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External Beam Radiotherapy in the Management of Low Grade Astrocytoma of the Brain

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Purpose: This study was designed to evaluate the effectiveness of postoperative radiotherapy for patients with low-grade astrocytomas and to define an optimal radiotherapeutic regimen and prognostic factors.

Materials and Methods: A total of 69 patients with low-grade astrocytomas underwent surgery and postoperative radiotherapy immediately following surgery at our institution between October 1989 and September 2006. The median patient age was 36 years. Forty-one patients were 40 years or younger and 28 patients were 41 years or older. Fourteen patients underwent a biopsy alone and the remaining 55 patients underwent a subtotal resection. Thirty-nine patients had a Karnofsky performance status of less than 80% and 30 patients had a Karnofsky performance status greater than 80%. Two patients were treated with whole brain irradiation followed by a coned down boost field to the localized area. The remaining 67 patients were treated with a localized field with an appropriate margin. Most of the patients received a dose of 50~55 Gy and majority of the patients were treated with a dose of 54 Gy.

Results: The overall 5-year and 7-year survival rates for all of the 69 patients were 49% and 44%, respectively. Corresponding disease free survival rates were 45% and 40%, respectively. Patients who underwent a subtotal resection showed better survival than patients who underwent a biopsy alone. The overall 5-year survival rates for patients who underwent a subtotal resection and patients who underwent a biopsy alone were 57% and 38%, respectively ($p<0.05$). Forty-one patients who were 40 years or younger showed a better overall 5-year survival rate as compared with 28 patients who were 41 years or older (56% versus 40%, $p<0.05$). The overall 5-year survival rates for 30 patients with a Karnofsky performance status greater than 80% and 39 patients with a Karnofsky performance status less than 80% were 51% and 47%, respectively. This finding was not statistically significant. Although one patient was not able to complete the treatment because of neurological deterioration, there were no significant treatment related toxicities.

Conclusion: Postoperative radiotherapy following surgery is a safe and effective treatment for patients with low-grade astrocytomas. The extent of surgery and age were noted as significant prognostic factors in this study. However, further effective treatment might be necessary in the future to improve long-term survival rates.

Key Words: Radiotherapy, Low-grade astrocytoma

Introduction

Low grade glioma is a heterogeneous group of central nervous system neoplasm that grows slowly, infiltrates widely, and may transform into fast growing high grade tumors in some instances.[1,2] Often referred to as benign, these tumors typically arise during the first five decades of life and have a long term survival of only 15% in a reported series of nearly 500 patients.[3]

Complete surgery is the treatment of choice, but, in many cases, the extent of surgery is limited by the involvement of eloquent and essential parts of the brain. Radiation therapy is a frequent procedure in the management of low grade astrocytoma.[4~6] The effectiveness of radiotherapy for low grade astrocytoma is controversial and the questions of dose response relationship and the optimal radiation dose to be delivered in these tumors are under discussion.

No prospective randomized studies comparing adjuvant postoperative radiotherapy to delayed radiotherapy at the time

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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.[7~9] The five year survival rate of patients with low grade astrocytomas who underwent surgery alone is approximately 20%. In contrast, five year survival rate for patients who received postoperative radiotherapy appears to be approximately 50%. However, this apparent benefit was limited only to the specific subgroup of patients in several studies.[3,10] There are also few series in which postoperative radiotherapy for astrocytomas has not improved survival over surgery alone.[11,12]

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

Materials and Methods

Total of sixty nine patients with low grade astrocytomas underwent surgery and postoperative radiotherapy immediately following surgery at our institution between October, 1989 and September, 2006. Two patients with pilocystic astrocytoma treated with radiotherapy were excluded from this study. The median age was 36 years with range of 19 to 73 years. Forty one patients were 40 years or younger and 28 patients were 41 years or older. Forty patients were male and 29 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 58 patients had CT or MRI to evaluate the residual tumor.

All of the patients underwent open craniotomy for histological confirmation. Of those patients, 14 patients underwent biopsy alone and remaining 55 patients had subtotal resection. Thirty nine patients had less than 80% of Karnofsky performance status and 30 patients had greater than 80%. The tumor was located predominantly in parietal lobe (34 patints), temporal lobe (25 patients) and frontal lobe (10 patients). Distribution of patients according to characteristics is shown in Table 1.

At our institution, treatment policy for low grade astrocytoma 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. Linear accelerator producing 6 MV photons was employed to treat patients. Two patients were treated with whole brain irradiation followed by coned down boost field to localized area. Remaining 67 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 delivered five times a week with 1.8 or 2 Gy per fraction, once a day. None of the patients were treated with hyperfractionation. The distribution of patients according to delivered dose and extent of surgery is shown in Table 2. One patient received less than 40 Gy because of termination of the radiotherapy with

Table 1. Patients Characteristics

Characteristics	No. of patients
Age	
Range	19~73
Median	36
40 or younger	41
>40	28
Sex	
Male	40
Female	29
Extent of surgery	
Subtotal resection	55
Biopsy alone	14
Performance status	
KPS*<80	39
KPS>80	30
Predominant location	
Parietal	34
Temporal	25
Frontal	10

*karnofsky performance status

Table 2. Distribution of Patients According to Delivered dose

Dose	Subtotal resection	Biopsy alone
<40 Gy	1	
40~45 Gy	2	
45~50 Gy	4	1
50~55 Gy	48	11
>55 Gy		2
Total	55	14

progression of neurological deterioration. Most of the patients received 50～55 Gy and majority of them were treated with 54 Gy. Two patients treated with whole brain irradiation followed by coned down boost field received 46 Gy to whole brain and 10 Gy to boost field with total of 56 Gy.

All of the patients were followed by radiation oncologist or their referring physicians following the completion of radiotherapy. Post- treatment CT or MRI was usually done 1 month and 6 months after the therapy to evaluate progression of the disease. Although 3 patients were treated with external beam reirradiation for documented recurrence, reirradiation results were not analyzed in this study. Survival was calculated from day one of radiotherapy and statistical comparison was made by Chi square test.

Results

The overall 5-and 7-year survival rates for entire 69 patients were 49% and 44%. Corresponding disease free survival rates were 45% and 40%, 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.[3,9)]

Patients who underwent subtotal resection showed better survival than those who underwent biopsy alone. The overall 5 year survival rates for patients with subtotal resection and patients with biopsy alone were 57% and 38%, respectively (Fig. 2). This was statistically significant with p-value less than 0.05. Also age at the time of presentation was examined as prognostic indicator. Forty one patients were 40 years or younger and 28 patients were 41 years or older. Forty one patients who were 40 years or younger showed better overall 5-year survival rate, compared with 28 patients who were 41 years or older (56% vs 40%, $p < 0.05$). This result is shown in Fig. 3.

Karnofsky performance status which is known as prognostic variable was evaluated also. The overall 5 year survival rates for 30 patients with greater than 80% of Karnofsky performance status and 39 patients with less than 80% were 51% and 47%, respectively. This was not statistically significant in our study. Although one patient was not able to complete the treatment because of neurological deterioration, there was no

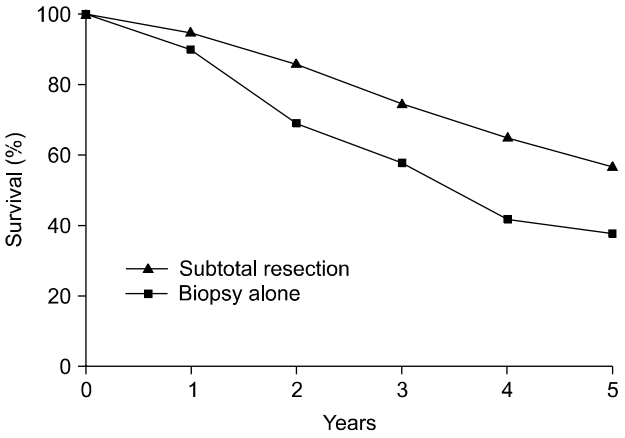

Fig. 2. Overall survival rates according to extent of surgery.

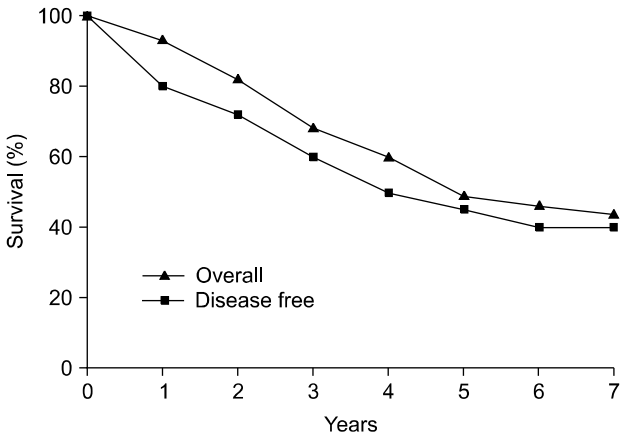

Fig. 1. Overall and disease free survival rates.

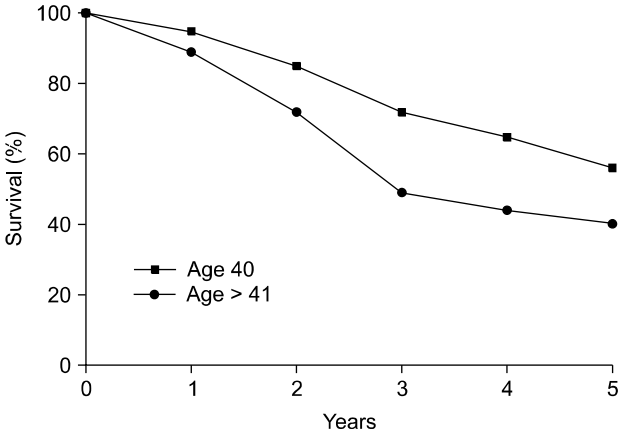

Fig. 3. Overall survival rates according to age.

significant treatment related toxicities.

Discussion and Conclusion

Different policies in general are pursued in the management of low grade astrocytomas after surgery or histological verification. The wait and watch policy is followed by some, and they initiate retreatment usually by surgery followed by radiotherapy on progression of the disease.[13] In histologically verified high grade astrocytoma, there is clear evidence from randomized studies that radiation prolongs survival.[14,15] However in low grade tumors, there is suggestion of survival benefit in only some retrospective studies particularly in patients with incompletely resected tumors.[3,16]

In our study, the overall 5-and 7-year survival rates for entire 69 patients were 49% and 44%. Corresponding disease free survival rates were 45% and 40%, respectively. Shaw et al. reported 40% of 5 year survival rate for low grade astrocytoma patients treated with postoperative radiation therapy.[17] Several studies also documented similar survival rates to our studies, ranging from 32% to 67%.[10,18]

Few studies compared moderate and high dose localized irradiation, although optimal radiation dose for treating low grade astrocytomas has yet to be defined. Rutten et al. reported that none of 9 patients with subtotally removed grade 2 astrocytomas who received >50 Gy were long term survivors compared to 11 of 16 patients who received <50 Gy.[19] In contrast, in the 90 patients studied by Fazekas, a gradual improvement in local control was noted at 20, 56%, and 69%, with equivalent dose of >850 ret, >1,150 ret, and >1,450 ret, respectively.[20] In randomized studies, however, no significant difference in long term survival was found between patients treated with low dose and high dose radiation.[21] Comparison of different doses of radiation was not made in this report, because majority of patients in this study were treated with 5,000~5,500 cGy.

Extent of surgery has been documented as prognostic variables in patients with low grade astrocytomas treated with surgery and postoperative radiotherapy in several studies.[22,23] Shaw et al. however reported no significant difference between patients treated with subtotal resection and biopsy alone followed by immediate postoperative radiotherapy.[17] In this study, there was significant difference in 5-year survival rate in patients treated with subtotal resection and irradiation (57%), compared with those treated with biopsy alone and irradiation (38%). Therefore we might suggest that resection should be attempted as much as possible to avoid major complications based on the result in our study. Although other authors reported a better survival for patients >50 years,[24] younger age (<40 years) was found to be a prognostic factor for survival by Shaw et al.[6] Forty one patients who were 40 years or younger showed better overall 5 year survival rate, compared with 18 patients who were 41 years or older (56% vs 40%) in this study. However it is not clear whether patients with low grade astrocytomas should be treated with different policy depending on age at the time of presentation. Also Plathow et al. showed better disease free survival in patients with Karnofsky performance status greater than 80%.[25] In our study, performance status was not a significant predictor of outcome.

In conclusion, postoperative radiotherapy following surgery is safe and effective treatment for patients with low grade astrocytomas. Extent of surgery and age were noted to be significant prognostic factors in our study. However, further effective treatment might be necessary in the future to improve long term survival rates.

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국문초록

뇌 성상세포종 환자의 외부 방사선치료

한양대학교 의과대학 치료방사선학교실

전 하 정

목 적: 뇌 성상세포종 환자에서 수술 후 외부 방사선치료의 효과를 평가하고 최적의 방사선 치료 방법 및 예후 인자를 알아보고자 하였다.

대상 및 방법: 1989년 10월부터 2006년 9월까지 본원에서 수술 후 방사선치료를 받은 69명의 뇌 성상세포종 환자를 후향적으로 분석하였다. 환자 나이의 중앙값은 36세이었다. 41명은 40세 이하이었으며 28명은 41세 이상이었다. 14명의 환자는 조직 검사만을 시행하였고 55명의 환자는 아절제술을 시행하였다. 카르노프스키 수행 점수는 39명은 80%미만 이었고 30명은 80%이상 이었다. 2명의 환자는 뇌전체를 조사받은 후 축소 조사야로 치료받았고 67명의 환자는 적당한 여유를 두고 부분조사를 시행하였다. 대부분의 환자는 5,000 내지 5,500 cGy를 조사받았다.

결 과: 전체 환자의 5년 및 7년 생존율은 40% 및 45%이었다. 5년 및 7년의 무병 생존율은 각각 45%와 40%이었다. 아절제술을 시행 받은 환자에서 조직검사만을 시행 받은 환자보다 보다 나은 생존율을 나타내었다. 아절제술을 시행 받은 환자와 조직 검사만을 시행 받은 환자의 5년 생존율은 각각 57% 및 38%이었다. 40세 이하 41명의 환자에서 41세 이상 28명의 환자보다 높은 5년 생존율을 보였다(56% vs 40%). 그러나 카르노프스키 수행 점수 80% 이상 환자와 80% 이하 환자의 5년 생존율은 통계적으로 유의한 차이를 나타내지 않았다(51% vs 47%). 비록 환자 한 명이 방사선 치료 중 치료를 중단 하였으나 유의한 방사선 치료에 의한 합병증은 관찰되지 않았다.

결 론: 뇌 성상세포종의 수술 후 외부 방사선 치료는 안전하고 효과적인 치료요법이었다. 수술의 정도 및 나이가 유의한 예후 인자임을 알 수 있었다. 그러나 성상세포종 환자의 장기 생존율을 높이기 위한 보다 효과적인 치료법이 향후 필요할 것으로 사료된다.

핵심용어: 방사선 치료, 뇌 성상세포종