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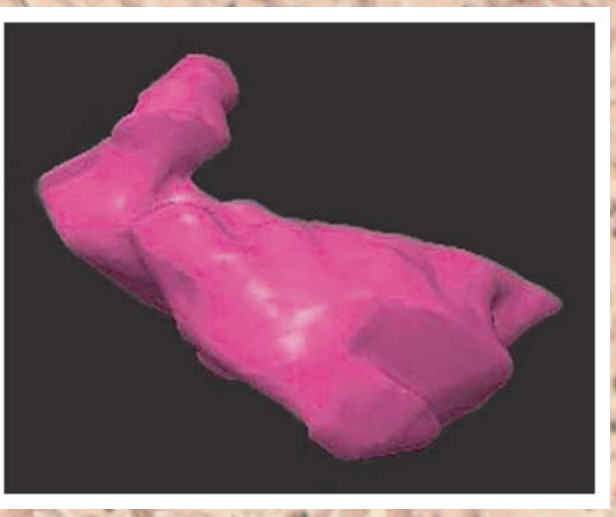

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Surgery of Malignant Gliomas Using Modern Technology

Martin Proescholdt, Christian Doenitz, Alexander Brawanski

Abstract: Recent evidence has demonstrated that the extent of surgical resection (EOR) is an important prognostic factor in patients with malignant gliomas. However, the infiltrative growth pattern and the functional anatomy of the brain consisting of eloquent cortical and subcortical structures pose a significant limitation to the surgical resection of these tumours. The gain of knowledge regarding function, biology, and pathophysiology of the brain has resulted in the advent of advanced technology to the neurosurgeon, allowing maximal resection with minimal operative morbidity. We have reviewed the current literature concerning intraoperative imaging, fluorescence-guided resection, and awake craniotomy to generate a comprehensive overview of the most recent developments in this field. In addition, we have provided data from our own institution confirming the beneficial effects of this multimodal approach. **Eur Assoc NeuroOncol Mag 2013; 3 (1): 11–4.**

Key words: resection, glioma, technology, MRI, awake craniotomy

Therapy of Malignant Gliomas – A Formidable Challenge

Gliomas of astrocytic, oligodendroglial, and ependymal differentiation comprise with an incidence of 6/100,000/year about 70 % of all intrinsic brain tumours [1]. The WHO classification system distinguishes 4 grades of malignancy [2] characterized by morphologic features such as mitotic activity, microvascular proliferation, and intratumoural necroses. The most frequent glioma of the adulthood, the glioblastoma multiforme, is a highly malignant neoplasm which displays an exceptionally poor prognosis with a median survival time of 15 months [3]. Two years after diagnosis, only 8.2 % of all patients are still alive [4]. The management of glioblastoma consists of 3 main elements: (1) microsurgical resection is followed by (2) concomitant treatment with radiotherapy plus (3) temozolomide chemotherapy [5]. In this context, the extent of surgical resection (EOR) has increasingly been recognized as an important prognostic factor in this patient population [6]. A prospective, randomized multicentre trial in glioblastoma patients has demonstrated that complete resection of the contrast-enhancing tumour leads to an overall survival of 16.7 months compared to 11.8 months after subtotal resection [7]. However, there are 2 major limitations to radical surgical resection: (1) glioblastomas display a highly infiltrative growth pattern [8] which renders complete resection virtually impossible. Careful histological studies revealed a tumour cell spread into the contralateral hemisphere in about 30 % of all patients at the time of diagnosis [9, 10]. Thus, even the most radical surgical approach will not lead to curative treatment [11]. (2) The functional anatomy of the brain consists of cortical and subcortical structures such as the primary motor cortex, Wernicke and Broca speech centres, or the internal capsule, which need to be preserved during surgical resection to avoid serious postoperative neurological deficits. Since patients with permanent neurological deficits have a significantly worse survival prognosis [12], the avoidance of any damage to these eloquent structures is mandatory in the surgical treatment of glioblastoma [13].

Preoperative Work-Up

Traditionally, surgery planning was conducted utilizing anatomical landmarks [14]. In the past, the identification of eloquent areas was performed in a generalized, rigid fashion based on the functional studies by Wilder Penfield, frequently leading to an inadequate assessment of the surgical risk in the individual patient [15]. The major reason for this inaccuracy is the significant individual variability of cortical organization [16]. In addition, recent studies have demonstrated a high degree of functional plasticity of the brain, which causes a significant shift of eloquent areas to distant sites especially under the condition of intracerebral tumour growth [17]. Preoperative application of functional MRI (fMRI) and Diffusion Tensor Imaging (DTI) allows the detection of eloquent cortical and subcortical structures with high sensitivity and specificity [18, 19]. With the advent of computer-based analysis tools allowing the fusion of patho-anatomical, functional, and metabolic imaging data, it is now possible to plan and execute a precise and safe resection trajectory, thus achieving maximal EOR with minimal surgical morbidity (Figure 1). In the case of a large, infiltrative tumour, which needs to be biopsied in order to establish a histological diagnosis, it is of paramount importance to target the area of the lesion with the suspected highest grade of malignancy. In a study conducted in 81 patients who received stereotactic biopsy followed by resection of the tumour within 60 days, the biopsy-based diagnosis was incorrect in 38 %, emphasizing the limitations of stereotactic biopsy as a diagnostic tool [20]. The application of Positron Emission Tomography (PET) scanning utilizing tracers such as $^{[F\text{-}18]}$fluoroethyltyrosine allows to detect metabolically active areas within a larger tumour mass. The integration of these molecular imaging data into the target planning process can significantly increase the diagnostic yield of stereotactic biopsies in patients with diffuse gliomas [21, 22]. In addition, the differentiation between tumour progress and radiation-induced necrosis or pseudoprogression can be facilitated by PET scanning, supporting adequate clinical management and avoidance of unnecessary treatment measures

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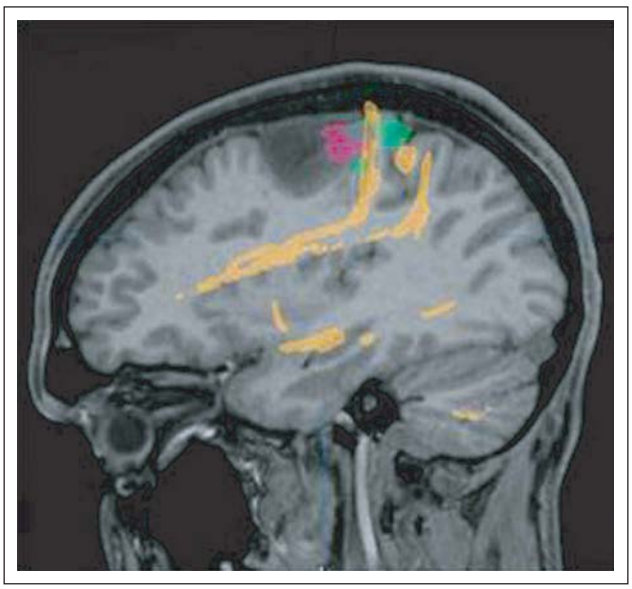

Figure 1. Fusion of [F-18]fluoroethyltyrosine: PET (red), functional MRI (green), and DTI tractography (yellow) in a patient with a left frontal anaplastic astrocytoma. Note the close vicinity of eloquent cortical and subcortical structures to the tumour borders.

such as repeated surgical resection [23]. Finally, detailed neuropsychological evaluation is helpful in unmasking subclinical tumour-related impairments to improve the prognostication of the postoperative course of the disease [24].

Intraoperative Technique

One of the most substantial obstacles to an extensive resection of gliomas is the infiltrative growth pattern of these tumours. The development of 5-aminolevulinic acid (5-ALA) as a tumour-specific fluorescence marker has caused a breakthrough in the resection of malignant gliomas [25]. The substance leads to an intracellular accumulation of fluorescent porphyrins which can be detected intraoperatively using a microscope equipped with a violet-blue excitation light source (Figure 2). A prospective, randomized controlled multicentre trial has demonstrated a significantly better EOR in the 5-ALA group compared to the control arm resected with conventional light [26]. The intraoperative localization of the tumour in addition to the adjacent, eloquent areas of the brain is greatly facilitated by the use of neuronavigation, which has also been termed frameless stereotaxy [27]. This technique is based on MRI imaging conducted with fiducial markers placed on particular landmarks of the patient's skull. Prior to craniotomy, an LED-emitting detection system linked to a computer containing the imaging data set is used to calibrate the surgical instrument set, which then allows the visualization of the resection process intraoperatively. This approach has significantly improved the safety and extent of resection in glioma patients [28, 29]. However, the accuracy of neuronavigation-based resection, which is solely based on preoperative imaging, decreases during the course of the procedure due to "brain shift" caused by the release of cerebrospinal fluid, brain swelling, and surgical manoeuvres [30]. To account for this aspect, real-time intraoperative imaging is required. Consequently, intraoperative MRI (iMRI) has been

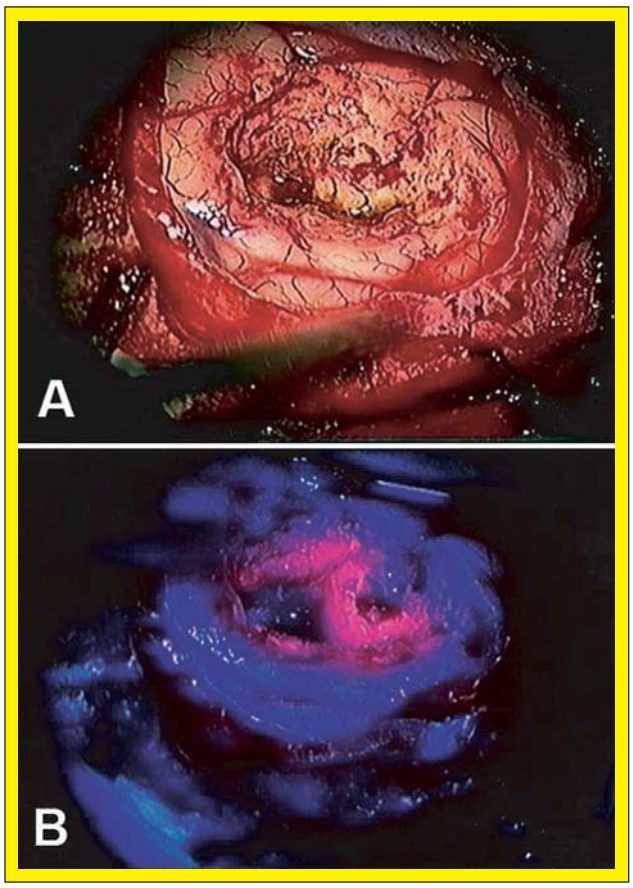

Figure 2. Resection cavity in a patient with glioblastoma following 5-aminolevulinic acid application as a fluorescence marker. **(A)** Under conventional light, inconspicuous adjacent white matter is visible. **(B)** Fluorescence illumination reveals a high-intensity signal indicating a residual tumour. Reprinted from [Stummer W, Novotny A, Stepp H, et al. Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients. J Neurosurg 2000; 93: 1003–13] with permission from the American Association of Neurological Surgeons.

developed as an advanced technique for imaging-based resection control in glioma surgery [31]. A recent, controlled, prospective clinical trial has demonstrated that the use of iMRI leads to a better extent of resection and improved 6-month survival rates in the iMRI group compared to the control population. Interestingly, the occurrence of postoperative neurological deficits was not significantly different between the 2 study groups [32]. However, iMRI is complex, requiring either transport of the patient to the scanner during the operation or a completely antimagnetic setting in the operating room. Surgery time is prolonged due to the scanning procedure and iMRI systems are expensive and not available in the majority of neurosurgical centres [33, 34]. A valid alternative is the use of intraoperative ultrasound (IOUS), which allows real-time detection of infiltrative tumour margins [35]. However, IOUS-based resection control, albeit possible, is influenced by surgery-related artefacts and depends significantly on the experience of the surgeon [36]. As an alternative to image-based surgery, awake craniotomy with intraoperative cortical and subcortical stimulation has been established as "gold standard" to achieve maximal EOR with minimal morbidity [37]. The procedure involves tumour resection in the awake patient, allowing serial neurocognitive tests concerning motor or language function combined with direct electri-

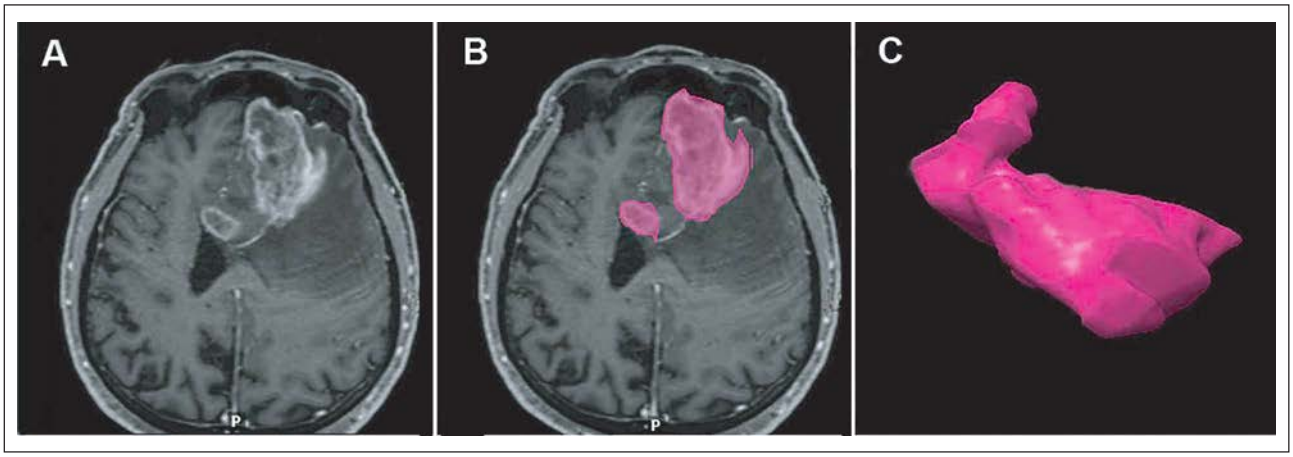

Figure 3. Quantification of the preoperative tumour volume in malignant gliomas. **(A)** Axial T1-weighted MRI scan of a patient with a left frontal glioblastoma. **(B)** The contrast-enhancing part of each section is outlined and subsequently fused to generate **(C)** a 3-dimensional segment which can be quantified volumetrically.

cal stimulation of the brain to unmask eloquent cortical and subcortical structures. Using this approach, a better EOR can be achieved while avoiding damage to functionally relevant brain structures [38, 39]. In order to avoid stress for the patient and to gain the best surgical results, a team of highly trained and experienced physicians consisting of anaesthesiologists, neuropsychologists, and neurosurgeons is mandatory [40]. In addition, especially if awake craniotomy is not an option, intraoperatively evoked potential monitoring is highly useful to detect damage to eloquent structures early during the procedure, allowing to correct the surgical trajectory in a timely fashion [41].

Results from a Single Centre – High-Tech Surgery, Is It Worthwhile?

Although it is self-evident to embrace the concept of high-tech surgery, limited resources in today's medical practice may prompt the question of whether this multimodal approach is of any clinical benefit to glioma patients. Employing the entire armamentarium outlined in this review except for iMRI, we volumetrically analyzed the EOR and clinical outcome in 44 patients with malignant gliomas (5 anaplastic astrocytoma, 39 glioblastoma) receiving surgical resection at our department. Mean age was 62.5 years, 61.4 % of all patients presenting with focal neurological deficits. Preoperative tumour size and EOR were quantified volumetrically based on MRI imaging (Iplan Cranio, Brainlab, Feldkirchen, Germany; Figure 3). In addition, surgical morbidity and mortality as well as the improvement of neurological performance were registered. There was no perioperative mortality, surgical morbidity was recorded in 9 % of all cases, caused by wound infection and CSF fistula, respectively. Complete resection (ie, no residual contrast enhancement in the postoperative scan) was achieved in 62 % of all cases, in 93 % of the patients an EOR > 90 % was accomplished. Of all patients presenting with neurological impairment, 52 % showed significant improvement. Only one patient developed transient double vision postoperatively, which completely dissipated after one week. These data confirm that the employment of advanced pre- and intraoperative technologies allows a safe and extensive resection in malignant glioma patients with a low rate of surgical morbidity.

Conclusion

Basic science research efforts during the decade of the brain has created an enormous gain of knowledge regarding function, biology, and pathophysiology of the brain [42]. This has caused a shift of paradigm in clinical neurosciences, including the surgical treatment of malignant gliomas. The advent of modern technology has revolutionized the preoperative workup, surgical trajectory planning, and intraoperative monitoring with significant benefits for the patients regarding neurofunctional improvement and overall survival. In the treatment of malignant glioma, combined efforts of all involved medical specialties are mandatory to achieve the best results for the individual patient [43, 44]. Modern neurosurgery can contribute to this treatment structure by providing maximal EOR combined with minimal morbidity.

Conflict of Interest

The authors report no conflict of interest.

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References:

1. Ricard D, Idbaih A, Ducray F, et al. Primary brain tumours in adults. Lancet 2012; 379: 1984–96.
2. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol (Berl) 2007; 114: 97–109.
3. Wen PY , Kesari S. Malignant gliomas in adults. N Engl J Med 2008; 359: 492–507.
4. Tran B, Rosenthal MA. Survival comparison between glioblastoma multiforme and other incurable cancers. J Clin Neurosci 2010; 17: 417–21.
5. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352: 987–96.
6. Sanai N, Polley MY, McDermott MW, et al. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011; 115: 3–8.
7. Pichlmeier U, Bink A, Schackert G, et al. Resection and survival in glioblastoma multiforme: an RTOG recursive partitioning analysis of ALA study patients. Neuro Oncol 2008; 10: 1025–34.
8. Claes A, Idema AJ, Wesseling P. Diffuse glioma growth: a guerilla war. Acta Neuropathol (Berl) 2007; 114: 443–58.
9. Sahm F, Capper D, Jeibmann A, et al. Addressing diffuse glioma as a systemic brain disease with single-cell analysis. Arch Neurol 2012; 69: 523–6.
10. Burger PC. Pathologic anatomy and CT correlations in the glioblastoma multiforme. Appl Neurophysiol 1983; 46: 180–7.
11. Dandy WE. Removal of the right hemisphere for certain tumors with hemiplegia: preliminary report. JAMA 1928; 90: 823–5.
12. Bauchet L, Mathieu-Daude H, Fabbro-Peray P, et al. Oncological patterns of care and outcome for 952 patients with newly diagnosed glioblastoma in 2004. Neuro Oncol 2010; 12: 725–35.

13. Stummer W, Tonn JC, Mehdorn HM, et al. Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. Clinical article. J Neurosurg 2011; 114: 613–23.

14. Berger MS, Hadjipanayis CG. Surgery of intrinsic cerebral tumors. Neurosurgery 2007; 61 (Suppl): 279–304.

15. Mazzola L, Isnard J, Peyron R, et al. Stimulation of the human cortex and the experience of pain: Wilder Penfield's observations revisited. Brain 2012; 135: 631–40.

16. Ojemann GA. Individual variability in cortical localization of language. J Neurosurg 1979; 50: 164–9.

17. Duffau H. Brain plasticity: from pathophysiological mechanisms to therapeutic applications. J Clin Neurosci 2006; 13: 885–97.

18. Gupta A, Shah A, Young RJ, et al. Imaging of brain tumors: functional magnetic resonance imaging and diffusion tensor imaging. Neuroimaging Clin N Am 2010; 20: 379–400.

19. Castellano A, Bello L, Michelozzi C, et al. Role of diffusion tensor magnetic resonance tractography in predicting the extent of resection in glioma surgery. Neuro Oncol 2012; 14: 192–202.

20. Jackson RJ, Fuller GN, Abi-Said D, et al. Limitations of stereotactic biopsy in the initial management of gliomas. Neuro Oncol 2001; 3: 193–200.

21. Pirotte B, Goldman S, Bidaut LM, et al. Use of positron emission tomography (PET) in stereotactic conditions for brain biopsy. Acta Neurochir (Wien) 1995; 134: 79–82.

22. Kunz M, Thon N, Eigenbrod S, et al. Hot spots in dynamic (18)FET-PET delineate malignant tumor parts within suspected WHO grade II gliomas. Neuro Oncol 2011; 13: 307–16.

23. Caroline I, Rosenthal MA. Imaging modalities in high-grade gliomas: pseudoprogression, recurrence, or necrosis? J Clin Neurosci 2012; 19: 633–7.

24. Wu AS, Witgert ME, Lang FF, et al. Neurocognitive function before and after surgery for insular gliomas. J Neurosurg 2011; 115: 1115–25.

25. Stummer W, Stocker S, Wagner S, et al. Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. Neurosurgery 1998; 42: 518–525.

26. Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 2006; 7: 392–401.

27. Willems PW, van der Sprenkel JW, Tulleken CA, et al. Neuronavigation and surgery of intracerebral tumours. J Neurol 2006; 253: 1123–36.

28. Kurimoto M, Hayashi N, Kamiyama H, et al. Impact of neuronavigation and image-guided extensive resection for adult patients with supratentorial malignant astrocytomas: a single-institution retrospective study. Minim Invasive Neurosurg 2004; 47: 278–83.

29. Wirtz CR, Albert FK, Schwaderer M, et al. The benefit of neuronavigation for neurosurgery analyzed by its impact on glioblastoma surgery. Neurol Res 2000; 22: 354–60.

30. Ohue S, Kumon Y, Nagato S, et al. Evaluation of intraoperative brain shift using an ultrasound-linked navigation system for brain tumor surgery. Neurol Med Chir (Tokyo) 2010; 50: 291–300.

31. Kubben PL, ter Meulen KJ, Schijns OE, et al. Intraoperative MRI-guided resection of glioblastoma multiforme: a systematic review. Lancet Oncol 2011; 12: 1062–70.

32. Senft C, Bink A, Franz K, et al. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol 2011; 12: 997–1003.

33. Oh DS , Black PM. A low-field intraoperative MRI system for glioma surgery: is it worthwhile? Neurosurg Clin N Amer 2005; 16: 135–41.

34. Seifert V. Intraoperative MRI in neurosurgery: technical overkill or the future of brain surgery? Neurol India 2003; 51: 329–32.

35. Gerganov VM, Samii A, Giordano M, et al. Two-dimensional high-end ultrasound imaging compared to intraoperative MRI during resection of low-grade gliomas. J Clin Neurosci 2011; 18: 669–73.

36. Hammoud MA, Ligon BL, elSouki R, et al. Use of intraoperative ultrasound for localizing tumors and determining the extent of resection: a comparative study with magnetic resonance imaging. J Neurosurg 1996; 84: 737–41.

37. Kim SS, McCutcheon IE, Suki D, et al. Awake craniotomy for brain tumors near eloquent cortex: correlation of intraoperative cortical mapping with neurological outcomes in 309 consecutive patients. Neurosurgery 2009; 64: 836–45.

38. De Benedictis A, Moritz-Gasser S, Duffau H. Awake mapping optimizes the extent of resection for low-grade gliomas in eloquent areas. Neurosurgery 2010; 66: 1074–84.

39. Pereira LC, Oliveira KM, L'Abbate GL, et al. Outcome of fully awake craniotomy for lesions near the eloquent cortex: analysis of a prospective surgical series of 79 supratentorial primary brain tumors with long follow-up. Acta Neurochir (Wien) 2009; 151: 1215–30.

40. Brydges G, Atkinson R, Perry MJ, et al. Awake craniotomy: a practice overview. AANA J 2012; 80: 61–8.

41. Kombos T, Picht T, Derdilopoulos A, et al. Impact of intraoperative neurophysiological monitoring on surgery of high-grade gliomas. J Clin Neurophysiol 2009; 26: 422–5.

42. Laws ER Jr. The decade of the brain: 1990 to 2000. Neurosurgery 2000; 47: 1257–60.

43. Hofer S, Roelcke U, Herrmann R. [New aspects of interdisciplinary therapy for malignant gliomas in adults]. Schweiz Med Wochenschr 1999; 129: 1332–41.

44. Taylor LP. Diagnosis, treatment, and prognosis of glioma: five new things. Neurology 2010; 75 (Suppl 1): S28–S32.