Pediatric giant cell glioblastoma: New insights into a rare tumor entity

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Little is known about giant cell glioblastoma (GCG) in pediatric patients. The present study identified 18 pediatric patients with centrally reviewed GCG from the HIT-GBM database of the Gesellschaft für Paediatrische Onkologie und Haematologie in Germany, Austria, and Switzerland. Clinical and epidemiological data were compared with those of 178 pediatric patients with centrally reviewed glioblastoma multiforme (GBM) from the same database. In this unique series, median age, male preference, and median clinical history did not differ significantly between pediatric GCG and GBM patients. GCG showed a stronger predilection for cerebral hemispheres than did GBM, which may only partly explain the higher percentage of gross total tumor resections in GCG patients. Most surprising, the widely distributed hypothesis that GCG may imply a better prognosis than GBM could not be substantiated for our pediatric series. Future studies with larger patient numbers and molecular pathological analyses are still needed to corroborate the present findings and further elucidate the biology of GCG in children. *Neuro-Oncology 11, 323–329, 2009 (Posted to Neuro-Oncology [serial online], Doc. D07-00214, December 2, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-099)*

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Glioblastoma multiforme (GBM) is a clinically, histologically, and genetically quite heterogeneous highly malignant brain tumor.[1] The current WHO classification of brain tumors recognizes two other distinct variants of classical GBM: gliosarcoma and giant cell glioblastoma (GCG).[2] The latter variant is characterized by a predominance of bizarre, multinucleated giant cells, an occasionally abundant reticulin network, and a high frequency of *TP53* mutations. It represents 5% of all glioblastomas,[3–5] and its incidence in adults is 0.8% of all brain tumors and even less in pediatric patients.[6] Clinically, despite a poor prognosis for GCG in most reports, this variant is associated with a longer survival compared with GBM in both adults[7–9] and children.[1,10–13]

The present study retrospectively analyzed data on pediatric patients with GCG who had been enrolled in the HIT-GBM trials in Germany, Austria, and Switzerland since 1994. Since very few data regarding pediatric GCG are available, the present study with 18 centrally reviewed pediatric GCG cases represents the largest patient cohort of this rare tumor entity to date. A systematic analysis of epidemiology, tumor characteristics, and potential prognostic parameters was performed compared with 178 pediatric HIT-GBM patients with centrally reviewed GBM. Results are critically reviewed in the light of the present literature.

Patients and Methods

Patient Characteristics and Inclusion/Exclusion Criteria

Patient data were obtained from the HIT-GBM database of the Brain Tumor Study Group of the Society of Pediatric Oncology and Hematology in Germany, Austria, and Switzerland (Gesellschaft für Paediatrische Haematologie und Onkologie). Inclusion criteria were histopathological diagnosis of GCG or classic GBM confirmed by central neuropathological review (German Brain Tumor Reference Center, Department of Neuropathology, Bonn, Germany) and patient age of 0–17 years at time of initial diagnosis. Pediatric patients with centrally reviewed histopathological diagnosis of gliosarcoma were excluded from the present study.

By applying these criteria, 196 patients were identified, 18 with GCG and 178 with GBM. The clinical characteristics of these patients are listed in Tables 1 and 2. Informed consent for statistical analyses had been given by all patients and/or their parents at time of enrollment in the various HIT-GBM trials, in accordance with the Declaration of Helsinki.

HIT-GBM Treatment Protocols

Eligible pediatric patients older than 3 years but younger than 18 years with high-grade glioma and/or diffuse intrinsic pontine glioma had been enrolled in the various HIT-GBM trials since 1994. In all these trials, best feasible tumor resection was recommended before starting chemo- and/or radiotherapy. Standard fractionated radiotherapy (54–59.4 Gy total dose; daily fractions of 1.8 Gy over 6–7 weeks) was also common for all HIT-GBM trials. In HIT-GBM-A, oral etoposide and trofosfamide were given during radiotherapy and continued for 1 more year after radiotherapy.[14] In HIT-GBM-B, cisplatinum, etoposide, and ifosfamide were given in two cycles concomitantly with radiotherapy followed by intravenous low-dose cyclophosphamide and subcutaneous interferon-γ.[15,16] In HIT-GBM-C, weekly vincristine injections were added to the concomitant HIT-GBM-B radiochemotherapy. Chemotherapy with cisplatinum, etoposide, ifosfamide, and vincristine was continued during maintenance treatment.[17] The concomitant radiochemotherapy of HIT-GBM-C was also adopted for HIT-GBM-D, followed by a maintenance therapy with prednisolone, vincristine, and lomustine (CCNU). The therapeutic efficiency of two courses of high-dose methotrexate before radiotherapy was studied for feasibility in a pilot study (HIT-GBM pilot D) and then as a randomized question in HIT-GBM-D.[18] Children younger than 3 years of age were primarily treated with surgery and chemotherapy alone following the HIT-SKK chemotherapy protocol for infant patients with brain tumors.[19]

Central neuropathological and central neuroradiological reviews were highly recommended in HIT-GBM-A and HIT-GBM-B and mandatory for the HIT-GBM-C and HIT-GBM-D trials. The extent of tumor resection was determined on the basis of early postsurgical imaging and/or the neurosurgical report. Gross total tumor resection was defined as 100% macroscopic removal of the tumor mass. The category "nontotal tumor resection" included subtotal (<100% but ⩾90%) and partial (<90%) resection as well as an open or stereotactic biopsy without tumor debulking.

Statistical Analysis

Statistical analysis was retrospectively performed using SPSS, version 12.0, (SPSS Inc., Chicago, IL, USA). Overall survival (OS) and event-free survival (EFS) were determined by Kaplan-Meier analysis and log-rank testing. An event was defined as tumor relapse or progression, occurrence of a secondary malignancy, or death from any cause. Patient groups were categorized within each histological subtype (GCG, GBM) by the following parameters: sex (male/female), age (<11 years/⩾11 years or <3 years/⩾3 years), tumor location (cerebral hemispheres/all other locations), and extent of tumor resection (gross total tumor resection/nontotal tumor resection). The prognostic relevance regarding EFS and OS of the histological subtype (GCG vs. GBM) was compared for the subgroups for age, sex, tumor location, and extent of tumor resection, as defined above. The survival analysis was completed for each histological subtype by a Cox regression analysis (stepwise entry, 0.05; removal, 0.1; maximal iterations, 20) for the resulting subgroups. To compare epidemiological frequencies and disease/treatment characteristics between GCG and GBM, either the two-sided chi-square test (sex ratio, localization, frequency of radiotherapy, frequency of gross total tumor resection, chemotherapy regimens) or the Mann-Whitney test (age, median clinical history) was performed. For all statistical analyses, the significance level was set as $p < 0.05$.

Results

By retrospective analysis of patient data from the HIT-GBM trials in Germany, Austria, and Switzerland, 196 pediatric patients were identified who suffered from either GCG or GBM. Only patients with central neuropathological review were entered in this analysis. Of the 196 patients, 178 patients (90.8%) had a GBM, and 18 patients (9.2%) GCG. Median follow-up time was 0.9 years in both tumor entities, with a range of 0–7.49 years for GBM and 0.12–3.16 years for GCG.

The gender distribution did not differ significantly between the two histopathological subtypes: GBM was found in 101 males and 77 females (male-to-female ratio, 1.3:1), and GCG in 12 males and 6 females (male-to-female ratio, 2.0:1; Table 1). The median age was 11 years for both tumors, but the age range of affected children and young adolescents varied between the subtypes (GBM patients, 0–17 years; GCG patients, 4–17 years). The absence of GCG in infants younger than 3 years of age was not significant ($p = 0.2560$) compared with

Table 1. Epidemiology, tumor characteristics, and survival data of 196 pediatric patients with GBM and GCG from the HIT-GBM trials, all confirmed by central neuropathological review. Gross total removal appears to have been performed more often in GCG than in GBM patients (not significant), probably because of the small number of GCG in deep midbrain or brainstem locations where complete surgical removal is usually impossible. No significant difference was found for the parameters of age, sex, median clinical history, and survival.

Characteristic	GCG	GBM	Statistical Significance
Number of cases	18	178	
Male-to-female ratio	2.0:1	1.3:1	No[a]
Median age/range (years)	11 (4–17)	11 (0–17)	No[b]
Median clinical history/range (months)	0.93 (0.3–6.9)	1.0 (0–8.2)	No[b]
Median follow-up/range (years)	0.93 (0.12–3.16)	0.93 (0–7.49)	No[b]
Tumor localizations[d]			
Cerebrum/cortex	14	81	$p = 0.009$[a]
Basal ganglia/thalamus/deep midbrain	1	29	No[a]
Cerebellum	2	12	No[a]
Brainstem	0	35	$p = 0.038$[a]
Overlapping	1	14	No[a]
Others	0	7	No[a]
Extent of resection			
Total	44%	26%	No[a]
Nontotal	56%	74%	
Chemotherapy regimen			
HIT-GBM-A	0	21	No[a]
HIT-GBM-B	2	17	No[a]
HIT-GBM-C	4	49	No[a]
HIT-GBM-D	12	59	$p = 0.005$[a]
HIT-SKK	0	10	No[a]
No chemotherapy	0	10	No[a]
Other regimen	0	12	No[a]
Radiotherapy			
Yes	18	154	
No	0	17	No[a]
Unknown		7	
Event-free survival			
Median (years)	0.54	0.53	No[c]
One year	19% ± 11%	23% ± 3%	No[c]
Two years	9% ± 9%	10% ± 2%	No[c]
Overall survival			
Median (years)	1.18	1.08	No[c]
One year	64% ± 13%	53% ± 4%	No[c]
Two years	18% ± 15%	29% ± 4%	No[c]

[a]chi^2 test; [b]Whitney-Mann test; [c]log rank test; [d]some patients had multiple lobes involved.

patients younger than 3 years of age with GBM, who represented 6% ($n = 12$) of all pediatric GBM patients (Fig. 1).

The median duration of the initial clinical history of GBM and GCG was similarly short (GBM: 1.0 month, range 0–8.2 months; GCG: 0.9 months, range 0.3–6.9 months). In patients with GCG, symptoms of raised intracranial pressure and hemiparesis were the leading initial symptoms, prevalent in 83% and 50% of the cases, respectively. Diplopia, aphasia, vertigo, and seizures were initially found only in a few GCG patients (Table 2).

GCG was predominantly found in the cerebral hemispheres (78%, $n = 14$; Table 1), whereas GBM also arose in other brain regions in substantial numbers (cerebral hemispheres: 46%, $n = 81$; basal ganglia/thalamus/deep midbrain: 16%, $n = 29$; cerebellum: 6.7%, $n = 12$; brainstem: 20%, $n = 35$; Table 1). The absence of GCG in the brainstem and the predominance of locations within the cerebral hemispheres were both significant compared with GBM ($p = 0.009$ and $p = 0.038$).

Interestingly, 44% of GCG patients (8 of 18 cases) but only 26% of GBM patients (46 of 178) underwent

Table 2. Detailed tumor and treatment characteristics of the 18 pediatric GCG patients from the HIT-GBM trials. If patients were alive at the last visit, the time of follow-up since initial diagnosis is specified in brackets.

Patient No.	Age (Years)	Gender	History (months)	Initial Symptoms and Signs	Localization	Volume (cm)	Resection	Radio (Gy)	Survival (Months)[a]
1	7	F	1.37	Hemiparesis, aphasia	Cerebellum left side		Partial	54	11
2	12	M	0.37	Vomiting, aphasia, hemiparesis	Thalamus, hypothalamus, corpus callosum		Subtotal	59.4	Alive (1.5)
3	7	M	0.30	Vomiting, headache	Frontal lobe		Partial	59.4	14
4	9	M	1.27	Vomiting, headache	Occipital lobe, lateral ventricle	5.8 × 5.2 × 8	Subtotal	59.4	Alive (11)
5	13	M	0.93	Hemiparesis, attention deficit	Corpus callosum, left frontal lobe	4.6 × 5.5 × 4	Biopsy	59.4	14
6	13	M	0.70	Headache, hemiparesis	Thalamus, cerebellar peduncles, pons		Biopsy	45	6
7	17	M	1.00	Vomiting, headache, hemiparesis	Frontal lobe	4 × 3.8 × 3.8	Total	59.4	Alive (21)
8	17	M	1.13	Vomiting, headache	Temporal lobe	5.4 × 4.2 × 6.6	Total	59.4	Alive (18)
9	4	M	1.57	Vomiting, headache	Cerebellum		Partial	55	10
10	6	F	0.87	Seizures	Occipital lobe	3 × 3 × 2.7	Total	Yes[a]	Alive (4)
11	16	F	3.53	Headache, hemiparesis, aphasia	Temporal and parietal lobe	6 × 5 × 5	Partial	59.4	Alive (12)
12	16	F	0.57	Vomiting, headache, hemiparesis	Frontal lobe		Total	Yes[a]	Alive (6)
13	11	M	0.33	Vomiting, headache, ataxia, diplopia, vertigo	Parieto-occipital lobe		Subtotal	59.4	10
14	17	M	0.77	Vomiting, headache, diplopia	Frontoparietal lobe	2.5 × 3.3 × 3.3	Total	59.4	Alive (9)
15	8	F	6.90	Headache, hemiparesis, vertigo	Parietal lobe	1.7 × 1.6 × 1.5	Total	59.4	Alive (37)
16	7	M	0.83	Vomiting	Occipital lobe		Total	59.4	23
17	13	F	1.57	Vomiting, headache	Temporo-occipital lobe	5.5 × 6 × 5	Subtotal	59.4	11
18	10	M	2.37	Vomiting, headache	Frontal lobe, parasellar region	3 × 3 × 2.5	Total	59.4	12

[a]All patients received radiotherapy at a dosage between 45 and 59, 4 gray; in two patients (10 and 12) the dosage was not reported.

gross total tumor resection (not significant, two-sided chi-square test). To study whether this tendency may be explained by the fact that GCG occurred predominantly in locations where complete tumor resection is supposedly facilitated (e.g., cerebral hemispheres), a subgroup of GBM patients with similar tumor locations was defined. In this subgroup, the percentage of gross total tumor resection indeed increased from 26% to 33% (45 of 136 patients), but was still lower than for GCG patients, albeit not significant (two-sided chi-square test).

In Kaplan-Meier survival analysis, gross total tumor resection provided a significantly better OS than did nontotal resection in both GCG patients ($p = 0.0115$; Fig. 2) and GBM patients ($p < 0.001$; Fig. 3). This was also true for EFS in GBM patients ($p < 0.001$; data not shown), while in GCG only a tendency was observed ($p = 0.1095$, not significant; data not shown). Tumor location in cerebral hemispheres, compared with all other locations, showed a significant prolongation of OS ($p = 0.0014$ and $p = 0.0262$) and EFS ($p = 0.0005$ and $p = 0.0305$) for both GBM patients and GCG patients, respectively. Other clinical parameters (gender and age) were also analyzed in a univariate setting but showed no significant impact on survival in either GCG and GBM patients (data not shown). In addition, Cox regression analyses for gender, age, location, and extent of tumor resection as defined above confirmed the independent impact of tumor localization on OS and EFS in GCG ($p = 0.013$ and $p = 0.020$).

All patients with GCG received radiotherapy, compared with only 154 of 171 patients with GBM (seven patients were excluded from this analysis due to missing data regarding radiotherapy; $p = 0.16$, not significant, two-sided chi-square test; Table 1). All GCG and 156 GBM patients received chemotherapy according to the HIT-GBM protocols (a detailed overview is given in Table 1). Twenty-two GBM patients were treated without or by an individually tailored chemotherapy.

Finally, both tumor entities, GBM and GCG, were compared regarding their prognosis. In Kaplan-Meier

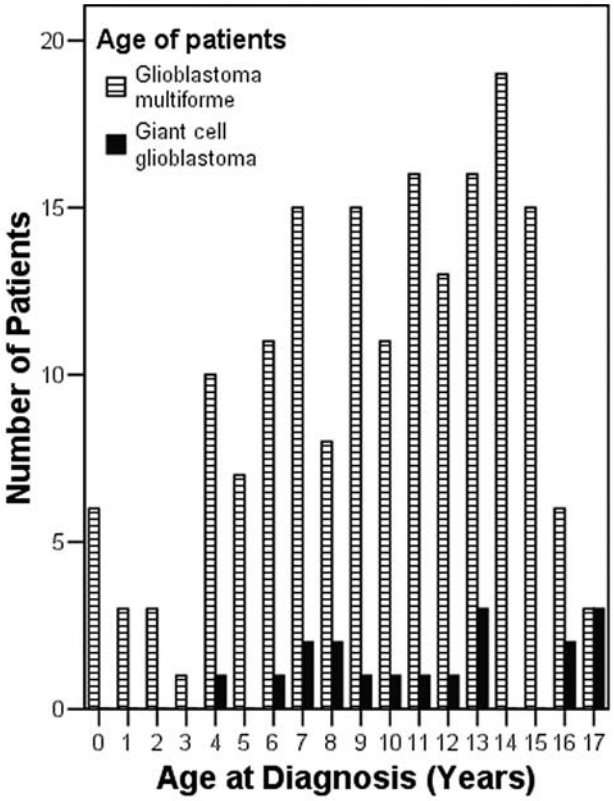

Fig. 1. Age at diagnosis of giant cell glioblastoma and glioblastoma multiforme in 196 pediatric patients from the HIT-GBM trials.

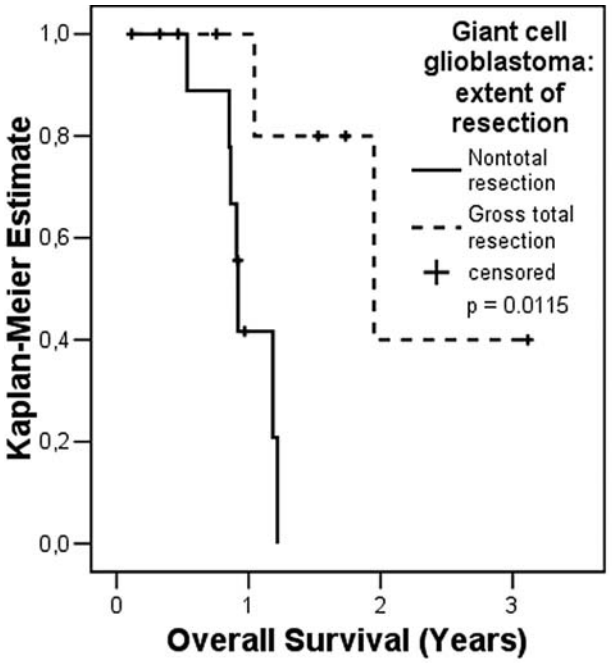

Fig. 2. Kaplan-Meier analysis of overall survival in 18 pediatric patients with giant cell glioblastoma in relation to the extent of tumor surgery (total vs. nontotal tumor resection). Difference in survival was significant ($p = 0.0115$) by log-rank test.

analyses, neither OS nor EFS showed significant differences between GCG and GBM. Median OS was 1.18 years for GCG and 1.08 years for GBM; median EFS was 0.54 years for GCG and 0.53 years for GBM (Table 1). The 1-year OS in GCG and GBM was 64% ± 13% and 53% ± 4%, respectively, and the 2-year OS was 18% ± 15% and 29% ± 4%, respectively (Table 1). The 1-year EFS in GCG and GBM was 19% ± 11% and 23% ± 3%, respectively, and the 2-year EFS was 9% ± 9% and 10% ± 2%, respectively (Table 1).

Discussion

According to the current WHO classification of brain tumors, GCG represents a distinct histological subtype of GBM.[2] Especially in pediatric patients, relatively little is known about the epidemiology and characteristics of this tumor entity because systematic reviews of larger case series are missing due to its rare incidence. The present study therefore aimed at further characterization of GCG in children. The access to the HIT-GBM database with the largest series of pediatric patients with centrally reviewed high-grade gliomas represents a unique prerequisite to perform this task.

According to previous pediatric case series with small patient numbers, it was suggested that GCG may represent about 5% of glioblastomas,[12,20–22] which constitute

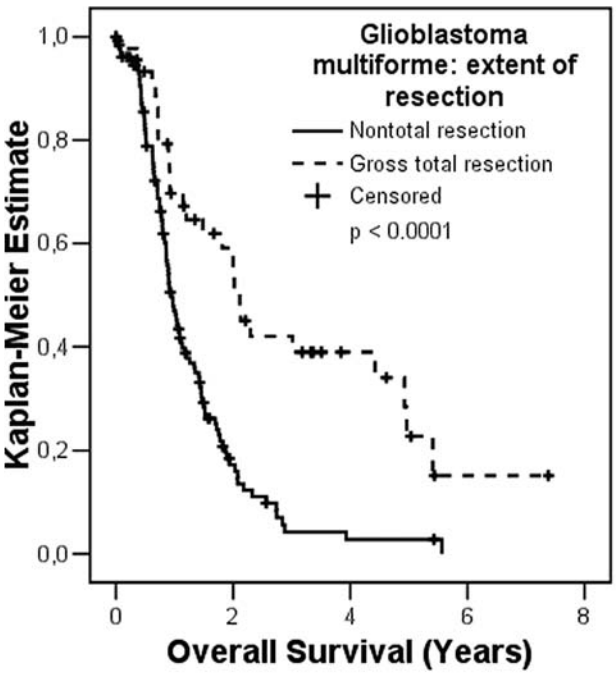

Fig. 3. Kaplan-Meier analysis of overall survival in 178 pediatric patients with glioblastoma multiforme in relation to the extent of tumor surgery (total vs. nontotal tumor resection). Difference in survival was significant ($p < 0.0001$) by log-rank test.

only 7%–9% of all pediatric brain tumors.[6,13] Now, based on our own data from 196 pediatric patients whose diagnosis of either classic GBM (n = 178) or GCG (n = 18) had been confirmed by central neuropathological review, we postulate a frequency of approximately 9% GCG among pediatric glioblastomas. This corresponds to 1 GCG among 11 newly diagnosed pediatric GBMs.

In our series, signs of increased intracranial pressure were found as leading symptoms of GCG in pediatric patients, since 83% of the patients initially reported headache and/or vomiting. Hemiparesis represented another initial symptom, being prevalent in 50% of our patients. In contrast, seizures previously reported as an early symptom in children with GCG[6] occurred only in a minority of our patients and therefore does not seem to represent a typical initial symptom of this tumor.

It was also previously reported that there may be a female predominance among children with GCG.[1,4] Similar to the findings in adult patients with GCG, our own data support a predominance of male patients (male-to-female ratio, 2:1) among children and young adolescents with GCG.[22] A less marked male predominance was also found for the pediatric GBM patients in our study (male-to-female ratio, 1.3:1). This observation is in concordance with a previous report in pediatric patients with GBM.[13] However, gender could not be identified as a prognostic marker for both GCG and GBM in our pediatric patients. This is in concordance with previous findings in adult patients.[22]

In our study, GBM was found at all ages within the pediatric population, with a median age of 11 years (range, 0–17 years). GCG patients showed the same median age (range, 4–17 years). The fact that only one patient younger than 6 years of age suffered from a GCG was not significant.

One of the central questions of the present study was to investigate whether pediatric patients with GCG may have a better prognosis than do pediatric patients with GBM, as had been suggested in previous studies mainly in adults[7–9] but also in children.[10,13] Based on our own series, we could not confirm a better survival for pediatric patients with GCG. Median OS and median EFS did not differ significantly for GCG and GBM, nor did survival after 1 and 2 years. We feel confident that our data are representative, since they are based on the largest series of pediatric patients with a high standard of quality control measures, as indicated by a 100% rate of central neuropathological review; however, in interpreting the unexpected present findings, one must consider that GCG is a rare tumor entity in children and that larger series of patients are still lacking.

Because supposedly better survival of GCG patients was previously linked to a higher degree of complete tumor resection than in GBM patients,[12] we also performed a subgroup analysis to investigate, first, whether there is a higher percentage of gross total tumor resection in our GCG patients and, second, whether this may result in a better survival of this subgroup compared with all GCG patients and also with GBM patients with completely resected tumors. Background for both questions was that previous reports suggested that GCG was more often completely resected than was GBM due to its predominance in locations within the cerebral hemispheres and its less infiltrative behavior.[4,6,10]

In our pediatric patients, a higher rate of total tumor resection was indeed found in GCG patients compared with their GBM counterparts (44% vs. 25%), although this difference was not significant. GCG tumors were also mainly located in both cerebral hemispheres, although a preference for frontal and temporal lobes could not be confirmed, as described previously.[1,12,23] Because tumor locations such as thalamus/deep midbrain, brainstem, or spine where complete tumor resection is usually impossible were very rarely found in our pediatric GCG patients (similar to previous reports in adults),[8,22] we tried to exclude these prognostically unfavorable tumor locations from our GBM control group in order to improve the match for the GCG group. We thought that by this selection any poor prognostic bias due to, for example, brainstem tumors in the GBM group would be widely ruled out. Although the rate of gross total tumor resection increased from 25% to 33% within the newly defined GBM control group, it was still lower than in the GCG group (44%). However, differences were not significant. Furthermore, there were also no significant differences between EFS and OS within the two subgroups of completely resected GCG and GBM (data not shown). Overall, the potentially higher rate of completely resected GCG does not obviously represent a marked survival advantage compared with GBM.

Nevertheless, besides tumor localization, gross total tumor resection resulted in a better survival both in GCG and GBM patients compared with patients with incompletely resected tumors. Other clinical parameters such as sex and age did not have a significant impact on survival. All these findings are in good agreement with several previous studies in which gross total tumor resection represented a powerful favorable predictor of outcome in children with high-grade gliomas.[13,24–28] Thus, we strongly recommend performing a gross total tumor resection in pediatric patients with high-grade gliomas, if feasible.

In conclusion, the present study encompassed the largest group of pediatric patients with GCG and GBM to date. Only patients with central neuropathological review were analyzed to ensure a high quality-control level for the data presented here. In our series, GCG represents a rare tumor entity in children, occurring approximately once among every 11 newly diagnosed pediatric glioblastomas. In contrast to other previous reports, we found a male, not a female, predominance among pediatric GCG patients, similar to adults. Furthermore, the widely distributed hypothesis that pediatric GCG may imply a better prognosis than pediatric GBM could not be substantiated by the present analysis: we found no significant differences in OS and EFS between GCG and GBM. Besides localization in the cerebral hemispheres, gross total tumor resection was a positive prognostic clinical parameter in pediatric GCG patients, but this was also true for pediatric GBM patients; there were no significant differences in survival between subgroups

with completely resected GCG and GBM. Future studies with larger patient numbers together with molecular pathological analyses are still needed to corroborate the findings of the present study and to further elucidate the biology of this rare tumor entity in children.

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