## Title

Optimizing glioblastoma resection: intraoperative mapping and beyond



## Journal

CNS Oncology, 3(5)

## ISSN

2045-0907

## Authors

Osorio, Joseph A
Aghi, Manish K

## Publication Date

2014-09-30

## DOI

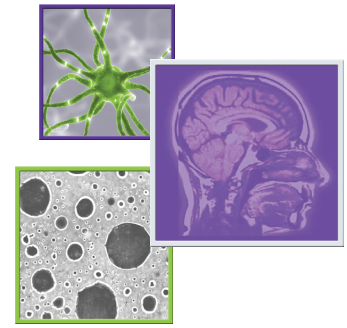
10.2217/cns.14.36

Peer reviewed

REVIEW

For reprint orders, please contact: reprints@futuremedicine.com

CNS Oncology



# Optimizing glioblastoma resection: intraoperative mapping and beyond

Joseph A Osorio*[,1] & Manish K Aghi[1]

**Practice points**

- Many retrospective studies have correlated extent of resection with improved patient survival for glioblastoma.
- Preoperative techniques to improve safety of maximal surgical resection include functional MRI, magnetoencephalography and diffusion tensor imaging.
- Intraoperative techniques to improve safety of maximal surgical resection include language and motor mapping.
- Intraoperative techniques to improve extent of resection include intraoperative MRI and 5-aminolevulinic acid administration.

**SUMMARY** The management of glioblastomas starts with surgical resection if possible, along with subsequent chemotherapy and radiation therapy. Several retrospective studies have suggested that extent of resection plays a role in the prognosis of glioblastoma patients. The importance of extent of resection must be balanced with preserving patient's functional status for tumors in eloquent areas. Here we review the preoperative imaging modalities such as functional MRI and magnetoencephalography (MEG), and the intraoperative techniques such as motor and language mapping, intraoperative MRI, and intraoperative techniques such as 5-aminolevulinic acid administration, that allow maximal safe operative resection of glioblastomas.

**KEYWORDS**
• glioblastoma • mapping
• MRI • resection
• tractography

## Background

Glioblastoma resection has evolved over time to incorporate the changes and advancement that have included both clinical research and technology advancement, most notably in the field of medical imaging and image processing. Through these advancements, both invasive and non-invasive treatments have steadily effected and at times improved time to progression, quality of life, and overall survival. The current standard of care for newly diagnosed glioblastomas is to proceed to an operative resection if it is safe and achievable, along with subsequent chemotherapy and radiation therapy.

The introduction that maximizing extent of surgical (EOR) resection could improve outcomes, was first introduced into the medical literature in 1976 by Onoyama *et al.* [1], where radiation treatment of glioblastoma was studied; tumor location was identified as potentially affecting survival and prognosis. Interestingly, they felt that this variable could be confounded by the extent of resection given that less eloquent brain regions and the nondominant hemisphere were producing longer survivals. Survival was longest in the right hemisphere when compared with the left hemisphere, and lowest when bilateral hemispheres were involved. Right frontal tumors also showed a survival

[1]Department of Neurological Surgery, University of California, 505 Parnassus Avenue, Room M779, San Francisco, CA 94143-0112, USA
*Author for correspondence: osorioj@neurosurg.ucsf.edu

Future Medicine part of fsg

advantage when compared with other right-sided lobed tumors [1]. Was it possible that surgeons were more likely to have larger EORs when knowing that patients would have less associated morbidity when operating on less eloquent locations? It was also noted as an aside that almost all patients who were long-term survivors had received maximal resection of the initial tumor burden. At this time, EOR was being defined using CT contrast studies.

Subsequent studies continued to identify EOR as a significant prognostic factor [2,3], but equally important was the overall quality of life of patients following extensive resections. Ammirati *et al.* showed that glioblastomas that received gross total resection (GTR), had overall more time in an independent status following the operation as compared with those who had a subtotal resection (STR) [4]. Not only has EOR affected overall survival, but subsequent studies showed that time to progression (TTP) was also prolonged and associated with greater extent of resection [5].

There have been few large-sized studies that have provided evidence for factors influencing survival, but the first was in 2001 where Lacroix *et al.* showed a median survival difference of 13 months compared with 8.8 months when separating glioblastoma patients by EOR divided by those that had 98% of tumor removed, with more extensive resections having a survival advantage [6]. Given the diffuse signal abnormality encountered in glioblastoma, including enhancing and nonenhancing tumor burden, Stummer *et al.* showed that survival depended on EOR of the enhancing tumor on MRI [7]. Survival benefit has been shown with EOR to be >78%, and continued with a step-wise benefit when looking at EOR >90, >95, >98 and when equal to 100% [8]. The largest data analysis to date includes 21,783 patients, and this study also demonstrated that GTR and radiation therapy (RT) compared with STR and RT had a median survival benefit of 11 months compared with 9 months, respectively [9].

When incorporating all of the data from over the past 30 years of published data, it is clear that achieving the maximal safe EOR is beneficial to patients with glioblastoma. In order to optimize a safe and maximal resection of patients with glioblastoma, there has been a significant amount of development and research that has gone into the preoperative optimization planning, as well as the intraoperative tools that can be utilized that will be discussed below.

## Preoperative tools to optimize resection

### • Functional MRI

Functional MRI (fMRI) is a technique that provides a merge of dynamic data with the ability to localize function onto an MRI, in a noninvasive way. It was initially validated using electrocortical stimulation [10]. This enabled fMRI to become a useful tool as a presurgical planning aid to identify dominant hemisphere cortical language areas [10]. Language lateralization scores directly correlate between fMRI and Wada testing, which was thea prior gold standard [11].

fMRI provides a preoperative tool with additional information on eloquent brain regions that can be used when determining operative risk prior to tumor resection [12–17]. When integrating this information into patients with brain tumors, mass lesion displacement of eloquent regions can be better understood using fMRI. Neuro-navigation has the capability of providing this information to the surgeon not only prior to operative resection, but also during the surgical procedure [18]. **Figure 1** is an example of an intraoperative screenshot showing neuronavigation. Like the DTI technique mentioned below, fMRI can potentially be incorporated into standard imaging done at most modern MRIs, although the complexity of the analysis reduces its availability to centers handling a sufficiently large number of brain tumor cases.

In terms of reimbursement for fMRI, in the USA, the CPT code process for fMRI began in early 2004 and was a coordinated effort of many professional societies such as American Society of Neuroradiology, American Society of Functional Neuroradiology, American College of Radiology, and American Academy of Neurology. These efforts yielded CPT codes 70555 (fMRI, requiring physician administration) and 96020 (neurofunctional testing selection). Hypothesized pitfalls with fMRI in glioblastoma include the change in the microenvironment that potentially exists within high-grade tumor tissue that is quite different from the normal tissue on which the technique was founded [19].

### • Magnetic source imaging

Magnetic source imaging (MSI) provides integrated functional and dynamic data from magnetoencephalography (MEG) to be merged with anatomical images obtained with an MRI [20]. MSI is a functional preoperative imaging technique that provides sensorimotor, visual and language functional data. When planning for

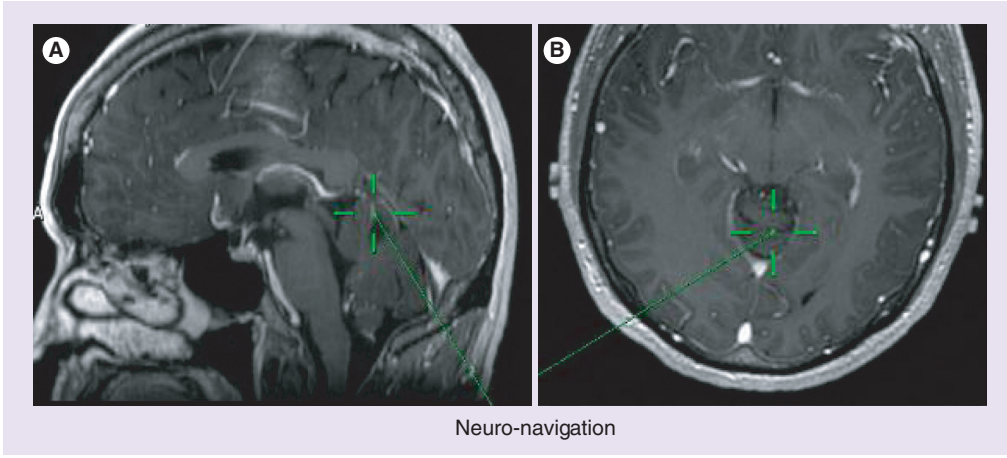



**Figure 1. Post-gadolinium enhanced T1 MRI showing a 49 year-old man with a cerebellar vermis high-grade glioma. (A)** Sagittal and **(B)** axial. Shown are the neuro-navigation (green) trajectories intra-operatively, demonstrating the supracerebellar–infratentorial approach that was used for operative resection of this tumor.
For color images please see www.futuremedicine.com/doi/full/10.2217/cns.14.36

tumor operations that lie within regions of eloquent brain regions, it is critical to identify accurately the operative corridors that could result in morbid outcomes during tissue resection for brain tumors. MSI provides an additional facet of information that can show usefulness when stratifying patients by risk preoperatively [21]. MSI is of value in understanding the anatomic boundaries individualized to each and every operation **(Figure 2)** [22,23]. Although MSI has provided additional information that could be used for preoperative planning, it is still not widely used and is utilized primarily in highly specialized medical centers, with only 34 centers in the USA possessing this technology as of 2014.

To date, there have been no good comparisons of the accuracy of fMRI versus MSI/MEG in predicting real anatomic locations of function identified by intraoperative mapping. It should be noted that, prior to the advent of fMRI and MSI, preoperative language mapping had required invasive techniques. The early gold standard used an invasive intracarotid amobarbitol procedure – the Wada test – that had potential morbidity [24]. However, identification of dominant hemisphere language function can now be acquired using noninvasive techniques like fMRI or MSI [22,23].

### • Diffusion tensor imaging

Axonal architecture can be captured using noninvasive imaging with diffusion tensor MRI, and this has been shown to be useful and confirmatory when evaluated using intraoperative cortical stimulation [25]. Diffusion MRI provides connectivity information, and subcortical pathways for motor, sensory, vision and language

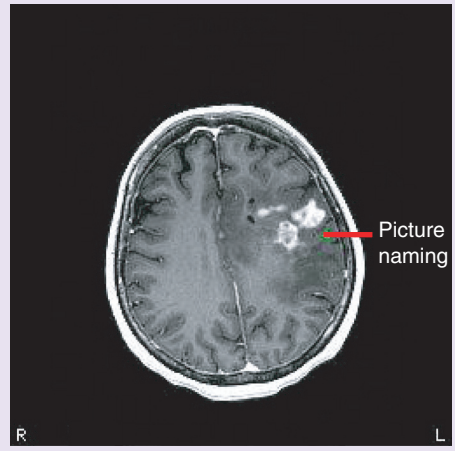



**Figure 2. Example of magnetoencephalography-derived images obtained from a 44-year-old male with a left frontal lobe high grade glioma.** Magnetoencephalography revealed a focus in the left frontal lobe associated with picture naming that was posterior the lesion. These images were loaded into operating room neuronavigation, and awake intraoperative language mapping was used to corroborate the preoperative magnetoencephalography.

pathways [26]. Figure 3 shows an example of an intraoperative screenshot, demonstrating diffusion tensor imaging (DTI) tracks.

Intraoperative stimulation using cortical stimulation is the traditional standard for identification of function in the cortex [27–30]. Although the technique is reliable, it does have limitations in its ability to stimulate subcortical extensions of functioning areas. Tumors or lesions that have mass effect on these tracts can not only cause displacement of these tracts, but can also make understanding location for these tracts difficult [31]. Tumor pathology has been shown to have an effect on the accuracy of the tumor-to-diffusion tracts, with nonenhancing lesions showing minimal intraoperative shift when compared with enhancing lesions [32].

Preoperative DTI has become a useful adjunct in providing subcortical pathway identification. Together with neuro-navigation techniques, DTI connectivity maps provide additional information that is useful in delineating areas that require identification for functional preservation during surgical resection. When mapping in the subcortical region, DTI is used to help identify the regions in question by allowing a visual spatial registration and improved localization so that mapping identification is maximized [33,34].

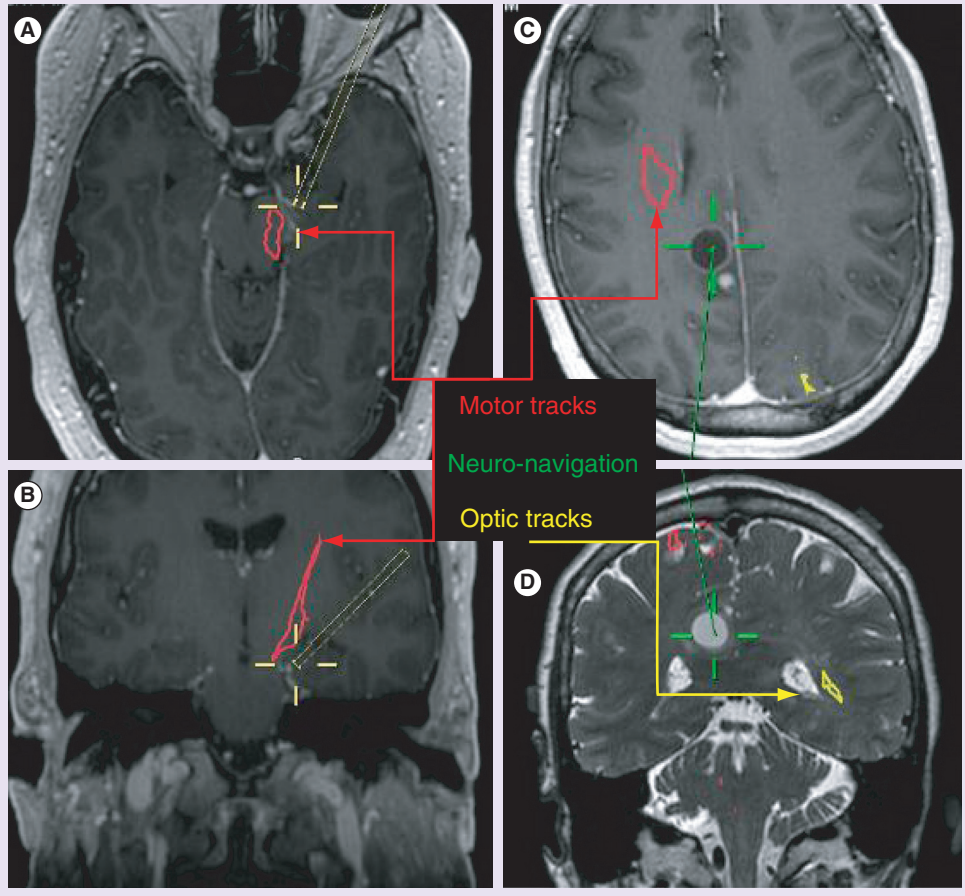



**Figure 3. Intraoperative screenshot, demonstrating diffusion tensor imaging tracks. (A)** Axial and **(B)** coronal post-gadolinium T1 enhanced MRI from a 36-year-old man with a lesion in the left amygdala. Motor (red) diffusion tensor imaging (DTI) tracks are shown at the level of the midbrain **(A)** and corona radiata and internal capsule **(B)**. **(C)** Axial post-gadolinium enhanced and **(D)** coronal T2 MRI showing a 66-year-old woman with a cystic glioblastoma and enhancing mural nodule in the right posterior cingulate gyrus. Optic radiations (yellow) and corticospinal tracts (red) were generated using DTI imaging and are shown as well as neuro-navigation (green).
For color images please see www.futuremedicine.com/doi/full/10.2217/cns.14.36

Further studies using DTI have shown an association of functional information and that of the structural DTI fiber tracking making the link between speech and naming by combining these techniques. These techniques not only make new associations within unknown relationships in the brain architecture, but also provide additional connectivity data that allow preservation of language function [25]. Further sequence development using q-ball reconstruction with diffusion MRI has shown improvements in sensitivity and accuracy of tracking methods providing reproducible and accurate advancements [35]. One study has shown that DTI and MSI can prove complementary in identifying and validating cortical centers and their associated subcortical pathways [23].

## Intraoperative tools to optimize resection

### • Intraoperative motor & language mapping

Early identification of the motor and sensory representations on the cortical brain tissue surface was first studied using cortical stimulation, and this was introduced in 1931 by Foerster *et al.*, and soon after proceeded by Penfield in 1937 [36]. Brain tumor lesions distort the traditionally identified anatomical representation of eloquent regions, so intraoperative stimulation has become a gold standard for direct identification of cortical function [29,37].

The method of direct stimulation depolarizes a focal area of cortex and induces a neuronal excitation that either creates an inhibition or excitation [38]. This method of excitation can be utilized intraoperatively to map both motor and language function not only on the cortex, but also subcortically [39,40]. The goal of operative resection of infiltrative glioblastomas is to achieve a resection that maximizes EOR safely without compromising eloquent tissue and sparing function. As has been shown previously, and highlighted in many articles including Sanai *et al.* [41] and Duffau *et al.* [42], intraoperative stimulation provides tract localization and when tissue is maximized and abutting these regions, transient deficits are experienced and recovered in the majority of patients. Negative results have proven useful when looking at the EOR in noneloquent or nonfunctional mapping regions and improved survival. There has been discussion about the potential use of a supratotal resection in nonfunctioning eloquent glioblastomas as an avenue for achieving maximal resection to improve survival [42]. In a study that looked at 250 dominant hemisphere glioma patients, after identification of intraoperative language function, deficits were noted immediately postoperatively in 14% of patients, but at the 6-month follow-up evaluation, only 1.6% of patients had persistent language deficits, and all other patients that had experienced postoperative changes had recovered [41]. These data alone characterize the strength of intraoperative mapping in sparing eloquent cortex and function.

To date, there have been no good studies analyzing the time and costs of intraoperative stimulation. A cost–benefit justification of the technique would need to show that the cumulative costs of mapping the brain when removing tumors in eloquent locations is justified by reducing the costs such as time in rehab, mechanical assistance devices, additional needed medications, and complications such as aspiration or venous thrombosis that are associated with postoperative motor and language deficits.

### • 5-aminolevulinic acid

In glioblastoma, the complete resection of the enhancing tumor has been shown to be an important prognostic factor, together with maximizing the extent of resection [7,8]. New techniques have been developed to aid the surgeon in identifying the boundaries of tumor tissue. 5-aminolevulinic acid (5-ALA) is a nonfluorescent amino acid precursor that, when introduced into a glioma patient, induces an accumulation of fluorescence in the tumor bed. It is believed that the fluorescence occurs in the tumor bed of glioma patients because of the disruption in the blood–brain barrier that leads to an accumulation in glioma tissue, therefore 5-ALA is not seen in healthy brain tissue [18,43].

Retrospective studies using 5-ALA have shown median overall survival benefit of 27 months over 17 months, and a decrease in complication rates of 18.5 versus 8% [43]. When comparing the complete removal of contrast-enhancing tumors, a 5-ALA study achieved a 65% complete removal, compared with 36% over white light microsurgery [44]. 5-ALA has shown to be a useful intraoperative aid in achieving not only improved EORs, but also influencing survival.

Although the data for 5-ALA use have shown promise, its limited use is still only utilized in

highly specialized medical centers. 5-ALA has shown promise as an intraoperative aid, but there are practical limitations that exist when using this technique as an operative tool. 5-ALA can be visualized only under fluorescence, therefore the operative arena lights must be turned off and this prohibits the surgeon from operating under minimal visualization of the surrounding tissues; this makes this technique strictly a validation tool. Furthermore, fluorescence is obscured by blood, therefore this can easily influence the interpretation of the fluorescence signal.

### • Intraoperative imaging: ultrasound & MRI

Contrast-enhanced ultrasound (CEUS) imaging of tissue perfusion is based on microtubule echo detection and visualizes tumors based on local perfusion variations. The technique has been used to classify the presence of glioblastoma in tumor borders with minimum average classification error of 17% [45]. Intraoperative MRI has been more frequently studied than intraoperative ultrasound. One randomized controlled trial showed no benefit of iMRI on EOR as compared with standard neuronavigation [46]. Another study in which iMRI was used if available found that the impact of iMRI on EOR was barely statistically significant ($p = 0.049$) while its impact on overall survival was not statistically significant [47].

## Recurrent glioblastoma

The improvements in both preoperative and intraoperative tools have resulted in longer survival for patients with glioblastoma. This has resulted in many patients surviving with good functional status, and also surviving to recurrence [48]. Although there has been significant advancement in both the surgical and nonsurgical treatment of glioblastoma, these malignant tumors are still associated with poor prognosis. Recent studies have demonstrated convincing evidence for supporting repeat craniotomy [48]. Similar to what has been shown in the population of newly diagnosed glioblastoma, the impact of EOR at repeat resection has shown a benefit in overall survival [48]. Importantly, the EOR from the time of initial craniotomy does not influence this benefit during repeat craniotomy. And a recent study has suggested that there is an EOR threshold of 80% at the time of repeat craniotomy in order for the craniotomy to exert an impact of overall survival [49], suggesting that the benefits of repeat craniotomy for recurrent glioblastoma are not limited to tumors with large mass effect or edema, or for cases where the diagnosis of treatment effect versus recurrence needs to be established.

Although operative repeat resection has shown a benefit as described above, a large portion of therapy at the time of recurrence involves nonoperative treatments. Aside from the developments in chemotherapy and radiation treatments for patients with recurrent glioblastoma, novel therapies are being developed that offer new avenues for improving outcomes in patients. Immunotherapy is a recent development that evokes specific immune responses against glioblastomas by developing tumor antigens and delivering them via heat-shock peptide protein vaccines [50].

## Conclusion & future perspective

The operative management of glioblastoma has undergone continued improvement and optimization over the recent years. This has resulted in an overall survival benefit, and also an improvement in the quality of life of patients. Postoperative patients are seeing better functional outcomes as a result of the changes that were discussed above. This is largely due to the preoperative and intraoperative developments that help identify tumor tissue, and also aid in locating and sparing adjacent eloquent and normal functioning brain. The result has been larger regions of extent of resection, which has provided the improvements in survival.

In the future, hopefully the techniques described here will be better integrated together in a seamless manner that maintains an efficient workflow in the operating room. While technically challenging, larger clinical trials will hopefully better define the specific roles of each individual technique in a manner that allows more standardized practice patterns.

## Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

*No writing assistance was utilized in the production of this manuscript.*

## References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest


1 Onoyama Y, Abe M, Yabumoto E, Sakamoto T, Nishidai T. Radiation therapy in the treatment of glioblastoma. *Am. J. Roentgenol.* 126(3), 481–492 (1976).

2 Payne DG, Simpson WJ, Keen C, Platts ME. Malignant astrocytoma: hyperfractionated and standard radiotherapy with chemotherapy in a randomized prospective clinical trial. *Cancer* 50(11), 2301–2306 (1982).

3 Simpson JR, Horton J, Scott C *et al.* Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. *Int. J. Radiat. Oncol. Biol. Phys.* 26(2), 239–244 (1993).

4 Ammirati M, Vick N, Liao YL, Ciric I, Mikhael M. Effect of the extent of surgical resection on survival and quality of life in patients with supratentorial glioblastomas and anaplastic astrocytomas. *Neurosurgery* 21(2), 201–206 (1987).

5 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.* 52(4), 371–379 (1999).

6 Lacroix M, Abi-Said D, Fourney DR *et al.* A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J. Neurosurg.* 95(2), 190–198 (2001).

7 Stummer W, Reulen HJ, Meinel T *et al.* Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. *Neurosurgery* 62(3), 564–576; discussion 564–576 (2008).

•• **Given the diffuse signal abnormality encountered in glioblastoma, including enhancing and nonenhancing tumor burden, it was demonstrated that survival depended on extent of resection (EOR) of the enhancing tumor on MRI.**

8 Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. *J. Neurosurg.* 115(1), 3–8 (2011).

• **Survival benefit has been shown with EOR >78%, and continued in a step-wise benefit when looking at EOR >90, >95, >98 and when equal to 100%.**

9 Zinn PO, Colen RR, Kasper EM, Burkhardt JK. Extent of resection and radiotherapy in GBM: a 1973 to 2007 surveillance, epidemiology and end results analysis of 21,783 patients. *Int. J. Oncol.* 42(3), 929–934 (2013).

10 Fitzgerald DB, Cosgrove GR, Ronner S *et al.* Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. *AJNR Am. J. Neuroradiol.* 18(8), 1529–1539 (1997).

11 Yetkin FZ, Swanson S, Fischer M *et al.* Functional MR of frontal lobe activation: comparison with Wada language results. *Am. J. Neuroradiol.* 19(6), 1095–1098 (1998).

12 Bogomolny DL, Petrovich NM, Hou BL, Peck KK, Kim MJ, Holodny AI. Functional MRI in the brain tumor patient. *Top. Magn. Reson. Imaging* 15(5), 325–335 (2004).

13 Hirsch J, Ruge MI, Kim KH *et al.* An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. *Neurosurgery* 47(3), 711–721; discussion 721–712 (2000).

14 Mueller WM, Yetkin FZ, Hammeke TA *et al.* Functional magnetic resonance imaging mapping of the motor cortex in patients with cerebral tumors. *Neurosurgery* 39(3), 515–520; discussion 520–511 (1996).

15 Vlieger EJ, Majoie CB, Leenstra S, Den Heeten GJ. Functional magnetic resonance imaging for neurosurgical planning in neurooncology. *Eur. Radiol.* 14(7), 1143–1153 (2004).

16 Guggisberg AG, Honma SM, Findlay AM *et al.* Mapping functional connectivity in patients with brain lesions. *Ann. Neurol.* 63(2), 193–203 (2008).

17 Tarapore PE, Martino J, Guggisberg AG *et al.* Magnetoencephalographic imaging of resting-state functional connectivity predicts postsurgical neurological outcome in brain gliomas. *Neurosurgery* 71(5), 1012–1022 (2012).

18 Hervey-Jumper SL, Berger MS. Role of surgical resection in low- and high-grade gliomas. *Curr. Treat. Options Neurol.* 16(4), 284 (2014).

19 Giussani C, Roux FE, Ojemann J, Sganzerla EP, Pirillo D, Papagno C. Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. *Neurosurgery* 66(1), 113–120 (2010).

20 Doss RC, Zhang W, Risse GL, Dickens DL. Lateralizing language with magnetic source imaging: validation based on the Wada test. *Epilepsia* 50(10), 2242–2248 (2009).

21 Ganslandt O, Buchfelder M, Hastreiter P, Grummich P, Fahlbusch R, Nimsky C. Magnetic source imaging supports clinical decision making in glioma patients. *Clin. Neurol. Neurosurg.* 107(1), 20–26 (2004).

22 Szymanski MD, Perry DW, Gage NM *et al.* Magnetic source imaging of late evoked field responses to vowels: toward an assessment of hemispheric dominance for language. *J. Neurosurg.* 94(3), 445–453 (2001).

23 Berman JI, Berger MS, Chung SW, Nagarajan SS, Henry RG. Accuracy of diffusion tensor magnetic resonance imaging tractography assessed using intraoperative subcortical stimulation mapping and magnetic source imaging. *J. Neurosurg.* 107(3), 488–494 (2007).

24 Wada J, Rasmussen T. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. 1960. *J. Neurosurg.* 106(6), 1117–1133 (2007).

25 Henry RG, Berman JI, Nagarajan SS, Mukherjee P, Berger MS. Subcortical pathways serving cortical language sites: initial experience with diffusion tensor imaging fiber tracking combined with intraoperative language mapping. *Neuroimage* 21(2), 616–622 (2004).

26 Yu CS, Li KC, Xuan Y, Ji XM, Qin W. Diffusion tensor tractography in patients with cerebral tumors: a helpful technique for neurosurgical planning and postoperative assessment. *Eur. J. Radiol.* 56(2), 197–204 (2005).

27 Berger MS. Functional mapping-guided resection of low-grade gliomas. *Clin. Neurosurg.* 42, 437–452 (1995).

28 Berger MS, Ojemann GA. Intraoperative brain mapping techniques in neuro-oncology. *Stereotact. Funct. Neurosurg.* 58(1–4), 153–161 (1992).

29 Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J. Neurosurg.* 71(3), 316–326 (1989).

30 Penfield W. The supplementary motor area in the cerebral cortex of man. *Arch. Psychiatr. Nervenkr. Z Gesamte Neurol. Psychiatr.* 185(6–7), 670–674 (1950).

31 Kamada K, Todo T, Masutani Y *et al.* Combined use of tractography-integrated functional neuronavigation and direct fiber stimulation. *J. Neurosurg.* 102(4), 664–672 (2005).

32 Shahar T, Rozovski U, Marko NF *et al.* Preoperative imaging to predict intraoperative changesin tumor-to-corticospinal tract

distance: an analysis of 45 cases using high-field intraoperative magnetic resonance imaging. *Neurosurgery* 75(1), 23–30 (2014).

33 Papagno C, Gallucci M, Casarotti A *et al.* Connectivity constraints on cortical reorganization of neural circuits involved in object naming. *Neuroimage* 55(3), 1306–1313 (2011).

34 Bello L, Gambini A, Castellano A *et al.* Motor and language DTI fiber tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. *Neuroimage* 39(1), 369–382 (2008).

35 Bucci M, Mandelli ML, Berman JI *et al.* Quantifying diffusion MRI tractography of the corticospinal tract in brain tumors with deterministic and probabilistic methods. *Neuroimage. Clin.* 3, 361–368 (2013).

36 Snyder PJ, Whitaker HA. Neurologic heuristics and artistic whimsy: the cerebral cartography of Wilder Penfield. *J. Hist. Neurosci.* 22(3), 277–291 (2013).

37 Ojemann GA. Individual variability in cortical localization of language. *J. Neurosurg.* 50(2), 164–169 (1979).

38 Ranck JB, Jr. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res.* 98(3), 417–440 (1975).

39 Taylor MD, Bernstein M. Awake craniotomy with brain mapping as the routine surgical approach to treating patients with supratentorial intraaxial tumors: a prospective trial of 200 cases. *J. Neurosurg.* 90(1), 35–41 (1999).

40 Skirboll SS, Ojemann GA, Berger MS, Lettich E, Winn HR. Functional cortex and subcortical white matter located within gliomas. *Neurosurgery* 38(4), 678–684; discussion 684–675 (1996).

41 Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N. Engl. J. Med.* 358(1), 18–27 (2008).

• **From 250 dominant hemisphere glioma patients, after identification of intraoperative language function, deficits were noted immediately postoperatively in 14% of patients, but at the 6 month follow-up evaluation only 1.6% of patients had persistent language deficits, and all other patients that had experienced postoperative changes had recovered. A theory of resection based on negative mapping.**

42 Duffau H. Is supratotal resection of glioblastoma in noneloquent areas possible? *World Neurosurg.* doi:10.1016j.wneu.2014.02.015. (2014) (Epub ahead of print).

43 Aldave G, Tejada S, Pay E *et al.* Prognostic value of residual fluorescent tissue in glioblastoma patients after gross total resection in 5-aminolevulinic acid-guided surgery. *Neurosurgery* 72(6), 915–920; discussion 920–911 (2013).

44 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.* 7(5), 392–401 (2006).

45 Ritschel K, Pechlivanis I, Winter A. Brain tumor classification on intraoperative contrast-enhanced ultrasound. *Int. J. Comput. Assist. Radiol. Surg.* doi:10.1007/s11548-014-1089-6 (2014) (Epub ahead of print).

46 Kubben PL, Scholtes F, Schijns OE *et al.* Intraoperative magnetic resonance imaging versus standard neuronavigation for the neurosurgical treatment of glioblastoma: a randomized controlled trial. *Surg. Neurol. Int.* 5, 70 (2014).

47 Napolitano M, Vaz G, Lawson TM *et al.* Glioblastoma surgery with and without intraoperative MRI at 3.0T. *NeuroChirurgie* doi:10.1016j.neuchi.2014.03.010 (2014) (Epub ahead of print).

48 Bloch O, Han SJ, Cha S *et al.* Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. *J. Neurosurg.* 117(6), 1032–1038 (2012).

49 Oppenlander ME, Wolf AB, Snyder LA *et al.* An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. *J. Neurosurg.* 120(4), 846–853 (2014).

50 Bloch O, Parsa AT. Heat shock protein peptide complex-96 (HSPPC-96) vaccination for recurrent glioblastoma: a Phase II, single arm trial. *Neuro. Oncol.* 16(5), 758–759 (2014).