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Esthesioneuroblastoma: A General Review of the Cases Published Since the Discovery of the Tumour in 1924

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Abstract. *Esthesioneuroblastoma (ENB) arises from the neuroepithelium in the olfactory rim of the nasal cavity. It accounts for about 3% of all intranasal tumours. Reviews since the first description by Berger and Luc in 1924 never reported more than a hundred cases, stressing the rarity of the tumour. However, a thorough literature review revealed a total of 945 reported cases. In our search we found a total of 1,457 cases chronicled in the literature of which perhaps 487 were cited in more than one paper, bringing the total of reported cases to 945. Author cases accounted for 198 and therefore collaborative efforts accounted for 747 cases. Sex distribution was 53.36% male and 46.64% female. Kadish classification was applied to 553 cases revealing 103 (18.29%) class A cases, 182 (32.33%) class B and 278 (49.38%) class C cases. This distribution was generally stable through the decades. Treatment could be classified in 898 cases. It consisted of surgery alone in 25.17% (226 cases), radiotherapy alone in 18.37% (165 cases), combined surgery and radiotherapy in 43.21% (388 cases) and chemotherapy in 13.2% (119 cases), followed in 11 cases (1.22%) by bone marrow transplant. In the reported cases an overall follow up could be evaluated in 477 cases, while in only 234 cases a five-year follow up was done. The outcome was 68.38% alive and disease free, 12.82% alive with disease and 18.80% dead. From these 20.51% had surgery only, 11.11 % radiotherapy and 68.38% combined surgery and radiotherapy. The best survival rates were obtained by combined therapy (72.5% vs. 62.5% surgery alone and 53.85% radiotherapy alone). Death rates were highest after radiotherapy alone (30.77% versus 18.75% in combined therapy and 12.50% after surgery alone). In conclusion, ENB is a rare but not exceptional tumour. It is best treated with combined surgery and radiotherapy. Unfortunately early diagnosis is still uncommon and no significant changes to the proportions of Kadish classes at first diagnosis have been noted in recent decades. A greater awareness of the tumour and earlier diagnosis seems the major focus for future research.*

Estesioneuroblastoma (ENB) is a rare tumour arising from the olfactory neuroepithelium in the olfactory rim of the nasal cavity and accounts for about 3% of all intranasal tumours(1). It was described for the first time by Berger and Luc in 1924(2) and given the name esthesioneuroepithelioma. The great histologic variability of the neoplasm has led to a large number of different names, such as estesioneurocitoma(3), estesioneuroblastoma(4), olfactory intranasal neuroblastoma(5), estesioneuroepithelioma, olfactory estesioneuroma(6), tumour of the olfactory placode(7) or neuroolfactory tumour(3) in order to stress one of the manifold histologic characteristics found in the examined cases. These include both olfactory rosettes together with a neuroblastic component for the esthesioneuroepithelioma, a mainly neuroblastic appearance in the estesioneurocitoma and pseudorosettes in the estesioneuroblastoma. Today most researchers have agreed on the term of estesioneuroblastoma, considering the neoplasm as originating from the neuroepithelial cells of the olfactory mucosa, which derive from the neural crest. The first cases described in American literature are those of Seaman(9) and Schall in 1951.

Seventy years after the first description of the estesioneuroblastoma we have done a general review of internationally indexed literature and its citations. The tumour has always been considered a rare and exotic entity, its incidence in the scientific literature is fluctuating and certainly many cases are not accounted for. Early reviews were done by Lewis(1955/139 total, 18 own cases), Leroux-Robert(75/128 total, 11 own cases), Kadish(76/121 total, 17 own cases), Shah(81/101 total, 31 own cases) and more

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Table I. *Stadiation according to Kadisch.*

Type	Extension
A	Tumour limited to the nasal cavity
B	Tumour interesting the nasal and paranasal cavities
C	Tumour extends beyond the nasal and paranasal cavities

Table II. *Stadiation according to Morita.*

Type	Extension
A	Tumour limited to the nasal cavity
B	Tumour interesting the nasal and paranasal cavities
C	Tumour extends beyond the nasal and paranasal cavities
D	Presence of metastases

Table III. *Stadiation according to Biller.*

	Extension
T1	Nasal and paranasal cavities, excluding the sphenoid
T2	Extension to periorbital tissue and cranial cavity
T3	Extension to the brain with good operability
T4	Non operable extension to the brain
N	Lymph nodes
M	Distant metastases

Table IV. *Classification according to Dulgherov.*

	Extension
T1	Nasal and paranasal cavities excluding the sphenoid
T2	T1 plus extension to the sphenoid
T3	Extension to the orbit and anterior fossa
T4	Extension to the brain

recently by Morita(1993), who collected 49 cases and Eden (1994) with 40 cases. These values seem to stress the rarity of the tumour. Perhaps by reviewing the indexed world literature 1457 cases could be found, 487 of whom had to be discarded as having been already reported in earlier papers. After deleting all review cases and those considered in more than one paper, 945 true new cases remained. 198 of these were true author's cases and 747 were referenced from collaborating institutions.

Pathology

General. Several theories on the origin of ENB have been formulated in the past. Jacobson's organ, an accessory olfactory site well developed in snakes and rudimental in man, has been cited, but its location in the anterior and basal part of the septum makes it an improbable origin. Some have suggested the sphenopalatine ganglion as the origin, also difficult due to its site. The ectodermal olfactory placode, often suggested as probable origin does not persist in postembryonal life and remnants have not been seen in ENB cases. Loci's ganglion, a small formation in the olfactory placode of probable endodermal origin, has been supposed by Martin(10) as an origin, while others suggest the nasal mucosa by itself or the sympathetic ganglia within it, due to the stromal tissue of the tumour(11). Some similarities between the ENB and the tumours arising from the APUD system (amine precursor uptake and decarboxylation) exist(12), but there are also major differences as the lack of production of adrenaline precursor or degradation molecules (like dopamine, vanilmandelic acid and emovanillic acid) and a different age distribution. ENB is a tumour of adulthood, while neuroblastoma of the adrenal gland peaks at about 5 years of age. Today the ENB is considered to arise from the basal neural cells of the olfactory mucosa(13)(14), which are staminal cells for the neuroreceptors and maintain a regular mitotic activity also in the adult.

Epidemiology. The incidence of the tumour is about equal in males and females (Table I). ENB can be seen in all ages from eighteen months (15) to 84 years (16). It has been described with an equal distribution in all human races.

In the field of comparative pathology ENB has been described in the animal as well as in man. Several descriptions have been made in mammals as mink [*Mustela vison*](17), dogs(18)(19), cats(20)(21), monkeys(22), horses(23) as well as rats and mice. Many authors consider ENB absent or extremely rare in non-mammals, but descriptions in fish and amphibia have been made. In the teleosts an olfactory neuroblastoma without distant metastasis and fair differentiation towards ciliated neural receptor cells has been described (in the domestic carp [*Cyprinus caprio*](24), in a *Sparus aurata*(25) and in the *Coregonus hoyi*(26)) suggesting that in these animals the tumour tends to reach a greater degree of differentiation. A case in an amphibian was described in the axolotl [*Siredon mexicana*](27).

As stated in the introduction, in our review we found 1457 cases reported in the literature, 487 of whom had to be discarded as having been already reported in earlier papers. In 25 cases it could not be stated for certain if they were original new cases, leaving 945 true new reported cases. 198 of these were true author's cases and 747 were referenced from collaborating institutions (Table X).

Table V. *Histological calssification according to Hyams.*

Grade	Lobular cytoarchitecture	Mitotic index	Nuclear polymorphism	Fibrillar matrix	Rosettes	Necrosis
I	preserved	zero	none	preminent	H.W.R.	none
II	preserved	low	low	present	H.W.R.	none
III	present or not	modest	modest	low	F.R.	rare
IV	present or not	high	high	absent	none	frequent

[H.W. R.- Homer-Wrigth Rosettes]
[F. R. - Flexner Rosettes]

In 551 cases the sex was given with a distribution of 294 (53.36%) males and 257 (46.64%) females (Table VI).

The rarity in the literature with isolated case reports has made it difficult for many authors to put their cases in a correct perspective. Exact local extension and clinical classification is often difficult and sometimes not possible. Considering authors classification or a sufficiently correct description of local extension, 563 cases out of 945 could be classified according to Kadish, with 103 class A(18,29%), 182 class B(32.33%) and 278 class C(49.38%) cases (Table XI).

Etiopathogenesis. No definite causative agent of esthesioneuroblastoma has been demonstrated in man. The tumour does not show familiar prevalence and is not linked to race or sex. Generally there is no evident relationship with tumours of the neuroepithelium linked to development, as in medulloblastomas or other neuroblastomas, also patients with retinoblastoma are known to have a generaly higher incidence of extraocular tumours, and Klein(28) describes a case of an ENB that arose in a girl with a successfully treated retinoblastoma.

ENB has been seen in hamsters after exposure to di-ethyl-nitrosoamine(29)(30), 2,6-dimethylnitrosomorpholine, N-nitrosopiperidine(31)(32)(33) and di-n-propylnitrosamine (34). The presence of Polyoma virus particles has been seen in neuroepithelial tumours in mice(35). Mice from a transgenic line that expressed the human adenovirus type 12E1A and E1B genes tend to develop olfactory neuroblastomas at approximately 6 month of age(36). In most cases type C retrovirus particles were seen in the tumour rosettes. In the same paper three cases of feline C-particle positive ENB's were reported. In cat spontaneous olfactory neuroblastomas type C retroviral particles have been shown. These particles have been classified as Feline Leukaemia Virus (FeLV) by polymerase chain reaction and immunohistochemistry. It may be interesting that these FeLV-positive cats did not have any other evidence of neoplasms or leukaemia(37).

In some cases the tumour seems to possess endocrinologic activity. Arnesen(38) reports a case of Cushing's syndrome secondary to ENB with resolution of the clinical disease after treatment of the neoplastic lesion. Myers(39) has published a case of ENB invading the oral cavity and showing antidiuretic hormone secretion. These links to neuroendocrine activity of the tumour are still to be studied, the staminal characteristic of the basal cells can probably favour a sufficient dedifferentiation with expression of other neuronal qualities by the neoplastic cell.

That the behaviour of the neuroreceptorial cell of the olfactory system still needs more research is perhaps demonstrated by a specific disease in which the migration of the olfactory cells is inhibited: Kallmann's syndrome. In this syndrome the original cells do not migrate normally during embryologic development and one can see a lack of neurosecretory cells in the hypothalamus with amenorrhea and agenesis of the olfactory bulbs and olfactory mucosa. Recently there has been evidence that the two cell populations, one neuroendocrine and one olfactory, divide early and migrate separately(40)(41), giving the possibility of atypical Kallmann-like cases with lack of neuroendocrine cells and normal olfactory function as well as bulbar agenesia and anosmia with a normal neuroendocrine activity(42)(43)(44). Only with this data one can explain the strange finding of Zappia(45), who reported an ENB in a person with Kallman's syndrome, and in which the olfactory cells were supposedly lacking.

Morbid Anatomy

Light microscopy. The lamina propria of the mucosa appears oedematous and largely infiltrated by nodes and cords of uniform appearing cells(46). The cell lumps are divided by fibrovascular connective tissue in which a small amount of inflammatory cells as well as leukocytes can be found. The covering respiratory epithelium is pseudostratified with the possibility of areas of squamous metaplasia and erosions.

The tumour cells have irregular, dark and vacuolated nuclei in which evident nucleoli can be seen. The cytoplasm is clear, eosinophilic and may be vacuolated as well. Necrotic areas are frequent and argentaffin as well as argirophilic granuli are present. The cells tend to form pseudorosettes by grouping themselves around a central vessel with high, cylindrical parallel cells in which the apical cytoplasm does not take up the stain. Sometimes true rosettes with a central

Table VI. *Sex distribution.*

	Male	Female
Number of cases	294	257
%	53.36%	46.64%

Table VII. *Local recurrence after surgery alone.*

Biller	12.5%
Elkon	44.0%
Kadish	50.0%
Foote	59.0%
Beitler	67.0%
O'Connor	75.0%
Dulgherov	86.0%

Table VIII. *Recurrence after surgery and radiotherapy.*

O'Connor	0.0%
Beitler	0.0%
Dulgherov	8.0%
Foote	12.5%
Elkon	29.0%
Kadish	40.0%

Table IX. *Survival at 5 years of follow-up.*

Bailey	18%
Skolnik	52%
Elkon	65%

round space surrounded by cylindrical cells can be seen. Mitoses can be found but are not predominant.

Two cell types have been described: Clear cells with vacuolated or compact nuclei with only a small amount of chromatin and large nucleoli, eosinophilic granular cytoplasm and dark cells, with compact dark nuclei and scarce cytoplasm, resembling neurones. A great amount of neurofibrillar material and dendritic processes are visible. Obert(47) proposed the diagnosis of ENB only if the following six characteristics are all present:

a) true rosettes or pseudorosettes,
b) lobular sepimentation by fibrovascular septa,
c) oval or round nuclei,
d) clearly defined nuclear chromatin,
e) scarce cytoplasm,
f) intercellular plexiform fibers.

The presence of neurofibrillar material is considered necessary to the diagnosis of neuroblastoma.

Hyams(48) tried to classify survival expectancy based on histologic data, grading the tumour as follows (Table V); grade one: well preserved lobular cytoarchitecture, mitotic index zero, no nuclear pleomorphism, evident fibrillar matrix, some Homer-Wright rosettes and absence of necrosis; grade two: well preserved lobular cytoarchitecture, low mitotic index, scarce nuclear pleomorphism, fibrillar matrix present, some Homer-Wright rosettes, no necrosis; grade three: lobular cytoarchitecture preserved partially, medium mitotic index, modest nuclear pleomorphism, only scarce fibrillar matrix, some Flexner corpuscles, areas of necrosis; grade four: lobular cytoarchitecture preserved partially, high mitotic index, clear nuclear pleomorphism, no fibrillar matrix, no rosettes, large areas of necrosis;

With FIF (formaldehyde induced fluorescence)(49) the neoplastic cells show a yellow-green fluorescence which can be seen also in the tumours derived from the APUD system.

Electron microscopy. Ultrastructural analysis of the cells shows cytoplasmatic dense core granules, described for the first time by McGouran(50), microtubuli, microfilaments and normal intracytoplasmatic organelles. A large number of intracytoplasmatic vacuoli resemble neurosecretory granules after degranulation.

Immunohistochemistry. Immunohistology is of major importance for diagnosis of ENB. Neurone Specific Enolase (NSE) is always present in ENB(51). The positivity for NSE together with the presence of "dense core granules" as well as neurite-like structures with microfilaments and microtubuli and positivity for a 68 kilodalton neurofilament subunit suggest further the neural origin of ENB.

The presence of NSE alone does not permit the diagnosis of ENB, as it can be found in normal or neoplastic nervous tissue as well as neuroendocrine cells and tumours derived from the APUD system(52). Cells of ENB can be positive for the S-100 protein(53) suggesting the presence elements derived from the Schwann cells, as normally present in the neuroolfactory epithelium.

Similarly sometimes positivity for glial fibrillary acidic protein (GFAP) can be seen, as well as for serotonin and vimentin, a mesenchymal cell marker(54).

Keratins and desmin are constantly absent, confirming that the tumour is not of epithelial origin(55). Positive reaction for synaptophysin, normally present in presynaptic vescicles of neurones and neuroendocrine neoplasms can be found(56), as well as positivity for chromogranin(57).

Cytogenetic analysis. Cytogenetic analysis as proposed by Castaneda(58) has shown a large number of chromosomal

Table X. *New ENB cases reported in literature (personal cases + new collection cases).*

Years	Total	Review	Possible new cases	True new cases	Collection cases	Personal cases
24-34	7	0	7	7	0	7
3544	12	0	12	12	0	12
45-54	28	0	28	18	6	12
55-64	51	0	51	59	26	33
65-74	230	175	55	64	46	18
75-84	560	270	290	276	230	46
85-94	569	42	527	509	439	70

Table XI. *Classification by 5-year interval of 59.6% 15631 of all new reported cases.*

Years	A	B	C
24-34	1	0	2
35-44	2	0	0
45-54	5	9	2
55-64	7	12	30
65-74	10	7	17
75-84	47	64	59
85-94	31	90	168
24-94	**103**	**182**	**278**

abnormalities such as pseudo-tetraploidia and abnormal metaphases. Most chromosomes are present three times and chromosome number five has been counted up to eight times. Multiple interstitial deletions and 2q+ and 5q+ changes have been described. Northern-blot analysis shows the presence of the proto-oncogenes c-*myc* and N-*myc*, but not of the protooncogene c-*fms*.

Clinical Behaviour and Classification

In 1973 Ogura and Schenk(59) called the ENB "the great impostor", in order to stress its polymorphism both in clinical behaviour and pathology, where the tumour has to be differentiated from lymphoma, melanoma, embryonal rhabdomyosarcoma, lymphoepithelioma, pericytoma and highly differentiated sarcoma(60), extramedullar plasmocytoma(61) and Ewing's sarcoma, as well as its high tendency to local recurrence. The tumour arises from the olfactory mucosa and remains initially confined to the upper nasal cavity, followed by local invasion of the paranasal sinuses and the endocranic cavity. In late cases distant metastases can be seen.

Early in its growth the ENB tends to invade the *lamina cribra* of the ethmoid, with endocranic extension, and the *lamina papiracea*, with invasion of the orbit. Early symptoms are correlated to the extension of the tumour, going from epistaxis, monolateral nasal airway obstruction and hyposmia to ophthalmic problems, maxillar area tumefaction and sinusitis-like cephalalgia. The rhinorrhea and the pain distribution especially can mislead the clinician to misdiagnose of "sinusitis". Maxillary sinus invasion can give hypoestesia or irradiated pain in the area of that sinus and the upper teeth. Ophthalmic problems secondary to orbital invasion are, among others, diplopia, prooptosis, epifora and reduction or the visus with scotopsia up to amaurosis. ENB will invade not only the orbit directly, but also the sphenoid sinus and the optic chiasma. In some cases a prevalent and early endocranic invasion gives a clinical situation of endocranic hypertension. In some rare cases no local symptomatology is evident and the first sign can be a metastasis in the neck. According to some authors, tumours with early endocranic invasion seem less frequently result in distant metastasis(62).

In 1976 Kadish(63) proposed his classification of ENB, which has been generally accepted (Table I). This classification was modified by Morita in 1993(64) maintaining classes A and B, while class C was divided into two classes (Table II).

Biller in 1990(65) proposed a classification according to the TNM system of the UICC (Union International Contre le Cancre), stressing that the types A and B of Kadish show little difference in clinical behaviour and introducing an evaluation of the possibility of surgical treatment (Table III).

To avoid the necessity of surgical exposure of the tumour in order to reach a sure staging, Dulgherov in 1992 proposed a TNM classification based on Computerised Tomography and Nuclear Magnetic Resonance (66) (Table IV).

Diagnostic Procedures

ENB arises in the vault of the nasal cavity and often remains hidden for a long time. After the first symptoms the diagnostic prosocol for ENB requires an accurate rhinoscopy with the use of flexible and rigid endoscopes. For the staging of the neoplasm after a positive endonasal biopsy, a thorough radiological examination with Computerised Tomography(67) is necessary. This must be done with contrast media, to distinguish the neoplastic soft-tissue from surrounding anatomic structures, and with both axial and coronal reconstruction centered on the cribriform plate. The contrast media shows a homogeneous distribution and enhancement in the neoplastic tissue. Standard radiograms do not add more useful information and are useless once diagnosis of ENB has been established. In the case of endocranic invasion,

Table XII. *Radiotherapy only: Follow-up for 1 year.*

	Patients	Disease -Free	Dead	Alive with Disease	Recurrence	Metastasis
24-34	0	0	0	0	0	0
35-44	0	0	0	0	0	0
45-54	0	0	0	0	0	0
55-64	2	1	1	0	1	0
65-74	1	0	0	1	1	0
75-84	3	0	3	0	3	1
85-94	1	0	1	0	0	1
total	**7**	**1**	**5**	**1**	**5**	**2**

Table XIII. *Radiotherapy and surgery: Follow-up for 1 year.*

	Patients	Disease -Free	Dead	Alive with Disease	Recurrence	Metastasis
24-34	0	0	0	0	0	0
35-44	0	0	0	0	0	0
45-54	0	0	0	0	0	0
55-64	4	2	2	0	3	1
65-74	3	2	0	1	1	0
75-84	4	2	1	1	1	1
85-94	13	8	5	0	4	3
total	**24**	**14**	**8**	**2**	**9**	**5**

Table XIII. *Radiotherapy and surgery: Follow-up for 1 year.*

	Patients	Disease -Free	Dead	Alive with Disease	Recurrence	Metastasis
24-34	0	0	0	0	0	0
35-44	0	0	0	0	0	0
45-54	0	0	0	0	0	0
55-64	4	2	2	0	3	1
65-74	3	2	0	1	1	0
75-84	4	2	1	1	1	1
85-94	13	8	5	0	4	3
total	**24**	**14**	**8**	**2**	**9**	**5**

Table XV. *Radiotherapy and surgery: Follow-up for 3 years.*

	Patients	Disease -Free	Dead	Alive with Disease	Recurrence	Metastasis
24-34	0	0	0	0	0	0
35-44	1	1	0	0	0	0
45-54	0	0	0	0	0	0
55-64	2	1	0	1	1	0
65-74	1	1	0	0	0	0
75-84	6	3	3	0	3	3
85-94	15	10	5	0	2	0
total	**25**	**16**	**8**	**1.**	**6**	**3**

Table XVI. *Surgery alone: Follow-up for 5 years.*

	Patients	Disease -Free	Dead	Alive with Disease	Recurrence	Metastasis
24-34	0	0	0	0	0	0
35-44	0	0	0	0	0	0
45-54	2	1	0	1	1	0
55-64	0	0	0	0	0	0
65-74	1	0	0	1	1	0
75-84	8	7	1	0	3	0
85-94	13	7	2	4	6	1
24-94	24	15	3	6	11	1
total	**48**	**30**	**6**	**12**	**22**	**2**

Table XVII. *Radiotherapy alone: Follow-up for 5 years.*

	Patients	Disease -Free	Dead	Alive with Disease	Recurrence	Metastasis
24-34	0	0	0	0	0	0
35-44	0	0	0	0	0	0
45-54	0	0	0	0	0	0
55-64	3	0	2	1	3	1
65-74	0	0	0	0	0	0
75-84	2	0	1	1	1	1
85-94	8	7	1	0	2	1
24-94	13	7	4	2	6	3
total	**26**	**14**	**8**	**4**	**12**	**6**

furthermore, Nuclear Magnetic Resonance can give useful information on the existence of invasion of the brain tissue, which is obviously of great importance for therapeutic decisions. NMR is not a substitute for tomography, dut to its scarce imaging of the bone.

Clinically a monolateral mass can be seen, resembling a polypoid tumour or a large hematic cyst. The mass can obstruct the nasal choanae and the upper and middle meatus and its colour ranges from grey to red. NMR gives a good possibility to separate neoplastic from inflammatory masses.

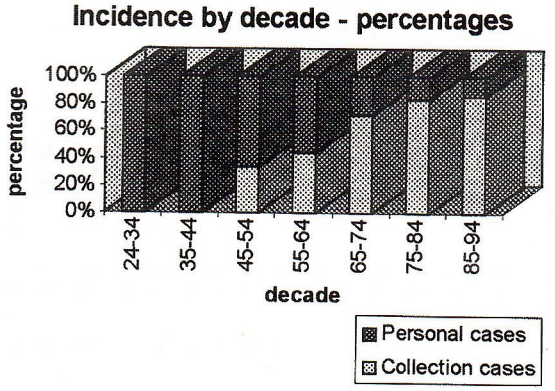

Figure 1. *Relative incidence by decade.*

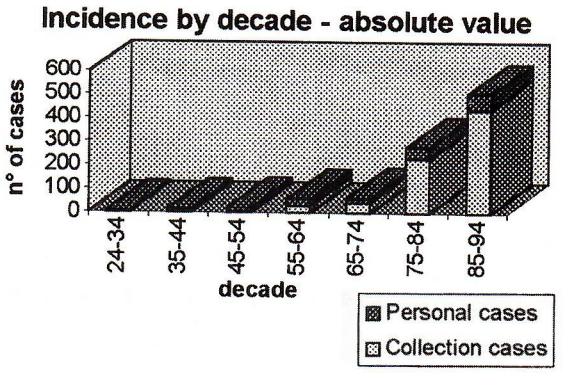

Figure 2. *Absolute incidence by decade.*

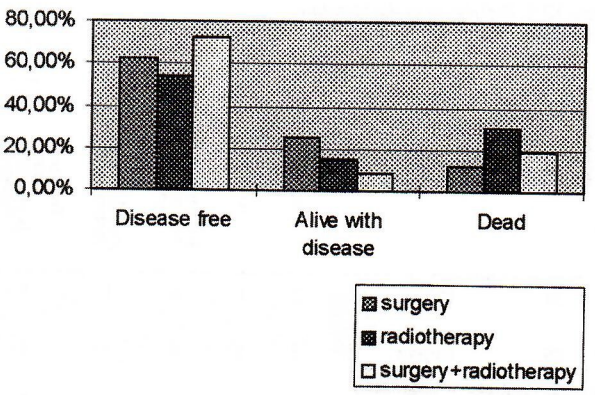

Figure 3. *Results at 5 years by therapy.*

Table XVIII. *Radiotherapy and surgery: Follow-up for 5 years.*

	Patients	Disease -Free	Dead	Alive with Disease	Recurrence	Metastasis
24-34	1	1	0	0	1	0
35-44	0	0	0	0	0	0
45-54	2	1	1	0	2	0
55-64	10	4	4	2	7	3
65-74	3	3	0	0	1	0
75-84	10	7	2	1	7	3
85-94	54	42	8	4	7	8
24-94	80	58	15	7	25	14
total	**160**	**116**	**30**	**14**	**50**	**28**

Tumours give a homogenous image due to their high cellularity(68). After the injection of gadopentate-dimeglumin as a contrast medium the tumour appears with a lower density than the normal cerebral tissue if T1-weighted and hyperdense if T2-weighted. The contrast medium tends to concentrate in the tumour tissue, as usual in highly vascularized neoplasms. This allows distinction from the generally sparsely vascularized epithelial tumours originating from the paranasal sinuses.

It should be stressed that a clear staging should always be done, we saw that of 945 new total cases only 573 (61 %) could be clearly classified from the case description - and this is true not only for the older literature!

Treatment

The optimal treatment for ENB has still to be found. The generally low incidence in each research centre has made large co-ordinated follow-up studies difficult if not impossible. Surgery, radiotherapy and chemotherapy have been used, not always with uniform results.

Surgery can be done on the primary lesion and on the neck as well as only on the neck. It can also follow radiotherapy after reduction of the main neoplastic tissue. Sometimes partial resection, is done to reduce tumour tissue and give the radiotherapy a greater chance. The surgical approach requires a paralateronasal incision with craniofacial resection. A "split-face" approach with en-block resection of the ethmoid and the tumour(69) is now the most diffuse technique. Endocranic invasion and the close relationship with the ethmoid's lamina cribrosa require a combined otolaryngological and neurosurgical approach with bicoronal incision and frontal lobe exposure.

Most authors consider the invasion of the optic chiasma, the cavernous sinus and/or the middle fossa, as well as the presence of distant metastases as a limit for surgery(70)(71)(72)(73), while invasion of the orbit or maxillary sinus are not.

Radiotherapy has been used as a treatment for the first documented case of ENB described by Berger, with good results. It is proposed for both the treatment of the primary lesions and the neck metastases and can precede or follow

Table XIX. *References in the literature.*

										ESTHESIONEUROBLASTOMA																
													Kadish stages			Therapy									
N.	Year	Author	Reference	Total reported cases	Review cases (or elsewhere included)	Probable new author' cases	True new cases (Collection + Personal)	New collection cases	Personal cases	M	F	Age	A	B	C	Surg	Rt	Surg + Rt	Chemot	Transplant	Disease-free	Alive with disease	Dead	Recurrence	Metastasis
1	24	Berger	2	1	0	1	1	0	1	1	0	50	0	0	1	0	1	0	0	0	1	0	0	0	0
2	26	Berger	3	1	0	1	1	0	1	0	1	52	0	0	1	0	0	1	0	0	1	0	0	1	0α
3	26	Treplan	96	2	0	2	2	0	2																
4	29	Portman	4	1	0	1	1	0	1			11	1	0	0	1	0	0	0	0	0	0	0	1	0
5	29	Tobeck	97	1	0	1	1	0	1																
6	30	Adler	98	1	0	1	1	0	1																
7	35	Mittelbach	99	2	0	2	2	0	2																
8	36	Wohlwill	100	1	0	1	1	0	1																
9	37	Eigler	101	1	0	1	1	0	1																
10	37	Escat	102	2	0	2	2	0	2																
11	37	Massier	103	1	0	1	1	0	1				1	0	0	0	0	1	0	0	0	0	0	0	0	0
12	41	Tavares	104	4	0	4	4	0	4																
13	43	Gricouroff	105	1	0	1	1	0	1				1	0	0	0	0	0	1	0	0	1	0	0	0	0
14	46	Da Costa	106	1	0	1	1	0	1																
15	46	Ribeiro	107			0	0																		
16	47	Eigler	108	1	0	1	1	0	1																
17	47	Jemmi	109	1	0	1	1	0	1																
18	47	Portman	110	2	0	2	2	0	2	1	0	11-52	1	1	0	0	1	1	0	0	0	0	1	1	0
19	49	Martin	110	1	0	1	1	0	1			14	0	1	0	0	0	1	0	0	1	0	0	1	0
20	49	Stout	111	6	0	6	6	6	0																
21	49	Wild	112	1	0	1	1	0	1																
22	50	Huet	113	1	0	1	1	0	1	0	1	51	0	1	0	0	0	1	0	0	0	0	0	0	0
23	50	Piquet	114	1	0	1	1	0	1	0	1	25	0	0	1	0	0	1	0	0	1	0	0	0	0
24	50	Rossert	115	1	0	1	1	0	1																
25	51	Aboulker	115	4	0	4	0	0	0																
26	51	Lenz	117	1	0	1	1	0	1																

continued

Table XIX. *(continued).*

N.	Year	Author	Reference	Total reported cases	Review cases (or elsewhere included)	Probable new author cases	True new cases (Collection + Personal)	New collection cases	Personal cases	ESTHESIONEUROBLASTOMA			Kadish stages		Therapy										
										M	F	Age	A	B	C	Surg	Rt	Surg + Rt	Chemot	Transplant	Disease-free	Alive with disease	Dead	Recurrence	Metastasis
27	51	Schall	5			0	0			0	3	22-76	2	1	0	3	0	0	0	0	3	0	0	0	0
28	51	Seaman	9	1	0	1	0	0	0	4	0		2	2	1	0	1	2	0	0	1	1	0	2	1
29	51	Terracol	118			0	0			1	0	20	0	1	0	1	0	0	0	0	0	0	0	0	0
30	52	Alves	119			0	0																		
31	52	Bosc	120	1	0	1	1	0	1	1	0	50	0	1	0	1	0	0	0	0	0	1	0	1	0
32	52	Hlasicova	121			0	0																		
33	53	Huet	122	1	0	1	0	0	0	1	0	14	0	1	0	1	0	0	0	0	1	0	0	0	0
34	54	Fruhling	123	4	0	4	0	0	0																
35	55	Fisher	124	1	0	1	1	0	1	1	0	31	0	0	1	0	0	1	0	0	0	0	1	1	1
36	55	McCormack	1	5	0	5	5	5	0	4	1	29-58	2	1	2	2	0	3	0	0	3	0	2	0	2
37	57	Giraud	125			0	0																		
38	57	Mendeloff	262	6	0	6	12	6	6	2	4	16-41	3	0	3	0	1	5	0	0	2	0	3	4	1
39	58	Riemen--schneider	126	1	0	1	1	0	1	1	0	67	0	0	1	0	1	0	0	0	0	0	1	0	
40	58	Sirtori	8	1	0	1	1	0	1																
41	59	Alvade	127	1	0	1	1	0	1	1	0	74	0	1	0	0	0	1	0	0	0	1		1	
42	59	Church	128	1	0	1	1	0	1				0	0	1	1	0	0	0	0	0	0	1	1	
43	59	Holland	129	1	0	1	1	0	1	0	1	78	0	0	1	1	0	0	0	0	0	0	1	0	
44	59	King	130	1	0	1	1	0	1	1	0	14	0	0	1	0	0	1	0	0	0	0	1	1	
45	59	Kramer	131			0	0																		
46	59	Kroath	132	1	0	1	1	0	1	1	0	28	0	0	1	0	1	0	0	0	0	0	0	0	
47	59	Lang	133	1	0	1	1	0	1	1	0	20	0	0	1	1	0	0	0	0	0	0	1	0	
48	59	Mettler	134	1	0	1	1	0	1																
49	60	David	135	1	0	1	1	0	1	1	0	36	0	0	1	0	0	1	0	0	0	0	1	1	
50	60	Mashberg	136	1	0	1	1	0	1	1	0	24	0	1	0	1	0	0	0	0	1	0	0	0	0
51	60	Obert	47	8	0	8	8	8	0	5	3	15-65	1.	1	6	1	2	5	0	0	0	3	4	6	
52	60	Palmer	137	1	0	1	1	0	1				0	1	0	1	0	0	0	0	1			0	0

continued

Table XIX. *(continued).*

ESTHESIONEUROBLASTOMA

N.	Year	Author	Reference	Total reported cases	Review cases (or elsewhere included)	Probable new author' cases	True new cases (Collection + Personal)	New collection cases	Personal cases	M	Kadish stages F	Age	A	B	Therapy C	Surg	Rt	Surg + Rt	Chemot	Transplant	Disease-free	Alive with disease	Dead	Recurrence	Metastasis
53	61	Bozzi	138			0	0																		
54	61	Dibble	139	2	0	2	2	0	2			18-36	0	2	0	0	0	2	0	0	1	0	0	2	
55	61	Eggston	140	2	0	2	4	2	2	1	1	33-69	0	0	2	0	0	2	0	0	2	0	0	2	
56	61	Largiader	141	1	1	1	1	0	1	0	1	17	0	1	0	0	0	1	0	0	1	0	0	1	
57	62	Calvet	142			0	0																		
58	62	Mollica	143			0	0																		
59	63	Aurby	144			0	0																		
60	63	Grimaud	145	2	0	2	2	0	2	1	1	30-63	0	1	1	1	1	0	0	0	1	0	1	1	
61	63	Hutter	146			0	0																		
62	63	Wallenborn	147	1	0	1	1	0	1	0	1	52	0	1	0	1	0	0	0	0	1	0	0	0	0
63	64	Andre'	148			0	0																		
64	64	Becker	149	5	0	5	5	5	0	3	2	32-70	1	1	3	1	1	3	0	0	5			3	
65	64	Dutz	150	1	0	1	1	0	1	1	0	61	0	0	1	0	0	1	0	0	0	1		1	
66	64	Gerard--Marchant	151	4	0	4	4	0	4	2	2	10-63	0	1	3	0	1	3	0	0	0	0	3	3	
67	64	Putney	152	1	0	1	1	0	1	0	1	70	0	0	1	0	0	0	0	0	0	0	1		
68	65	Fitz-Hugh	153	6	0	6	6	6	0	3	3	9-62	1	1	4	0	0	6	0	0	4		1	0	0
69	65	Grahne154	1	0		1	1	0	1	1	0	60	0	0	1	0	1	0	1	0	0	0	1	1	1
70	65	Lewis	155	18	0	18	18	18	0	11	7	12-79				7	2	9	0	0	0	9	9	12	4
71	66	Solnik	80	104	102	2	2	0	2	1	1	27-35	0	0	2	1	0	1	0	0	0	2	0	2	
72	66	Tingwald	7	73	73	0	0	0	0										2						
73	68	Kolze	156	1	0	1	1	0	1	0	1	68	0	0	1	0	1	0	0	0	0	1	0	0	0
74	69	Castro	157	7	0	7	14	7	7				3	2	2	0	1	5							
75	70	Bidstrup	158	5	0	5	5	5	0				3	0	2	1	3	1							
76	70	McGavran	50	2	0	2	4	2	2																
77	72	Schenck	159	8	0	8	8	8	0				1	3	4	2	0	6							

continued

Table XIX. *(continued).*

N.	Year	Author	Reference	Total reported cases	Review cases (or elsewhere included)	Probable new author' cases	ESTHESIONEUROBLASTOMA: True new cases (Collection + Personal)	New collection cases	Personal cases	M	F	Age	Kadish stages: A	B	Therapy: C	Surg	Rt	Surg + Rt	Chemot	Transplant	Disease-free	Alive with disease	Dead	Recurrence	Metastasis
78	73	Hamilton	160	1	0	1	1	0	1																
79	74	Kahn	161	1	0	1	1	0	1	1	0	44	0	0	1			1				1		1	
80	74	Tyler	162	3	0	3	3	0	3				2	1	0	0	2	1							
81	75	Bailey	163	3	0	3	3	0	3				3	0	0	1	0	2							
82	75	Leroux--Robert	164	11	0	11	11	11	0				1	8	2	1	1	9							
83	76	Berard	165	1	0	1	1	0	1	0	0	56	0	0	1	0	0	1	0	0	0	0	1	1	1
84	76	Jensen	166	3	0	3	3	0	3				0	3	0	0	1	2							
85	76	Kadish	63	17	0	17	17	17	0	7	10	3-77	7	5	5	8	4	5	0	0	13		4		3
86	76	McKay	167	2	0	2	2	0	2				1	0	1	0	0	2							
87	76	Oberman	168	7	0	7	7	7	0	2	5	8-72	2	5	0	2	1	4	1	0	3	1	3	4	
88	76	Osamura	169	1	0	1	1	0	1	0	1	66	1	0	0										
89	77	Cantrell	14	12	0	12	12	12	0				1	5	6		4	8							
90	77	Djalilian	170	18	0	18	18	18	0							9	9	0							
91	77	Micheau	11	6	0	6	6	6	0																
92	77	Taxy	171	2	0	2	2	0	2	0	2	16-18	0	2	0			2	1	0	1	0	1	1	
93	77	Withers	172	1	0	1	1	0	1				0	1	0	1	0	0							
94	78	Manelfe	173	5	0	5	5	0	5	4	1	6-60	1	3	1		4	3	4				1	3	
95	79	Baker	174	9	0	9	9	9	0							1	1	7							
96	79	Canty	175	2	0	2	2	0	2	2	0	23-69	0	1	1	0	0	1	0	0	1	1	0	2	1
97	79	Chaudhry	176	2	0	2	2	0	2	1	1	47-73	1	1	0			1			1	1			
98	79	Elkon	78	97	97	0	0	0	0																
99	80	Ahmad	177	0	0	0	0																		
100	80	Daly	74	7	0	7	14	7	7				2	1	4		3	4			4				
101	80	Fayos	178	9	0	9	9	9	0								1	8	6		3				
102	80	Homzie	179	173	173	0	0	0	0																

continued

Table XIX. *(continued).*

N.	Year	Author	Reference	Total reported cases	Review cases (or elsewhere included)	Probable new author cases	True new cases (Collection + Personal)	New collection cases	Personal cases	ESTHESIONEUROBLASTOMA																
													Kadish stages			Therapy										
										M	F	Age	A	B	C	Surg	Rt	Surg + Rt	Chemot	Transplant	Disease-free	Alive with disease	Dead	Recurrence	Metastasis
103	80	Singh	180	1		1	1	0	1										1						
104	80	Walters	181	1	0	1	1	0	1	0	1	25	0	0	1	1	1		1		0	1	0		
105	81	Albert	182	1	0	1	1	0	1										1						
106	81	Chapman	183	4	0	4	8	4	4									4	1		4				
107	81	Jung	184	1	0	1	1	0	1																
108	81	Shah	89	31	0	31	31	31	0	18	13	12-79	6	6	19	13	2	16			16		15	24	
109	82	Appelbblatt Mc-Clatchey	185	21	0	21	21	21	0				9	8	4	5	2	14							
110	82	Ijaduola	186	1	0	1	1	0	1																
111	82	Silva	187	31	0	31	31	29	2	14	15		3	7	5	9	7	17	8	0			12	13	5
112	83	Olsen	188	21		21	0			10	11	12-64				8	3	10	2		13		8	15	
113	83	Srigley	189	1	0	1	1	0	1																
114	83	Wang	190	24	0	24	24	24	0				9	8	7	7	5	12			15				
115	84	Harrison	191	8	0	8	8	8	0							2	1	5	1		4				
116	84	Johns	192	2	2	2	2	0	2				0	0	2	2									
117	84	Meyrowitz	193	1	0	1	1	0	1																
118	84	Tamada	194	17	0	17	18	17	1							2	8	6	4		9				
119	84	Wade	83	5		5	0												5						
120	84	Weiden	195	1	0	1	1	0	1										1						
121	85	Choi	51	10		10	0			9	1	16-61	2	4	4	6		8			4		4		
122	85	Millse Frierson	196	21	0	21	21	21	0				1	11	9		1	20			10				
123	85	Newbill	197	6	0	6	6	6	0										6						
124	85	O'Connor Jr	87	1	0	1	1	0	1	0	1	46	0	0	1	1	1	1	1	1	1				
125	85	Spalke	198	1	0	1	1	0	1																
126	86	Acker	199			0	0																		
127	86	Carpentier	200	1	0	1	1	0	1										1						
128	86	Guerrier	201	4	0	4	8	4	4	3	1	16-72	0	3	1	1	1	2	0	0	2	0	0	0	

continued

Table XIX. *(continued).*

				ESTHESIONEUROBLASTOMA																					
												Kadish stages				Therapy									
N.	Year	Author	Reference	Total reported cases	Review cases (or elsewhere included)	Probable new author cases	True new cases (Collection + Personal)	New collection cases	Personal cases	M	F	Age	A	B	C	Surg	Rt	Surg + Rt	Chemot	Transplant	Disease-free	Alive with disease	Dead	Recurrence	Metastasis
129	86	Levine	202	26	0	0	0	0	0			19-66													
130	86	Rodas	203	1	0	1	1	0	1										1						
131	86	Schroth	204	1	0	1	1	0	1																
132	86	Taxy	205	2	0	2	2	0	2																
133	87	Axe	206			0	0																		
134	87	Franklin	207	1	0	1	1	0	1																
135	87	Leguillou	208	45	0	45	45	45	0																
136	87	Mohanti	209	1	0	1	1	0	1										1						
137	87	Paling	210	1	0	1	1	0	1	1	0	71	0	0	1										
138	87	Wante	86	1	0	1	1	0	1	0	1	58	0	0	1			1	1		1				1
139	87	Whang-Peng	211	1	0	1	1	0	1																
140	88	Falkson	212	1	0	1	1	0	1	1	0	25	0	0	1		1		1		1				
141	88	Heros	213	2	0	2	2	0	2	1	1	23-28	1	0	1	1	1	1	2		0		2	2	
142	88	Regenbogen	214	2	0	2	2	0	2	0	2	25-69	0	0	2										
143	88	Spaulding	85			0	0																		
144	88	Stewart	215			0	0																		
145	88	Urdaneta	82	7	0	7	7	7	0	4	3	6-44	2	1	3		3	4	4		4		3	3	
146	88	Wick	216			0	0																		
147	88	Wigand	217	1	0	1	1	0	1																
148	88	Woodhead	218	24	0	24	24	24	0	14	10	9-67													
149	89	Anavi	219	1	0	1	1	0	1	0	1		0	0	1			1	0		1	0	0	1	
150	89	Arita	220	2	0	2	4	2	2	2	0	28-52	0	0	2	1		1	1		1	1		2	
151	89	Fahlbush	221	8	0	8	8	8	0	4	4	17-62	0	0	8	1		7			4		4	4	
152	89	Held	222	1	0	1	1	0	1																
153	89	Hurst	67	9	9	0	0	0	0	5	4	19-66	0	2	7			9	7		8				

continued

Table XIX. *(continued).*

N.	Year	Author	Reference	Total reported cases	Review cases (or elsewhere included)	Probable new author cases	ESTHESIONEUROBLASTOMA: True new cases (Collection + Personal)	New collection cases	Personal cases	M	Kadish stages: F	Age	A	B	Therapy: C	Surg	Rt	Surg + Rt	Chemot	Transplant	Disease-free	Alive with disease	Dead	Recurrence	Metastasis
154	89	Llombart--Bosh	223	1	0	1	1	0	1	0	1	67	0	0	1								1	1	
155	89	Lochrin	224	7	0	7	7	7	0	2	5	12-78	0	3	4		2	5	3		4		2	3	
156	89	O'Connor	225	15		15	0			6	9	4-67	2	7	6	4	4	7			10				
157	89	Schulz--Wendtland	226	1	0	1	1	0	1	1	0		0	0	1		1	1							
158	89	Som	227	2	2	0	0	0	0							2									
159	89	Stewart	88	5	5	0	0	0	0	3	2	35-55	0	0	5			5	5	5	1	1	3		
160	90	Biller	65	13	0	13	13	13	0																
161	90	Delank	228	7	0	7	7	7	0	4	3	13-75	1	2	4		3	3	1						
162	90	Fondelli	15	1	0	1	1	0	1			1	0	0	1										
163	90	Goldsweig	84	1	0	1	1	0	1	0	1	37	0	1	0	1		1	1	0				1	
164	90	Meneses	229	5	0	5	5	0	5	1	4	15-59	0	0	5	1	1	3	1	0	4	0	1	2	
165	90	Polonowski	230	1	0	1	1	0	1																
166	90	Schmidt	231	4	0	4	4	4	0	3	1	41-54	0	1	3		1	3	2						
167	91	Ahern	232	7	0	7	7	7	0	4	3	39-83	4	1	2	2	1	4	2	0	2	1	4	2	
168	91	Beitler	79	14	14	14	14	14	0	8	6	22-66	2	4	8	3	5	6	0	0	7	3	4	9	
169	91	Castaneda	58	1	0	1	1	0	1	1	0	16	0	0	1			1	1	0			1	1	
170	91	Fellinder	233	1	0	1	1	1	0																
171	91	Ho H.W.	234	1	0	1	1	0	1	0	1	47	0	0	1	1									
172	91	Perkkio	235	1	0	1	1	0	1	0	1	5	1	0	0		1		1				1		
173	91	Roux	236	7		7	7	7	0	4	3	29-65	0	2	5	4		3	4	0	4		3		
174	91	Sartoris	73	2	0	2	4	2	2	1	1	48-59													
175	91	Vandevanter	237	1	0	1	1	0	1	1	0	46	0	0	1	1									
176	92	Berman	238	1	0	1	1	0	1	0	1	11	0	0	1			1	1	0	1				
177	92	Davis	239	4	0	4	4	4	0				0	0	4	1	4		4	0	3		1	1	
178	92	Dilhuydy	240	2	0	2	2	2	0																

continued

Table XIX. *(continued).*

							ESTHESIONEUROBLASTOMA																			
											Kadish stages					Therapy									
N.	Year	Author	Reference	Total reported cases	Review cases (or elsewhere included)	Probable new author' cases	True new cases (Collection + Personal)	New collection cases	Personal cases	M	F	Age	A	B	C	Surg	Rt	Surg + Rt	Chemot	Transplant	Disease-free	Alive with disease	Dead	Recurrence	Metastasis
179	92	Dulguerov	66	26	0	26	26	26	0	12	12	4-73	9	7	6	7	4	12	2	0	15	2	7	11	
180	92	Feifel	241	1	0	1	1	0	1	0	1	47	0	0	1	0	1	0	0	0	0	0	1	1	
181	92	Jugie	242	1	0	1	1	0	1	0	1	46	0	1	0	1									
182	92	Klein	28	1	0	1	1	0	1	0	1	18	0	0	1	1							1		
183	92	Lemoine	243	12	0	12	12	12	0	7	5	18-73	1	8	3	1	1	9	0	0	6	0	5	3	2
184	92	Lloreta-Trull	244	24	0	24	24	24	0	11	13	13-82									12	2	7		
185	92	Mack	245	2	0	2	2	0	2	1	1	13-47	0	0	2			2	2	0	0	1	1	2	
186	92	Shanley	246	1	0	1	1	0	1	0	1	63	0	0	1										
187	92	Zappia J.J.	45	1	0	1	1	0	1	1	0	16	0	1	0	1	0	0	0		1				
188	93	Cheng Li	247	5	0	5	5	5	0	2	3	17-76	0	2	3										
189	93	Du	55	1	0	1	1	0	1	1	0	54	0	1	0			1	0	0	1				
190	93	Knobber	248	5	0	5	5	5	0	1	4	19-81	0	1	4										
191	93	Koh-Ichi	249	7	0	7	7	7	0	5	2	17-73	1	4	2		1	6	2	0	2		5	6	
192	93	Lund	250	20	0	20	20	20	0	12	8	14-67				9	1	10	0	0	11	2	2		
193	93	Morita	64	49	0	49	49	49	0	27	22	3-78	4	13	32	24	4	21			26			19	
194	93	Vanhoenacker	251	1	0	1	1	0	1	1	0	14	0	0	1			1							
195	93	Zappia J.J.	16	21	0	21	21	21	0	13	8	14-84	0	9	12	5	3	12	4	0	14	2	5	5	
196	94	Arnesen	38	1	0	1	1	0	1	0	1	36				1								1	
197	94	Derdeyn	252	6	0	6	6	6	0	1	5	19-66	0	1	5	5									
198	94	Eden	253	40	0	40	40	40	0							23	38		15	5					
199	94	Kempf	254	6	0	6	6	0	6	4	2					6		1	1		4	1	1	1	1
200	94	Kurihara	255	4	0	4	4	0	4									4			3		1	1	
201	94	Louboutin	256	2	0	2	2	0	2																
202	94	McCaffrey	257	24	0	24	24	24	0																
203	94	Myers	39	1	0	1	1	0	1																
204	94	Schuster	258	15	0	15	15	15	0							10									

continued

Table XIX. *(continued).*

				ESTESIONEUROBLASTOMA																							
																Kadish stages			Therapy								
N.	Year	Author	Reference	Total reported cases	Review cases (or elsewhere included)	Probable new author cases	True new cases (Collection + Personal)	New collection cases	Personal cases	M	F	Age	A	B	C	Surg	Rt	Surg + Rt	Chemot	Transplant	Disease-free	Alive with disease	Dead	Recurrence	Metastasis
205	94	Silva	259		0	0	2	0	2																
206	94	Som	673	3	0	3	0	0	0																
207	94	Tscherning	260	1	0	1	1	0	1	1	0	3						1	1				1	1	
208	94	Valles-San--Leandro	261	1	0	1	1	0	1																
				1457	487	970	945	747	198	294	257		103	182	278	226	165	388	119	11	288	40	149		
													563			898					477				

surgery. The irradiated area(74) should include the entire nasal fossa, both maxillary sinuses, the ethmoid and should generally be extended to the sphenoid sinuses and the anterior cranial fossa. The overall dose is about 5000cGy given at rates of 200cGy/day for 5 days a week. Radiotherapy has been proposed as primary treatment in ENB(75) and an epidemiological study done at the Mayo-Clinic for the years from 1951 to 1990 showed no significant difference in survival rates between patients who had only radiotherapy and those on whom only surgery on the primary lesion was performed(76).

On the other hand a combined approach with postsurgical radiotherapy seems to yield better control, especially of local recurrence. Local recurrences after surgery alone were reportedly as high as 59%, with 9% distant metastasis, while after a combined surgical and radiotherapeutical approach the local recurrences fell to 12.5%. These results are reported by several authors, also if the values are quite different from one study to the other. Dulgherov reports 86% local recurrence after surgery and 8% after surgery and radiotherapy, while Kadish reports values of 50% after surgery alone and 40% after surgery followed by radiotherapy. On the other hand, O'Connor(77) saw 75% of recurrences after surgery and none after a combined approach, and Elkon(78) reported values of 44% and 29%. Finally Beitler(79)reports values of 67% for surgery alone and 0% for the combined approach (Table VII ans VIII).

At present there is no general agreement on the treatment of the primary lesion. Skolnik(80) considers radiotherapy only in cases of local recurrence after surgery or if surgery is technically impossible, Elkon and Million(81) consider surgery and radiotherapy alone as equivalent on stage A and stage B lesions, while in stage C tumours a combined approach is suggested. Urdaneta(82) and Wade(83), considering the progresses done in both therapies, value a combined approach in all cases as the best choice.

It becomes evident from this data, that treatment of ENB must always be personalised according to the known polymorphism in the growth of the tumour.

Today most of the reported data suggest the use of a wide surgical resection followed by radiotherapy as the best choice for the control of the primary lesion. The fear expressed by Biller of the risk of a rise in local metastasis after surgery cannot be confirmed.

For the treatment of the neck lymph nodes a functional neck dissection (with conservation of the sternocleidomastoid muscle) is proposed if there are metastatic lymph nodes as seen by clinical examination or imaging techniques such as echography or NMR, while a prophylactic dissection in a negative neck is not generally agreed upon, considering the non epithelial origin of the tumour.

Recently chemotherapy has entered the treatment protocol for ENB. The agents most frequently used are cisplatinum, etoposide, adriamycin, cyclophosphamid, vinciristin, 5-fluoro-uracyl, doxorubicin and thiothepa. This therapy should not be considered as a first choice, but is generally confined to inoperable lesions or large, otherwise untreatable, recurrences. In some cases preliminary chemotherapy, followed by surgery and radiotherapy has been proposed in stage C patients(84) (85). To reach the intracranial extension of the tumour the antimitotic agent can be given locoregionally by an intraarterial catether introduced through the common carotid artery(86). Unfortunately the technique requires high-cost implantable infusion pumps, but the placement of the catheter is easy and can be done in general centers. It has a low morbidity and did not show significant

side effects. Recently a protocol with high doses of chemotherapy followed by autologous medullar transplant has been proposed, similar to those used in breast cancer(87)(88).

The data of the treatment as reported in the literature could be classified in 898 cases. It consisted of surgery alone in 25.17% (226 cases), radiotherapy alone in 18.37% (165 cases), combined surgery and radiotherapy in 43.21% (388 cases) and chemotherapy in 13.2% (119 cases). In 11 cases (1.22%) a bone marrow transplant was performed.

Survival Rates According to the Literature

Survival rates vary widely in the literature (Table IX). Survival appears to be closely correlated to the stage of ENB. In the papers of Elkon and Shah survival for stage A patients ranges from 75% to 83%, for stage B from 68% to 33% and for stage C from 41% to 45%(89). The results of the Mayo-Clinic survey suggest a major importance of Hyam's grade in predicting outcome, more than that of age, sex and Kadish's staging. The overall report of life expectancy in ENB patients is slowly rising, this may be due to both earlier diagnosis and better surgical and radiotherapeutical approaches. The tendency to give late local recurrences and distant metastases must perhaps always be kept in mind.

In the reported cases an overall follow up could be valued in 477 cases, while in only 234 cases a five year follow up was done. The outcome was 68.38% alive and disease free 12.82% alive with disease and 18.80% dead. Of these 20.51% had surgery only, 11.11% radiotherapy and 68.38% combined surgery and radiotherapy. The best survival rates where obtained with combined therapy (72.5% *vs.* 62.5% surgery alone and 53.85% radiotherapy alone). Death rates were highest after radiotherapy alone (30.77% *versus* 18.75% in combined therapy and 12.50% after surgery alone) (Tables XII-XVIII) (Figures 1-3).

Discussion

Seventy years from the first description of the Estesioneuroblastoma we felt it useful to undertake a general review of the topic. The tumour is still considered not only rare but exceptional, few cases are reported sporadically and no clear therapeutic protocol has been agreed upon. Other reviews have been done before, the most complete being those of Skolnik in 1966 (2 own cases and 102 cases found in the literature from 1924 to 1966), Elkon in 1979 (97 new cases from 1966 to 1979), and more recently Morita (49 cases) and Eden (40 cases).

From a general review of the indexed world-literature much interesting data emerges. First, one has to distinguish between the author's own cases, new cases collected from the author's own or collaborating institutions and cases collected from the literature. Furthermore, the multidisciplinary approach to therapy, as regards surgery and radiation, can result in the presence of the same cases in several publications, as for example in a surgical and in a radiotherapy journal, by two different teams of researchers, one interested in the surgical procedure and one reporting the results of radiotherapy or chemotherapy.

Since about 15-20 years ago the descriptions of the cases have become multiform and often little comparable data can be obtained. Follow-up ranges from a few months to years, age is often reported only as raw general data (*i.e.* from-to) and stadiation started with Kadish's work. Some early cases can be presumptively and retrospectively staged by their description. We must always keep in mind that all specific statements must be done only on comparable data. While the total reported cases are more than 1400, only 945 can be classified as truely new cases. From this in only 551 sex distribution was clear. Kadish classification had been done in 563 cases and survival rates in even less. This has to be kept in mind while observing the tables, since the sum of the data never reaches the total of new cases, but all percentages are reported to the total number of comparable cases in that specific topic.

Each author has his specific field of interest which ranges from histopathology to diagnosis and therapy. This makes the data extremely difficult to compare and order. On the other hand, the selection of comparable data is of the utmost importance in obtaining information on the epidemiology of the neoplasm, its clinical behaviour and therapeutic outcome. A further major problem consists in the extreme parcellization of the data, often just one or two cases are reported, and sometimes from the discussion it emerges that the author does not seem to be aware of some of the published indexed literature. Many cases perhaps find their way only into national, regional papers with no relevance to the world scientific community and are lost for further reference.

Finding so many published cases in the referenced literature was in fact a real surprise for us. Generally case reports behave in a specific way. In the beginning, few cases are reported as a new nosologic entity. After that one can see a rapid rise in reports with a following decline in interest in isolated cases. At this point only large reviews and discussions find their way into the indexed literature, leaving isolated case reports to student's work and very exceptional situations. Neuroblastoma reports accordingly progressed continuously through the decades, with new case reports rising rapidly since 1970, while review reports peaked in the early '80's. The new case reports show only a minor rise in personal cases, while better institutional collaboration has permitted large new case collections. Collected cases amount for more than 80% of the new cases reported in the last decade.

One explanation for this phenomenon becomes evident from the examination of the literature. Even large review series never contain more than a hundred cases and the general impression remains that of an extremely rare and

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exotic tumour. This may explain the still high interest in the neoplasm and the fortunately high percentage of reporting.

As already stated, ENB was first described as such by Berger in 1924, but already before his basic paper, the Germans Schmidt in 1900(90) and Sussenguth in 1909(91), the Austrian Chiari in 1901(92), the American Clark in 1905(93) and the French Anglode in 1920(94) described "nasal gliomas" which could well have been equal to the olfactory neuroblastoma of Berger. Both Chiari and Sussenguth already proposed the olfactory origin of the neoplasm!

Besides the paper of Clark, Estesioneuroblastoma remained confined to European interest since 1951, when Schall describes the first case in the American literature, 27 years after Berger and after World War II. The first description by Berger in France in 1924 was followed in 1926 by Terplan in Germany. In 1941 Tadares was the first Portuguese author to report ENB and in 1947 Jemmi introduced the nosologic entity into Italian literature. Haslican in 1952 reported the first case in Czech literature, Lang in 1959 in the first and Largiader in 1961 Brazillian. From then most cases are found in the English speaking literature, but recently rising interest can be seen in Japan. In fact larger populations, as those from the Far East, previously not extensively studied, are now highly represented in the case reports. This is of special interest in order to compare the incidence of the neoplasm in the different populations.

With the better diagnostic possibilities today one should expect a shift from late to early cases at first diagnosis. This unfortunately is not true. Observing the evolution of the new case reports we see a relatively stable situation since the mid 50's with about half of all cases still in the Kadish C stage. This may be partially due to the introduction of CT and NMR in the clinical evaluation. Some cases, originally considered stage B, may now reveal an unexpected invasiveness, but there is still space for a greater awareness of the tumour.

In conclusion, we would like to stress some facts on ENB:

a) It is still a rare but not exceptional tumour, which must be suspected in all masses of the nasal cavities. In young patients with recurrend epistaxis a flexible fiber-endoscopy should always be considered.

b) Histology is tricky and the Pathologist should be alerted by the clinician if there is suspicion of ENB.

c) The best treatment appears to be combined surgery and radiotherapy. Surgery should be always done on the primary lesion in stage A and B cases, while stage C cases must be considered case by case. Surgery on a positive neck should always be considered, while a prophylactic neck dissection is not generally agreed upon.

d) Chemotherapy, both general and locoregional, has to be considered as a last resort only.

e) Survival rates are rising and a survival rate of now about 65% after 5 years with a combined approach justifies more aggressive treatment.

In order to favour a better collection of cases a world registry could be useful for histological reference and case recording.

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