Low Grade Astrocytoma- Need Postoperative Radiotherapy or Not ?

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The precise role of radiotherapy for low grade gliomas including the optimal radiation dose and timing of treatment remains unclear. The information given by a retrosepctive analysis may be useful in the design of prospective randomized studies looking at radiation dose and time of surgical and radiotherapeutic treatment.

The records of 56 patients (M:F=29:27) with histologically verified cerebral low grade gliomas (47 cases of grade 1 or 2 astrocytomas and 9 oligodendrogliomas) diagnosed between 1979 and 1989 were retrospectively reviewed. The extent of surgical tumor removal was gross total or radical subtotal in 38 patients (68%) and partial or biopsy only in the remaining 18 patients (32%). Postooperative radiation therapy was given to 36 patients (64%) of the total 56 patients with minimum dose of 5000 cGy (range=1250 to 7220 cGy).

The 5-and 10-year survival rates for the total 56 patients were 44% and 32% respectively with a median survival of 4.1 years. According to the histologic grade the 5- and 10-year survivals were 52% and 35% for the 24 patients respectively with grade I astrocytomas compared to 20% and 10% for the 23 patients with grade II astrocytomas. Survival of oligodendroglioma patients was greater than those with astrocytoma (65% vs 36% at 5 years), and the difference was also remarkable in the long term period of follow up (54% vs 23% at 10 years). Those who received high-dose radiation therapy ($\geq$ 5400 cGy) had significant better survival than those who received low-dose radiation ($<$ 5400 cGy) or surgery alone ($p<0.05$). The 5- and 10-year survival rates were, respectively 59% and 46% for the 23 patients receiving high-dose radiation, 36% and 24% for the 13 patients receiving low-dose radiation, and 35% and 26% for the 20 patients with surgery alone. Survival rates by the extent of surgical resection were similar at 5 years (46% vs 41%), but long term survival was quite different ($p<0.01$) between total/subtotal resection and partial resection/biopsy (41% and 12%, resepctively).

Previously published studies have identified important prognostic factors in these tumor: age, extent of surgery, grade, performance status, and duration of symptoms.

But in our cases statistical analysis revealed that grade I histology ($p<0.025$) and young age ($p<0.001$) were the most significant good prognostic variables.

Key Words: Brain tumor, Low-grade glioma, Radiotherapy

INTRODUCTION

Low-grade gliomas constitute about 15 to 20% of all intracranial gliomas, they are the astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas[1]. These tumors typically arise during the first four decades of life and have a long-term survival of only 15% in a recently reported series of nearly 500 patients[2]. To date their optimal treatment and its timing remains controversal. It is essential for understanding the pathology, natural history, and modern treatment option to make a rational decision regarding the proper course of treatment for a patient with low-grade glioma. A number of retrosepctive studies have suggested a beneficial role for radiotherapy in low grade astrocytomas incompletely resected at surgery[2~5]. In low grade oligodendrogliomas, the role of radiotherapy is less clear[6~8].

Methods for the management of supratentorial low-grade glioma patients range from obervation alone to surgery plus postoperative radiation. There is not a role for the routine use of postoperative radiation therapy in younger patients with pilocytic astrocytomas. In contrast, postoperative

radiation therapy appears to improve survival, particularly in adults with ordinary astrocytomas and oligodendrogliomas. Treatment decisions are primarily depending on patient age and histologic type.

The 5-year survival of patients with supratentorial low-grade astrocytomas who undego surgery alone is about 20%, and for patients who receive postoperative radiotherapy 5-year survival appears to be about 50%. However, in several series, this apparent benefit was limited only to the subgroup of adult patients[2,9]. The 5-year survival with surgery alone versus surgery plus postoperative radiotherapy was 31% vs 85% in one series of oligodendroglioma patients who had subtotal resection[10] and 85% vs 100% in another series where all oligodendroglioma patients had gross total removal[7]. There are also a few series in which postoperative radiotherapy for astrocytomas or oligodendrogliomas has not improved survival over surgery alone[6].

Interpreting the available low-grade glioma radition therapy literature is difficult. Proponents of observation argue for the benign course of the disease, as well as both the lack of proven benefit and the potential morbidity of therapy, particularly radiation therapy[11,12]. Those favoring intervention cite the poor long-term survival time[2], the propensity of ordinary low-grade gliomas to grow or to undergo malignant transformation over time, and the reduced morbidity of modern radiation therapy[13].

The series presented herein is limited to patients with supratentorial low grade gliomas treated with megavoltage postoperative irradiation. Nearly all patients had CT scans at the time of diagnosis and in follow-up. The survival rates were obtained according to various factors, and statistical analyses of those data were performed to reveal the prognostic variables.

MATERIAL AND METHODS

1. Patient Characteristics

Between January 1979 and December 1989, total 56 patients with supratentorial low-grade gliomas underwent surgery and 36 patients of them were treated postoperative radiotherapy at Kyung Hee University Hospital (Table 1). The 29 males and 27 females ranged in age from 6 to 71 years (median age, 42 years). All patients underwent open craniotomy. The extent of surgical tumor removal was gross total or radical subtotal in 38 patients (68%) and partial or biopsy only in the remaining 18 patients (32%). Postoperative radiation therapy was given to 36 patients (64%) of the total 56 patients, with minimum dose of 5000 cGy (range 1250 to 7220 cGy). Location and size of the primary tumor were detemined by a review of the preoperative CT scan and of the operative report. The sites of involvement are commonly included the frontal, temporal, and parietal lobes. Enhancement on the preoperative CT scan after the injection of contrast media was present in 23 patients (41.1%), absent in 29 (51.8%), and not done or unkown in the remaining 4 (7.1%).

Table 1. Patient Characteristics With Low Grade Astrocytomas (N=56)

Parameter	Number	Percent
Age (years)		
0~20	18	32.1
21~40	22	39.3
41~71	16	28.6
Sex (M:F)	29:27	52:48
Tumor location		
Frontal	25	44.6
Temporal	18	32.1
Parietal	9	16.1
Occipital	4	7.1
CT enhancement		
yes	23	41.1
no	29	51.8
not done	4	7.1
Extent of surgery		
Total/subtotal	38	67.9
Partial/biopsy	18	32.1
Radiation therapy		
Over 54 Gy	23	41.1
less 54 Gy	13	23.2
No	20	35.7
Histology		
grade I astrocytoma	24	42.9
grade II astrocytoma	23	41.1
oligodendroglioma	9	16.0
Survival status		
death from tumor	32	57.1
death from other	4	7.2
alive without tumor	12	21.3
alive with tumor	4	7.2
lost	4	7.2

2. Pathology

All pathologic material was reviewed by a pathologist, who was unware of the patient's clinical course. Histologic grading basically followed the Daumas-Duport's method[14] which includes a

summed score based on the presence or absence of four equally weighted histologic features-nuclear abnormalities, mitoses, vessel proliferation, and necrosis. By definition, grade I tumors have none of these four features, whereas grade II tumors have one feature, usually nuclear abnormalities. The distribution of grade in the study population were as follows; grade I astrocytomas-24 patients (43%), grade II astrocytomas-23 patients (41%), oligodendroglioma-9 patients (16%).

3. Postoperative Radiotherapy

Total 36 patients of 56 operation were treated with Co-60 machine. The irradiated volume was the whole brain with a partial brain boost in 7 patients (19%), and a partial brain field only in the remaining 29 patients (81%). The total dose, calculated at the midplane for opposed treatments or at the intersection of field centers for non-opposed treatments, ranged from 1250 to 7220 cGy (median dose, 5000 cGy). Two-thirds of the patients received a total dose of $\geq$ 5400 cGy (the high-dose group), whereas the remaining third received $<$ 5400 cGy (the low-dose group).

4. Survival Analysis

Survival was determined from the initiation of surgical and/or radiotherapeutic treatment. Follow-up information was available on 52 patients, with a range in follow-up time of 2.5 to 11.8 years, and a median of 5.5 years, for 16 patients who remain alive. Survival curves were estimated based on the method of Kaplan and Meier. The differences between subgroups were analyzed statistically by means of the log-rank test. Multivariate analysis of survival was not attempted due to the limited size and number of deaths in the study population.

RESULTS

1. Survival

The 5-and 10-year survivals for the total 56 patients were 44% and 32%, respectively, with a median survival of 4.1 years. Although, prognosticaly, the nonirradiated patients (n=20) represented a more favorable subgroup than those who received postoperative radiation therapy (n=36), the 5-year survival was 52% for those with radiation therapy and only with 30% for those with surgery alone ($p<0.05$) shown in Fig. 1.

Fig. 2 shows the survival curves for patients with the various histologic grading. They are significantly different ($p<0.025$) with an estimated 5-year survival of 52% for the 24 patients with grade I astrocytomas, 20% for the 23 patients with grade II astrocytoma, and 65% in the 9 patients with oligodendroglioma. Survival of oligodendroglioma patients was greater than those with astrocytoma (65% vs 36% at 5 years), and the difference was also remarkable in the long term period (54% vs 23% at 10 years).

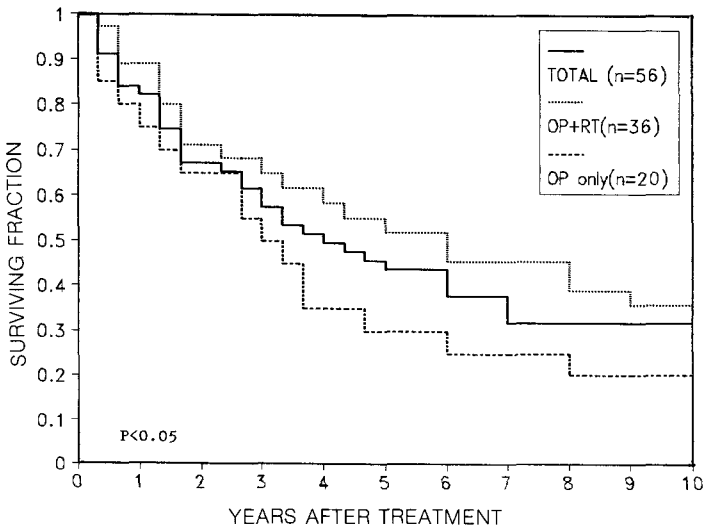

Fig. 1. Survival curves for patients with low grade glioma who were irradiated and those who were not after initial surgery.

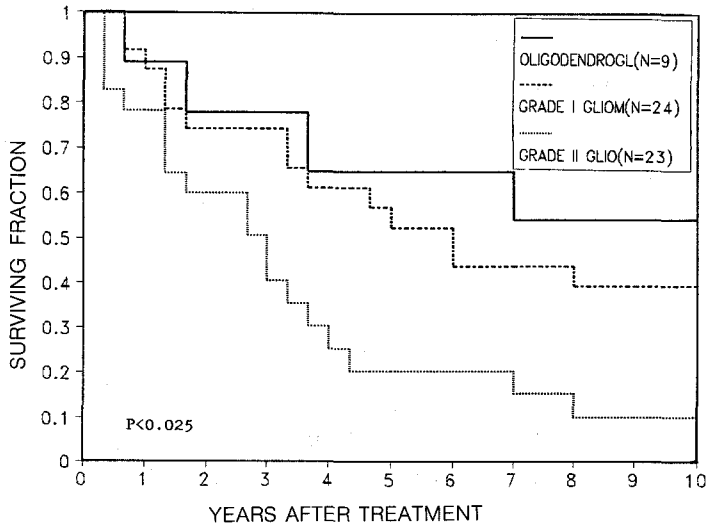

Fig. 2. Survival curves for patients with tumors classified by histologic grade.

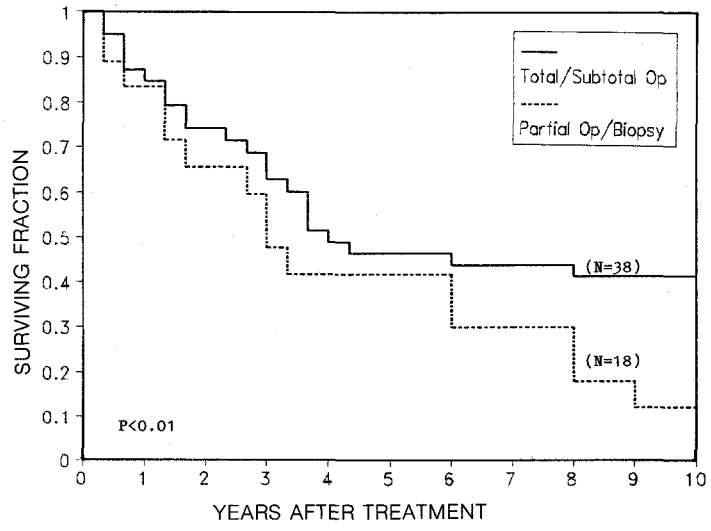

Fig. 3. Survival curves for patients with low grade glioma by the extent of surgical tumor removal.

Survival rates according to the extent of surgical resection were similar at 5 years (46%vs 41%), but long term survival was quite different ($p<0.01$) between total/subtoal resection and partial resection/biopsy (41% and 12%, resepctively) in Fig. 3.

Those who received high-dose radiation therapy ($\geq$ 5400 cGy) had significant better survival times than those who received low-dose radiation ($<$ 5400 cGy) or surgery alone ($p<0.05$). The 5-and 10-year survival rates were, respectively 59% and 46% for the 23 patients receiving high-dose radiation, 36% and 24% for the 13 patients receiving low-dose radiation, and 35% and 26% for the 20 patients with surgery alone (Fig. 4). Statistical analysis revealed that grade I histology ($p<0.025$) and young age of patient ($p<0.001$) were the most significant prognostic variables associated with a good survival shown in Fig. 5.

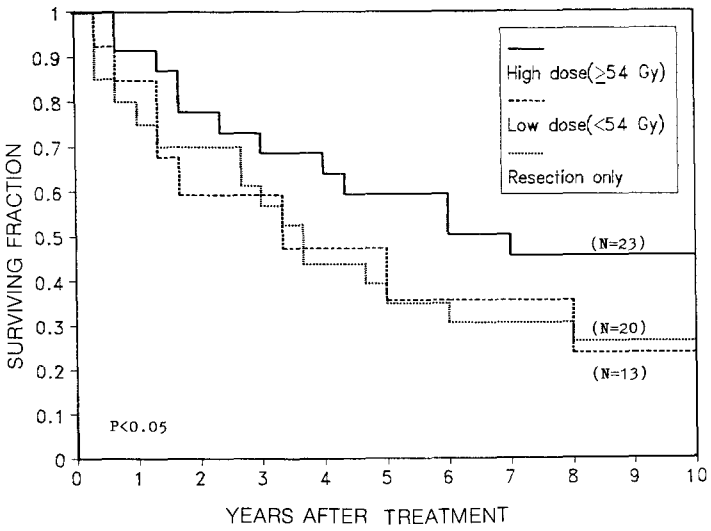

Fig. 4. Survival curves for patients with low grade glioma by the amount of postoperative radiation therapy received.

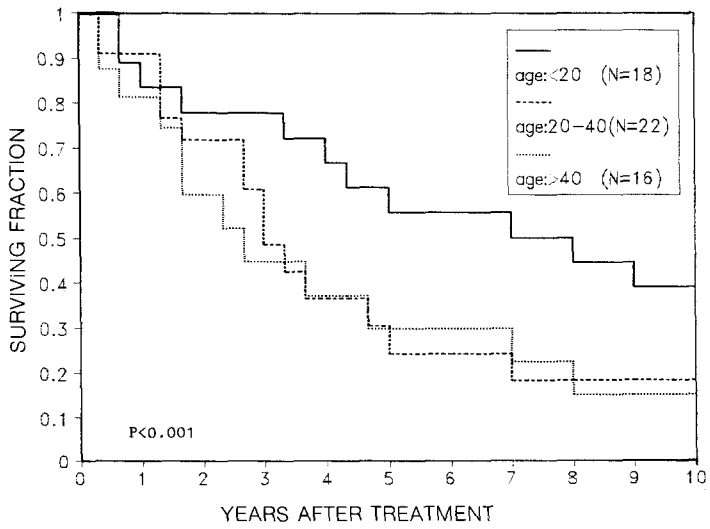

Fig. 5. Survival curves for patients with tumor by age.

2. Patterns of Failure and Outcome

Sixteen of the 56 patients remain alive, four with disease progression and 12 without evidence of disease. According to histologic grade, 4 patients with oligodendrogliomas are alive and disease free (follow-up 2.5 to 9.8 years), 6 of 24 patients with grade I astrocytomas, and 2 of 23 patients with grade II astrocytomas. Thirty-six patients have died, 32 of known disease progression, and 4 from other causes unrelated to their low-grade gliomas. Overall, 36 patients had documented treatment failure, based on either neurologic or CT scan progression. For the 36 patients in whom treatment failure occurred, the median and 5-year survival were 24 months and 23%, respectively. Three patients were retreated with additional radiation therapy. Their survival times following retreatment were 6, 12, and 15 months. Twenty-one of the 36 patients with treatment failures had preoperative and postoperative

Table 2. Low Grade Glioma: 5-year Survival After Surgery Alone Compared With Postoperative Radiotherapy

Author	Year	No. of Patients (S/S+RT)	5-year survival(%) S Alone	S+RT
Bouchard	1966	147(42/105)	26	49
Stage	1974	45(17/28)	20	42
Leibel	1975	108(37/71)	19	46
Fazekas	1977	47(15/32)	13	41
Omsted	1978	15(5/10)	0	50
Laws	1984	241(167/74)	34	49
Garcia	1985	80(23/57)	21	50
Soffietti	1989	85(53/32)	28	25
Shaw	1989	126(19/117)	32	68
Hong	1992	56(20/36)	30	52

CT scans, and simulation and portal films available to determine failure patterns. All 21 patients developed disease progression within their radiation portals.

DISCUSSION

About one half of brain tumors are gliomas, 25% of which are low-grade astrocytomas. Cerebral lesions are more common in adults, whereas lesions at other sites occur typically during the first 3 decades[15]. Astrocytomas arise from astrocytes that display different degrees of cytologic maturation[16]. They are variously classified according to grade or histologic subgroups, currently four grading systems are in common use[11,17~19]. Patients with well-differentiated or grade 1 tumors have pilocytic astrocytomas, whereas those with anaplastic or grade 2 and 3 tumors have ordinary astrocytomas, oligodendrogliomas. or mixed oligoastrocytomas. New methods of identifying prognostically favorable or unfavorable groups of low-grade gliomas, such as bromodeoxyuridine labelling, DNA ploidy analysis, and cytogenetic or molecular genetic studies, appear promising[20~22]. Neuro-imaging studies of the brain in patients with low-grade gliomas vary considerably depending on the underlying pathology. MRI of low-grade gliomas typically shows a defined area of increased signal on T2-weighted images corresponding to the hypodense as well as enhancing areas on CT[23]. This characteristic finding frequently makes MRI superior to CT for radiation therapy treatment planning.

Recent studies have divided the low-grade gliomas into two distinct groups, the pilocytic astrocytomas and the ordinary astrocytomas. Patients with pilocytic astrocytomas enjoy 10-year survivals of 80% or more following complete or even incomplete excision. On the other hand, ordinary astrocytomas are associated with 10-year survivals of 20%. The favorable pilocytic astrocytomas are well circumscribed, noninfiltrative tumors ameanable to cure with complete excision. Unfavorable ordinary astrocytomas are poorly defined, infiltrative, and incurable with even complete excision, as evidenced by the 11% 10-year survival in surgically treated patients[24].

One of the earliest studies was that of Levy and Elvidge[25], who reviewed 176 cases and found that germistocytic type of astrocytoma has a poorer prognosis than that of other variants, and that patients with cerebellar astrocytomas did better than those with cerebral lesions, even in the face of incomplete removal. Several years later, the importance of analyzing radiotheraputic outcome by histologic type was recognized by Bouchard[26], who reported one half of radiated supratentorial astrocytoma and oligodendroglioma patients were 5-year survivors. Although he also described the favorable outcome of patients with cerebellar tumors of the pilocytic type, there was no recognition of a favorable cerebral counterpart. In authors' results according to histologic grade the survivals were significantly different ($p<0.025$) with an estimated 5-year survival of 52% of patients with grade I astrocytomas, 20% of those with grade II astrocytomas, and 65% for oligodendrogliomas. It was similar to that recent series have reported the survival of radiated patient with supratentorial low-grade gliomas by histologic type, with 5-year results as follows; 57% for mixed oligoastrocytoma[27], 57% to 100% for oligodendrogliomas[7,15,28], and 50% for ordinary astrocytomas[9,10].

The results of surgery alone for patients with supratentorial low-grade ordinary astrocytomas were variable ranges from 0 to 34%, typically about 20% in 5-year survival rates. The result of surgery plus postoperative radiation therapy in patients who underwent subtotal resection or biopsy; their 5-year survival rate range from 28% to 76% and average about 50%. Several series have noted a significantly improved survival of patients with ordinary astrocytomas receiving postoperative radiation therapy, particularly in adults as compared with children. Garcia et al[9] reported that improved survival with radiation therapy was limited to adults at or older than 30 years of age. In contrast, Shaw's results were the benefits not only in

adults at or older than 35,but also in patients less than 27 years of age[29]. The majority of previous 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 survival ranging from 28% to 76%. In our cases although the non-irradiated patients represented prognostically a more favorable subgroup than those who received postoperative radiation therapy, the 5-year survival was 52% for those with radiation therapy compared to 36% for those with surgery alone ($p<0.05$).

The low-grade gliomas are a diverse group of brain tumors in which the outcome for patients receiving radiotherapy following subtotal removal or biopsy is primarily dependent upon histologic type[30]. The estimated 5- and 10-year survivals for the total group of 49 patients in their series were 62% and 14%. However, by histologic type, the estimated 5-year survival was 100% for patients with pilocytic astrocytomas, 83% for those with mixed oligoastrocytomas or oligodendrogliomas, and 40% in patients with ordinary astrocytomas. Shaw et al[29] reported multivariate analysis in 167 patients with low-grade pilocytic astrocytomas, ordinary astrocytomas, and mixed oligoastrocytomas showed histologic type to be the most significant prognostic variable. The 41 patients with pilocytic astrocytomas had a 5-year survival rate of 85%, compared with 51% for the 126 patients with ordinary astrocytomas or mixed oligoastrocytomas. There was no improvement in survival with postoperative radiation therapy for the overall group of 41 patients with pilocytic astrocytomas. In the patients with ordinary astrocytomas and mixed oligoastrocytomas, the survival distributions were similar (52% 5-year survival rate) for the 23 patients who had gross total resection and the 103 with subtotal resection biopsy. It was concluded that postoperative radiation therapy should be routinely given to patients with ordinary astrocytomas and oligoastrocytomas, regardless of the extent of surgical resection. However, other series have shown a survival advantage to gross total resection and question the value of postoperative radiation[31].

The major issue for the patients with an unfavorable low-grade glioma not whether to irradiate, but rather how much radiation to give. Shaw et al[21] have demonstrated in a careful retrospective analysis that postoperative radiotherapy significantly prolongs the survival of patients with supratentorial low-grade nonpilocytic astrocytoma. The 10-year survival with dose of 53 Gy or more given postoperatively was 40% in a recent series, with similar survival reported in other modern radiotherapy series. Several recent series have addressed the issues of treatment field and total dose selection for patients receiving radiation therapy for supratentorial low-grade gliomas, since the survival distribution of patients receiving partial brain versus whole brain radiation are similar, partial brain treatment fields, encompassing the tumor with a 2-cm margin, should be used in order to minimize the likelihood of long-term radiation sequele[30]. Failure pattern analyses in radiated low-grade glioma patients support this approach[13,30]. Selection of total dose is a more controversal issue, but at present, doses in the range of 45 to 65 Gy may be considered reasonable and are supported by the literature. Rutten et al[32] 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. In contrast, in the 90 patients studied by Fazekas[3], 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. In one Mayo Clinic series, the 5-year survival rate was 68% with dose $>$ 53 Gy compared with 47% of doses $<$ 53 Gy and 32% undergoing surgery alone[29]. At our presented cases those who received high-dose radiation therapy ($\geq$ 5400 cGy) had significant better survival times than those who received low-dose of radiation ($<$ 5400 cGy), or surgery alone ($p<0.05$). The 5-and 10-year survival rates were, respectively 59% and 46% for the 23 patients receiving high-dose radiation, 36% and 24% for the 13 patients receiving low-dose radiation, and 35% and 26% for 20 patients with surgery alone as similar to Mayo Clinic series.

The ideal volume to treat patients with low-grade gliomas has not been defined, although available data from this and previous studies suggest a localized field may be optimal. Perhaps of more importance, analysis of failure patterns in 21 of the 36 patients with treatment failures revealed all recurrences to be within the radiation portals. Other gliomas series have either failed to show a survival difference between localized versus whole brain radiation[28] or have demonstrated a poorer survival with the use of whole brain radiation[10]. Management decision in children must be individualized, reserving radiation therapy for

patients with symptomatic residual tumor following incomplete resection in a setting where close follow-up with radiation given at a time of symptomatic, radiographic, or neurologic progression is felt to be an unsafe strategy[33].

The previous studies have been retrosepctive analyses in which the irradiated and nonirradiated groups of patients have not been similar in important characteristics (e.g., age, performance status). The pathological classification of lesions has been different. The location and size of the tumors have been different, and the extent of operation has not been uniform (biopsy vs complete resection). Finally, the parameters of the treatment being tested have not been standarized with respect to total dose, duration of therapy, field size, etc.

The role of postopoerative radiotherapy in the treatment of supratentroiral oligodendrogliomas remains also controversal. For patients with oligodendrogliomas of all grades who underwent less than gross total resection, better 5-year survival (72%) was associated with the addition of postoperative radiation therapy in doses over 50 Gy[34]. Similar results have been also noted in three other series[7,8,35]. In contrast, three additional series reported no evidence of benefit to postoperative radiation therpy in patients with oligodendrogliomas[28,36,37]. In our small cases of 9 patients with postoperative radiotherapy the 5-year survival was 67% similar to other results

The differential diagnosis in a patient who has received radiotherapy for a low-grade glioma and subsequently develops progression based on neurologic examination and CT or MRI scans includes tumor versus radionecrosis[38]. Although it is impossible to distinguish tumor from radiation effect or frank radionecrosis on the basis of CT or MRI scans, the positron emission tomography (PET) may differentiate between tumor and necrosis[39]. Malignant transformation, a typical feaure of ordinary astrocytomas, is parituclarly common in low-grade tumors of germistocytic type[18].

Ultimately, the majority of observed, operated, or radiated patients with supratentorial low-grade gliomas will develop progression or regrowth of tumor. A variety of treatment options remain for patients with recurrent supratentorial low-grade gliomas. These include reoperation, reirradiation, interstitial implantation, radiosurgery, chemotherapy, and P-32 instillation for recurrences. Therefore, reoperation may be therapeutic in the minority of instances when neurologic and CT and MRI "progression" are due to radionecrosis. Leibel et al[40] have reported that patients who have resection of radionecrotic brain tissue following interstitial implantation of high-grade gliomas are neurologically improved and may enjoy a prolonged survival. The role of radiation therapy in the retreatment of brain tumors is not well established, but reirradiation of patients with late recurrence of brain tumors may offer neurological improvement and prolonged survival without excessive risk of radionecrosis by precise treatment planning[41]. We retreated three patients with additional radiation therapy who had recurrent tumors, their survival times following retreatment were 6, 12, and 15 months. Interstitial irradiation has been used for the treatment of small, relatively circumscribed tumors; 5-year survival rates have ranged from 44% to 78%[42]. These survival rates are similar to the more favorable results reported for surgery plus postoperative radiation theapy. More recently, the results of stereotactic radiation therapy using doses of 16 to 50 Gy in one or two fractions for supratentorial low-grade gliomas were reported[43]. As demonstrated by CT complete or partial response was observed in the majority of patients (12/14) apparently without damaging surrounding norml tissues.

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= 국문초록 =

저분화 성상세포종-수술후 방사선치료가 필수적인가 ?

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저분화 성상세포종에 대한 방사선 치료의 역할이나 적정 방사선량, 치료시기등은 논란의 여지가 많다. 후향적 분석결과로 얻은 정보는 방사선량이나 외과적 또는 방사선 치료에 의한 시술시기 등의 관점에서 전향적인 연구계획을 세우는데 도움이 된다.

저자들은 1979년부터 1989년까지 경희대학병원에서 수술로 확진된 저분화 성상세포종 환자중 천막하부를 제외한 총 56(남 : 여=29:27)명에 대한 치료결과를 후향적으로 분석하였다. 수술절제범위는 38명(68%)에서 근치수술하였고, 18예(32%)는 부분절제 또는 조직생검만 시행하였다. 총 56예 중 수술후 방사선치료를 받은 환자는 36명(64%)이었고, 방사선량은 최저 5000 cGy를 국소조사하였다. 총 56예의 5년 및 10년 생존율은 각각 44%와 32%였으며, 중간 생존기간은 4.1년이었다. 조직소견에 따른 5년 및 10년 생존율은 grade I(23명)이 각각 52%와 35%이고, grade II(23명)는 20%와 10%였다. Oligodendroglioma 환자는 성상세포종보다 생존율이 높았으며(5년 생존율=65% vs 36%)장기간 생존율은 각각 54%와 23%로 현저한 차이가 있었다. 다량의 방사선치료를 받은 (≥54 Gy)환자는 소량의 방사선(<54 Gy)이나 수술만 받은 환자보다 5-년 및 10-년 생존율이 높았다($p<0.05$). 수술범위에 따른 5년 생존율은 46%와 41%로 비슷하였으나, 10년 생존율은 근치수술한 경우가 41%, 부분절제 또는 조직생검한 경우는 12%로 현저한 차이가 있었다($p<0.01$).

과거 여러 저자들의 연구에 의하면 환자나이, 수술범위, 방사선치료유무, 악성도, 증상 발현기간, 수행능력 상태등이 성상세포종의 중요 예후인자라고 보고하였으나, 본 저자들의 예에서는 grade I조직소견($p<0.025$)과 환자나이($p<0.001$)가 가장 중요한 예후인자였으며 향후 무작위화한 전향적인 연구가 필요할 것으로 생각된다.