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The influence of different classification standards of age groups on prognosis in high-grade hemispheric glioma patients

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ABSTRACT

Although age is thought to correlate with the prognosis of glioma patients, the most appropriate age-group classification standard to evaluate prognosis had not been fully studied. This study aimed to investigate the influence of age-group classification standards on the prognosis of patients with high-grade hemispheric glioma (HGG). This retrospective study of 125 HGG patients used three different classification standards of age-groups (≤50 and >50 years old, ≤60 and >60 years old, ≤45 and 45–65 and ≥65 years old) to evaluate the impact of age on prognosis. The primary end-point was overall survival (OS). The Kaplan–Meier method was applied for univariate analysis and Cox proportional hazards model for multivariate analysis. Univariate analysis showed a significant correlation between OS and all three classification standards of age-groups as well as between OS and pathological grade, gender, location of glioma, and regular chemotherapy and radiotherapy treatment. Multivariate analysis showed that the only independent predictors of OS were classification standard of age-groups ≤50 and >50 years old, pathological grade and regular chemotherapy. In summary, the most appropriate classification standard of age-groups as an independent prognostic factor was ≤50 and >50 years old. Pathological grade and chemotherapy were also independent predictors of OS in post-operative HGG patients.

1. Introduction

Gliomas are the most frequently occurring primary tumors of the central nervous system [1]. Grade III and grade IV tumors, which are called high-grade gliomas (HGGs) have a poor prognosis and no effective therapeutic strategies [2]. Despite tremendous progress in this field over the past decade, the median survival in patients with glioblastoma multiforme (GBM) is approximately 1 year [3]. The current standard of care for HGGs includes a combination of surgery and adjuvant focal, external beam radiation, and is largely palliative in nature [4]. Some challenges with the current standard of care therapy include the findings that sublethal doses of radiation promoted the migration of glioma cells, leading to locoregional relapses [5]. Addition of a daily oral dose of the chemotherapeutic agent, temozolamide (TMZ) significantly improved the survival rate from 6%–10% compared with patients treated with adjuvant radiotherapy alone [6,7]. However, development of drug resistance and toxicity is the major drawbacks with this chemotherapy regimen [8]. Moreover, tumor recurrence is almost inevitable even after a therapeutic strategy using a combination of the most extensive tumor resection possible along with post-operative adjuvant radiochemotherapy [3,9–11].

A number of studies have investigated the factors predicting tumor recurrence and survival in HGG patients. Some molecular markers which have been used for prognostic purposes as well as to identify glioma subtypes include 1p/19q chromosomal codeletion, isocitrate dehydrogenase (IDH) mutations, methylation of O-6-methylguanine-DNA-methyltransferase promoter (MGMT), amplification of the epidermal growth factor receptor (EGFR) gene, and overexpression of vascular endothelial growth factor A (VEGF-A) [12–14]. Additionally, age, histopathology, molecular pathology and imaging, the extent of tumor resection and Karnofsky Performance Scale (KPS) scores have been shown to be correlated with prognosis [15–17].

The median age of onset of HGG is 64 years old and patients >70 years old comprise almost 20% of all newly diagnosed glioblastoma cases in the United States [18]. Elderly patients are more prone to complications, their ability to tolerate surgery, chemotherapy and radiotherapy is inferior to that of young patients, and they are generally excluded from most clinical trials. Elderly patients have also been shown to express higher levels of VEGF compared with younger patients, and this has been suggested to contribute to the fact that they have a worse prognosis than young patients [19]. A number of studies have evaluated age as a prognostic factor. A single institutional review of 70 patients with intracranial anaplastic

Abbreviations: AIC, Akaike information criterion; CI, confidence interval; EGFR, epidermal growth factor receptor; GBM, glioblastoma multiforme; HGG, high-grade glioma; HR, hazard ratio; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Scale; MGMT, O-6-methylguanine-DNA-methyltransferase; OS, overall survival; SD, standard deviation; TMA, temozolamide; VEGF-A, vascular endothelial growth factor A.

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oligodendroglioma showed that patients <50 years old had a significantly longer median survival compared with patients >50 years old [15]. Other studies also demonstrated that in addition to KPS scores, extent of surgery, and histological characteristics, age was a significant prognostic factor [20,16,21]. In contrast, data from some studies suggested that age was not a prognostic factor in glioma patients [17,22].

Since there was a significant variation in the age classification standards used in the different studies, we hypothesized that the conflicting data from previous studies may be due to differences in the age classification standards. In this study, we aimed to evaluate the influence of different classification standards of age-groups on the prognosis of patients with high-grade hemispheric glioma.

2. Patients and methods

2.1. Clinical data

This study gathered clinical and imaging data from a total of 125 patients with high-grade hemispheric glioma who received surgery and then were pathologically verified at the Division of Neurosurgery of the First Affiliated Hospital of Fujian Medical University between June 2002 and June 2012. The extent of resection was determined using post-operative enhanced MRI within 3 days of surgery. The inclusion criteria are as follows: 1) presence of fully-resected high-grade hemispheric glioma under the operating microscope, 2) availability of clear radio-chemotherapy data and follow-up data, and 3) availability of clear pathological data. The exclusion criteria are as follows: 1) presence of infratentorial glioma, brain glioma or WHO grade I, II glioma, 2) absence of histopathological data and 3) absence of follow-up data. Patients who underwent partial resection or biopsy were also excluded (partial resection is indicated by the presence of an enhancing lesion which occupies more than 80% of the surgical cavity). Most of the study patients received post-operative radio-chemotherapy. The chemotherapy treatment plan included ≥4 cycles of temozolomide (TMZ; 150 mg/M2KOF/day); radiation therapy, with a single dose of 2 Gy up to a total dose of 54–58 Gy was concomitantly administered after the second cycle of chemotherapy. The irradiated area covered the operating region plus a safety margin of 2 cm. Chemotherapy was carried out at our clinical center, while radiotherapy was performed at different clinical centers. The accumulated numbers of irradiation ranged from 0 to 30, and a single irradiation dose to an individual ranged from 0 to 2.65 Gy. Pathological grades were based on the 2007 WHO classification standard of brain tumors [23].

Classification of patients by age was based on three different methods: (1) ≤50 or >50 age-groups as previously described by Yang et al. [15]; (2) ≤60 or 60 age-groups as previously described by Allahdini et al. [17]; and (3) ≤45, 45–65, or ≥65 age-groups as previously described by Lacroix et al. [24].

The primary outcome was overall survival (OS), which was defined as the time period from the first surgery until death or until the final follow-up visit. The study was terminated on June 1st, 2012. A total of 39 patients were still alive at the end of follow-up and 86 patients had died (28 grade III cases, 58 grade IV cases).

Informed consent was obtained from all study patients and the study was approved by the medical ethics committee of the Fujian Medical University.

2.2. Statistical analyses

Categorical variables were shown as number and percent, while continuous variables were shown as mean and standard deviation (SD). Subjects were followed-up from the time of surgical operation until death or until the last follow-up. Kaplan–Meier survival analyses were used to estimate the probability of survival with different age-groups as cut-off points. Log-rank tests were performed to compare survival rates among age-groups. Cox proportional hazard regression models were performed to calculate hazard ratio (HR) with 95% confidence interval (CI) for risk of death. In order to identify significant effects of each variable with multiple categories, tests of global null hypothesis by likelihood ratio tests were further used by comparing intercept-only model to the model with the variable being tested.

The multivariate Cox regression model included significant variables identified by univariate analysis, except for age-groups. Subsequently, a backward selection procedure was performed; variables with p-values of less than 0.05 were included in Model I. After the multivariate Cox regression model (Model I) was constructed, three separate models were created by applying age-groups with different cut-off points. These included Model II: ≤45 years, 46–64 years, and ≥65 years; Model III: ≤50 years and >50 years; and Model IV: ≤60 years and >60 years. The Akaike information criterion (AIC) was calculated to determine the best cut-off point of age among three multivariate models. The model with the lowest AIC value was considered as the best model. All statistical analyses were performed with SAS software version 9.2 (SAS Institute Inc., Cary, NC). A two-tailed $p < 0.05$ indicated statistical significance.

3. Results

The study population comprised 78 males (62.4%) and 47 (37.6%) females. The ratio of males to females was 1.66:1. The age range of the study subjects was 16–78 and the mean age was 48.1 years (SD = 14.6 years). Analysis of age of the study patients showed that 43.2% of the subjects was under 45 years old, 47.2% was >50 years old, and 21.6% of subjects was >60 years old (Table 1). A total of 38 patients did not receive any chemotherapy, 53 patients (42.4%) received irregular chemotherapy, and 34 patients (27.2%) received regular chemotherapy. Sixty patients did not receive any radiotherapy and 65 patients received radiotherapy. There were 56 patients classified as WHO grade III, and 69

Table 1
Distribution of demographic and clinical characteristics and estimated risk of death in patients with gliomas of cerebral hemisphere.

Characteristics	n	(%)	HR[b]	(95% CI)	p
Gender					
Male	78	(62.4)	1.00		
Female	47	(37.6)	0.61	(0.39–0.97)	0.036
Chemotherapy					
No	38	(30.4)	1.00		
Irregular	53	(42.4)	0.62	(0.38, 1.01)	0.055
Regular	34	(27.2)	0.40	(0.22, 0.71)	0.002
Radiotherapy					
No	60	(48.0)	1.00		
Yes	65	(52.0)	0.51	(0.33, 0.79)	0.002
Grade					
III	56	(44.8)	1.00		
IV	69	(55.2)	3.06	(1.93, 4.86)	<0.001
Karnofsky Performance Scale[a]	71.8	(10.4)	0.98	(0.97, 1.00)	0.021
Laterality					
Left	68	(54.4)	1.00		
Right	48	(38.4)	0.87	(0.56, 1.36)	0.544
Location					
Lobar	103	(82.4)	1.00		
Non-lobar	18	(14.4)	1.87	(1.06, 3.31)	0.030
Size (cm^3)[a]	67.1	(46.9)	1.00	(0.99, 1.00)	0.504
Age group 1					
≤45 years	54	(43.2)	1.00		
46–64 years	56	(44.8)	2.21	(1.37, 3.57)	0.001
≥65 years	15	(12.0)	3.05	(1.57, 5.94)	0.001
Age group 2					
≤50 years	66	(52.8)	1.00		
>50 years	59	(47.2)	2.47	(1.59, 3.82)	<0.001
Age group 3					
≤60 years	98	(78.4)	1.00		
>60 years	27	(21.6)	2.77	(1.68, 4.55)	<0.001

Abbreviation: HR = hazard ratio; CI = confidence interval.
[a] Data were shown as mean (standard deviation).
[b] HR and 95% CI were calculated by Cox regression analysis.

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