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CLINICAL INVESTIGATION **Head and Neck**

OUTCOME AND PROGNOSTIC FACTORS IN OLFACTORY NEUROBLASTOMA: A RARE CANCER NETWORK STUDY

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Purpose: To assess the outcome in patients with olfactory neuroblastoma (ONB).
Methods and Materials: Seventy-seven patients treated for nonmetastatic ONB between 1971 and 2004 were included. According to Kadish classification, there were 11 patients with Stage A, 29 with Stage B, and 37 with Stage C. T-classification included 9 patients with T1, 26 with T2, 16 with T3, 15 with T4a, and 11 with T4b tumors. Sixty-eight patients presented with N0 (88%) disease.
Results: Most of the patients (n = 56, 73%) benefited from surgery (S), and total excision was possible in 44 patients (R0 in 32, R1 in 13, R2 in 11). All but five patients benefited from RT, and chemotherapy was given in 21 (27%). Median follow-up period was 72 months (range, 6–315). The 5-year overall survival (OS), disease-free survival (DFS), locoregional control, and local control were 64%, 57%, 62%, and 70%, respectively. In univariate analyses, favorable factors were Kadish A or B disease, T1–T3 tumors, no nodal involvement, curative surgery, R0/R1 resection, and RT-dose 54 Gy or higher. Multivariate analysis revealed that the best independent factors predicting the outcome were T1–T3, N0, R0/R1 resection, and total RT dose (54 Gy or higher).
Conclusion: In this multicenter retrospective study, patients with ONB treated with R0 or R1 surgical resection followed by at least 54-Gy postoperative RT had the best outcome. Novel strategies including concomitant chemotherapy and/or higher dose RT should be prospectively investigated in this rare disease for which local failure remains a problem. © 2010 Elsevier Inc.

Olfactory neuroblastoma, Esthesioneuroblastoma, Radiotherapy, Surgery, Chemotherapy.

INTRODUCTION

Esthesioneuroblastoma or olfactory neuroblastoma (ONB) is a rare malignant disease of the olfactory neuroepithelium, including the superior one third of the nasal septum, cribriform plate, and superior turbinates, extending to base of the skull and to the intracranial space (1–3). It constitutes only 3% of all intranasal neoplasms, and its etiology remains unclear (4). ONB can be observed in both children and adults. Its incidence peaks first between ages 11 and 20 years, then between ages 51 and 60 years (5). Evidence in the literature comes mainly form retrospective studies carried out over long periods in which diagnostic workup changed dramatically from conventional radiology to computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)/CT, and/or functional MRI. On the basis of current evidence, a combined otolaryngologic and neurosurgical anterior craniofacial resection followed by postoperative radiotherapy is the main treatment modality in patients with localized ONB (6–9). Using combined modality treatment, many series report good locoregional control (6, 7, 10, 11); however, when negative surgical margins are obtained, adjuvant radiation therapy (RT) remains questionable according to some authors (12,

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13). The role of chemotherapy in the treatment of ONB is controversial, both postoperatively and before resection (14–20).

We report herein the results of a retrospective multicenter study of a large cohort of patients with ONB from 13 European and North American centers, aiming to assess treatment approaches and different prognostic factors in this rare disease.

METHODS AND MATERIALS

A series of 77 patients treated for ONB in 13 European and North American centers between 1971 and 2004 were included in this retrospective study of the Rare Cancer Network (www.rarecancer.net).

Inclusion criteria consisted of nonmetastatic ONB eligible for curative treatment, adult (≥18 years) or adolescent patients (three patients aged 15 years, one patient aged 14 years), no previous history of cancer other than nonmelanoma skin cancer or in situ cervix cancer, and good performance status (World Health Organization scale 0–1). The study was approved by the Ethical Committee of the University of Lausanne. Staging was assigned according to the TNM classification system of the International Union against Cancer 2002 (21), and to the Kadish system (22). No information on histological grade, according to Hyams classification (1), was collected.

Initial symptoms were mainly nasal obstruction with or without recurrent epistaxis, severe frontal headache, impaired vision, anosmia, or chewing pain with a median duration of 3 months (range, 1–24) before treatment. Pretreatment evaluation included a medical history, examination with panendoscopy (oro-pharyngolaryngoscopy, bronchoscopy, and esophagoscopy), CT scan (n = 71), and/or MRI (n = 35) of the head and neck region. Only four patients (treated between 1971 and 1978) had neither CT scan nor MRI. Additional diagnostic procedures for distant metastases, including CT of the chest, liver ultrasound, and/or bone scintigraphy were only performed if clinically indicated. Laboratory studies included blood chemistry (electrolytes, liver and kidney function tests), and a complete blood count was performed.

Patient characteristics are summarized in Table 1. Median age was 52 years (range, 14–85), and male/female ratio was 40/37. According to Kadish classification, there were 11 patients (14%) with Stage A (nasal cavity only), 29 (38%) with Stage B (paranasal sinus involved), and 37 (48%) with Stage C (extension beyond paranasal sinus). TNM classification included 9 patients (12%) with T1, 26 (34%) with T2, 16 (21%) with T3, 15 (19%) with T4a, and 11 (14%) with T4b tumors. Sixty-eight patients presented with N0 (88%) disease.

Overall survival (OS), disease-free survival (DFS), and actuarial locoregional (LRC) and local control (LC) rates were calculated using the product-limit method (23). Time to any event was measured from the date of pathological diagnosis. The events were death (all causes) for OS and death (all causes) or relapse for DFS. For the LRC rate, the event consisted of local or regional relapse (local relapse for LC). Patients without relapse were censored at their last follow-up. Confidence intervals (CI) were calculated from standard errors. Differences between groups were assessed using the log-rank test (24). Multivariate analyses were done using the Cox stepwise-regression analysis to determine the independent contribution of each prognostic factor (25).

RESULTS

Most of the patients (n = 56, 73%) benefited from surgery (S). Treatment consisted of a combination of S, radiation therapy (RT), and chemotherapy (CT) in 12 patients (16%), S + RT in 40 (52%), S alone in 5 (6%), RT + CT in 9 (12%), and RT alone in 11 (14%). Total excision was possible in 44 of 56 operated patients (R0 in 32, R1 in 13, R2 in 11). All but five patients benefited from RT with a median dose 60 Gy (range, 30–70 Gy) in median 2 Gy/fraction during median 42 days. RT was delivered using two-dimensional (2D) RT in 31 patients (40%), three-dimensional (3D) RT in 38 (50%), and intensity-modulated RT (IMRT) in 3 (4%). Planning treatment volume included the tumor bed in 61 (85%), tumor bed and involved lymph nodes in 11 (15%) patients. No cervical elective nodal irradiation was performed. Two or three cycles (range, 2–12) CT was given in 21 patients (27%) using several combinations including platinum (n = 9), doxorubicin (n = 7), or both (n = 5). Median follow-up period was 72 months (range, 6–315).

Median time to locoregional progression was 110 months (range, 0–310). Local progression was observed in 24 (31%), regional (alone in 7 patients, 9 with local relapses, 2 with distant metastases, and 2 with local and distant metastases) in 20

Table 1. Characteristics of 77 patients with olfactory neuroblastoma

	n	%
Sex		
Male	40	52
Female	37	48
Kadish classification		
A	11	14
B	29	38
C	37	48
T classification		
1	9	12
2	26	34
3	16	21
4a	15	19
4b	11	14
N classification		
0	68	88
1	4	5
2	5	7
Treatment		
Surgery + RT	40	52
Surgery + RT + CT	12	16
RT alone	11	14
RT + CT	9	12
Surgery alone	5	6
Type of surgery		
Total	44	57
Subtotal	12	16
No Surgery	21	27
Surgical margins		
R0	32	57
R1	13	23
R2	11	20
Radiotherapy technique		
2D RT	31	40
3D RT	38	50
Intensity-modulated RT	3	4
No RT	5	6

Abbreviations: 2D = two dimensional; 3D = three dimensional; CT = chemotherapy; RT = radiation therapy.

Table 2. Univariate analyses in 77 patients with olfactory neuroblastoma (log-rank test)

	n	5-yr OS	95% CI	*p* value	5-yr DFS	95% CI	*p* value	5-yr LRC	95% CI	*p* value	5-yr LC	95% CI	*p* value
All patients	77	64	52–76		57	45–69		62	49–75		70	58–82	
Sex													
Female	37	61	44–78	0.34	49	32–66	0.77	57	39–75	0.40	66	49–83	0.08
Male	40	67	51–83		53	35–71		67	49–85		73	55–91	
Age (years)													
Median (>51)	39	69	53–85	0.89	59	42–76	0.99	62	44–80	0.74	68	50–86	0.78
(≤51)	38	60	43–77		55	39–71		64	46–82		73	57–89	
Quartile (>61)	19	60	34–86	0.07	50	34–76	0.08	43	14–72	0.15	52	19–85	0.59
(≤61)	58	66	53–79		59	46–72		67	53–81		74	62–86	
Kadish classification													
A	11	80	54–100	0.10*	68	38–98	0.32*	68	38–98	0.86*	68	38–98	0.92*
B	29	76	59–93		56	36–76		63	43–83		68	48–88	
C	37	52	34–70		43	25–61		58	38–78		73	56–90	
A + B	40	76	61–91	0.03†	59	42–76	0.15†	65	49–81	0.60†	69	53–85	0.78†
T -classification													
1–3	55	72	59–85	0.01	60	56–74	0.01	67	53–81	0.15	73	59–87	0.10
4	22	47	25–69		30	8–52		44	16–72		62	39–85	
N -classification													
0	68	68	56–80	0.01	55	42–68	0.0005	65	52–78	<0.0001	72	60–84	0.005
+	9	27	0–68		28	0–60		32	0–68		52	7–97	
Chemotherapy													
No	56	65	52–78	0.49	56	42–70	0.47	68	54–82	0.10	75	63–88	0.04
Yes	21	59	32–86		34	6–62		37	8–66		52	29–65	
Surgery													
Total	44	70	55–85	0.004‡	53	37–69	0.07‡	63	47–79	0.22‡	68	52–84	0.53‡
Subtotal	12	67	40–94		56	26–86		68	37–99		82	59–100	
No surgery	21	51	27–75		48	24–72		56	31–81		68	42–94	
Total+subtotal	56	69	56–82	0.001§	54	40–68	0.02§	65	51–79	0.08§	71	58–84	0.30§
Surgical margins													
R0, R1	45	71	56–86	0.004	54	38–70	0.05	64	48–80	0.22	69	53–85	0.62
R2, no surgery	32	56	38–74		48	29–67		58	38–78		73	55–91	
Total RT dose (n = 72)													
≥54 Gy	57	71	58–84	0.08	61	47–75	0.02	72	58–86	0.003	79	67–91	0.002
<54 Gy	15	43	17–69		19	0–41		29	10–48		41	19–63	

Abbreviations: CI = confidence interval; DFS = disease–free survival; LC = local control; LRC = locoregional control; OS = overall survival; RT = radiotherapy.

* A vs. B vs. C.

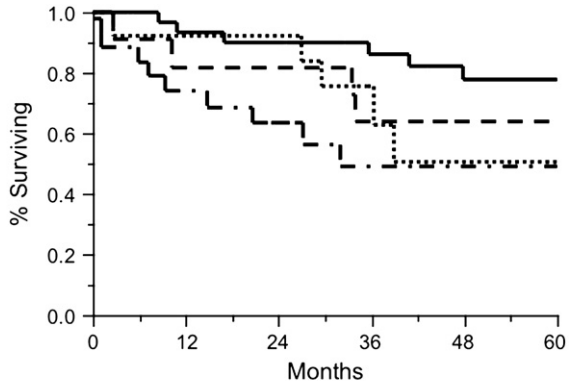
† A + B vs. C.

‡ Total vs. subtotal vs. no surgery.

§ Surgery vs. no surgery.

(26%), and distant metastases in 15 (19%) patients. Among the 68 patients without initial nodal disease (N0), there were 8 local, 4 regional, 8 distant, 7 locoregional, 3 local and distant, 1 distant and regional, and 2 locoregional and distant relapses, giving a total of 5 nodal relapses (7%) without local progression (4 regional alone and 1 regional and distant). In 9 patients with positive lymph nodes (N1 or N2), there were no isolated local or distant relapses, 1 isolated regional relapse, 4 locoregional relapses, and 1 regional and distant relapse (2 regional relapses without local progression; 22%). Salvage treatment consisted of surgery and/or RT. In patients with local recurrence, surgery alone was performed in 8 patients, surgery and postoperative RT in 1, palliative chemotherapy in 4, and supportive care in 11 patients. Treatment of regional relapse consisted of neck dissection in 1 patient, RT in 1 patient, and palliative chemotherapy in 5 patients. Causes of death included disease progression in 32, postoperative complications in 2, radiation-induced brain necrosis in 1, and intercurrent disease in 3 patients. The 5-year OS, DFS, LRC, and LC was 64% (95% CI, 52%–76%), 57% (95% CI, 45%–69%), 62% (95% CI, 49%–75%), and 70% (95% CI, 58%–82%), respectively. In univariate analyses (Table 2; Figs. 1 and 2), factors favorably influencing the outcome were the Kadish A or B disease, T1–T3 classification, no nodal involvement (N0), curative surgery, R0/R1 resection in operated patients, and total RT dose ≥54 Gy in irradiated patients. Multivariate analysis (Table 3) revealed that the independent best prognostic factors predicting the outcome were T1–T3, N0, R0 or R1 resection, or total RT dose (≥54 Gy).

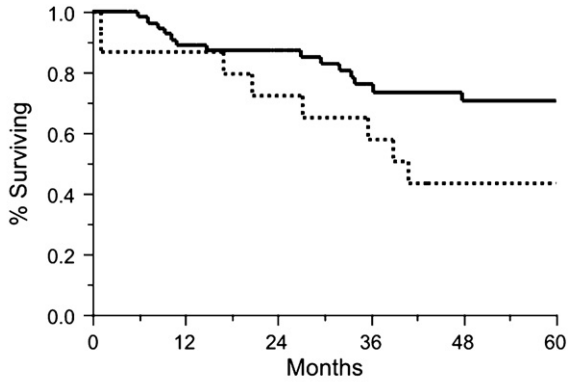
Late toxicity assessment was performed according to the European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group grading system (26). There were seven (9%) patients with severe late



Patients at risk

R0	32	29	27	23	20	19
R1	13	12	11	8	5	4
R2	11	10	9	8	6	5
No surgery	21	16	11	8	7	6

Fig. 1. Overall survival at 5 years according to surgical margin (log-rank test, $p = 0.006$): R0 resection (solid line; $n = 32$), R1 resection (dotted line; $n = 13$), R2 resection (dashed line; $n = 11$), or no surgery (dashed/dotted line; $n = 21$).



Patients at risk

RT ≥ 54 Gy	57	49	44	32	28	27
RT < 54 Gy	15	13	11	9	7	6

Fig. 2. Overall survival at 5 years according to total radiotherapy (RT) dose in 72 patients treated with RT (log-rank test, $p = 0.08$): ≥54 Gy (solid line; $n = 57$) vs. <54 Gy (dotted line; $n = 15$).

toxicity: one (1%) patient with Grade 3 retinopathy, and six (8%) with Grade 4 (osteonecrosis in five [osteoradionecrosis in 4, postoperative necrosis in 1] and lethal frontal brain necrosis in another). In six patients treated with RT, planning was 3D in three patients (total dose: 60 Gy, 60 Gy, and 64 Gy), and 2D in three (total dose: 56 Gy, 67.5 Gy, and 70 Gy). No details can be given with regard to RT dose delivered to critical structures because of the retrospective nature of the study.

DISCUSSION

ONB is a relatively uncommon disease, and data are based only on published series including small numbers of patients treated over a long period of time (6, 7). Our collaborative group, called Rare Cancer Network, is active in the field of oncology to collect sufficient data from many European and North American centers to analyze various prognostic factors with enough statistical power and offer treatment recommendations (www.rarecancer.net).

The majority of ONB is found with more advanced disease according to the Kadish classification (48% of Stage C in our series), which is in line with other series (6, 10, 13). The reason for this is the difficulty of diagnosis because of unspecific unrecognized initial symptoms (nasal obstruction, recurrent epistaxis, *etc.*). In addition to CT, initial diagnostic workup may include MRI and/or PET to better define the local extent of the disease (27, 28).

Local recurrence and/or distant progression remains the main problem in the management of ONB and can occur many years after initial diagnosis and treatment (14). Salvage treatment consists of surgery, surgery and postoperative RT, RT alone, palliative chemotherapy, or supportive care depending on the type of relapse and the initial treatment of the patient. In Dulguerov et al.'s (7) meta-analysis, local, regional, and distant recurrence rates were reported in 29%, 16%, and 17%, respectively. In a recent report from the Princess Margaret Hospital of a series of 39 patients treated for ONB, local recurrence was documented in 12 patients (30.7%), regional in 7 (17.9%), and distant in 3 (7.7%); with a 5-year OS and DFS of 87.9% and 76%, respectively (15). In our experience, which is in accordance with Dulguerov's meta-analysis, local progression and distant metastases were observed in 31% and 19%, respectively. However, our regional relapse rate was higher (26%). In the same meta-analysis including 390 patients from 26 studies, the 5-year OS and DFS were reported to be 45% and 41%, respectively. In our series, the 5-year OS and DFS were 64% and 57%, respectively. This difference can be explained by the fact that the meta-analysis and our series included patients treated over more than 3 decades, using various therapeutic approaches, compared with single-center experience from the Princess Margaret Hospital (15). The most important prognostic factors influencing the outcome reported in ONB are Hyams grade (1), positive lymph nodes (7), and Kadish stage (7, 11). In our series including 77 patients from 13 European and North American centers, best prognostic factors found in uni- and multivariate analyses were early-stage disease without lymph node involvement, R0/R1 resection, and postoperative RT with at least 54 Gy.

In ONB, the mainstay of the treatment is surgery. The current accepted practice is open or endoscopic craniofacial surgical resection (7, 8, 11, 13, 16). Adjuvant RT is indicated for Kadish Stage B and C (7–12), whereas Kadish A disease can be managed by surgery alone (20). In our series, combined surgery and postoperative RT gave the best outcome, particularly when the total RT dose was ≥54 Gy. In patients without nodal disease at presentation ($n = 68$) and without elective neck irradiation, there were only five (7%) nodal relapses with local progression. In those with N+ disease ($n = 9$), following involved-neck RT, only two patients developed nodal relapses without local progression. With only RT-related toxicity being important, more conformal techniques such as intensity-modulated RT (IMRT) and/or proton therapy allow

Table 3. Multivariate analyses in 77 patients with olfactory neuroblastoma (Cox model)

	Overall survival		Disease-free survival		Locoregional control		Local control	
Parameter	RR	*p* value	RR	*p* value	RR	*p* value	RR	*p* value
Surgery (S) (R0/R1* vs. R2/no S)	2.04	0.0003	1.63	0.004	1.69	0.02	–	NS
T classification (T1–T3* vs. T4)	1.56	0.01	1.57	0.009	–	NS	–	NS
N classification(N0* vs. N+)	–	NS	1.79	0.02	2.00	0.01	–	NS
Total RT dose (Gy) (≥54* vs. <54†)	4.00	0.001	3.57	0.002	3.57	0.007	3.45	0.005

Abbreviations: NS = not significant; RR = relative risk; RT = radiation therapy.
* Better outcome.
† Including patients not receiving RT.

higher doses to target volumes and spare critical sensitive structures (29–33). In our series, treatment consisted of surgery and postoperative RT in 52% of the patients. Conventional 2D-RT was given in 40% of the patients, and 3D- or IMRT was given in 54% of the patients. Radiation-induced complications reported are not negligible, ranging from 30% to 40% (2, 11). In our series, 9% of patients developed RT-related severe late toxicity, which is low compared with other series, probably because of the increased number of patients treated with 3D-RT.

The role of CT is not well defined. Some institutions use pre- or postoperative CT; however, no consensus has been reached regarding optimal practice. Retrospective data suggest that patients with high-grade, Kadish Stage C disease may benefit from adjuvant CT (17, 18, 34). Neoadjuvant chemotherapy can be used to reduce tumor burden to achieve R0/R1 surgical resection (11, 35). There is no standard CT regimen in ONB. However, in patients with high-grade disease, platinum-based CT, combined or not with RT, is reported to be efficient (34).

In this multicenter retrospective study, patients with ONB had the best outcome, particularly when treated with R0 or R1 surgical resection followed by at least 54-Gy postoperative RT. Given the low incidence of isolated regional relapses, elective neck irradiation is not recommended, whereas in patients with positive lymph nodes at diagnosis, involved neck irradiation is warranted. Local recurrence remaining the major problem in the management of ONB, and novel strategies including combined CT and/or dose escalation made possible by advanced radiation techniques such as IMRT or proton therapy should be prospectively investigated.

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