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Aesthesioneuroblastoma

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Abstract

Forty patients were treated or followed up for aesthesioneuroblastoma between 1980 and 1995 at Institut Gustave Roussy, France. There were three T_1, seven T_2, 15 T_3 and 15 T_4 lesions. The cervical metastatic rate at presentation was 18 per cent. Distant metastases were detected by bone marrow biopsy and bone scan in three patients at presentation. Treatment modalities included surgery alone in eight patients, radiotherapy alone in three patients, combined modality surgery plus radiotherapy in 11 patients, chemotherapy alone in two patients, chemotherapy plus radiotherapy in 10 patients, and multimodality therapy chemotherapy plus surgery plus radiotherapy in six patients.

The five-year survival rate was 51 per cent. Multimodality treatment offered better survival (63 per cent at five years) and disease-free interval (54 months). Overall local, regional, and distant failure rates were 58 per cent, 15 per cent and 40 per cent respectively. Distant metastases commonly occurred in bone (82 per cent). Cervical metastasis was an unfavourable prognostic indicator (0 per cent survival at two years).

In conclusion, aesthesioneuroblastoma is sensitive to chemotherapy and radiotherapy. Multimodality therapy should be used initially.

Key words: Neuroblastoma; Olfactory mucosa; Surgery, operative; Radiotherapy; Chemotherapy

Introduction

Aesthesioneuroblastoma is a rare neuroectodermal tumour originating from the olfactory epithelium, first described by Berger and Luc in 1924, and since then approximately 300 cases have been reported (Jekunen *et al.*, 1996). These tumours are often found in the upper nasal cavity and ethmoidal region and rapidly spread through the cribriform plate to involve intracranial structures. These neuroendocrine tumours are rarely associated with hormone excess syndromes such as Cushing syndrome (Arnesen *et al.*, 1994) or inappropriate secretion of ADH (Al Ahwal *et al.*, 1993). Histological identification is sometimes more difficult because these tumours exhibit little or no differentiation (Mills and Frierson, 1985) and can often be mistaken for other malignancies such as undifferentiated carcinoma, lymphoma, melanoma, or sarcoma (Oslen and DeSanto, 1983; Levine *et al.*, 1986; Schwaab *et al.*, 1988). Special histological stains and ultrastructural analysis may be required to confirm the histological diagnosis (Schenck and Ogura, 1972). These tumours are locally aggressive and have a metastatic potential to regional lymph nodes, and distant sites. Kadish *et al.* (1976) developed a staging considering the local extent of the tumour. We employed a staging system classification which seemed to correspond well with the present diagnostic and surgical trends. We retrospectively reviewed our experience with aesthesioneuroblastoma to identify the prognostic factors and analyse the outcome of treatment modalities.

Materials and methods

From 1980 to 1995, 45 patients were identified as having aesthesioneuroblastoma in the department of Head and Neck Surgery of the Institut Gustave Roussy. Five patients who refused treatment were excluded, and the remaining 40 patients were studied in this retrospective review. Twenty-one patients (48 per cent) were initially treated elsewhere, but received adjuvant (surgery, one patient; radiotherapy, four patients), or salvage treatment (nine patients), or were only followed up (seven patients) at the Institut Gustave Roussy. All the clinical, radiological and pathological reports of the 40 treated cases were reviewed. The age of the patients ranged from one to 67 years (median, 38); 22 were women and 18 were men. The symptoms and signs in patients at initial presentation are shown in Table I. The site of origin of tumour was noted as upper nasal cavity and ethmoid in 37 patients, maxillary sinus in

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TABLE I
FREQUENT SIGNS OR SYMPTOMS

Symptoms/Signs	n	%
Nasal obstruction	20	50
Epistaxis	10	25
Infraorbital neuralgia	9	23
Polypoid mass	8	20
Proptosis	8	20
Reduction of visual acuity	7	18
Diplopia	5	13
Anosmia	3	8
Frontal syndrome	2	5
Syndrome of inappropriate secretion of ADH	1	3

two patients, and frontal lobe in one patient. Tumours were staged according to local extension (Table II); three patients had a T_1, seven patients had a T_2, 15 patients had a T_3, and 15 patients had a T_4 stage tumour. Neck node involvement was noted in seven patients (18 per cent); in these patients, the primary was T_1 in one, T_3 in two, and T_4 in four patients. Cervical metastases were ipsilateral in five, and bilateral in two patients. Distant metastases were revealed by bone scans in three of 40 patients; bone marrow biopsies in these three patients showed aplasia. None of the patients with palpable nodes had distant metastases at the time of initial presentation.

Statistical methods

The X^2 test, Mann-Whitney U test, Student's *t*-test, and statistical ANOVA were used for statistical analysis of the data. Overall and disease-free survivals were calculated by the method of Kaplan and Meijer (1958). Comparison of survival between subgroups of patients was performed with the log-rank statistical test (Peto and Pike, 1973). The $p \leqslant 0.05$ was considered statistically significant.

Treatment

Treatment modalities employed for 40 patients included radiotherapy alone in three patients, surgery alone in eight patients, chemotherapy alone in two patients, chemotherapy plus radiotherapy in 10 patients combined modality (surgery plus post-operative radiotherapy) in 11 patients, and multi-modality (chemotherapy plus surgery plus post-operative radiotherapy) in six patients.

The common surgical procedures employed in 25 patients are shown in Table III.

In all, chemotherapy was employed in 16 patients including five patients who had neck nodes at presentation. The drugs employed were adriamycin, vincristine, dacarbazine (DTIC), cisplatin, cyclophosphamide, cytosine arabinoside, in various

TABLE II
PATIENT DISTRIBUTION ACCORDING TO T STAGE

Stage (T)	n	%
T_1: Tumour confined to nasal cavity and ethmoid	3	8
T_2: Tumour extending to the adjacent paranasal sinuses	7	18
T_3: Tumour extending to cribriform plate or orbit	15	38
T_4: Tumour extending to intracranial fossa or brain	15	38

TABLE III
SURGICAL PROCEDURES

Surgical approach	n
Lateral rhinotomy	10
Craniofacial resection	7
Neurosurgery plus lateral rhinotomy (two-staged)	3
Sublabial approach	2

combinations. The response at primary and neck nodes were judged clinically and radiologically, and was graded as follows; complete response—75–100 per cent regression of the tumour, partial response —50–75 per cent regression of tumour, and no response—less than 50 per cent regression or progression of tumour. Of 16 patients, five (31 per cent) attained a complete response at the primary site, and 11 (69 per cent) had no response. The response at the nodes was complete response in three patients, and no response in two patients.

Treatment to the neck in seven patients who had palpable nodes at presentation consisted of conservative neck dissections (ipsilateral–two; bilateral–one) in three patients, and radiotherapy in four patients. Post-operative radiotherapy to the neck was employed in two patients. Of 33 patients who had no palpable nodes at diagnosis, 27 received irradiation as definitive or adjuvant treatment to the primary tumour. Twelve of 27 patients were treated at our institute, and the area irradiated included the first station cervical nodes. In 15 patients who were treated elsewhere, the irradiated field did not include the first station cervical nodes.

Results

Survival

The overall survival in 40 patients who were treated for aesthesioneuroblastoma was 54 per cent, and 51 per cent at three, and five years respectively (Table IV) with a median survival of 34 months (range: two to 126, mean: 42.6 ± 33). The disease-free survival at three, and five years was 43 per cent, and 38 per cent respectively, with a median disease-free interval of 10 months (range: 0–126; mean: 23.8 ± 4.7).

The presence of cervical metastases at diagnosis was found to be the only significant risk factor for survival. The overall survival at two years in patients with cervical metastases at presentation was dismal compared to 78 per cent in patients without positive palpable neck nodes (Table IV) ($p < 0.0001$). Other factors including T stage, and treatment modality did not have significant impact on survival (Table IV) ($p > 0.05$).

When chemotherapy was employed, the grade of response of the primary was found to be a significant prognostic indicator in patients who had unresectable tumours; the survival and disease-free interval were significantly better in those who had a complete response rather than no response to chemotherapy (50 per cent *vs* 14 per cent at five years, $p = 0.02$; median disease-free interval: 36 *vs* 0.5 months; $p = 0.007$). Of three patients who had a complete

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TABLE IV
FACTORS AFFECTING SURVIVAL

Factors	Overall survival (%) 1 year	2 years	3 years	5 years	Difference in survival at 3 and 5 years
Whole series	80	62	54	51	
T stage					NS
T1	100	33	33	33	
T2	100	86	64	64	
T3	73	73	65	65	
T4	73	47	33	25	
Nodal status					
NO	87	78	65	65	$p < 0.0001$
Palpable nodes	42	0	0	0	
Surgery					NS
Surgical resection	88	68	59	59	
No surgery	67	55	55	37	
Response to CT					
CT + RT group					$p < 0.02$
CR	100	100	100	50	
NR	42	14	14	14	
Multimodality group					NS
CR	100	100	100	100	
NR	100	75	75	75	
Treatment modality					NS
RT alone	100	100	66	66	
CT alone	50	50	0	0	
CT + RT	60	40	40	13	
Surgery alone	88	75	58	58	
Surgery + RT	90	55	45	45	
Multimodality	83	83	63	63	

RT = radiotherapy; CT = chemotherapy; Multimodality = CT + surgery + postoperative RT; CR = complete response; NR = no response; p value <0.05 was considered as statistically significant; NS = statistically nonsignificant.

response, one patient was alive with no evidence of disease (NED) at 37 months, one patient died of distant metastases but with local control at 62 months, and one patient was alive with local recurrence at 44 months. In contrast, six of seven patients who had no response died of disease within one and a half years, and one patient was alive with local failure (overall survival, range: two to 99 months; mean: 22; median: 12). Although the response of primary to chemotherapy did not show significant survival advantage in patients treated with the multimodality regimen (Table IV), the disease-free interval was significantly better in patients treated by the multimodality regimen than in those who did not receive chemotherapy prior to surgery (mean: 54 *vs* 23 months; t test: $p < 0.05$).

Local failure

Local failure occurred in more than half of the patients in this series (23 patients, 58 per cent) (Table V). Tumour was continuous after treatment in eight patients, and delayed recurrences occurred in 15 patients. Local failure occurred alone in 10 patients, whereas in the remaining 13 patients local failure was associated with neck relapses and/or distant metastases. The median time to local failure was six months (range: 0–28: mean: seven).

TABLE V
PATTERNS OF FAILURE

Type of failure	n
Local	10
Distant	8
Local + Regional	2
Local + Distant	8
Local + Regional + Distant	3
Regional + Distant	1

TABLE VI
FACTORS AFFECTING LOCAL FAILURE

Factors	Local Failure n	%	p value
T stage			NS
T_1	3/3	100	
T_2	4/7	57	
T_3	7/15	47	
T_4	9/15	60	
Nodal status			NS
N_0	17/33	51	
Palpable nodes	6/7	86	
Surgery			
Surgical resection	11/25	44	$p = 0.02$
No surgery	12/15	80	
Response to CT			
CT + RT group			$p = 0.01$
CR	1/3	33	
NR	7/7	100	
Multimodality group			NS
CR	0/2	100	
NR	2/4	50	
Treatment modality			NS
RT alone	1/3	33	
CT alone	2/2	100	
CT + RT	8/10	80	
Surgery alone	4/8	50	
Surgery + RT	5/11	45	
Multimodality	2/6	33	

RT = radiotherapy; CT = chemotherapy; CR = complete response; NT = no response; Multimodality = CT + surgery + post-operative RT; The factors were analysed by Chi-square test; p value <0.05 was considered as statistically significant; NS = statistically nonsignificant.

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TABLE VII
LOCAL FAILURE IN RELATION TO SURGICAL APPROACH AND T STAGE

Type of surgery	T1	T2	T3	T4	All T
Lateral rhinotomy	1/1 (100%)	2/3 (67%)	4/6 (67%)	–	7/10 (70%)
Craniofacial	–	–	0/4 (0%)	2/3 (67%)	2/7 (28%)
Neurosurgery + Lateral rhinotomy	–	–	–	2/3 (67%)	2/3 (67%)
Neurosurgery	–	–	0/1 (0%)	0/2 (0%)	0/3 (0%)
Sublabial	–	0/2 (0%)	–	–	0/2 (0%)

The local failure rate was significantly high in those who had no surgical resection of the primary (80 per cent *vs* 44 per cent; $p = 0.02$) and particularly in those who had no response rather than a complete response to chemotherapy (100 per cent *vs* 33 per cent; $p = 0.01$) (Table VI). When the incidence of local recurrence was studied according to the type of surgical approach employed (Table VII), lateral rhinotomy had the highest failure rate (70 per cent; $p = 0.07$). When employed for tumours eroding the cribriform plate (T_3) craniofacial resections provided a significantly better local control than the lateral rhinotomy procedure (four out of four, 100 per cent *vs* two out of six, 33 per cent; $p = 0.03$). When the tumour extended to the intracranial fossa or frontal lobe (T_4), craniofacial surgery was successful only in one of three patients (33 per cent).

Fifteen of 23 patients underwent salvage attempts for a locally recurrent disease with success in six patients. Five of these six salvaged patients were alive with NED, whereas one patient died of distant metastases (follow-up: 24–100 months; mean 68 months; median: 65 months). Of 17 patients whose local recurrences were not controlled, 14 patients succumbed to disease between two and 62 months (median: 14 months; mean: 18 months) whereas three patients were alive with local recurrence at 66, 72, and 99 months respectively.

TABLE VIII
FACTORS AFFECTING DISTANT METASTASES

Factors	Distant Failure n	%	*p* value
T stage			NS
T_1	2/3	66	
T_2	1/7	14	
T_3	5/15	33	
T_4	8/15	53	
Nodal status			$p = 0.006$
N_0	17/33	51	
Palpable nodes	6/7	86	
*CT**			
CT	6/15	40	NS
No CT	7/22	32	
*Response to CT**			NS
CR	1/5	20	
NR	5/10	50	

CT = chemotherapy; CR = complete response; NR = no response; * = three patients with distant metastases at initial presentation were excluded. The factors were analysed by the Chi-square test; *p* value <0.05 was considered as statistically significant; NS = statistically nonsignificant.

Neck failure

Neck relapses occurred in six of 40 patients (15 per cent) (Table V) within a median interval of 10 months (range: three to 42; mean: 18 months). Neck failure occurred in four of 33 (12 per cent) patients who had N_0 necks, and in two of seven (29 per cent) patients who had palpable neck nodes at the time of initial presentation.

Of four patients who had N_0 necks at diagnosis, neck failure occurred with continuous local control in one patient, whereas it was associated with simultaneous local failure in three patients. These four patients received treatment to a primary elsewhere, and radiotherapy (exclusive or post-operative) employed in three of them did not include the first station cervical nodes. The locoregional relapses were successfully salvaged by surgery and post-operative radiotherapy, with two patients living with NED and one patient dying of distant metastases. The fourth patient with isolated neck failure died of distant metastases during the course of radiotherapy to the neck. The neck relapses in two patients whose cervical metastases at diagnosis had been treated with chemotherapy followed by radiation, could not be salvaged, and both patients succumbed to locoregional plus distant failure. The median survival in patients with neck failure was 21 months (range: six to 100 months; mean: 32 months).

The incidence of neck failure was 0 per cent (0/12) in those who received elective irradiation to the first station cervical nodes compared to 19 per cent (four out of 21 patients) in those who did not have elective irradiation to the neck ($p > 0.05$). There was a trend towards decreased incidence of neck failure when chemotherapy was employed in patients who had no cervical metastases at diagnosis (0 per cent (0/14) *vs* 26 per cent (seven out of 19; $p = 0.06$).

Distant metastases

Distant metastasis was the most frequent pattern of failure (Table V) and occurred in 16 patients (40 per cent). Metastases alone occurred in four (25 per cent) patients whereas it was associated with local and or regional failure in 12 patients (Table V). Distant metastasis was synchronous with a primary in three patients, and time to metastasis in the remaining 13 patients was one to 20 months (median: seven months; mean: eight months). The most common site of metastasis was bone (11 patients) followed by meninges (three patients), skin (two patients), lungs (one patient), and breast (one patient).

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Cervical metastasis at diagnosis was found to be the only significant risk factor for distant failure. The distant metastases rate was 51 per cent without cervical metastases at presentation, and increased to 86 per cent with the presence of cervical metastases at presentation ($p = 0.006$) (Table VIII). The other factors including T stage of primary tumour, chemotherapy, and grade of response to chemotherapy did not influence significantly the incidence of distant metastases ($p > 0.05$) (Table VIII). Distant metastases significantly affected the survival: the three-year overall survival in patients with metastases was six per cent compared to 90 per cent in those without metastases ($p < 0.0001$). All patients with metastases succumbed to disease with 14 patients dying before two years (survival range: four to 44 months; mean: 16 months; median: 14 months).

Last follow-up

At the conclusion of this study 17 patients were alive with NED between 24 and 126 months (median: 60 months), three patients were alive with local failure between 66 and 99 months (median: 72 months), and 20 patients died of their disease between two and 62 months (median: 16 months). The cause of death was local failure alone in four patients, distant failure alone in five patients, local plus distant failure in eight patients, regional plus distant failure in one patient, and local, regional and distant failure in two patients.

Discussion

Aesthesioneuroblastoma is a rare, locally aggressive and persistent disease with a potential to metastasize to cervical lymph nodes and distant sites. Because of the rarity of this malignancy, no definitive consensus regarding the optimal treatment has been reached and considerable controversy exists over its optimal management (Foote *et al.*, 1993). The literature suggests that addition of radiotherapy to surgery improves the local control rates and survival (Eden *et al.*, 1994). In our study the overall survival for 40 patients was 54 per cent at three years and 51 per cent at five years. There was no statistically significant difference in the survival and local control rates between patients treated with single modality (radiotherapy or surgery) and combined modality therapies (surgery plus post-operative radiotherapy) (Table IV). The addition of chemotherapy to the combined modality improved overall survival (63 per cent at five years), disease-free interval (54 months), and local control rate (66 per cent).

The response of tumour to chemotherapy (complete response or no response) did not significantly influence the survival when the patients underwent surgery. In contrast, a significantly better survival was noted in patients with complete regression of tumour when chemotherapy was employed prior to definitive radiotherapy for a locally advanced or unresectable tumour (survival: 50 per cent (complete response) *vs* 14 per cent (no response) at two years; $p = 0.02$) (Table IV). The grade of response was also a prognostic indicator in terms of incidence of distant metastases as evidenced by a reduced distant metastasis rate in patients with a complete response (Table VIII).

There is a likelihood of synchronous and metachronous cervical node metastasis. Although the exact incidence of synchronous cervical metastasis remains ill-defined, the review of Davis and Weisser (1992) revealed an incidence between 17 and 48 per cent. We noted cervical metastases in 28 per cent of patients at the time of presentation, and in contrast to the reports published, we did not find any association between an advanced clinical stage and incidence of cervical metastases. The presence of cervical metastases at presentation was a poor prognostic sign as evidenced in this study by a dismal survival at two years.

Beitler *et al.* (1991) reviewed the literature and reported an incidence of delayed cervical node metastasis of 19 per cent in patients who did not have cervical node metastases at presentation. They found 10 neck failures with the primary continuously controlled in nine per cent of patients, and suggested that these patients could be potentially cured by elective neck treatment. In our series, we noted delayed neck failure in four of 33 (12 per cent) patients who did not have cervical metastases at presentation. Only one of these four patients had the primary continuously controlled whereas in the remaining three, the neck failure occurred with local recurrence. We observed no delayed neck failures in patients who had no cervical metastases at presentation when radiotherapy (definitive or adjuvant) included electively the first station cervical nodes, or when chemotherapy was employed as a part of the initial treatment. Since the isolated cervical metastasis rate in our study was negligible (three per cent), it was difficult to set conclusive guidelines for management of occult neck disease.

Achieving acceptable rates of local control remains a significant problem in patients with aesthesioneuroblastoma. A local recurrence rate of 53 per cent in our series was similar to that in other reports (Bailey and Barton, 1975; Oslen and DeSanto, 1983). The treatment modalities employed were not uniform in our patients, because the majority of them had received initial treatment elsewhere. Combined or multimodality treatments were often employed for patients at an advanced clinical stage, and we noted that the local recurrence rate was less when a multimodality regimen was employed (50 per cent *vs* 33 per cent).

Pre-operative radiological investigations, such as computed tomography (CT) scan and magnetic resonance imaging (MRI), may reveal early involvement of the cribriform plate and aid in the proper selection of surgical approach. When employed for tumours eroding the cribriform plate, lateral rhinotomy is an inadequate surgical procedure with a 66 per cent local recurrence rate. Craniofacial surgery is

a more appropriate procedure for tumours in such a location as evidenced in our series by the absence of local recurrences.

The 40 per cent rate of distant metastasis in the current series was much higher than that reported in the literature (Oslen and DeSanto, 1983; Eden *et al.*, 1994). The principal site of distant metastasis in our series was bone (82 per cent), vertebrae being the most common location (86 per cent). Asymptomatic bone metastases were incidentally revealed by bone scans performed after noting aplasia on bone marrow biopsy at initial presentation in three patients. Hence, bone marrow biopsies and bone scans should be systematically included in the diagnostic tools of metastases. The significant risk factor for development of distant metastases was the presence of cervical metastases at initial presentation ($p = 0.006$). It remains unclear whether the high risk patients really benefit from aggressive local and systemic treatment in terms of disease control and survival. The distant metastases significantly affected the survival ($p < 0.0001$), and none of the patients with distant metastases in this study survived in spite of attempts at salvage. However, the experience of Eden *et al.* (1994), suggested that high-dose chemotherapy and autologous bone marrow transplantation can provide a durable control of local and distant failures.

Conclusions

Aesthesioneuroblastoma is a locally aggressive tumour with a potential to metastasize to cervical lymph nodes and distant sites. Bone marrow biopsies and bone scans should be included in diagnostic investigations. Aesthesioneuroblastoma is sensitive to chemotherapy and radiotherapy. The presence of cervical metastases at presentation, and the response of the primary tumour to chemotherapy seemed to be the predictors of treatment outcome and survival. Multimodality regimens including chemotherapy, surgery and post-operative radiotherapy increase relapse-free and overall survivals. Craniofacial resections allow a wide access and should provide better tumour-free margins. The incidence of metachronous isolated cervical metastasis is less than five per cent and hence we could not recommend elective neck dissections. However, the first station cervical nodes should receive elective radiation post-operatively.

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