ORIGINAL PAPER/*ARTYKUŁ ORYGINALNY*

# Reoperations of patients with low-grade gliomas in eloquent or near eloquent brain areas

## *Ponowne operacje chorych z glejakami wysoko zróżnicowanymi położonymi w okolicach elokwentnych mózgu lub w pobliżu okolic elokwentnych mózgu*

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## Abstract

**Background and purpose:** Reoperations of patients with recurrent low-grade gliomas (LGG) are not always recommended due to a higher risk of neurological deficits when compared to initial surgery. The purpose of the present study was to evaluate surgical outcomes of patients operated on for recurrent LGG.
**Material and methods:** Sixteen patients who had surgery for recurrent LGG out of 68 LGG patients who underwent surgery at the Department of Neurosurgery in Sosnowiec, Poland between 2005 and 2011 were enrolled in the study.
**Results:** A large tumour volume prior to the initial surgery was the most significant parameter influencing LGG progression (96.6 $cm^3$ vs. 47.9 $cm^3$, $p = 0.01$). Increased incidence of epileptic seizures and decreased mental ability according to Karnofsky score were the most common symptoms associated with tumour recurrence. In the group of patients with malignant transformation, the relative cerebral blood volume (rCBV) was considerably increased (1.21 vs. 2.41, $p < 0.01$). No statistically significant difference was found in terms of the extent of resection between initial surgery and reoperation. Similarly, no significant difference was found in the number of patients with a permanent neurological deficit after initial surgery and reoperation.

## Streszczenie

**Wstęp i cel pracy:** Ponowne operacje chorych z odrostem wysoko zróżnicowanego glejaka mózgu (WGM), zwłaszcza zlokalizowanego w obszarach elokwentnych mózgu, nie zawsze są zalecane. Powodem tego jest przekonanie, że ryzyko wystąpienia deficytów neurologicznych jest większe niż podczas pierwszej operacji. Celem pracy była ocena wyników leczenia chorych operowanych ponownie z powodu odrostu WGM.
**Materiał i metody:** W okresie od 2005 r. do 2011 r. w Klinice Neurochirurgii w Sosnowcu operowanych było 68 chorych z rozpoznaniem WGM. Do analizy włączono 16 chorych operowanych ponownie z powodu odrostu guza.
**Wyniki:** Jednym z najistotniejszych parametrów decydujących o progresji WGM była duża objętość guza przed pierwszą operacją (96,6 $cm^3$ *vs* 47,9 $cm^3$; $p = 0,01$). Głównym objawem odrostu guza była zwiększona częstość napadów padaczkowych oraz pogorszenie sprawności intelektualnej ocenianej w skali Karnofsky'ego. Wśród guzów, w przypadku których doszło do zezłośliwienia odrostu, obserwowano istotny wzrost względnej mózgowej objętości krwi (rCBV) (1,21 *vs* 2,41; $p < 0,01$). Nie stwierdzono statystycznie istotnej różnicy pod względem doszczętności resekcji między pierwszą i ponowną

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**Conclusions:** Reoperations of the patients with recurrent LGG are not burdened with a higher risk of neurological sequelae when compared to initial surgery. The extent of resection during the surgery for LGG recurrence is comparable to initial surgery. The increase of rCBV seems to be a significant biomarker that indicates malignant transformation.

**Key words:** low-grade glioma, tumour progression, reoperation, relative cerebral blood volume.

operacją. Nie stwierdzono statystycznie istotnej różnicy w liczbie chorych z utrwalonym deficytem neurologicznym po pierwszym zabiegu i po ponownej operacji.
**Wnioski:** Ponowne operacje chorych z odrostem WGM, również tych zlokalizowanych w obszarach elokwentnych mózgu, nie są obarczone większym ryzykiem powikłań neurologicznych w porównaniu z pierwszą operacją. Stopień resekcji osiągany przy operacjach odrostu WGM jest porównywalny z zakresem resekcji po pierwszej operacji. Istotnym parametrem wskazującym na zezłośliwienie procesu nowotworowego jest wzrost rCBV.

**Słowa kluczowe:** glejaki wysoko zróżnicowane, progresja nowotworu, reoperacja, względna mózgowa objętość krwi.

## Introduction

Low-grade gliomas (LGG), despite the fact that they are histologically benign, tend to undergo malignant transformation which significantly shortens the patient's lifespan. The most important factors that affect LGG patients' survival include age, the extent of resection, histological type and initial volume of the tumour [1-12]. Recent years have brought a number of publications, which stress that the extent of resection is a significant, independent factor that affects overall survival and progression-free survival (including time to malignant transformation) of patients after surgery for LGG [1,6,9, 10,12]. Importantly, the introduction of neuronavigation, functional MRI and intraoperative neurophysiological monitoring facilitated the extension of resections of LGG that occupy eloquent areas, mainly motor cortex and speech areas, while allowing the preservation of permanent, iatrogenic neurological deficits within acceptable limits [9,13-19]. Still, for most of the LGG located within eloquent brain areas only partial resection is feasible [9,13,14,20,21]. The decision to leave a part of the tumour within an eloquent area is usually made based on neuronavigation and neurophysiological monitoring indications in order to avoid new, severe and permanent neurological deficits that might be rendered by extended resection. Interestingly, while the benefits of extensive initial resection of LGG raise no doubts, still the indications for reoperation of recurrent LGG are a matter of debate. Scepticism arises mainly from the conviction that the risk of injury is even greater with reoperation. Some authors advise that patients with recurrent tumour should undergo chemo- or radiotherapy instead [1,22-26].

The aim of our prospective, observational case study, based on a series of patients previously diagnosed with LGG, was to evaluate the surgical outcome of secondary surgery for recurrent tumour.

## Material and methods

Sixty-eight patients who underwent surgery for WHO grade II LGG [27] in the Department of Neurosurgery of the Silesian Medical University in Sosnowiec between January 2005 and July 2011 were included in our study. Subsequent analysis involved 16 patients (24%) who were reoperated on for recurrent tumour. Cases with any diameter enlargement and/or new contrast enhancement in the tumour remnants in follow-up magnetic resonance imaging (MRI) in FLAIR sequence at least 3 months after the initial surgery were considered recurrent.

Patients prior to initial as well as secondary surgery underwent a series of imaging studies that involved MRI with T1- and T2-weighted and FLAIR sequences along with functional (BOLD-fMRI), diffusion-tensor imaging (DTI) and perfusion (PWI) studies. Perfusion data were subsequently used to calculate relative cerebral blood volume (rCBV), a quotient of maximal CBV within the lesion to CBV in normal white matter in the contralateral hemisphere. Tumour volume was calculated based on FLAIR images. According to the classification proposed by Sawaya *et al.* [28], anatomical regions occupied by tumours were subsequently divided into non-eloquent brain, near-eloquent brain and eloquent brain. All operations were performed with neuronavigation (BrainLab AG, Munich, Germany). All the patients with tumours within or near the sensorimotor cortex or motor speech representation addition-

ally went through functional imaging studies in order to visualize active regions within eloquent areas of cortex and white matter tracks. All the patients with tumours in the vicinity of the motor cortex had motor evoked potentials (MEP) monitored during surgery. MEP monitoring involved transcranial stimulation (TES), direct cortical stimulation (DCS) and direct subcortical white matter stimulation (DSCS). All electrophysiological studies were performed with Inomed ISIS apparatus (Teningen, Germany) with the "train" stimulation pattern (4 to 6 single 0.5-ms stimuli with 3 to 4 ms intervals). Current of a few to several mA (3-30 mA range) was used for DCS and DSCS and current of 100 to 150 mA (max. 220 mA) for TES was used.

Postoperative MRI was performed within 48 hours after surgery. The extent of resection was evaluated based on pre- and postoperative FLAIR images. According to Sawaya *et al*. [28], the extent of resection was classified as gross total (> 95%), subtotal (85-95%) and partial (< 85%).

Follow-up imaging studies were performed in 6-month intervals and involved T1- and T2-weighted images, FLAIR sequences, MR spectroscopy (MRS) and PWI studies. Intellectual performance and patient independence were assessed with the Karnofsky performance scale (KPS). Neurological examination involved assessment of seizures and headaches frequency along with neurological deficits (hemiparesis, speech disturbances and hemianopsia) evaluation. Deficits that subsided within 3 months after surgery were considered transient while those that lasted more than 3 months were deemed permanent.

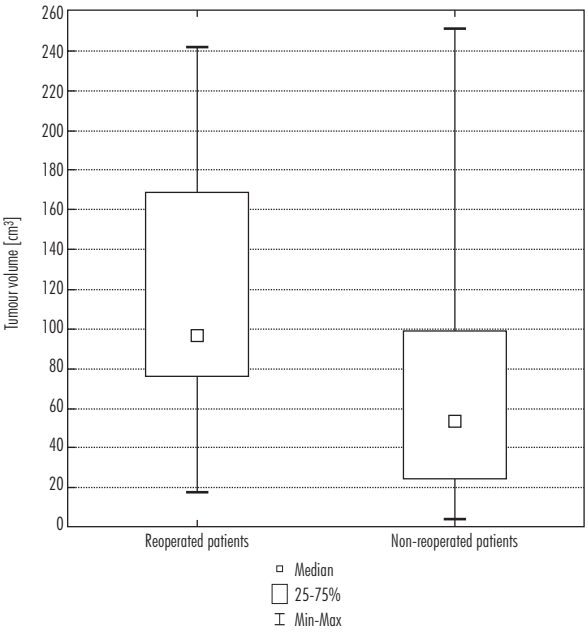


**Fig. 1.** Comparison of tumour volumes prior to initial surgery in 16 patients who underwent reoperation and 46 patients without reoperation ($p = 0.01$)

## Statistical analysis

Statistical analysis was performed with the STATISTICA 9.0 software package (StatSoft, USA). Distribution of quantitative variables was primarily evaluated with the Shapiro-Wilk test. Variables were characterized with median and interquartile range values. For statistical analysis, Mann-Whitney *U*-test or Student *t*-test were used based on variable distribution. For qualitative variables, intergroup differences were evaluated with the $\chi^2$ test (with Yates correction for small groups). Results of pre- and postoperative studies were compared with nonparametric Wilcoxon pair-rank test or Student *t*-test for dependent variables. For all of the analyses, the significance level was set at 0.05. Kaplan-Meier analysis was used for calculation of survival curves and for assessment of predictive values of evaluated variables.

## Results

In our cohort of 68 patients operated on for LGG, we found 22 cases of progression (32%) that included 11 patients (16%) with malignant transformation. Median follow-up time for all of the patients was 34 months (interquartile range: 21-49 months). Five-year progression-free survival for all of the patients was 35%; accordingly, malignant transformation-free survival was 53%. Sixteen patients underwent reoperation, three patients died from progression, and three other patients opted against surgery and remain in a stable neurological condition.

Our cohort of 16 patients who were reoperated on included 8 men aged 24 to 59 years and 8 women aged 24 to 48 years (median age for all of the patients was 34 years with interquartile range of 29-42 years). Overall performance assessed with KPS prior to the initial surgery for the majority of the patients, i.e. 13 patients (82%), was either 90 or 100 points. Eleven patients (69%) had tumours localized in one of the brain eloquent areas (the most common location being the motor cortex), 4 (25%) of them in near-eloquent areas and 1 patient (6%) outside eloquent areas. Median preoperative tumour volume was 96.6 $cm^3$ (interquartile range, 75.4-168 $cm^3$). Importantly, in the remaining 46 patients who underwent surgery for LGG in the

same period and showed no signs of recurrence, median preoperative tumour volume was 47.9 $cm^3$ (interquartile range, 27.1-98.4 $cm^3$). The difference in tumour volumes between these groups was statistically significant ($p = 0.01$) (Fig. 1). During initial surgery, none of the 16 patients had gross total resection. Subtotal resection was achieved in 3 patients (19%) while the remaining 13 patients (81%) had partial resection. Fourteen patients (88%) had histopathological diagnosis of fibrillary astrocytoma, one patient (6%) had oligoastrocytoma and one other (6%) had oligodendroglioma. Two patients developed permanent neurological deficits after surgery.

Median time between initial surgery and reoperation was 19 months (interquartile range, 15-33 months). The increased incidence of seizures, found in 7 patients (50%), was the most common symptom of tumour recurrence. The extent of resection after reoperation was assessed as gross total in 1 patient (7%), in 4 others as subtotal (27%) and in the remaining 10 patients (66%) as partial. For technical reasons, one of the patients had no postoperative MRI, i.e. analysis of the extent of resection after secondary surgery was performed in 15 cases. Postoperative histopathological diagnoses were as follows: 6 patients (38%) had LGG WHO grade II while the remaining 10 patients (62%) had either WHO grade III or IV tumours. Five patients (36%) developed permanent neurological deficits after secondary surgery.

Tables 1 and 2 summarize comparisons of selected clinical and radiological data between the groups of patients with either grade II or grade III/IV tumours. Notably, we found a statistically significant deterioration of intellectual performance and independence assessed with KPS prior to reoperation in patients with malignant transformation (WHO grade III or IV) when compared to the patients without malignant transformation (Table 1). Moreover, patients with malignant transformation showed significantly higher rCBV values (Table 2). No differences in the extent of resection between patients with grade II and III/IV tumours during primary as well as secondary surgery were found (Table 2).

Accordingly, Table 3 presents comparisons of selected clinical and radiological data between primary and secondary surgery in our group of 16 patients analysed. Importantly, no significant differences in numbers of patients with permanent neurological deficits after primary and secondary surgery were found. Similarly, we found no significant differences in volumes of tumours after primary and secondary surgery in patients with either recurrent grade II tumours, with malignant transformation of the tumour, or in the entire group with recurrent LGG. No statistically significant differences were found with regard to the extent of resection between primary and secondary surgery while rCBV values in the group of patients with malignant transformation were significantly higher prior to reoperation when compared to the values prior to the primary surgery.

## Discussion

Twenty-two patients (32%) out of 68 patients who underwent surgery for LGG between 2005 and 2011 showed signs of tumour progression, i.e. 5-year progression-free survival in our group was 35%. Various authors have reported progression-free survival values between 19% [11] and 55% [2], but in the majority it approximates 50% [1,4,5,7,12,29,30]. Median for the time free from progression in patients treated for LGG varies between 2 [31-33] and 5.5 years [10] but again the majority of authors report 5 years [5,6,21]. The most important factors that significantly increase progression-free survival include: age (≤ 40 years) [12], histopathology of the tumour (oligodendroglioma/oligoastrocytoma vs. astrocytoma) [5], preoperative volume of the tumour [1,10,30], postoperative volume of the tumour [10,30] and the extent of resection [6,12,33]. In our cohort of 16 patients, median progression-free survival time was relatively short at 19 months (interquartile range, 15 to 33 months), a value close to the one reported by Schmidt *et al*. [33]. These authors, however, found a significant relationship between progression-free survival and the extent of resection. In patients with gross total resection (> 90%), median time to reoperation was 49 months while in those with subtotal resection it was only 25 months. In our group all of the patients who underwent reoperation had either subtotal or partial resection of the tumour and a vast majority of them (88% of patients) had a final diagnosis of fibrillary astrocytoma. Moreover, prior to the first surgery the volume of the tumours in this group was significantly higher when compared to the remaining 46 patients treated for LGG. LGG progression in our study cohort was related then to subtotal resection, histopathological diagnosis of astrocytoma and finally to the size of the tumour.

A significant fraction of LGGs undergo malignant transformation to WHO grade III or IV tumours. Various studies report the percentage of malignant transformations varying from 13 to 86% [1,6,8,10,21,31,32, 34-36]. Here we report that 50% of our patients with radiological signs of progression had malignant trans-

**Table 1.** Comparison of selected variables between patients with WHO grade II and WHO grade III/IV among 16 patients operated on for low-grade glioma recurrence – data are reported as *n* (%) or median (interquartile range)

| Variable | WHO grading after surgery | | Total | *P*-value (grade II vs. III/IV)* |
|---|---|---|---|---|
| | grade II | grade III/IV | | |
| No. of patients (%) | 6 (38) | 10 (62) | 16 (100) | |
| Age [years] | 38 (33-48) | 33 (27-36) | 34 (29-42) | NS# |
| Sex | | | | |
| Female | 4 (66%) | 4 (40%) | 8 (50%) | NS |
| Male | 2 (34%) | 6 (60%) | 8 (50%) | |
| Side; *n* (%) | | | | |
| Left | 5 (83) | 5 (50) | 10 (63) | NS |
| Right | 1 (17) | 5 (50) | 6 (37) | |
| Time to secondary surgery [months] | 19 (4-37) | 19 (11-28) | 19 (15-33) | NS# |
| KPS score prior to initial surgery | | | | |
| 70 | 1 (17%) | 1 (10%) | 2 (12%) | NS |
| 80 | 0 (0%) | 1 (10%) | 1 (6%) | |
| 90 | 1 (17%) | 2 (20%) | 3 (19%) | |
| 100 | 4 (66%) | 6 (60%) | 10 (63%) | |
| Symptoms prior to initial surgery | | | | |
| Headache | 1 (17%) | 3 (30%) | 4 (25%) | NS |
| Epilepsy | 5 (83%) | 9 (90%) | 14 (88%) | NS |
| Neurological deficits | 2 (34%) | 4 (40%) | 6 (37%) | NS |
| Permanent neurological deficit after initial surgery | 1 (17%) | 1 (10%) | 2 (12%) | NS |
| KPS score prior to secondary surgery | | | | |
| 70 | 3 (50%) | 0 (0%) | 3 (19%) | < 0.05 |
| 80 | 0 (0%) | 5 (50%) | 5 (31%) | |
| 90 | 2 (33%) | 5 (50%) | 7 (44%) | |
| 100 | 1 (17%) | 0 (0%) | 1 (6%) | |
| Symptoms prior to secondary surgery** | | | | |
| Headache | 2 (34%) | 2 (25%) | 4 (29%) | NS |
| Epilepsy | 1 (20%) | 6 (67%) | 7 (50%) | NS |
| Neurological deficits | 2 (40%) | 2 (22%) | 4 (29%) | NS |
| Permanent neurological deficit after secondary surgery** | 2 (40%) | 3 (33%) | 5 (36%) | NS |
| Radiotherapy | 3 (50%) | 8 (80%) | 11 (69%) | NS |

**P-values for $\chi^2$ test with Yates correction, except for those indicated with # (Student t-test).*
***Patients with permanent deficits after initial surgery that did not regress were excluded.*
*NS – non-significant; KPS – Karnofsky Performance Scale*

formation. In 16 patients who were reoperated on, this value was even higher, at 62%. Smith *et al.* [10] reported that the most important risk factor for malignant transformation is a large preoperative volume of the tumour. McGirt *et al.* [6], on the other hand, proved that patients after gross total resection survive longer

**Table 2.** Comparison of magnetic resonance imaging results between patients with WHO grade II and WHO grade III/IV among 16 patients operated on for low-grade glioma recurrence – data are reported as *n* (%) or median (interquartile range)

| Variable | WHO grading after surgery | | Total | *P*-value |
|---|---|---|---|---|
| | grade II | grade III/IV | | (grade II vs. III/IV)* |
| Tumour volume prior to initial surgery [$cm^3$] | 100.9 (73.6-219.5) | 96.6 (77.3-127.7) | 96.6 (75.4-168.0) | NS |
| rCBV prior to initial surgery | 1.28 (1.11-1.71) | 1.96 (1.27-2.61) | 1.60 (1.11-2.40) | NS |
| Contrast enhancement prior to initial surgery | | | | |
| Yes | 1 (17%) | 5 (50%) | 6 (37%) | NS# |
| No | 5 (83%) | 5 (50%) | 10 (63%) | |
| Tumour volume after initial surgery [$cm^3$] | 50.1 (13.8-121.3) | 35.0 (20.5-52.4) | 35.0 (17.9-67.4) | NS## |
| % of resection after initial surgery | 7770.8 (45-88) | 70.8 (41.0-78.2) | 74 (43-83) | NS |
| Resection degree after initial surgery | | | | |
| Gross total | 0 (0%) | 0 (0%) | 0 (0%) | NS# |
| Subtotal | 2 (34%) | 1 (10%) | 3 (19%) | |
| Partial | 4 (66%) | 9 (90%) | 13 (81%) | |
| Tumour volume prior to secondary surgery [$cm^3$] | 93.5 (74.4-229.8) | 58.9 (40.9-113.9) | 76.2 (44.2-120.4) | NS |
| rCBV prior to secondary surgery | 1.21 (1.01-1.50) | 2.41 (1.66-2.91) | 1.81 (1.29-2.67) | < 0.01## |
| Contrast enhancement prior to secondary surgery | | | | |
| Yes | 3 (50%) | 7 (70%) | 10 (63%) | NS# |
| No | 3 (50%) | 3 (30%) | 6 (37%) | |
| Tumour volume after secondary surgery* [$cm^3$] | 22.2 (14.3-88.0) | 36.2 (18.2-74.7) | 24.1 (14.3-88.0) | NS |
| % of resection after secondary surgery** | 79 (54-86) | 62 (12-70) | 70 (41-89) | NS## |
| Resection degree after secondary surgery** | | | | |
| Gross total | 0 (0%) | 1 (11%) | 1 (7%) | NS# |
| Subtotal | 3 (50%) | 1 (11%) | 4 (27%) | |
| Partial | 3 (50%) | 7 (78%) | 10 (66%) | |

** P-values for Student t-test except for those indicated with # ($\chi^2$ test with Yates correction) or ## (Mann-Whitney U-test)*
***Comparison of 15 patients*
*rCBV – relative cerebral blood volume*

without malignant transformation when compared to patients after subtotal or partial resection. Lastly, Chaichana *et al.* [1], based on multifactor analysis, reported histopathological diagnosis of fibrillary astrocytoma, size of the tumour and the extent of resection as the most important risk factors for LGG malignant transformation with tumours ≥ 3 cm in diameter at the highest risk of malignant transformation. Importantly, gross total resection significantly lowered that risk. Medians for the time free from malignant transformation according to Smith *et al.* [10], McGirt *et al*. [6] and Schmidt *et al*. [33] were 10.1 years, 8.8 years and 47 months (range from 6 to 88 months), respectively. According to Chaichana *et al.* [1] 5-year malignant transformation-free survival was 74% while in our group it was 53%.

The occurrence of contrast enhancement in the follow-up MRI suggests malignant transformation. According to Schmidt *et al*. [33] the occurrence of contrast enhancement within the tumour has 65% sensitivity and 80% specificity for malignant transformation.

**Table 3.** Comparison of selected variables from initial and secondary surgery in 16 patients operated on for low-grade glioma recurrence – data are reported as *n* (%) or median (interquartile range)

| Variable | WHO grading prior to reoperation | | Total |
|---|---|---|---|
| | grade II | grade III/IV | |
| rCBV prior to initial surgery | 1.28 (1.11-1.71) | 1.96 (1.27-2.61) | 1.60 (1.11-2.40) |
| rCBV prior to secondary surgery | 1.21 (1.01-1.50) | 2.41 (1.66-2.91) | 1.81 (1.29-2.67) |
| *P*-value | NS# | 0.05## | NS## |
| Tumour volume after initial surgery [$cm^3$] | 50.0 (13.8-121.3) | 35.0 (20.5-52.4) | 35.0 (17.9-67.4) |
| Tumour volume after secondary surgery* [$cm^3$] | 22.2 (14.3-88.0) | 36.2 (18.2-74.7) | 24.1 (14.3-88.0) |
| *P*-value | NS# | NS## | NS## |
| % of tumour removal after initial surgery | 77 (45-88) | 70 (41-78) | 74 (43-83) |
| % of tumour removal after secondary surgery* | 79 (54-86) | 62 (12-70) | 70 (41-89) |
| *P*-value | NS## | NS# | NS## |
| Degree of resection after initial surgery | | | |
| Gross total | 0 (0%) | 0 (0%) | 0 (0%) |
| Subtotal | 2 (34%) | 1 (10%) | 3 (19%) |
| Partial | 4 (66%) | 9 (90%) | 13 (81%) |
| Degree of resection after secondary surgery* | | | |
| Gross total | 0 (0%) | 1 (11%) | 1 (7%) |
| Subtotal | 3 (50%) | 1 (11%) | 4 (27%) |
| Partial | 3 (50%) | 7 (78%) | 10 (66%) |
| *P*-value | NS### | NS### | NS### |
| Permanent neurological deficit after initial surgery | 1 (17%) | 1 (10%) | 2 (12%) |
| Permanent neurological deficit after secondary surgery | 2 (40%) | 3 (33%) | 5 (36%) |
| *P*-value | NS### | NS### | NS### |

*#Student t-test for dependent variables; ##Wilcoxon pair rank test; *Comparison performed for 15 patients; ###$\chi^2$ test with Yates correction*
*rCBV – relative cerebral blood volume*

The presence of contrast enhancement is a radiological representation of neoangiogenesis within the tumour that undergoes malignant transformation.

An important parameter that reflects tumour angiogenesis is rCBV. This marker closely correlates with histological grading of astrocytic tumours' malignancy and constitutes an important prognostic factor for outcome [20,37-39]. Amongst the patients with malignant transformation, rCBV values were significantly higher when compared to patients without malignant transformation (2.41 vs. 1.21, $p < 0.01$). No significant difference in contrast enhancement on control MRI between these two groups was found, although in patients with malignant transformation the number of patients with contrast enhancement was higher (70% vs. 50%).

The higher incidence of epileptic seizures was the main clinical sign of LGG progression. In our group, 50% of patients had higher incidence of seizures during progression, despite antiepileptic treatment. Schmidt *et al*. [33] also reported similar incidence of seizures, with 53% of patients with recurrent LGG showing higher incidence of seizures. Additionally, we found that patients with malignant transformation showed significant deterioration of their overall performance assessed with KPS, when compared to the remaining patients who undergo surgery for recurrent tumour ($p < 0.05$).

The introduction of neuronavigation and intraoperative electrophysiological monitoring into the surgical repertoire applicable for the treatment of LGG localized within eloquent areas allowed surgeons to increase

the extent of resection on one hand with simultaneous limitation of permanent neurological deficits on the other. The risk of permanent neurological deficits after surgery for LGG is relatively low at 2% to 5% [6,9,10], even including tumours within eloquent areas of the brain [9,20]. Sanai *et al.* [9] in a group of 104 patients with insular tumours reported permanent deficits in less than 2% of the cases (with the median of the extent of resection at 84.5%). No significant influence of the extent of resection on the incidence of new neurological deficits after surgery was reported [6,10,20]. Still, for the majority of the LGGs localized within brain eloquent areas, only partial resection is feasible. The resection stops whenever cortical and subcortical stimulation signals the presence of speech or motor centres. This is the origin of the conviction that further extension of resection during reoperation increases the risk of new neurological deficits. Based on that belief, some authors suggest chemo- or radiotherapy instead of reoperation [19,22-26]. Duffau *et al.*, on the other hand, state that reoperation should always be considered for patients with recurrent LGG, even in cases when the recurrent tumour is located within eloquent areas of the brain. Based on their research, Duffau and his group proposed a theory of functional reorganization of brain eloquent centres in patients after surgery for slowly growing tumours. According to this theory, the functional structure of the central nervous system consists of parallel, interconnected neuronal networks that are capable of reciprocal compensation of function in the event that one of them is dysfunctional [40,41]. The recurrence of the tumour residue within an eloquent area usually expands into this area. Based on the aforementioned theory, Duffau *et al*. state that owing to the functional plasticity of the brain in response to the tumour recurrence within a few years, the reshaping of functional tissue occurs [42-44]. Thus, a reoperation of the tumour within an eloquent area as well as the expansion of the extent of resection without the risk of new neurological deficits is possible [21,44]. Thus, a concept of a multistage surgical approach in the treatment of LGGs within eloquent areas emerged based on the theory of functional plasticity of the brain [44].

Martino *et al.* [21] analyzed the outcomes of 19 patients with recurrent LGG within one of the eloquent areas of the brain. All of the patients in their group underwent subtotal or partial resection during initial surgery. Accordingly, all reoperations, with a single exception of a gross total resection, were either subtotal or partial resections. The majority of patients, i.e. 16 out of 19 patients, showed either improvement or stabilization of preoperative neurological deficit after reoperation. According to these authors, surgery for LGG within eloquent areas in several (usually two or three) stages significantly improves survival measurements in this group of patients. Median follow-up time in their group averages 6.6 years. The outcomes in our group of 16 patients with LGG are similar. One should remember, however, that our cohort included LGG cases outside of eloquent areas of the brain (total of 5 patients). We failed to increase the extent of resection in the majority of the patients when compared to the initial operation. Notably, however, reoperations did not influence the neurological status of our patients.

## Conclusions

1. The risk of tumour progression in patients after surgery for LGG reaches 68%, while the risk of malignant transformation within 5 years averages 47%.
2. Fifty percent of patients with LGG progression show signs of malignant transformation of the tumour.
3. A significant factor that influences the progression of LGG is a large volume of tumour prior to the initial surgery.
4. The most common symptoms of LGG progression are the increase of seizure incidence and intellectual deterioration measured with KPS.
5. A high value of rCBV is a significant parameter that suggests malignant transformation in patients with LGG recurrence.
6. Reoperation of patients with LGG recurrence, even those with tumours within eloquent areas of the brain, does not carry higher risk of neurological deficits when compared to the initial surgery.
7. The extent of resection during surgery for recurrent LGG is comparable with the extents of resection achievable during initial surgery.

## Disclosure

Authors report no conflict of interest.

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