Journal of Clinical Neuroscience 30 (2016) 65–70

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

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

Clinical Study

A national perspective of adult gangliogliomas

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ARTICLE INFO

Article history:
Received 16 December 2015
Accepted 27 December 2015

Keywords:
Chemotherapy
Extent of resection
Ganglioglioma
Gross-total resection
Overall survival
Radiation

ABSTRACT

Gangliogliomas (GG) are rare tumors of the nervous system. Patient characteristics and clinical outcomes of low and high-grade GG have been difficult to elucidate in the adult population. This study aims to further elaborate on GG treatment and overall survival utilizing a larger cohort than previously published. The USA National Cancer Database was utilized to evaluate adult (age 18 years and older) patients diagnosed with GG between 2004 and 2006. Descriptive statistics and Kaplan–Meier overall survival estimates were provided. A total of 198 adult GG patients were diagnosed between 2004 and 2006. Of these, 181 (91.4%) were low-grade and 17 (8.6%) high-grade GG. Overall, the median age was 36 years; approximately 50% of patients were female, and 86.5% Caucasian. Most patients (59%) had near/gross total resection. Radiation and chemotherapy were prescribed in 18 (9.1%) and 11 (5.7%) patients, respectively. Radiation (64.7% *versus* 3.9%, $p < .0001$) and chemotherapy (47.1% *versus* 1.7%, $p < .0001$) were more frequently given to patients with high-grade tumors than low-grade. The median overall survival of high-grade GG was 44.4 months (95% confidence interval [CI]: 10.5–92.5) while the corresponding estimate for low-grade tumors was not reached. Older age (hazard ratio [HR] 1.72, 95% CI: 1.26–2.34) and high tumor grade (HR 3.91, 95% CI: 1.43–10.8) were found to be associated with poor survival. Adult GG have a temporal lobe predilection and overall gross total resection rate of 59%. Older patients with high-grade tumors had an increased hazard of mortality. High-grade GG were significantly more likely to be treated with radiation therapy and chemotherapy.

1. Introduction

Gangliogliomas (GG) are the most common glial-neuronal neoplasm and are characterized by a mix of neoplastic astrocytes and atypical ganglion cells. They are benign, slow-growing neoplasms that account for 1% of all brain tumors [1]. According to recent reports, the incidence of GG is between 1.3% and 10% of all primary brain tumors in adults and up to 10% of primary brain tumors in children [2–5]. The World Health Organization classifies GG into three distinct categories: gangliocytoma (often referred to as low-grade; grade I and II), anaplastic (grade III), and ganglioblastomas (grade IV) [6]. Grade III and IV GG are sometimes referred to as high-grade tumors. Gangliocytomas are characterized by their uniform mature neural ganglion cell structure resembling neurocytoma [7]. Anaplastic GG and ganglioblastomas are typically malignant transformations of previously diagnosed benign tumors and are characterized by prominent hypercellularity, high mitotic activity, and necrosis [6,8–10].

GG may arise from anywhere in the central nervous system, but approximately 80% of these tumors are found in the frontal and temporal lobe and patients therefore present with seizures [11]. Although fairly distributed between the sexes, GG are more prevalent in younger populations, with 60–80% of patients being less than 30 years old. Clinical presentation depends on tumor location, however most patients (62–100%) with supratentorial GG present with seizures. GG located in temporal lobes frequently present with medically intractable partial complex seizures [11,12].

Surgery is the treatment of choice for GG. These neoplasms are often well circumscribed, which increases the likelihood of gross total resection (GTR), which has been shown to significantly reduce seizure frequency and prolong survival [13,14]. Adjuvant radiation therapy and chemotherapy are typically reserved for grade III or grade IV patients or those with incomplete surgical resections or recurrence. Evidence on radiation efficacy remains inconclusive; some studies show that radiation improves overall survival while others demonstrate no difference at all [2,12–14]. Similarly,

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http://dx.doi.org/10.1016/j.jocn.2015.12.028
0967-5868/

chemotherapy is not routinely used to manage GG and there is a paucity of studies reporting clinical outcomes in GG patients following adjuvant chemotherapy [7]. Our study aims to utilize the USA National Cancer Database (NCDB) to report the largest series worldwide of adult patient and tumor characteristics, as well as treatment patterns to analyze their effects on outcomes.

2. Methods

2.1. Patient population

A retrospective cohort of 198 adult (age 18 years and older) GG patients diagnosed between 2004 and 2006 from the NCDB were included in this analysis; 181 (91.4%) of these cases were low-grade tumors, and the remaining 17 (8.6%) were high-grade tumors. NCDB is a nationwide database containing outcomes data from more than 1500 cancer programs accredited by the Commission on Cancer in the United States and Puerto Rico. We used the *International Classification of Disease for Oncology, Third Edition* histology codes 9505 (GG) and 9404 (gangliocytoma). A detailed description of our inclusion criteria and the data variables utilized for this query are as follows: (1) histology 9492, 9505 [variable: *histology*], (2) GG/gangliocytoma tumors were primary site tumors [data: *sequence_number*], (3) underwent surgical procedure [data: *rx_summ_surg_prim_site*], (4) had survival data [data: *vital_status*], (5) diagnostic confirmation [data: *diagnostic_confirmation*], and (6) grade that was specifically documented as either low-grade or high-grade [data: *cs_sitespecific_factor1*]. Grade specific data according to *cs_sitespecific_factor1* was only available for cases diagnosed from 2004 onwards.

2.2. Variables

Patient characteristics include age in years, sex, race/ethnicity, extent of surgical resection (near/gross total, partial, and biopsy), tumor size (mm), and tumor location. A detailed description of treatment with radiation (for example, external beam, intensity-modulated radiation therapy, stereotactic radiosurgery) and chemotherapy (single *versus* multiple agents), and the time of these therapies from diagnosis were also documented. All treatments documented in the NCDB are the ones prescribed as the initial course of treatment after surgery. While the estimate of median overall survival has not been reached, we provide a preliminary description of overall survival. The overall estimate of survival is defined as the time from diagnosis to date of death or date of last contact for those patients with censored date of death.

2.3. Statistical methods

Descriptive statistics were reported for all patients, as well as by subgroup according to tumor grade (low *versus* high). Continuous variables were described using means, medians, standard deviation, and interquartile range, whereas categorical variables were reported in terms of frequencies. Bivariate analysis between patient and tumor characteristics, as well as treatment and tumor grade, were conducted using Wilcoxon rank sum and Fisher's exact tests where appropriate. Survival was estimated by the Kaplan–Meier life method and a multivariate Cox proportional hazards model was used to evaluate the association of clinical and patient characteristic with survival. Hazard ratio (HR), 95% confidence intervals (CI) and p values are reported throughout. A p value cut-off of 0.05 was considered statistically significant. All statistical analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Demographics

A total of 198 adult patients were diagnosed with GG/gangliocytoma tumor between 2004 and 2006. Most cases were low-grade tumors (91.4%). Overall, the median age of diagnosis was 35.5 years, with 49% of patients being female, 86.5% Caucasian, and 13.5% of non-Caucasian descent (Table 1). Most (59%) patients underwent near/gross total resection, 20% partial resection, and 21.0% biopsy. The median size of tumors was 25.5 mm and a large proportion of tumors were located in the temporal lobe (32.8%), followed by frontal (21.2%), and parietal lobes (10.1%). Patients in the low and high-grade cohorts were comparable according to

Table 1
Demographic and tumor characteristics for patients diagnosed with ganglioglioma, 2004–2006

Variable	All patients N = 198	Low-grade tumors N = 181 (91.4%)	High-grade tumors N = 17 (8.6%)	p value
Age at diagnosis, years				.12
Mean (SD)	37.6 (14.7)	37.0 (14.5)	43.4 (16.4)	
Median [IQR]	35.5 [49–25]	34.0 [48–25]	39.0 [56–33]	
Female, N (%)	97 (49.0)	88 (48.6)	9 (52.9)	.73
Race, N (%)				1.0
Caucasian	167 (86.5)	152 (86.4)	15 (88.2)	
Non-Caucasian	26 (13.5)	24 (13.6)	2 (11.8)	
Extent of resection, N (%)				.87
Near/gross total	115 (59.0)	106 (59.2)	9 (56.3)	
Partial resection	39 (20.0)	35 (19.6)	4 (25.0)	
Biopsy	41 (21.0)	38 (21.2)	3 (18.8)	
Tumor size, millimeters				.03
Mean (SD)	31.9 (23.8)	30.9 (24.0)	42.5 (19.6)	
Median [IQR]	25.5 [40–20]	25 [40–18]	38 [55–25]	
Unknown	68 (34.3)	68 (34.3)	0 (0)	
Tumor location summarized, N (%)				.52
Supratentorial	146 (73.4)	133 (73.5)	13 (76.5)	
Infratentorial	17 (8.6)	17 (9.4)	0 (0)	
Other	35 (17.7)	31 (17.1)	4 (23.5)	

Missing data: race (2.5%), extent of resection (1.0%), Hispanic (11.1%).
IQR = interquartile range, SD = standard deviation.