Radiotherapy Results of Malignant Astrocytoma and Glioblastoma Multiforme

Doo Ho Choi, M.D., Hae Kyung Lee, M.D. and Seong Eon Hong, M.D.

Department of Therapeutic Radiology, College of Medicine, Kyung Hee University, Seoul, Korea

A retrospective analysis was performed on 53 patients with brain malignant astrocytoma and glioblastoma multiforme treated with surgical resection and postoperative radiotherapy in the period between January 1980 and June 1991.

There were 13 patients with malignant astrocytoma, 40 patients with glioblastoma multiforme. Survival rates were analyzed according to histologic grade, age, performance status, extent of surgical resection, tumor location, symptom duration, total radiation dose and addition of chemotherapy after radiation therapy.

5 year actuarial survival rate for malignant astrocytoma was 29.4%, for glioblastoma multiforme was 2.8%. Histologic grade, age, performance status, total radiation dose were statistitically significant prognostic factors.

Key Words: Radiotherapy, Malignant astrocytoma, glioblastoma multiforme

INTRODUCTION

Malignant gliomas comprise 33 to 45% of primary brain tumors, and of these, nearly 85% are glioblastoma multiforme[1,2]. Prospective clinical studies have shown both the efficacy and the shortcomings of conventional radiotherapy in the treatment of malignant gliomas. 5 year survival rate for patients with malignant astrocytomas was 18%, 5% for those with glioblastoma multiforme[1,3].

It has been reported that pretreatment characteristics affect the outcome of patients with malignant glioma, and the most important prognostic factors are histology, age, and performance status[4~8].

To assess the effect of postoperative radiotherapy, chemotherapy and importance of prognostic factors, a retrospective analysis was performed for a group of patients with malignant astrocytoma and glioblastoma multiforme treated at our hospital during the period from January 1980 through June 1991.

MATERIALS AND METHODS

From January 1980 through June 1991, 53 patients with histologically confirmed malignant astrocytoma and glioblastoma multiforme of brain were treated postoperatively at the Department of Therapeutic Radiology, College of Medicine, Kyung Hee University. All patients except five were followed until the time of analysis or to the time of death, five patients were lost to follow up at 3, 3, 4, 4, and 5 months after treatment (Table 1).

The age ranged from 18 to 72 years, and there were 29 males and 24 females. Thirteen patients had malignant astrocytoma, 40 patients had glioblastoma multiforme according to three-tired classification by Ringerz[9] (Table 2). The peak age incidence of glioblastoma multiforme was in the

Table 1. Patient Entry and Follow-up Status (1980. 1-1991. 6)

	No. of patients	F/U months (median)
Followed	48	3-119 (14)
alive	5	26-110 (78)
dead	43	3-58 (11)
Lost	5	3-5 (4)
Total	53	3-119 (12)

Table 2. Patients Characeristics

Characteristics	No. of patients (%)
Age (median	18-72 years (52 years)
Sex	
Male	29 (55)
Female	24 (45)
Histology	
Malignant astrocytoma	13 (25)
Glioblastoma multiforme	40 (75)

sixth decade and there were relatively even distribution of ages in malignant astrocytoma (Table 3). on the basis of operative report, the extent of surgery was categorized as biopsy only, partial resection, or total resection. Postoperative scans were not reviewed to verify the surgeon's assessment of the extent of tumor removal (Table 4).

Initial functional status by ECOG performance score were as followings: ECOG 0-2; 9 patients with malignant astrocytoma, 21 patients with glioblastoma multiforme. ECOG 3-4; 4 patients with malignat astrocytoma, 19 patients with glioblastoma multiforme. The duration of symptoms before diagnosis was mostly within 3 months in glioblastoma multiforme patients (Table 5). Main tumor location were presented in the Table 6, most common site were frontal and parietal lobe.

All the patients were treated with cobalt-60 photon and usual fraction was 180-200 cGy/day, 5 fractions in a week. Radiation portals were whole brain or tumor volume with generous margin according to tumor size or location, followed by reduced field. Total planned dose ranged from 5000 cGy to 7000 cGy, and there were 7 patients with radiation dose less than 5000 cGy (Table 7). Two of 13 malignant astrocytoma patients and 13 of 40 glioblastoma multiforme patients received nitrosourea based chemotherapy as an adjuvant to surgery and radiation therapy.

Survival was counted from the day of operation. Kaplan-Meier method[10] was used to calcurate and log-rank test[11] was used to compare survival data.

Table 3. Histologic Grades by Age

Age	MA*	GM**	Total
0~29	4	2	6
30~39	1	7	8
40~49	3	8	11
50~59	3	14	17
60~	2	9	11

* MA: Malignant astrocytoma
**GM: Glioblastoma multiforme

Table 4. Extent of Surgical Resection

Extent	MA*	GM**	Total (%)
Total resection	2	12	14 (27)
Partial resection	9	23	32 (60)
Biopsy only	2	5	7 (13)

* MA: Malignant astrocytoma
**MG: Glioblastoma multiforme

Table 5. Symptoms Duration by Months

Duration	MA*	GM**	Total (%)
1~3	5	32	37 (70)
4~6	5	4	9 (17)
7~	3	4	7 (13)

* MA: Malignant astrocytoma
**GM: Glioblastoma multiforme

Table 6. Tumor Location

Location	Malignant astrocytoma	Glioblastoma	Total (%)
Frontal L*	4	15	19 (36)
Parietal L	5	14	19 (36)
Temporal L	2	8	10 (18)
Occipital L	1	2	3 (6)
Others	1	1	2 (4)

L*: Lobe

Table 7. Radiation Dose

Dose (cGy)	MA*	GM**	Total (%)
-5500	3	19	22 (42)
5501-6000	5	12	17 (32)
6001-	5	9	14 (26)

* MA: Malignant astrocytoma
**GM: Glioblastoma multiforme

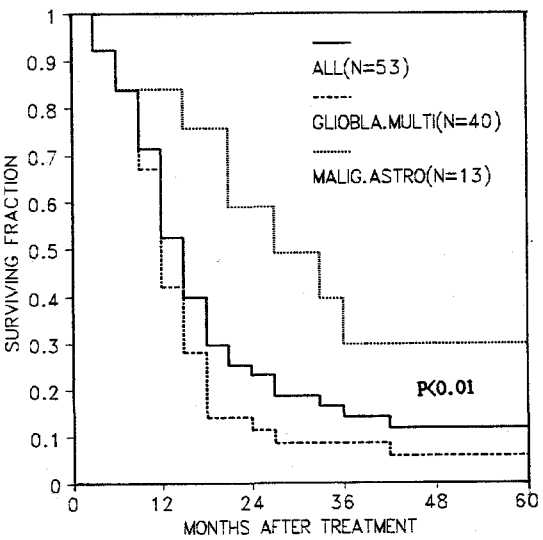

Fig. 1. Actuarial survival according to histologic grade.

RESULTS

The 5 year survival rate for total 53 patients was 8.6%, and were 29.4%, 2.8% for patients with malignant astrocytoma and glioblastoma multiforme, respectively (Fig. 1). Median survival for patients with malignant astrocytoma was 27 months compared with 11 months in the patients with glioblastoma multiforme. Of the 13 patients with malignant astrocytoma, 4 patients were still aliver for 26, 51, 58, 119 months after treatment, but only one patient of the 40 glioblastoma multiforme was alive for more than 60 months. This case had the characteristics of young age, total tumor resection, frontal location, addition of chemotherapy after radiation therapy. The survival rate difference between two groups of patients was statistically significant ($p<0.01$).

The age of the patients at diagnosis had a significant effect on outcome (Fig. 2). The 2 year survival rates were 47.1%, 9.6%, and 0% for patients less than 44, 45 to 59 and aged 60 or more, respectively ($p<0.01$). There was no patient survived longer than 27 months among patients with aged 45 or more. The extent of surgical resection had an influence on prognosis, but the survival difference was statistically not significant ($p>0.1$). The 2 year survival rate for patients who underwent a total resection was 50% compared with 9.6% for those who underwent a partial resection, and 0% for patients undergoing only a biopsy (Fig. 3). All patients with biopsy only died within 24 months, one of 32 patients with partial resection and 3 of 14 patients with totally resected survived after 60 months.

Performance status at the time of initial treatment had also an important prognostic factor. In

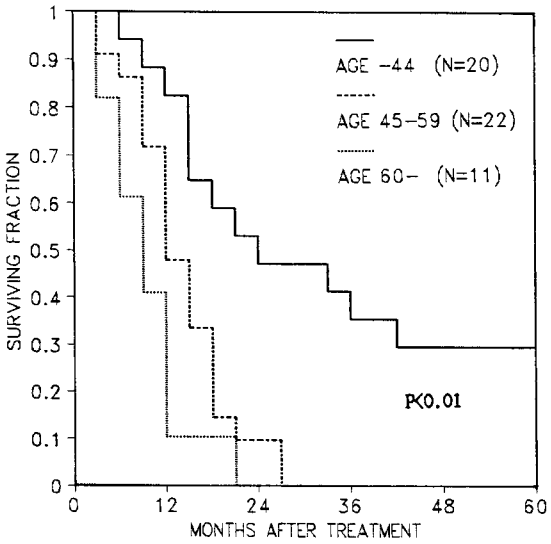

Fig. 2. Actuarial survival according to age.

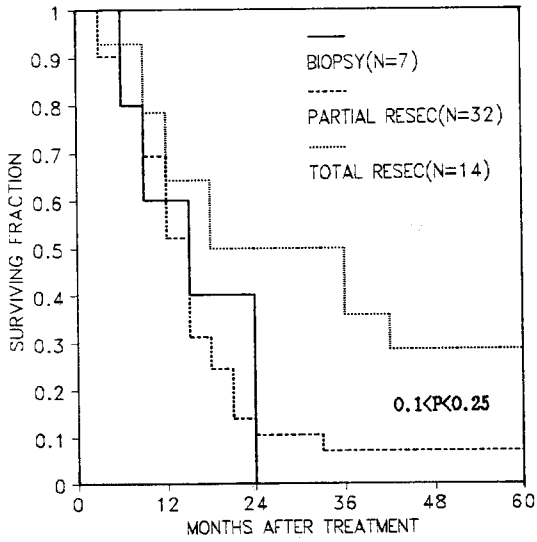

Fig. 3. Actuarial survival according to operation extent.

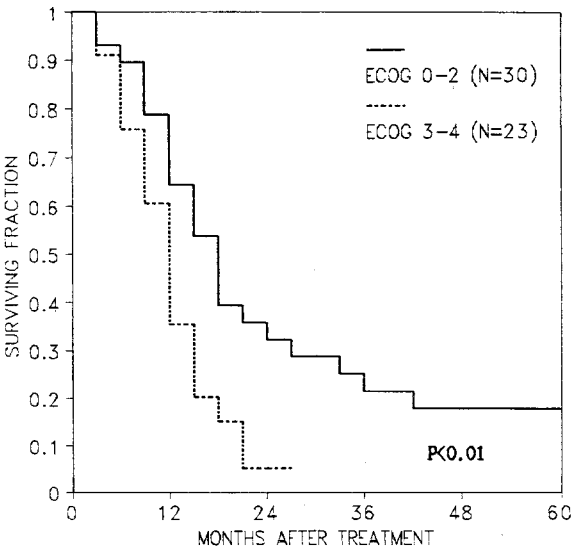

Fig. 4. Actuarial survival according to performance score.

our retrospective analysis, patients with an initial ECOG score 0-2 had a 2 year survival rate of 64.5%, compared with 5.1% for a ECOG score 3-4 ($p<0.01$) (Fig. 4). Patients with symptomatic intervals of less than 3 months had a slightly shorter survival experience than those with longer duration of symptoms without statistical significance (Fig. 5). Survival influenced according to tumor location, especially frontal versus temporal and parietal tumor was shown in Fig. 6. Two year survival rate of patients with frontal tumor was 41.2% compared with 11.2% for those with temporal and parietal tumor (statistically not significant). Regarding radiation dose, survival rate was improved significantly by increasing radiation dose above 56 Gy ($0.02<p<0.01$). However there was no survival difference

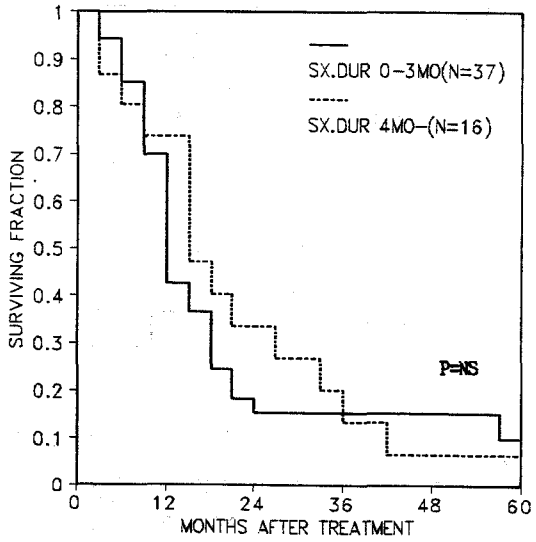

Fig. 5. Actuarial survival according to symptoms duration at diagnosis.

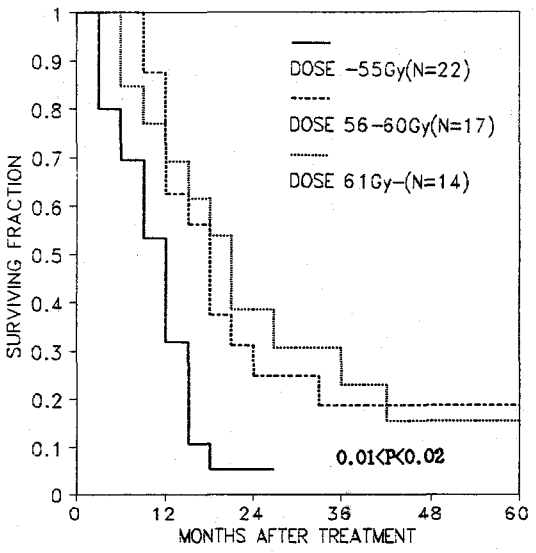

Fig. 7. Actuarial survival according to total radiation dose.

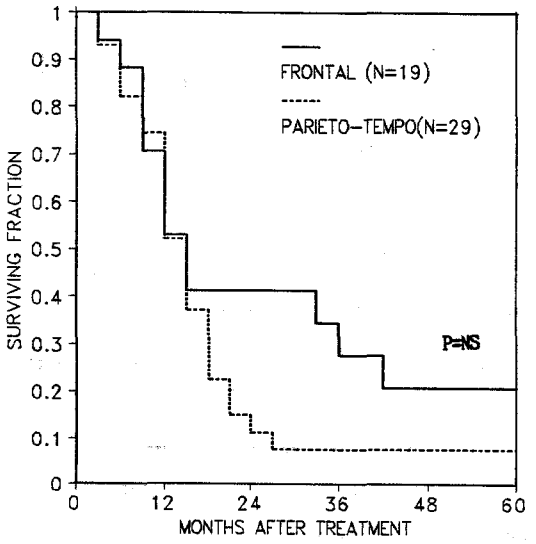

Fig. 6. Actuarial survival according to tumor location.

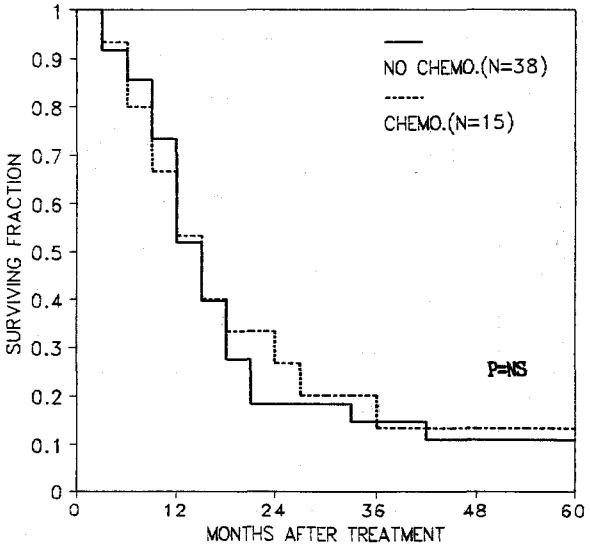

Fig. 8. Survival rate of chemotherapy and non-chemotherapy group.

between 56-60 Gy and more than 61 Gy (Fig. 7). In the chemotherapy group, survival was not improved compared with non-chemotherapy group (Fig. 8).

DISCUSSION

The value of postoperative radiation therapy in the treatment of patients with resected brain malignant astrocytoma and glioblastoma multiforme is documented by published survival data. In 1977, Sheline examined a number of published series and compared the results using surgery alone to surgery and postoperative radiation therapy[12]. His observations documented a benefit for the addition of radiation therapy in the malignant glioma for up to 4 years. 1978, Wallker reported the results of Brain Tumor Study Group protocol 6901 that in a randomized comparison conclusively documented the benefit of adding postoperative radiation therapy to surgery[13]. Median survival was increased from 17 to 37.5 weeks for those adequately treated. One year survival was increased from 3 to 24%, however at 18 months none of the patients treated with only surgery were alive and 4% of patients receiving radiation therapy and surgery were still alive.

Our results confirm the value of the postoperative radiation therapy and compare favorably with the published figures. Survival curves according to histologic grade shown in Fig. 1 emphasize the importance of histologic grading in determining prognosis and separation of glioblastoma multiforme from malignant astrocytoma. The presence of tumor necrosis requred for the definitive diagnosis of glioblastoma multiforme is the histologic feature most reliably prognostic of an unfavorable clinical course[14]. Our results suggest that patients with malignant astrocytoma have a 1 in 4 chance of potential cure if they are adequately treated with postoperative radiation therapy, similar result shown by Rutten at al[15].

Analysis of our material showed the survival advantage for patients who were treated to doses above 56 Gy (Fig. 7), and there was no survival difference between 56-60 Gy and above 61 Gy group. Walk et al.[16], examined the dose effect relationship of radiotherapy in the treatment of malignant glioma, they concluded that a clear cut dose effect relationship exist, median survival from 28 weeks to 42 weeks as dose increasing from 5000 cGy to 6000 cGy. In 1983, Chang at al., reported the results of an RTOG-ECOG study[17] in which patients were randomized to receive 60 Gy in 6-7 weeks or 70 Gy in 7-8 weeks. The results showed no statistically significant benefit for the higher dose of radiation[5], a median survival of 9.3 months for those patients receiving 60 Gy and 8.2 months for those receiving 70 Gy. Combining the results of these large randomized trials suggests that with conventional fractionation the optimal dose for glioblastoma multiforme is in the order of 60 Gy, presumably the optimal dose for malignant astrocytoma is similar this remains to be established.

Survival was significantly different among 3 age groups as shown in Fig. 2. An improved prognosis with younger age was identified both in patients with malignant astrocytoma and glioblastoma multiforme[7,17]. Age remained a significant factor even after adjustment for histology, performance status, and other identifiable prognostic variables[6,18].

Analysis according to extent of surgical resection, it is likely that maximal tumor excision can extend life by reducing tumor burden and delaying regrowth. Our results represented superior survival outcome in the patients of total resection compared to the patients of partial resection and biopsy only, statistically not significant difference (Fig. 3). The RTOG/ECOG studies demonstrated a relationship between survival and extent of surgery. Initial report by Chang et al[5] gave 18 months survival rate of 15, 25, and 34% for biopsy only, partial resection and total resection respectively, Others[19,20] evaluated the prognostic importance of residual tumor, not always positive result[21].

Performance status at the time of initial treatment was also an important variable (Fig. 4). In the RTOG/ECOG study the 18 months survival was 34% for those with a Karnofsky performance status (KSP) of 70-100 as compared with 13% for a KSP of 40-60 and 10% for 20-30[5]. Tumor location specifically frontal versus parietal tumors, was shown in a combined RTOG analysis to be prognostic for patients with both malignant astrocytoma and glioblastoma multiforme, and the duration of symptoms before diagnosis, which appears to be indicative of the rate of tumor growth, has been verified as a prognostic factors[5,6,8]. Our results represented median survival benefit (Fig. 5, 6), but these factors were statistically not significant.

A large number of prospective trials have evaluated the combination of chemotherapy and radiotherapy in patients with malignant gliomas. No cooperative group study for adults has shown a

significant improvement in overall survival when the combination of chemotherapy and radiation therapy was compared with radiation therapy alone, except improved outcome for patients with specific subgroup[22]. Chemotherapy appeared to prolong the overall and event-free survival in children with glioblastoma multiforme in a randomized trial conducted by the Children's Cancer Study Group[23].

From our results and other reports, since there were no or few longterm survivors in patients with glioblastoma multiforme treated with conventional therapy, more effective therapeutic modalities are needed to improve the prognosis. Some methods adding radiation sensitizers[24], brachytherapy to conventional therapy[25], or altered fractionation shedules[26] are in progress. The use of interstitial brachytherapy has been a major advance in the treatment of glioblastoma multiforme.

REFERENCES

1. **Mahley SM, Mettlin C, Natarajan N, et al**: National survey of patterns of care for brain-tumor patients. J Neurosurg 71:826-836, 1989
2. **Nelson DF, Gonzalez DG, Bleehen N**: Brain sites. Int J Radiat Oncol Biol Phys 4:S135-S145, 1988 (suppl)
3. **Leibel SA, Sheline GE**: Radiation therapy for neoplasms of the brain. J Neurosurg 66:1-22, 1987
4. **Shapiro WR**: Therapy of adult malignant brain tumors: What have the clinical trials taught us ? Semin Oncol 13:38-45, 1986
5. **Chang CH, Horton J, Schonfeld D, et al**: Comparison of postoperative radiotherapy and combined postopertive radiotherapy and chemotherapy and multidisciplinary management of malignant gliomas. A joint radiation therapy oncology group and eastern cooperative oncology group study. Cancer 52:997-1007, 1983
6. **Byar DP, Green SB, Strike TA**: Prognostic factors for malignant glioma: Oncology of nervous system. Boston, MA, Marinus Nijhoff. 1983, pp 375 -395
7. **Nelson DF, Nelson JS, David DR, et al**: Survival and prognosis of patients with astrocytomas with atypical or anaplastic features. J Neuro-oncol 3:99 -103, 1985
8. **Medical Research Council Brain Tumor Working Party**: Prognostic factors for high grade gliomas: Development of a prognostic index. J Neuro-oncol 9:47-55, 1990
9. **Ringerz N**: "Grading of gliomas". Acta Pathol Microbiol Scand 27:51-64, 1950
10. **Kaplan E, Meier P**: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457 -481, 1958
11. **Peto R, Pike MC, Armitage P, et al**: Design and Analyis of randomized clinical trial requiring prolonged observation of each patient. II. analysis and examples. Br J Cancer 35:1-39, 1977
12. **Sheline GE**: Radiation therapy of brain tumors. Cancer 39:873-881, 1977
13. **Walker MD, Alexander JE, Hunt WE, et al**: Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. J neurosurg 49:333-343, 1978
14. **Nelson JS, Schoenfeld D, Tsukada Y, et al**: Histologic criteria with prognostic significance for malignant glioma. Modern radiotherapy in multidisciplinary management. New York, Masson. 1982, pp 1-4
15. **Ruthen EH, Kazem J, Sloof JL, et al**: Post-operative radiation therapy in the treatment of brain astrocytoma: A retrospective study of 142 patients. Int J Radiat Oncol Biol Phys 7:191-195, 1981
16. **Walker MD, Strike TA, Sheline GE**: Analysis of dose effect relationship in the treatment of malignant gliomas. Int J Radit Oncol Biol Phys 5:1725-1731, 1979
17. **Choi DH, Kim IH, Ha SW**: Radiotherapy result of brain astrocytoma and glioblastoma multiforme. J Korean Soc Ther Radiol 6:163-168, 1988
18. **Burger PC, Green SB**: Patient age, histologic features, and length of survival in patients with glioblastoma multiforme. Cancer 59:1617-1625, 1987
19. **Green SB, Wood JR, Shapiro WR**: Resection of malignant glioma. The prognostic importance of residual tumor size as measured on CT scans. a brain tumor cooperative group (BTCG) study (abstr). Proceeding of the Meeting of the American Society of Clinical Oncology 6:A267, 1987
20. **Suh CO, Kim KE, Suh JH**: Radiotherapy results of brain astrocytoma. J Korean Soc Ther Radiol 2: 177-84, 1984
21. **Michael DP, Philip HG, Theodore LP, et al**: Highly anaplastic astrocytoma: A review of 357 patients treated between 1977 and 1989. Int J Radiat Oncol Biol Phys 23:3-8, 1992
22. **Laramore GE, Marz KL, Nelson JS, et al**: Radiation Therapy Oncology Group (RTOG) survival data on anaplastic astrocytomas of the brain: Does a more aggressive form of treatment adversely impact survival ? Int J Radiat Oncol Biol Phys 17:1351 -1356, 1989
23. **Sposto R, Ertel IJ, Jenkin RDT, et al**: The effectiveness of chemotherapy for treatment of high grade astrocytomas in children: Results of randomized trial. J Neuro-oncol 7;165-177, 1989
24. **Newman HFV, Bleehen NM, Ward R, et al**: Hypoxic cell radiosensitizers in the treatment of high grade gliomas: A new direction using combimed Ro 03 -8799 (pimoidazole) and SR 2508 (etanidazole).

Int J Radiat Oncol Biol Phys 15:677-684, 1988
25. **Loeffler JS, Alexander E, Wen P, et al**: Results of stereotactic brachytherapy used in the initial management of patient with glioblastoma. J Natl Cancer Inst 82:1918-1921, 1990
26. **Nelson DF, Curran WJ, Nelson JS, et al**: Hyperfractionation in malignant glioma report on a dose searching phase I/II protocol of the Radiation Therapy Oncology Group (RTOG). Proc Am Soc Clin Oncol 9:90, 1990 (abstr)

= 국문초록 =

악성 성상세포종과 교아세포종의 방사선 치료성적

경희대학교 의과대학 치료방사선과학교실

최 두 호 · 이 혜 경 · 홍 성 언

1980년 1월부터 1991년 6월까지 경희대학교 부속병원 치료방사선과에서 수술후 방사선치료를 받은 뇌의 악성 성상세포종과 교아세포종 환자 53명을 대상으로 후향적 분석을 실시하였다.

48명이 추적 가능하였으며 5년생존율은 악성 성상세포종이 29.4% 였고 교아세포종이 2.8% 였으며 중앙생존기간은 각각 27개월, 11개월이었다. 조직 분화도, 나이, 수행능력, 방사선량이 통계학적으로 유의하게 의미있는 예후인자로 나타났다. 종양절제 정도, 증상발현 기간, 종양의 위치에따라 생존율의 차이를 보였으나 통계적인 유의성은 없었다.