대한방사선종양학회지 2009;27(4):189~193 DOI: 10.3857/jkstro.2009.27.4.189

Treatment and Prognosis for an Esthesioneuroblastoma over a 20-Year Period: Impact of Treatment Era

Chang Hoon Song, M.D.*, Il Han Kim, M.D.*,§,‖, Hong-Gyun Wu, M.D.*,§,‖, Dong Wan Kim, M.D.†, and Chae-Seo Rhee, M.D.‡

Departments of *Radiation Oncology, †Internal Medicine, ‡Otorhinolaryngology and Head and Neck Surgery, and §Cancer Research Institute, Seoul National University College of Medicine, ‖Institute of Radiation Medicine, Medical Research Center, Seoul National University, Seoul, Korea

Purpose: To report on the changes in the patterns of care and survival over time for esthesioneuroblastoma.
Materials and Methods: We retrospectively analyzed 42 previously untreated and histologically confirmed esthesioneuroblastoma patients seen between March 1989 and June 2007. According to Kadish's classification, 3 patients (7%) were stage A, 6 (14%) at stage B, and 33 (79%) at stage C. Of the 33 Kadish C patients, 19 and 14 patients were treated from 1989 through 2000 and from 2001 through 2007, respectively. Treatment included surgical resection, radiotherapy, chemotherapy, or a combination of these methods. Chemotherapy was administered to 8 of 19 patients (42%) seen from 1989 through 2000, whereas all of the 14 patients seen from 2001 through 2007 received chemotherapy ($p<0.001$). No patient was treated by three-dimensional conformal radiotherapy (3D-CRT) from 1989 through 2000, however 8 of 14 patients (67%) seen from 2001 through 2007 underwent 3D-CRT ($p<0.001$). The median follow-up time for surviving patients was 6.5 years (range, 2.2~15.8 years).
Results: The 5-year overall survival (OS) and progression-free survival (PFS) rates for the entire cohort were 53% and 39%, respectively. The 5-year OS was 100% for Kadish stages A or B and 39% for stage C ($p=0.007$). For patients with stage C disease who were treated from 1989 to 2000 and from 2001 to 2007, the 5-year OS rate was 26% and 59% ($p=0.029$), respectively and the corresponding 5-year PFS rate was 16% and 46% ($p=0.001$), respectively. Intraorbital extension and treatment era (1989~2000 vs. 2001~2007) were found as independent factors for OS and PFS in a multivariate analyses.
Conclusion: The results of this study suggest that treatment era, which features a distinction in treatment modality and technique with the introduction of 3D-CRT, may be the cause of improved OS and PFS in Kadish stage C patients. To achieve better outcomes for patients with Kadish stage C, combined chemoradiotherapy, especially 3D-CRT, is recommended in addition to surgery.

Key Words: Esthesioneuroblastoma, Olfactory neuroblastoma, Radiotherapy, Chemotherapy

Introduction

Esthesioneuroblastoma or olfactory neuroblastoma is a rare malignancy originating in the upper nasal cavity and accounts for only about 3% of all intranasal tumors.[1] The disease usually occurs in the fifth to sixth decades of life, although it is unclear whether there is a unimodal or a bimodal peak in incidence by age.[1] There appears to be no predilection for gender.[2] As in other intranasal tumors, initial symptoms are non-specific and include nasal obstruction, epistaxis, hyposmia, and exophthalmos in correlation to the extent of tumor. The most commonly used staging system was developed by Kadish et al.[3] This system divides tumors into 3 stages: stage A tumors are limited to the nasal cavity; stage B tumors involve the nasal cavity and paranasal sinuses; and stage C tumors extend beyond the nasal cavity and paranasal sinuses.

Submitted September 29, 2009, accepted October 28, 2009
Reprint requests to Il Han Kim, M.D., Department of Radiation Oncology, Seoul National University College of Medicine, 28, Yeongeon-dong, Jongno-gu, Seoul 110-744, Korea
Tel: 02)2072-2528, Fax: 02)742-2073
E-mail: ihkim@snu.ac.kr
Presented at the 50th annual meeting of the American Society for Therapeutic Radiation Oncology, September 21-25, 2008, Boston, MA, USA.
This work was supported by grant No. M2070202001-07N0202-00111 from the 2008 National Nuclear R&D Program of the Korean Science & Engineering Foundation (KOSEF).

Due to the rarity of esthesioneuroblastoma and inconsistent treatment, the optimal management is still controversial. Surgery or radiotherapy is still used by some institutions as a single modality,[4] while many other institutions favor surgery followed by radiotherapy.[5,6] The use of combined modality treatment with surgery, radiotherapy, and chemotherapy in various combinations has been increasingly adopted over the past few years.[7,8]

Because our previous study[9] comprised of patients treated between 1979 and 1997 showed a disappointing outcome compared with contemporary literatures, we examined outcomes and prognostic factors in patients treated recent 20 years.

Materials and Methods

From March 1989 to June 2007, a total 42 patients with esthesioneuroblastoma were treated with curative intent at the Seoul National University Hospital. The diagnosis of esthesioneuroblastoma was based on histopathologic features and confirmed with immunohistochemical staining in 78% of patients. Medical records of all patients were reviewed for clinicopathologic features, therapeutic modalities, and tumor recurrence. Available clinical and radiologic informations about tumor extent were used to stage patients who were initially seen with primary disease using Kadish staging system retrospectively.[3] The entire group comprised an even proportion of 50% men and 50% women. The median age at diagnosis was 38 years (range, 4 to 65 years). The symptoms at presentation were varied with the most common symptom of nasal obstruction (Table 1).

Table 1. Presenting Symptoms and Signs of Esthesioneuroblastoma in all 42 Patients

	No. of patients (%)
Nasal obstruction	22 (52)
Epistaxis	14 (33)
Headache	13 (31)
Visual disturbance	10 (24)
Rhinorrhea	9 (21)
Proptosis	8 (19)
Hyposmia-anosmia	7 (17)
Facial pain	6 (14)
Facial mass	2 (5)
Epiphora	1 (2)
Mental change	1 (2)

Twenty patients (48%) underwent surgery, either without further therapy (n=4), combined with radiotherapy (n=8), chemotherapy (n=3), or both of radiotherapy and chemotherapy (n=5). Seventy-five percent of surgery was craniofacial resection (CFR). Clear resection margins were obtained in 5 patients of these 15 patients who received CFR. Five patients were managed with extracranial surgical excision. Clear margins of resection were achieved in 3 patients who received extracranial surgical excision.

Thirty-one (74%) patients received radiotherapy. Radiotherapy was conducted postoperatively in 12 patients, preoperatively in 1 patient, and as a definitive treatment in 18 patients. Irradiated doses ranged from 41.8 to 78.3 Gy with the median value of 55.8 Gy. In two patients, radiotherapy was discontinued at 45 Gy and 46.8 Gy respectively because of tumor progression and patient's request. Twenty-three of 31 (74%) patients were treated with conventional radiation techniques while 8 patients with three-dimensional conformal radiotherapy (3D-CRT).

Twenty-eight (67%) patients received any kind of chemotherapy as their initial treatment. Nineteen patients received neoadjuvant chemotherapy, three of whom were also treated with adjuvant chemotherapy after the completion of radiotherapy. Objective response was observed in 11 of 19 patients (58%). Chemotherapy was the only form of treatment in 4 patients. Twenty-one (75%) patients received etoposide, ifosfamide, and cisplatin and 4 patients (14%) etoposide and cisplatin.

The median follow-up for surviving patients was 6.5 years (range, 2.2 to 15.8 years). Overall survival (OS) and progression-free survival (PFS) rates were estimated by using the Kaplan-Meier method and compared by log-rank test. All time-to-failure end points were calculated from the initiation of first treatment. Receiver operating characteristic curves were generated to define the cutoff point of treatment era. Age, sex, performance status, treatment era, skull base penetration, intraorbital extension (IOE), trimodality treatment including surgery, chemotherapy and radiotherapy, craniofacial resection, resection margin status, surgeon, radiation dose, 3D-CRT, any kind of chemotherapy, and neoadjuvant chemotherapy were evaluated for prognostic factors in univariate analysis. Marginally significant factors ($p<0.15$) on univariate analysis were subjected to multivariate analysis with forward-stepwise

logistic regression to assess their relative importance. Cross tabulations for identified factors were done with Pearson's chi square test or Fisher's exact test.

Results

The 5-year OS and PFS rates for all patients were 53% and 39%, respectively. No one is dead in nine patients with stage A or B, whereas 21 of 33 patients with stage C were died at the time of analysis. Due to the great discrepancy of survival in Kadish stage C, following analyses were limited to 33 patients with Kadish stage C.

IOE, treatment era (1989～2000), and trimodality treatment were significant for impaired OS (p=0.006, p=0.029, and p=0.041, respectively). The 5-year OS was 59% for patients treated in the later era (2001～2007) and 26% for patients treated from 1989 to 2000 (Fig. 1). IOE and treatment era remained significant in the multivariate analysis. Patients with IOE had a 3.6-fold risk of death (83% vs. 52%; 95% confidence interval [CI], 1.4 to 8.9; p=0.007) and patients who have been treated between 1989 and 2000 had a 3.0-fold risk of death compared with patients treated from 2001 to 2007 (84% vs. 36%; 95% CI, 1.1 to 8.3; p=0.030).

IOE, treatment era, and trimodality treatment were also significant univariate factor for the PFS (p=0.003, p=0.001, and p=0.012, respectively). The 5-year PFS was 46% for patients treated in the later era (2001～2007) and 16% for patients treated from 1989 to 2000 (Fig. 2). In addition to these factors, introduction of chemotherapy was also important for PFS (p=0.045). Multivariate analysis for PFS also revealed IOE and treatment era as an independent factor (p＜0.001 and p=0.001, respectively).

Surgically induced complications occurred in 3 patients. Two patients suffered from wound abscess. One patient experienced rhinorrhea of cerebrospinal fluid. Radiation necrosis on brain was developed in one patient.

Discussion and Conclusion

Esthesioneuroblastoma often presents with vague symptoms such as nasal obstruction, epistaxis, and headache. Therefore, many patients were found at an advanced stage.[3,10,11] Most patients of this study were also Kadish C stage. We observed a 5-year OS rate of 53% and a PFS rate of 39% for stage C patients. Treatment outcomes of the current study were comparable with other historic controls[5,6,12,13] and favorable compared to our previous report.[9] Our previous study was comprised of patients who were treated during 1979 and 1997. The 5-year OS rate improved from 20% for former study to 53% for current study. Multivariate analyses in current study also revealed that IOE and treatment era were independent factors for OS and PFS. To find out differences between groups, cross tabulations for each IOE and treatment era were made. There was no difference according to IOE. Cross-tabulations for the two treatment eras (1989～2000 vs. 2001～2007) revealed no differences between them concerning age, sex, performance status, skull base penetration, trimodality treatment, radiotherapy, surgery, craniofacial resection, and

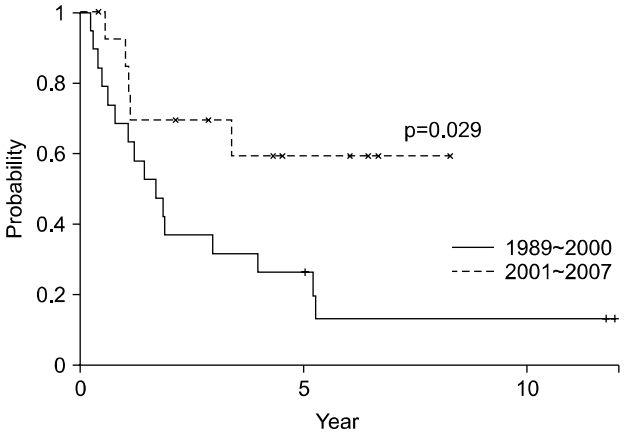

Fig. 1. Overall survival curves according to the two treatment eras (1989～2000 vs. 2001～2007) in Kadish stage C.

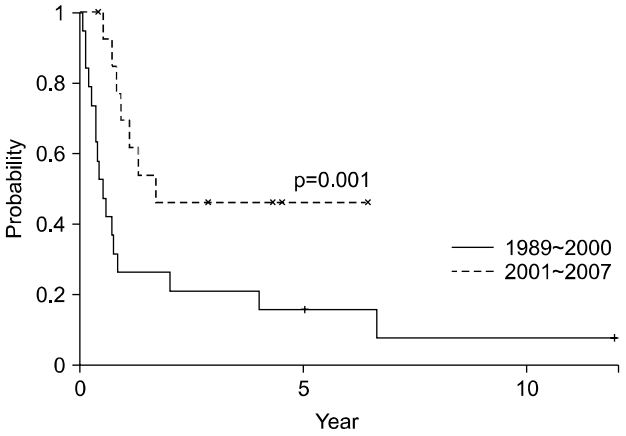

Fig. 2. Progression-free survival curves according to the two treatment eras (1989～2000 vs. 2001～2007) in Kadish stage C.

resection status (Table 2). Chemotherapy was given to 8 of the 19 patients (42%) in the era of 1989～2000, whereas all of the 14 patients in the era of 2001～2007 received chemotherapy ($p<0.001$, Table 2). No one was treated with 3D-CRT from 1989 through 2000, however 8 of the 14 patients (67%) between 2001 to 2007 underwent 3D-CRT ($p<0.001$) (Table 2). Furthermore, patients who received surgery were lesser in the era of 2001～2007 compared to the era of 1989～2000 (p=0.073) (Table 2). However, chemotherapy and 3D-CRT failed to show significant association with OS and PFS in univariate analyses. Therefore, we cannot simply ascribe improved outcomes in the era of 2001～2007 to chemotherapy or 3D-CRT. However, it might be explained by gradual evolutions of treatment quality and technique of radiotherapy, chemotherapy, or surgery. Spaulding et al.[14] already mentioned about the importance of the treatment era. In their study, PFS rate for Kadish C stage improved from 0% for patients in the era of 1959～1975 to 43% for those in the era of 1975～1985. As in our experience, IOE was a significant predictor of PFS in the experience of Gruber et al.[15] To our surprise, IOE was associated with distant metastasis ($p<0.001$), not with local failure (p=0.451). Based on our observation, we recommend chemotherapy in case of IOE.

Table 2. Cross-tabulations according to the Two Treatment Eras in Kadish Stage C

Parameter		No.	Treatment era		p-value
			1989～2000	2001～2007	
Age	<50	22	13	9	0.803
	≥50	11	6	5	
Sex	M	19	11	8	0.966
	F	14	8	6	
SBP*	No	11	6	5	0.803
	Yes	22	13	9	
IOE†	No	21	13	8	0.506
	Yes	12	6	6	
Trimodality	No	29	18	11	0.288
	Yes	4	1	3	
Radiotheapy	No	7	5	2	0.670
	Yes	26	14	12	
3D-CRT‡	No	18	14	4	<0.001
	Yes	8	0	8	
Chemotherapy	No	11	11	0	<0.001
	Yes	22	8	14	
Surgery	No	19	8	11	0.073
	Yes	14	11	3	
Resection status	R_0, R_1	7	5	2	0.670
	R_2, Bx	26	14	12	

*skull base penetration, †intraorbital extension, ‡three-dimensional conformal radiotherapy

In conclusion, we have shown better OS and PFS in stage C esthesioneuroblastoma patients treated in the later era (2001～2007) compared to those treated in the earlier era (1989～2000). We could not find any differences between two eras except chemotherapy and 3D-CRT. Based on our observation, to improve outcomes for Kadish C esthesioneuroblastoma, we recommend combined chemoradiotherapy, especially 3D-CRT, in addition to surgery.

References

1. **Ferlito A, Rinaldo A, Rhys-Evans PH.** Contemporary clinical commentary: esthesioneuroblastoma: an update on management of the neck. Laryngoscope 2003;113:1935-1938
2. **Simon JH, Zhen W, McCulloch TM, et al.** Esthesioneuroblastoma: the University of Iowa experience 1978～1998. Laryngoscope 2001;111:488-493
3. **Kadish S, Goodman M, Wang CC.** Olfactory neuroblastoma: a clinical analysis of 17 cases. Cancer 1976;37:1571-1576
4. **Rinaldo A, Ferlito A, Shaha AR, Wei WI, Lund VJ.** Esthesioneuroblastoma and cervical lymph node metastases: clinical and therapeutic implications. Acta Otolaryngol 2002;122:215-221
5. **Resto VA, Eisele DW, Forastiere A, Zahurak M, Lee DJ, Westra WH.** Esthesioneuroblastoma: the Johns Hopkins experience. Head Neck 2000;22:550-558
6. **Constantinidis J, Steinhart H, Koch M, et al.** Olfactory neuroblastoma: the University of Erlangen-Nuremberg experience 1975～2000. Otolaryngol Head Neck Surg 2004;130:567-574
7. **McElroy EA Jr, Buckner JC, Lewis JE.** Chemotherapy for advanced esthesioneuroblastoma: the Mayo Clinic experience. Neurosurgery 1998;42:1023-1027
8. **Koka VN, Julieron M, Bourhis J, et al.** Aesthesioneuroblastoma. J Laryngol Otol 1998;112:628-633
9. **Wu HG, Kim IH.** Treatment and results of olfactory neuroblastoma. J Korean Soc Ther Radiol Oncol 2000;18:177-181
10. **Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM.** Esthesioneuroblastoma: prognosis and management. Neurosurgery 1993;32:706-714
11. **Levine PA, Gallagher R, Cantrell RW.** Esthesioneuroblastoma: reflections of a 21-year experience. Laryngoscope 1999;109:1539-1543
12. **McLean JN, Nunley SR, Klass C, Moore C, Muller S, Johnstone PA.** Combined modality therapy of esthesioneuroblastoma. Otolaryngol Head Neck Surg 2007;136:998-1002

13. **Chao KS, Kaplan C, Simpson JR, et al.** Esthesioneuroblastoma: the impact of treatment modality. Head Neck 2001; 23:749-757
14. **Spaulding CA, Kranyak MS, Constable WC, Stewart FM.** Esthesioneuroblastoma: a comparison of two treatment eras. Int J Radiat Oncol Biol Phys 1988;15:581-590
15. **Gruber G, Laedrach K, Baumert B, Caversaccio M, Raveh J, Greiner R.** Esthesioneuroblastoma: irradiation alone and surgery alone are not enough. Int J Radiat Oncol Biol Phys 2002;54:486-491

국문초록

감각신경모세포종의 20년에 걸친 치료와 예후 분석: 치료 시기에 따른 차이

서울대학교 의과대학 방사선종양학교실*, 내과학교실†, 이비인후학교실‡,
암연구소§, 서울대학교 방사선의학 연구소‖

송창훈*·김일한*,§,‖·우홍균*,§,‖·김동완†·이재서‡

목 적: 감각신경모세포종의 시대에 따른 치료방침과 생존율의 변화를 보고하고자 하였다.

대상 및 방법: 1989년 3월부터 2007년 6월 사이에 감각신경모세포종으로 진단을 받고 처음으로 치료를 받은 42명의 환자를 후향적으로 분석하였다. Kadish 병기에 따르면, 3명(7%)의 환자가 A병기, 6명(14%)의 환자가 B병기, 33명(79%)의 환자가 C병기였다. 33명의 C병기 환자 중, 19명은 1989년부터 2000년에, 14명은 2001년부터 2007년까지 치료 받았다. 치료는 수술, 방사선치료, 항암화학요법 및 이들의 조합이었다. 1989년부터 2000년까지 치료를 받은 19명 중 8명(42%)이 항암화학요법을 받은 것에 비해, 2001년부터 2007년까지 치료를 받은 환자 14명은 모두 항암화학요법을 받았다($p<0.001$). 삼차원입체조형방사선치료는 1989년부터 2000년에는 아무도 받지 않았으나 2001년부터 2007년도에 치료를 받은 14명 중 8명이 받았다($p<0.001$). 생존환자에 대한 중앙 추적기간은 6.5년(범위, 2.2~15.8년)이었다.

결 과: 전체 환자에 대한 5년 생존율과 무진행생존율은 각각 53%와 39%였다. Kadish A혹은 B 환자의 5년 생존율은 100%이고 Kadish C병기의 5년 생존율은 39%였다($p=0.007$). C병기 환자 중 1989년부터 2000년까지 치료받은 환자와 2001년부터 2007년까지 치료받은 환자의 5년 생존율은 각각 26%와 59%였다($p=0.029$). 상응하는 5년 무진행생존율은 각각 16%와 46%였다($p=0.001$). 다변량분석에서 안와내침범과 치료시대(1989~2000 vs. 2001~2007)가 생존율과 무진행생존율에 영향을 주는 독립인자로 확인되었다.

결 론: 본 연구의 결과 C병기 환자에서 삼차원입체조형방사선치료의 도입과 같은 치료방법과 기술의 진화를 반영하는 치료시기가 향상된 생존율과 무진행생존율의 원인이 될 수도 있음을 제시 하였다. C병기 환자에서 더 나은 결과를 얻기 위해서는 수술에 더하여 항암화학요법과 방사선치료 병용요법, 특히 삼차원입체조형방사선치료가 추천된다.

핵심용어: 감각신경모세포종, 후각신경아세포종, 방사선치료, 항암화학요법