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High Dose Level Radiation Therapy for Local Tumour Control in Esthesioneuroblastoma

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Esthesioneuroblastoma is an uncommon tumour of neural crest origin arising in the nasal cavity. This paper is a retrospective review of 7 patients with esthesioneuroblastoma treated at a single institution from May 1974 to July 1990. 5 patients were treated with radiation therapy alone and 2 patients were irradiated after surgical resection. No local or regional occurrence was observed in any patient at 6 months, or at 1, 3, 6, 11.5 and 12 years following treatment. One patient died of intercurrent disease 6 years after radiation therapy. 2 patients died of disease, 1 of distant metastasis at 6 months and the other patient of meningeal carcinomatosis and distant metastases 1 year after treatment. One patient is alive with distant metastases 1 year after treatment. None of the patients experienced significant complications of irradiation. High-dose irradiation (60 Gy or more) alone or in combination with resection is an effective local treatment modality for esthesioneuroblastoma.

Key words: esthesioneuroblastoma, olfactory neuroblastoma, radiation therapy
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INTRODUCTION

ESTHESIONEUROBLASTOMA (ENB) is an uncommon tumour of neural crest origin which arises in the nasal cavity. Since the first description by Berger and colleagues in 1924 [1], over 200 well-documented cases have been reported in the world literature. Owing to the rarity of this neoplasm, no single physician or institution has accumulated a broad experience with this tumour. However, a correlation between local tumour extent, metastatic disease and reduction in patient survival has been demonstrated [2]. On this basis, a staging system has been proposed [2]. ENB has a bimodal age distribution with a peak in the 11–20 years age group and then a second higher peak in the 51–60 years age group [3, 4].

Typical histological features used to identify olfactory neuroblastoma from undifferentiated carcinoma and other intranasal malignancies are neuroepithelial cells arranged in pseudorosettes, a surrounding stroma composed of undifferentiated cells and fibrillar cords, marked microvascularity with neuroepithelial cells around the blood vessels, a conspicuous absence of mitotic figures, occasional interstitial calcification, and finally, a basic similarity to adrenal or sympathetic ganglionic neuroblastoma and retinoblastoma [2, 5]. The usual localisation of these tumours, high in the nasal vault, and their vascularity account for the two most common symptoms: unilateral nasal obstruction and epistaxis. Pain is rare until local invasion of adjacent structures occurs; headaches occur with central nervous system involvement. Tearing, proptosis and diplopia are late signs of orbital involvement. The treatment of ENB reported in the literature includes primary surgical therapy [6, 7], primary radiation therapy [2, 3, 8, 9] or combined radiation and surgery [10–12]. Recently, some authors advocated planned pre-operative radiation followed by surgery [12–14].

This paper presents the results of treatment of patients who received radiation therapy alone or combined with surgery.

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MATERIALS AND METHODS

Between May 1974 and July 1990, 7 patients with ENB were treated with radiation therapy at the University Hospital St. Rafaël, Leuven, Belgium.

From each case report, age, sex and local, regional and metastatic tumour spread were reported. Details of surgical and radiotherapy treatment were obtained (Table 1). Follow-up periods ranged from 6 months to 12 years.

We have adopted the staging system suggested by Kadish and colleagues [2]: stage A, involvement of the nasal cavity only; stage B, involvement of the nasal cavity and one or more paranasal sinuses; stage C, involvement beyond the nasal cavity, including involvement of the orbit, base of the skull or intracranial cavity, cervical nodes or distant metastatic sites. In our series, 6 patients had extended stage C ENB. One patient had a tumour in the lower region of the right orbit, but without macroscopic disease in the nasal cavity. Staging investigations consisted of a thorough history and physical examination, looking especially for signs of intra-orbital, intracranial or metastatic disease. CAT scans (when available) of the primary region were performed. Surgery was performed in 2 patients: in patient 2, a limited resection of the bottom of the right orbit was performed, and patient 4 had a total ethmoidectomy and partial maxillectomy. Radiation therapy was delivered using Cobalt 60 in 6 patients and 6 MV X-rays in 1 patient with a 2-field or 3-field technique. All patients were treated with continuous-course irradiation. Treatment was administered once a day, five frac-

Table 1. Treatment and results in 7 patients

Patient	Age (years)	Sex	Extent of disease	Stage	Surgery	Radiation therapy	Follow-up	Complications
1	19	Male	Nasal cavity, right ethmoid sinus, sphenoid sinus, right orbit	C	None	60 Gy, 2 Gy/fr. Co 60, 3-fields	No evidence of disease at 12 years	None
2	49	Female	Right orbit*	C	Partial right orbital excision	60 Gy, 2 Gy/fr. Co 60, 2-fields	No evidence of disease at 11.5 years	None
3	74	Male	Nasal cavity, right ethmoid sinus, right maxillary sinus, sphenoid sinus, right submaxillar lymph node	C	None	60 Gy, 2 Gy/fr. Co 60, 3-fields	Died of intercurrent disease at 6 years	None
4	51	Male	Nasal cavity, ethmoid sinuses, left maxillary sinus, cribiform plate	C	Ethmoidectomy and partial maxillectomy	50 Gy, 2 Gy/fr. 6 MV X-rays, 3 fields	No evidence of disease at 3 years	None
5	22	Male	Nasal cavity, left ethmoid sinus, left maxillary sinus, base of skull, left orbita	C	None	65 Gy, 2 Gy/fr. Co 60, 3-fields	Died of distant metastases at 1 year	None
6	37	Male	Nasal cavity, sphenoid sinus, base of skull	C	None	64 Gy, 2 Gy/fr. Co 60, 2-fields	Pleural metastases and supraclavicular lymph node involvement at 1 year	None
7	17	Male	Nasal cavity, maxillary sinus, right orbit	C	None	60 Gy, 2 Gy/fr. Co 60, 3-fields	Died of distant metastases at 6 months	None

*Limited extension in the orbit only.

tions per week, usually at 2 Gy per fraction. Minor orbital invasion was present in patient 2, and most of the lacrimal tissue, one third of the eyeball and the crystalline lens were excluded from the irradiation fields. On ophthalmoscopic examinations, no evidence of radiation cataracts or radiation retinopathy was present. Chemotherapy was never included in the primary treatment.

RESULTS

The results of treatment are given in Table 1. No patient had a local or regional recurrence within the irradiated fields. 4 of the 7 patients were disease-free at 3, 6, 11.5 and 12 years after radiation therapy and 3 are still alive. One patient died of intercurrent disease without local recurrence at 6 years following radiotherapy (patient 3). 3 patients had a tumour recurrence. One patient developed pleural metastases and a supraclavicular lymph node involvement (outside the irradiated areas) 1 year after treatment, and has just begun chemotherapy (patient 6). 2 patients died with distant metastases without local relapse. One of these patients developed skin and bone marrow metastases and died 6 months after radiation therapy (patient 7). The other patient died of bone marrow metastases and meningeal carcinomatosis at 1 year after irradiation without evidence of local recurrence (patient 5). There were no significant complications of radiation therapy. Even in the 2 patients followed up for more than 10 years, no cataract was seen, despite the irradiation to a portion of the orbit.

DISCUSSION

ENB remains a very uncommon neoplasm of the nasal cavity and one which is often misdiagnosed because of its histological pattern and rarity. While some have questioned the prognostic significance of the staging system suggested by Kadish and colleagues that we have adopted in our series [2], it provides a common reference point for comparisons of therapy. Nevertheless, in our series, patient 2 presented a small tumour only in the orbit, without nasal involvement. By applying the staging system of Kadish [2] for this uncommon presentation, patient 2 was a stage C ENB, but from a prognostic point of view should be considered rather as a stage A ENB. Patient 2 had no evidence of disease 11.5 years after partial right orbital excision and external radiation therapy. The 6 other patients had locally very extended stage C tumours.

The debate regarding optimal therapy for ENB has not yet been resolved, with proponents for radiotherapy alone, surgery alone or combined modality therapy including chemotherapy [2–4, 7, 15]. In 1966, Skolnik and colleagues [15] reviewed 97 cases reported in the literature from 1924 (the date of the first description of ENB) until 1966. For the 50 patients followed for 5 or more years, he found an advantage in 5-year survival for patients treated with surgery compared with radiotherapy (64 versus 38%). Nevertheless, there was no indication of the extent of disease, and one may assume that many of the patients with advanced disease received palliative treatment with combined treatment or radiotherapy.

More recently, in Elkon's 1979 world literature review [3], the analysis of the overall group suggests that either surgery or radiotherapy as initial treatment is as good as combined treatment in stage A and B disease, with 3-year crude survival of 88.9 and 88.3%, respectively. The overall control rates for stage A ENB were 70% for stage B, the overall control rate was 7/11 (64%) for radiotherapy alone, 4/8 (50%) for surgery alone, and 12/21 (57%) for combined radiotherapy and surgery. In stage C, combined treatment would seem to offer patients the best chance for cure, with 52.9% surviving for 3 years. Of the 21 patients with stage C disease, 15 were treated by combined therapy: 6 patients died with disease and 2 are living with disease.

Kadish and colleagues [2], in a review of 17 patients, suggested

limited surgery followed by radiation therapy in stage A ENB. For lesions limited to the nasal cavity and paranasal sinuses (stage B), Kadish suggested pre-operative radiation therapy and limited surgery, and, for stage C ENB, Kadish suggests high-dose radiation therapy of 60–65 Gy in 7 weeks followed by surgical resection of residual disease, if operable. Of 17 patients in this series, 13 (76%) were alive without disease. The local control rates were 7/7 patients with stage A ENB (100%), 4/5 patients (80%) with stage B ENB, and 2/5 patients (40%) with stage C ENB.

Spaulding's review of 30 patients in 1988 [4] demonstrated local control for stage B ENB of 100% with a combination of radiotherapy and surgery, but has not demonstrated a significant improvement in treatment results with aggressive upfront management of stage C ENB (craniofacial resection or chemotherapy), at the cost of a non-significant increase in complications of therapy.

Ahmad and associates [8] obtained local control in 66.6% (6/9 patients) of patients with ENB treated with radiation therapy alone.

The local control in our series was obtained in 7/7 patients with stage C ENB, treated with radiotherapy alone or a combination of limited surgery and postoperative external radiation therapy. Our results for local control are extremely good compared to others series: Olsen's [7] failure rate was 62% and Elkon's [3] failure rate was 38%, with doses of postoperative irradiation of 50 Gy. Alternatively, in Ahmad's series [8], none of the patients who received a tumour dose of 60 Gy or more postoperatively developed local recurrence. In our series, 6 patients received doses between 60 and 64 Gy, and only 1 patient (patient 4) received 50 Gy. These few reports suggest that large fields and doses of external radiation therapy of 60 Gy or more may obtain a better local control in ENB.

In the presence of palpable disease in the neck, a neck dissection should be done for residual disease after radiotherapy to levels above 60 Gy. In the presence of neck nodes, both neck sides should be treated. In clinical negative neck areas, the dose should be in the region of 50 Gy [16].

Haematogenous metastases from ENB occur in up to 24% of cases in the Appleblatt's review [17], and according to Elkon's review [3], distant metastases occurred in 30% of patients with stage B and 48% of those with stage C disease during its course. In our series, 3/7 (43%) patients presented distant metastases (the 3 patients were stage C ENB). In view of the high incidence of distant metastasis, a few authors [4, 13, 17–24] have reported the use of chemotherapy as part of the treatment of ENB. Weiden and colleagues [19] reported their experiences with 1 patient treated with three cycles of cisplatin and 5-fluorouracil, followed by radiation and three additional cycles of the same chemotherapeutic regimen. Repeat CT scans demonstrated persistent soft tissue masses, and resulted in a left intranasal etmoidectomy being performed. The pathological report showed mucosal tissue and underlying bone with chronic inflammation and fibrosis, but not malignancy. 5 patients reported by Levine and colleagues [13] had no tumour in the specimen, and 6 had only foci of microscopic residual disease after chemotherapy and radiotherapy. Polonowski and associates [18] reported 1 patient with recurrent ENB after surgery and radiation therapy, treated with four 6-day cycles of combination chemotherapy cisplatin and 5-fluorouracil. Complete tumour regression was noted on repeat CT scans, and confirmed by histopathological examination after surgical removal. Roux and colleagues [21] presented 7 patients with ENB, treated with several chemotherapeutic agents (cisplatin and 5-fluorouracil). Five-year distant failure rate was significantly decreased compared to other series. Morita and associates [22] reported 49 patients with ENB, treated at the Mayo Clinic. The 5-year survival rate was 80% for the low-grade tumours and 40% for the high-grade tumours. For these authors, the poor prognosis associated with high-grade tumours may also indicate the addition of chemotherapy. These few reports suggest the potential efficacy of planned combined modality therapy, including early chemotherapy in locally advanced ENB or high-grade tumours. Nevertheless, further investigations are necessary to confirm the general efficacy of chemotherapy in ENB. In Spaulding's review [4], with the addition of chemotherapy and craniofacial resection in stage C ENB, no significant improvement in relapse-free survival could be documented.

From the above data and the data presented in our series, it is reasonable to assume that ENB can be eradicated with radiotherapy. Large fields and doses of 60 Gy or more are needed, as has been proved by the long term local control in some patients. Irradiation alone or in combination with resection is an effective treatment modality not only for stage A and B, but also for stage C. Extremely careful treatment planning has to be carried out to avoid complications of high-dose irradiation in the nasal and orbital region.

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Testicular Lymphoma: a Population-based Study of Incidence, Clinicopathological Correlations and Prognosis

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In a Danish population-based non-Hodgkin's lymphoma registry, 2687 newly diagnosed patients were registered from 1983 to 1992. 39 had testicular involvement (TL) (incidence 0.26/10^5/year). Median age was 71 years. 24 cases had localised and 15 had disseminated disease. Histologically, all cases were diffuse (65% diffuse centroblastic type). Of the 27 tested, 11% were of T- and 89% of B-immunophenotype. In localised cases, where surgery was supplemented by combination chemotherapy (CCT), the relapse rate was 15.4%. The relapse rate for cases with localised disease treated with other regimens (orchiectomy and/or radiotherapy) was 63.6% ($P < 0.05$). Median relapse-free survival was 28 and 14 months, respectively. Overall 5-year survival for all cases was 17%. Adverse prognostic factors at the univariate level were stage IV, constitutional symptoms, serum lactic dehydrogenase elevation and performance score (WHO 3–4). It is suggested that the treatment of stage I_E/II_E TL should include early CCT and CNS prophylaxis.

Key words: non-Hodgkin's, lymphoma, testicular, surgery, therapy
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INTRODUCTION

SINCE THE first description of testicular lymphoma as a clinical entity in 1866 [1], a large number of publications have described the natural history of this lymphoma. Of these reports, only very few contain population-based data [2, 3].

Primary testicular non-Hodgkin's lymphoma (NHL), defined as testicular involvement at the time of diagnosis, is a rare disease, representing 1–8% of all testicular cancer [4]. It mainly affects older men, is histologically highly malignant (usually of centroblastic diffuse type), with a tendency to bilateral testicular involvement and an association with Waldeyer's ring, skin and CNS [4].

It is still debated whether truly (i.e. without microscopic spread) primary testicular NHL does exist as an independent entity, or whether it should be regarded as the first symptom of a more widespread disease. Rare cases have been reported where patients have achieved long-term disease-free survival after orchiectomy as the sole treatment.

This report is a clinicopathological analysis of 39 unselected cases based on the data from a Danish population-based lymphoma registry.

PATIENTS AND METHODS

The Danish population-based registry, LYFO registry, covering western Denmark (2.8 million inhabitants), was started on 1 January 1983, and is still ongoing. The organisation of the registry has been described elsewhere [5]. For this study, the data from 2687 consecutive cases of NHL, registered between 1 January 1983 and 30 September 1992, were analysed. 39 patients (1.4%), all with testicular involvement at the time of diagnosis, were included.

Clinical data

At the time of diagnosis, the registered parameters included date of birth, date of diagnosis, occupation, associated diseases,

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