Surgical treatment versus concurrent chemoradiotherapy as an initial treatment modality in advanced olfactory neuroblastoma

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< Table of Contents >

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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Olfactory neuroblastoma is very aggressive tumor with a high locoregional recurrence rate and distant metastasis. Surgical treatment, including craniofacial resection, has been the main treatment modality. However, locoregional recurrence and distant metastasis frequently developed, other various treatment approaches have been tried. One of the treatment choices is concurrent chemoradiotherapy. We investigated to evaluate our experiences regarding the treatment outcome of patients with advanced olfactory neuroblastoma undergoing surgical treatment (n=10) and CCRT (n=6). We retrospectively analyzed 16 patients treated for advanced olfactory neuroblastoma within the past ten years. The five-year disease-free survival rate of the patients who underwent surgical treatment was 68%. The disease free survival rate for patients who received CCRT was 42%. The difference in the survival rate was not statistically significant, and no difference in the recurrence rate between the two groups. In conclusion, complete surgical resection, including craniofacial resection (CFR), and

postoperative radiotherapy seem to be essential in the treatment of advanced olfactory neuroblastoma. However, olfactory neuroblastoma responds well to CCRT and CCRT has little cosmetic problem. Therefore, we suggest that CCRT mat be considered as one of the primary treatment modalities in the patients with advanced olfactory neuroblastoma.

Key words: Olfactory neuroblastoma, Craniofacial resection, Concurrent chemoradiotherapy

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I. INTRODUCTION

Olfactory neuroblastoma, first described in 1924, is a rare, malignant tumor of the olfactory neuroepithelium. It accounts for about 3% to 5% of all tumors of the nasal cavity and paranasal sinuses.[1] The Kadish Staging systems have been most commonly used and Stage C and D is classified with advanced stage. In advanced olfactory neuroblastoma, the tumor is a locally aggressive neoplasm that frequently invades the skull base and orbit.[2,3,4] CFR, combined with radiotherapy and/or chemotherapy, has resulted in a significantly improved survival rate and the five-year survival rate improved from 37.5% to 82% after adding CFR.[2] However, irrespectively of any type of aggressive therapy, locoregional recurrence as well as distant metastasis frequently develops even long after initial therapy, and serious morbidity from CFR generally manifests as postoperative complications including cerebrospinal fluid (CSF) leakage,

wound infection, extended hospital stay, and cosmetic issues.[5,6] The role of radiotherapy and chemotherapy in the treatment of olfactory neuroblastoma is controversial, but recent studies reported various treatment approches.[3,6,7] The purpose of this study is to review our experiences with advanced olfactory neuroblastomas and to compare surgical treatment and concurrent chemoradiotherapy(CCRT) outcomes.

II. PATIENTS AND METHODS

1. Patient demographics and tumor characteristics

We retrospectively reviewed the medical records of 16 patients with advanced olfactory neuroblastoma for demographic information, presenting symptoms, treatment regimens, tumor extent, regional and distant metastasis, surgical margin, tumor recurrence, salvage therapy and survival at four general hospitals in South Korea between 1995 and 2004. The patient group was comprised of ten male and six female patients. The patients' ages ranged from 8 to 70 years, with a mean value of 43.4 years. Computerized tomography (CT) and magnetic resonance imaging (MRI) were used to evaluate the tumor's extent, and staging was determined according to the modified Kadish classification (Table 1).[8] Twelve patients were diagnosed as stage C disease, and four patients were diagnosed as stage D disease. The pathologic specimens of each patient were reviewed and confirmed as olfactory neuroblastoma. There were no significant differences of gender ratio ($p=0.175$), age ($p=0.607$) and stage ($p=0.957$) between two different treatment groups.

Table 1. Stages of olfactory neuroblastoma according to Kadish and modified by Morita.

Stage	Tumor localization
A	Tumor confined to the nasal cavity
B	Tumor confined to the nasal cavity and paranasal sinuses
C	Tumor beyond the nasal cavity and paranasal sinuses, including involvement of the cribriform plate, base of the skull, orbit or intracranial cavity
D	Tumor with metastasis to cervical lymph nodes or distant metastasis

Patient No.	Sex/Age	Stage	Treatment	Recurrence	Salvage therapy	Final Status	Survival (months)
1	M/25	C	CFR+RT	Nodal/Primary	RND+RT+CT	NED	54
2	M/34	C	CFR	Primary	RT	NED	85
3	M/70	C	CFR	Nodal	RT+RND	DOR	116
4	F/39	C	CFR+RT			NED	42
5	M/47	D	EN+RT+CT			NED	24
6	M/61	C	CFR	Distant	RT	DID	26
7	M/48	C	CFR+RT			NED	18
8	M/51	C	CFR+RT+CT			NED	12
9	F/40	D	MM+RND+RT	Primary	CT	DID	34
10	F/64	D	CFR+RT			NED	7

Table 2. Patient charateristics receiving surgery as an initial treatment (n= 10).

RT, radiotherapy; CT, chemotherapy; CFR, craniofacial resection; MM, medial maxillectomy; EN, endoscopic mass excision; RND, radical neck dissection; NED, no evidence of disease; DOD, death of disease; DID, death of intercurrent disease; FUL, follow up loss.

2. Treatment modality

CCRT was used as an initial treatment in six patients (Table 3). The main

chemotherapy regimen comprised 75 mg/m^2 etoposide per day administered on Days 1-5 and 20mg/m^2 cisplatin per day administered on Days 1-5. In addition, 1000 mg/m^2 ifosfamide per day was administered on Days 1-5 in one patient with Stage D disease. In child patient (No 1, see table 3), 400mg/m^2 cytoxan and 40mg/m^2 adriamycin were administered per day on Days 1-5 and 1.5mg/m^2 vincristine administered on Days 1 and 5. Two cycles of chemotherapy were concurrently performed during intensity modulated radiotherapy (IMRT), and radiotherapy doses ranged from 4000 to 5430 cGy in primary lesions. Patients eligible for salvage therapy received radiotherapy doses ranging from 4000 to 6500 cGy in primary lesions, and from 4500 to 5000 cGy in cervical lesions. The dose of radiotherapy was determined depending on the aim of treatment. Cytoxan, adriamycin and vincristine were selected as components of the salvage chemotherapy regimen. If patients did not respond to these regimens, they received second-line chemotherapy, including the first choice regimens etoposide, ifosfamide, and cisplatin. A complete response (CR) was defined as the absence of detectable disease based on clinical, radiologic, and histologic criteria. A partial response (PR) was defined as a decrease over 50% in tumor area for period over 4 weeks. Disease progression was defined as an increase over 25% in the overall tumor area or as the appearance of new lesions.

Pt. no.	Sex/Age	Stage	Regimens	Cycles	RT Dose (cGy)	Recurrence	Salvage Therapy	Response	Final Status	Survival (Mo.)
1	F/8	C	VC,AD,CX	6	4000			CR	NED	173
2	F/27	D	Ifo,VP,DDP	6	5430			CR	DID	44
3	F/63	C	VP,DDP	3	4000	Primary	Conservative	PR	DOD	27
4	M/24	C	VP,DDP	5	4500	Distant	Conservative	PR	FUL	12
5	M/61	C	VP,DDP	5	4500	Distant	RT	CR	DOD	25
6	M/33	C	VP,DDP	2	5040			CR	NED	19

Table 3. Patient characteristics treated with concurrent chemoradiotherapy (n=6).

RT, radiotherapy; CT, chemotherapy; CCRT, concurrent chemoradiotherapy; VC, Vincristine; AD, Adriamycin; CX, Cytoxan; Ifo, Ifosfamide; VP, Etoposide; DDP, Cisplatin; CR, complete response; PR, partial response; NED, no evidence of disease; DOD, death of disease; DID, death of intercurrent disease; FUL, follow up loss.

3. Follow up, recurrence and local control

The mean follow-up period was 44.9 months, which was calculated from the first day after completing each primary treatment. Time until first recurrence was defined as the time between the initial date of treatment and the date when the recurrence was discovered. Local control was defined as abscence of clinical, radiologic or pathologic

evidence of persistent or recurrent tumor within the original tumor bed after therapy. Survival calculations included patients who died without olfactory neuroblastoma and excluded those lost during follow-up. The disease-specific survival rate was calculated from the day of diagnosis according to the Kaplan-Meier method.

III. RESULTS

1. Surgical treatment

Ten patients with advanced olfactory neuroblastoma underwent surgical therapy as a primary treatment modality. The disease-free five-year survival rate was 68% in all patients (Figure 1). Eight patients are still living, but two patients died of disease-related causes.

When tumor infiltration to the skull base or brain was found, radical surgery (CFR) was performed.(n=8) When the tumor was confined to the nasal cavity without invasion of the skull base, conservative surgery (medial maxillectomy, endoscopic mass excision) was used.(n=2)

Five patients (50%) had failure after initial treatment. Two patients had nodal recurrences and two patients had regional recurrences. Three of these patients had grossly or microscopically positive surgical margins at the time of their initial radical surgery. One patient had subdural metastasis at 13 months and died shortly after initial treatment. The mean time to initial recurrence or metastasis after treatment was 28.6 months (range, 10 to 72 months), and the mean survival after recurrence or metastasis following the initial treatment was 32.4 months. Four of the eight patients (50%) who underwent CFR had recurrence or metastasis, three (75%) of which did not receive postoperative radiotherapy.

Salvage therapy was conducted in all five patients with recurrence or metastasis and proved successful in 60%. In the two patients with regional recurrence, salvage radiotherapy was performed, but one of the patients died. In the two patients with

nodal recurrence, salvage therapy, including radiotherapy and neck dissection, was successful. One patient (No. 3, see Table 2) had nodal recurrence on the left neck (level I) at 70 months post-CFR. Salvage radiotherapy (6000 cGy) was performed, and the nodal lesion completely remitted. At post-CFR 89 months, there was local nodal recurrence on the left neck (level II), and a left radical neck dissection was performed.

In the patients who underwent surgical treatment, five out of ten (50%) had complications related to the surgical treatment (Table 4). In two patients, wound infection (including frontal abscess) developed, and CSF leakage developed in one patients.

2. Concurrent chemoradiotherapy

CCRT was performed in six patients and the disease-free five-year survival rate was 42% in all patients (Figure 1). Four patients died, three as a result of disease-related causes. However, the p-value (0.2588) did not show statistical significance with regard to survival between patients receiving surgical treatment and those receiving CCRT. Three patients (50%) had locoregional recurrence or distant metastasis. One patient had regional recurrence nine months after the initial treatment. Two patients had spinal metastasis at 2 months and 21 months after initial treatment, respectively. The mean time to initial recurrence or metastasis after initial treatment was 10.5 months (range, 2 to 21 months) and the mean survival period after recurrence or metastasis was 10.7 months. Among the patients treated with CCRT, patients with distant metastasis received salvage therapy with booster radiotherapy; however, the patients did not survive.

Etoposide and cisplatin were the main chemotherapy regimens in five patients. In one patient, vincristine, adriamycin and cytoxan were used. The median number of chemotherapy cycle administered was 5 (range, 2 to 6 cycles). The radiotherapy doses ranged from 4000 to 5430 cGy in primary lesions. All six patients achieved objective responses, which included four complete responses (66%) and two partial reponses (34%). No patient experienced primary tumor progression while receiving CCRT. Only one patient, who experienced complete response, had distant metastasis developed at 21 months after initial treatment including five cycles of chemotherapy (Etoposide, Cisplatin) and 4500 cGy radiotherapy. Of the two patients who achieved partial response, in one patient, regional recurrence occurred at 9 months after three cycles of chemotherapy (etoposide, cisplatin) and 4000 cGy radiotherapy. Another patient underwent five cycles of chemotherapy (etoposide, cisplatin) and 4500 cGy radiotherapy but distant metastasis developed at 2 months after treatment.

Four out of six patients (67%) developed complications related to the chemotherapy or radiotherapy (Table 4). Two patients developed neutropenia, and one patient developed osteoradionecrosis. No patients had abnormal electrolyte level and endocrinologic dysfunction after chemoradiotherapy.

Figure 1. Disease-free survival in the patients with advanced olfactory neuroblastoma that underwent surgical treatment or received CCRT

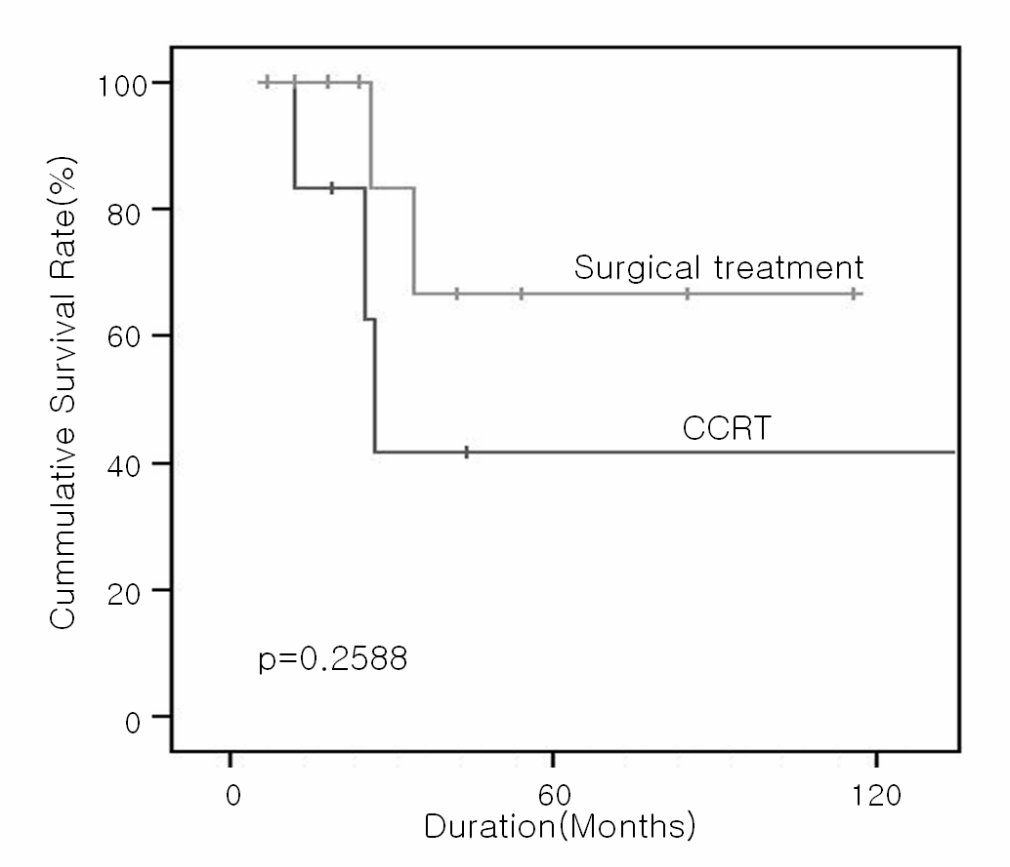

Table 4. Complications related to the treatment.

Complication	Patient No.
Surgical complication	
CSF leakage	1
Meningitis	1
Brain abscess	1
Wound infection	2
CCRT complication	
ORN	1
Neutropenia	2
Epistaxis	1

CSF, Cerebrospinal fluid; ORN, Osteoradionecrosis

IV. DISCUSSION

Olfactory neuroblastoma is a rare tumor with an initially nonspecific symptomatology resembling that of chronic sinusitis. Therefore, up to 70% of patients present with advanced tumor stages at the time of initial diagnosis.[9] In this study, 89% of patients had advanced stage disease at diagnosis and no patients presented in stage A (data not shown). This type of tumor arises from olfactory epithelium high in the nasal cavity and extends to the paranasal sinus in close proximity to the cribriform plate. Olfactory neuroblastoma is an aggressive malignancy that frequently invades the skull base and orbit; the locoregional recurrence rate is relatively high.[2,9] Therefore, the initial treatment modality is important to the patient's survival. A multimodal therapeutic strategy including surgery with postoperative radiotherapy or chemotherapy has been recommended for advanced stage disease.[2,3,10-12] For smaller-sized tumors, an endoscopic mass excision or other limited external intervention had been used. CFR, which enables en bloc resection, has been shown to improve disease-free survival.[2-4,13,14] However, CFR has elicited serious problems such as post-operative complications, an extended hospital stay and cosmetic issues.

It has been reported that the results of radiotherapy alone were equivalent to those of both surgery alone or combination therapy[15] and in locally advanced or unresectable tumors, a significantly better survival was noted in patients with complete regression of the tumor when chemotherapy was employed prior to definitive radiotherapy.[7,16] In addition, multiple reports have suggested that olfactory neuroblastomas are responsive to platinum-based chemotherapy regimens.[7,17] However, the role of radiotherapy or

chemotherapy remains unclear and has been proposed as just adjuvant treatment in advanced olfactory neuroblastoma.

In this study, we tried to compare the treatment outcome of the surgical therapy including CFR and CCRT in patients with advanced stage olfactory neuroblastoma. The disease-free five-year survival rate of the patients who underwent surgical treatment was 68% and 80% of those patients are still living. The rate of recurrence or distant metastasis was 50%, but salvage therapy was successful in 60% of patients with recurrence or metastasis. For smaller-sized tumors, endoscopic mass excision or other limited external interventions had been used, but the surgical margin was statistically significant to the patient's recurrence. Therefore, en bloc resection of the tumor, including a negative surgical margin, has to be considered when surgically treating advanced olfactory neuroblastoma. CFR was performed in 80% of patients as an initial treatment. Three patients who underwent CFR without postoperative radiotherapy developed locoregional recurrence and distant metastasis and only one patient who was managed with CFR and postoperative radiotherapy had local recurrence. Therefore, surgery with postoperative radiotherapy seems to be superior to any single-modality treatment in advanced stages of olfactory neuroblastoma.

Some authors[18,19] have reported that the major benefits of chemotherapy lie in the treatment of patients with advanced olfactory neuroblastoma. The response rate of the previous studies, ranged from 63% to 71%, and a significantly better survival rate was noted in patients with complete regression of a locally advanced or unresectable tumor when chemotherapy was employed prior to definitive radiotherapy.[14] In our study, the disease-free five-year survival rate of the patients who received CCRT was 42%, and 50% of those patients died as a result of disease-related causes. Three of the six

patients (50%) treated with CCRT had regional recurrence and distant metastasis. However, in our limited data, it did not appear that the treatment modality significantly altered survival or recurrence rate in advanced olfactory neuroblastoma (p=0.2588). There was no difference in the recurrence or complication rate between surgical treatment and CCRT. Among the patients who received concurrent chemoradiotherapy, 66% experienced complete response and 34% experienced partial response. Moreover, there was only one recurrence at the primary tumor bed, and another two recurrences were outside the irradiation field (i.e. spinal metastasis). Surgical treatment and post-operative radiotherapy have been known to be a main treatment modality, but CCRT has therapeutic efficacy as a primary treatment.

Achieving acceptable rates of local control remains a significant problem in patients with advanced olfactory neuroblastoma. The rate of recurrence and distant metastasis after initial treatment was 50% in our study, despite combination therapy. In patients with locoregional recurrence, salvage therapy was successful in 60% patients, but in the patients with distant metastasis, none survived. Therefore, combined or multimodality treatment should be considered in patients with advanced olfactory neuroblastoma and adequate salvage therapy may be important to increase the patients' survival and to prevent tumors' further recurrence.

V. CONCLUSION

In our limited experience, we found that complete surgical resection (including CFR) and postoperative radiotherapy played an important role in the treatment of advanced olfactory neuroblastoma. In many cases local failure developed after surgery, postoperative radiotherapy is essential. CCRT is expected to be the promising modality, because olfactory neuroblastoma responds well to CCRT and CCRT has little cosmetic problem. There is no significant difference in the treatment outcomes between surgical treatment and concurrent chemoradiotherapy. Therefore, we suggest that CCRT may be considered as another primary treatment modality in the patients with advanced olfactory neuroblastoma.

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Abstract(in Korean)

진행된 후신경아세포종의 초치료로서 수술요법과 동시 항암 약물-방사선요법의 비교

<지도교수 : 윤 주 헌>

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정 의 석

후신경아세포종은 높은 국소재발 및 원격전이율을 보이는 매우 침윤성이 높은 종양으로 두개안면절제술을 포함한 수술요법이 주된 치료방법이었다. 하지만, 국소재발율과 원격전이가 흔해 동시 항암 약물-방사선 요법을 포함한 다른 여러 치료 방법이 시도되어 왔다. 그러나, 동시 항암 약물-방사선요법은 치료 결과에 있어서 아직까지 효과가 불분명하였다. 이에 저자는 수술요법과 동시 항암 약물-방사선 요법을 시행한 진행된 후신경아세포종 환자들에 대한 경험을 평가하고자 하였다. 10년 동안의 진행된 후신경아세포종으로 진단받아 치료받은 16명의 환자를 후향적으로 분석하였다. 수술요법을 시행한 환자의 5년 무병 생존률은 68%였다 (n=10). 동시 항암 약물-방사선 요법을 시행한 환자의 5년 생존률은 42%였다 (n=6). 두 군간의 생존율 차이의 통계학적 유의성은 없었고 재발률의 차이 또한 유의하지 않았다. 결론적으로 두개안면절제술

등의 완전한 수술적 절제와 수술 후 방사선치료가 진행된 후신경아세포종의 치료에 필수적인 것으로 보여지며, 동시 항암 약물-방사선요법이 또 하나의 초치료로서 적절한 치료방법이 될 수 있을 것이다.

핵심되는 말: 후신경아세포종, 두개안면절제술, 동시 항암 약물-방사선요법

PUBLICATION LIST

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