ONCOLOGY

Radiotherapy alone for local tumour control in esthesioneuroblastoma

Il ruolo della radioterapia come unico trattamento nel controllo locale dell'estesioneuroblastoma

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SUMMARY

Esthesioneuroblastoma is an uncommon tumour. Due to its low incidence, this neoplasm is difficult to evaluate and its treatment remains a matter of debate. Although the role of post-operative radiation is relatively well-defined, little is reported regarding the role of radiotherapy as the only treatment modality. A retrospective analysis of the literature has been conducted. With reference to the treatment of esthesioneuroblastoma, 55 patients submitted only to radiotherapy have been selected from publications of internationally indexed literature between 1979 and 2006. According to the Kadish classification, 6 patients were in stage A, 12 in stage B, and 37 in stage C. Response to therapy for each stage was assessed. There was no evidence of disease in: 6/6 stage A patients with a median follow-up period of 103.6 months, 7/12 stage B patients with a median follow-up period of 120 months, and 7/37 stage C patients with a median follow-up period of 77.3 months. A total of 27 patients died due to tumour-related causes and 5 due to intercurrent disease, while 3 patients were alive with disease (local recurrence and cervical lymph node metastasis). In conclusion, esthesioneuroblastoma is a malignant tumour which grows both locoregionally and distantly. For this reason, despite the satisfying results regarding response to radiotherapy alone in stage A patients, irradiation should be used only in early lesions arising below the cribriform plate, whereas all other cases require aggressive and multimodal therapy.

Key words: Nose • Malignant tumours • Olfactory neuroblastoma • Esthesioneuroblastoma • Radiotherapy

RIASSUNTO

L'estesioneuroblastoma è un tumore raro. La bassa incidenza rende difficile la valutazione dei risultati terapeutici su questa neoplasia ed il suo trattamento rimane oggetto di discussione. Sebbene il ruolo della radioterapia post chirurgica è ben accetto poco è stato riportato in letteratura circa il suo ruolo come unica modalità di trattamento. È stato condotto uno studio retrospettivo sui dati riportati in letteratura. Con riferimento al trattamento dell'estesioneuroblastoma, 55 pazienti sottoposti unicamente al trattamento radioterapico sono stati selezionati da lavori internazionali pubblicati tra il 1979 e il 2006. In accordo con la classificazione di Kadish, 6 pazienti erano alla stadio A, 12 erano alla stadio B, 37 erano alla stadio C. Per ogni stadio è stata valutata la risposta alla radioterapia. I risultati hanno evidenziato assenza di ripresa di malattia in 6/6 pazienti allo stadio A in un periodo medio di follow-up di 103,6 mesi, 7/12 pazienti alla stadio B con un periodo medio di follow-up di 120 mesi e 7/37 pazienti alla stadio C con un periodo medio di follow-up di 77,3 mesi. 27 pazienti sono morti per cause correlate alla malattia tumorale e 5 a causa di malattie intercorrenti. In tre pazienti viventi, la malattia ha presentato ricorrenze locali e metastasi ai linfonodi cervicali. In conclusione, l'estesioneuroblastoma rappresenta un tumore maligno la cui crescita è sia locoregionale che a distanza. Per tale motivo, malgrado i soddisfacenti risultati ottenuti dalla radioterapia usata come unico trattamento nei pazienti allo stadio A, la terapia radiante dovrebbe essere utilizzata soltanto in pazienti con lesioni precoci che si sviluppano al di sotto della lamina cribriforme, in tutti gli altri casi è necessario un trattamento aggressivo combinato.

Parole chiave: Naso • Tumori maligni • Neuroblastoma olfattorio • Estesioneuroblasoma • Radioterapia

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Introduction

Tumours arising from the olfactory neuroepithelium of the nasal cavity are known as esthesioneuroblastomas (ENB). Since the first case of ENB, described by Berger and Luc, in 1924, as "esthesioneuroepitheliome olfactif", more than 1,000 cases of this tumour have been reported in the literature world-wide [1]. Therefore, it can be considered an uncommon neoplasm rather than a rare tumour [2]. In fact, it represents about 5% of all nasal malignant tumours [3]. Treatment of ENB remains a matter of debate due to the infrequent occurrence and the varying biologic activity of this tumour, ranging from a less aggressive tumour leading to a long survival, to a highly aggressive neoplasm, presenting rapid wide-spread metastasis, with limited survival. Another factor contributing to the controversy is the lack of a staging system related to prognosis.

Some attempts to classify ENB have been made. In 1976,

Kadish et al. [4] developed a classification based on local extension, consisting of 3 groups (Table I).

Table I. Kadish classification [4].

Stage A	Tumour confined to nasal cavity
Stage B	Tumour involving nasal cavity and paranasal sinuses
Stage C	Tumour spreading beyond nasal cavity and sinuses

In 1992, Dulguerov and Calcaterra [5] described a classification based on the TNM system and on high resolution imaging findings:

T1 tumour involving the nasal cavity and/or paranasal sinuses (excluding the sphenoid sinus), sparing the most superior ethmoidal cells;
T2 tumour involving the nasal cavity and/or paranasal sinuses (including the sphenoid sinus) with extension to, or erosion of, the cribriform plate;
T3 tumour extending into the orbit or protruding into the cranial fossa, without dural invasion;
T4 tumour involving the brain;
N0 no cervical lymph node metastasis;
N1 any form of cervical lymph node metastasis;
M0 no metastasis;
M1 distant metastasis.

Surgical resection is considered the treatment of choice. Moreover, there is a general tendency to treat patients with post-operative radiotherapy (RT) or radiosurgery.

We observed a case of ENB, incidentally diagnosed during nasal polypectomy, and achieved an unexpected successful follow-up 8 years after RT alone.

Thereafter, in order to evaluate the outcome of RT alone for ENB, a review has been made of the international literature.

Material and methods

With reference to the treatment of ENB, a retrospective analysis has been made of the publications appearing in internationally indexed literature (PubMed database) between 1979 and 2006. Among these publications, only cases treated with radiotherapy (RT) alone were considered. Excluded were studies lacking data such as staging, doses of RT, duration of follow-up, and outcome.

The first publication is a review of case reports from 1941 to 1977 [6]; the others discuss the experience of universities [5-13] and of oncology treatment centres [14-16].

When available, we acquired information such as age and sex of patients. In the review concerning 13 patients treated by RT, alone, we found the age and sex of 4 cases identified in the original paper by Kadish et al. [4].

In Table II, the following data are outlined for each study: year of publication, first Author, study setting, period of the study, total number of cases reported, number of cases undergoing RT alone, sex, age, initial extent of disease (staging, cervical metastasis, distant metastasis), doses of RT, length of follow-up, and outcome.

Response to therapy was classified as: disease-free, alive with disease, died due to intercurrent disease, died due to local progression or recurrence, cervical metastasis, and distant metastasis.

Table II. Retrospective analysis of literature.

1	Year of publication	Authors	Reference	Setting	Period of study	Total reported cases	Cases with RT alone	M	F	Age	A	B	C	Cervical metastasis at presentation	Distant metastasis at presentation	Doses of RT (CGY)	Follow-up (months)	Disease-free	Alive with disease	Died of intercurrent disease	Died of disease	Local recurrence	Cervical metastasis	Distant metastasis
	1979	Elkon D., et al.	6	Review of case reports published since 1966	1941 1977	97	13	X		51	X		C			5300	42	X						
								X		3			X			6000-6500	13				X	X		
									X	28			X	X		6000-6500	6	X			X		X	
									X	51			X			6000-6500	2				X	X		
											X					5000	6	X						
											X					6000	84	X						

(continues)

(Continuation of Table II)

											X				4500	216	X								
											X				5100	12				X	X		
											X				5500	90	X						
											X				5000-6000	36				X		X	
											X				7000	132	X						
												X			2300	30				X			X
												X			4600	24	X						
2	1980	Ahmad K., Fayos J.V.	7	University of Michigan Medical Center (UMMC), MI, USA	1963 1978	9	1		X	61		X			5066	75				X	X		
3	1988	Urdaneta N., et al.	8	Yale University of Medicine, New Haven, CT, USA	1959 1984	7	2		X	44	X				4575	200	X						
									X	44		X			5600	120	X						
4	1988	Schwaab G., et al.	14	Institut Gustave-Roussy, Villejuif, France	1956 1984	40	6	X		36			X		6200	36				X		X	X
								X		18		X			6200	36				X	X		
								X		22			X		6200	120		X			X		
									X	62			X	X	6200	8				X		X	
								X		16			X		6200	90	X						
									X	16			X	X	6200	4				X		X	
5	1989	O'Connor T.A., et al.	9	University of California, Los Angeles, CA, USA	1969 1986	15	3					X			6500	132	X						
													X	X	4500	24-216				X			X
													X		8000	24-216				X	X		
6	1992	Dulguerov P., Calcaterra T.	5	UCLA Medical Center, Los Angeles, CA, USA	1970 1990	24	4		X	73			X		5500-6500	40				X	X		
									X	62		X			5500-6500	20				X		X	
								X		29		X			5500-6500	72	X						
								X		41	X				5500-6500	194	X						
7	1994	Guedea F., et al.	10	University Hospital St. Rafael, Leuven, Belgium	1974 1990	7	5	X		19			X		6000	144	X						
								X		74			X	X	6000	72			X				
								X		22			X		6500	12				X			X
								X		37			X		6400	12				X			X

(continues)

(Continuation of Table II)

								X		17			X			6000	6				X			X
8	1996	Slevin N.J., et al.	15	The Christie Hospital, Manchester, U.K.	1984 1993	9	5		X	60			X			5000	72	X						
									X	46			X			4750	72		X			X	X	
									X	62			X			4500	24			X				
									X	84			X	X		4000	3				X		X	X
									X	63		X				5000	78	X						
9	2001	Simon J.H., et al.	11	University of Iowa College of Medicine, Iowa City, Iowa, USA	1978 1999	13	2	X		79			X			5940	6			X				
								X		81			X			3000	15				X	X		
10	2002	Hwang S.K., et al.	12	Seoul National University Hospital Seoul, Korea	1979 2000	21	3	X		36			X			Average 5580	4				X	X		
									X	14			X			Average 5580	4				X	X		
								X		62			X			Average 5580	8				X	X		
11	2003	Eich T.H.	16	Treatment Centers of Radiotherapy and Paediatric Oncology, Germany	1979 2001	47	7		X	73			X			5800	8				X		X	
								X		65			X			7000	6				X			X
									X	65			X			6500	11			X				
									X	58			X			6600	125	X						
									X	68			X		X	4000	2				X	X		
									X	80			X			5000	94			X				
								X		12			X			5500	39		X				X	
12	2004	Bueso P. , et al.	13	Hospital Clinico Universitario de Zaragoza en Aragon, Spain	1981 2003	8	3	X		82			X			6000-6500	87	X						
								X		80			X	X		6000-6500	108	X						
								X		67			X			6000-6500	36				X	X		
13	2006	Benfari G.		E.N.T. Dept. “G. Ferreri” – University of Roma, Italy	1998	1	1		X	62	X					5500	96	X						

From 1941 to 2006, 5 cases were described, all of whom treated with RT alone. We added our case to the patients previously reported in the literature, thus 55 patients form the basis for this analysis.
It was possible to determine age and sex distribution in only 43 patients. The median age was 49.4 years (range 3-84). Sex was equally distributed (21 females and 22 males).
All patients were staged according to the Kadish classification since it has been used by most Authors. On the basis of the Kadish classification, 6 (10. 9%) patients were stage A, 12 (21.8%) were stage B, and 37 (67.2%) were stage C. Of the 37 stage C patients, 6 presented cervical metastasis and 2 showed distant metastasis at the beginning of RT.
RT doses ranged between 2300 and 8000 cGy (mean value 5510.7 cGy). Forty-two patients received doses ranging from 5000 to 6600 cGy, 10 received 2300-4750 cGy and 2 had 7000 cGy. Only one patient received 8000 cGy.
The mean follow-up period was 56.1 months (range 2-216). The two cases reported by O'Connor et al. [9] with a long interval follow-up times of 24-216 months, were not calculated for the mean value.

Results

Survival

Overall, 10 patients were disease-free (36.3%), with a mean survival of 105.6 months. Disease-free rates were 15% under 5 years, 45% from 5 to 10 years, and 40% more than 10 years.
Local tumour control was obtained in 6/6 (100%) stage A patients with a median follow-up period of 103.6 months (range 6-200), 7/12 (58.3%) stage B patients with a median follow-up period of 120 months (range 72-216), and 7/37 (18.9%) stage C patients with a median follow-up period of 77.3 months (range 24-144).

Failure analysis

Of the 55 patients, 3 (5.4%) were alive with disease, due to local recurrences and cervical lymph node metastasis; 5 (9%) died due to non-tumour-related causes (intercurrent disease); 27 (49%) patients died due to tumour-related causes.
In the stage B group, 3 patients died due to progression at the original tumour site or to local recurrence at 12, 36 and 75 months, respectively. Two patients died due to cervical lymph node metastasis, one at 20 months and the other at 36 months.
In the stage C group, 3 patients were alive with disease at 39.7 and 120 months, respectively. Ten patients died due to therapy-refractive tumour progression or local recurrence, with a median survival time, in 9 cases, of 13.7 months (range 2-40); 4 died due to loco-regional metastasis, with a median survival time of 4.5 months (range 4-8); 6 died due to distant metastasis, with a median survival time in 5 cases of 13. 2 months (range 6-30); 4 died due to cervical and distant metastases, with a median survival time of 19.5 months (range 3-36).

Discussion

Several interesting findings emerged from this study.
– Radiotherapy alone was effective in 36.3% of patients;
– survival rates tend to decrease with increasing tumour stage: 100% for stage A, 58.3% for stage B, 18.9% for stage C patients;
– survival is not correlated with radiation doses. Most patients who died of the disease had received radiotherapy doses ranging from 5000 to 6500 cGy, doses recommended in the literature;
– presence of palpable neck nodes and/or distant metastasis, at presentation, is an important prognostic factor for survival. Of 6 patients with regional lymph node metastasis, at presentation, 4 died of the disease with a median survival time of 5.2 months; the same outcome was observed in 2/2 patients with distant metastasis;
– ENB is characterized by a variable and often prolonged natural history [19]. This prerogative is emphasized by one patient who is still alive with the disease at 120 months.

Results obtained are not dissimilar from those of a meta-analysis in the literature performed between 1990 and 2000 [3] reporting the treatment modalities for esthesioneuroblastomas: surgery alone, surgery and radiotherapy, radiotherapy alone, a combination of surgery, radiotherapy and chemotherapy, and chemotherapy alone. Survival according to treatment modality was as follows: 65% for surgery plus radiation; 51% for radiation plus chemotherapy; 48% for surgery alone; 47% for surgery plus radiation plus chemotherapy; 37% for radiation alone. Surgical procedures for ENB consist of a craniofacial resection or endoscopic nasal resection. Most Authors recommend a craniofacial resection [3-17] although the experience at Graz University demonstrated optimal results with combined endoscopic surgery and Gamma-knife radiosurgery performed in Kadish stage A to C patients[18]. We have obtained analogous, satisfying results of treatment with endoscopic surgery combined with RT in Kadish stage A and B patients[20].
It is important to emphasize the evolution of RT from 1941 to 2006. It is difficult to make a comparison between the various RT techniques. Today's RT and its associated physical basis are much more sophisticated with regard to those of the mid-20th Century.

Conclusions

ENB is a malignant neoplasm which grows both loco-regionally and at distance. More detailed guidelines are needed to help physicians in the treatment of this disease. Aim of the present study was to perform a retrospective analysis of the outcomes obtained with RT alone in the management of ENB.
This study confirms previous observations: more severe prognostic factors are the extension of the tumour beyond Kadish stage A, and the finding of metastasis at presentation. Moreover, it highlights the long natural history of ENB: recurrence may be detected years after completion of treatment.
Despite the satisfying results regarding response to RT alone in stage A patients, this conclusion should be interpreted cautiously due to the limited number of stage A patients.
In our opinion, irradiation should be used only in early lesions arising below the cribriform plate with little or no bony destruction, whereas all other cases require aggressive and multimodal treatment (radical surgery followed by RT and, in selected cases, chemotherapy).

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