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Clinical Study

Impact of histopathological transformation and overall survival in patients with progressive anaplastic glioma

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ABSTRACT

Progression of anaplastic glioma (World Health Organization [WHO] grade III) is typically determined radiographically, and transformation to glioblastoma (GB) (WHO grade IV) is often presumed at that time. However, the frequency of actual histopathologic transformation of anaplastic glioma and the subsequent clinical impact is unclear. To determine these associations, we retrospectively reviewed all anaplastic glioma patients who underwent surgery at our center at first radiographic progression, and we examined the effects of histological diagnosis, clinical history, and molecular factors on transformation rate and survival. We identified 85 anaplastic glioma (39 astrocytoma, 24 oligodendroglioma, 22 oligoastrocytoma), of which 38.8% transformed to GB. Transformation was associated with shorter overall survival (OS) from the time of diagnosis (3.4 *vs.* 10.9 years, $p = 0.0005$) and second surgery (1.0 *vs.* 3.5 years, $p < 0.0001$). Original histologic subtype did not significantly impact the risk of transformation or OS. No other factors, including surgery, adjuvant therapy or molecular markers, significantly affected the risk of transformation. However, mutations in isocitrate dehydrogenase 1 (IDH1) was associated with longer time to progression (median 4.6 *vs.* 1.4 years, $p = 0.008$) and OS (median 10.0 *vs.* 4.2 years, $p = 0.046$). At radiographic progression, tissue diagnosis may be warranted as histologic grade may provide valuable prognostic information and affect therapeutic clinical trial selection criteria for this patient population.

1. Introduction

Anaplastic diffuse glioma (astrocytoma, oligodendroglioma and oligoastrocytoma) are malignant World Health Organization (WHO) grade III tumors that almost universally recur after initial treatment [1–3]. Recurrence or progression is most commonly determined radiographically [4,5], and in this setting, transformation to glioblastoma (GB) is often presumed, particularly when certain radiographic features, such as gadolinium enhancement, are present. However, the reliability of common MRI sequences such as contrast-enhancement, diffusion-weighted imaging and perfusion-weighted imaging to distinguish grades of glial tumors is not yet validated [6–12]. The actual frequency of histopathologic transformation when MRI suggests progression is unclear.

We conducted a retrospective analysis of anaplastic glioma patients who underwent surgery (biopsy or resection) at our institution at first radiographic recurrence. We also examined the effect of clinical and molecular prognostic factors and treatment on the risk of transformation to GB and on patient survival. We sought to determine the frequency of reported histopathologic transformation of anaplastic gliomas to GB at first relapse, the determinants that affect the risk of transformation, and the survival of patients as a function of histologic grade at recurrence.

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2. Materials and methods

2.1. Clinical parameters

Through review of a prospectively collected database of all patients treated at our brain tumor center, we identified patients aged 18 years or older who were diagnosed with an anaplastic (WHO grade III) glioma (astrocytoma, oligodendroglioma or oligoastrocytoma), underwent surgery at our institution between 1993–2012 at first radiographic progression, and had diagnostic tumor samples from the time of both initial diagnosis and radiographic progression. We excluded patients in whom a second surgery was performed due to suspicion of tumor undersampling and when a second surgery was performed without evidence of progression. We also excluded patients whose second surgical specimen demonstrated entirely treatment-related necrosis.

We relied upon the pathology reports generated by Massachusetts General Hospital neuropathologists. Common practice in the division for uncertain diagnoses is that a consensus panel of neuropathologists makes an assessment and renders the formal pathology report.

Tumors were diagnosed and graded according to the current WHO criteria [13] at the time of the procedure. We catalogued patient demographics, Karnofsky Performance Status (KPS) scores, MRI findings, treatment history, overall survival (OS), and time to first progression (TTP), and histopathologic diagnoses. Isocitrate dehydrogenase (IDH) mutation status was obtained by immunohistochemistry using an IDH1 R132H antibody [14] or SNaPshot genotyping [15]. Loss of 1p and 19q material was determined by fluorescence in situ hybridization. The institutional review board approved the study prior to its initiation.

2.2. Statistical methods

Variables in the analysis included age at diagnosis, KPS at second surgery, histologic subtype at diagnosis, tumor grade, type of surgery at diagnosis and at recurrence, OS from time of initial diagnosis, OS from time of recurrence, TTP from diagnosis, contrast enhancement of the original tumor, new contrast enhancement at recurrence, post-surgery treatment (radiotherapy and chemotherapy regimens), IDH1 mutation, and 1p/19q co-deletion. The chi-squared test of analysis of variance and the Fisher's exact test were used to compare categorical and continuous variables across the selected groups. Cumulative survival probabilities were estimated using the Kaplan–Meier method. The logrank test was used to compare survivals of groups. In addition, in survival comparisons, proportional hazards regression models were fitted, and age was included as a covariate. Multivariate analysis was limited by small sample sizes in each subgroup. In all cases, two-sided p values < 0.05 were considered statistically significant.

3. Results

We included 85 patients with an initial diagnosis of WHO grade III anaplastic glioma who underwent a second surgery at our institution (Table 1). Of these, 39 (46%) were astrocytomas, 24 (28%) were oligodendrogliomas, and 22 (26%) were oligoastrocytomas. The median follow up time of the entire cohort was 6.0 years (range 0.6–32.6 years). The median OS of the entire cohort was 8.2 years (95% CI 4.6–10.8 years) and median TTP was 20.5 months (95% CI 17–34 months).

At first recurrence, 33 (38.8%) patients transformed to GB, and 52 (61.2%) remained grade III. The patients in the two groups were balanced in terms of demographic characteristics and initial treatment (Table 1). Of note, a majority of patients received adjuvant chemotherapy in addition to or concurrent with radiation therapy after diagnosis (67 patients, 85% of the entire cohort), while only 12 patients (14%) received radiation alone and six patients (7%) received chemotherapy only. All of the patients treated with chemotherapy alone had the 1p/19q co-deletion. Concurrent radiation and temozolomide per standard protocol for GB [16] (with 12 adjuvant temozolomide cycles) was used for 31 patients (36%). Temozolomide was the chemotherapeutic agent most commonly used at diagnosis, (33 patients, 39%), followed by procarbazine, lomustine, vincristine (PCV) chemotherapy (22 patients, 26%). Other regimens used at diagnosis included temozolomide plus PCV (1), BCNU (2), tamoxifen (1), propylthiouracil plus tamoxifen (1), bevacizumab plus irinotecan (1), topotecan (1), irinotecan (1) and imatinib plus celebrex (1).

Table 1
Clinical and molecular characteristics of patients with progressive anaplastic glioma

Characteristic	No transformation (n = 52)		Transformation to grade IV (n = 33)	
Age, years				
Median	40.1		40.6	
Range	19–73		21–66	
Sex				
Male	31 (59.6%)		19 (57.6%)	
Female	21 (40.4%)		14 (42.4%)	
KPS at recurrence	88.5		78.9	
	No. of Patients	%	No. of Patients	%
Pathology				
Astrocytoma	20	38.5	19	57.6
Oligodendroglioma	18	34.6	6	18.2
Oligoastrocytoma	14	26.9	8	24.2
Molecular subgroups				
1p/19q co-deleted	10/27	52.6	1/8	12.5
IDH-1 mutation	12/27	44.4	12/27	44.4
Radiology				
Contrast enhancement of initial tumor	27/36	75	15/22	68.2
New contrast enhancement	7/12	58.3	7/7	100
Surgery				
Initial resection	40	76.9	24	72.7
Biopsy	12	23.1	9	27.3
Treatment at Diagnosis				
Radiation only	8	15.4	4	12.1
Chemotherapy only	5	9.6	1	3
Radiation and chemotherapy	18	34.6	18	54.6
Chemoradiation per Stupp protocol[1]	21	40.4	10	30.3
Clinical trials after recurrence				
Enrolled in clinical trials	27	46.2	24	72.7
Mean number of clinical trials	0.93		0.54	

[1] Stupp R, et al. N Engl J Med. 2005 Mar 10;352(10):987–96.

3.1. Risk of transformation

At the time of first recurrence, 19 of 39 (49%) astrocytomas, 6 of 18 (33%) oligodendrogliomas and eight of 22 (36%) oligoastrocytomas transformed to GB. The original histologic subtype did not significantly impact risk of transformation ($p = 0.16$). In addition, there were no significant differences between purely astrocytic tumors *versus* tumors with any oligodendroglial histology ($p = 0.12$) or between purely oligodendroglial tumors *versus* tumors of any astrocytic histology ($p = 0.14$) in the risk of transformation. Although astrocytomas were twice as likely in our series, to transform into GB than were oligodendrogliomas, this trend did not reach statistical significance.

Contrast-enhancement of the tumor on initial MRI was not associated with risk of transformation ($p = 0.76$). Notably, most of the tumors in this cohort (73%) displayed contrast enhancement at diagnosis. Nineteen tumors had no gadolinium enhancement