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CLINICAL STUDY

Hemispheric infiltrative grade II gliomas in adults: association of residual tumour volume and extent of tumour resection with malignant transformation

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ABSTRACT

OBJECTIVES: Evaluation of the impact of surgical treatment on malignant transformation (MT) of adult supratentorial infiltrative grade II gliomas (G2G) in a series of chemotherapy and radiotherapy-naïve patients.

BACKGROUND: Despite G2G are slow-growing tumours, they typically undergo MT with a subsequent fatal disease course. An extensive resection alone likely changes their biological behaviour and defers MT; however, this impact is not unequivocally confirmed.

METHODS: Thirty-eight chemotherapy and radiotherapy-naïve adult patients operated from 2005 till 2014 for a G2G were investigated. Based on postoperative magnetic resonance imaging (MRI) and/or positron emission tomography follow-up (FU) scans, the patients were classified as "transformers" (15 patients in whom MT occurred during the FU-period) and "non-transformers" (23 patients).

RESULTS: The follow-up period of "non-transformers" was longer ($p < 0.0001$). After adjustment for known risk factors – age, male sex, astrocytoma histology, preoperative tumour volume, preoperative contrast enhancement and positive isocitrate dehydrogenase 1 gene mutation status – a larger log postoperative tumour volume ($p = 0.031$) and a smaller extent of resection ($p = 0.0086$) were associated with a shorter MT-free survival.

CONCLUSION: In our series, less extensive resections were associated with a shorter time to MT. Our data support an adoption of techniques enabling extensive G2G resections, such as intraoperative imaging and awake resections, into everyday routine *(Tab. 1, Fig. 2, Ref. 40)*. Text in PDF *www.elis.sk*

KEY WORDS: grade II glioma, malignant transformation, resection, prognosis, tumour volume.

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Abbreviations: ASCO – American Society of Clinical Oncology, EOR – extent of resection, FLAIR – Fluid attenuated inversion recovery, FU – follow-up, G2G – grade II gliomas, HR – hazard ratio, IDH1 – isocitrate dehydrogenase 1, KPS – Karnofsky Performance Status, LOH – loss of heterozygosity, MRI – magnetic resonance imaging, MT – malignant transformation, PCV – Procarbazine, CCNU, and Vincristine, PET – positron emission tomography, PWI – perfusion-weighted imaging, rCBV – relative cerebral blood volume, RTOG – Radiation Therapy Oncology Group, SUV – standardized uptake value, WHO – World Health Organization

Introduction

Adult supratentorial infiltrative grade II gliomas (G2G) are usually slow-growing tumours; however, after several years they usually undergo a malignant transformation (MT) with a subsequent fatal disease course (1). Maximal safe surgical resection is nowadays considered to be the treatment of the first choice (2) – an extensive reduction of glioma cells likely defers MT and prolongs the overall survival of G2G patients (3). Nevertheless, current guidelines (2) are mostly based on data from retrospective uncon-

trolled studies, and despite some retrospective data are close to a patient randomization (3, 4), no real prospective randomized controlled trial comparing a resection with biopsy has been conducted (5). However, such trial would be highly problematic due to the ethical aspect of randomization and will likely never be performed. Importantly, the positive impact of an early surgical treatment on G2G prognosis is questioned even in some recent publications (6–8). Hence, further enlargement of the current body of evidence is still needed.

One of the most prominent questions remains whether the surgical treatment alone may significantly alter biological behaviour of G2G and defer MT. Notably, a significant association between a smaller residual tumour volume and a longer time to MT was not confirmed in some recent surgical series (9–11). The aim of this work was to evaluate the impact of the surgical treatment on MT of G2G in a series of chemo- and radiotherapy-naïve patients.

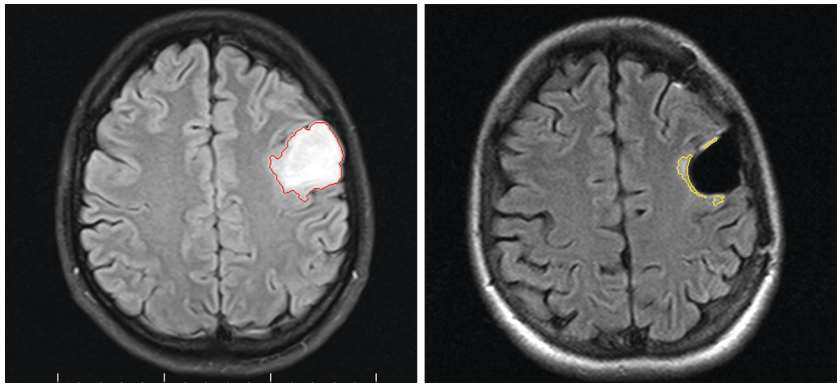

Fig. 1. Left-sided frontal grade II oligodendroglioma. Tumour volume segmentation in preoperative (left) and postoperative (right) axial FLAIR MRI images. The red and yellow lines show the segmentation borders.

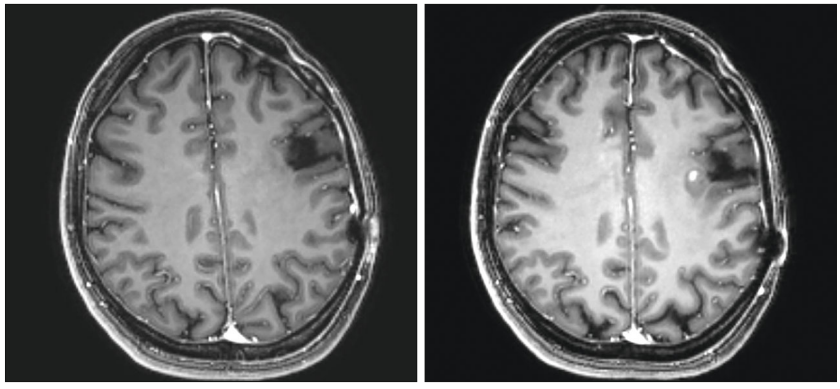

Fig. 2. Postoperative FU contrast enhanced T1-weigted MRI scans of the patient showed in Figure 1. No contrast enhancement is present on the MRI performed 13 months after the surgery (left). Malignant transformation appeared on FU MRI scans 25 months after the surgery (right) – the MT is represented by the new contrast enhancement.

Patients and methods

Selection of study population and inclusion criteria

Till the end of year 2014, our regional tumour board (Bratislava Brain Tumour Board, Bratislava BTB) recommended a watch-and-wait approach as the initial post-resection strategy in a large majority of G2G patients. However, our treatment strategy changed after the first presentation of the long-term results of the Radiation Therapy Oncology Group (RTOG) trial 9802 "Phase III study of radiation therapy with or without procarbazine, CCNU, and vincristine (PCV) in low grade glioma" at the American Society of Clinical Oncology (ASCO) 2014 meeting (12). Reflecting the aforementioned new data, since 2015 Bratislava BTB indicated upfront postoperative radiotherapy and chemotherapy in G2G patients much more frequently than before the RTOG 9802 trial results were reported. Nevertheless, considering that adjuvant treatment changes the biological behaviour of the residual glioma cells, our series of chemo- and radiotherapy-naïve patients, who underwent the first surgery before 2015 represents a scientifically valuable study group. It enables a retrospective evaluation of the impact of surgical treatment alone on MT of G2G. Since a relatively long follow-up (FU) is needed to evaluate the natural postoperative behaviour of these slow-growing lesions, patients operated during the decade before 2015 were included.

The inclusion criteria for our study were as follows: 1) histopathological verification of supratentorial infiltrative grade II glioma in adult patients (18 years or older) operated in the period from 2005 till 2014 using the World Health Organization (WHO) 2007 classification (13); 2) surgical treatment performed at the Department of Neurosurgery of Faculty of Medicine of Comenius University and University Hospital Bratislava; 3) absence of postoperative radiotherapy, chemotherapy, reoperation (due to a residuum progression) or any other form of adjuvant treatment which could change the natural behaviour of the residual tumour. Oncological management of all the patients was recommended by Neuro-oncology Clinic of the 2nd Department of Neurology of Faculty of medicine of Comenius University and University hospital Bratislava (in most cases confirmed by Bratislava BTB).

Preoperative evaluation

Preoperative magnetic resonance imaging (MRI) protocol included T1-weighted sequence (pre- and post-contrast imaging), T2-weighted sequence, Fluid attenuated inversion recovery (FLAIR) sequence, and diffusion weighted imaging (DWI). Semi-automated segmentation using an intensity gradient-based thresholding program (TomoCon, TatraMed s.r.o.) was used to calculate glioma volumes. Tumour (pseudo)borders were segmented from adjacent

brain on axial FLAIR sequence, manual editing was used when adjustments were necessary (Fig. 1).

Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose and/or ^{11}C-methionine was performed when a high-grade glioma was suspected based on preoperative MRI (^{11}C-methionine PET was used since year 2013).

Patient admission notes were used for the evaluation of preoperative Karnofsky Performance Status (KPS).

Postoperative evaluation and follow-up investigations

The first postoperative MRI was performed within 72 hours after surgery. Volumetry of the tumour remnants was performed similarly to preoperative tumour volume calculation, using a semi-automated segmentation based on FLAIR sequence. In cases, where a resection-related ischemia hindered the delineation of tumour residuum on FLAIR sequence, diffusion weighted imaging and T2-weighted imaging, as well as FLAIR sequence performed 3 months after the surgery were evaluated in order to precisely identify and delineate residual tumour tissue. The extent of resection (EOR) was defined as percentage of removed FLAIR abnormality (Fig. 1).

Patient hospital discharge documentations, and later outpatient clinical reports were used in order to evaluate the presence or absence of a new permanent postoperative neurological deficit.

Data on the presence or absence of the isocitrate dehydrogenase 1 gene (IDH1) mutation were collected; the IDH1 mutation status was evaluated by immunohistochemistry.

All the patients were followed up using the standardized MRI protocol, including MRI spectroscopy and perfusion-weighted imaging (PWI). Positron emission tomography (using 18-fluorodeoxyglucose and/or 11C-methionine) was performed in all cases, in which there was any suspicion of MT based on MRI.

Malignant transformation was determined radiologically. It was defined as: 1) detection of (one or more) new areas of pathological contrast enhancement (Fig. 2) or significant growth of previously stable baseline enhancement; 2) "malignant" PWI – increased values of relative cerebral blood volume (rCBV) > 1.75 (14); 3) "malignant" PET features - ^{18}F-fluorodeoxyglucose PET tumour-to-cortex standardized uptake value (SUV) ratio > 0.6 and tumour-to-white matter SUV ratio > 1.5 (15), or ^{11}C-methionine PET tumour-to-cortex SUV ratio > 1.9 (16).

Patient series and definition of subgroups

Thirty-eight patients (22 males, 16 females) fulfilled the inclusion criteria, KPS score of all the patients was ≥ 80. The data on IDH1 mutation was available in all but two patients. According to the postoperative MRI and PET follow-up scans, patients were divided into two main subgroups: 1) patients in whom MT occurred ("transformers") and 2) patients without MT during FU period ("non-transformers").

In transformers, the FU-period was defined as the time between the surgery and MRI or PET investigation showing the transformation to high-grade glioma (time to event). In non-transformers, the FU-period was defined as the time between surgery and the last available MRI scan; if these patients were treated for a radiological progression (without any sign of a MT), the FU-period was defined as the time between surgery and the last available MRI, based on which the adjuvant treatment (chemotherapy, and/or radiotherapy and/or reoperation) was indicated.

Statistical analyses

The collected demographic and clinical data were summarized using descriptive statistics. Continuous variables were tested for normality with Shapiro-Wilk test. Since most continuous variables showed departures from normality, the data were summarized as medians with the respective ranges. Mann-Whitney test was then used to test for a difference in data distribution between transformers and non-transformers. Categorical variables are presented as counts and relative frequencies, and their associations with MT were analysed with Pearson's chi-square test or Fisher's exact test if the assumptions of the chi-square test were not met.

Survival analysis (i.e. "MT-free survival" analysis) was used to compare the distribution of the times from surgery to MT (in months) for both measures of postoperative tumour burden - postoperative tumour volume and the EOR. Patients without MT at the time of latest FU were censored at that time, contributing to the analysis only at times prior to the last FU MRI. Hazard ratios (HR) and 95% confidence intervals were estimated performing a simple Cox proportional-hazards regression model, separately for each predictor of interest. The volumetric data were $\log_{10}$ transformed, and resection percentages were arcsin square root transformed. Multiple Cox regression was then performed for each predictor to adjust the univariate MT-free survival estimates for other known prognostic factors associated with MT and/or shorter survival: higher age (17), male sex (18), astrocytoma histology (17), larger preoperative tumour volume on a log scale (19), preoperative contrast enhancement (20) and IDH 1 mutation negativity (21). Statistical analyses were performed using StatsDirect 3.0.191 software (Stats Direct Ltd., Cheshire, UK) and Statistica 13 software (TIBCO Software Inc. US). All p-values were considered significant at a two-tailed p-value of < 0.05.

Results

There were no perioperative deaths, and no moderate or severe permanent postoperative deficits. The median FU-period for the whole series was 37.5 months (range 2–148); the median FU-period for "transformers" was significantly shorter ($p < 0.0001$) as compared to "non-transformers". The radiological, histological, and surgical data of both groups are summarized in the Table 1.

Factors associated with malignant transformation

In 15 patients (39.5 %), postoperative MRI and/or PET investigation revealed a MT during the FU. In univariate analyses, a significant association between MT and preoperative tumour diameter ($p=0.0014$), preoperative tumour volume ($p=0.0003$), smaller EOR ($p=0.0152$) and residual tumour volume ($p=0.0002$) was found.

In the first multivariate model, after an adjustment of EOR for age, male sex, astrocytoma histology, log preoperative tumour volume, preoperative contrast enhancement and IDH 1 status, a

Tab. 1 Univariate analysis of factors associated with malignant transformation.

Characteristic		Total	Non-transformers	Transformers	p	Odds Ratio
Count (%)		38 (100%)	23 (60.5%)	15 (39.5%)	n.a.	
Age (years)	median	35	40	31	0.0839	
	range	19–58	19–58	22–53		
Sex	male	22 (57.9%)	14 (60.9%)	8 (53.3%)	0.7425	1.36
	female	16 (42.1%)	9 (39.1%)	7 (46.7%)		
Follow-up (months)	median	37.5	50	15	< 0.0001	
	range	2–148	23–148	2–45		
Histology*	astrocytoma	20 (52.6%)	11 (47.8%)	9 (60.0%)	0.4795	
	oligoastrocytoma	9 (23.7%)	5 (21.8%)	4 (26.7%)		
	oligodendroglioma	10 (23.7%)	7 (30.4%)	2 (13.3%)		
IDH 1 mutation**	yes	30 80.0%)	21 91.3%)	9 (60.0%)	0.1608	0.21
	no	6 (15.8%)	2 (8.7%)	4 (26.7%)		
	unknown	2 (5.3%)	0 (0%)	2 (13.3%)		
Preoperative MRI contrast enhancement	yes	5 (13.2%)	1 (4.4%)	4 (26.7%)	0.0685	8.00
	no	33 (86.8%)	22 (95.6%)	11 (73.3%)		
Tumour diameter (mm)	median	45.2	42.9	56	0.0014	
	range	15–81.5	15–66.1	33.6–81.5		
Tumour volume (cm3)	median	24.7	13.8	59.2	0.0003	
	range	1.3–163.3	1.3–83	5.1–163.3		
Residual tumour volume (cm3)	median	2.1	1.1	7.1	0.0002	
	range	0–53	0–31.5	1.1–53		
Extent of resection	median	91.7	93	87.1	0.0152	
	range	11.7–100	31.7–100	11.7–96.5		

n.a. – not applicable, IDH1 – isocitrate dehydrogenase 1, MRI – magnetic resonance imaging, * Histopathological diagnosis was established according to WHO 2007 diagnostic consensus criteria , ** IDH 1 mutation was evaluated in all patients grouped in the non-transformers group, and in all but two patients grouped in the transformers group

significant association between a smaller EOR and a shorter MT-free survival was found (p=0.0086). A significant association between MT and negative IDH1 status (p=0.009) and larger log preoperative tumour volume (p=0.027) was observed as well.

In the second/alternative multivariate model, after an adjustment of log postoperative tumour volume for aforementioned risk factors, a significant association between a shorter MT-free survival and larger residual tumour (p=0.031) as well as negative IDH1 status (p=0.007) was observed. No association between MT-free survival and remaining risk factors was found in any of the multivariate analyses.

Discussion

Malignant transformation of G2G is a catastrophic event, causing worsening of neurocognitive functions and premature death (22). While the positive impact of an extensive resection on overall survival of G2G patients was confirmed in many series (3, 4, 9–11, 19, 23–33), the impact of surgical treatment on MT-free survival was studied less frequently (3, 9–11, 19, 23, 26–28, 30, 32, 33). In numerous studies, greater EOR has been associated with a longer time to MT (3, 19, 23, 26–28, 30, 33), raising the possibility that extensive resections significantly modify biological behaviour of G2G. On the other hand, a significant association between an extensive tumour removal and MT has not been confirmed in some recent studies (9–11), or was confirmed only in IDH1 negative, but not in IDH1 mutated G2G (32). Interestingly, in the seminal work of Smith et al (19), MT-free survival was predicted by EOR, but not by postoperative residual G2G volume.

Understanding of factors associated with MT of G2G may help to guide the treatment strategies (34). Importantly, due to the absence of a proper randomized trial on prognostic significance of G2G resections certain doubts persist - the role of the EOR and residual tumour volume as prognostic factors remains still controversial within the neuro-oncology community (2). Due to these reasons, more evidence supporting a positive impact of extensive G2G resections on deferring MT might further reduce the uncertainties regarding the indication of early G2G surgeries.

The results of our study indicate that extensive G2G resections defer MT. Both the lower EOR and the larger residual tumour volume were significantly associated with MT. This finding underscores the role of surgical treatment of G2G. In addition, it supports the need for the introduction of surgical methods enabling the most extensive and safe G2G resection, such as awake brain surgery and intraoperative imaging modalities, into everyday routine. In addition, considering the potential benefits of MT deferring on G2G patient prognosis, our results support the role of an additional resection, when a resectable residuum is found on postoperative MRI. According to recent data, this strategy may be especially important in grade II astrocytomas (24), where the residual volumes as little as 1 cm^3 lead to significantly worse overall survival (20).

The most important characteristic of our study group is the fact that only G2G patients after a single resection were included. Radiotherapy and chemotherapy undoubtedly change the biological behaviour of G2G and may confound the natural progression of these tumours (35). In our study, we attempted to control for this bias by including chemotherapy and radiotherapy-naïve G2G

patients only, considering the fact that even performing multivariate analyses, outside of a randomized controlled trial it is virtually impossible to eliminate the bias completely (36). Of note, since the presentation of the RTOG 9802 trial results the early postoperative chemo- and radiotherapy became the standard of care especially in high-risk G2G patients (37), a series of adjuvant therapy-naïve G2G represents an important study material. It allows to study the natural postoperative progression of G2G unaffected by chemotherapy, radiotherapy, or reoperation, which is relatively rare nowadays.

As many retrospective studies, our work has several limitations. Firstly, the G2G (all operated before 2015) were classified histopathologically using WHO 2007 diagnostic consensus criteria, and the subtype were not revised using a molecular analysis and the new WHO 2016 classification (38). However, IDH1 mutation, that is much more common than IDH2 (39), was evaluated in all but 2 patients as expected IDH1 positivity was negatively associated with MT. In addition, despite 1p/19q loss of heterozygosity (LOH) was not used for establishing oligodendroglioma diagnosis, our own results indicate a strong correlation between 1p/19q LOH and classic oligodendroglial histomorphology (40). Secondly, MT was diagnosed radiologically and was not confirmed in all cases by biopsy. However, as no adjuvant treatment was applied, new contrast enhancement or significant growth of previously stable baseline enhancement could not be attributed to radiation effects. Hence, including chemo- and radiotherapy naïve patients only likely contributed to much higher reliability of radiological criteria for MT determination. Lastly, our study group was relatively small, partly due to the strict inclusion criteria selected in order to eliminate the aforementioned bias represented by adjuvant treatment, and also due to the small size of the Slovak population (5.45 million people). Nevertheless, despite the aforementioned limitations, our study indicates a strong preventive effect of extensive tumour tissue resection on deferring MT of G2G.

Conclusion

In our series, both the lower EOR and larger residual tumour volume were significantly associated with a shorter MT-free survival. Techniques enabling extensive and safe G2G resections, such as intraoperative imaging devices and awake resections, should be adopted into everyday routine in neurosurgical units specialized for G2G treatment. However, considering the limitations of our work, future studies are necessary to confirm our results, especially in grade II oligodendrogliomas.

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