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Prognostic Factors in Elderly Patients With Supratentorial Malignant Gliomas

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Abstract

The prognostic factors were retrospectively analyzed in 30 patients aged 70 years or over with supratentorial malignant gliomas treated by surgery in our hospital. The histological diagnosis was confirmed as grade 3 in 13 patients and grade 4 in 17. Seventeen patients received adjuvant radiation therapy. Only 10 patients underwent chemotherapy. Survival time was analyzed with the Kaplan-Meier method. Prognostic factors were obtained from the Cox proportional hazards model. Univariate analysis showed preoperative Karnofsky performance status (KPS) score of 70 or greater and radiation therapy were significantly associated with longer survival. However, multivariate analysis revealed that preoperative KPS score of 70 or greater was the only independent prognostic factor and radiation therapy lost its significance due to selection bias. Neurological deterioration and medical complications occurred in six and seven patients, respectively. Performance status rather than histological grade is the key prognostic factor in elderly patients with supratentorial malignant gliomas. Patients with good preoperative KPS score should be aggressively treated with extensive resection and radiotherapy.

Key words: malignant astrocytoma, elderly patient, radiation therapy, survival time, performance status

Introduction

Evidence is growing that the incidence of malignant gliomas has increased substantially in the elderly population, especially in industrialized countries, over the past three decades.[9,11,12,14,18,36,44] Numbers of primary brain tumors have nearly doubled in the 65- to 74-year-old population and have more than doubled in the 75- to 84-year-old population.[11] These increasing trends may result from a combination of a true increase in the incidence, a gain in life expectancy, and exposure to increasing environmental carcinogens,[18] as well as improved diagnostic procedures and better access of the elderly to health care.[36]

Aggressive treatment has been questioned for elderly patients.[21,32,35] In addition, elderly patients have frequently been undertreated or untreated.[5,26] Surprisingly, a retrospective cohort study in Minnesota found that the proportion of elderly patients receiving no treatment increased from 4% between 1980 and 1989 to 18% between 1990 and 1995.[26] However, elderly patients with brain tumors should be treated based on sound scientific data and not ad hoc decisions.[4] Several prognostic factors have been identified in patients with malignant glioma, including age, performance status, histological grade, and extent of resection.[10,13,20-25,30-33,38] Age is considered a strong negative factor on survival.[10,21-25,32,35,38] However, age should not be a reason for exclusion from aggressive treatment,[5,27,39,45] because the few investigations of the treatment of malignant gliomas in the elderly[4,10] have not defined the prognostic factors in this subgroup.

The present retrospective study tried to identify the independent variables that are significant predictors of survival time in elderly patients with malignant astrocytomas.

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Methods

I. Patient population

The clinical records were retrospectively reviewed of 30 elderly patients, 17 men and 13 women aged 70 to 81 years (median 73.0 years) at first admis-

sion, who were surgically treated for histologically confirmed supratentorial malignant astrocytomas at our University Hospital between April 1980 and December 2005. The most frequent symptoms were dementia in 14 patients, hemiparesis in 13, and visual disturbance in eight. The histological diagnosis was glioblastoma multiforme (grade 4) in 17 patients, and anaplastic astrocytoma or anaplastic oligodendroglioma (grade 3) in 13. At the end point of the study on August 31, 2006, two patients were alive and 28 had died. The clinical characteristics are summarized in Table 1.

II. Treatment characteristics

All patients were treated using standard microneurosurgical techniques. Our standard surgical policy was debulking as far as possible and preservation of neurological functions. Needle biopsy was not performed in this series. Gross total resection, defined as the complete absence of residual enhanced tumor on early postoperative magnetic resonance imaging or computed tomography, was

Table 1 Clinical characteristics of the patients

Case No.	Age (yrs)	Sex	Survival (mos)	Tumor grade	Resection	KPS (%)		Surgical result	Radiation	Chemo-therapy	Complication	
						Preop.	Postop.				Surgical	Medical
1	76	M	12	4	partial	80	80	NC	no	no		
2	73	M	2	4	partial	40	30	worse	no	no	aphasia	septicemia
3	76	F	18	4	gross total	90	90	NC	yes	no		
4	77	F	8	4	partial	70	50	worse	no	no	consciousness disturbance	
5	70	M	12	4	partial	70	80	improve	yes	yes		
6	74	F	4	4	gross total	60	70	improve	yes	yes		
7	70	F	14	4	partial	60	90	improve	no	no		
8	71	M	18	4	gross total	80	100	improve	yes	yes		
9	71	M	24	4	gross total	70	90	improve	yes	yes		
10	72	F	5	4	partial	60	100	improve	no	no		
11	70	M	5	4	partial	60	50	worse	yes	no	hemiparesis	pulmonary embolism
12	81	F	8	4	gross total	70	80	improve	no	no	hematoma	
13	71	M	4	4	partial	50	50	NC	no	no		pneumonia
14	72	F	3	4	partial	50	50	NC	no	no		ketoacidosis
15	70	M	12	4	partial	60	60	NC	yes	no		
16	76	M	4	4	partial	50	50	NC	yes	no		
17	78	F	10	4	gross total	70	70	NC	no	no		
18	76	M	9	3	partial	80	60	worse	no	no	hemiparesis	
19	71	F	17	3	partial	70	70	NC	yes	yes		
20	76	F	6	3	gross total	50	80	improve	no	no		
21	70	F	22	3	gross total	80	80	NC	yes	yes		
22	73	M	7	3	gross total	80	60	NC	yes	no		pneumonia
23	73	F	11	3	partial	60	50	worse	no	no	hemiparesis	pneumonia
24	72	M	36	3	gross total	80	80	NC	yes	yes		
25	70	M	72	3	gross total	80	50	worse	yes	no	hemiparesis	
26	71	M	13	3	gross total	60	80	improve	no	no		pneumonia
27	71	M	8	3	partial	60	60	NC	yes	no		
28	74	M	5	3	gross total	50	100	improve	yes	yes		
29	70	F	12	3	gross total	80	80	NC	yes	yes		
30	70	M	20	3	partial	80	80	NC	yes	yes		

KPS: Karnofsky performance status, NC: no change.

achieved in 14 patients, and partial resection in 16. Reoperation for recurrent tumor was performed in six patients. Postoperative adjuvant radiotherapy was routinely initiated 2 or 3 weeks after tumor removal, except for patients aged over 80 years or patients in poor neurological or general condition. Linac external beam conventional radiation therapy was administered to the residual tumor or tumor cavity with a margin of 2 cm using 2 Gy daily, 5 days a week, up to a total of 40 Gy. The dosage was boosted to a total of 54 to 60 Gy to the whole brain or to the extended local tumor. Radiation therapy was completed in 17 patients, consisting of local plus whole brain irradiation in six and local plus extended local irradiation in 11. Stereotactic booster irradiation was carried out in six patients using either gamma knife (4) or NOVARIS methods (2). Chemotherapy with nimustine hydrochloride (ACNU) was given to 10 patients with good postoperative Karnofsky performance status (KPS) score (≥ 70).

III. Statistical analysis

Survival time was retrospectively analyzed using the Kaplan and Meier method, and survival curves for the various subgroups were compared using the log-rank test. The Cox proportional hazards model was used to identify the multivariate independent predictors of survival. The five clinical parameters examined were tumor grade (grade 3 vs. grade 4), extent of tumor resection (gross total resection vs. partial resection), preoperative and postoperative KPS scores (KPS ≥ 70 vs. KPS <70), and radiation therapy (with vs. without).

Results

No operative death occurred in our series. One patient required immediate reoperation for postoperative hematoma evacuation, but fully recovered. Postoperative improvement of symptoms was observed in 10 patients, but no improvement was found in 14. Six patients suffered postoperative neurological deterioration; deteriorated hemiparesis in four patients, and aphasia and consciousness disturbance in one patient each. Three of these cases of postoperative neurological deterioration were transient, but another three persisted. Medical complications occurred in seven patients within 30 postoperative days; pneumonia in four patients, pulmonary embolism in one, diabetic ketoacidosis in one, and septicemia in one. Mean preoperative and postoperative KPS scores were 66.7 and 70.7, respectively.

Patients had survival times of 2 to 72 months. The median survival was 10.5 months. Survival curves of patients with the independent prognostic factors were fitted to stratified proportional hazard models using the Kaplan and Meier method (Fig. 1). Univariate analysis showed preoperative KPS score ≥ 70 and radiotherapy were significant ($p < 0.05$)

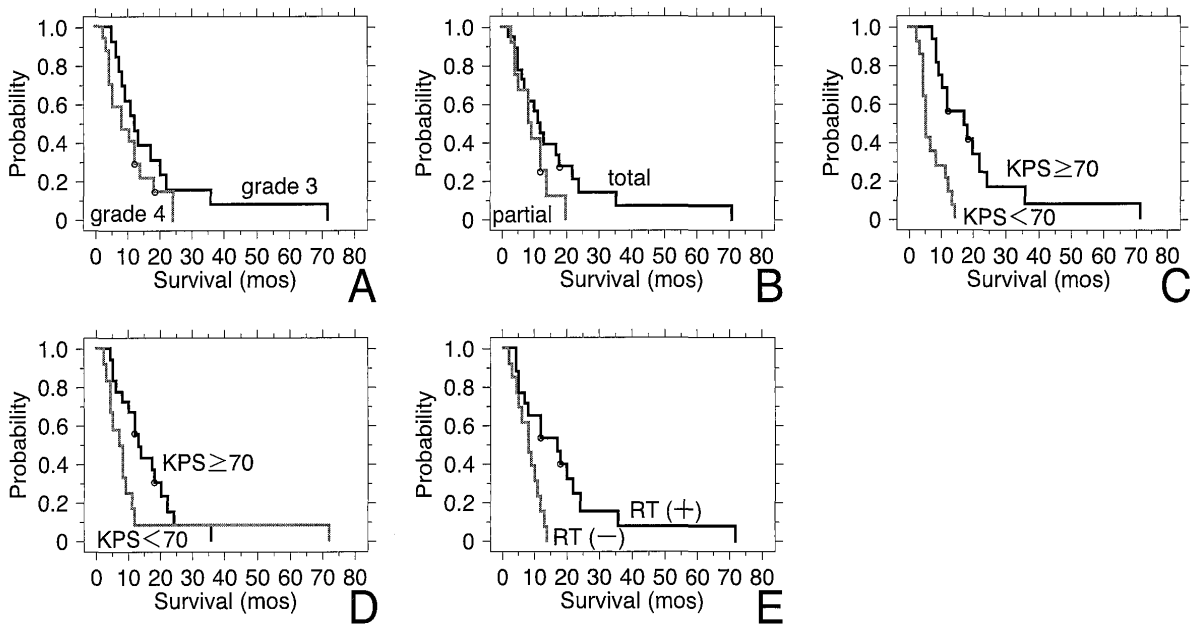

Fig. 1 Kaplan-Meier estimated survival curves of the 30 elderly patients with malignant astrocytomas stratified by the tumor grade (A, p = 0.1383), extent of resection (B, p = 0.1705), preoperative Karnofsky performance status (KPS) score (C, p = 0.0001), postoperative KPS score (D, p = 0.1796), and radiation therapy (RT) (E, p = 0.0043).

Table 2 Multivariate analyses of survival predictors

	p Value	Hazard radio (95% confidence interval)
Grade 3	0.2209	0.549 (0.210–1.435)
Total resection	0.7819	1.155 (0.413–3.203)
Preop. KPS ≥70*	0.0177	0.297 (0.109–0.810)
Postop. KPS ≥70	0.1550	0.522 (0.204–1.287)
Radiotherapy	0.0917	0.437 (0.167–1.144)

*Statistically significant difference ($p<0.05$) from preoperative Karnofsky performance status (KPS) score (<70).

predictors of longer survival duration. However, multivariate analyses showed preoperative KPS score (≥70) was the only independent predictor of survival (Table 2). Median survival was 14.5 months in patients with preoperative KPS score ≥70, compared to 5 months for those with preoperative KPS score <70.

Discussion

The present study analyzed the prognostic factors of elderly patients with supratentorial malignant gliomas. Univariate analysis demonstrated that the preoperative KPS score ≥70 and radiation therapy were significant prognostic factors, whereas multivariate analyses showed radiation therapy lost its statistical significance due to selection bias, so the preoperative KPS score ≥70 was the only independent prognostic factor. According to our results, only patients with good preoperative KPS score may benefit from aggressive treatment, including extensive resection and full-dose irradiation. Similarly, aggressive surgery and radiation therapy extended survival in elderly patients with good performance status.[30,31,34,42,45] However, few reports have considered the importance of combination treatment with surgery, radiation therapy, and chemotherapy, regardless of the pretreatment KPS score.[33]

Previous reports of improved survival benefit for patients receiving radical resection of malignant astrocytomas have been criticized for selection bias. Patients receiving partial resection or biopsy were often older, had a lower performance status, and so had a lower chance of receiving adjuvant therapies. A recent small randomized trial included 23 patients aged greater than 65 years with malignant glioma assigned to only biopsy or resection with radiation therapy.[43] The median survival time was significantly longer in patients who underwent resection (5.6 months) than in those who underwent biopsy (2.8 months). In general, surgical treatment for elderly patients carries the risk of high mortality and morbidity. Overall morbidity, including neurological and general complications, occurs in 30% to 50% of the elderly subpopulation.[7,15,21,41] Medical complication rates seem to become higher with increasing age compared with neurological morbidity.[6] Our overall complication total was 14 of 30, with more medical complications than neurological complications. The decision to carry out radical surgery on elderly patients with malignant gliomas should be based on careful consideration of the patient's condition, including performance, mental and neurological status, and tumor location. Geriatric medicine often considers 65 years and older as elderly, although the definition varies.[4] We used an age limit of 70 years, because 65 years and younger are no longer considered as elderly. In our series, the oldest patient who underwent surgery was an 81-year-old woman. However, we now consider that radical treatment should be indicated only for patients aged 80 years or younger.

Our single-institution retrospective study was based on a relatively small number of patients. Histological grade was not an independent prognostic factor, which is consistent with the recent largest series of the Glioma Outcome Project, which showed very little difference in survival time between patients with grade 3 and grade 4 malignant gliomas.[25] A diagnosis of grade 3 tumor might be a result of tissue sampling error of glioblastoma, or grade 3 tumor in the elderly may behave just as aggressively as glioblastoma, with indistinguishable biological properties.

There is now considerable concern over the optimal adjuvant therapies for elderly patients with malignant gliomas. Although the elderly appear to be susceptible to radiation-induced brain injury, radiation therapy remains the gold standard even for elderly patients with malignant gliomas.[3,17] Radiotherapy was the only prognostic factor for survival in this subgroup, and radiotherapy was recommended for all elderly patients.[28] Other studies have also shown a survival advantage for radiotherapy, although the benefit is observed only in patients aged 70 years or younger, and patients with good performance status or resection.[1,34,42] The survival benefit of radiotherapy was minimal, but improvement in symptoms was found.[1,29] Short-course radiotherapy is also recommended for the elderly.[1–3,37,42] A prospective randomized trial found no difference in survival between patients receiving standard radiation therapy (60 Gy in 30 fractions over 6 weeks) or short-course radiation therapy (40 Gy in 15 fractions over 3 weeks).[37] In our series, we

used a stereotactic radiosurgery boost for recurrence in six patients, who were likely to have good performance status or longer survival period. Stereotactic radiosurgery boost appears useful for treatment of recurrent malignant gliomas,[2,19] but the effectiveness in the elderly subpopulation should be clarified.

Chemotherapy as the only adjuvant therapy has not been advocated for the elderly because malignant gliomas are chemoresistant and nitrosourea-based chemotherapies are associated with significant myelosuppression.[4] Recently, temozolomide has been introduced to the clinical setting. A randomized multicenter trial demonstrated an increase in 2-year survival from 10% to 26% in glioblastoma patients aged 71 years and younger with the addition of temozolomide to radiotherapy.[40] The effectiveness and safety of temozolomide treatment have been demonstrated in the elderly.[5,8] Temozolomide single-agent therapy improves neurological status and is as effective as irradiation in increasing survival in elderly glioblastoma patients with or without resection.[8,16] Therefore, temozolomide would be now considered a viable alternative to radiation therapy, especially in elderly patients.[4,5,8,16] Prospective randomized studies are now investigating the optimum therapeutic options for efficacy, toxicity, convenience, and quality of life for the elderly.[4]

The present study indicates that performance status rather than histological grade is the key prognostic factor in elderly patients with supratentorial malignant gliomas. Elderly patients with a good preoperative KPS can be treated aggressively with extensive resection and radiotherapy. Elderly patients with poor performance status should not undergo surgery or radiation, but administration of temozolomide should be considered.

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Commentary

The authors retrospectively analyzed 30 patients aged 70 years old or over with supratentorial malignant gliomas treated by surgery. They found that KPS score of 70 or greater and radiation therapy were significantly associated with longer survival with univariate analysis and that KPS score of 70 or greater was the only independent prognostic factor with multivariate analysis. So, the authors suggested that patients with good preoperative KPS score should be aggressively treated with resection and radiotherapy. This is a nice statistical research with detailed analysis. But clinically the prognostic factor is complex. I think the only limitation of this study is the sample size. If more cases were added into this study, other positive prognostic factors would be found. We expect a further larger sample size study.

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This paper notes the apparent increased incidence in industrialized countries of malignant gliomas in elderly patients, which may represent either a true increased incidence, or may simply indicate increased access to diagnostic scans in this population. It also draws attention to the fact that, in many countries, elderly patients may be considered unsuitable for surgical resection or for adjuvant treatment solely on the grounds of age because it is assumed they have a uniformly poor prognosis as well as poor tolerance of invasive therapies. The authors describe in this series of 30 patients the results of what is intensive treatment and which is, at least judged by European practice, unusually radical treatment. Their conclusion is that performance status, rather than histological grade, should indicate whether the individual patient should be treated by extensive resection and radiotherapy. In selected patients there can be relatively good results. They conclude that such treatment is not suitable for those with poor performance status.

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