Radiotherapy Result of Brain Stem Tumors

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Twenty five patients with tumors of the brain stem were treated with radiotherapy between 1979 and 1987. Histological diagnosis could be obtained in 6 cases, and other 19 patients were diagnosed by neurologic findings and CT or MRI. Eighteen patients were treated by radical radiotherapy and 6 patients received both operation and radiotherapy, while 1 patient received chemotherapy after radiotherapy. Total dose ranged from 50 Gy to 55 Gy.

By an clinical scoring scale at 2 months after radiotherapy, no complete response was obtained, but 16 cases achieved partial response, 2 cases were stable, and 4 cases were deteriorated. The overall survival rate at 3 years was 36%. Age, performance status at diagnosis, degree of cranial nerve involvement, CT pattern of post-contrast enhancement, and clinical response by scoring scale were correlated with survival.

Key Words: Brain stem tumor, Radiotherapy, Clinical response, Survival

INTRODUCTION

The brain stem is constituted by the midbrain, pons, and medulla oblongata[1,2], and performs several vital functons such as the control of respiration. Because of critical location, the tumors were seldom biopsied[3~5] and the majority of patients were treated with radiotherapy without histologic confirmation. The reported 5 year survival rate following radiotherapy ranged from 0% to 40%[1,6,7]. Most of patients died within 2 years after diagnosis. However, 20~30% of patients were reported to survive several years and might be cured of tumors[8,9]. The present study was conducted to ascertain the patterns of clinical response and survival after radiotherapy and to identify prognositic factors that would be valuable for individualized treatment.

Survival from the onset of irradiation was calculated by the life table method[11]. The logrank test was used to compare survival rate[12].

MATERIALS AND METHODS

Twenty seven patients with tumors of the brain stem were treated at the Department of Therapeutic Radiology, Seoul National University Hospital between 1979 and 1987. Of them, two patients with incomplete radiotherapy were excluded from analysis. The median follow-up period of survivors was 57 months.

The male to female ratio was 3 : 2. The age ranged from 4 to 44 years old and their median age was 8 years old (Table 1). The location of the tumor was the pons in 19 patients, midbrain in 4 cases, medulla oblongata in 1 case, and cerebellar peduncle in 1 case, but many tumors had extents of two sites or more. The clinical diagnosis was obtained by CT scan alone in 9 patients and by CT and MRI in 10 patients. Biopsy was done in 5 patients and partial removal was performed in 1 case. Thus the histologic diagnosis was made in 6 cases; all were astrocytoma of varying grade; grade I in 3 cases, grade II in 2 cases, and grade III in 1 case.

Radiation was delivered with Co-60 gamma rays or 6 MV X-rays using two parallel opposed fields with adequate margin. The total radiation dose was 50 Gy~55 Gy with conventional fractionation schedule. One cycle of chemotherapy with vincristine, CCNU, procarbazine, hydroxyurea, Cis-platinum, Ara-C, DTIC, and prednisolone was combined after radiotherapy for one patient.

Clinical response was evaluated at 2 months after completion of radiotherapy according to a scoring scale in which included tumor size reduction by CT scan, change of neurologic status, and change of steroid dose; overall score of 6 was defined as complete response, 2 to 5 as partial response, −1 to +1 as stable, and less than −2 as deterioration[10] (Table 2). Tumor response was assessed by CT scan at 2 months after radiotherpy;

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Table 1. Patient Characteristics

Characteristics		No. of Pts
Age	0 – 9	14
	10 – 19	6
	20 –	5
Sex	Male	15
	Female	10
Total		25

Table 2. Clinical Scoring Scale

Score	Mass in CT	N.E.	Steroid
+3	Gone	Normal	
+2	> 50% reduced	Improved	
+1	< 50% reduced		Decreased
0	No change	No change	No change
−1			Increased
−2	Increased	Worsened	

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Table 3. Clinical Response by a Scoring Scale at 2 Months after Radiotherapy

Response	No. of Pts (%)
Complete response	–
Partial response	16 (64)
Stable	2 (8)
Deterioration	4 (16)
Unknown	3 (12)
Total	25

Table 4. Tumor Response by CT Scan at 2 Months after Radiotherapy

Results	No. of Pts (%)
Complete remission	–
Partial remission	8 (32)
Minimal remission	3 (12)
Stable	8 (32)
Progression	4 (16)
Unknown	2 (8)
Total	25

complete remission was defined as complete disappearance of mass, partial remission as reduction of mass over 50% without development of new lesion, minimal remission as reduction of mass from 10% to less than 50%, and stable as mass change within ±10%.

RESULTS

Clinically 64% (16/25) of patients obtained partial response and 8% (2/25) maintained stable condition (Table 3). But among 22 patients whose response were evaluable, PR was 72.2% and stable condition was 9.1%. The response duration ranged from 1 to 76 months and its median was 8 months. As for the tumor response by CT scan alone 32% of cases showed PR, 12% showed MR, 32% remained stable, and 16% of them progressed (Table 4).

The 1-, 2-, and 3-year survival rate were 56%, 40%, and 36%, respectively. All death were, due or related, to uncontrolled or recurrent tumor at primary site as possible as we could identify. Dissemination into subarachnoidal space was found in one patient.

Table 5 showed the median survival period and 3 year survival rate as a function of various factors. Patients older than 10 years of age, with good performance status, with minimal cranial nerve involvement, with diffuse enhancement on CT, or with clinical response at 2 months after radiotherapy had better survival (Fig. 1~4). According to symptom and sign, there was no significant difference in survival. The response on CT alone was not associated with survival (Fig. 5).

Nine patients deteriorated within 10 days after radiotherapy started, but most of them recovered in several days and continued radiotherapy with supportive care. One patient sufferd from chronic otitis media after radiotherapy with 5,500 cGy, but survives more than 78 months.

DISCUSSION

Although some reported survival was in excess of 40% at 5 years, our 3 year survival rate of 36% is consistent with the majority of treatment results of brain stem tumor[7,10,13~17].

In our studies, patients older than 10 years of age, with minimal cranial nerve involvement, with good performance status, with diffuse enhancement on CT, or with clinical response at 2 months after radiotherapy had better survival,

Table 5. Survival by the Various Factors

Factor	Number of patients	Median survival (months)	3 year survival (%)
Age (year)			
= < 10	15	9	13
> 10	10	54	70**
Performance status			
ECOG 1	6	42	83
ECOG 2	7	16	43
ECOG 3	7	9	14
ECOG 4	6	7	0**
Tumor location			
Midbrain	4	36	75
Pons	19	10	21*
Cranial nerve involvement			
Unilateral			
All	19	17	40
< 3[a]	11	48	64**
Bilateral	4	12	25**
Tumor density on PCT[b]			
Hypodensity	15	12	20
Mixed density	7	22	43
Hyperdensity	3	61	100*
CT enhancement pattern			
Non-enhancement	12	12	17
Diffuse enhancement	7	48	86
Ring enhancement	6	10	17**
Tumor response on CT			
PR[c]	8	42	75
NR[d]	12	10	25*
Clinical response by scoring scale			
PR[c]	16	20	40
NR[d]	6	9	17**

** : $p < 0.05$, * : $0.05 < p < 0.1$

a : Number of involved cranial nerve was less than 3.

b : Pre-enhancement CT

c : Partial response or remission

d : Stable and deterioration

which overlapped a number of prognostic factors reported by others for the brainstem tumor[1,7,14]. The presence of an early, highly focal neurologic deficit might reflect the invasive and destructive nature of a rapidly growing neoplasm. Cranial nerve paresis might reflect the malignant nature of tumor[1] and was more likely seen in the pons lesions[15]. Benignancy of midbrain tumors was more often than pons tumors[2,6]. Therefore, histological grade seemed to have an essential prognostic value, and it was reported that none of 18 patients with biopsied malignant tumors survived 16 months, whereas half of 14 children with well differentiated astrocytomas survived 5 years[9]. In one study, the survival difference between low and high grade tumors approached statistical significance: and became highly significant with time in a serial [7,8]. Although the histology could be verified in 6 cases only in our study, brain stem tumors can now be safely biopsied stereotactically.

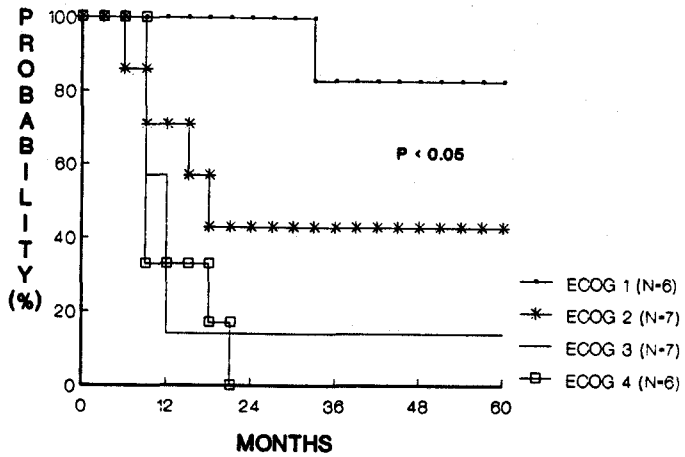

Fig. 1. Survival according to performance status. The 3 year survival rate of ECOG 1, 2, 3, and 4 was 83, 43, 14, and 0%, respectively.

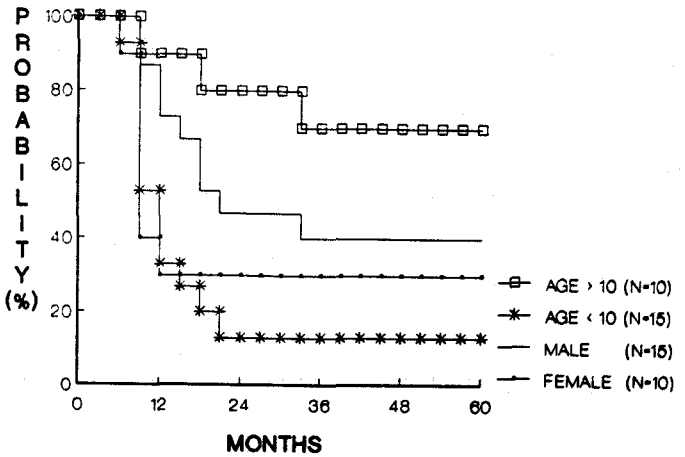

Fig. 2. Survival according to age and sex. According to sex, there was no differnce on survival, but 3 year survival rate of patients older than 10 years of age was significantly higher than that of younger (70% vs 13%).

Because MRI is better than CT in delineating the extent and heterogeneous appearance of brain stem tumor, MRI guided multiple stereotactic biopsies may be of value for estimating prognosis and planning treatment[7,19,20]. But there still ramains a representativeness of small specimen for the tumor.

Brain stem tumors were known to exhibit a number of patterns in CT appearance, particulary in regard to contrast enhancement[1,21~23], and various patterns by CT were correlated with histologic grade of tumor. One reported that, unlike supratentorial gliomas, enhancing brainstem tumors were often of low grade and non-enhancing ones were of high grade[24]. While other reported that enhancing tumors included both low and high grade tumors[22], non-enhancing hypodense tumors were grade II or III, and diffusely enhancing tumors included both low and high grade by other[25]. Our results didn't show clear relationship between the patterns of contrast enhancement and histologic grade. The prognosis for hypodense tumor was

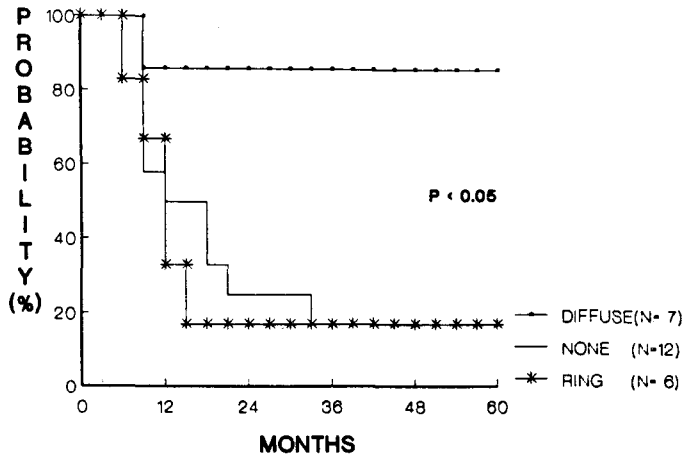

Fig. 3. Survival by CT pattern of post-contrast enhancement. Diffuse enhanement showed excellent survival rate (86%) compared with other groups (17%, each).

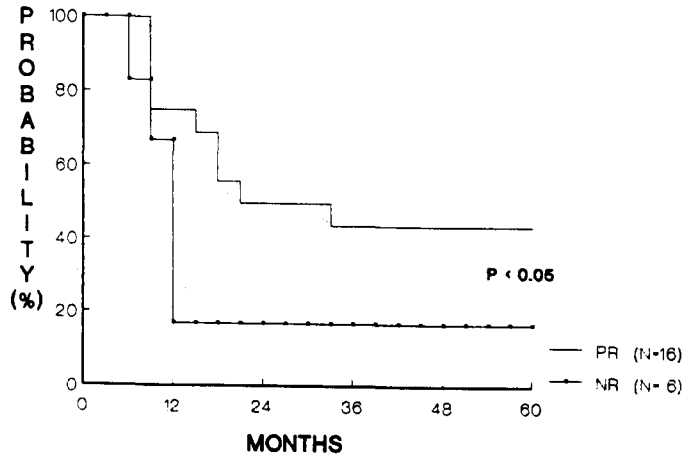

Fig. 4. Survival by clinical response based on a scoring scale in which included neurologic finding, change in steroid dose, and CT response. Patients with partial response (PR) at 2 months showed better outcome than patients with no response (NR).

reported to be worse than that for a non-hypodense tumor, which indicated infiltration of brain stem structures by neoplasm[5]. This seemed to be in agreement with our results.

Of tumors with diffuse contrast ehnancement, 57% showed partial response, whereas in the tumors of non-enhancement 30% showed partial response. Ring enhancing tumors showed a limited radiation response (1/6 cases)[1]. It was suggested that the tumor that might be controlled by conventinal radiotherapy was either a small to middle sized non-enhancing tumor or a diffuse enhancing tumor. Among the evaluable patients of this analysis the partial remission rate by CT was 40% and the clinial partial response rate according to a scoring scale was 73%. Clearly the prognostic value of the latter was more significant. So, CT scan actually gave some information on prognosis, but was not decisively relied upon.

The value of extensive removal of brain stem

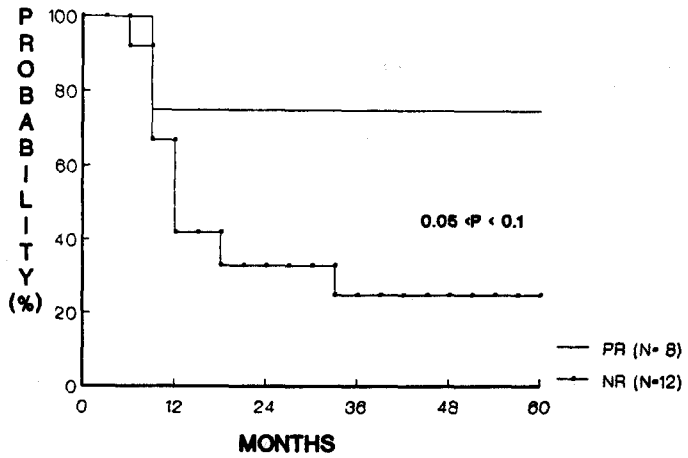

Fig. 5. Survival by response on CT scan. The 3 year survival rate of partial remission (PR) group and no remission (NR) group was 75% and 25%, respectively.

tumors became clearer. Although extensive removal was not indicated in diffuse brain stem tumors[3], 10~15% of brain stem tumors that are focal and enhancing could often be subtotally removed with low morbidity and no mortality[3,5].

Because the results of conventional radiotherapy of brain stem tumor was generally poor, new treatment protocols as combination with chemotherapy or hyperfractionated radiotherapy are now being investigated[17,26~28]. Although the effectiveness of such therapy were not well documented, recent reports suggested that there was no detrimental acute or subacute effects on normal brain. Results of these trials were not significantly better; 1- and 2-year survival rates of malignant gliomas were slightly better with hyperfractinated radiotherapy. Hyperfractionation prolonged the time to tumor progression and survival time for many patients with brain stem glioma[29]. Since radiotherapy is the only means of therapy in almost all brain stem gliomas, it seems that a further escalation of total dose, upto 70 Gy or more, with hyperfractionated radiotherapy can be entertained, but that there remains a group of patients who will be only moderately helped by this technique and for whom more aggessive treatment will be warranted.

In our studies, one patient expired with CSF seeding. Improving local control in brain stem tumors, CSF metastasis may become a more clinical relevant problem. The patients with high grade neoplasms which more frequently demonstrate CSF metastasis would be the most likely candidates for trial of craniospinal therapy[6,28].

Our 3 year survival rate (being only 36%) again indicated a poor prognosis of brain stem tumors. We think that surgery should be used for confirmation of histologic diagnosis and may play an important role in volume reduction in selected patients. We believe that radiotherapy will remain the mainstay of treatment for this tumor and are encouraged to search for ways to improve results of treatment such as altered radiotherapy schedules or other approaches, possibly including the use of systemic chemotherapy in combination of radiotherapy.

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═국문초록═

뇌간 종양의 방사선 치료 성적

서울대학교 의과대학 치료방사선과학교실

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1979년부터 1987년까지 뇌간 종양 환자 25명이 방사선 치료를 받았다. 6예는 조직학적으로, 19예는 이학적 및 신경학적 진찰, CT 및 MRI 등에 의하여 임상적으로 진단하였다.

18예는 근치적 목적의 방사선 치료를, 6예는 수술후 방사선 치료를, 1예는 방사선 치료후 항암제 병용요법 등을 각각 받았다. 방사선 치료는 통상적 분할치료법에 의하여 50~55 Gy를 조사하였다. 치료 완료후 두달째 임상적 scoring scale에 따른 완전관해는 없었고, 부분관해 16예(64%), 무변화 2예, 종양진행 4예가 각각 관찰되었다.

생명표법에 의한 1, 2, 3년 생존율은 각각 56%, 40%, 36%였으며, 연령, 진단당시 전신상태, 뇌신경 장애정도, 조영제 투입후 시행한 뇌단층 촬영 소견, scoring scale에 의한 임상적 관해양상 등의 요인이 생존율에 유의한 영향을 주는 예후인자였다.