Original article

Surgical treatment of supratentorial high-grade glioma: what is the best strategy? The fruit of seven years' experience

S. SIMPATICO, P. CAIAZZO, A. DE BELLIS, D. SIMPATICO*, M. DE BELLIS

UOSC di Neurochirurgia, Ospedale "S. Maria", Loreto Mare (Napoli), Italy
** Istituto di Biologia Molecolare, Università degli Studi, Napoli, Italy*

SUMMARY: ***Aim.*** *Patients with high-grade gliomas (grade IV gliomas and glioblastomas) have a median survival of approximately 12 months, a rate that has not substantially improved over the years, despite advances in medicine and surgery. It is therefore vital to elucidate the effects of surgery on the quality of life of patients harbouring high-grade glioma, identifying factors associated with prolonged and reduced functional outcome with a view to guiding treatment strategies and prolonging functional independence. For this reason we set out to review the data pertaining to the patients surgically treated for high-grade glioma over the last seven years.*
Materials and methods. *156 patients (90 men and 66 women) of average age 66.6 years (range 26-79 years) with high-grade glioma have been surgically treated by our team over the last seven years (2006-2012). The aim of surgery was generally gross total removal. Subtotal resection was performed primarily when the tumour involved the eloquent brain, as confirmed by intraoperative mapping and/or monitoring. Stereotactic biopsy was performed for inoperable tumours. Resections were retrospectively classified as either gross total removal or subtotal resection by an independent neuroradiologist comparing pre- and post-operative contrast CT/MR scans, and pre-surgical Karnofsky performance status scores were compared with those at 6- and 12-month follow-up.*
Results. *Gross total removal was achieved in 80 out of the 156 cases (51%), subtotal resection (more than 10% residual mass detected) in 43 patients (28%), and stereotactic biopsy was performed in 33 patients (21%). There were 5 cases of perioperative death (3%), and 27 patients (17%) developed new or increased motor, visual, or language deficit. 90 patients then underwent conventional radiotherapy. Local chemotherapy was administered in five cases via carmustine wafers. Oral chemotherapy with temozolomide was administered to 69 patients, of whom 45 (65%) received radiotherapy and temozolomide according to the protocol used in the study of Stupp et al. (N Engl J Med, 2005). 38 young patients (< 55 years), treated only with gross removal surgery, survived 12 months on average. 22 young patients with multimodal treatment (surgery, radiotherapy and temozolomide) survived 18 months on average. 53/156 patients fell into the older age category (above 55 years), and were treated with surgery, chemo-irradiation and the adjuvant temozolomide. Their survival was significantly lower than that of younger patients, at an average of 11 months*
Conclusion. *Survival prospects for patients with glioblastoma remain very poor, which makes it important to understand the effects that surgery has on quality of life and, more specifically, functional independence for patients with high-grade glioma. Indeed, although several early-phase clinical trials of targeted therapies in high-grade glioma have been completed or are underway, either singly or in combination with standard chemotherapy and/or radiation therapy, surgery remains the primary intervention at the present time.*

KEY WORDS: *High-grade glioma, Multidisciplinary approach, Quality of life, Surgical treatment.*

Correspondence: Dr. Stefano Simpatico, UOSC di Neurochirurgia, Ospedale "S. Maria", via Amerigo Vespucci, 80141 Napoli (NA), Italy, ph. +39-(0)81-2542730 and 2542831, e-mail: stefanosimpatico@libero.it
Progress in Neuroscience 2013; 1 (1-4): 105-110. *ISSN: 2240-5127*
Article received: 16 April 2013. doi: 10.14588/PiN.2013.Simpatico.105

LIST OF ACRONYMS AND ABBREVIATIONS: AGT = O6-Alkyl Guanine Transferase; CNS = Central Nervous System; CT = Computed Tomography; DCC = Deleted in Colorectal Cancer; ΔEGFR = delta Epidermal Growth Factor Receptor; EGF/R = Epidermal Growth Factor/Receptor; FU = Follow-Up; GTR = Gross Total Removal; HGG = High-Grade Gliomas; KPS = Karnofsky Performance Status; MDM2 = Mouse Double Minutes 2; MGMT = O6-Methyl Guanine Methyl Transferase; MRI = Magnetic Resonance Imaging; PDGF/R = Platelet-Derived Growth Factor/Receptor; PTEN = Phosphatase and TENsin homolog; QOL = Quality of Life; STR = SubTotal Resection; VEGF/R = Vasogenic Growth Factor/Receptor; WHO = World Health Organization.

□ INTRODUCTION

High-grade gliomas (grade IV gliomas and glioblastomas), also called malignant gliomas, are the most common primary brain tumours in the adult population. Their annual incidence is 5-10 per 100,000 people, and gliomas account for 42% of all primary CNS tumours and 77% of all malignant primary CNS tumours. Patients with these devastating cancers have a median survival of approximately 12 months, a rate that has not substantially improved over the years, despite advances in medical and surgical therapy. Indeed, high-grade gliomas have a propensity to invade and infiltrate surrounding normal brain parenchyma, making curative resection difficult, to say the least. Pragmatically speaking, therefore, it is therefore vital to elucidate the effects of surgery on the QOL of patients harbouring high-grade glioma. Indeed, the identification and consideration of factors associated with prolonged functional outcome (preoperative KPS score ≥ 90, seizures, primary glioblastoma, gross total resection, temozolomide) and decreased functional outcome (older age, coronary artery disease, new postoperative motor deficit) may help guide treatment strategies aimed at improving QOL for patients with glioblastoma, with a view to prolonging functional independence.

Although significant changes in the overall treatment paradigms have remained elusive, several additions to the surgeon's armoury over the past several decades have led to improved outcomes in this respect. Patients who only receive "supportive care", usually corticosteroid and anticonvulsant drugs, have a median survival of approximately 14 weeks or less, while, historically speaking, those treated with surgery alone have a median survival duration of less than 6-12 months, which is extended to approximately 9 months through the addition of postoperative radiotherapy. Although the value of glioma resection in obtaining histological diagnosis and decompression are unquestionable, there have been no significant advances in either surgical technique or preoperative planning. What is more, the effect of the extent of glioma resection on progression and/or survival remains unclear.

Aims. With a view to shedding light on the issues raised above, we set out to review the data pertaining to the patients surgically treated for high-grade glioma over the last seven years.

□ MATERIALS AND METHODS

We analysed 156 patients surgically treated for high-grade glioma between 2006 and 2012. The sample comprised 90 males and 66 females, whose age ranged from 26 to 79 years (average 66.6 years).

All patients treated presented a neurological deficit or mass effect hypertension ascribable to their tumour. In order to alleviate/reverse these symptoms, the aim of surgery was therefore generally to achieve GTR of the tumour wherever possible. When intraoperative mapping and/or monitoring (awake/speech language mapping, direct cortical motor stimulation, and motor-evoked or somatosensory-evoked potentials) indicated that the tumour involved the eloquent brain, STR was performed. Stereotactic biopsy was used for tumours considered to be inoperable.

In order to determine whether this difference had any effect on functional outcome and/or survival, the extent of resection was retrospectively classified from contrast CT/MR imaging reports obtained < 48 hours after resection as either GTR or STR by an independent neuroradiologist blinded to patient outcomes. STR and GTR were defined, respectively, as those tumours with residual and no residual enhancement achieved upon comparison of pre- and postoperative MR/CT images[7].

Cases were further classified according to whether the glioblastoma was primary, i.e., of *de novo* origin, or secondary, i.e., arising in patients with a prior history of a lower grade glioma[12].

As genomic data was not routinely obtained at our institution, the designation of primary *vs.* secondary glioblastoma was based on clinical criteria alone. To determine the survival and QOL of GTR *vs.* STR patients, follow-up with KPS (60-90%) was performed at 6 and 12 months.

□ RESULTS

A total of 156 patients were surgically treated for high-grade glioma in the frontal, temporal, parietal posterior/occipital or anterior gyrus cinguli (reported in order of frequency)[22, 23].

GTR was achieved in 80 patients (51%), and STR in 43 cases (28%). STR was defined as mass reduction with more than 10% residual mass detected with contrast-CT scan performed 24 hours post-surgery. 33 patients (21%) were merely biopsied via stereotaxis. There were 5 cases of perioperative death (3%), and 13 (8%), 3 (2%), and 11 (7%) patients developed new or increased motor, visual or language deficits, respectively, following surgery.

90 patients (75 after surgery: 55 GTR and 20 STR, and 15 after biopsy) were administered conventional radiotherapy after their operation, whereas 5/75 was treated with local chemotherapy with carmustine wafer.

69 patients were given oral chemotherapy with temozolomide: 45 (65%) of these received temozolomide with radiotherapy after surgery, according to the protocol used in the study by Stupp et al.[27], 24 (35%) only temozolomide after surgery.

Patients were classed into two age ranges: < 55-year age (60 patients) and 55-75-year age (96 patients). 38 young patients treated with gross removal surgery alone survived for an average of 12 months. This contrasted with the 22 young patients treated by a triple-pronged approach (surgery, radiotherapy and temozolomide), who survived 18 months on average. 53 patients, who fell into the older age group (55 years and above), were treated with surgery and chemo-irradiation with concomitant adjuvant temozolomide and survived for an average of 11 months. The survival of patients in this older age group was significantly lower than in younger patients (Table 1).

STR, rather than GTR, had to be performed in 31 out of the 53 older patients, but, in our experience, the extent of surgery did not influence the prognosis in our elderly population. 4 patients underwent repeat surgery for glioblastoma recurrence.

There seems to be no significant difference between GTR (38 young patients) and surgery (STR/GTR) with multiple therapy (75 patients, of whom 22 young) group in terms of QOL (KPS: 60-90%) at 6-month follow-up (Table 2).

In our experience, temozolomide, if well tolerated, does however improve QOL in both age groups (KPS 70-90 after surgery in non-eloquent areas).

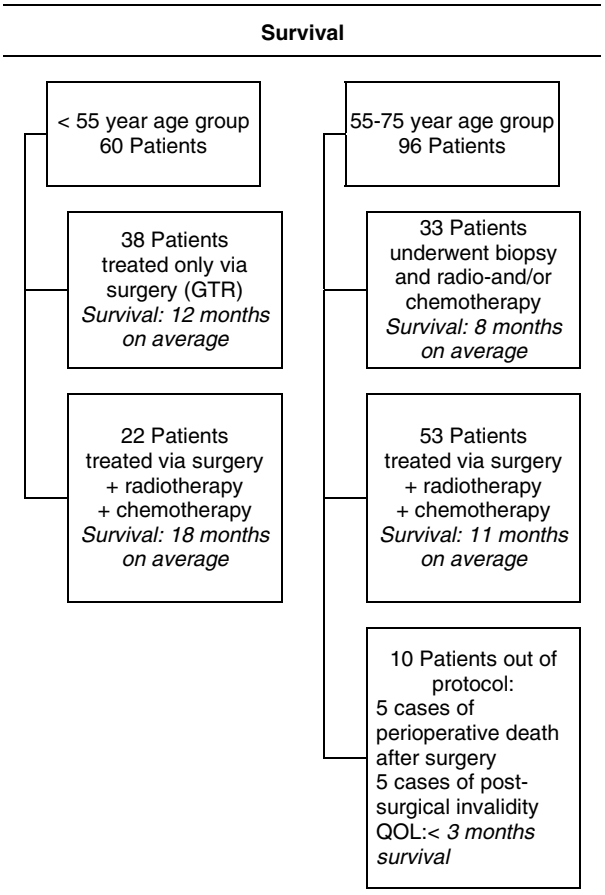

Table 1. Survival of 156 patient treated for high-grade glioma.
Legend: GTR = Gross Total Removal; QOL = Quality of Life.

□ DISCUSSION

Evaluation of the effects of extensive resection on clinical outcomes for patients with high-grade glioma has been primarily limited to survival studies[3,7]. Recent reports have shown that GTR of malignant gliomas is correlated with prolonged survival[5,10,11], which may increase by as much as a median of 40%, as compared with STR[22]. We found similar results, showing that GTR yields an approximate increase in prolonged functional independence of 45%.

Current neurosurgical innovations aim to improve our anatomical, physiological, and functional understanding of the surgical region of interest, with a view to preventing potential neurological morbidity during resection. Emerging imaging technologies, as well as state-of-the-art intraoperative techniques, can facilitate a greater extent of resection while minimizing the associated morbidity profile. Specifically, the value of mapping motor and language pathways is well

High-grade glioma outcomes: our experience

GTR only (*38 Patients*)	GTR/STR with radio-chemotherapy (*75 Patients*)	Biopsy with radio-chemotherapy (*33 Patients*)
6 month FU 20 Patients (52%) KPS 60-90	6 month FU 40 Patients (53%) KPS 60-90	6 month FU 13 Patients (39%) KPS 60-90
12 month FU 9 Patients (23%) KPS 60-90	12 month FU 25 Patients (33%) KPS 60-90	12 month FU 3 Patients (9%) KPS 60-90

Table 2. Follow-up (6-12 months) of 146 patients (10 patients was out of protocol) that we treated for for high-grade glioma between 2006 and 2012. *Legend*: FU = Follow-Up; GTR = Gross Total Removal; KPS = Karnofsky Performance Status; STR = SubTotal Resection.

established for the safe resection of intrinsic tumours. In eloquent areas in our sample, all microsurgical removals were approached via one or more transcortical corridors[17,19]. In general, we carry out a limited craniotomy to expose the tumour and up to 2 cm of surrounding brain. Indeed, the goal of surgery is often directed towards the central necrotic region and the imaging-defined enhanced margin. To limit morbidity due to removal of functional brain tissue, however, the infiltrative tumour cells found in the surrounding brain are generally not considered part of the surgical target, making it more likely for tumours to recur after treatment at this site[17].

Surgery for high-grade glioma is highly dependent on imaging. MRI can provide an anatomical definition of the lesion and functional capacity of critical cortical regions, enabling their precise localization within the brain. Perfusion MR imaging and MR spectroscopy can potentially overcome the limitation posed by sampling error, enabling non-invasive histopathological grading of the entire lesion *in vivo*. The common use of stereotactic guidance, intraoperative imaging, functional magnetic resonance imaging, and physiological monitoring has also enhanced the surgeon's ability to achieve aggressive tumour removal while protecting the patient from neurological impairment[17].

We firmly believe that a tumour causing mass effect and neurological deterioration is a clear indication for surgical removal, whereas an infiltrating lesion that produces no mass effect and no neurological involvement is a more perplexing decision[22]. Although microsurgical resection seems to remain the surgery of choice in all gliomas[8], there is no general consensus in the literature regarding the efficacy of whole or partial resection in improving patient outcome[16].

Nevertheless, maximum possible tumour resection within safe limits can decrease tumour burden and thereby enhance the effects of adjuvant therapies[2,6], as well as improving mass effect symptoms, reducing the frequency of seizures, and providing tissue for pathological and genomic studies to better identify and test novel therapies[10]. This, however, may be considered academic if survival and/or quality of life are not dramatically enhanced by such an invasive procedure. To this end, the literature reports recent attempts to define the main survival time associated with subtotal *vs*. gross total resection in high-grade gliomas. The difference was defined as modest, with an increase, from 11.3 to 14.2 months in WHO grade IV tumours (12 studies analysed only these poor grade tumours)[18]. This would seem to indicate that a "wait and see" policy can be advocated, particularly in young patients affected by chronic epilepsy who present small volume expanding lesions in critical areas but no mass effect and CT/MRI contrast enhancement. Indeed, although early resection of potentially curable tumours is favoured, several Authors have observed that delaying surgery in minimally symptomatic patients is not associated with poorer outcome[13,25].

Nowadays the most efficacious means of managing glioblastoma is certainly a double or triple-pronged attack. Current initial management of grade IV glioma consists of maximal feasible surgical resection followed by post-surgical radiotherapy, the latter being the standard treatment with a grade 1 level of evidence[15]. Concurrent temozolomide chemotherapy is also commonly used to adjuvate radiotherapy, despite ongoing controversy surrounding the role of chemotherapy in the initial management of this disease[20]. Temozolomide is an orally administered alkylating agent that has 100% bioavailability and the unique ability to deplete the DNA repair enzyme AGT. To prevent repair of DNA damage and increase the potential effectiveness of chemotherapy, MGMT, the enzyme responsible for DNA repair following alkylating agent chemotherapy, can be silenced by

methylation of its promoter. In one study, this combination (temozolomide and radiotherapy) prompted a 6.4-month median survival benefit in patients demonstrating methylation of the MGMT promoter, as compared to an insignificant benefit in patients who did not[9].

As regards surgery, to date there is still a lack of evidence in the literature on whether surgical resection improves patient survival, although Pang et al. state that "there are benefits, albeit short-term ones, to expect after surgical resection, and these should be borne in mind"[21]. Although the modern neurosurgical literature (1990 to the present) contains no definitive answers as to the role of the extent of resection in outcome for glioma patients, it does provide some clues. Since 1990, twenty-nine studies have applied statistical analysis to examine the extent of the effect of resection in improving survival and delaying tumour progression among patients with grade IV glioma[3]. Though greater resection was not found to have a significant effect on tumour progression or overall survival in all cases, every study showed that resection, whether whole or partial, did confer a survival benefit[10].

HGG is predominantly seen in advanced age[4], which remains a very strong and independent negative prognostic factor in glioblastoma. This has prompted an increase in the aggressiveness of treatment provided to the elderly, although the gain seen in our older age group seems very modest at best. Hence, the prognosis of older patients still remains very poor, despite the multimodal treatment available today. In order for progress in glioblastoma treatment to come about, therefore, more frequent genetic mutation studies are required. According to the last two editions of WHO classification, two types of genetic variations bring about high-grade glioma growth, namely oncogenic activation factors (EGF/R, MDM2, PDGF/R) and oncosuppressor disactivation factors (10p, 10q, 19q, DCC, p16, TP53, PTEN). Mutation or inhibition of these factors can lead to tumour development in the prostate, colon, breast or brain[9,14,26].

Epidermal growth factor receptor gene amplification is the most common genetic alteration seen in high-grade glioma, and about 50% of EGF/R-amplified tumours also harbour a constitutively active mutant form of the receptor, ΔEGFR. ΔEGFR greatly enhances tumour growth, which makes it an attractive target for anti-glioma therapies. However, recent clinical experiences with EGFR kinase inhibitors have been disappointing, because resistance is common and tumours eventually recur. That being said, there is still hope for the future, represented by controlled trials of a glioma IV grade treatment that allows tumoral and seric determination of important factors like EGF, EGF/R, VEGF and VEGF/R[24]. The ultimate aim of trials such as these is to provide more effective, more individualized therapy with fewer collateral effects[1,26].

□ CONCLUSION

Survival for patients with glioblastoma remains very poor. This makes it vital for us to determine the effects of surgery on QOL and, more specifically, functional independence for these patients. We believe it is imperative to obtain 60-90% KPS in the follow-up period to high-grade glioma treatment (6-12 months), as anything less would be unacceptable. In this respect, while surgery remains the primary intervention, coadjuvant therapies do seen to help, especially in young people. Several early-phase clinical trials of targeted therapies in high-grade glioma have been completed or are underway, either singly or in combination with standard chemotherapy and/or radiation therapy[13], but the current chemotherapeutic standard for glioblastoma patients is temozolomide (75 mg/m^2/die) as coadjuvant drug during radiotherapy (60 Gy/30 fractions)[8,22].

Nevertheless we still remain unable to treat the disease or guarantee survival, which will only come about through progress and increased understanding of the biology and genetics of glioma, together with truly useful experimental models. To this end, gene expression profiling has proven to be a highly effective method of obtaining global signatures reflecting the biological state of the tumour and its underlying pathogenic mechanisms, providing markers for use in diagnosis and clinical management. By identifying the weaknesses of the tumour, in future we should be in a position to offer very real opportunities for the development of effective targeted treatments for patients with these devastating diseases[14].

□ REFERENCES

1. Arribas Alpuente L, Menendez Lopez A, Yaya Tur R. Glioblastoma: changing expectations? Clin Transl Oncol 2011; 13 (4): 240-248.

2. Barker FG 2nd, Prados MD, Chang SM, Gutin PH, Lamborn KR, Larson DA et al. Radiation response and survival time in patients with glioblastoma multiforme. J Neurosurg 1996; 84 (3): 442-448.
3. Brown PD, Maurer MJ, Rummans TA, Pollock BE, Ballman KV, Sloan JA et al. A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: the impact of the extent of resection on quality of life and survival. Neurosurgery 2005; 57 (3): 495-504.
4. Chaichana KL, Chaichana KK, Olivi A, Weingart JD, Bennett R, Brem H et al. Surgical outcomes for older patients with glioblastoma multiforme: preoperative factors associated with decreased survival. Clinical article. J Neurosurg 2011 ; 114 (3): 587-594.
5. Chaichana KL, Halthore AN, Parker SL, Olivi A, Weingart JD, Brem H et al. Factors involved in maintaining prolonged functional independence following supratentorial glioblastoma resection. J Neurosurg 2011; 114 (3): 604-612.
6. Engelhard HH. The role of interstitial BCNU chemotherapy in the treatment of malignant glioma. Surg Neurol 2000; 53 (5): 458-464.
7. Gulati S, Jakola AS, Johannesen TB, Solheim O. Survival and treatment patterns of glioblastoma in the elderly: a population-based study. World Neurosurg 2012; 78 (5): 518-526.
8. Hassaneen W, Levine NB, Suki D, Salaskar AL, de Moura Lima A, McCutcheon IE et al. Multiple craniotomies in the management of multifocal and multicentric glioblastoma. J Neurosurg 2011; 114 (3): 576-584.
9. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005; 352 (10): 997-1003.
10. Keles GE, Anderson B, Berger MS. The effect of extent of resection on time to tumor progression and survival in patients with glioblastoma multiforme of the cerebral hemisphere. Surg Neurol 1999; 52 (4): 371-379.
11. Keles GE, Chang EF, Lamborn KR, Tihan T, Chang CJ, Chang SM et al. Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma. J Neurosurg 2006; 105 (1): 34-40.
12. Komotar RJ, Starke RM, Connolly ES, Sisti MB. Evaluating the benefit of repeat surgery for recurrent glioblastoma multiforme. Neurosurgery 2010; 67 (6): N16-N17.
13. Krex D, Klink B, Hartmann C, von Deimling A, Pietsch T, Simon M et al. Long-term survival with glioblastoma multiforme. Brain 2007; 130 (Pt 10): 2596-2606.
14. Lassman AB, Rossi MR, Raizer JJ, Abrey LE, Lieberman FS, Grefe CN et al. Molecular study of malignant gliomas treated with epidermal growth factor receptor inhibitors: tissue analysis from North American Brain Tumor Consortium Trials 01-03 and 00-01. Clin Cancer Res 2005; 11 (21): 7841-7850.
15. Laws ER, Parney IF, Huang W, Anderson F, Morris AM, Asher A et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. J Neurosurg 2003; 99 (3): 467-473.
16. McGirt MJ, Chaichana KL, Gathinji M, Attenello FJ, Than K, Olivi A et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. J Neurosurg 2009; 110 (1): 156-162.
17. Moliterno JA, Patel TR, Piepmeier JM. Neurosurgical approach. Cancer J 2012; 18 (1): 20-25.
18. Nomiya T, Nemoto K, Kumabe T, Takai Y, Yamada S. Prognostic significance of surgery and radiation therapy in cases of anaplastic astrocytoma: retrospective analysis of 170 cases. J Neurosurg 2007; 106 (4): 575-581.
19. Ojemann GA: Organization of language cortex derived from investigations during neurosurgery. Semin Neurosci 1990, 2: 297-305.
20. Omar AI, Mason WP. Anaplastic astrocytomas. Handb Clin Neurol 2012; 105: 451-466.
21. Pang BC, Wan WH, Lee CK, Khu KJ, Ng WH. The role of surgery in high-grade glioma - is surgical resection justified? A review of the current knowledge. Ann Acad Med Singapore 2007; 36 (5): 358-363.
22. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery 2008; 62 (4): 753-764.
23. Sanai N, Polley MY, Berger MS. Insular glioma resection: assessment of patient morbidity, survival, and tumor progression. J Neurosurg 2010; 112 (1): 1-9.
24. Sathornsumetee S, Reardon DA, Desjardins A, Quinn JA, Vredenburgh JJ, Rich JN. Molecularly targeted therapy for malignant glioma. Cancer 2007; 110 (1): 13-24.
25. Stummer W, van den Bent MJ, Westphal M. Cytoreductive surgery of glioblastoma as the key to successful adjuvant therapies: new arguments in an old discussion. Acta Neurochir 2011; 153 (6): 1211-1218.
26. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352 (10): 987-996.
27. Talacchi A, Corsini F, Gerosa M. Surgical approaches to tumors of the anterior gyrus cinguli. Neurosurgery 2010; 66 (6 Suppl Operative): 245-251.

Disclosure. *The authors declare that they know of no conflict of interest, financial or otherwise, arising from this article.*