Esthesioneuroblastoma

What is the Optimal Treatment?

Jesper G. Eriksen, Lars Bastholt, Annelise S. Krogdahl, Olfred Hansen and Karsten E. Joergensen

From the Departments of Oncology (J.G. Eriksen, L. Bastholt, O. Hansen), Pathology (A.S. Krogdahl) and Oto-rhino-laryngology (K.E. Joergensen), Odense University Hospital, Denmark

Correspondence to: Dr Jesper G. Eriksen, Department of Oncology, Odense University Hospital, DK-5000 Odense, Denmark

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A retrospective review was conducted on 13 patients with esthesioneuroblastoma (ENB), treated at our institution from 1977 to 1997. According to the Kadish classification, one patient was in stage A, 5 patients were classified as stage B and 7 patients were in stage C. Five-year disease-specific survival was found to be 51%. Forty-six percent of the patients experienced relapse and despite intensive salvage therapy, median survival after recurrences was only 12 months. This indicates the need for good primary control in local as well as distant disease. The role of pre- versus postoperative radiotherapy to secure good local control is discussed and compared with the literature, and treatment guidelines are proposed. The tumours were graded according to the Hyams' classification and its importance as a prognostic factor is briefly discussed.

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Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is an uncommon tumour type of neural crest origin arising in the nasal vault (1). Since Berger first described it in 1924, more than 945 cases of this tumour have been reported in the world literature, mostly as single case reports (2).

ENB accounts for approximately 6% of intranasal cancers (3) and shows a variety of symptoms and a heterogeneous histopathology. Because of its rarity, no consensus has been reached regarding treatment of this tumour. Traditionally, ENB is staged as suggested by Kadish (Table 1) (4).

We present our experience with this uncommon tumour type and compare it with that in the world literature.

MATERIAL AND METHODS

From 1977 to 1997 a total of 15 patients diagnosed with ENB was registered in our department. The search was cross-checked with files from the Department of Pathology and the National Board of Health. Data on age, sex, stage of disease according to the Kadish classification systems, symptoms, pathology, treatment, complications and follow-up were registered. All histological slides were reviewed and studied immunohistochemically and graded according to Hyams' histological classification system (Table 2) (5). Available data on causes of death (including autopsy reports) were also registered.

RESULTS

Female (6) to male (9) ratio among the 15 patients was 1 : 1.5. For one patient, only data on histopathology were available because the clinical file was lost, and one patient had never been treated. The following data are based on the remaining 13 patients.

Median age was 49 years (range 14–83 years). Aetiology was unknown in all cases. Presenting symptoms were nasal obstruction in 46% of the cases, headache or blurred vision in 38%, discharge or epistaxis in 23%. The results of grading and immunohistochemistry are presented in Table 3.

Eighty-seven percent of the tumours stained positive for synaptophysin, 27% were positive for neurofilament protein, 67% were positive for chromogranin A and 100% for neural cell adhesion molecule (N-CAM). All the tumours stained positive for Class III beta-tubulin. These are all markers for neuronal and neuroendocrine tumours. S-100 protein is a marker of the sustentacular network, which surrounds the neuroblasts in a diagnostically distinctive fashion. These sustentacular cells were found in 47% of the tumours. As expected, only one tumour

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Table 1

Stages according to Kadish and modified by Morita. To make our figures comparable with the literature, we have calculated stages C and D together, as is done in almost all the larger reviews

Stage	Tumour localization
A	Tumour confined to the nasal cavity
B	Tumour confined to the nasal cavity and paranasal sinuses
C	Tumour confined beyond the nasal cavity and paranasal sinuses, including involvement of the cribriform plate, base of the skull, orbit or intracranial cavity
D	Tumour with metastasis to cervical lymphnodes or distant sites

showed scattered positive cells in CD99-staining (Ewing sarcoma-marker). Neuroblastoma-antigen reactivity was found in only two tumours and alpha-smooth-muscle antigen was never expressed. These antibodies can be used in the differential diagnosis of small cell tumours; 60% strongly expressed cytokeratins, indicating epithelial differentiation. The KI-67 index, a marker of cell proliferation activity, was also identified (Table 3).

Staging procedures included clinical examination, with inspection of the nasal vault and pharyngeal regions supported by findings during surgery. Preoperative CT-scans were performed in 85% of the cases.

According to the Kadish classification, one patient was diagnosed as stage A, 5 patients as stage B and 7 patients were registered as stage C. Two patients had lymph node metastases at the time of presentation and were classified as stage D. For the purpose of comparing the results with those in the literature, we have listed stage C (5 patients) and D (2 patients) as one group, namely stage C.

Different approaches to treatment depending on stage and general health situation were applied (Table 4). Treatment generally consisted of surgery for stage A, surgery combined with primarily postoperative radiotherapy with 55–60 Gy for stage B and surgery, radiotherapy and chemotherapy for stage C tumours, where chemotherapy is often applied preoperatively and radiotherapy with 55–60 Gy postoperatively. The most frequently used cytotoxic agents were cisplatin, doxorubicin and vincristine.

Median follow-up time was 4.6 years (range 0.7–11.6 years) and 5-year crude survival was 45% (see Fig. 1), with a median overall survival of 4.6 years (0.7–11.9 years). Median recurrence-free survival was 4.2 years (0.5–11.9 years), defined as the time from the start of treatment until recurrence or death is verified.

One-year disease-specific survival was 77% and at 5 years 51% of the patients were still alive. Two long-term survivors both lived for more than 10 years without evidence of disease—one was classified as stage A and the other stage B. Both were primarily diagnosed with low-grade tumours with a KI-67 index of less than 10%. Both had tumours with a strongly S-100-positive sustentacular network.

If we look at the stages, we find that our only stage A patient lived for more than 11 years after diagnosis and died of pneumonia at 94 years of age, without evidence of recurrence. In stage B, 3 patients out of 5 (60%) were still alive 5 years after diagnosis—two of them with positive S-100 staining and KI-67 of less than 10%. Only one patient died of ENB within 5 years (KI-67 $>$ 10% and S-100 negative). In stage C, only 1 out of 7 patients (14%) was alive 5 years after diagnosis; 5 of the 7 patients died of ENB within the first 5 years, 6 of them with high-grade tumours, and one with low-grade. The patient who survived for more than 5 years had a tumour without a sustentacular network and a proliferation rate greater than 10%.

Overall, out of 13 patients (46%) 6 died of ENB, recurrence being observed in 5 of these patients, while one patient was never free of tumour. Metastases were all distant (distant lymph nodes, brain, breast, bone marrow and leptomeningeal infiltration). Median time to recurrence was 6 months (range 2–11 months) and median survival after recurrence was 12 months (range 3–37 months). Four patients in our review are still alive, and all are without evidence of disease.

DISCUSSION

ENB is a very rare tumour and evaluation of the therapy given is therefore difficult. Owing to changes in diagnostic procedures and treatment over time, comparison of results can be problematic. The present paper is no exception, presenting 13 patients collected over a period of 20 years.

Table 2

The histological grade according to Hyams' classification. Grade 1+2: low-grade; Grade 3+4: high-grade; H-W: Homer-Wright pseudorosettes; +/−: present or absent

	Grade 1	Grade 2	Grade 3	Grade 4
Lobular architecture	Present	Present	+/−	+/−
Mitotic activity	Absent	Present	Prominent	Marked
Nuclear pleomorphism	Absent	Moderate	Prominent	Marked
Rosettes	H-W +/−	H-W +/−	Flexner +/−	Absent
Necrosis	Absent	Absent	Occasional	Common

Table 3

Histological grading according to Hyams' classification and result of the immunohistochemical staining

Pt. no.	Syn	NF	Chr.A	β-tubulin	S-100	CK	N-CAM	CD99	NB	Actin	KI-67	Grade
1	+++	–	–	+++	++	–	+++	–	–	–	<10%	1–2
2	+++	(+)	+++	+++	+++	–	+++	–	–	–	<10%	1
3	+++	(+)	+++	+++	+	+++	+++	–	–	–	<10%	1
4	–	–	–	++	–	+++	+	–	–	–	>10%	3
5	++	–	++	+++	++	–	+++	–	–	–	>10%	3–4
6	–	–	–	+++	–	+++	+++	–	–	–	>10%	3
7	+++	–	++	+++	+++	–	+++	–	–	–	<10%	2
8	++	–	–	(+)	–	+++	+++	–	–	–	>10%	4
9	+	(+)	+	++	–	++	(+)	+	++	–	>10%	3–4
10	+++	(+)	+++	+++	–	–	+++	–	–	–	>10%	4
11	+++	–	+++	+++	++	+++	+++	–	–	–	<10%	2
12	+++	–	+++	++	–	+++	+++	–	–	–	>10%	4
13	+++	–	+++	+++	++	–	+++	–	–	–	<10%	1–2
14	++	–	–	+++	–	+++	+++	–	+	–	>10%	3
15	+++	–	+++	+++	–	++	+++	–	–	–	<10%	1

Number of positive staining cells: +++ signifying most, ++ many and + scattered positive cells.
Abbreviations: Syn = synaptophysin; NF = neurofilament protein; Chr.A = chromogranin A; CK = cytokeratins; N-CAM = neural cell adhesion molecule; CD99 = Ewing's sarcoma tumour marker; NB = neuroblastoma tumour marker; Actin = α-smooth muscle actin.

Our group of patients is very representative of the pattern of this disease (6–8), and the distribution of patients in each Kadish stage also reflects the literature (9–11), as do primary site of the tumour and the presenting symptoms.

The results of the immunohistochemical and histological examinations show that all cases discussed here are of neuroendocrine/neural origin and it is concluded that all these tumours are cases of ENB, and that a broad panel of antibodies is necessary to verify the diagnosis. Although S-100 protein-positive sustentacular cells are often seen in ENB, it is also known that poorly differentiated tumours generally are devoid of these sustentacular cells. As seen in the present study, they are mostly grades 3 and 4 tumours, lacking such S-100 protein reactive cells. In our study sustentacular cells were less frequently found than has been reported by others (12).

When comparing the KI-67-staining and the degree of differentiation, it can be seen that poor differentiation (Hyams' grade 3 + 4) is associated with a high proliferation index and well-differentiated tumours with a low one. These results compared with overall survival indicate that long-term survival is correlated with well-differentiated tumours, and probably a lesser tendency to metastasize. Most of these tumours are also classified as Kadish stages A and B. Unfortunately, this material was too small for us to perform reliable statistical analyses, but similar results have been observed in other solid tumour types (13, 14). Nevertheless, our results with the proliferation index and Hyams' grade compared with overall survival suggest that this classification can be used as a prognostic factor in the treatment of ENB, but this has to be verified in a large-scale study. This is also illustrated by the fact that, among the Hyams' grades 1 and 2 patients treated, median overall survival is 103 months and 5-year overall survival is 80%. Among grades 3 and 4 patients, median overall survival is only 25 months and 5-year overall survival is as low as 12%.

ENB tends to grow locoregionally, but unlike squamous cell carcinomas of the head and neck, distant metastases are not unusual (15). The majority of recurrences occur within the first few years after treatment (16, 17). Spaulding (8) found median time to relapse, for all stages, to be 11 months. Forty-six percent of our patients developed recurrence, which in the literature is reported to be between 38% and 86% (6, 8, 18).

Six patients with residual tumour or recurrent disease presented with distant metastases and they all died from ENB 3 to 37 months after relapse, despite intensive salvage therapy. Median survival after recurrence was 12 months. From these data it is reasonable to propose intensive primary therapy in selected patients. Not only to secure local control, but also to minimize the risk of metastatic disease.

Surgical excision is traditionally used on patients with localized disease, i.e. stage A (7, 19), often performed through a lateral rhinotomy. Some recommend combination with radiotherapy (10). This must be preferred, if local resection with safe margins cannot be obtained. Craniofacial surgery can be used to secure free margins. Spaulding et al. have reported an increase from 70% to 87% in the 2-year survival for stage A + B, after introduction of craniofacial resection (8).

The combination of surgery and adjuvant radiotherapy to clinical target volume (CTV) is mandatory for stage B patients (5, 9, 10, 16, 20, 21).

Table 4

Patients treated at Odense University hospital 1977–1997

Pt. no.	Age	Sex	Stage	Year of diagnosis	Treatment	Recurrence	RFS	Status Jan.'99	OS
1	83	F	A	1978	S	–	139	DOR	139
2	14	M	B	1986	CT+S+RT	–	143	NED	143
3	60	F	B	1986	S+RT	–	107	DOR	107
4	58	M	B	1986	S+RT	–	25	DOR	25
5	32	F	C	1988	CT	Progres.	6	DOD	22
6	56	F	B	1990	S+RT	+	6	DOD	43
7	46	F	B	1990	S+RT	–	103	NED	103
8	62	M	C	1991	S+RT	+	2	DOD	8
9	29	M	C	1992	S+CT+RT	–	72	NED	72
10	55	M	C	1993	CT+RT	+	5	DOD	10
11	41	F	C	1995	S+CT+RT	+	5	DOD	9
12	64	M	C	1996	CT+RT+S	–	27	NED	27
13	46	M	C	1996	S+RT+CT	+	11	DOD	14

Abbreviations: S = surgery, RT = radiotherapy, CT = chemotherapy; NED = No evidence of disease; DOD = dead of disease; DOR = dead of other reasons; DFS = disease-free survival, OS = overall survival; Progres. = progression under treatment.

Recent reports using chemotherapy in stage B have shown that ENB also is a chemo-sensitive tumour (22).

CTV (primary tumour site and subclinical lymph node metastases) should receive 45–50 Gy and GTV (gross tumour volume) should receive 55–60 Gy. Optimal dosage, however, has never been properly determined (6, 8, 16, 23).

The combination of surgery and radiotherapy will improve local control. Dulguerov (7) found, for all stages, that with surgery alone 86% of patients developed recurrence, and after radiotherapy alone 60%. However, after combined therapy only 17% experienced a relapse. Foote (9) found the same tendency, although not so pronounced: 72% 5-year local control when surgery alone was performed and 86% for the group that received combined surgery and radiotherapy. In the two papers, there are differences in the stage of disease, however, with a marked tendency to use combined therapy in stage C patients.

Chemotherapy as a treatment modality was introduced in the early 1980s, using combinations of cyclophosphamide, epirubicin, vincristine and cisplatin. Today the best results are achieved using combinations of these drugs (8, 10, 24–28). We used a combination of cisplatin, doxorubicin and vincristine, which is reported to give good results with acceptable toxicity (29).

Chemotherapy, first of all, is used in stage C patients, combined with wide surgical resections and radiotherapy. Introduction of surgery by craniofacial resection and chemotherapy for stage C has increased the 2-year crude survival considerably and today multimodality therapy is accepted in these patients. Eden and colleagues have reported an increase in 2-year crude survival from 50 to 88% (8).

The order in which these treatment modalities should be applied has not been determined. Traditionally, radiotherapy is given after surgery (2), but good results are also reported using preoperative radiotherapy (8, 10, 30). For the surgeon, it can be difficult to determine the margins of the tumour when radiotherapy is given preoperatively, and a risk of incomplete resection exists. On the other hand, the risk of seeding of tumour cells during surgery is probably less when surgery is performed after radiotherapy. One of our patients actually had his first recurrence close to the wound after surgical resection of a cerebral metastasis, performed before radiotherapy. Preoperative radiotherapy could also provide good local tumour control, optimizing the chance of total resection of the tumour with minimal cosmetic damage. A review of the literature, combined with our own experience, cannot clarify this subject any further (8, 17, 20–22).

Generally, our group of patients was treated as recommended in the literature. All patients in stage B underwent surgery and postoperative radiotherapy, while patients in stage C were treated more individually.

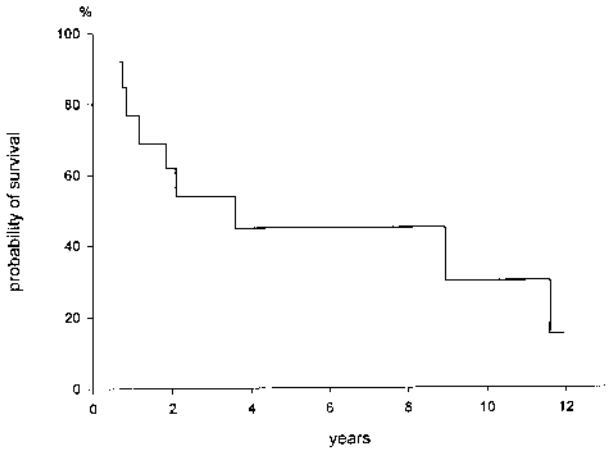

Fig. 1. Crude survival for ENB-patients, 1977–1997.

The 5-year disease-specific survival in our study was 51% and all recurrences occurred within the first year after start of treatment, somewhat below the results reported by most other authors. In the literature the 5-year recurrence-free survival is reported to be between 52% and 90% (7, 10, 24, 31–33).

Taking these data into consideration, local control and minimization of risk of metastatic spread are essential if we want to increase survival after ENB. Our own data show, together with the literature, that effective primary treatment is essential. Therefore it seems reasonable to suggest the following therapeutic guidelines:

Stage A: Surgery—in selected cases combined with radiotherapy.

Stage B: Radiotherapy to CTV, followed by surgical resection. The results of adjuvant chemotherapy have to be further elucidated.

Stage C: Preoperative chemotherapy and/or radiotherapy followed by surgical procedures. The use of adjuvant postoperative chemotherapy has to be further elucidated, as well as timing of radiotherapy and surgery.

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