J. Korean Soc Ther Radiol Oncol 2000;18(2):79~84

Postoperative Radiotherapy for Low Grade Glioma of the Brain

Ha Chung Chun, M.D. and Myung Za Lee, M.D.

Department of Therapeutic Radiology, Hanyang University College of Medicine, Seoul, Korea

Purpose : To evaluate the effectiveness and tolerance of postoperative external beam radiotherapy for patients with low grade glioma of the brain and define the optimal radiotherapeutic regimen.

Materials and Methods : Between June, 1985 and May, 1998, 72 patients with low grade gliomas were treated with postoperative radiotherapy immediately following surgery. Median age was 37 years with range of 11 to 76 years. Forty one patients were male and 31 patients were female with male to female ratio of 1.3:1. Of those patients, 15 underwent biopsy alone and remaining 57 did subtotal resection. The distribution of the patients according to histologic type was as follows: astrocytomas-42 patients (58%), mixed oligodendrogliomas-19 patients (27%), oligodendrogliomas-11 patients (15%). Two patients were treated with whole brain irradiation followed by cone down boost and remaining 70 patients were treated with localized field with appropriate margin. All of the patients were treated with conventional once a day fractionation. Most of patients received total tumor dose of 5000~5500 cGy.

Results : The overall 5 and 7 year survival rates for entire group of 72 patients were 61% and 50%. Corresponding disease free survival rates for entire patients were 53% and 45%, respectively. The 5 and 7 year overall survival rates for astrocytomas, mixed oligodendrogliomas, and oligodendrogliomas were 48% and 45%, 76% and 56%, and 80% and 52%, respectively. Patients who underwent subtotal resection showed better survival rates than those who did biopsy alone. The overall 5 year survival rates for subtotal resection patients and biopsy alone patients were 67% and 43%, respectively. Forty six patients who were 40 years or younger survived better than 26 patients who were 41 years or older (overall survival rate at 5 years, 69% vs 45%). Although one patient was not able to complete the treatment because of neurological deterioration, there was no significant treatment related acute toxicities.

Conclusion : Postoperative radiotherapy was safe and effective treatment for patients with low grade gliomas. However, we probably need prospective randomized trial to define optimal treatment timing and schedule for low grade gliomas and select patient group for different treatment philosophies.

Key Words : Radiotherapy, Low grade glioma, Astrocytoma, Oligodendroglioma

INTRODUCTION

The low grade gliomas of the brain are pathologically and clinically diverse group of central nervous system neoplasms which include the astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas. Often referred to as benign, these tumors typically arise during the first four decades of life and have a long term survival of only 15% in a reported series of nearly 500 patients.[1)]

The role of radiation therapy in the management of patients with low grade gliomas has not been clearly defined. No prospective randomized studies comparing adjuvant postoperative radiotherapy to delayed radiotherapy at the time of progression or recurrence have been completed. Thus, therapeutic recommendations are now based on the limited number of retrospective studies which have been reported for this disease.[2~4)]

The five year survival rate of patients with low grade astrocytomas who undergo surgery alone is approximately 20%. In contrast, five year survival rate for patients who receive postoperative radiotherapy appears to be approximate-

Submitted February 29, 2000 accepted April 20, 2000
Reprint requested to : Ha Chung Chun, M.D., Department of Therapeutic Radiology, Hanyang University Hospital
Tel : 02)2290-8617, Fax : 02)2290-8617
E-mail : rthcchun@email.hanyang.ac.kr

ly 50%. However, this apparent benifit was limited only to the specific subgroup of patients in several studies.[1,5] Postoperative radiotherapy also appears to be associated with improved survival in patients with oligodendrogliomas. The five year survival rate with surgery alone versus surgery plus postoperative radiotherapy was 31% vs 85% in one series.[6] There are also few series in which postoperative radiotherapy for astrocytomas or oligodendrogliomas has not improved survival over surgery alone.[7,8]

We retrospectively analyzed the records of low grade glioma patients who were treated with postoperative radiotherapy immediately following surgery to evaluate the effect of radiotherapy and tolerance.

MATERIALS AND METHODS

Between June, 1985 and May, 1998, 72 patients with low grade gliomas underwent surgery and postoperative radiotherapy immediately following surgery at our institution. The median age was 37 years with range of 11 to 76 years. Forty six patients were 40 years or younger and 26 patients were 41 years or older. Forty one patients were male and 31 patients were female with male to female ratio of 1.3:1. All of the patients were evaluated by CT scan or MRI preoperatively and 49 patients had pospoperative CT or MRI to evaluate residual tumor.

All patients underwent open craniotomy for histological confirmation. Of those patients, 15 patients underwent biopsy alone and remaining 57 patients did subtotal resection.

The distribution of patients according to histological types in the study population were as follows: astrocytomas-42 patients (58%), mixed oligodendroglioma-19 patients (27%), oligodendroglioma-11 patients(15%). Two patients with pilocytic astrocytoma who were treated with radiotherapy were excluded from this study. The distribution of patients according to extent of surgery and histological types are shown in Table 1.

Table 1. Distribution of Patients according to Extent of Surgery and Histological Type

Surgery \ Histology	Astrocytoma	Mixed oligodendroglioma	Oligodendroglioma
Biopsy alone	10	2	3
Subtotal resection	32	17	8
Total	42	19	11

At our institution, treatment policy for low grade glioma of the brain is postoperative radiotherapy immediately following surgery instead of wait and watch policy until progression or recurrence of the disease. Thus all of the patients in this study received postoperative radiotherapy at least 6 weeks after surgery. Majority of patients initiated radiotherapy two to three weeks following stable condition after surgery.

Until 1987, Cobalt 60 teletherapy unit was employed to treat the patients. Thereafter 6 MeV Linear Accelerator was used. Two patients were treated with whole brain followed by coned down boost to localized area. Remaining 70 patients were treated with two lateral parallel opposed fields targeting on primarily involved region with 1.5 to 2 cm margin based on preoperative CT scan or MRI. Treatment was given 5 times a week with 180 or 200 cGy per fraction, once a day. None of the patients were treated with hyperfractionation. The distribution of patients according to total delivered dose and histological type is shown in Table 2. One patient received less than 4000 cGy because of termination of the radiotherapy with progression of neurological deterioration. Most of the patients received 5000~5500 cGy and majority of them were treated with 5400 cGy. Two patients who were treated with whole brain field and coned down boost field received 4600 cGy to whole brain and 1000 cGy to boost field with total of 5600 cGy.

All of the patients were followed by us or their referring physicians folllowing the completion of radiotherapy. Post-treatment CT or MRI was usually done 1 month and 6 month after the therapy to evaluate progression of the disease. Although 4 patients were treated with external beam reirradiation for documented recurrence or progression of the disease, reirradiation result was not analyzed in this study. Survival was calculated from day one of the radiotherapy

Table 2. Distribution of Patients accoridng to Delivered Dose and Histology

Dose \ Histology	Astrocyoma	Mixed oligodendroglioma	Oligodendroglioma
<4000 cGy	1		
4000~4500 cGy	2	1	
4500~5000 cGy	5	3	2
5000~5500 cGy	32	15	6
5500~6000 cGy	2		3
Total	42	19	11

and statistical comparison was made by Chi square test.

RESULTS

The overall 5 and 7 year survival rates for entire group of 72 patients were 61% and 50%, respectively. Corresponding disease free survival rates for entire group of patients were 53% and 45%, respectively. These results are shown in Fig. 1. Because of inadequate follow up data in this study, we were not able to define exact site of relapsed region, that is, infield recurrence vs recurrence out of the field. However, we believe majority of recurrences were developed in the irradiated field based on other reported series.[1, 4,]

As shown in Fig. 2, the overall survival rates at 5 and 7 years for patients with astrocytomas were 48% and 45%, respectively. Corresponding overall survival rates for mixed oligodendrogliomas were 76% and 56%, respectively. Patients with oligodendrogliomas showed 5 and 7 year overall survival rates of 80% and 52%. There was a trend of further decrease of survival rate after 5 years in patients with oligodendroglioma component compared with patients with astrocytoma patients.

Patients who underwent subtotal resection showed better survival than those who did biopsy alone. The overall 5 year survival rates for subtotal resection patients and biopsy alone patients were 67% and 43%, respectively(Fig. 3). This was statistically significant with p value less than 0.05. Also age at the time of presentation was examined as prognostic indicator. Forty six patients who were 40 years or younger showed better overall 5 year survival rate, compared with 26 patients who were 41 years or older (69% vs 45%, Fig. 4).

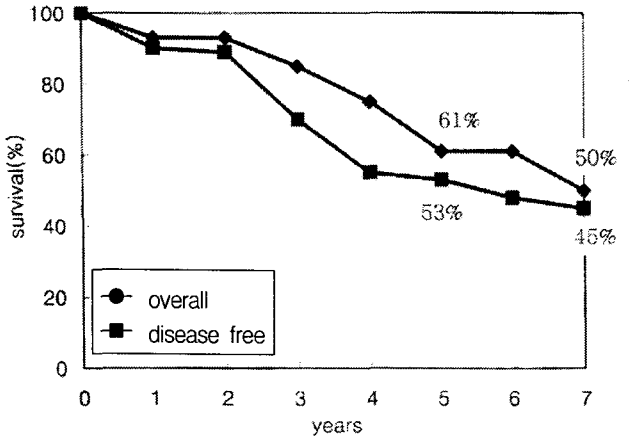

Fig. 1. Overall and disease free survival rates for entire group of patients.

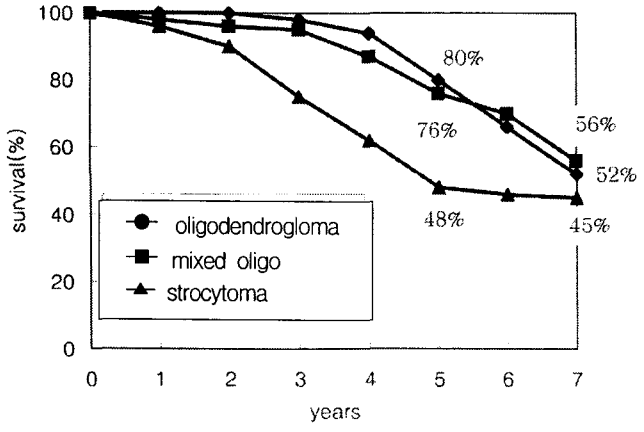

Fig. 2. Overall survival rates according to histological type.

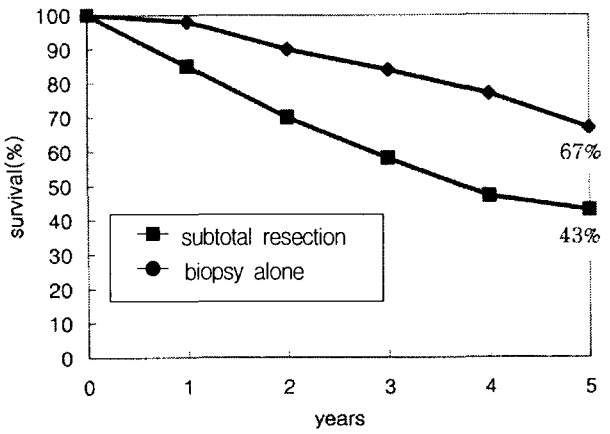

Fig. 3. Overall survival rates according to extent of surgery.

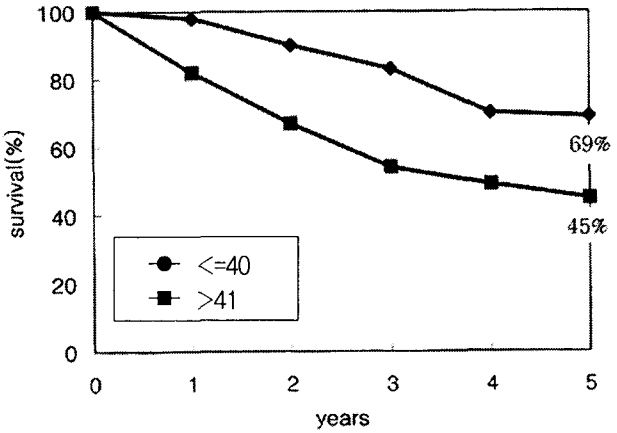

Fig. 4. Overall survival rates according to age.

Karnofsky performance scale which is known as prognostic variable was not evaluated because of inadequate data in records. Although one patient was not able to complete the treatment because of neurological deterioration, there was no significant treatment related toxicities.

DISCUSSION

The low grade gliomas are a diverse group of central nervous system neoplasms in which the outcome for patients receiving radiotherapy following subtotal removal or biopsy is primarily dependent upon histologic type. Shaw et al. reported 5 and 10 year survival rates for 49 patients of 62% and 14%.[10] However, by histologic type, the estimayed 5 year survival was 100% for patients with pilocytic astrocytomas, 83% for those with mixed oligo-astrocytomas or oligodendrogliomas, and 40% in patients with ordinary astrocytomas. Our result showed slightly lower 5 year survival rate than that in this study. This was probably due to the fact that pilocytic astrocytoma patients were not included in our study. The majority of reported series dealing with patients receiving postoperative radiotherapy for low grade gliomas have failed to separate survival as a function of histologic type. This accounts for the wide range of 5 year survivals in these studies, ranging from 28% to 76%.[4, 11, 12] Also several series reported the survival of irradiated patients with low grade gliomas by histologic type.[5, 6, 13] Five year survival rates were as follow, 57% for mixed oligo-astrocytomas, 57% to 100% for oligodendrogliomas and 50% for astrocytomas.

The optimal radiation dose for treating low grade gliomas has yet to be defined. Few studies compared moderate and high dose localized irradiation, with the hypothesis that higher doses will improve local control and ultimately long term survival. Rutten et al. reported that 0 of 9 patients with subtotally removed grade 2 astrocytomas who received >5000 cGy were long term survivors compared to 11 of 16 patients who received <5000 cGy.[14] In contrast, in the 90 patients studied by Fazekas, a gradual improvement in local control was found at 20%, 56%, and 69%, with equivalent doses of >850 ret, >1150 ret, and >1450 ret, respectively.[14]

However, in randomized studies, no significant difference in long term survival was noted between patients treated with low dose and high dose radiation.[16] Because majority of patients in our study were treated with 5000~5500 cGy, comparison of different doses of radiation was not made in this series. Extent of surgery has been recognized as prognostic variables in patients with low grade gliomas treated with surgery and postoperative radiotherapy in several studies.[6,9,17] However, Shaw et al. reported no significant difference between patients treated with subtotal resection and biopsy alone followed by immediate postoperative radiotherapy.[10] In our study, there was significant difference in 5 year survival rate in patients treated with subtotal resection and irradiation (67%), compared with those treated with biopsy alone and irradiation (43%). Thus we suggest that maximum resection should be attempted with avoiding major morbidities based on the result in our study. Also age at the time of presentation was noted to be significant prognostic variable with 5 year survival rates of 69% for 40 years or younger and 45% for 41 years or older, respectively. However, it is not clear whether patients with low grade gliomas should be treated with different policy depending upon age at the time of presentation.

There is at present no consensus on the policy of treatment for patients with low grade gliomas. Surgery is usually attempted and either biopy or subtotal resection is undertaken.

After surgery or histopathologic verification, different policies in general are being pursued. The wait and see policy is followed by some,[18] and they initiate retreatment usually by surgery followed by radiotherapy on progression of disease. The other school treats the patients with planned immediate postoperative radiotherapy.[5, 14, 19] Some institutions follow no definite policy, and sometimes postoperative radiotherapy is used, perhaps in difficult clinical situations.[20] In some situations radiation therapy is being advocated even without biopsy, particularly when any surgical intervention is encountered with the risks of unacceptable complications.[21] Because treatment policy in our institution was immediate postoperative radiotherapy following surgery, conclusion of this issue was not able to be made in this study. In conclusion, postoperative radiotherapy was safe and effective treatment for patients with low grade gliomas. However, we probably need prospective randomized study to define the optimal treatment timing and schedule for patients with low grade gliomas and select the patient group for different treatment philosophies.

REFERENCES

1. **Laws ER, Taylor WF, Clifton MB, et al.** Neurosurgical management of low grade astrocytoma of the cerebral hemispheres. J Neurosurg 1984; 61:665-673
2. **Lote K, Egeland T, Hager B, et al.** Survival, prognostic factors, and therapeutic efficacy in low grade glioma: A retrospective study in 378 patients. J Clin Oncol 1997; 15: 3129-3140
3. **Whitton AC, Bloom HJG.** Low grade glioma of the cerebral hemisphere in adults: A retrospective analysis of 88 cases. Int J Radiat Oncol Biol Phys 1990; 18:783-786
4. **Sheline GE.** Radiation therapy of brain tumors. Cancer 1977; 39:873-881
5. **Garcia DM, Fulling KH, Marks JE.** The value of radiation therapy in addition to surgery for astrocytomas of the adult cerebrum. Cancer 1985; 55:919-927
6. **Scanlon PW, Taylor WF.** Radiotherapy of intracranial astrocytomas-analysis of 417 cases treated from 1960 through 1969. Neurosurgery 1979; 5:301-308
7. **Bullard DE, Rawlings CE, Phillips B, et al.** Oligodendroglioma-analysis of the value of radiation therapy. Cancer 1987; 60:2179-2188
8. **Uihlein A, Colby MY, Layton DD, et al.** Comparison of surgery and surgery plus irradiation in the treatment of supratentorial gliomas. Acta Radiol 1968; 5:67-78
9. **Shibamoto Y, Kitakabu Y, Takahashi M, et al.** Supratentorial low grade astrocytoma. Correlation of computed tomography findings with effect of radiation therapy and prognostic variables. Cancer 1993; 72:190-195
10. **Shaw EG, Scheithauer BW, Gibertson DT, et al.** Postoperative radiotherapy of supratentorial low grade gliomas. Int J Radiat Oncol Biol Phys 1989; 16:663-668
11. **McCormick BM, Miller DC, Budzilovich GN, et al.** Treatment and survival of low grade astrocytoma in adults. Neurosurgery 1992; 31:636-642
12. **Mirabell R, Balart J, Matias-Guiu X, et al.** Radiotherapy for supratentorial low grade gliomas: Results and prognostic factors with special focus on tumor volume parameters. Radiother Oncol 1993; 27:112-116
13. **Muller W, Schroder R.** Supratentorial recurrences of gliomas-morphological studies in relation to time intervals with astrocytomas. Acta Neurochirugica 1977; 37:75-91
14. **Rutten EHJ, Kazem I, Sloof JL, et al.** Postoperative radiation therapy in the management of brain astrocytomas-retrospective study of 142 patients. Int J Radiat Oncol Biol Phys 1981; 7:191-195
15. **Fazekas JT.** Treatment of grades I and II brain astrocytomas-role of radiotherapy. Int J Radiat Oncol Biol Phys 1977; 2:661-666
16. **Karim ABL, Matt B, Hatlevoll R, et al.** A randomized trial on dose response in radiation therapy of low grade cerebral glioma: EORTC study 22844 1996; 36:549-556
17. **Berger M, Deliganiz A, Dobbins J, et al.** The effect of extent of resection on recurrence in patients with low grade cerebral gliomas. Cancer 1994; 74:1784-1791
18. **Afra D, Muller W.** Recurrent low grade gliomas: Dedifferentiation and prospects of reoperation. In :Karim ER, Laws ER, eds. Principles and practice in neuro-oncology. Heidelberg : Springer-Verlag. 1991:189-203
19. **Shaw EG, Daumas-Duport C, Scheithauer BW, et al.** Radiation therapy in the management of low grade supratentorial astrocytomas. J Neurosurg 1989; 70:853-861
20. **Janny P, Cure H, Mohr M, et al.** Low grade supratentorial astrocytomas. Management and prognostic factors. Cancer 1994; 73:1937-1945
21. **Rojan B, Pickuth D, Ashley S.** The management of histologically unverified presumed cerebral gliomas with radiotherapy. Int J Radiat Oncol Biol Phys 1994; 28:405-413

국문 초록

뇌 신경교종의 수술 후 방사선치료

한양대학교 의과대학 치료방사선과학교실

전 하 정 · 이 명 자

목 적 : 뇌 신경교종에 대한 방사선치료 효과를 평가하고 최적의 방사선 치료 방법을 알아보고자 함이 본 연구의 목적이다.

대상 및 방법 : 1985년 6월 부터 1998년 5월까지 본원 치료방사선과에서 수술후 외부 방사선 치료를 받은 72명의 뇌 신경교종 환자를 후향적으로 분석하였다. 환자 나이의 중앙값은 37세였으며 남녀비는 41명대 31명였다. 15명의 환자에서는 조직검사만을 시행하였고 나머지 57명의 환자에서는 아절제술을 시행하였다. 조직검사 소견에 따른 환자의 분포는 성세포종 환자가 42명였으며 혼합 핍지신경교종 환자는 19명, 핍지신경교종 환자는 11명였다. 2명의 환자는 뇌전체를 조사받은후 축소조사야로 치료를 받았고 70명의 환자는 처음부터 부분 조사를 시행하였다. 모든 환자는 하루에 한 번 전통적인 방사선 분할요법으로 치료하였다. 대부분의 환자는 5000~5500 cGy의 총 방사선양을 조사받았다.

결 과 : 72명 전체 환자의 5년 및 7년 생존율은 61% 및 50%였고 무병 생존율은 5년과 7년에서 각각53% 및 45%였다. 성세포종, 혼합 핍지신경교종 및 핍지신경교종의 5년과 7년 생존율은 각각 48% 와 45%, 76% 와 56%, 및 80% 와 52%였다. 아절제술을 시행한 환자는 조직검사만을 시행한 환자와 비교하여 높은 생존율을 나타내었다. 아절제술을 시행한 57명 환자의 5년 생존율은 67%였고 조직검사만을 시행받은 15명 환자의 5년생존율은 43%였다. 40세 이하 46명의 환자는 5년생존율이 69%로서 41세 이상 26명의 환자에서의 5년생존율 45%보다 좋은 생존율을 나타내었다. 비록 환자 한명이 치료중 치료를 중단하였으나 유의한 방사선치료에 의한 급성합병증은 관찰되지 않았다.

결 론 : 뇌 신경교종의 수술후 방사선치료는 안전하고 효과적인 치료요법였다. 그러나 뇌 신경교종 환자에서 최적의 방사선 시기 및 계획을 수립하고 서로 다른 치료방침에 맞는 환자를 구분하기 위하여 보다 잘 짜여진 선행적 임상연구가 필요하리라 사료된다.

핵심용어 : 방사선치료, 신경교종, 성세포종, 핍지신경교종