Journal of Clinical Neuroscience 21 (2014) 1709–1713

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Treatment and survival of patients harboring histological variants of glioblastoma

Alicia Ortega, Miriam Nuño, Sartaaj Walia, Debraj Mukherjee, Keith L. Black, Chirag G. Patil *

Center for Neurosurgical Outcomes Research, Maxine Dunitz Neurosurgical Institute, Department of Neurosurgery, Cedars-Sinai Medical Center, Advanced Health Sciences Pavilion, 127 S. San Vicente Boulevard, Suite A6600, Los Angeles, CA 90048, USA

ARTICLE INFO

Article history:
Received 9 April 2014
Accepted 4 May 2014

Keywords:
Chemotherapy
Giant cell glioblastoma
Glioblastoma
Gliosarcoma
Overall survival

ABSTRACT

It is unclear whether the survival difference observed between glioblastoma (GBM), giant cell glioblastoma (gcGBM), and gliosarcoma (GSM) patients is due to differences in tumor histology, patient demographics, and/or treatment regimens. The USA National Cancer Database was utilized to evaluate patients diagnosed with GBM, gcGBM, and GSM between 1998 and 2011. Kaplan–Meier survival estimates and Cox proportional hazards models were utilized to estimate overall survival. A cohort of 69,935 patients was analyzed; 67,509 (96.5%) of these patients had GBM, 592 (0.9%) gcGBM, and 1834 (2.6%) GSM. The median age for GBM and GSM patients was 61 *versus* 56 years for gcGBM ($p < 0.0001$). Higher extent of resection ($p < 0.0001$) and radiation ($p = 0.001$) were observed in gcGBM patients compared to other histologies. Multivariate analysis showed that gcGBM patients had a 20% reduction in the hazards of mortality (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.69–0.93) compared to GBM, while GSM patients trended towards higher hazards of mortality (HR 1.04, 95% CI 0.96–1.12) than the GBM cohort. Previous studies have suggested a disparity in the survival of patients with GBM tumors and their histological variants. Using a large cohort of patients treated at hospitals nationwide, this study found a 20% reduction in the hazards of mortality in gcGBM patients compared to GBM. Similarly, gcGBM patients had a 24% reduction in the hazards of mortality compared to the GSM cohort. GSM patients had a 3% increase in the hazards of mortality compared to GBM.

1. Introduction

Glioblastoma (GBM) is a glioma characterized by rapid, aggressive growth and it accounts for the greatest proportion of malignant primary brain tumors in adults [1]. Approximately 54% of all malignant brain tumor cases are GBMs [1]. This disease is characterized by a set of genomic alterations and also by aggressively infiltrating, hyperchromatic cells that have a great deal of variation in tumor size and shape, making it difficult to differentiate distinct variants [1,2]. However, giant cell glioblastoma (gcGBM) and gliosarcoma (GSM) have been identified as unique GBM subtypes, as they possess distinct histological identities that are relevant for clinical outcomes and yet still belong under the overarching entity of GBM [3]. Treatment for GBM and its histological variants typically involves radiation and chemotherapy [1].

GSM is a rare malignancy involving both glial and sarcomatous tissue. This variant is associated with an incidence between 1% and 8% of GBM and is thought to possess a slightly lower overall survival when compared to classic GBM [4–6]. GSM possesses many genomic alterations similar to classic GBM. Unlike classic GBM, however, in which epidermal growth factor receptor (EGFR) mutations and amplification are dominant features, GSM tumors are characterized by infrequent EGFR mutations. GSM tumors also have a predilection for the temporal lobe and are distinguished pathologically from classic GBM tumors when considering clinical progression [1,4]. gcGBM is a rare histological variant of GBM characterized by giant, multinucleated cells and lymphocytic infiltration [7]. Similar to GSM, gcGBM tumors also display infrequent EGFR mutations. Furthermore, gcGBM cells, while sharing many similarities in genomic alterations with GBM, experience significantly more polyploidy when compared with classic GBM samples [1]. Approximately 5% of all GBM cases are gcGBMs [8–10]. gcGBM is traditionally thought to be characterized by a younger patient population than GBM and GSM [7–9,11,12].

Recent small studies have purported that when compared to GBM, gcGBM has a higher overall survival rate, while GSM is associated with an inferior prognosis [2,4,7,10,13,14]. However, due to the lack of reported case series of gcGBM, it is unclear whether this proposed superior survival is due to a histological difference

* Corresponding author.
E-mail address: chirag.patil@cshs.org (C.G. Patil).

http://dx.doi.org/10.1016/j.jocn.2014.05.003
0967-5868/

between gcGBM and GBM or is simply a consequence of favorable patient characteristics, such as age at diagnosis, extent of tumor resection, and/or treatment regimens, to name a few. Thus, in this study we aimed to elicit the nature of the differences between GBM, gcGBM, and GSM patients and the association of these disparities with overall survival.

2. Methods

2.1. Patient population

A retrospective cohort of 69,935 adult (age 18 years and older) GBM patients diagnosed between 1998 and 2011 from the USA National Cancer Database (NCDB) were included in this analysis; 67,509 of these patients had classic GBM histology, 592 gcGBM, and the remaining 1834 were classified as GSM. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. This nationwide database contains outcomes data from more than 1500 cancer programs in the United States and Puerto Rico. Using the International Classification of Disease for Oncology, Third Edition, histology codes 9440 (GBM not otherwise specified), 9441 (gcGBM), and 9442 (GSM), an initial cohort of patients was identified within the NCDB. Patients under the age of 18 or without microscopic confirmation of tumor were excluded from the analysis. Survival data were available for 41,035 (58.7%) patients who were diagnosed prior to 2006.

2.2. Variables

Patient information on age in years, race, median household income, extent of surgical resection, tumor location, and tumor size were extracted. Extent of resection was defined as near/gross total resection, partial resection, or biopsy according to the surgery of primary site codes in the NCDB. A detailed description of treatment with radiation (including external beam, intensity-modulated radiation therapy, or stereotactic radiosurgery) or chemotherapy (single *versus* multiple agents) was documented. The outcome of overall survival was defined as the time from diagnosis to date of death or date of last contact for those patients with censored date of death. Patients diagnosed after 2006 did not have survival data available for analysis.

2.3. Statistical methods

Descriptive statistics were reported for all patients as well as by subgroups according to histology. Continuous variables were described using means and medians, whereas categorical variables were reported in terms of frequencies. Univariate analyses of demographic or clinical factors were conducted using Wilcoxon rank sum and Fisher's exact tests where appropriate. Kaplan–Meier survival estimates and log-rank tests were utilized for all patients with survival data. Multivariate analysis was performed using adjusted hazard ratios (HR) to identify factors associated with survival for this same subset of subjects (n = 41,037). HR, 95%

Table 1
Demographics and tumor characteristics of patients diagnosed with glioblastoma tumors, 1998–2011

Variable	All patients n = 69,935	Tumor histologies			*p* value
		Glioblastoma n = 67,509 (96.5%)	Giant cell glioblastoma n = 592 (0.8%)	Gliosarcoma n = 1834 (2.6%)	
Age at diagnosis, years					
Mean (SD)	60.8 (12.95)	60.9 (12.9)	54.5 (15.5)	60.4 (12.9)	<0.0001
Median [IQR]	61 [70–52]	61.0 [70–52]	56 [67–45]	61 [70–52]	
Female	29,225 (41.8)	28,208 (41.8)	253 (42.7)	764 (41.7)	0.89
Race					
White	63,842 (91.3)	61,683 (91.4)	528 (89.2)	1631 (88.9)	<0.0001
Black	3642 (5.2)	3466 (5.1)	32 (5.4)	144 (7.6)	
Native American	102 (.2)	100 (.15)	0 (0.0)	2 (.1)	
Asian	1097 (1.6)	1053 (1.6)	22 (3.7)	22 (1.2)	
Other	488 (.7)	471 (.7)	5 (.8)	12 (.7)	
Hispanic	3555 (5.1)	3424 (5.1)	33 (5.8)	97 (5.7)	0.64
Median household income, USD					
<$30,000	7876 (11.9)	7601 (11.9)	71 (12.7)	204 (11.9)	0.02
$30,000–$35,00	12,042 (18.3)	11,609 (18.31)	80 (14.3)	353 (20.5)	
$35,000–$45,999	18,217 (27.7)	17,581 (27.7)	181 (32.3)	455 (26.5)	
>$46,000	27,564 (41.9)	26,627 (41.9)	229 (40.8)	708 (41.2)	
Extent of resection					
Biopsy	30,462 (44.2)	29,501 (44.3)	214 (36.7)	747 (41.2)	<0.0001
Partial resection	18,520 (26.9)	17,934 (26.9)	141 (24.2)	445 (24.52)	
Near/Gross total Resection	19,952 (28.9)	19,101 (28.7)	228 (39.1)	623 (34.3)	
Tumor size, cm					
Mean (SD)	5.0 (6.6)	5.0 (6.6)	5.5 (1.6)	5.2 (6.7)	0.02
Tumor location					
Frontal lobe	18,881 (27.0)	18,272 (27.1)	180 (30.4)	429 (23.4)	<0.0001
Temporal lobe	19,428 (27.8)	18,571 (27.5)	177 (29.9)	680 (37.1)	
Parietal lobe	11,886 (17.0)	11,554 (17.1)	97 (16.4)	235 (12.8)	
Occipital lobe	3368 (4.8)	3275 (4.9)	22 (3.7)	71 (3.9)	
Overlapping lobe	9333 (13.4)	9022 (13.4)	62 (10.5)	249 (13.6)	
Infratentorial lobe*	637 (.9)	599 (.9)	<10 (1.5)	29 (1.6)	
Other**	6402 (9.2)	6216 (9.2)	45 (7.6)	141 (7.7)	

Missing data rates: race (1.1%), income (6.1%), resection (1.4%), tumor size (29.0%).
Data are presented as number (%) unless otherwise specified.
IQR = interquartile range, SD = standard deviation, USD = United States dollars.
* Brain stem, cerebellum.
** Brain not otherwise specified, cerebrum.