

Multidisciplinary Management of Adult Low Grade Gliomas

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Rezumat

Managementul multidisciplinar al gliomelor cu grad scăzut de malignitate

Background: Gliomele emisferice cu grad scăzut de malignitate ale adulților acoperă un spectru patologic clar definit de o serie de simptome neurologice și de caracteristici histopatologice și moleculare. Managementul optim al acestor tumori încă reprezintă un subiect de dezbateri aprinse în ciuda progreselor înregistrate în medicină în ultimii 20 de ani.

Materiale și metode: Autorii au evaluat literatura de specialitate încercând să găsească un numitor comun în ceea ce privește tratamentul multidisciplinar al gliomelor cu grad scăzut de malignitate. După parcurgerea literaturii de specialitate autorii au suprapus concluziile trase cu experiența personală pentru a evalua aplicabilitatea tratamentelor propuse de diferiți autori și pentru a propune un algoritm propriu de tratament al acestor pacienți.

Rezultate și concluzii: Progresul înregistrat în microchirurgie și monitorizarea intraoperatorie permit o rezecție agresivă a acestor tumori cu o îmbunătățire semnificativă în supraviețuire și calitatea vieții. Factorii de risc ai metodelor de tip "wait and see" precum și neurotoxicitatea radioterapiei sunt eclipsați de beneficiile unei rezecții chirurgicale atente urmată de chimioterapie. O strategie de management modernă și corect efectuată ar trebui să includă o rezecție chirurgicală maximală care să

menajeze structurile critice ale encefalului și amânarea cât mai mult a radioterapiei. Rolul temozolomidei încă nu este elucidat – el urmând să fie stabilit de studii care sunt încă în desfășurare.

Cuvinte cheie: low grade glioma, gliome cu grad scăzut de malignitate, astrocitom, oligodendrogliom, oligoastrocitom, management multidisciplinar, temozolomida

Abstract

Background: Adult hemispheric low grade gliomas (LGG) cover a pathologic spectrum which has specific clinical, histological and molecular characteristics. The optimal management of these tumors is still a controversial topic in international literature.

Methods: We evaluated scientific papers from the literature (Medline and Cochrane Library to date) and we compared the results found there with our experience, trying to create a pattern of treatment of our own.

Results and conclusions: The advances in microsurgical and neuromonitoring techniques, as well as in neuroimaging, allow for a more aggressive resection of LGG with a significant improvement in overall survival and quality of life. The potential risks of the "wait and see" policy and the neurotoxicity of radiotherapy are challenged by the benefits of careful surgical resection and up-front chemotherapy. The present day treatment strategy, based on recent evidence, should include a maximal surgical resection when possible, with the full preservation of the patients' ability, and delayed radiotherapy. The role of temozolomide in the management of LGG and the identification of the therapeutic modality with the best quality

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of life profile will be determined by ongoing trials. The further characterization of prognostic relevance of molecular markers and data from advanced imaging techniques needs an intensification of research and validation efforts.

Abbreviations: LGG: low grade gliomas, WHO: World Health Organization, OS: overall survival, PFS: progression-free survival, MRI: Magnetic resonance imaging, MRS: Magnetic resonance spectroscopy, MPFS: malignant progression-free survival, rCBV: Relative Cerebral Blood Volume, QOL: quality of life, FLAIR: Fluid attenuated inversion recovery, MGMT: O6-methylguanine DNA methyltransferase enzyme, DSC MR imaging: Dynamic Susceptibility Contrast Perfusion MR imaging, 1H-MRS: Proton Magnetic Resonance Spectroscopy, IDH1: isocitrate dehydrogenase 1 gene, SPECT: Single-photon emission computed tomography, PET: Positron emission tomography, DTI-FT: Diffuse Tensor Imaging-fiber tracking technique, DES: direct electrical stimulation, EEG: Electroencephalography, EcoG: Electrocorticography, MEP: motor evoked potentials, EMG: Electromyography, AED: anti-epileptic drugs, TMZ: Temozolomide, EORTC: European Organization for Research and Treatment of Cancer, NCCTG: North Central Cancer Treatment Group, RTOG: Radiation Therapy Oncology Group, ECOG: Eastern Cooperative Oncology Group, EOR: extent of resection, Gy: Gray (unit), GyE: gray equivalent, RT: radiation therapy, IMRT: image-guided intensity modulated radiotherapy, FSRT: fractionated stereotactic radiotherapy, SRS: proton therapy or stereotactic radiosurgery, LET: high-linear energy transfer beams, RBE: relative biological effectiveness, CTCAE: Common Terminology Criteria for Adverse Events, PCV: procarbazine, lomustine, and vincristine chemotherapy

Key words: low-grade glioma, astrocytoma, oligodendroglioma, oligoastrocytoma, mixed glioma, molecular cytogenetics, chemotherapy, temozolomide, neuroimaging, health-related quality of life, cognitive functioning

Introduction

Diffusely infiltrating low grade gliomas (LGG) (see Fig. 1) include grade II astrocytomas, oligodendrogliomas and oligoastrocytomas (World Health Organization (WHO) grade 2) (1). Low grade gliomas represent up to 30% of all gliomas and most of the patients diagnosed with this condition are between the second and fourth decade of life. LGGs are commonly located in or close to eloquent areas (2), which makes their management a very difficult matter.

At presentation, the most frequent symptom is a seizure based disorder (72-89% of cases) (3), which is followed by headache and nausea (10-44% of cases) (4,5), mental status changes (3-30% of cases) (4,5) and focal neurological deficits (2-30% of patients) (5). Despite the typical symptoms described in the literature many patients may have a normal gross neurological examination at diagnosis.

Most LGGs show an aggressive pattern of behavior (6,7). The average survival period for low grade gliomas is about 10 years. The 5-year overall survival (OS) and progression-free survival (PFS) rates in randomized studies range from 58% to 72% (for the OS) and 37% to 55% (for the PFS)(8). Poor prognosis factors include age above 40 years, astrocytic tumor histology, tumor size bigger than 6 cm, tumor crossing of the midline, and neurological deficit at diagnosis (9).

The optimal treatment of patients with Low Grade Gliomas has yet to be determined. No class I, II or III evidence exists regarding the optimal management of these patients. The therapeutic approaches have included the “wait and watch” strategy, needle or open biopsy, surgery, radiotherapy and chemotherapy. Over the last decade, several studies have brought new and significant information for defining the role and the timing of each therapeutic approach.

Conservative management for adult supratentorial LGG

There is no evidence from randomized clinical trials about

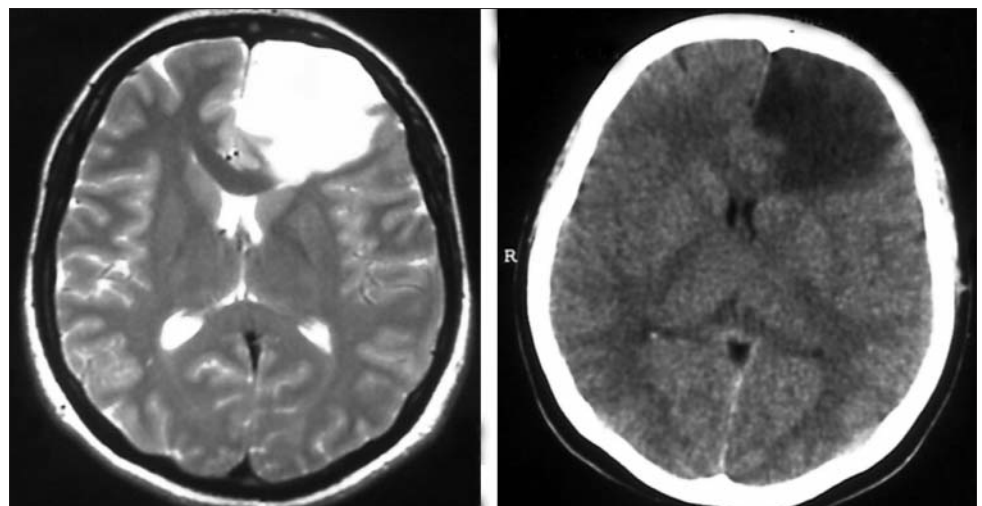


Figure 1. CT Aspect of a patient with LGG

either the role of conservative management in LGG or the timing of surgical treatment. We consider that the surgical intervention should not be unnecessarily delayed when unfavorable prognostic factors are identified: age > 40 years, tumor size > 6 cm, tumor crossing the midline, poor performance status, drug resistant epilepsy. However, there is no evidence that these patients will do better with an early intervention either (10).

If the surgeon chooses the “watch and wait” strategy, the patient will be monitored using MRI scans in the 3rd year, 6th year and then yearly, unless clinical condition warrants any early scan. The patient is also neurologically tested for baseline purposes. Comparison of MRI images over the years documents the changes in lesion size. Many papers have shown gradual enlargement of the lesion (7,11) at a rate that was influenced by genetic alterations in the tumor cell populations (12). A larger preoperative tumor volume was significantly associated with shorter overall survival (OS), progression free survival (PFS), and malignant progression-free survival rates (MPFS) (13). Sequential measurement of LGG volume allows for accurate determination of growth rates and identification of patients whose tumors are at high risk of early transformation (7,14).

Due to the lack of histological data in the setting of a “wait and see” approach, the prognostic data derived from newer MRI techniques are of paramount importance. Therefore using only conventional MRI scans lowers the certainty of LGG diagnosis. A study of 174 cases of supratentorial glial lesions diagnosed using MRI before biopsy, shows that only in 20 cases (30%), the histological analysis changed the presumptive diagnosis of LGG (15), other studies have shown even greater discordance (16). A recent study retrospectively analysing 35 patients with histologically diagnosed LGG have shown that a rCBV threshold of 1.75 could differentiate between a prolonged survival group (mean time to progression of approx. 10 years) from a poor prognostic group (mean time to progression less than one year) (11), and in a recent follow up study authors have shown that rCBV elevations can precede malignant transformation and new contrast enhancement by up to 12 months (17) Such information is useful for guidance regarding when to abandon a “watch and wait” strategy or whether it is prudent to start treatment initially.

Does patient outcome suffer due to a “watch and wait” strategy? There is no randomized trial on conservative management versus early surgery to answer this question. Current literature has not demonstrated that patients are harmed by considerable delay in primary intervention, therefore the surgeon’s choice of conservative management will be influenced by many variables: natural history of disease, patient’s compliance with treatment, the presence of unfavorable prognosis factors, patient age, associated morbidities, clinical performance status, location and size of lesion, certainty of diagnosis of WHO II gliomas, the presence of clinical and radiological signs of progression etc.

Surgery

In accordance with modern oncology concepts, an increasing

number of authors find histological validation to be mandatory to solve the dilemmas of differential diagnosis, grading malignancy and assessing the molecular profile of tumors (E.g. 1p/19q loss and MGMT status) before deciding the further management. Needle biopsy targeting regions with elevated choline levels or regions with increased angiogenesis (maximum relative CBV derived from DSC MR imaging) can partly overcome the limits of this technique and significantly increase diagnostic yield. However, the diagnostic accuracy of 1H-MRS-supported and MRI-guided procedures was only 67% and 79% in a recent study (18,19,20).

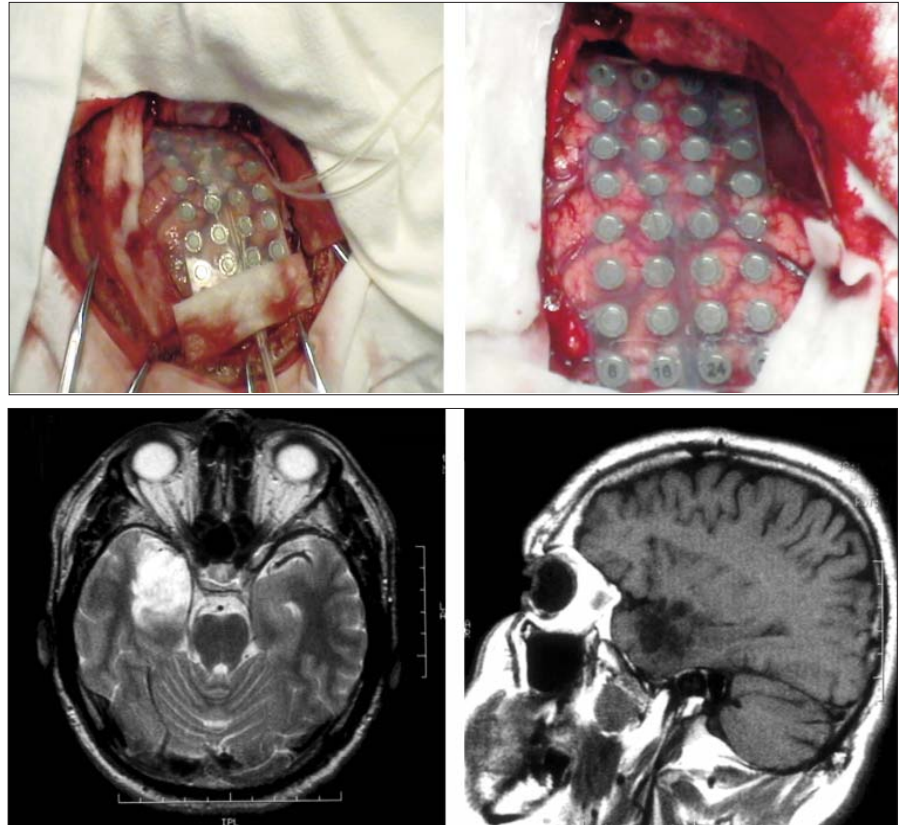
Surgical resection of LGGs is still a matter of debate, but a growing number of recent studies support its role (21, 22, 23). Surgical resection allows obtainment of representative tissue to reach a correct histological and molecular diagnosis. The relevance of chromosome 1p/19q loss of heterozygosity, MGMT methylation, and mutation affecting codon 132 of the isocitrate dehydrogenase 1 (IDH1) gene are important in the histotype definition and the prognostication of the response to certain chemotherapeutic agents, having therapeutic implications (24,25,26,27). In addition, surgery has the potential to improve neurological symptoms, obtaining better seizure control, and could decrease the rate of recurrence and malignant transformation, thereby having a beneficial effect on survival. Surgery however has its own unavoidable risks, which could permanently affect the patient’s quality of life

Patients with significant neurological deficits who present mass effect or poor seizure control, despite poly-therapy, are usually candidates to surgical resection, even though there are higher surgical risks in terms of morbidity and mortality, but the alternative is progressive neurological deterioration or even death in the near future.

The tumor location predominantly close or within eloquent cortex (in 82.6% of cases (2), the diffuse pattern of growth, the frequently normal neurological examination and the relatively long natural history of the lesion impose preservation of neurological functions of the patient while simultaneously advocating for a maximum resection of tumor mass. To achieve these goals, it is mandatory to perform a series of neuropsychological, neurophysiological, neuroradiological and intraoperative investigations in order to identify and preserve at the time of surgery essential cortical and subcortical areas.

The preoperative neuroradiological examination, including basic morphological MR images (T1, T2 and FLAIR), metabolic sensitive techniques (MR spectroscopy, SPECT or PET), functional MRI (for motor and language tasks) and anatomic studies (such as Diffuse Tensor Imaging-fiber tracking techniques (DTI-FT) for visualizing the relationship between the fiber tracts and tumor mass) provides all-embracing information about the anatomical and functional boundaries of the lesion to be resected, but this information needs to be confirmed intraoperatively by direct electrical stimulation (DES) (see Fig. 2) that identifies with certainty functional regions and allows the surgeon to maximize the extent of resection while reducing the risks of permanent neurological deficits.

Figure 2. Aspects showing the direct electrical stimulation technique and a patient in which it was used



The use of neuronavigation, intraoperative MRI and brain mapping techniques (EEG, ECoG, MEP, EMG, and DES) decreases the percentage of postoperative permanent deficits a staggering ten times (from 23% to 2.3% when subcortical stimulation is used) and increases the percentage of patients in which a total (no abnormalities seen on post op FLAIR images) and subtotal resection (a postoperative volume on volumetric post op FLAIR images less than 10 ml) is achieved (from 11%, when no brain mapping was available, to 52.8%) (21, 22, 28, 29,30)

Total and subtotal resections have a positive impact on seizures in patients with insular LGG within a range of 76% to 89% with reduction in the number of anti-epileptic drugs (AED) administered (31). Suppression of AEDs is possible in 30% of cases. Seizure recurrence after initial postoperative seizure control was associated with tumor progression (32,33, 34). Gross-total resection, preoperative seizure control on antiepileptic medication and duration of seizures of less than 1 year emerged as predictors of complete seizure freedom in a recent study examining 773 patients who underwent surgery for LGG across 20 published series (35).

There are no randomized trials that have examined the effect of the extent of surgery on OS and PFS, but many recently published articles stress the importance of the extent of resection in controlling tumour growth and determining survival. In a recent study authors analysing 216 adults undergoing initial resection of hemispheric LGG showed that postoperative tumour volume was a significant predictor of OS

and PFS, and extent of resection was a significant predictor of MPFS. Patients with at least 90% removal had 5 and 8-year overall survival (OS) rates of 97% and 91%, whereas patients with less than 90% removal had 5- and 8-year OS rates of 76% and 60%. Patients with complete resection had 5- and 8-year OS, PFS and MPFS rates of 98% and 98%, 78% and 48%, and 96% and 79% (21).

A total or subtotal resection is difficult to be achieved in large and diffuse tumors. When the lesion presents a mass effect, a partial resection may still be useful (21,36). The majority of these patients is referred to stereotactic biopsy only followed by adjuvant therapies. To make a radical surgery possible in this group of patients, preoperative chemotherapy (TMZ, for 6 month) was proposed (37); this combined treatment was feasible, efficient and well-tolerated in ten initially inoperable patients (38). In patients that underwent a partial removal, chemotherapy could have been used for further decrease of postoperative tumor volume to a value associated with a better prognosis (26,28,39). A two stage surgical procedure could be necessary in patients who lose their intra-operative responsiveness (the second surgery is usually made after a period up to four to six months to let brain plasticity take place). In recurrent tumors, from all the available therapeutic options, surgery, usually combined with other therapeutic modalities, is the treatment of choice when a total or subtotal resection is possible.

A significant improvement in OS associated with a more extensive resection of diffuse LGG has been documented in

all series since 2005 in which an objective extent of resection could be correlated with survival (34,21,22,36,40,41, 42,43,44). A complete or “supra-total” resection (resection extending beyond the area of MR imaging signal abnormalities up to 20 mm), in one step or a “planned multistage surgical approach”, awake surgery with cortico-subcortical mapping using direct electrostimulation, maximization of the extent of resection and preservation of QoL were the fundamental elements associated with significant delay of anaplastic transformation and implicitly with improvement of OS (45,46, 47,48).

Radiotherapy

The optimal role of radiotherapy in the management of LGG still needs to be established. The four phase III randomized trials performed until now brought significant information about indications for irradiation, timing, dose and toxicity of radiotherapy, irradiation technique, and adjuvant chemotherapy after radiation. The highly variable outcome of LGG led to the identification of prognostic factors and, based on them, to the definition of risk groups. The two randomized, multicentre trials of the European Organization for Research and Treatment of Cancer (EORTC) 22844 (49) and 22845 (50) including 534 patients allowed the development of a prognosis score. The unfavorable prognosis factors identified by a multivariate analysis were: age ≥ 40 years, astrocytic tumor histology, tumor size > 6 cm, tumor crossing the midline, and neurological deficit at diagnosis. The favorable prognosis score (0 to 2 risk factors) was associated with a median survival of 7.72 years compared with a high risk score (3 to 5 risk factors) where median survival was of 3.20 (51).

Analysing long-term efficacy of immediate postoperative radiotherapy versus deferred radiotherapy until the time of progression for LGG in 314 adults; the authors concluded that radiotherapy could be deferred for patients with low-grade glioma who are in a good condition, provided they are carefully monitored (52). Patients with large unrespectable tumors or having a high risk score are commonly treated with immediate radiotherapy.

Two randomized trials investigated radiation doses in patients with LGG. Although some studies reported a better survival for doses greater than 50 Gy (53), the EORTC 22844 and North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group (NCCTG/RTOG/ECOG) studies did not show any advantage for higher versus lower doses (54,55).

In the NCCTG/RTOG/ECOG trial, the survival was compared in 203 adult patients treated with low-dose (50.4 Gy/28 fractions) versus high-dose (64.8 Gy/36 fractions) localized radiation therapy (RT), and the authors found that survival at 2 and 5 years is non-significantly better with low-dose RT (survival at 2 and 5 years was 94% and 72%, respectively, with low-dose RT and 85% and 64%, respectively, with high-dose RT). In the 379 adult patients with cerebral LGGs randomized in the EORTC 22844 trial to receive irradiation postoperatively (or post-biopsy) with either 45 Gy in 5 weeks or

59.4 Gy in 6.6 weeks with a median follow-up time of 74 months no significant difference in terms of survival (58% for the low-dose arm and 59% for the high-dose arm) or the progression free survival (47% and 50%) was observed between the two arms of the trial.

The extent of resection (EOR) and radiation dose were reported as being significant for OS and PFS (the median survival of patients with partial resection who received ≤ 50 Gy was 16.5 months while those who received > 50 Gy and suffered a total/subtotal resection was 109.2 months) (53), but the relationship between postoperative tumor volume and radiation dose has not been studied in a randomized trial to date. However, if higher doses are used, an increased radiotherapy related toxicity is observed. In the NCCTG/RTOG/ECOG trial, the 2-year actuarial incidence of grade 3 to 5 radiation necrosis was 2.5% with low-dose RT and 5% with high-dose RT (55), or lower levels of functioning and more symptom burden following completion of radiotherapy are reported in patients of the EORTC 22844 trial (56).

The analysis of the 65 survivors with (LGG) who completed neuropsychological follow-up at a mean of 12 years after first diagnosis showed a progressive decline in attentional functioning, even those who received fractions doses that are regarded as safe (≤ 2 Gy), comparative with patients that did not receive radiotherapy (57).

New techniques that use conformal or focal delivery of radiation like image-guided intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy, fractionated stereotactic radiotherapy (FSRT), proton therapy or stereotactic radiosurgery (SRS), sparing in a higher grade of surrounding normal tissues, should significantly improve treatment outcomes. The intensity modulated radiotherapy and volumetric modulated arc therapy techniques can reduce the dose to the bilateral hippocampi below the dosimetric threshold of 7.3 Gy, value associated with neurocognitive function impairment providing local control rates comparable to those provided by two-dimensional and three-dimensional radiotherapy, so it was shown in 39 children with LGG (58). Although these preliminary results indicate some benefit, incorporation of these two techniques into clinical trials is needed.

Stereotactic radiosurgery has been performed for patients particularly selected with recurrent LGG or residual or unresectable small tumor, providing long-lasting tumor control with comparable toxicity (59), but confirmation by prospective trials is lacking. An increase in the incidence of radiotherapy related side effects was reported in larger target volumes (median size: 28 cm³) and higher doses (median dose: 20 Gy) (60).

Fractionated stereotactic radiotherapy combines the advantage of low risk of radiation related side effects, due to dose fractionation, with comparable effectiveness, including small and larger tumors, as compared with the others stereotactic radiotherapy techniques (61). Hypofractionated stereotactic radiotherapy (H-FSRT) brings a lower level of neuro-toxicity than SRS, but the incidence of radiation related side effects seems larger as compared to FSRT due to higher single doses. Comparatively with FRST, the H-FSRT has the

benefit of a shortening of the overall treatment time, which becomes useful in terminally ill patients.

The use of particle charged radiotherapy (proton or carbon ion) has been implemented for treatment of cerebral glioma. Particle irradiation exhibits enhanced effectiveness and accurate delivery, especially in deep seated lesions, in comparison to conventional photon therapy. Additionally to proton ions, the carbon ions, as high-linear energy transfer (LET) beams, express superior relative biological effectiveness (RBE), that is more pronounced for resistant tumors compared to sensitive tumors. Mizoe et al reported promising results regarding the effectiveness and safety of coadjuvant therapy (x-ray conventional radiotherapy, chemotherapy [Nimustine hydrochloride], and carbon ion radiotherapy (range from 16.8 to 24.8 GyE) in 48 patients with malignant gliomas (62). Carbon ion radiotherapy is routinely performed with acceptable neurotoxicity in patients with chordomas and chondrosarcomas of the skull base showing superior results (63).

No acute (arising during the first 90 days after radiotherapy) toxicities bigger than grade II of Common Terminology Criteria for Adverse Events v4.0 (CTCAE) was reported in 33 patients with gliomas and meningiomas that underwent particle radiotherapy delivered with active raster scanning (64).

Two ongoing trials are investigating particle radiotherapy in patients with cerebral gliomas. Within CLEOPATRA trial, authors are investigating the effectiveness of a carbon ion boost comparatively to a proton boost in patients with macroscopic tumour residues following surgery, photon radiotherapy (50 Gy) and chemotherapy with temozolomide (65). Within the second one, the CINDERELLA trial, the impact of re-irradiation using carbon ion therapy versus FSRT in patients with recurrent gliomas (including WHO grade II gliomas) that underwent a prior course of standard photon radiotherapy is being evaluated (66).

Chemotherapy

The adjuvant chemotherapy after radiation has been analysed in RTOG 9802 trial, which included 251 high risk patients who were randomized to radiotherapy (RT) alone (54 Gy) or RT + procarbazine, lomustine, and vincristine (PCV) chemotherapy (6 cycles of standard dose). The PFS was reported as being improved for patients that underwent a combined treatment, but not OS. The combined regimen seemed to provide a survival gain in 2-year survivors probably due to chemotherapy (67).

In recent years temozolomide (TMZ) chemotherapy has been studied more extensively due to its ease of administration and a favorable quality-of-life profile (68). Some prospective

randomized trials have been launched to determine whether temozolomide can substitute radiation therapy and whether there is a benefit from combining these two therapeutic modalities. The phase II RTOG 0424 trial of a temozolomide-based chemoradiotherapy regimen for high-risk LGG compares the 3-year survival of this regimen to the 3-year survival of the EORTC high-risk low-grade glioma population described by Pignatti et al. The phase III ECOG E3F05 trial should primarily determine whether the addition of temozolomide to fractionated radiotherapy improves the PFS or the OS of patients with low-grade gliomas requiring treatment. Secondly, the trial should evaluate the toxicities and quality of life in patients receiving radiation therapy alone or radiation therapy plus temozolomide chemotherapy, and to estimate the consequences of the presence or absence of 1p and 19q deletion on PFS and OS, in general, and particularly in patients receiving chemotherapy.

Response rate after chemotherapy may vary markedly in LGG with prevalence of minor responses. In a retrospective observational study including 149 adult patients with progressive LGG treated with up-front TMZ chemotherapy, seventy-seven patients (53%) experienced an objective response and loss of chromosome 1p/19q predicted both a durable chemosensitivity and a favorable outcome (26). Oligodendrogliomas, especially pure tumors, with a loss of heterozygosity on chromosome 1p/19q show a particular responsiveness to chemotherapy (PCV and TMZ) and radiotherapy (response rates as high as 90 – 100%) (69).

Conclusions

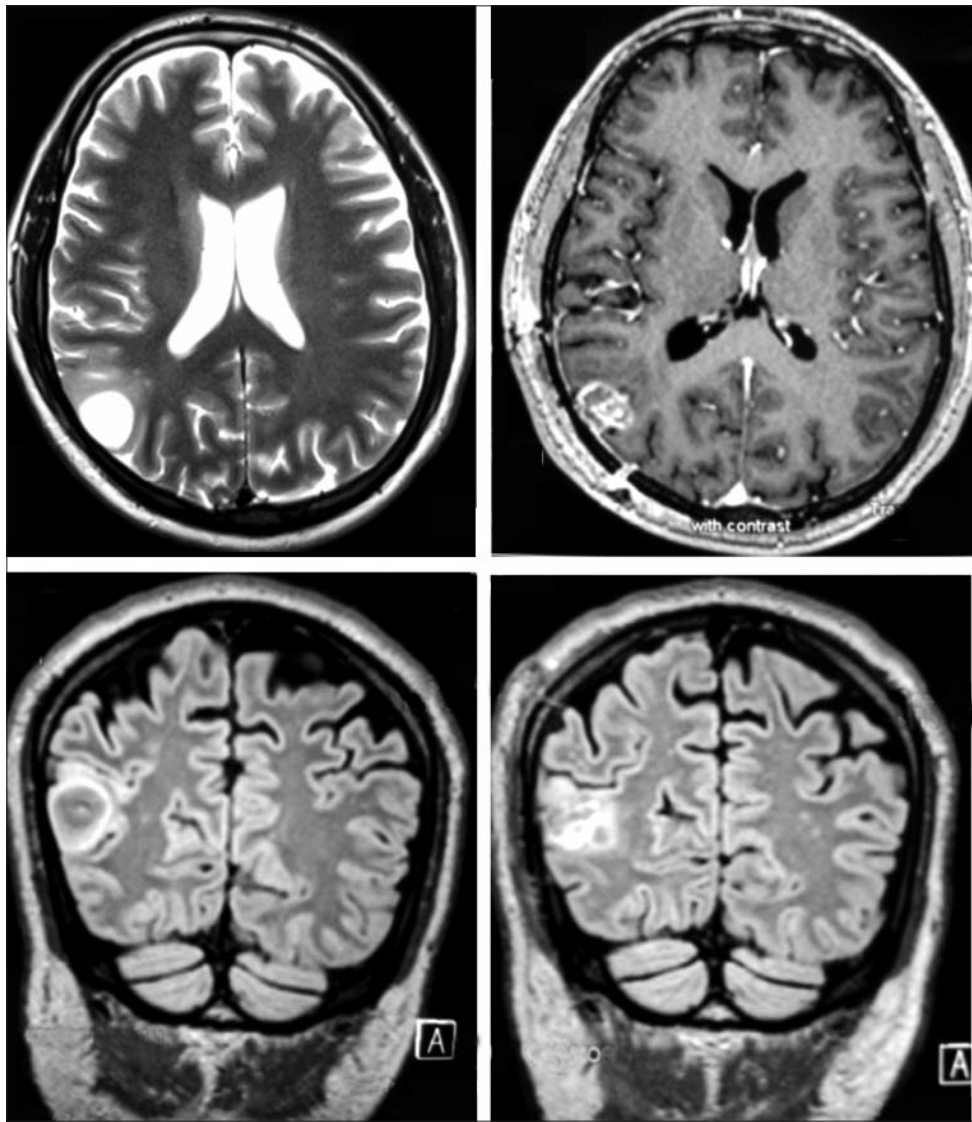
The advances in microsurgical and neuromonitoring techniques as well as in neuroimaging allow a more aggressive resection of LGG with a significant improvement in overall survival and quality of life. The potential risks of a “wait and see” approach and the neurotoxicity of radiotherapy are challenged by the benefits of surgical resection and up-front chemotherapy. The present day treatment strategy, based on currently emerged evidence, should include a maximal surgical resection when possible with the full preservation of the patients’ ability, and delayed radiotherapy until de time of progression. The role of temozolomide in the management of LGG and the identification of the therapeutic modality with the best quality of life profile should be determined by ongoing trials. The further characterization of prognostic relevance of molecular markers and data from advanced imaging techniques needs an intensification of research and validation efforts.

Last but not least, the authors emphasize the importance of early detection of such tumors as it allows for total resections with a perfect outcome for the patient and 0% recurrence. (See Figs, 3, 4)

Figure 3. A 31 year old male patient, incidentally diagnosed with Low Grade Glioma. The images are taken one year post-op



Figure 4. Preop (left) and Postop (right) Images of the above mentioned patient



References

1. Louis D, Ohgaki H, Wiestler O, Cavenee W, eds. World Health Organization Classification of Tumors of the Central Nervous System, 4 edn. Lyon: IARC; 2007.
2. Duffau L, Capelle L. Preferential brain locations of low grade gliomas. Cancer. 2004;100(12):2622-6.
3. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients

- with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol.* 2007;6(5):421-30.
4. Wessels PH, Weber WE, Raven G, Ramaekers FC, Hopman AH, Twijnstra A. Supratentorial grade II astrocytoma: biological features and clinical course. *Lancet Neurol.* 2003;2 (7):395-403.
 5. Yeh SA, Lee TC, Chen HJ, Lui CC, Sun LM, Wang CJ, et al. Treatment outcomes and prognostic factors of patients with supratentorial low-grade oligodendroglioma. *Int J Radiat Oncol Biol Phys.* 2002;54(5):1405-9.
 6. Lang FF, Gilbert MR. Diffusely infiltrative low-grade gliomas in adults. *J Clin Oncol.* 2006;24(8):1236-45.
 7. Rees J, Watt H, Jäger HR, Benton C, Tozer D, Tofts P, Waldman A. Volumes and growth rates of untreated adult low-grade gliomas indicate risk of early malignant transformation. *Eur J Radiol.* 2009;72(1):54-64. Epub 2008 Jul 15.
 8. Claus EB, Black PM. Survival rates and patterns of care for patients diagnosed with supratentorial low-grade gliomas: data from the SEER program, 1973-2001. *Cancer.* 2006;106(6):1358-63.
 9. Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, et al. European Organization for Research and Treatment of Cancer Radiotherapy Cooperative Group. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol.* 2002;20(8):2076-84.
 10. Van den Bent MJ. Low grade gliomas: how should patients be managed? In: Williams C (ed) Evidence based oncology. London: BMJ Publishing; 2003. p. 561-64.
 11. Law M, Oh S, Babb JS, Wang E, Inglese M, Zagzag D, et al. Low-grade gliomas: dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging-prediction of patient clinical response. *Radiology.* 2006;238(2):658-67. Epub 2006 Jan 5.
 12. Ricard D, Kaloshi G, Amiel-Benouaich A, Lejeune J, Marie Y, Mandonnet E, et al. Dynamic history of low-grade gliomas before and after temozolomide treatment. *Ann Neurol.* 2007; 61(5):484-90.
 13. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. *J Clin Oncol.* 2008; 26(8):1338-45.
 14. Rees J, Watt H, Jäger HR, Benton C, Tozer D, Tofts P, et al. Volumes and growth rates of untreated adult low-grade gliomas indicate risk of early malignant transformation. *Eur J Radiol.* 2009;72(1):54-64. Epub 2008 Jul 15.
 15. Callovini GM. Is it appropriate to redefine the indication for stereotactic brain biopsy in the MRI Era? Correlation with final histological diagnosis in supratentorial gliomas. *Minim Invasive Neurosurg.* 2008;51(2):109-13.
 16. Scott JN, Brasher PM, Sevicik RJ, Rewcastle NB, Forsyth PA. How often are nonenhancing supratentorial gliomas malignant? A population study. *Neurology.* 2002;59(6):947-9.
 17. Law M, Young RJ, Babb JS, Peccerelli N, Chheang S, Gruber ML, et al. Gliomas: predicting time to progression or survival with cerebral blood volume measurements at dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *Radiology.* 2008;247(2):490-8. Epub 2008 Mar 18.
 18. Chernov MF, Muragaki Y, Ochiai T, Taira T, Ono Y, Usukura M, et al. Spectroscopy-supported frame-based image-guided stereotactic biopsy of parenchymal brain lesions: comparative evaluation of diagnostic yield and diagnostic accuracy. *Clin Neurol Neurosurg.* 2009;111(6):527-35. Epub 2009 May 7.
 19. Cha S, Tihan T, Crawford F, Fischbein NJ, Chang S, Bollen A, et al. Differentiation of low-grade oligodendrogliomas from low-grade astrocytomas by using quantitative blood-volume measurements derived from dynamic susceptibility contrast-enhanced MR imaging. *AJNR Am J Neuroradiol.* 2005;26(2): 266-73.
 20. Guillemin R, Menuel C, Duffau H, Kujas M, Capelle L, Aubert A, et al. Proton magnetic resonance spectroscopy predicts proliferative activity in diffuse low-grade gliomas. *J Neurooncol.* 2008;87(2):181-7. Epub 2007 Dec 28.
 21. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. *J Clin Oncol.* 2008;26(8):1338-45.
 22. Claus EB, Horlacher A, Hsu L, Schwartz RB, Dello-Iacono D, Talos F, et al. Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. *Cancer.* 2005;103(6):1227-33.
 23. Sanai N, Berger MS. Extent of resection influences outcomes for patients with gliomas. *Rev Neurol (Paris).* 2011;167(10): 648-54. Epub 2011 Sep 7.
 24. Van den Bent MJ, Dubbink HJ, Marie Y, Brandes AA, Taphoorn MJ, Wesseling P, et al. IDH1 and IDH2 mutations are prognostic but not predictive for outcome in anaplastic oligodendroglial tumors: a report of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *Clin Cancer Res.* 2010; 16 (5):1597-604. Epub 2010 Feb 16.
 25. Labussiere M, Wang XW, Idbaih A, Ducray F, Sanson M. Prognostic markers in gliomas. *Future Oncol.* 2010;6(5):733-9.
 26. Kaloshi G, Benouaich-Amiel A, Diakite F, Taillibert S, Lejeune J, Laigle-Donadey F, et al. Temozolomide for low-grade gliomas: predictive impact of 1p/19q loss on response and outcome. *Neurology.* 2007;68(21):1831-6.
 27. Everhard S, Kaloshi G, Crinière E, Benouaich-Amiel A, Lejeune J, Marie Y, et al. MGMT methylation: a marker of response to temozolomide in low-grade gliomas. *Ann Neurol.* 2006;60(6): 740-3.
 28. Bello L, Gallucci M, Fava M, Carrabba G, Giussani C, Acerbi F, Baratta P, Songa V, Conte V, Branca V, Stocchetti N, Papagno C, Gaini SM. Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. *Neurosurgery.* 2007 Jan; 60 (1): 67-80; discussion 80-2.
 29. Duffau H. Surgery of low-grade gliomas: towards a functional neurooncology. *Curr Opin Oncol.* 2009 Nov;21(6):543-9.
 30. Bello L, Fava E, Carrabba G, Papagno C, Gaini SM. Present day's standards in microsurgery of low-grade gliomas. *Adv Tech Stand Neurosurg.* 2010;35:113-57.
 31. Simon M, Neuloh G, von Lehe M, Meyer B, Schramm J. Insular gliomas: the case for surgical management. *J Neurosurg.* 2009; 110(4):685-95.
 32. Duffau H, Moritz-Gasser S, Gatignol P. Functional outcome after language mapping for insular World Health Organization Grade II gliomas in the dominant hemisphere: experience with 24 patients. *Neurosurg Focus.* 2009;27(2):E7.
 33. You G, Sha ZY, Yan W, Zhang W, Wang YZ, Li SW, et al. Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. *Neuro Oncol.* 2012;14(2):230-41. Epub 2011 Dec 19.
 34. Chang EF, Potts MB, Keles GE, Lamborn KR, Chang SM, Barbaro NM, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. *J Neurosurg.* 2008;108(2):227-35.
 35. Englot DJ, Berger MS, Barbaro NM, Chang EF. Predictors of

- seizure freedom after resection of supratentorial low-grade gliomas. A review. *J Neurosurg.* 2011; 115 (2): 240-4. Epub 2011 Apr 29.
36. Ius T, Isola M, Budai R, Pauletto G, Tomasino B, Fadiga L, et al. Low-grade glioma surgery in eloquent areas: volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients: clinical article. *J Neurosurg.* 2012;117(6):1039-52. Epub 2012 Oct 5.
 37. Duffau H, Taillandier L, Capelle L. Radical surgery after chemotherapy: a new therapeutic strategy to envision in grade II glioma. *J Neurooncol.* 2006;80(2):171-6. Epub 2006 Apr 28.
 38. Blonski M, Taillandier L, Herbet G, Maldonado IL, Beauchesne P, Fabbro M, et al. Combination of neoadjuvant chemotherapy followed by surgical resection as a new strategy for WHO grade II gliomas: a study of cognitive status and quality of life. *J Neurooncol.* 2012 Jan; 106 (2): 353-66. Epub 2011 Jul 22.
 39. Ricard D, Kaloshi G, Amiel-Benouaich A, Lejeune J, Marie Y, Mandonnet E, et al. Dynamic history of low-grade gliomas before and after temozolomide treatment. *Ann Neurol.* 2007;61 (5):484-90.
 40. Yeh SA, Ho JT, Lui CC, Huang YJ, Hsiung CY, Huang EY. Treatment outcomes and prognostic factors in patients with supratentorial low-grade gliomas. *Br J Radiol.* 2005;78 (927): 230-5.
 41. McGirt MJ, Chaichana KL, Attenello FJ, Weingart JD, Than K, Burger PC, et al. Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas. *Neurosurgery.* 2008; 63 (4): 700-7; author reply 707-8.
 42. Ahmadi R, Dictus C, Hartmann C, Zörn O, Edler L, Hartmann M, et al. Long-term outcome and survival of surgically treated supratentorial low-grade glioma in adult patients. *Acta Neurochir (Wien).* 2009;151(11):1359-65. Epub 2009 Jul 3.
 43. Schomas DA, Laack NN, Rao RD, Meyer FB, Shaw EG, O'Neill BP, et al. Intracranial low-grade gliomas in adults: 30-year experience with long-term follow-up at Mayo Clinic. *Neuro Oncol.* 2009;11(4):437-45. Epub 2008 Nov 18.
 44. Capelle L, Fontaine D, Mandonnet E, Taillandier L, Golmard JL, Bauchet L, et al. Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases. *J Neurosurg.* 2013;118(6):1157-68. Epub 2013 Mar 15.
 45. Pallud J, Varlet P, Devaux B, Geha S, Badoual M, Deroulers C, et al. Diffuse low-grade oligodendrogliomas extend beyond MRI-defined abnormalities. *Neurology.* 2010;74(21):1724-31.
 46. Yordanova YN, Moritz-Gasser S, Duffau H. Awake surgery for WHO Grade II gliomas within "noneloquent" areas in the left dominant hemisphere: toward a "supratotal" resection. Clinical article. *J Neurosurg.* 2011;115(2):232-9. Epub 2011 May 6.
 47. Robles SG, Gatignol P, Lehericy S, Duffau H. Long-term brain plasticity allowing a multistage surgical approach to World Health Organization Grade II gliomas in eloquent areas. *J Neurosurg.* 2008;109(4):615-24.
 48. Duffau H. The challenge to remove diffuse low-grade gliomas while preserving brain functions. *Acta Neurochir (Wien).* 2012;154(4):569-74. Epub 2012 Jan 26.
 49. Karim AB, Maat B, Hatlevoll R, Menten J, Rutten EH, Thomas DG, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. *Int J Radiat Oncol Biol Phys.* 1996;36(3):549-56.
 50. Karim AB, Afra D, Cornu P, Bleehen N, Schraub S, De Witte O, et al. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: an interim analysis. *Int J Radiat Oncol Biol Phys.* 2002;52(2):316-24.
 51. Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, et al. European Organization for Research and Treatment of Cancer Radiotherapy Cooperative Group. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol.* 2002;20(8):2076-84.
 52. Van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet.* 2005;366(9490):985-90.
 53. Leighton C, Fisher B, Macdonald D, Stitt L, Bauman G, Cairncross J. The dose-volume interaction in adult supratentorial low-grade glioma: higher radiation dose is beneficial among patients with partial resection. *J Neurooncol.* 2007;82(2):165-70. Epub 2007 Feb 14.
 54. Karim AB, Maat B, Hatlevoll R, Menten J, Rutten EH, Thomas DG, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. *Int J Radiat Oncol Biol Phys.* 1996;36(3):549-56.
 55. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. *J Clin Oncol.* 2002;20 (9):2267-76.
 56. Kiebert GM, Curran D, Aaronson NK, Bolla M, Menten J, Rutten EH, et al. Quality of life after radiation therapy of cerebral low-grade gliomas of the adult: results of a randomised phase III trial on dose response (EORTC trial 22844). *EORTC Radiotherapy Co-operative Group. Eur J Cancer.* 1998;34 (12): 1902-9.
 57. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol.* 2009;8(9):810-8. Epub 2009 Aug 7.
 58. Paulino AC, Mazloom A, Terashima K, Su J, Adesina AM, Okcu MF, et al. Intensity-modulated radiotherapy (IMRT) in pediatric low-grade glioma. *Cancer.* 2013;119(14):2654-9. Epub 2013 Apr 30.
 59. Heppner PA, Sheehan JP, Steiner LE. Gamma knife surgery for low-grade gliomas. *Neurosurgery.* 2008;62 Suppl 2:755-62.
 60. Cho KH, Hall WA, Gerbi BJ, Higgins PD, McGuire WA, Clark HB. Single dose versus fractionated stereotactic radiotherapy for recurrent high-grade gliomas. *Int J Radiat Oncol Biol Phys.* 1999;45(5):1133-41.
 61. Combs SE, Thilmann C, Edler L, Debus J, Schulz-Ertner D. Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. *J Clin Oncol.* 2005;23(34):8863-9.
 62. Mizoe JE, Tsujii H, Hasegawa A, Yanagi T, Takagi R, Kamada T, et al. Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas: combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy. *Int J Radiat Oncol Biol Phys.* 2007 Oct 1; 69 (2): 390-6. Epub 2007 Apr.
 63. Schulz-Ertner D, Karger CP, Feuerhake A, Nikoghosyan A, Combs SE, Jäkel O, et al. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. *Int J Radiat Oncol Biol Phys.* 2007;68(2):449-57. Epub 2007 Mar 23.

64. Rieken S, Habermehl D, Haberer T, Jaekel O, Debus J, Combs SE. Proton and carbon ion radiotherapy for primary brain tumors delivered with active raster scanning at the Heidelberg Ion Therapy Center (HIT): early treatment results and study concepts. *Radiat Oncol.* 2012;7:41.
65. Combs SE, Kieser M, Rieken S, Habermehl D, Jäkel O, Haberer T, et al. Randomized phase II study evaluating a carbon ion boost applied after combined radiochemotherapy with temozolomide versus a proton boost after radiochemotherapy with temozolomide in patients with primary glioblastoma: the CLEOPATRA trial. *BMC Cancer.* 2010;10:478.
66. Combs SE, Burkholder I, Edler L, Rieken S, Habermehl D, Jäkel O, et al. Randomised phase I/II study to evaluate carbon ion radiotherapy versus fractionated stereotactic radiotherapy in patients with recurrent or progressive gliomas: the CIN-DERELLA trial. *BMC Cancer.* 2010;10:533.
67. Shaw EG, Wang M, Coons SW, Brachman DG, Buckner JC, Stelzer KJ, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. *J Clin Oncol.* 2012;30(25):3065-70. Epub 2012 Jul 30.
68. Liu R, Solheim K, Polley MY, Lamborn KR, Page M, Fedoroff A, et al. Quality of life in low-grade glioma patients receiving temozolomide. *Neuro Oncol.* 2009;11(1):59-68. Epub 2008 Aug 19.
69. Jenkins RB, Blair H, Ballman KV, Giannini C, Arusell RM, Law M, et al. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. *Cancer Res.* 2006;66(20):9852-61.