Clinical and Radiological Prognostic Factors of Anaplastic Oligodendroglioma Treated by Combined Therapy

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Abstract

The clinical and radiological prognostic factors were investigated in 32 patients with newly diagnosed anaplastic oligodendroglioma treated by combined therapy using surgery, postoperative radiation therapy, and adjuvant chemotherapy between September 1994 and December 2002. Surgery aimed at total removal was followed by radiotherapy, and 3 weeks later by adjuvant chemotherapy repeated at 6- to 7-week intervals. Survival analysis showed that younger age, absence of preoperative headache, good postoperative Karnofsky Performance Status (KPS) score (≥ 80), and relatively small tumor volume ($< 50 \text{ cm}^3$) were predictors for longer survival in univariate analysis ($p < 0.05$). Age and good postoperative KPS score were independent prognostic factors in multivariate analysis ($p < 0.05$). Median survival was 58 months after diagnosis, and the 5-year survival rate was 49%.

Key words: anaplastic oligodendroglioma, clinical prognostic factor, combined therapy, radiological prognostic factor

Introduction

The term oligodendroglial tumor includes both oligodendroglioma and anaplastic oligodendroglioma according to the World Health Organization (WHO) classification of tumors. Oligodendroglial tumors account for about 3.2% of all central nervous system tumors, of which 28.2% are anaplastic oligodendrogliomas in Korea.²⁰⁾

The survival of patients is affected by the tumor location, histological grade, age at surgery, extent of surgical removal, tumor size, postoperative Karnofsky Performance Status (KPS) score, and timing of radiation therapy, based on univariate or multivariate analysis.^{5,7,11,19,24)} However, these findings were not based on only cases of pure anaplastic oligodendroglioma, but on cases of both oligodendroglioma (WHO grade II) and anaplastic oligodendroglioma (WHO grade III). The addition of adjuvant chemotherapy to surgery and postoperative radiotherapy, using nitrosoureas, gives better results with increased long-term survival in patients with malignant glioma.^{4,12)} The clinical and radiological prognostic factors in patients with newly diagnosed anaplastic oligodendroglioma treated by

combined therapy are unclear,¹²⁾ although the prognostic factors of anaplastic oligodendroglioma, which is related by pathology, chromosome, and genes, are known.^{3,9,10,17)}

The present study investigated patients with newly diagnosed anaplastic oligodendroglioma treated by combined therapy with surgery, postoperative radiotherapy, and adjuvant chemotherapy to identify the clinical and radiological prognostic factors.

Materials and Methods

I. Patient population

We evaluated 526 consecutive cases of gliomas treated at the Samsung Medical Center from September 1994 to December 2002. Among them, all patients treated under a diagnosis of oligodendroglioma (WHO grade II) or anaplastic oligodendroglioma (WHO grade III) were reviewed. This study included the patients with histologically-proven anaplastic oligodendroglioma treated by combined therapy. Secondary anaplastic oligodendroglioma (malignant transformation) was excluded, so only newly diagnosed anaplastic oligodendroglioma was included. The histological diagnosis was re-evaluated by two independent neuropathologists and graded according to the 2000

WHO classification.¹³⁾ Anaplastic oligoastrocytoma was identified if the tumor contained anaplastic features and geographically distinct astrocytic and oligodendroglial components, which were excluded. Cases of disagreement were re-reviewed by both pathologists until a consensus was reached.

II. Combined therapy

Combined therapy consisted of surgery, postoperative radiotherapy, and adjuvant chemotherapy, in that order. Surgery was performed at the authors' institution and the aim was complete tumor removal. Conventional external field radiation (1.8 Gy/day, 5 days/week, total dose 56–60 Gy) was initiated in the 3rd to 4th postoperative week. Chemotherapy was performed at the authors' institution. Three weeks after completing irradiation, patients began PCV chemotherapy (procarbazine, lomustine [CCNU], vincristine) with the following schedule: CCNU, 110 mg/m² orally on day 1; procarbazine, 60 mg/m² orally on days 8 through 21; and vincristine, 1.4 mg/m² i.v. on days 8 and 29. The PCV chemotherapy was repeated at 6- to 7-week intervals for six courses or until tumor progression.

When the recurrent tumors were detected, reoperation was performed if the tumor was surgically accessible, and then PCV chemotherapy was repeated for four courses.

III. Clinical and radiological parameters

The date of diagnosis and date of death (or last known status) were recorded for all patients. The following factors were evaluated for prognostic significance: age at diagnosis, sex, duration of symptoms, headache, seizure, neurological deficit at diagnosis, KPS score, tumor location, cystic change, enhancement on magnetic resonance (MR) imaging, midline shift, brain edema, contralateral involvement, calcification on computed tomography (CT), tumor volume, and extent of resection.

The presence of headache was recorded as the initial symptom and any history. The presence of seizure was recorded as a history of epilepsy prior to diagnosis, and occurrence of seizure at any time before or after the diagnosis of anaplastic oligodendroglioma. The KPS score was examined 1 week after operation (postoperative and preradiotherapy). The extent of tumor removal was assessed on the postoperative enhanced T₁-weighted MR image within 48 hours after surgery, and graded as gross total resection (no obvious residual tumor), subtotal resection (residual tumor <50%), or biopsy (residual tumor >50%). Subtotal resection and biopsy were grouped together as less than total resection for statistical evaluation. Tumor volume was calculated

as an ellipse. The horizontal (X), vertical (Y), and height (Z) dimensions were obtained and then used in the formula $(\pi/6)(XYZ)$ to find the volume. Tumor location was considered as the area or lobe in which the tumor was predominantly located. Other factors such as brain edema, calcification on CT, contralateral involvement, cystic change, enhancement, and midline shift were observed on the preoperative MR image.

IV. Statistical analyses

Statistical calculations used the commercially available SPSS 10.0 software package (SPSS, Chicago, Ill., U.S.A.). The end point of this study was overall survival as measured from the date of operation that confirmed the diagnosis of anaplastic oligodendroglioma to the last follow-up visit or death. Univariate analysis constructed probability curves according to the Kaplan-Meier method for the 22 variables for comparison by the log rank test. Variables with a p value of less than 0.05 in the univariate analysis were subsequently introduced into a multivariate stepwise proportional hazards regression analysis (Cox model) to identify the parameters independently associated with survival.

Results

I. Patient population

Thirty-two patients, 16 males and 16 females (median age 41.5 years), with confirmed newly diagnosed anaplastic oligodendroglioma were treated by combined therapy. Median patient follow up was 35.3 months. Median survival time from diagnosis was 58 months (Fig. 1). The overall 5-year survival rate was 49.38%. At the last follow up, 12 patients had died of the disease.

II. Clinical prognostic factors

The clinical factors associated with survival according to univariate analysis are reported in Table 1. Age at diagnosis (Fig. 2), headache as initial symptom (Fig. 3), and KPS score at 1 week postoperation (Fig. 4) were all statistically significant. Sex, duration of symptoms, seizure, and neurological deficit at diagnosis were not significant factors. Extent of resection and timing of radiotherapy were also not significant factors.

III. Radiological prognostic factors

The radiological factors associated with survival according to univariate analysis are reported in Table 2. Small tumor volume (<50 cm³) was predictive of better survival (Fig. 5). Tumor location, cystic change, enhancement, midline shift, brain edema,

Fig. 1 Actuarial survival curve depicting the overall survival of the patients with newly diagnosed anaplastic oligodendroglioma treated by combined therapy. Censored patients are marked (+).

Fig. 2 Kaplan-Meier graph of the cumulative probability of survival for the younger age group (< 50 years, dashed line) and older age group (≥ 50 years, solid line). Censored patients are marked (+). $p = 0.0083$ for univariate analysis, 0.025 for multivariate analysis.

Table 1 Association of clinical parameters with survival times

Variable	No. of patients (n = 32)	5-Year survival rate (%)	p Value (univariate)
Age at diagnosis ^{*,**}			
< 50 yrs	22	59.34	0.0083
≥ 50 yrs	10	19.69	
Sex			
male	16	40.38	0.9696
female	16	64.78	
Duration of symptoms			
< 8 wks	24	49.75	0.3961
≥ 8 wks	8	43.75	
Headache [*]			
yes	16	42.21	0.0397
no	16	57.78	
Seizure			
yes	17	52.94	0.2430
no	15	45.95	
Neurological deficit			
yes	11	43.29	0.3867
no	21	53.47	
KPS score at 1 wk after operation ^{*,**}			
< 80	11	22.27	0.0277
≥ 80	21	63.53	
Extent of resection			
gross total resection	13	40.40	0.6727
no gross total resection	19	52.31	
Timing of radiation therapy			
≤ 4 wks after operation	19	52.29	0.4416
> 4 wks after operation	13	44.44	

^{*} $p < 0.05$ (univariate analysis), ^{**} $p < 0.05$ (multivariate analysis). KPS: Karnofsky Performance Status.

Fig. 3 Kaplan-Meier graph of the cumulative probability of survival for patients with (solid line) and without (dashed line) headache at diagnosis. Censored patients are marked (+). $p = 0.0397$ for univariate analysis, 0.125 for multivariate analysis.

Fig. 4 Kaplan-Meier graph of the cumulative probability of survival for patients with high Karnofsky Performance Status (KPS) score (≥ 80 , dashed line) at 1-week postoperation and low KPS score (< 80 , solid line). Censored patients are marked (+). $p = 0.0277$ for univariate analysis, 0.047 for multivariate analysis.

Table 2 Association of radiological parameters with survival times

Variable	No. of patients (n = 32)	5-Year survival rate (%)	p Value (univariate)
Tumor location			
frontal	15	62.50	0.2119
nonfrontal	17	57.65	
Cystic change			
yes	20	39.19	0.1519
no	12	76.39	
Enhancement			
yes	26	42.69	0.1183
no	6	100.0	
Midline shift			
yes	23	48.79	0.9397
no	9	76.19	
Brain edema			
yes	24	60.12	0.2152
no	8	54.69	
Contralateral involvement			
yes	7	66.67	0.6522
no	25	38.64	
Calcification			
yes	20	74.07	0.2699
no	12	36.07	
Tumor volume ^{*,**}			
$< 50 \text{ cm}^3$	25	62.11	0.0057
$\geq 50 \text{ cm}^3$	11	18.18	

^{*} $p < 0.05$ (univariate analysis), ^{**} $p = 0.051$ (tendency for better survival, but did not achieve statistical significance as an independent prognostic variable in multivariate analysis).

Fig. 5 Kaplan-Meier graph of the cumulative probability of survival for patients with large tumor volume ($\geq 50 \text{ cm}^3$, solid line) and small tumor volume ($< 50 \text{ cm}^3$, dashed line). Censored patients are marked (+). $p = 0.0057$ for univariate analysis, 0.051 for multivariate analysis.

contralateral involvement, and calcification were not significant factors.

IV. Multivariate analysis for survival

Age at diagnosis, headache, KPS score at 1 week postoperation, and tumor volume with corresponding p values of less than 0.05 in the univariate analysis were introduced into multivariate analysis. Age at diagnosis and KPS score at 1 week postoperation had statistical significance as independent prognostic variables ($p = 0.025, 0.047$). Small tumor volume ($< 50 \text{ cm}^3$) showed a tendency for better survival, but did not achieve statistical significance ($p = 0.051$). Absence of headache as the initial symptom was not identified as a statistically significant parameter.

Discussion

Combined loss of 1p and 19q is a statistically significant multivariate predictor of overall survival in patients with anaplastic oligodendrogliomas, and is also significantly associated with both chemosensitivity and longer recurrence-free survival after chemotherapy.³⁾ The phosphatase and tensin homolog deleted by the chromosome 10 (PTEN) alteration is associated with poor prognosis.¹⁷⁾ Recent evidence suggests that molecular genetic analysis may provide a more powerful method for separating

anaplastic oligodendrogliomas into therapeutically and prognostically significant subgroups. However, the clinical and radiological prognostic factors are still important for predicting the survival of patients with anaplastic oligodendroglioma. These factors may very well provide information in addition to the new molecular methods.

I. Age

Age has been reported as the most important predictor of survival, which is related, not unexpectedly, to the natural history of glioma, as a high rate of malignant transformation, higher proliferation index, and larger tumor volume all occur with increasing age.^{1,2,7,19,22)} Several criteria have been used in the past to define "younger age" (21,⁷⁾ 40,⁹⁾ 45,²²⁾ 49,¹⁹⁾ and 50 years^{12,14)}. For this study, younger age was anything under 50 years because the goal was to identify the oldest patient with anaplastic oligodendroglioma. Age was a statistically significant parameter (univariate and multivariate) for longer survival in the present patients with newly diagnosed anaplastic oligodendroglioma treated by combined therapy. The prognostic importance has been reaffirmed by this study.

II. Headache

Seizure is well known to be a good prognostic factor for patients with glioma, whereas headache was generally known to be unrelated with better survival.^{9,22)} Headache is a typical symptom of increased intracranial pressure (ICP). So we simply used headache as indirect evidence of preoperative increased ICP. Some authors showed that no preoperative increased ICP sign could be a good prognostic factor (univariate) in anaplastic oligodendroglioma patients.¹¹⁾ The present analysis showed that absence of headache at diagnosis was a statistically significant parameter (univariate) for survival whereas seizure was not. We failed to find any evidence of how headache and seizure were correlated. These two parameters did not overlap. Headache might be related to tumor volume but we could not prove any relationship between these two parameters. Additionally, we could not categorize the type of headache. Although the reason is hard to explain, patients with headache might have had increased ICP before surgery and this could influence the survival of patients with newly diagnosed anaplastic oligodendroglioma treated by combined therapy.

III. KPS score at 1 week after operation

The current study suggests that KPS score is the most consistent predictor of survival in patients

with anaplastic gliomas.^{6,8,12,21}) There are many baselines for KPS score as a prognostic factor: preoperative,^{11,12}) postoperative,^{11,18,22}) below 90,¹²) below 80,^{11,21}) and below 70.^{22,24}) We chose KPS score at 1 week postoperation as the baseline because we wanted to investigate both postoperative and pre-radiotherapy KPS score. Scoring below 80 was a statistically significant prognostic (univariate and multivariate) parameter. The prognostic importance has been reaffirmed by this study.

IV. Tumor volume

There was no correlation between the preoperative tumor size and length of life in patients with malignant glioma,^{16,23}) but smaller tumors (≤ 4 cm) were associated with improved survival when compared with tumors in general.^{7,12}) This study found that tumor volume (< 50 cm³) is a significant prognostic factor (univariate and tendency for better survival in multivariate analysis). Therefore, tumor volume is related to the prognosis for patients with newly diagnosed anaplastic oligodendroglioma treated by combined therapy.

V. Multivariate analysis and other known predictors

Age at diagnosis and KPS score at 1 week postoperation were independent predictors for better survival in patients with newly diagnosed anaplastic oligodendroglioma treated by combined therapy. This study failed to show any statistical significance for headache history and tumor volume which were associated with better survival in univariate analysis. However, small tumor volume (< 50 cm³) may constitute a favorable prognostic factor, even if this factor did not achieve statistical significance ($p = 0.051$) in the multivariate analysis where the number of patients was small.

These investigations did not reveal the favorable survival association with frontal localization reported in some series.^{5,9,15}) Although gross total tumor removal had an effect on survival in patients with anaplastic oligodendroglioma,¹²) our results could not show any prognostic significance of total removal in patients with newly diagnosed anaplastic oligodendroglioma treated by combined therapy.

This small and single institutional study identified younger age, absence of headache, good KPS score, and small tumor volume as clinical and radiological prognostic factors for good survival in patients with newly diagnosed anaplastic oligodendroglioma treated by combined therapy. Further studies with more patients, longer follow up, and combination with molecular analysis will provide more information about this rare disease.

Acknowledgments

We are grateful to Yeon Lim Suh, M.D. (Department of Pathology, Samsung Medical Center) and Yoon-La Choi, M.D. (Department of Pathology, Samsung Medical Center) for their review of pathology, and Sun Woo Kim, Ph.D. (Samsung Biomedical Research Center, Samsung Medical Center) for her expert advice in the statistical work of this study. We also thank Hyun Jeong Lim and Jeong A. Lee for editing the manuscript.

This study was supported in part by Samsung grant # SBRI (C-A4-210-1), and Sungkyunkwan University School of Medicine.

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Commentary

Anaplastic oligodendroglioma is a rare disease which is difficult to treat. Some factors such as age and KPS of patients, location, presence of calcifications and extent of resection of the tumor are thought to have impact on survival. If possible, radical resection will lead to better prognosis, and most anaplastic oligodendrogliomas respond to chemotherapy and radiotherapy. So aggressive therapy with chemotherapy and radiotherapy may lengthen survival. A number of techniques have been developed to improve the results of treatment, such as intraoperative navigation, intraoperative functional mapping, BCNU degradable implants and iodine-125 seeds.

I suggest that the responsible and exact prognostic factors should be better identified by further studies with more cases, or international multicenter retrospective review, so we can make more correct judgment in the study of prognostic factors of anaplastic oligodendrogliomas. The authors' work provides us with useful information about some clinical and radiological predictors and prognostic factors of anaplastic oligodendrogliomas, which are helpful for us in the management of such lesions.

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The authors report on their vast experience concerning surgery and postoperative treatment of anaplastic oligodendroglioma. They discuss in detail all factors, either clinical or radiological and pathological, associated with a longer survival. They identify a few of them as good indicators, namely absence of preoperative headache, small volume of the tumor (both presumably connected with normal intracranial pressure), age, and good postoperative Karnofsky score. Being a single institution study, the number of patients is not enormous, not enough to allow finer statistical elaborations; on the other hand, this has the advantage of a more uniform treatment and clear conclusions.

I appreciate reading it, and would like to see it published. I only have two comments about the paper.

1) Among anaplastic oligodendrogliomas, the unique CT/MRI finding that has been suggested to be a poor indicator of survival is “ring enhancement” (in other words a glioblastoma-like appearance) (ref. 3 of this article). It would be nice to compare the authors’ results with these findings, and understand the reasons for the differences. 2) One of the chemotherapies that are reputed very useful in oligodendrogliomas is temozolamide. Why, at recurrence of the tumor and after adjuvant PCV, did not the authors use this drug that is now widely employed? The reasons should be reported.

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