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The Efficiency of Radiation Therapy in the Treatment of Intracranial Oligodendrogliomas : Factors Influencing the Prognosis

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Purpose : Oligodendrogliomas (ODG) are a rare, slow growing, tumor in the brain, which can be cured by complete surgical resection, but as yet it is not known if postoperative adjuvant radiation therapy (RT) is essential. We analyzed the treatment results of patients with irradiated ODG to investigate the efficacy of RT in terms of survival rates and other influencing prognostic factors.

Methods and Materials : Between March 1983 and December 1997, 42 patients with ODG were treated with RT at our hospital. The RT was performed daily at a dose of 1.8~2.0 Gy, at 5 fractions per week, to a total dose of between 39.6 Gy and 64.8 Gy (mean 53.3 Gy). The ages of the patients ranged between 5 and 62 years, with a median age of 39 years. The mean follow-up period was 63.4 months (8-152 months). The Kaplan-Meier method was used to assess the survival, and 5 year survival rates (5-YSR). Log rank tests and Cox regression analyses were used to define the significance of prognostic factors.

Results : The majority of ODG in this study were located in the cerebral hemisphere (83.3%). ODG are slightly more common in men than women, and commonly occurs in middle age, between the 3rd and 4th decades. It has been recommended that RT is commenced within 4 weeks following surgery (5-YSR; 86% vs. 49%; $p<0.03$). Histologically well differentiated, as opposed to poorly differentiated, tumors were found to have a more favorable prognosis ($p<0.02$). The actuarial 5-YSR was 65.3% (median survival 90 months). 5-YSR for the various extents of surgical excision, followed by external RT, was superior to that of biopsy only followed by external RT (69.9% vs. 26.6%, $p<0.01$). Tumor size and location, overall elapsed irradiation days, age, sex, whole brain irradiation as a course of treatment and chemotherapy, had no influence on the 5-YSR ($p>0.05$).

Conclusion : A local involved field irradiation with conventional fractionation, commencing within 4 weeks following surgical excision of the tumor, was beneficial for the 5-YSR, but a total radiation dose exceeding 60 Gy did not improve the 5-YSR.

Key Words : Oligodendroglioma, Radiation therapy, Prognostic factor

Introduction

Oligodendrogliomas (ODG) represent 2 to 5% of intracranial gliomas.[1~4] Although many authors agree that radical resection increase survival rates,[3~21] a few studies have examined postirradiation results in patients with cerebral oligodendrogliomas. The interpretation of these studies is difficult because of the limited numbers of patients, variability in the radiation dose and technique, and a lack of histologic confirmation.[3, 4] The merits of postoperative radiation therapy in the management of patients with ODG has not, therefore, been adequately determined.

In this study, we evaluated the effectiveness of radiation therapy and other factors influencing survival after treatment such as tumor size and location, pathologic subtypes, extent

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of surgery, radiation doses and techniques, postoperative intervals before radiation therapy (RT), and chemotherapy.

Materials and Methods

Between 1983 March and 1997 December, 42 patients received radiation therapy for cerebral ODG at the department of radiation oncology of our hospital. The results obtained were retrospectively analyzed through medical records and telephone calls to the patients and/or their relatives. The number of ODG patients treated at our department was 42 (5%) of 847 primary brain tumors irradiated during the same periods. The decision whether or not to give postoperative RT depended upon the opinions of the neurosurgeon and the consulting radiation oncologist. All patients had a Karnofsky performance status of at least 70. There were 25 (59.5%) males and 17 (40.5%) females with ages ranging from 5 to 62 years (median 39 years). Of the 42 patients, 21 (50%) were in their third and fourth decades. The intracranial locations of lesion were 36 (85.7%) in the cerebral hemisphere, 4 (9.5%) in the ventricles and one (2.3%) in each of the thalamus and the cerebellum (Fig. 1). Twenty-two (52.4%) patients received a subtotal resection. Eleven (26.2%) underwent partial resection, five (11.9%) had total tumor resection and another 5 had a stereotactic biopsy only. One of these patients had a total resection of tumor followed by a subtotal resection just before the RT due to the tumor recurrence. Two (4.8%) patients were found to have transformations of diagnosis from ODG to glioblastoma multiforme following repeated operations at 46 and 53 months after initial surgery, respectively. Pathologic subtypes and grades are shown in Table 1. The number of pure ODG and mixed tumors with an astrocytic component were 36 (85.7%) and 6 (14.3%). In terms of tumor size by CT or MRI, 31 (73.8%) cases showed the longest diameter over 5 cm and ten (23.8%) showed 2 to 5 cm. The remaining was less than 2 cm diameter. One (2.3%) of 5 stereotactic biopsy cases was treated with by radiosurgery (2 cm in diameter). Table 2 shows postoperative intervals before starting RT, the irradiation technique and the total radiation doses. RT was performed using a 6 MV linear accelerator (NEC, Japan; Mevatron MX, Siemens). The daily doses used was 1.8~2.0 Gy, at 5 times a week, to total 39.6~64.8 Gy/5~8 weeks (median; 54 Gy). Eighteen (42.9%) patients received whole brain irradiation (40~45 Gy/4~5 weeks) as a part of their RT followed by a boost to the primary tumor area (10~15 Gy/~2 weeks). Twenty-three (54.8%) patients were treated by the local involved field irradiation technique (54~60 Gy/6~7 weeks). Radiosurgery (2 cm secondary collimator, 20 Gy at 80% margin of the tumor) was done in one case (2.3%). Table 3 shows details of the chemotherapy. The follow-up period for survivors ranged from 8~152 months with a mean follow-up of 63.4 months.

The endpoint used for this study was survival. Survival

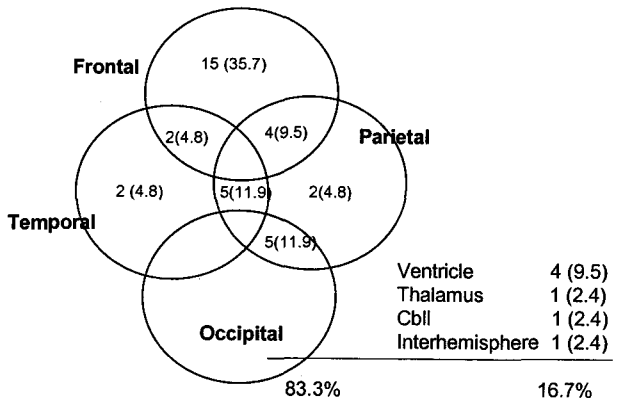

Fig. 1. The intracranial location of the oligodendrogliomas.

Table 1. Tumor Pathology of 42 Oligodendromas

Grade	Pure	Mixed
1	14	2
2	6	2
2~3	5	1
3	7	1
4	4	
Total (%)	36 (85.7)	6 (14.3)

Table 2. Treatment Variables

Postoperative intervals (POI : weeks) before RT	
POI ≤4	30 (71.4%)
4< POI ≤8	9 (21.4%)
8< POI	3 (7.2%)
Total radiation doses (TRD : Gy) except one radiosurgery	
40 ≤ TRD< 50	2 (4.9%)
50 ≤ TRD< 55	20 (48.8%)
55 ≤ TRD< 60	13 (31.7%)
60 ≤ TRD	6 (14.6%)
Radiation therapy (RT)	
· involved field RT following shrinking technique (40~75.6 Gy/5~8 wks)	23 (54.8%)
· whole brain RT (40~45 Gy/4~5 wks) + boost (10~15 Gy/1~2 wks)	18 (42.9%)
· radiosurgery (2 cm, 25 Gy)	1 (2.3%)

Table 3. Treated Chemotherapy Regimens

	Regimens		No (%)
No			29 (69)
Yes	BCNU*	3 (7.2)	13 (31)
	PCV†	3 (7.2)	
	IFN†	1 (2.3)	
	unknown	6 (14.3)	

*Carmustine (Bis-chlorethyl-nitrosourea)
†Procarbazine+CCNU (lomustine)+Vincristine

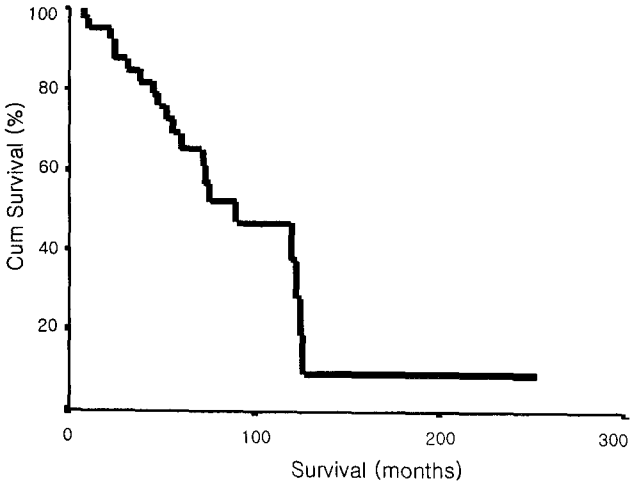

Fig. 2. Actuarial 5 year survival rates of oligodendrogliomas.

distributions were estimated using Kaplan-Meier curves. The log-rank test was used to assess the strength of association between survival time and single variable corresponding to factors thought to be prognostic survival. Cox regression was used to assess the association between survival and multiple indicators of patients, tumor, and treatment characteristics, etc.

Results

ODG occurred most frequently in the frontal lobes (50%) followed by the parietal (38%) and temporal (21.4%) locations (Fig. 1). The majority of tumors in this study were located in the cerebral hemispheres (83.3%). ODG was slightly more common in men than in women, occurring commonly in middle age with 3rd to 4th decade predominance. The actuarial five-year survival rate (5-YSR) was 65.3% (median 90 months) (Fig. 2). The 5-YSR of surgical excision of the tumor and external RT was superior to that of biopsy alone and RT (69.9% vs 26.7%, $p<0.01$) (Table 4).

Table 4. Prognostic Factors Influencing Survival

Prognostic factor	5-year SR (%)	p value*	p value†
Age (years)			
≤50	74.07	0.9172	0.44
>50	66.27		
Gender			
Male	77.25	0.3481	0.4962
Female	57.01		
KPS			
≤70	46.3	0.0011	
>70	86.0		
Tumor size (cm)			
≤6	72.03	0.2279	0.8736
>6	52.91		
Tumor location			
central	55.56	0.8828	0.7546
other	66.43		
Pathology subtype			
pure	64.66	0.7033	0.1135
mixed	66.67		
Pathology grade			
1~3	60.0	0.0510	0.0121
4	41.67		
Surgery			
biopsy	26.67	0.0623	0.0044
any excision	69.89		
Post operative interval before RT (weeks)			0.6877
<4	86.12	0.0327	
≥4	49.1		
Whole brain RT			
yes	55.56	0.2015	0.7289
no	74.71		
Whole brain dose (Gy)			
<40	73.38	0.0121	0.4689
≥40	33.33		
Total tumor dose (Gy)			
<60	74.86	0.0103	0.0256
≥60	33.33		
Chemotherapy			
yes	76.92	0.8127	0.5657
no	60.16		

*p value in univariate log-rank test
†p value in multivariate cox regression test

It is recommended that external RT be started within 4 weeks of surgery (5-YSR; 86% vs 49%; $p<0.0327$) (Table 4). Histologically well differentiated tumors have a more favorable prognosis than poorly differentiated tumors ($p<0.02$). Tumor size, location, over all number of elapsed irradiation days, age, sex, whole brain irradiation as a course of treatment and chemotherapy were not found to influence

the 5-YSR (p>0.05) (Table 4). An involved field local irradiation with conventional fractionation schemes and starting a RT within 4 weeks of surgical excision benefited 5-YSR, but a total radiation dose over 60 Gy did not improve 5-YSR (74.9% vs 33.3%; p<0.02) (Table 4).

Discussion

ODG accounts for fewer than 5% of adult primary brain tumors, and occur most commonly between the ages of 25 and 49 years.[1~4, 15] More than 80% of ODG arise in the white matter of the cerebral hemispheres, commonly in frontal, temporal, and parietal lobes.[1, 15] Approximately 15% are found in the third or lateral ventricles, and the remainder arise in the posterior fossa.[1] Calcification is a common feature occurring in 60% of cases, and peritumoral edema is minimal.[15~17] Our data also occupied 5% incidence of primary brain tumors irradiated at our department and its peak incidence was in the 3rd to 4th decades. Most of the tumors were located in the cerebral hemispheres (83.3%) and the others (16.7%) were at the ventricles, thalamus and cerebellum etc.

A complete follow-up was done during this study. Twenty-six (61.9%) of the 42 patients were alive at the end of the study. The age at death varied from 15 to 62 years, the survival duration ranged from 8 to 126 months, and the 5-YSR was 65.3% (median 90 months). Generally, the median survival duration of patients with low-grade mixed ODG is reported as 7 years and 5- and 10-year survival rates to be 63% and 33%, respectively.[1, 2, 15] Many ODG are admixed with astrocytoma or ependymoma components. The presence of the other histologic component between 10 % to 25% is required to make diagnosis of mixed ODG. Anaplastic ODG and mixed gliomas may contain hemorrhagic and/or necrotic areas. Smith et al and others reported statistically better 5- and 10-year survival rates in pure low grade ODG (73% and 49% respectively) than in mixed ODG (62% and 33%) or low grade astrocytoma (47% and 18%).[5, 11] Our study, however, revealed no differences in survival between the pure and mixed types (p>0.114) as did the study of Wallner et al.[13]

Log rank test and cox regression were performed to identify those factors that influenced time to death (Table 4). Time to tumor recurrence was not evaluated because of the accuracies associated with determining this variable retrospectively. Age, gender, tumor size, location, whole brain irradiation technique and the addition of chemotherapy had no significant effect on survival (p>0.05), but the types of surgical excision (surgery vs biopsy), postoperative interval before RT($\leq$4 weeks vs >4 weeks), total radiation doses (< 60 Gy vs $\geq$60 Gy) and tumor grades (grade 1~3 vs grade 4) showed a statistical significant effect on survival (p< 0.05). ODG have an infiltrative growth pattern, and complete excision can be achieved only rarely.[6, 7, 15] Following resection of the tumors, most patients are left with gross residual tumor, and long term survival rate is low without effective adjuvant therapy. Some investigators have shown increased survival after postoperative irradiation while others have reported no significant survival benefit by adding RT.[3, 8~11] Therefore, RT should be limited to recurrent tumors that can not be removed because of their location. In such cases, RT should be given as late as possible.[8] All reported studies, however, have been retrospective and have spanned long time intervals, so that changes in treatment technique over time could have influenced the results. The radiation doses used were variable, indicating a significant heterogeneity in the therapy with some patients obviously under treated. However, RT has several other effects besides potentially delaying tumor recurrence or improving survival.[6, 7, 19~21] The results of contemporary supratentorial low grade ODG series revealed survival advantages for patients receiving RT. The median survival times were in the range 2.2 to 5.6 years without radiation and 3.2 to 11.2 years with RT.[15] RT may also decrease the likelihood of malignant transformation or at least may delay its onset. Reichenthal et al observed a 9% incidence of malignant transformation in patients who received postoperative RT versus 18% in those who had surgery alone.[18] Two (4.8%) of our cases transformed to glioblastoma multiforme at 46 months and 53 months after the initial diagnosis.

The extent of the radiation field, whole-brain with or without a boost versus partial-brain, did not appear to have any prognostic value in our patients. Following wide field irradiation, complication risk can rise depending on the radiation doses treated. So, it is recommended to treat only partial-brain fields encompassing the tumor, defined on high resolution CT scans or MR images, with a 1~2 cm surrounding tumor margin. Regarding the potential benefit of higher doses of RT compared with lower doses, the retrospective data have been mixed. Medbery et al found tumor

progression in 89% of patients receiving less than 50 Gy compared with 53% for those who received 50 Gy or more.[20] North and colleagues had no survivors among patients receiving less than 40 Gy compared with a 66% 5-YSR for those receiving 45 to 59 Gy and 22% for those who had more than 59 Gy and up to 66 Gy.[21] The analysis of Shaw et al also suggested an improvement in survival with doses of 53 Gy or more versus lower doses.[19] Patients in the present study who received postoperative irradiation doses over 60 Gy didn't make the survivals prolong ($p<$ 0.0256). Our data revealed also even any degree of surgical resection is superior to that of biopsy alone ($p<0.004$). Until further information becomes available, doses of 50 to 60 Gy are reasonable depending on the degree of postoperative residuals. A randomized trial by the European Organization for the Research and Treatment of Cancer (EORTC) to observe the timing of RT (early versus delayed) showed no difference in the 5-year overall survival rate, which was 63% with early RT and 66% with delayed RT.[23] Progression was documented by worsening of the imaging studies with or without evidence of change in the neurologic examination. The 5-year progression free survival rate was 44% with early RT versue 37% with delayed RT. They reported that differences were not significantly different. With nearly 5 years median follow-up, 65% of patients in the delayed RT arm eventually required RT. Our suggestion that starting the RT within 4 weeks following surgical excision of the tumor benefit for the 5-YSR might be needed more cases accumulation and follow-up data.

Anaplastic ODG is considered a chemosensitive tumor. Cairncross et al have reported that both newly diagnosed or recurrent, as well as metastatic anaplastic ODG, predictably respond to chemotherapy.[3, 22] However, our 13 (31%) cases of chemotherapy group were treated with heterogenous regimens as shown in table 3 and revealed no significant survival benefits (5-YSR; with chemotherapy (76.9%) vs without chemotherapy (60.2%) ($p>0.56$).

Finally, this study is limited by the relatively small size of the patients population, resulting in limited power to demonstrate a casual effect. The circumventing the weakness of this is to conduct a randomized prospective trial in which surgical resection with or without adjuvant radiation therapy and chemotherapy.

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국문초록

뇌내 희돌기교종의 방사선치료 성적 및 예후인자

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목 적 : 희돌기교종은 천천히 자라는 낮은 빈도의 뇌 종양으로서 수술로 치유되지만 완전절제가 어려워 수술후 방사선치료가 추천되고 있다. 희돌기교종 환자의 방사선치료후 생존율과 이 생존율에 영향을 미치는 예후 인자들을 알아보기 위해 이 연구를 하였다.

대상 및 방법 : 1983년 3월 부터 1997년 12월 까지 177개월 동안에 가톨릭대학교 강남성모병원 치료방사선과에서는 조직학적 진단이 확진된 총 42예(남 : 여 = 25 : 17)의 희돌기교종 환자에 대한 방사선치료를 실시하였다. 방사선치료는 6 MV 선형가속기를 이용하여 180 cGy/일, 주 5회 씩, 총 조사선량 39.6~75.6 Gy (중앙값 54 Gy)를 실시하였다. 환자의 나이는 5~62세(중앙값 39세)에 분포하였으며 추적조사 기간은 8~152개월(평균 63.4개월)이었다. 방사선치료 종료일을 기준으로 생존율(Kaplan-Meier 법)과 이 생존율에 영향을 미치는 인자들을 후향적으로 분석하였다.

결 과 : 방사선치료후 5년 생존율(5YSR)은 65.3% 이었다(중앙값 90개월). 종양의 수술적 제거를 실시한 경우가 조직생검 만을 한 경우 보다 생존율이 좋았으며(5YSR; 69.9% vs 26.7%; $p<0.01$), 수술후 방사선치료를 4주 이내에 실시한 군이 4주 이후의 경우보다 생존율이 좋은 것으로 나타났다(5YSR; 86% vs 49%; $p<0.03$). 종양에 대한 방사선 총 조사선량이 60 Gy 이상인 군에서는 60 Gy 이하 치료한 군에 비하여 생존율의 증가를 보이지 않았다(5YSR; 74.9% vs 33.3%; $p<0.02$). 조직학적 악성 분화도가 높을수록 생존율은 낮았으며($p<0.01$). 종양의 크기, 뇌내 종양의 위치, 전뇌 방사선조사의 유무, 방사선치료에 소요된 총 기간, 성별, 나이, 화학요법 치료 유무 등에 따른 생존율 변화의 차이는 없는 것으로 분석되었다($p>0.05$).

결 론 : 희돌기교종 환자의 방사선치료는 국소적으로 병소부위에 수술후 4주 이내에 실시하여 생존율 증가를 관찰할 수 있었다. 또한 전통적인 분할 방사선치료 시 총 방사선조사선량이 60 Gy 이상은 생존율을 증가시키지 못하였다.

핵심용어 : 희돌기교종, 방사선치료, 예후인자