Radiotherapy for the Low-grade Astrocytomas

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= Abstract =

Purpose: To evaluate the efficacy of radiotherapy for the low-grade astrocytomas and confirm the variables influencing treatment results.

Materials and Methods: Forty-six patients with low-grade astrocytoma received radiotherapy after surgical removal (36 patients) or biopsy (10 patients) from 1979 to 1990. Twenty patients had grade I histology and 26 had grade II. External radiotherapy was done by conventional schedule with the total dose of 45 to 60 Gy (median; 54 Gy). The median follow-up period was 5 years.

Results: The 2- and 5-year survival rates were 80% and 72%, respectively and the 2- and 5-year progression-free survival was 75% and 63%, respectively. The survival was influenced significantly by the histologic grade, the histologic type, and performance status. Major complication was not found.

Conclusion: In spite of good survival, the local failure was still the major problem. Age and the extent of surgery as well as three favorable factors should be considered in the future treatments.

Key Words : Low-grade astrocytoma, Radiotherapy

INTRODUCTION

Astrocytoma is a group of tumors heterogeneous in incidence, gross or microscopic features, and natural behaviours. Slowly growing or less aggressive tumors are referred to as the low-grade or benign and rapidly progressive tumors as the high-grade or malignant [1]. The behavioural variety leads to uncertainties of treatment and prognosis even in the low-grade astrocytomas.

The proposed managements have been so various that it ranged from observation to surgery plus radiotherapy[2-7]. The consensus concerning the prognostic importance of patient's age or performance status, tumor location, histologic grade or type, and the extent of surgery has also not been reached largely because treatment methods have evolved.

To evaluate the efficacy of radiotherapy and confirm the variables influencing the outcome, we analyzed the results, mainly in terms of survival, failure and complication of the patients with the low-grade astrocytoma, retrospectively.

MATERIALS AND METHODS

Forty-eight patients with the low-grade

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Table 1. Histologic Grade according to the Histologic Type

Histologic Type	Histologic Grade		all
	I	II	
Pilocytic	10	0	10
Ordinary(Non-pilocytic)			
Fibrillary	9	16	25
Gemistocytic	0	4	4
Protoplasmic	0	0	0
Mixed	0	4	4
Mixed oligoastrocytoma	1	2	3
Total	20	26	46

astrocytoma[8] received radiotherapy from 1979 to 1990 at the Seoul National University Hospital , in which brainstem or optic nerve primaries were not included. After pathologic review by one of us (JGC) according to the WHO classification system[9], two cases were excluded because one was changed to high grade astrocytoma and another to oligodendroglioma. Another two patients were up-graded in histology from I to II. The histologic grades and types are shown in the Table 1. The proportion of the pilocytic and the non-pilocytic type was nearly same (approx. 50% : 50%) in the cases with the grade I histology but there only were the non-pilocytic types in the the grade II histology.

Of 46 eligible patients, there were 24 males and 22 females. Age ranged from 2 to 58 yrs (median of 29 yrs) and two peaks were observed in the first and fourth decades. As for the performance status, 25 cases (55%) , 13 (28%), 6 (13%), and 2 (4%) had ECOG scales of 1, 2, 3, and 4, respectively. Headache was the most common symptom at presentation and was followed by less frequent symptoms of nausea and vomiting, seizure, motor or sensory deficit, visual disturbance, mentality change, cranial nerve involvement, and psychologic problem.

The tumor locations in decreasing order were the frontal lobe (33%), cerebellum (30 %), basal ganglia or thalamus (17%), parietal lobe (13%), and temporal lobe (7%). Twenty percents of the tumors were found in the midline of the brain and remainders were evenly distributed in the right (37%) and left (43%) sides.

Tumor histology was confirmed by biopsy (10 patients) or resection (subtotal in 30 and gross in 6). Conventional radiotherapy was delivered from 3-4 wks after surgery using a telecobalt unit or a linear accelerator. The total dose was 45-60 Gy (median of 54 Gy). Treatment fields encompassed the tumors with the margin of 2-3 cm. Reductions in the field size were done after 35-45 Gy for large tumors. Whole brain fields were used in 10 patients.

Survival time was calculated from the operation date. The follow-up period ranged from 3 to 166 months with the median of 60 months for all and from 36 to 166 months for the survivors. Survival and progression-free survival (PFS) rates were obtained by the Kaplan-Meier method[10] and comparison of survival data was done by the log rank test[11]. The Cox proportional hazard regression model was used for multivariate analysis[12].

RESULTS

Survival

The 2- and 5-yr survival rates were 80% and 72%, respectively and the 2- and 5-yr progression-free survival was 75% and 63%, respectively (Fig. 1). Approx. 2/3 of deaths were observed within first 2 years after the operation.

The 5-yr survival was significantly influenced by 3 variables among the 10 tested (Table 2); histologic grade, histologic type, and performance status. The survival patterns by these three variables are shown in Figures 2-4. The age at diagnosis was marginally significant because the younger (< 30 yr) patients had better 5-yr survival than the older ($p=0.08$).

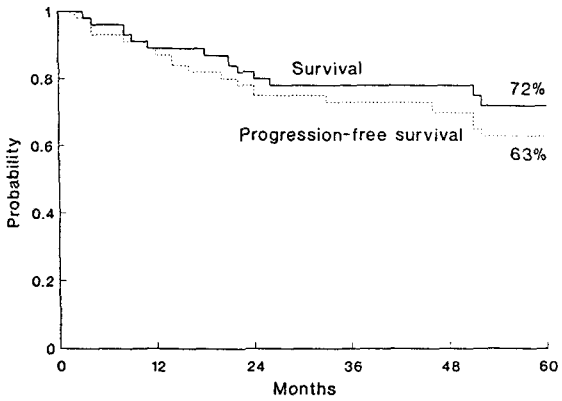

Fig. 1. The overall and the progression-free survival for all the eligible patients (n=46) with the low-grade astrocytoma.

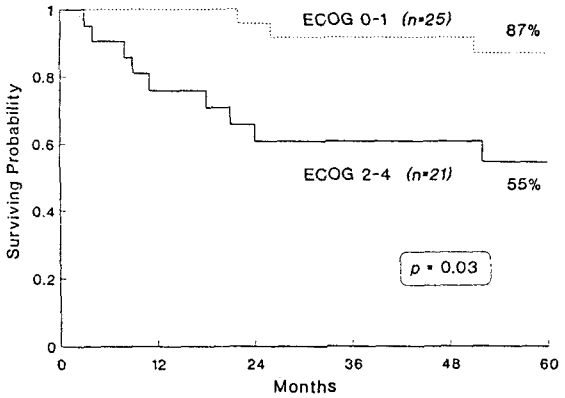

Fig. 2. Survival of the low-grade astrocytomas by the performance status before radiotherapy.

Table 2. Prognostic Values of the Variables by the Log Rank Test

Variable		No. of patients	5-YSR* (%)	p#
Sex	Male	24	70	
	Female	22	76	N.S.
Age(yr)	<30	27	81	
	≥30	19	60	0.08
Performance	ECOG 0-1	25	87	
	ECOG 2-4	21	55	0.03
Tumor location	Supratentorial	32	67	
	Infratentorial	14	85	N.S.
Tumor size	≤3cm	13	75	
	>3cm	33	71	N.S.
Extent of surgery	Biopsy	10	70	
	Subtotal	30	68	0.30
	Gross total	6	100	
Histologic type	Pilocytic	10	100	
	Non-pilocytic	36	65	0.03
Histologic grade	I	20	95	
	II	26	62	0.003
Total dose	<53Gy	12	91	
	≥53Gy	36	64	0.12
Radiation filed	Partial brain	36	76	
	Whole brain@	10	61	0.15

* : 5-year survival rate
\# : log rank test
@ : Reduced at 35-45 Gy.

But gender, presenting symptom, tumor location and size, the extent of surgery, the total radiation dose, or field size did not affect the survival.

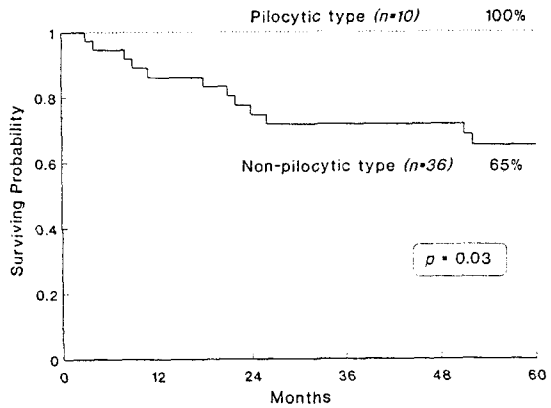

Fig. 3. Survival of the low-grade astrocytomas by the histologic type.

The histologic grade, type, and performance status also influenced the 5-year survival significantly by multivariate analysis with odds ratio of 22.77, 10.13, and 3.67, respectively.

Failure

The uncontrolled primary tumor or recurrent tumor was the cause of death in all 14 dead patients. All recurrences occurred at the primary tumor sites. At the time of analysis, 5 patients had progression of the primary or recurrent tumors. Histologic change to higher grade or malignant transformation was not found among 4 patients who got reoperation. The results of the reoperations were disease-

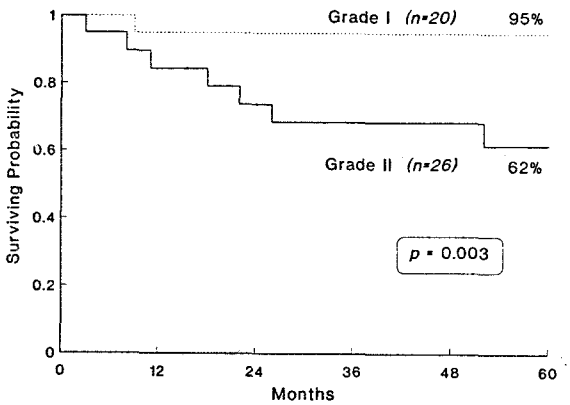

Fig. 4. Survival of the low-grade astrocytomas by the histologic grade classified by the WHO system.

free status in 1 case, alive with disease in 2 cases, and rapidly deteriorated to death in 1 case. Sufferring from the short-term memory deficit was noted in 3 patients who received 45, 50, and 56 Gy. Radiation necrosis, clinically or histologically, was not confirmed in any case.

DISCUSSION

The optimal treatment of the low-grade astrocytoma remains to be defined. The argue for observation or surgery alone was supported by benign course of the disease and moreover both the lack of proven benefit and the potential morbidity of radiotherapy[2,13,14]. The assertion for aggressive radiotherapy was based on observation that the long-term survival was poor after surgery alone, e.g. 15-yr survival of 15% by the Mayo Clinic[3]. The efficacy of radiotherapy was suggested by a report[7] that the 5-yr survival improved from 37 % to 60% and also 10-yr survival from 11% to 41% after combining surgery and radiotherapy ($p=0.048$). The 2- and 5-yr survival rates of 80% and 72% of our own seemed to be compatible with the survival patterns of others[15-21]. In the tumors resected subtotally and treated with radiotherapy[6], 5-yr survival rate was improved from 19% to 46% in adult and from 50% to 81% in children. This benefit was not observed in some reports[3,21]. But it was not clear whether survival was affected by differences in the extents of surgery between patients who received surgery alone and patients who received surgery and radiotherapy. The importance of the histologic types was suggested by a multivariate analysis[22] showing 5-yr survival of 85% for the pilocytic type and 51% for the non-pilocytic ordinary or mixed types. The survival gain after radiotherapy was not observed in the patients with pilocytic type as a whole but might be observed in some patients who had biopsy or subtotal resection. Our study shows better survival for the pilocytic type. The better survival for grade I histology in our study might partly be explained by the WHO classification system because grade I tumors included the favorable pilocytic type[9]. A marked survival advantage for grade I over grade II histology was also proven by others [1,6]. Although categorized as a low-grade astrocytoma, the gemistocytic types behave as anaplastic astrocytomas and 80% of those transform into glioblastoma multiforme[1]. So it was not unexpected opinion that the gemistocytic types be classified and treated as anaplastic astrocytomas[23], because the presence, at least 20%, of gemistocytes in gliomas regardless of pathologic background was poor prognostic sign. We cannot explain the reason why in the present study the gemistocytic types had no difference in the behaviour or survival from the non-gemistocytic types. The better survival with higher oligodendroglial component was shown by the report[24] that the 5-yr survival rates for the ordinary astrocytomas, mixed oligo-astrocytomas, and oligodendrogliomas were 46%, 63%, and 72%, respectively. We could not obtain data supporting this idea in this study.

Many studies indicated benefit of the gross resection in the survival[3,5,6,21], which was denied by the Mayo Clinic recently[25]. The extent

of surgery, meanwhile, did not result in a significant difference in survival in this study. Patient selection might have contributed this result. The age at the time of operation marginally influenced survival. It has been noted that the benefit of radiotherapy for the ordinary astrocytomas was greater in adults than in chlidren[3,6,22,25-27]. It has recently been disputed that the suggestion of limited efficacy of radiotherapy[4] in adults (≥ 30 yr)[22]. Seizures have been associated with better survival[3,28,29], while it was not shown in this analysis. This may be related to earlier presentation and diagnosis. Furthermore, these patients rarely had deep-seated tumors[28]. But other presenting symptoms trended toward a poorer prognosis.

The optimal radiation dose has not been defined yet and is a controversial issue[22,25] The report that the 5-yr survival was 68% with dose of 53 Gy or more and 47% with dose less than 53 Gy[25] was not consistent with the analysis from ordinary astrocytomas showing that crude survival rate was 68% with dose of 50 Gy or less but was 0% with dose exceeding 50 Gy[15]. The hypothesis that higher doses would lead to higher local control and better survival is under clinical trial by the Mayo-NCCTG (50 Gy vs. 65 Gy) and the EORTC (45 Gy vs. 60 Gy) currently. The poor survival in the patients who had high dose (> 53 Gy) in our results could be explained by the fact that the large part of patients had the unfavorable histology (i.e., non-pilocytic type). The optimal field size has not been defined. The survival data in this study did not depend on the field size. But considering that all the relapses were found within the radiation portals, partial brain fields encompassing the tumor with a 2-3 cm margin seems to be suitable and it would lessen the probablility of delayed-onset sequelae.

In conclusion, we obtained a good survival for the low-grade astrocytoma after radiotherapy. Better was the survival in patients with the pilocytic type, the grade I histology, and good performance status. But the local failure was still the major problem. We will take advantage of age and extent of surgery as well as three favorable factors to improve treatment results.

REFERENCES

1. **Russell DS, Rubinstein LJ:** Pathology of tumors of the nervous system. London, Arnold. 1989; pp. 95-169
2. **Cairncross JG, Laperriere NJ:** Low grade glioma-to treat or not to treat? Arch Neurol 1990; 46:1238
3. **Laws ER, Taylor WF, Clifton MB, et al.:** Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres. J Neurosurg 1984; 61:665-673
4. **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
5. **Fazekas JT:** Treatment of grades I and II brain astrocytomas-the role of radiotherapy. Int J Radiat Oncol Biol Phys 1977; 2:661-666
6. **Leibel SA, Sheline GE, Wara WM, et al.:** The role of radiation therapy in the treatment of astrocytomas. Cancer 1975; 35:1551-1557
7. **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
8. **Kernohan JW, Mabon RF, Svien HJ, et al.:** Symposium on new and simplified concept of gliomas. Proc Staff Mtgs Mayo Clinic 1949; 24: 71-75
9. **Zulch KL:** Histologic typing of tumours of the central nervous system. International Histologic Classification of Tumors. No. 21, Geneva, World Health Organization, 1979
10. **Kaplan EL, Meier P:** Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958; 53:457-481
11. **Mantel N, Haenszel W:** Statistical aspects of the analysis of data from retrospective studies

of disease. J Natl Cancer Inst. 1959; 22:719–748

12. **Cox DR:** Regression models and life tables. J R Stat Soc [B] 1972; 34:187–220
13. **Maire JP, Coudin B, Caudry M, et al.:** Neuropsychologic impairment in adults with brain tumors after radiation therapy, "In" Brain Oncology, Chatel M, Darcel F, Pecker J (eds), Dordrecht, Martinus N, 1987; 329–334
14. **Morantz RA:** Radiation therapy in the treatment of cerebral astrocytoma. Neurosurgery 1987; 20:975–982
15. **Rutten EHJM, Kazem I, Slooff 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
16. **Whitton AC, Bloom HJG:** Low–grade gliomas of the cerebral hemispheres in adults–a retrospective analysis of 88 cases. Int J Radiat Oncol Biol Phys 1990; 18:783–786
17. **Kleinberg L, Wallner K, Malkin NG:** Good performance status of long–term disease–free survivors of intracranial gliomas. Int J Radiat Oncol Biol Phys 1993; 26:129–33
18. **Jubelirer SJ, Rubin M, Shim C:** An analysis of 38 cases of low–grade cerebral astrocytoma in adults. W V Med J 1993; 89:102–105
19. **McCormack BM, Miller DC, Budzilovich GN:** Treatment and survival of low–grade astrocytoma in adults. Neurosurgery 1992; 31:636–642
20. **Rekate HL, Rakfal SM:** Low–grade astrocytomas of childhood. Neuro Clin 1991; 9:423–440
21. **Uihlein A, Colby MYJ, Layton DD, et al.:** Comparison of surgery and surgery plus irradiation in the treatment of supratentorial gliomas. Acta Radiol 1966; 5:67–78
22. **Shaw EG, Scheithauer BW, Gilbertson DT, et al.:** Postoperative radiotherapy of supratentorial low–grade gliomas. Int J Radiat Oncol Biol Phys 1989; 16:663–668
23. **Krouwer HGJ, Davis RL, Silver P, et al.:** Gemistocytic astrocytomas–a reappraisal. J Neurosurg 1991; 74:399–406
24. **Shaw EG, Scheithauer BW, O'Fallon JR:** Management of supratentorial low–grade gliomas. Semin Radiat Oncol 1991; 1:23–31
25. **Shaw EG, Daumas–Duport C, Scheithauer BW, et al.:** Radiation therapy in the managenemt of low–grade supratentorial astrocytomas. J Neurosurg 1989; 70:853–861
26. **Medbery CA III, Straus KL, Steinberg SM, et al.:** Low–grade astrocytomas–treatment results and prognostic variables. Int J Radiat Oncol Biol Phys 1988; 15:837–841
27. **Piepmeier JM:** Observations on the current treatment of low–grade astrocytic tumors of the cerebral hemisphere. J Neurosurg 1987; 67: 177–181
28. **North CA, North RB, Epstein JA, et al.:** Low–grade cerebral astrocytomas–survival and quality of life after radiation therapy. Cancer 1990; 66:6–14
29. **Soffietti R, Chio A, Giordana MT, et al.:** Prognostic factors in well–differentiated cerebral astrocytomas in the adults. Neurosurgery 1989; 24:686–692

국문초록=

양성 성상세포종의 방사선치료

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목 적 : 양성 성상세포종에 대한 방사선치료의 효과를 평가하고 방사선치료 결과에 지대한 영향을 미치는 인자를 규명한다.

방 법 : 1979년 부터 1990년 까지 서울대학교병원에서 개두술(36예) 또는 조직생검(10예) 등을 통하여 양성 성상세포종임을 확인한 후 방사선치료를 시행한 46명의 치료성적을 분석하였다. 20명은 세계보건기구에서 설정한 조직 분화도 I 등급이었고 26명은 II 등급이었다. 방사선치료는 통상적 분할 치료법에 따랐으며 총방사선량은 45 내지 60Gy(중앙값 54Gy)이었다. 추적관찰기간의 중앙값은 60 개월이었다.

결 과 : 전체환자 46명의 2년 및 5년 생존율은 80% 및 72%이었고, 2년 및 5년 무진행 생존율은 75% 및 63%이었다. 조직학적 분화도가 유의성이 가장 큰 예후 인자임이 확인되었으며 조직학적 유형과 운동수행능력 또한 생존율에 영향을 미침을 확인하였다. 방사선 치료에 따른 중증의 합병증은 발생하지 않았다.

결 론 : 생존율은 양호하였으나 치료 실패의 주요소는 국소적 종양치유 실패였다. 확인된 3종의 양호한 예후인자와 아울러 연령 및 수술적 절제범위 등도 향후 치료방침 결정시 고려되어야 할 것이다.

중심단어 : 양성 성상세포종, 방사선치료