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The assessment of prognostic factors in surgical treatment of low-grade gliomas: A prospective study

Krzysztof Majchrzak[a,*], Wojciech Kaspera[a], Barbara Bobek-Billewicz[b], Anna Hebda[b], Gabriela Stasik-Pres[b], Henryk Majchrzak[a], Piotr Ładziński[a]

[a] Department of Neurosurgery, Medical University of Silesia, Sosnowiec, Poland
[b] Radiodiagnostic Department, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland

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ABSTRACT

Objective: A prospective volumetric analysis of extent of resection (EOR) was carried out to assess surgical outcomes in adults diagnosed with hemispheric low grade gliomas (LGGs).
Materials and methods: 68 consecutive patients diagnosed with LGGs were enrolled in the study. Pre- and post-operative tumor volumes and EOR were measured based on FLAIR MRI. Dynamic susceptibility contrast perfusion magnetic resonance imaging (DSC MRI) was used for the assessment of relative cerebral blood volume (rCBV). Three outcome measures were assessed: overall survival (OS), progression-free survival (PFS), and malignant degeneration-free survival (MFS).
Results: In 6 (9%) patients permanent neurologic deficits were observed. No statistically significant dependence between the EOR and the occurrence of permanent deficits was found. The eloquent or close to the eloquent location was statistically connected with lower EOR ($p = 0.023$). The preoperative volume of tumors treated with gross total resection was significantly smaller than the volume of tumors in subtotal or partial resection groups ($p = 0.020$, $p < 0.001$, respectively). OS was predicted by age at diagnosis ($p = 0.032$), and rCBV ($p = 0.002$). Progression and malignant transformation occurred in 22 (32%) and 11 (16%) out of 68 patients. PFS was predicted by preoperative tumor volume ($p = 0.005$), postoperative tumor volume ($p = 0.008$), the EOR ($p = 0.001$), and by the rCBV ($p = 0.033$). MFS was predicted by preoperative tumor volume ($p = 0.034$), the EOR ($p\,p = 0.020$), and by rCBV ($p = 0.022$). Postoperative tumor volume was associated with a trend of improved MFS ($p = 0.072$). The univariate analysis shows the statistical trend for the relationship between histological subtype and PFS and MFS ($p = 0.079$, $p = 0.078$, respectively). Multivariate analysis selected preoperative tumor volume and rCBV as independently associated with PFS ($p = 0.009$, $p = 0.019$, respectively) and MFS ($p = 0.023$, $p = 0.035$, respectively). EOR was associated with a trend of improved PFS, and MFS ($p = 0.069$, $p = 0.094$, respectively).
Conclusions: Tumor resection of LGG with the use of intraoperative monitoring and neuronavigation is associated with a low risk of new permanent deficits, but EOR significantly decreases with the size of the tumor and/or its location in/close to the eloquent areas. Smaller preoperative tumor volume and greater EOR are significantly associated with longer OS, PFS and MFS. Preoperative rCBV is one of the important prognostic factors significantly connected with survival. Prognosis in LGGs is still under discussion. Other factors such as age, histopathological subtype and KPS should not be underestimated.

1. Introduction

Unlike its anaplastic equivalents, low-grade gliomas (LGGs) offer a better prognosis [1]. The 5-year overall survival rates in patients with diagnosed LGG range from 27% to 97% [2–8]. The results of the majority of retrospective reports on prognostic factors in surgical LGG treatment are still discussed mainly because of significant methodologic limitations [9–11]. According to a few prospective clinical trials that have been published recently, age, extent of resection (EOR), histopathologic grade and tumor size are the most crucial factors influencing the survival rate [11]. Some authors also indicate other factors that may influence the survival of LGG patients. Among these factors are the following: functional status [2,4,7,8,12,13], epilepsy as a single presenting symptom [2,7], duration of symptoms [8], tumor location [4,6,7]. Though histologically benign, LGGs may transform into malignancy significantly shortening overall survival. Transformation of some parts of LGGs into malignancy is based primarily on increased

* Corresponding author. Tel.: +48 502507101.
E-mail address: majchrzak.mr@gmail.com (K. Majchrzak).

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cell nuclear pleomorphism and vascular hyperplasia [3,14–17]. The measurement of the relative cerebral blood volume (rCBV) obtained by dynamic susceptibility contrast enhanced magnetic resonance imaging (DSC MRI) provides information on angiogenic processes. This parameter correlates well with the histopathologic grading of gliomas and may constitute one of the crucial factors in prognosing their treatment outcomes [16,18,19]. The influence of surgical intervention on the final treatment outcome is the most controversial issue. The main reason for such controversy is the lack of exact criteria specifying and defining the EOR. Such criteria are frequently based on intraoperative assessment of resection. Generally, it is believed that a greater EOR significantly influences the improvement in overall survival rates and progression-free survival (PFS) [2,4,6–8,12,13,20]. Currently, tumor volume measurements based on fluid-attenuated inversion recovery MR imaging (FLAIR MRI) is the most exact way of assessment of EOR [6,21]. A case-series prospective study with volumetric assessment of the EOR was conducted to assess the treatment outcomes in adults diagnosed with hemispheric LGGs.

2. Materials and methods

2.1. Patient population

68 surgically treated patients (aged ≥18 yrs) were enrolled in the study. Patients were treated between January 2005 and July 2011 in a single neurosurgical center with the diagnosis of low-grade astrocytoma (LGA), oligoastrocytoma (LGOA) or oligodendroglioma (LGO) supratentorially, and histologically described according to the WHO criteria as grade 2 [22]. Patients with pilocytic astrocytoma, gemistocytic histology or gliomatosis cerebri were exluded [23]. In our study genetic evaluation was not performed. The Karnofsky Performance Scale (KPS) was used for grading functional status of each patient. The occurrence of headaches, epileptic seizures and neurological deficits was taken into consideration in the neurological assessment. In 70% of cases the first operator was the senior author (H.M.). The remaining 30% of patients were operated on by the first two authors (K.M., W.K.), always accompanied by the senior author.

Conventional MRI (T1 and T2-weighted images) with FLAIR sequences, functional MRI (fMRI), diffusion-tensor MRI (DTI), magnetic resonance spectroscopy (MRS), and DSC MRI were performed in all patients before surgery. On the basis of conventional MRI and DSC MRI preoperative tumor volume, and rCBV measurements were calculated (technical details concerning MRI are given below). Tumor location was defined according to the Sawaya et al., as noneloquent brain (grade I), near-eloquent brain (grade II), and eloquent brain (grade III) based on their location relative to brain function [24]. On the basis of rCBV results, patients were divided into two groups with low (≤1.75) and high (>1.75) rCBV values. All patients with tumors located according to MRI in eloquent or close to eloquent areas were operated on with the use of neuronavigation (BrainLab AG, Munich, Germany), with imaging (based on fMRI) of activity areas of eloquent brain cortex and tractography of the optic radiation and motor white matter tracts based on DTI. Tumors located in/close to the motor cortex were also monitored by motor evoked potentials (MEP) using transcranial electrical stimulation (TES), direct cortical stimulation (DCS), and direct electrical stimulation of the subcortical white matter tracts (DSCS). The examination was performed using a 16-channel intraoperative monitoring device (ISIS, Inomed, Teningen, Germany). The 'train' stimulation was supplied to the motor cortex or motor pathways of the white matter depending on which kind of stimulation was performed. Stimulation impulse consisted of 4–6 single stimuli, lasting 0.5 ms at the intervals of 3–4 ms. In the case of direct electrical stimulation (DCS, DSCS) the current used ranged from 3 to 30 mA and for transcranial stimulation (TES) the current of 100–150 mA (max. 220 mA) was used. In the cases of noneloquent localization only neuronavigation was used.

The assessment of EOR was performed based on the Sawaya et al. classification comparing the MRI results (preoperative and postoperative FLAIR MRI) performed up to 48 h following surgery [24]. Resection was then recorded as (1) GTR, gross total (>95%), (2) STR, subtotal (85–95%), or (3) PTR, partial (<85%). Control magnetic resonance spectroscopy (MRS) and perfusion MRI were performed at 6-month intervals. The follow-up protocol also consisted of neuroexam performed 24 h after surgery, at the time of discharge and every month during the first year and every quarter in the follow-up period. The occurrence of new transient or permanent neurological deficits was taken into consideration in the assessment of neurological condition following resection. Deficits that disappeared within 3 months after surgical procedure were considered to be transient and those lasting more than 3 months after surgery were considered to be permanent deficits. Three outcome measures were assessed: (1) overall survival (OS), defined as the time between initial surgery and death; (2) progression-free survival (PFS), defined as the time from surgery to increase in tumor size on follow-up FLAIR imaging and/or demonstration of gadolinium enhancement on follow-up imaging or malignant degeneration; and (3) malignant degeneration-free survival (MFS) defined as the time from surgery to progression on follow-up MRI imaging and higher-grade tumor on subsequent biopsy or revision resection.

2.2. Conventional MRI and tumor volume measurements

MRI examination was performed with the 1.5T Magnetom Avanto (Siemens AG, Erlangen, Germany) and the 3.0T Achieva scanner (Philips medical systems, Best, The Netherlands). A commercial head coil was used for imaging. At the first stage of the examination standard MRI sequences were performed. T1-weighted images (repetition time/echo time [TR/TE], 568/16 ms), T2 FLAIR (8000/86/inversion time [TI] 2370 ms), T-2 weighted images (4390/94) were obtained using Magnetom Avanto. Additionally, after DSC MRI, T1-weighted images were obtained (450/16) in patients before and after contrast enhancement (CE).

T1-weighted images were obtained using Achieva (Philips) (495/10), T2 FLAIR (9000/125), T2-weighted images (3000/80) and T1-weighted images after CE (636/10) after DSC MRI scans. Tumor volume was determined based on hyperintense region on T2 FLAIR and was approximated as an ellipsoid.

2.3. Dynamic susceptibility contrast enhanced magnetic resonance imaging

DSC MRI was obtained using echo-planar imaging (EPI) during CE. Imaging parameters for Avanto were the following: TR/TE 1560/30 ms, field of view (FOV) 250 mm × 250 mm, 21 slices–thickness 5 mm, matrix 128 × 128, voxel size 2.0 × 2.0, intersection gap 20%, flip angle 90o. Time acquisition (TA) was 1 min 26 s. Multihance contrast medium was administered at the fifth image at the volume of 0.2 mL/kg at an injection rate of 6 mL/s. Imaging parameters for Achieva were the following: TR/TE 16/24 ms, FOV 230 × 187 × 144 mm, 36 slices – thickness 4 mm, matrix 64 × 52, voxel size 3.59 × 3.59, no gap, flip angle 7°. TA was 1 min 29 s. Paramagnetic contrast medium was administered at the fifth image at the volume of 0.1 mL/kg at the injection rate of 6 mL/s.

2.4. rCBV measurements

To analyse DSC MRI data standard software provided by the producer was used. Color overlay maps of cerebral blood volume (CBV)