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Olfactory Neuroblastoma and Neuroendocrine Carcinoma of the Anterior Skull Base: Treatment Results at the M.D. Anderson Cancer Center

Abstract—Updated information on the pathologic characterization and treatment of olfactory neuroblastoma (ON) and neuroendocrine carcinoma (NEC) diseases is presented. A series of patients with ON or NEC was evaluated and retrospectively staged using the UCLA system. The parameters evaluated were symptoms, age, sex, risk factor assessment, stage of disease, treatment, and clinical outcome. The median follow-up was 3 years (range, 18 months to 23 years). The predominant therapy (63%) for ON was combined surgery and radiotherapy. Surgery alone or in combination with ancillary treatment was used in 58% of patients with NEC. For the most recent years of the study, patients with NEC have been treated successfully with combined chemotherapy and radiotherapy. Seventy percent of the patients with ON and 75% of the patients with NEC were clinically free of disease during the defined follow-up period. Surgical therapy consisting of a craniofacial resection combined with postoperative radiotherapy has resulted in good local and long-term control of ON. Our experience indicates that combined chemoradiation is an appropriate therapeutic approach for NEC. (*Skull Base Surgery*, 6(1):1–8, 1996)

Olfactory neuroblastoma (ON) is a malignant neoplasm originating in the upper nasal vault in the region of the cribriform plate. This rare tumor was first described in 1924.¹ In 1982, a study from our institution noted the histologic difference between ON and another rare malignancy of the sinonasal region, neuroendocrine carcinoma (NEC).² Subsequently, surgery in combination with radiotherapy, and in some instances primary chemotherapy, has been the preferred treatment for these two diseases.

When indicated, we have used an anterior skull base resection combined with resection of the appropriate paranasal sinus region, which gives better local control rates than a transfacial resection alone. In addition, our survival rates have improved with this form of treatment. This article reports our treatment of these two diseases, and describes why these tumors should be considered as clinically separate diseases.

MATERIALS AND METHODS

All patients with a diagnosis of ON or NEC treated at the University of Texas M.D. Anderson Cancer Center between 1954 and 1992 were identified by the Department of Patient Studies. A case series analysis evaluated the following parameters: presenting symptom, age, sex, risk factor assessment, extent of disease at diagnosis based on physical examination and radiologic tests, and review of the pathology specimen. All tumors were staged according to the proposed UCLA staging system (Table 1). When the original computed tomography, magnetic resonance image, or polytomography study was available, it was reviewed to retrospectively stage the disease. If the original radiologic study was not available, the medical record was used to stage the disease. When available, the original pathology specimen was reviewed by a pathologist to confirm the histologic diagnosis.

The cases were reviewed for clinical outcome, with special interest directed at type of treatment, extent of surgery, if applicable, extent of disease at pathologic examination, recurrence at the primary, regional, or distant locations, and long-term survival.

Table 1. UCLA 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

RESULTS

Thirty-two patients were identified for this review, 20 patients with ON and 12 with NEC. Figure 1 shows the findings characteristic of ON: irregular groups of tumor cells separated by acellular fibrillar material, tumor cells that form Homer-Wright rosettes or olfactory rosettes, and tumor cells with scant cytoplasm and uniform nuclear chromatin with or without nucleoli (Fig. 2). NEC exhibits poorly differentiated nests of cells separated by thin branches of cellular connective tissue, tumor cells with scant to moderate cytoplasm, finely granular nuclear chromatin, the absence of prominent nucleoli and fibrillar "cob web"-like material, and the presence of tumor intimately associated with benign glandular epithelium (Figs. 3, 4). NEC is a distinct category with poor histologic differentiations and neuroendocrine features.

For living patients, the median follow-up was 3 years (range, 18 months to 23 years). The median age at diagnosis was 40 years for patients with ON (range, 10 months to 79 years) and 53 years for patients with NEC (range, 16 to 79 years). The male to female ratio for ON was 1.9:1 and for NEC, 1.4:1. The origin of the disease, based on clinical findings, was the ethmoid sinuses (55% for ON, 42% for NEC) or nasal cavity (30% for ON, 50% for NEC). The predominant presenting symptom for both ON and NEC was nasal obstruction (65% and 75%, respectively), and the second most common symptom was epistaxis. Examination characteristically revealed a nasal mass in more than 80% of patients in both groups. Cranial nerve involvement (excluding CN I) was surprisingly rare, occurring in less than 10% of patients in both groups. There was no statistical association between the use of tobacco or other known carcinogens and the development of these tumors. The UCLA stages of disease for all patients are presented in Table 2. Regional metastasis at

Figure 1. Nasal neuroblastoma. Note irregular groups of tumor cells separated by acellular fibrillar "cob web"-like material. Hematoxylin and eosin stained (original magnification $\times 200$).

Figure 2. High power magnification of tumor in Figure 1. Note occasional prominent nucleoli. Hematoxylin and eosin stained (original magnification $\times 400$).

the time of diagnosis was uncommon in both groups: two patients with ON and one patient with NEC had neck metastasis.

A treatment summary is presented in Table 3. The predominant treatment for patients with ON was surgery; 11 (55%) patients with ON had surgery, either as their primary treatment or in combination with either pre-operative or postoperative radiotherapy. A craniofacial resection (CFR) technique was used in 6 of these 11 patients (55%). Surgery alone or in combination with ancillary treatment was used in seven of the patients (58%) with NEC. CFR was used in only two of these seven patients (29%).

Radiotherapy was given as a postoperative adjuvant treatment for seven patients with ON; the median dose

was 60.0 Gy (range, 45.0 to 70 Gy). When radiotherapy was used as a primary treatment modality ($n = 6$), the median dose was 60.2 Gy (range, 50.0 to 70.0 Gy). Only one patient received radiation therapy prior to surgery, with a dose of 59.4 Gy. Two patients with NEC were treated with post-operative adjuvant radiotherapy and received 50.0 and 55.0 Gy. Two patients with NEC treated by radiotherapy alone received 60.0 and 65.0 Gy. Four patients treated with combined chemotherapy and adjuvant radiotherapy received a median radiation dose of 50.0 Gy (range, 45.0 to 60.0 Gy). Three of these four patients also received radiation treatment of their necks, with a median dose of 45.0 Gy.

In the group of ON patients who underwent surgery, pathologic examination showed that seven (64%) had

Figure 3. Neuroendocrine carcinoma. Note nests of tumor cells separated by thin connective tissue branches. Hematoxylin and eosin stained (original magnification $\times 200$).

Figure 4. High-power magnification of tumor in Figure 3. Note finely granular chromatin of tumor cell nuclei and cellular branches of connective tissue. Hematoxylin and eosin stained (original magnification $\times 400$).

sinus involvement, five (46%) had cribriform plate involvement, three had dural involvement (27%), two had brain invasion (18%), and two had orbit invasion (18%). Four patients with NEC (57%) had sinus involvement, but none had cribriform, dura, brain, or orbital involvement.

For the 17 patients who underwent a surgical procedure at our institution, the incidence of complications was 12%. There was one perioperative death, a patient with ON who underwent a CFR, developed massive cerebral edema, and died 2 days after surgery. A patient with ON treated by a combined ethmoidectomy and maxillectomy developed meningitis, which was treated with antibiotics and responded without further complications.

There was one case of a squamous carcinoma which developed in the field of radiation 22 years after primary treatment with radiotherapy for a T1 ON located in the ethmoid sinus and superior nasal vault. The patient subsequently underwent a CFR for the squamous carcinoma and is alive without evidence of either disease 3 years after the CFR. Another complication of radiotherapy included a case of unilateral blindness and III cranial nerve palsy in a patient treated by induction chemotherapy followed by radiotherapy for a T3 ON.

Twenty-seven of the 32 patients received radio-

therapy at some point during their treatment. Of these patients, 10 (37%) developed osteoradionecrosis of their skull base or paranasal sinus region. The median dose was 60.0 Gy (range, 13.9 to 70.0 Gy). Of these 10 patients, only 3 had a temporalis muscle or free tissue transfer to cover the undersurface of the surgical defect. Seven patients who underwent either radiotherapy alone or surgery combined with radiotherapy without flap coverage of the surgical defect developed osteoradionecrosis. Five patients developed radiation-induced central nervous system sequelae, including cerebral necrosis and encephalomalacia.

Eleven patients (55%) with ON did not develop recurrence during the time of follow-up, whereas nine (45%) did develop recurrence. The median time to recurrence was 6 months for a primary recurrence ($n = 4$) and 30 months for the development of regional disease ($n = 4$). Only one patient in this group developed distant metastasis; this patient was a 10-month-old female for whom the metastasis proved to be fatal. In the four (18%) patients who developed regional disease, all responded to salvage therapy that included chemotherapy, radiation therapy, and surgery (Table 3). The chemotherapeutic agents, chosen empirically, included vincristine, cyclophosphamide, etoposide (VP-16), cisplatin, and 5-fluorouracil (5-FU).

One patient with NEC developed a primary recurrence at 34 months. This patient received successful salvage surgical therapy. Two patients developed distant metastasis, both within 12 months of initial treatment. Both were treated with a combination of etoposide and vincristine. One patient died from disease despite chemotherapy, while the other was treated successfully by chemotherapy alone. No patients developed regional metastasis. Nine patients (75%) with NEC had no evidence of recurrence during the follow-up period.

Table 2. Stage of Disease at Presentation

T Stage	Olfactory Neuroblastoma ($n = 20$)		Neuroendocrine Carcinoma ($n = 12$)	
	#	%	#	%
T1	6	30.0	4	33.3
T2	4	20.0	3	25.0
T3	5	25.0	4	33.3
T4	5	25.0	1	8.3

Table 3. Patient Characteristics

Pt.	Age (yr)	Sex	Year Seen	T Stage	Treatment	Surgical Procedure	Type	Recurrence		Final Outcome	Time (yr)*
								Time*	Treatment		
1	74	M	1956	T1	S	Partial maxillectomy, turbinectomy	Local	5 mos	S	DOC w/o disease	5.08
2	24	M	1963	T1	XRT	Olfactory Neuroblastoma	Local	7 mos	XRT	D unk	10.75
3	28	F	1970	T1	XRT		Local	4 mos	S		23.33
4	10 mos	F	1971	T1	C		2nd prim	21 yrs	C+S		1.08
5	17	F	1974	T1	S + XRT		DM	6 mos	C	DOD	18.75
6	39	M	1988	T1	S + XRT		Local	9 mos	C	NED	4.17
7	16	M	1970	T2	XRT		No			NED	21.83
8	41	M	1986	T2	XRT		No			NED	6.58
9	49	F	1987	T2	S + XRT		No			NED	5.08
10	38	M	1991	T2	XRT + S		No			NED	3.17
11	60	M	1973	T3	S + XRT		No			DOC w/o disease	0.67
12	23	M	1979	T3	C + XRT		No			DOD	0.67
13	45	F	1979	T3	XRT		Local	6 mos	none	LWD (lost to follow-up)	0.50
14	48	M	1990	T3	S		No			DOD	2 days
15	41	M	1992	T3	S + XRT + C		Reg.	22 mos	S	NED	2.33
16	3	F	1974	T4	XRT + C	Neuroendocrine Carcinoma	No			NED	14.92
17	57	M	1981	T4	S + XRT		Reg.	62 mos	XRT	DOC w/o disease	8.33
18	29	M	1983	T4	S + XRT		Reg.	3 mos	C	NED	9.33
19	43	F	1985	T4	S + XRT		Reg.	39 mos	XRT	LWD	9.33
							Reg.	62 mos	S + C		
20	79	M	1992	T4	XRT		Local	97 mos	S + XRT	DOC w disease	0.33
							No				
1	53	F	1973	T1	S	Neuroendocrine Carcinoma	Local			NED	20.92
2	53	M	1987	T1	S		No	33 mos	S	NED	6.00
3	63	F	1991	T1	XRT		No			NED	2.33
4	54	M	1991	T1	C + XRT		DM	16 mos	C	DOD	1.50
5	22	M	1992	T2	S + XRT		No			NED	2.50
6	69	M	1992	T2	S		No			NED	2.00
7	44	M	1985	T2	S + XRT		No			NED	9.33
8	51	M	1980	T3	XRT		No			NED	11.75
9	21	F	1982	T3	S + C + XRT		No			DOD	0.42
10	73	M	1988	T3	C + XRT		DM	7 mos	C	NED	6.00
11	79	F	1990	T3	C + XRT		No			DOC w/o disease	1.58
12	16	F	1992	T4	C + XRT		No			NED	2.00

*All times calculated from start of treatment.
Abbreviations: S, surgery; XRT, radiotherapy; DOC, dead from other cause; D unk, dead of unknown cause; C, chemotherapy; NED, no evidence of disease; DM, distant metastasis; DOD, dead from disease; LWD, living with disease; 2nd prim, second primary; Reg., regional.

Because of the small number of patients in each group in this study, a Kaplan-Meier survival analysis could not be performed. Instead, a crude mortality analysis shows that for the 20 patients with ON, 10 (50%) were alive, at the time this report was prepared. Three patients (15%) were dead of other causes and were without disease. Two patients (10%) were living with disease (one was lost to follow-up), one (5%) died from other causes with disease, and three (15%) died from disease. One patient (5%) died from an unknown cause. Using an arbitrary definition of survival without disease during the defined follow-up period as treatment success, 70% (14 of 20) of the patients in this group had successful outcomes.

In the group of 12 patients with NEC, 8 (67%) were living without disease at the time this report was prepared. One patient (8%) died from another cause without disease. Two patients (17%) were living with disease, and one patient (8%) died from disease. Therefore, the rate of treatment success in the group of patients with NEC was 75% (9 of 12).

For each tumor stage, the number of patients was too small to determine meaningful survival data. However, when the data were analyzed by effectiveness of treatment, it became apparent that patients who received surgery for ON had effective local control and longer survival than those who did not have surgery. Six of 11 patients who had surgery had a CFR. One of these patients had stage T2 disease, two had stage T3, and three had stage T4. There was only one local recurrence, which occurred in a T4 patient. In the group of seven patients with NEC who had surgery, two underwent a CFR. One had stage T1 disease, and the other had stage T2 disease. Neither of those patients had local recurrence.

DISCUSSION

Olfactory neuroblastoma is a malignant neoplasm originating in the upper nasal vault in the region of the cribriform plate. This tumor is believed to arise from the neurons or basal cells of the olfactory mucosa. This layer can be above or below the cribriform plate.² This rare tumor was first described in 1924 by Berger et al, who called it "*L'esthesioneuroepithelioma olfactif*."¹ It first appeared in the English language literature in 1951, when Schall and Lineback described three cases of a primary intranasal neuroblastoma treated at the Massachusetts Eye and Ear Infirmary.³ Since that time a considerable number of terms have been used to describe this tumor, including olfactory neurocytoma, olfactory neuroepithelioma, neuroendocrine carcinoma, esthesioneuroepithelioma, esthesioneurocytoma, neuroblastoma, and esthesioneuroblastoma.² These terms were based on various histologic criteria that were thought to give some indication of the tumor's clinical behavior. Currently, the term most used to describe these tumors is esthesioneuroblastoma, although we contend that olfactory neuro-

blastoma is a more accurate term. Hyams has developed a classification scheme that differentiates olfactory neuroblastoma into Grades 1 through 4 based upon the degree of differentiation.⁴

Silva et al reported the cases of tumors of the nasal cavity presenting at M.D. Anderson.² They included tumors previously classified as neuroblastomas, unclassified malignant neoplasms, or unclassified carcinomas. They included nine cases of neuroblastomas originating in the nasal cavity, further subdivided into three neuroblastomas with olfactory differentiation and six neuroblastomas without olfactory differentiation. Since the publication of that paper, tumors of this cell type treated at the M.D. Anderson have been classified as olfactory neuroblastomas and not esthesioneuroblastomas. It was concluded that a staging system previously proposed by Kadish did not offer prognostic value. However, it must be realized that only five patients with neuroblastoma were staged and reviewed.

The cell of origin of NEC is believed to be the glandular epithelium of the exocrine glands found in the normal olfactory mucosa.² The olfactory mucosa usually extends only up to the superior turbinate. The findings of Silva et al suggested that ON and NEC are distinctly different tumors; that NEC develops more inferior in the nasal cavity, arises from a different cell type than ON, is predominately a disease of older patients, very seldom presents with regional disease, is more prone to distant metastasis than ON, has a longer delay in the development of metastasis than ON, and causes death earlier than ON. On the other hand, ON develops more superior in the nasal vault, is more prone to present with metastasis, and is more common in younger patients.

Since the publication by Silva et al,² studies of ON from other institutions have been published. A recent paper by Dulgerov and Calcaterra, from UCLA, reviewed 24 patients with esthesioneuroblastoma.⁵ The authors proposed a new staging system (Table 1) that more appropriately evaluates the most aggressive elements of this disease, and compared their staging system to the previous staging systems by Kadish et al⁶ and Biller et al.⁷ Although their findings, like ours, did not reach statistical significance, their staging system had a higher association between stage and disease-free survival duration than either of the two earlier staging systems. Our series confirms the usefulness of this improved staging system. In our study only one ON patient with T1 disease died, while more patients with more advanced tumors died from their disease or with disease present.

In two more recent publications, Zappia et al⁸ at the University of Michigan used the Kadish staging system, and Morita et al⁹ at the Mayo Clinic used a modification of the Kadish staging system. Because of the small number of patients treated at each institution, neither of these studies found a significant correlation between advanced stage and disease-free survival duration, although there was an association between recurrence and death from

disease in both these studies in patients with advanced Kadish stage C disease. The Mayo Clinic material presented the largest number of patients (49) from a single institution and did show a correlation between clinical outcome and high-grade tumors using Hyams' classification. It is important to note that this series included NEC in its analysis, despite the dissimilarity between these two entities.

The literature indicates that the standard therapy for the treatment of ON is combined surgical resection and radiotherapy. The currently recommended treatment for ON that is believed to be surgically resectable is a CFR that attempts to remove the involved structures of the nasal vault, paranasal sinuses, orbit, cribriform plate, fovea ethmoidalis, involved dura, involved brain, and, in some cases, the olfactory tracts.^{5,8,9} Blacklock et al¹⁰ described the technique of CFR used at M.D. Anderson for the treatment of paranasal sinus neoplasms that transgress the skull base. There is disagreement in the literature regarding the timing of radiation therapy. The University of Virginia group uses preoperative radiation therapy in combination with chemotherapy,^{11,12} while investigators from the Mayo Clinic, University of Michigan, and UCLA prefer radiation therapy after surgery.^{5,8,9} Biller's group at Mt. Sinai has had success with CFR alone.⁷

The initial treatment for ON that we believe is resectable (T1 to T3) is CFR combined with postoperative radiotherapy to the primary field. We do not treat the regional lymphatics with either an elective neck dissection or radiotherapy. For advanced tumors that involve the brain or cavernous sinus and are believed to be surgically unresectable with clear margins, we have recently begun using empiric treatment with vincristine and cyclophosphamide followed by radiotherapy, with the potential for surgery if the lesion responds in a manner that makes surgery possible. The group of patients who have received this therapy is not presented in this study because the duration of follow-up was too short for meaningful analysis.

The reports in the literature of NEC of the paranasal sinus region are limited to less than 10 cases.¹³⁻¹⁵ Because of the small number of cases, there is no accepted standard of treatment. As demonstrated by this series, we have had success with surgery and radiotherapy. The role of CFR in the treatment of NEC is probably limited to those cases that clearly demonstrate cribriform plate, dura, or brain involvement, although in our series of patients who had surgery, none had extensive disease. For patients with disease that we feel is unresectable, we are now using induction chemotherapy with etoposide and vincristine, followed by radiotherapy. Three patients in this series have been treated successfully and have not required surgery. We have successfully treated several more NEC patients at our institution with this regimen, but their follow-up has been too brief to qualify for this study.

This analysis of the M.D. Anderson series of patients

confirms that NEC can be differentiated histologically from ON. It occurs in older patients, and it seldom involves the cribriform plate, confirming the hypothesis that it originates lower in the nasal vault. NEC is more likely to develop eventual distant metastasis than ON, although this study does not confirm that NEC presents more commonly with distant metastasis. In addition, NEC has responded well to combined chemotherapy plus radiotherapy, while it is apparent that ON is best treated by surgery and radiation therapy. Although CFR has produced excellent local control rates for ON, the exact indications for CFR are not clear. Early T1 lesions may not require CFR, while patients with T4 lesions are probably best served with induction chemotherapy. The timing of surgery in conjunction with radiotherapy is also still in question. Only future multicenter trials will be able to address this issue in a more definitive manner.

CONCLUSION

ON and NEC are distinctly different tumors of the nasal cavity and anterior skull base. Our series shows that surgery, including CFR, followed by radiotherapy produces good local control and long-term survival in patients with ON. NEC may best be treated by chemotherapy followed by radiation with surgery used for salvage; if surgery is used as a primary modality, a CFR may not be required.

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REVIEWERS' COMMENTS

We appreciate having the opportunity to comment on this study by Dr. Austin and his colleagues. They present a series of patients with either olfactory neuroblastoma or neuroendocrine carcinoma of the anterior skull base. This is a large series, carefully analyzed, from a major referral center. The pathologic differences in these lesions were described by Silva et al, at M.D. Anderson Cancer Center in 1982.¹

Nevertheless, problems arise because of the rarity of the tumor. These 32 patients presented over 38 years. There were significant differences in the technology available for imaging, as well as differences in the chemotherapy and surgery. Even a major referral center does not see many patients.

Although we make the pathologic distinctions between olfactory neuroblastoma and neuroendocrine carcinoma, we treat the tumors by the same protocol. The patient is first treated with two cycles of chemotherapy (etoposide and cis-platinum). If the tumor disappears or regresses dramatically by imaging, the patient is then radiated according to a high-dose proton/photon protocol. The patient then receives two additional cycles of chemotherapy. If the tumor does not regress significantly, and if the tumor is resectable by craniofacial resection, then surgical resection is recommended before radiation therapy.³ We have not noticed differences in the biologic behavior or clinical outcome between these two pathologic types. Ordonez and Mackay,² who also reviewed the M.D. Anderson Cancer Center experience with these tumors, detailed the pathologic distinctions, but emphasized that there is a continuum with significant overlap. Our clinical approach emphasizes the overlap.

Since these tumors are well defined pathologically, especially with immune peroxidase stains and electron microscopy, and since imaging allows careful determination of the extent of the tumor before treatment, a multicenter pooling of data might be realistic. The North American Skull Base Society is an organization which could organize this study.

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