Brainstem Tumors

—Results of 20 Patients Treated with Radiation Therapy—

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A total of 20 patients (male: female=10:10, adult:children=8:12) with brainstem tumors had been received radiation therapy in the Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine between 1980 and 1990. Thirteen of 20 patients were treated with conventional radiation therapy (before 1989, 180~200 cGy per fraction, 5 days a week, total dose 4680~5400 cGy), and seven patients were treated with hyperfractionated radiation therapy (in 1990, 100 cGy per fraction, twice daily 10 fractions a week, total dose 7200 cGy). Median follow up periods for conventional radiation therapy group and hyperfractionated radiation therapy group were 36 months and 10 months, respectively. Four of 20 patients had histopathologic diagnosis prior to treatment; 3 cases were low grade astrocytoma and 1 case was high grade astrocytoma. Overall 2-year actuarial survival rate was 30%. The prognosis of patients with a longer duration of symptom and sign was better (60% vs 12%), and the adult (52%) was better than children (14%). There was no significant difference between the focal (29%) and diffuse (26%) type. The initial clinical response was better in the hyperfractionated radiation therapy group. Because of the relatively small number of patients and short follow up period in hyperfractionated radiation therapy group, there was no comparison between two group.

Key Words: Brainstem glioma, Radiation therapy, Hyperfractionation

INTRODUCTION

Brainstem tumors comprise 10~15% of all childhood CNS tumors[1] and less than 2% in adult. Tumors that arise primarily from brainstem vary histologically from differentiated astrocytomas to glioblastoma multiforme[2,3]. Most brainstem tumors are diffuse in nature, mainly involving pons, and produce cranial nerve dysfunction[4], ataxia, and long tract signs. When brainstem tumors occur focally in the pons, medulla or midbrain, grow more slowly than diffuse tumors. Therefore prognosis of brainstem tumors should be different according to the tumor nature. However, before the advent of magnetic resonance imaging (MRI), delineation of brainstem tumors was very difficult due to artifact from the skull base on CT image. Consequently, most patients were diagnosed clinically together with a CT scan and received radiation therapy without any surgical intervention, even biopsy. Most patients show rapid neurologic improvement, but usually fail locally within 1 to 2 years[6]. Overall 5 years survival rate was approximately 30% in most series[2,5,6].

Chemotherapy trials didn't improve survival. Age, histology and tumor type were suggested as a prognostic factors. Now, in MRI era, more biopsies are tried to determine pathologic grade and to individualize the treatment. Recent studies[7,8] suggested that hyperfractionated radiation therapy has improved survival in diffuse type or high grade tumors. We performed retrospective study of twenty cases with brainstem tumors to evaluate the treatment outcome and prognostic factor. Also we present an early experience with hyperfractionated radiation therapy.

MATERIAL AND METHOD

Between 1980 and 1990, 20 previously untreated adults and children with brainstem tumors were referred to the Department of Radiation Oncology, Yonsei University Medical College. All patients had intrinsic lesions involving the brainstem documented by either CT or MRI scans; all the lesions had the

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radiographic appearance of glioma. No patients presented with multicentric or disseminated lesions. No patients received chemotherapy. Before 1989, conventional radiation therapy was performed in the 13 cases. Total radiation doses were 47~60 Gy with daily 180~200 cGy, 5 times per week. In 1990, hyperfractionated radiation therapy with 100 cGy fractions given twice daily with a minimum 4 hours break between treatments had been tried in 7 cases. Total radiation doses were 7200 cGy, 10 times per week. In the conventional radiation therapy group, there were 7 males and 6 females ranging from 3 to 35 years of age. Tumors were classified by CT and/or MRI imagies as being either diffuse or focal.

diffuse: involved more than one geographic area of brainstem.

focal: involved focal brainstem component.

The radiographic tumor pattern was focal in 7 patients and diffuse in 6 patients, respectively. Two patients underwent biopsies and their histologic diagnoses were documented as low grade astrocytoma. In the hyperfractionated radiation therapy group, there were 3 males and 4 females ranging from 4 to 34 years of age. Focal and diffuse tumor patterns were one and six, respectively. Two patients underwent biopsies and proved as one low grade astrocytoma and one high grade astrocytoma (Table 1). The duration of symptoms prior to diagnosis ranged from 1~24 months (median 2 months). The primary site of tumor was pons only in 8 patients. In the 9 patients, tumors involved the pons plus other site extension, namely pons plus cerebellum or pons plus midbrain etc. Treatments were given with opposed lateral field encompassing the radiographically visible tumor plus a 2~3 cm margin. Doses were specified at the mid-plane distance: megavoltage linear accelerator with 4 MV X-ray or Co-60 was used.

Response to therapy was determined by both the neurologic examination and a comparison of enhancing CT scan and/or MRI. Clinical response was divided into four categories.

CR (Complete Response): normal or complete disappearance of clinical symptom and sign

PR (Partial Response): definitely improved clinical symptom and sign

SD (Stable Disease): unchanged clinical symptom and sign

PD (Progressive Disease): worsening of clinical symptom and sign

The length of survival was calculated from the date irradiation began. One patient was lost to

Table 1. Patient Characteristics YUMC (1980~1990)

	Conventional (N=13)	Hyperfractionated (N=7)	Total (N=20)
Adult (>18)	5	3	8
M : F	3 : 2	1 : 2	4 : 4
Child (<18)	8	4	12
M : F	4 : 4	2 : 2	6 : 6
Age Mean	10	10	10
Range	3-35	4-34	3-35
Type			
Diffuse	6	6	12
Focal	7	1	8
Pathology			
Proven	2	2	4

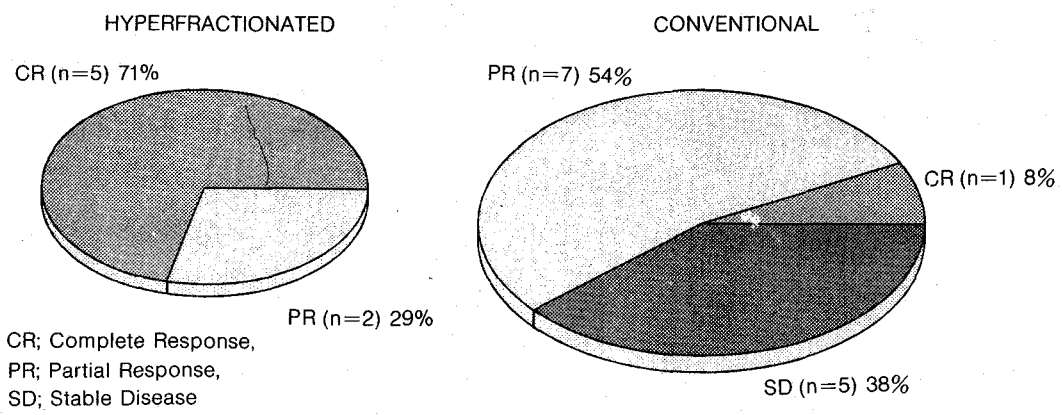

Fig. 1. Results of clinical response.

follow-up after treatment. The minimum follow-up was 2 months and maximum follow-up was 7 years 6 months. Actuarial survival rates were calculated using the Kaplan-Meier method. Because of the relatively small number of patients, analysis of risk factors. influencing survival was difficult.

RESULT

The clinical response was better in the hyperfractionated radiation group. In the hyperfractionated group, complete response rate was 71% and partial response rate was 29% but only 8% of CR rate in the conventional radiation group and majority of them appeared PR (54%) and SD (38%) (Fig. 1). The overall 2-year actuarial survival rate was 30%. The 2-year actuarial survival rate was 40% with conventional therapy group and 18%. with hyperfractionated group, respectively. This was no statistical signifciance (Fig. 2). In the conventional radiation therapy group, median survival time was 10 months. Nine patients were dead 2, 7, 7, 8, 8, 10, 10, 18, 38 months after treatment. there were five patients of long term survivor (Table 2). They were old age and had long symptom duration (2 weeks to 2 years), relatively. Three patients of them had focal type and poor clinical response. In the hyperfractionated radiation therapy group, at the follow-up period four patients were dead 4, 10, 10, 17 months after radiation therapy and three patients were alive at 14, 6, 9 months. The median survival time was 10 months. The patient with only one focal type was alive until 6 months follow up. The 2-year actuarial survival rate was better for adult (52%) than children (14%) but there was no statistical significance (Fig. 3).

Actuarial survival times were evaluated in terms of the rapidity of onset of signs and symptoms. For the 14 patients whose first sign or symptom occurred less than 2 months before diagnosis, the 2-year actuarial survival was 12%, whereas in the 6 patients with an interval of greater than 2 months, it was 60%. However, this was no statistical significance because of small number of cases (Fig. 4). The 2-year actuarial survival rate was 29% with focal type and 26% with diffuse type, respectively. There appeared to be no difference between them (Fig. 5). In the hyperfractionated radiation therapy

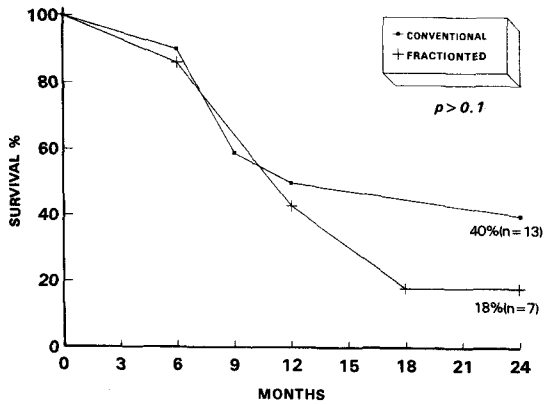

Fig. 2. 2-year survival by the treatment modality.

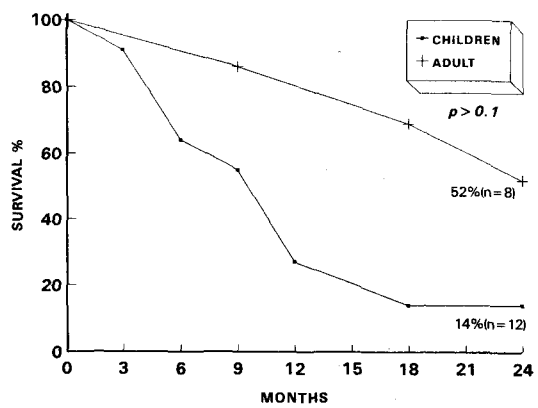

Fig. 3. 2-year survival by the age.

Table 2. Long Term Survivors with Conventional RT

Age	Sex	Symptom duration	Site	Biopsy	Type	Response after 54 Gy RT	Survival duration
35	F	2wk	pons	no	focal	SD	4yr3mo alive
11	M	1yr	pons	no	focal	PD	3yr2mo dead
26	F	6mo	post. fossa	no	focal	SD	7yr6mo alive
25	M	2yr	pons, midbrain	no	diffuse	PR	4yr9mo alive
3	M	1yr	pons, midbrain, medulla	no	diffuse	PR	5yr7mo alive

SD: unchanged neurologic examination PD: worsening of neurologic examination
PR: definitely improved neurologic examination

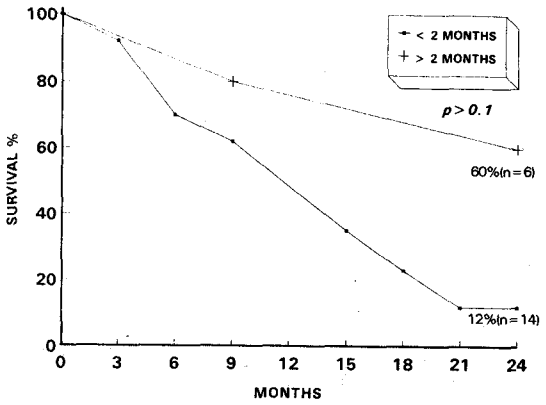

Fig. 4. 2-year survival by the symptom duration.

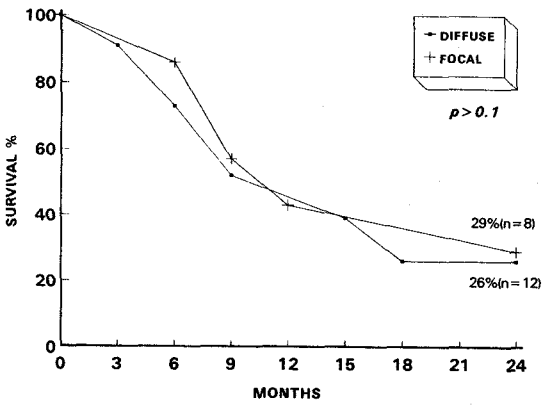

Fig. 5. 2-year survival by the tumor type.

group, long term toxicity has been minimal to date.

DISCUSSION

Nearly a half of brainstem tumors arises in the pons, with the medulla and midbrain being the next most frequent sites[2]. The surgical approach to brainstem tumors is hazardous and the degree of resectability extremely limited. Thus, in most instances, clinical and radiographic diagnosis alone has been regarded as sufficient and radiation therapy without pathologic diagnosis was standard treatment for brainstem tumors. Five-year survival rates of radiation therapy alone without histopathologic diagnosis have varied between 0~50%[2,5,6], which suggested that this variation was related the proportion of malignant tumor[3]. The overall 2-year survival rate for the 20 patients in this study was 30%, similar to that in all recent reports[2,5,6]. However, in several recent reports, either direct or stereotactic biopsy was done safely and good clinicopathologic correlations were obtained with little morbidity. Childrens Cancer Study Group (CCSG) reported that the survival rate was 20% in the patients not explored, 11% in the patients explored but not undergoing resection, and 75% in the patients undergoing partial resection[9]. And dorsally exophytic brainstem tumors carry a good prognosis as long as the patient receives maximum subtotal resection only[10]. But radiation remains the only routinely used therapeutic modality in the most brainstem tumors. Dose should not exceed 5500 cGy to the tumor area because of brain tissue tolerance. So survival rate of 20% to 30% at three years is more consistent with the results of recent large studies[5,9,11].

Littman[11] reported that among the 18 patients with well differentiated gliomas had five-year actuarial survival of 55%. In a recent CCSG trial[9], 74 children with brainstem gliomas were randomized to radiation alone versus postradiation CCNU, vincristine and prednisone. No statistical difference in the 5-year survival rate was apparent (17% versus 23%). Radiation sensitizers have not improved the response in either group patients[12].

Since the principal cause of treatment failure has always been an inability to achieve local control of primary tumor[6], hyperfractionated radiation therapy used for the further dose escalation. The CCSG pilot study (100 cGy fractions given twice daily to total dose 7200 cGy) appears to have improved survival[13]. Edwards et al[7] of a multiinstitution hyperfractionated trial involving 34 children and 19 adults showed a median survival time of 64 weeks and 92 weeks, respectively. In the hyperfractionated trial, survival was prolonged significantly. Parker et al[14] analyzed 16 children who receiving 120 cGy of RT twice daily, to a total dose of 6480 cGy. Median survival was 11 months, which was not different from the results obtained with conventional radiotherapy. Memorial Sloan-Kettering Cancer Center[15] reported 11 patients treated with hyperfractionated radiation (100 cGy fractions given twice daily to total dose of 7200 cGy), as well as with pre and post radiation chemotherapy. Median survival was 17 months. Linstadt et al[8] also reported on 14 patients treated with 100 cGy fractions give twice daily to total doses ranging between 6600~7800 cGy (median dose 7200 cGy). The 3-year actuarial survival rate was 59%, and median time to progression was 31 months (134 weeks). They recommended to perform a biopsy of the lesion when the operative risk is

acceptably low, and focal tumors proved as very low-grade astrocytomas can be treated with conventional irradiation regimen. Patients with unbiopsied or more aggressive gliomas are irradiated twice daily with 100 cGy fractions to total dose in the range of 7200 cGy.

In present study, clinical response was better in the hyperfractionated group. In the conventional fractionated radiation therapy group, there was five patients of long term survivor. They all had either long symptom duration or focal type tumors on CT scan and showed poor response to radiation therapy. Therefore we thought they might be a low grade gliomas or benign granulomatous lesion. On the other hand, in the hyperfractionated group, all except one had short symptom duration and more extensive diffuse type tumor on MR imaging suggesting high grade gliomas. Their median survival time was 10 months. Therefore, survival differences between two RT grups in our study were maybe due to different component of tumor histology rather than radiation regimen.

The principal prognostic factors in brainstem gliomas were location and histology of the tumor. Some authors[16] have suggested that long term survival depends on location. The mean survival of patients with tumors of the upper brainstem is longer than that of patients with tumors of the lower brainstem, because most of the upper brainstem tumors were low grade and lower tumors were high grade. However, Epstein and McCleary[18] reported that astrocytomas of the cervicomedullary junction carry a more favorable prognosis. In our study, adequate evaluation according to the primary tumor location cannot performed because of small number of cases and uncertainty of tumor extension of CT image in old cases. Age was the significant prognostic factor. For the 53 patients with hyperfractionated radiotherapy, the median survival time was 92 weeks for adults and 64 weeks for children[7]. Our result was also better survival for adult, but no statistical significance ($p>0.1$). The prognosis was worse with diffuse type of tumor than with focal type[7].

The period of survival was significantly shorter in children who presented with cranial nerve palsies and such children were more likely to have malignant tumors[17]. The CT appearance also has prognostic significance. Two CT features correlated with a significantly decreased survival time; a hypodense tumor prior to contrast administration and a tumor that involved the entire brainstem[15]. But CT had limitation to detect brainstem lesion. so we suggested that MRI is mandatory and future study should contain analysis of prognosis according to the MR imaging. The longest survival occured in patients with dorsally exophytic tumors that fill the fourth ventricle. These patients are remarkable in that their survival rate at 4.5 years may be greater than 90%[10]. The prognostic factors in brainstem tumors are tumor histology and tumor type. So, we think that neuroradiologic evaluation with MRI is mandatory and aggressive surgical approach for pathologic diagnosis is worth for better correlation of prognosis and selection of optimal treatment.

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= 국문초록 =

20예의 뇌간종양 환자의 방사선치료 결과

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김우철 · 서창옥 · 표홍렬 · 노준규 · 김귀언

1980년부터 1990년까지 연세의료원 암쎈터 치료방사선과에서 방사선 치료를 받은 20예(남자 : 여자=10:10, 성인 : 소아=8:12)의 뇌간종양 환자의 치료결과를 분석하여 보았다. 총 20예의 환자 중 13예에서는 보통 분할 방사선치료(분할 당 180~200 cGy, 주 5회, 총 4680~5400 cGy)를 시행하였고 나머지 7예에서는 과분할 방사선치료(분할 당 100 cGy, 1일 2회, 주 10회 총 7200 cGy)를 시행하였다. 중앙 추적 기간은 보통 분할 방사선 치료군과 과분할 방사선 치료군에서 각각 36개월과 10개월이었다. 20예의 환자중 4예에서는 치료전 병리학적 진단을 얻을 수 있었다. 이중 3예는 저분화 성상세포종양 이었고 1예는 미분화 성상 세포종양이었다. 전체 대상환자의 실제 2년 생존율은 30%이었다. 예후인자로 나이, 증상 발현기간, 종양 형태 등을 분석해 보았는데, 증상 발현기간이 긴 환자에서 짧은 환자보다 예후가 좋았고, 성인에서 소아보다 예후가 좋았다. 종양 형태간에는 차이가 없었다. 보통 분할 방사선 치료군보다 과분할 방사선 치료군에서 초기 임상적 치료 반응이 좋았다. 보통 분할 방사선 치료군과 과분할 방사선치료군을 비교하는 것은 환자의 숫자가 적고, 과분할 방사선치료군의 추적 기간이 짧아 어려웠다.