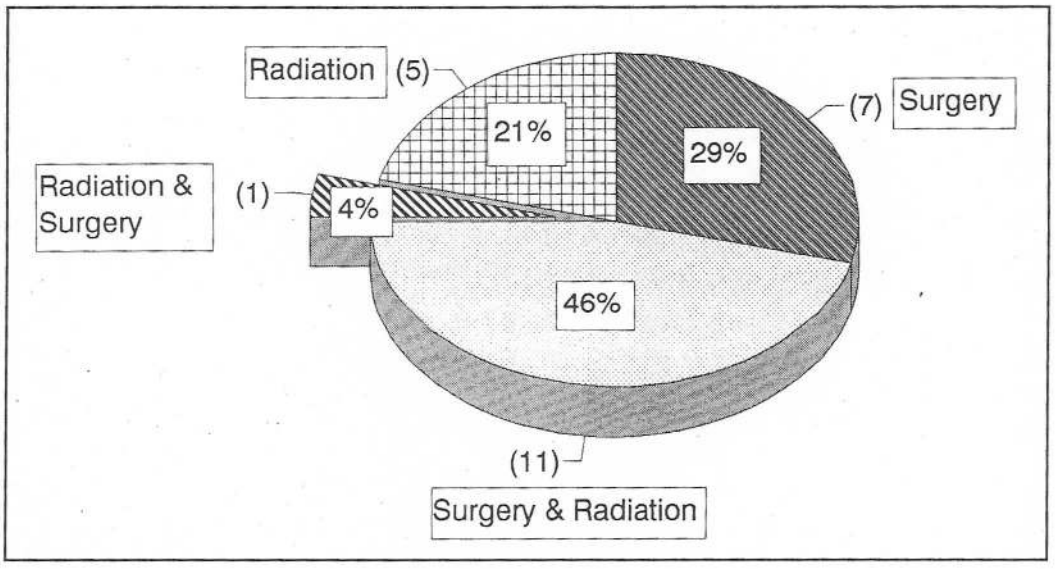

Fig. 3. Treatment modalities.

both of whom have died. By the time the distant metastasis occurred, the patients had also recurred in the nasal cavity. Neither neck disease nor distant metastasis reached statistical significance for association with poor prognosis, probably due to the small population sample.

Treatment Results According to Stages

Table V shows the results of treatment for patients classified by the staging system of Kadish, *et al.*[12] Group A consisted of 9 patients, 8 of whom remained disease-free (88%, follow-up 8.21 years). Seven patients were in group B, 4 of whom have remained free of disease (58%, follow-up 8.33 years). Six patients were staged as group C and only 3 have remained disease-free (50%, follow-up 4.6 years).

The classification of patients according to the staging system of Biller, *et al.*[5] is shown in Table VI. The distribution is skewed towards stage T1 with 16 patients in this group. Twelve of these patients have remained free of disease (75%, follow-up 7.7 years). Four patients were classified as T2 and 2 remain disease-free (50%, follow-up 5.2 years). Stages T3 and T4 consisted of one patient each. The T3 patient was cured (100%, follow-up 3.6 years) and the T4 patient died.

The results of treatment for patients classified according to the staging system proposed by the authors are shown in Table VII. Nine patients had disease limited to the nasal cavity or paranasal sinuses with the presence of free air space superior to the lesion as demonstrated by X-ray and were staged as T1. Seven of these patients remained free of disease (77%, follow-up 10 years). In seven patients, the tumor extended to the cribriform plate without eroding it and were therefore staged as T2. Of these, 5 patients have remained free of disease (71%, follow-up 6.7 years). Four patients had cribriform plate erosion and were staged as T3. Half of the T3 patients remained disease free (50%, follow-up 9.5 years). Two patients had brain substance invasion and were thus staged as T4. One of these 2 patients is free of disease (50%, follow-up 3.6 years).

When the association between disease-free status and stage was examined statistically, the system proposed by the authors had a higher chi-squared score than the staging systems of Biller and Kadish. However, none of the staging systems achieved significance at the 5% level, probably due to the small population sample.

Complications

Complications occurred in 7 patients (29%). Complications related to surgery occurred in 3 patients

TABLE V.
Results of Treatment: Staging After Kadish.

	Surgery	Radiation Therapy	Combined	Total
Group A	0/1	1/1	7*/7	8/9 (88%)
Group B	2*/3	1/2	1/2	4/7 (58%)
Group C	0/1	0/2	3/3	3/6 (50%)
Total	2/5 (40%)	2/5 (40%)	11/12 (92)%	

*Patients salvaged after local recurrence.

TABLE VI.
Results of Treatment: Staging After Biller.

	Surgery	Radiation Therapy	Combined	Total
Biller T1	2*/4	2/3	8*/9	12/16 (75%)
Biller T2	0/1	0/1	2/2	2/4 (50%)
Biller T3			1/1	1/1 (100%)
Biller T4		0/1		0/1 (0%)
Total	2/5 (40%)	2/5 (40%)	11/12 (92%)	

*Patients salvaged after local recurrence.

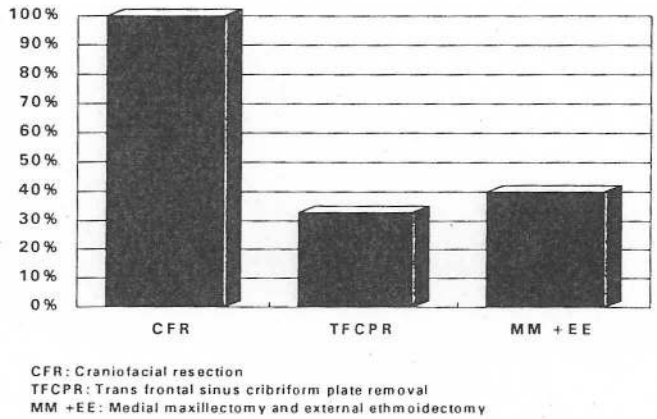

Fig. 4. Results of different surgical procedures.

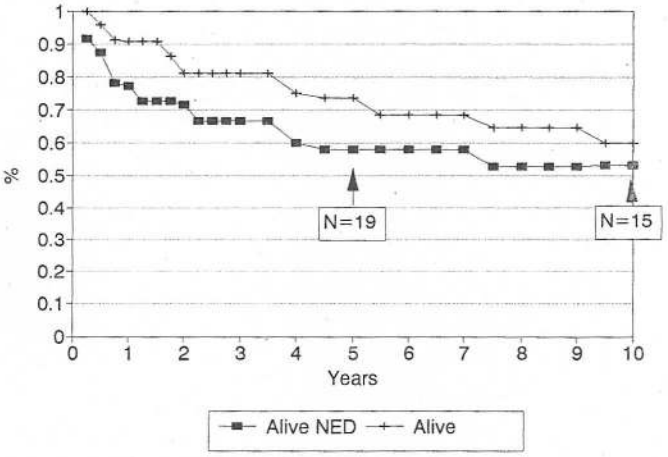

Fig. 5. Relapse-free survival.

(15%). They included 2 postoperative cerebrospinal fluid (CSF) leaks, 1 lacrimal drainage system obstruction treated by placing a Jones tube, and 1 frontal mucocele 6 years after the initial surgery.

Complications related to radiation occurred in 4 patients (24%). All resulted in a poor-to-nonfunctional eye. Three patients had radiation retinopathy, one of them also developed postradiation cataract. The fourth patient developed an orbital *Pseudomonas* infection that required an orbital exenteration for control.

DISCUSSION

Berger, *et al.*[4] described esthesioneuroblastomas as originating from the olfactory epithelium, a statement largely echoed in the literature. Esthesioneuroblastomas appear similar to central and peripheral neuroblastomas by light and electron microscopy.[3,9] They are composed of cells almost devoid of cytoplasm, sometimes arranged in a rosette formation.[15,18] Mitoses are rare.[15,21] A fibrillar background, which is thought to be necessary for the histopathological diagnosis, is present.[15,18] The fibrils have been shown by electron microscopy to represent cellular cytoplasmic processes.[15] Membrane-bound granules are found within the cytoplasmic processes[6,21,25] and are also thought to be diagnostic of neuroblastoma.[25] Neurosecretory granules are not found in the normal olfactory epithelium.

Immunohistochemistry shows labeling of these tumors by neurofilament protein, neuron-specific enolase, and S-100 antisera.[2,6,25] Similar labeling has been demonstrated in peripheral neuroblastoma[9] and normal human epithelium.[24] Esthesioneuroblastomas have been shown by biochemical and histochemical techniques, to contain the enzymes necessary for the synthesis of catecholamines.[14,24] No such enzymes are present in the normal olfactory epithelium.

In summary, esthesioneuroblastomas are nerve-related tumors, similar in many respects to neuroblastomas. Although esthesioneuroblastomas have been traditionally held to originate from the olfactory epithelium, several cellular characteristics, such as the lack of neurosecretory granules and enzymes involved in catecholamine synthesis within the normal olfactory epithelium, question this point of view.

If esthesioneuroblastomas do not originate from olfactory mucosa, the possibility exists for the tumors to arise below the level of the cribriform plate. This can occur even if esthesioneuroblastomas stem from the olfactory epithelium, since the distribution of the olfactory mucosa is not necessarily in continuity, but appears to intermix with respiratory nasal mucosa[16,17] and extend below the nasal roof.

The proposed new staging system includes a stage for tumors that do not extend to the cribriform plate (T1). These tumors might be excised through a facial approach, without a craniotomy. Whether this is an appropriate treatment option remains to be investigated. In our population, only 3 T1 patients underwent a tumor excision through a lateral rhinotomy, without cribriform plate removal; 2 patients remained disease-free and 1 patient had a recurrence. Three T1 patients had a removal of the cribriform plate and all remained disease free.

For stages T2 to T4, the surgical treatment should include a craniotomy with craniofacial resection of the cribriform plate and overlying dura, combined with a transnasal approach leading to en bloc tumor removal. Of 12 patients with stages T2 to T4,

TABLE VII.
Results of Treatment: UCLA Staging.

	Surgery	Radiation Therapy	Combined	Total
T1	1/2	2/3	4/4	7/9 (77%)
T2	1*/2		4*/5	5/7 (71%)
T3	0/1	0/1	2/2	2/4 (50%)
T4		0/1	1/1	0/1 (50%)
Total	2/5 (40%)	2/5 (40%)	11/12 (92%)	

*Patients salvaged after local recurrence.

the cribriform plate was removed in 7 and all have remained disease-free. Only 1 of 5 patients without cribriform plate resection has remained recurrence-free. Therefore, a frontal craniotomy to assess the superior extent of the tumor is recommended. If the tumor is resectable, the cribriform plate and overlaying dura should be removed and the tumor delivered en bloc through the nasal approach.

After the first description of combined craniofacial resection for the treatment of esthesioneuroblastomas by Doyle and Payton,[7] this surgical technique has been slow to be universally accepted. Appelblatt, *et al.*[1] reviewed 21 patients, 3 of whom had a craniotomy; 1 of these 3 patients developed distant metastasis and died with the local status unspecified. Olsen and DeSanto[20] reviewed 21 patients, 6 of whom had a craniofacial resection; 5 of these 6 patients experienced a recurrence or died. Harrison[10] reviewed 8 patients, 5 of whom had a craniofacial resection; 2 of these 5 patients experienced a recurrence and eventually died. Levine, *et al.*[13] reviewed 16 patients treated by craniofacial resection and radiation. Their results were better: 1 patient developed distant metastasis and 1 patient recurred locally.

Our experience with craniofacial resection of esthesioneuroblastoma has been extremely favorable. Seven patients who had undergone this treatment at UCLA have all remained free of disease. Most of these patients underwent combined treatment with surgery followed by radiation. Craniofacial resection is advocated as a unique treatment modality by Biller, *et al.*[5] Whether this is a valid treatment option cannot be ascertained from our data.

Radiation as the sole treatment modality for this neoplasm is probably to be proscribed, as only 40% of patients treated by radiation alone were disease-free. On the other hand, combined treatment with surgery and radiation has achieved the best results in our series: 11 (93%) of 12 patients treated with combined treatment remained disease-free. Therefore, we recommend combined treatment with surgery followed by radiation for all stages of esthesioneuroblastoma.

CONCLUSION

A new staging system that uses CT and MRI scans is proposed. This staging system correlates better with outcome than previously published staging classifications.

Local control of esthesioneuroblastoma could be achieved with craniofacial en bloc tumor resection followed by postoperative radiation therapy.

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