Original article

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Long-term prognostic assessment of 185 newly diagnosed gliomas
--Grade III glioma showed prognosis comparable to that of grade II glioma--

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Running head: Grade III glioma showed comparable prognosis to grade II

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Abstract

Objective: We evaluated the prognoses of newly diagnosed gliomas through WHO Grades II, III and IV to assess the overall tendency of treatment results for glioma in our institute. Furthermore, statistical analysis was performed to determine factors influencing the prognosis.

Methods: A total of 185 newly diagnosed glioma patients were operated on from 2000 to 2006. The primary endpoint was the overall survival from the date of surgery. The factors assessed as to whether they influenced the prognosis were the WHO grades of sex, age, location of the lesion, pre-operative Karnofsky Performance Status (KPS), extent of resection and whether or not radiation therapy was performed.

Results: The WHO grades influenced the survival significantly ($P < 0.0001$). The Grades II and III showed no statistically significant difference in survival ($P = 0.174$), whereas Grades III and IV showed a significant difference ($P < 0.0001$). The factor influencing survival as well as the grades was the KPS ($P < 0.0001$). The comparison of survival over WHO grades in the same KPS group was performed for 2 KPS groups (KPS = 100, KPS 80–90), and these also showed significant differences ($P = 0.0009$ and 0.0143, respectively).

Conclusions: Despite the different distributions of the KPS, the Grade III glioma patients showed survival comparable to that of the Grade II. On the other hand, the Grade IV glioma patients showed significantly poorer survival compared with Grade II or III.

Text

Introduction

Traditionally, researchers have categorized gliomas into two groups, the 'malignant' or 'high-grade' group and the 'low-grade' group, especially when discussing their prognoses. WHO Grade II gliomas, sometimes combined with Grade I gliomas, are considered to be 'low-grade', and WHO Grades III and IV combined are considered to be 'high-grade' or 'malignant'. This categorization is fairly convenient when determining adjuvant therapeutic modalities because the 'malignant' group is almost always treated by concomitant radiation therapy (RT) and chemotherapy.

Though the prognosis of gliomas in general had been considered to be poor, recent developments in diagnostic technologies and treatment modalities seem to have contributed to its improvement. This has resulted in the fact that some 'malignant' glioma patients may be able to expect long-term survival under certain conditions. However, there has been little discussion as to whether the old 'low-grade and malignant' categorization is appropriate when evaluating prognostic tendencies of gliomas at present.

In our institute, in striving to achieve extensive but safe resection of tumors, a number of new technological methods have been introduced in recent years, one of which is the intra-operative magnetic resonance imaging (iMRI) (1), which was introduced in 2000. After 6 years of surgical operations using iMRI and the accompanying treatment experiences, we felt the urge to evaluate the prognoses of the glioma patients whom we treated. In addition, we thought that it would be very informative to compare the overall survival of each WHO grade group. We evaluated the prognoses of newly diagnosed glioma through Grades II, III and IV to assess the overall tendency of treatment results for glioma in our institute.

Patients and methods

A total of 304 glioma patients operated on at our hospital from 1 January 2000 to 30 June 2006 were reviewed. The histological diagnoses were available for all cases and were classified according to the grading system defined by the 2000 WHO classification for tumors (2) of the central nervous system. We excluded WHO Grade I cases (11 patients) as they have extremely good prognoses. In order to assess the significance of the first surgery, we also excluded the patients who had undergone initial treatment at other institutes and were referred to our institute for the treatment of recurrent lesions. As a result, the prerequisite for inclusion in this analysis was to be newly diagnosed WHO Grades II, III and IV glioma patients who underwent operations in our institute from 1 January 2000 to 30 June 2006. A total of 185 patients were included in this analysis.

The detailed description of the patients is shown in Table 1, and the histological variation of each WHO grade group is shown in Table 2. Among these patients, 153

(82.7%) were operated on by using iMRI-guided navigation. The extent of resection was assessed by comparing pre- and post-operative iMRI (3). The pre-operative tumor volume was defined as an area of contrast-enhanced T1-weighted images (4), or, if the tumor does not show contrast enhancement, as an area of increased signal intensity on T2-weighted images corresponding to the mass lesion. An area of abnormal signal intensity was computed for each slice and multiplied by the slice width (1.5 mm), and a cumulative value was obtained by adding the values for the individual slices (5).

All surgical specimens were collected, processed and prepared for histological diagnosis in our neuropathologic laboratory. The specimens were thoroughly prepared with regular hematoxylin–eosin staining and necessary immunohistochemical antibodies were applied including MIB-1 antibody. For the entire study period, every diagnosis was conducted by one sole neuropathologist, Prof. Osami Kubo, who is one of the councillors of the Japanese Society of Neuropathology.

Adjuvant therapy included fractionated external-beam RT (50–60 Gy total, 2 Gy fraction for 5 days per week, unless modulated); and concomitant chemotherapy based on nimustine hydrochloride (ACNU) (6) with or without vincristine and/or procarbazine, temozolomide or autologous vaccine therapy. The clinical administration of temozolomide had not been approved during the study period (except the last few months); thus, it was not used as the first-line chemotherapy for primary glioma patients in this study. Patients to be treated with RT were selected by the following criteria. If the diagnosis was Grade III or IV, radiation was primarily recommended. If the diagnosis was Grade II, radiation was recommended if the patient's post-operative MRI showed any residual tumor and/or the MIB-1 index was 5% or higher. Maintenance therapy followed the initial therapy. In case of recurrence, the salvage therapy included re-operation using other chemotherapeutic agents or RT if the initial therapy did not include it.

The primary endpoint was the overall survival from date of surgery. Comparison of survival among WHO grades was performed using Cox's proportional hazard models.

Next, the patient's background was assessed to investigate whether there was any other factor that influenced the survival more than the WHO grades. The factors assessed were the WHO grades of sex, age, location of the lesion (U, supra-tentorial unilateral lesion; B, supra-tentorial bilateral lesions; I, infra-tentorial lesion), pre-operative Karnofsky Performance Status (KPS), extent of resection and whether or not RT was performed. These seven background factors were used as variables to apply Cox's proportional hazard models.

Results

The median observation time was 13.0 months. Kaplan–Meier survival curves were drawn for WHO Grades II, III and IV (Fig. 1). There was a significant difference in survival among grades ($P < 0.0001$). The number of the patients at risk at 0, 12, 24, 36, 48, 60 and 72 months is also indicated in Fig. 1.

Subsequently, the survival of each WHO grade was compared and statistically analyzed by using Cox's proportional hazard models. Grades II and III showed no statistically significant difference ($P = 0.174$), whereas Grades III and IV showed a significant difference ($P < 0.0001$).

As for the influence of background factors on survival, the P values were $P < 0.0001$ for WHO grades, $P = 0.525$ for sex, $P = 0.997$ for age, $P = 0.727$ for location, $P < 0.0001$ for KPS, $P = 0.374$ for the extent of resection and $P = 0.804$ for RT. Only the KPS showed as much influence on survival as the WHO grades.

Discussion

At the outset, it should be clarified that the data presented here were genuinely from a single institute. It may be apparent that the fraction of Grade III was much greater than that of other institutes or other studies, and the Grade III/IV patients were much younger than generally expected. One of the features of our institute is that most of the operative patients were referred from other hospitals or institutes. As is well known, the Grade IV gliomas develop symptoms much more rapidly than Grade II or III, and often need immediate treatment as soon as they are found. Furthermore, there is a tendency for Grade IV gliomas to be found in older age groups when compared with Grade II or III. Sometimes, those patients are not considered for operative therapy because of their age. Thus, those who were referred to our hospital tended to be younger and to contain a smaller fraction of Grade IV. As a result, we had a greater fraction of Grade III patients than Grade IV.

Our data clearly showed that the Grade III group, normally categorized in the malignant glioma entity, showed survival comparable to that of Grade II glioma, which is in the low-grade glioma entity. On the contrary, Grade III and IV glioma, usually combined as malignant glioma, showed significantly different survival.

We have used the same (or at least very similar) treatment strategy for the Grades III and IV gliomas. Once histologically diagnosed as Grade III or IV, the patients were always given RT and concomitant chemotherapy. On the contrary, Grade II glioma patients were not always treated by RT or chemotherapy as is explained in the Patients and Methods section. We have come to an interesting fact: though treated similarly, Grades III and IV showed significantly different prognoses; on the contrary, Grades II and III gliomas were treated based on different therapeutic strategies, and showed comparable prognoses in terms of survival.

As for background factors, the KPS influenced the survival as much as the grades. We examined the distribution of the patients for grades and KPS, shown in Table 3. It indicates that there are a certain number of patients in each WHO grade for the KPS = 100 and the KPS 80–90. Then, comparison of survival over grades was performed for the two KPS groups with KPS = 100 and KPS 80–90; this comparison also showed significant differences ($P = 0.0009$ and 0.0143, respectively). This supported the conclusion that the difference of survival among grades was independent of the deviations among patients' backgrounds.

Subsequently, the survival of each WHO grade in the KPS = 100 group was compared and statistically analyzed using Cox's proportional hazard models. The *P* values for grade II versus III and Grade III versus IV were 0.532 and 0.0294, respectively. Despite the fact that the patients' backgrounds have some biases throughout the grades, Grade III achieves survival comparable to Grade II, if diagnosed, treated and observed properly. On the contrary, Grade IV still remains in the uncontrollable disease category.

Conclusions

The results indicated that the Grade III glioma patients have prognoses comparable to that of the Grade II patients and the Grade IV glioma patients showed significantly poorer prognoses compared with Grade II or III. Among the patients' background factors, the KPS influenced the survival of gliomas as much as the WHO grades. However, the comparison of survival among the same KPS groups also showed significant differences over grades, indicating that the differences of survival over grades are independent of patients' background factors.

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Conflict of interest statement

None declared.

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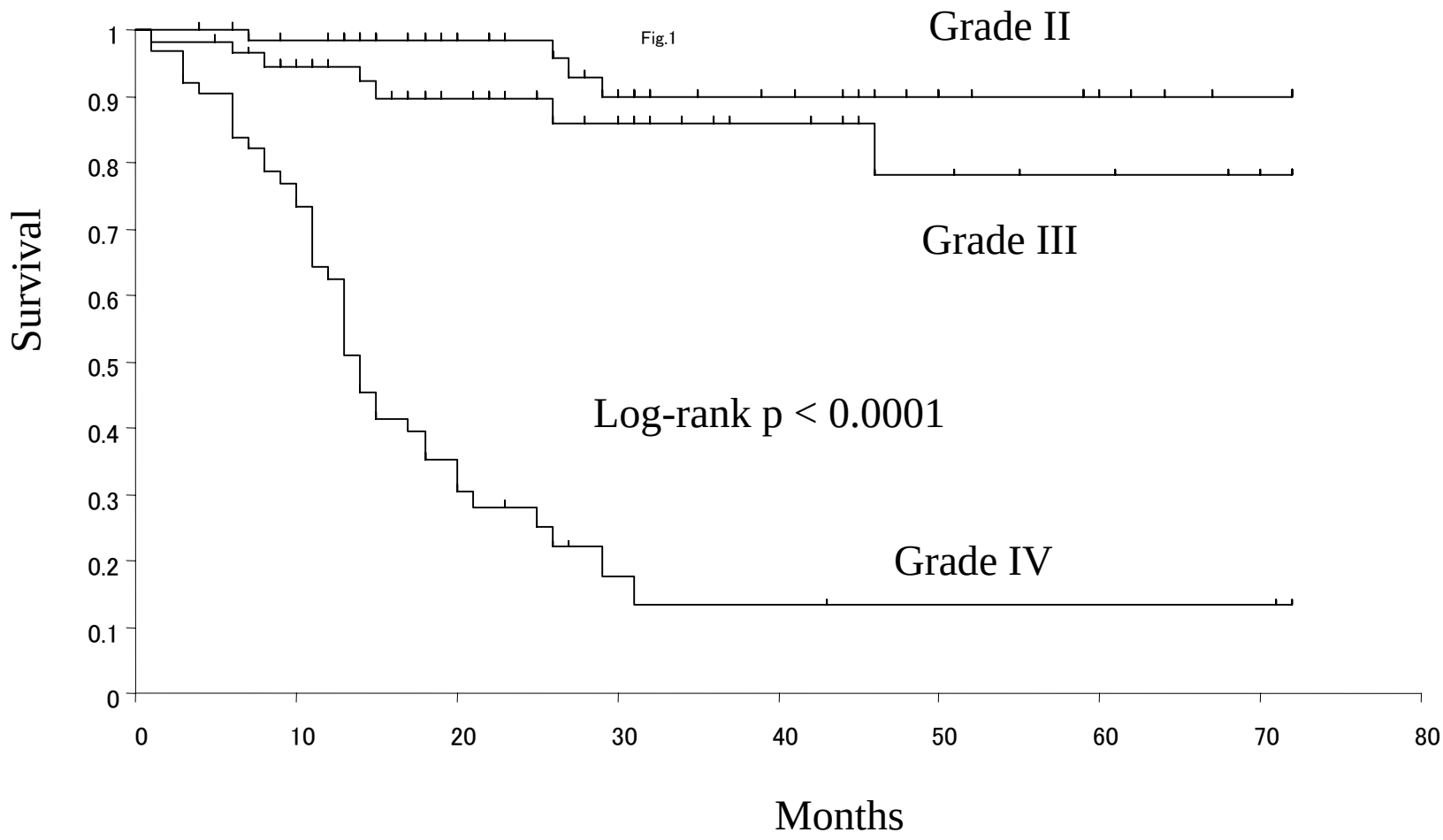

Months	0	12	24	36	48	60	72
Number of patients at risk							
Grade II	66	58	38	20	14	7	3
Grade III	57	40	27	15	9	7	4
Grade IV	62	34	10	3	2	2	1

Table 1. Characteristics of the patients in each WHO grade group

	Total	Grade II	Grade III	Grade IV
Number of cases	185	66	57	62
Sex				
Men	106	34	34	38
Women	79	32	23	24
Age (years old)				
Median	44.0	35.0	39.0	54.5
Range	8 - 78	11 - 70	22 -78	8 - 78
Location				
U	168	61	51	56
B	7	1	4	2
I	10	4	2	4
KPS				
Median	100.0	100.0	100.0	80.0
Range	10 - 100	70 - 100	50 - 100	10 - 100
Extent of resection (%)				
Median	95.0	95.0	95.0	95.0
Range	biopsy - 100	biopsy - 100	biopsy - 100	biopsy - 100
RT	131	26	51	54

U = unilateral supra-tentorial lesion, B = bilateral supra-tentorial lesions, I = infra-tentorial lesion
KPS Karnofsky performance status
RT Number of patients who received radiation therapy

Table 2. Histological variation in each WHO grade group

WHO grade	Histological diagnosis	Cases
Grade II	Astrocytoma	30
	Oligoastrocytoma	27
	Oligodendroglioma	5
	Ependymoma	3
	Pleomorphic xanthoastrocytoma	1
Grade III	Anaplastic astrocytoma	30
	Anaplastic oligoastrocytoma	21
	Anaplastic oligodendroglioma	3
	Anaplastic ependymoma	3
Grade IV	Glioblastoma	62

Table 3. Distributions of patients for KPS and grades

KPS	Grade II	Grade III	Grade IV
100	55	34	12
80 – 90	9	15	22
60 – 70	2	7	16
40 – 50	0	1	8
< 30	0	0	4