Maintaining neurological function in brain tumor resection

Hugues Duffau*: Hugues Duffau is professor and chairman at the Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center (Montpellier, France). He trained at the Pitié-Salpêtrière Hospital in Paris, France, and has won multiple awards, including being honored with the Grand Prix of Surgical Oncology by the French National Academy of Medicine in 2012. Duffau is a prominent member of multiple editorial boards and has authored over 200 articles within the field of neuro-oncology. He is currently director of a team researching plasticity of the CNS, human stem cells and glial tumors at INSERM U1051, Montpellier, France.

How do the risks to neurological function vary with resection of different brain tumor types?

The rationale of surgical resection is different in high-grade glioma (HGG) and low-grade glioma (LGG).

In HGG, it is not rare to observe a pre-operative deficit, especially in older patients. Thus, the goal is to avoid worsening this deficit, or even to improve it by decreasing the mass effect. In other words, in most cases the neurosurgeon will perform almost exclusively a resection of the central portion of the glioma and will leave the major part of the peripheral tumoral infiltration, which explains the need for systematic adjuvant treatment. Therefore, the onco-functional balance does not lean in favor of 'maximal' surgery, but in the vast majority of cases, it supports resection of only the enhanced part of the glioma (if possible), with no margin in order to prevent any postoperative impairment, even temporary impairment – with

the goal of performing radiotherapy and/or chemotherapy as soon as possible in the best neurological conditions.

By contrast, in LGG presurgical deficit is exceptional, even when the tumor involves eloquent areas. Indeed, the glioma is discovered because of inaugural seizures in more than 90% of cases, or incidentally, usually in young patients. Therefore, a limiting factor on the effectiveness of surgery is preserving a normal quality of life (including a normal professional life). On the other hand, from an oncological point of view, in principle it is hard to be content with a single 'tumor-ectomy' (i.e., removal of the part of the lesion visible on imaging), and it is instead preferred to remove the part of the brain invaded by a chronic and diffuse tumoral disease, eventually extended beyond the fluid-attenuated inversion recovery–MRI abnormalities [1]. Indeed, the recent literature clearly demonstrates that the risks of malignant transformation, as well as overall survival, are significantly related to the

News & Views

News

Journal Watch

Ask the Experts

Interview

Conference Scenes

*Neurochirurgie, Hôpital Gui de Chauliac, CHU Montpellier, 80 Avenue Augustin Fliche, 34295 Montpellier, France; h-duffau@chu-montpellier.fr

extent of resection. Such results support the achievement of (if possible) a total or supratotal resection (i.e., to take a margin around the fluid-attenuated inversion recovery signal abnormalities) [2]. In summary, the onco-functional balance pleads in favor of early and maximal LGG removal.

How would one most effectively approach resection of diffuse glioma? What are the main considerations in preoperative planning?

As glioma is a diffuse tumoral disease, the rationale should be to remove the brain invaded by tumoral cells (on the condition that this part of the CNS is not crucial for cerebral functions), rather than to think that it is possible to remove a ‘tumor mass’, especially in LGG. In other words, achieving a debulking ‘within the glioma’ does not prevent potential postsurgical deficit. As a consequence, the resection should be performed according to functional boundaries rather than to ‘oncological boundaries’ – which in essence mean nothing in gliomas. Because of a high level of inter-individual anatomo-functional variability (which is increased in [low-grade] gliomas owing to mechanisms of brain plasticity induced by the slow growth of the tumor), anatomical landmarks are of course useful, but definitely not enough when planning a resection. This is the reason why functional mapping should be performed in all cases [3]. Preoperatively, noninvasive functional MRI and diffusion tensor imaging may provide helpful data, but these methods suffer from serious limitations. Neurosurgeons have the tendency to believe that data provided by functional MRI and diffusion tensor imaging are the ‘absolute truth’. Yet, functional neuroimaging is based on biomathetical reconstruction, with results that may change according to the model, which explains its lack of reliability at the individual level. This is especially true when regarding cognitive function – for example, only 82% reliability is reported for the tracking of language pathways [4]. Furthermore, neuroimaging is not able to differentiate areas crucial for brain functions from regions that could be functionally compensated. Thus, there is a double risk of not selecting a patient for diffuse LGG surgery because functional MRI

activations are visible very near to or within the tumor, while it may in fact be possible to remove it with no permanent deficit, or of inducing a permanent deficit due to a false negative.

What benefits does intraoperative cortical–subcortical stimulation during awake surgery provide?

The first principle in (low-grade) glioma surgery should be to tailor the resection according to functional boundaries, with no margin, to maximize tumor removal while preserving critical structures. Owing to the limitations of functional neuroimaging, intraoperative electrostimulation mapping in awake patients is actually the more reliable method of identifying eloquent regions. This is an easy, safe, nonexpensive, reliable and reproducible technique, allowing the identification of crucial (nonfunctionally compensable) structures at the level of the cortex, white matter pathways (subcortical connectivity) and deep gray nuclei – and thus allowing real-time anatomo–functional correlations throughout the resection to be performed [5]. In the past decade, brain mapping has led to an impressive improvement of both functional and oncological outcomes in glioma surgery. First, patients who classically would not be selected for surgery purely on the basis of anatomical criteria (e.g., gliomas involving the ‘Broca’s area’), can now benefit from resection without a dogmatic *a priori* against surgical feasibility owing to tumor location. The use of intraoperative electrostimulation allowed a significant increase in surgical indications for LGG involving so-called ‘eloquent areas’, when compared with a control group of patients who underwent resection under general anesthesia with no mapping [6]. For example, surgical resection is possible with no permanent neurological worsening for gliomas within Broca’s area, Wernicke’s area, insula, left dominant inferior parietal lobule, retrocentral area and even the precentral region [7].

Furthermore, the rate of permanent neurological deficits was shown to be significantly less thanks to awake mapping. In other words, the functional risk is less than 2% in the recent series using direct electrostimulation [8,9]. This rate is very reproducible among the teams using awake

mapping worldwide. Indeed, a recent meta-analysis studying more than 8000 patients who underwent surgical resection for brain glioma (both LGG and HGG) demonstrated that the use of intraoperative mapping allowed a statistically significant reduction in permanent deficit, despite an increased rate of resection within eloquent areas [10].

Finally, this meta-analysis also showed that the extent of resection was increased thanks to the use of intraoperative electrical mapping [10]. Interestingly, it was recently confirmed in the largest surgical series ever reported, with more than 1000 LGGs, that the extent of resection significantly affected overall survival [11]. Therefore, because the traditional dilemma in LGG (i.e., survival versus quality of life) is now solved, at least in the vast majority of cases, surgical resection is today the first therapeutic option to consider in LGGs – as recommended by the European Guidelines [12].

What evidence is there in favor of using intermittent general anesthesia (i.e., asleep–awake–asleep protocol) for brain tumor resection?

Although it is technically possible to keep the patient awake from the beginning to the end of the surgical procedure, notably for rapid resection of small tumors, the asleep–awake–asleep protocol offers many advantages. First, the comfort of the patient is not optimal during opening and closure, in particular due to the craniotomy. In addition, the cooperation of the patient is not required outside the brain. Thus, it seems more logical to open the skull in asleep patients. Second, the bleeding is less when the opening and closure of the skull are performed under general anesthesia, especially in cases of wide boneflap, tailored to voluminous tumors. Third, there is a time constraint during the awake period in which real-time functional feedback is provided by the patient throughout the resection because tiredness will progressively occur (usually after two hours of active collaboration). It implies that the patient should not already be tired by the opening, explaining why it is better to be asleep during the first part of surgery and to wake the patient only when his/her participation is mandatory, that is, just before the cortical mapping. It also means that in

very big tumors, such as left fronto-temporo-insular gliomas, for technical reasons (e.g., dissection in contact with the Sylvian vessels), it is basically impossible to remove the lesion in 2 h. As a consequence, the goal is not to debulk the tumor from inside during the awake period, but to find the functional boundaries while the patient is able to cooperate and then to disconnect the part of the brain invaded by the tumoral disease, without attempting to remove it. Indeed, it will be possible to finish the resection of this part of the CNS under general anesthesia (since, by definition, it is not crucial for function as it was previously disconnected), with no limitation of time. Because this additional resection can take several hours, there is no reason for the patient to still be awake. Finally, this asleep–awake–asleep technique is very safe and reliable, on the condition that the neuro-anesthesiologist team is experienced in this kind of management in that the team performs such a procedure very regularly [13].

How does intraoperative monitoring differ when trying to preserve visual function?

For a long time there was no attempt to map visual function during brain surgery. Neurosurgeons used anatomical landmarks only, with the aim of trying to avoid damage to optic radiations, but as previously mentioned, anatomy lacks reliability, especially at the subcortical level, thus explaining the high rate of campimetric deficits in the classical literature. Although visual field deficits have received less attention, they can nonetheless be disabling, in particular, due to the fact that it is forbidden in many countries to drive with a hemianopia. Recently, it was proposed that the patient should be woken, even in the right ‘nondominant’ hemisphere, in order to test visual function and to map the optic radiation by performing direct subcortical stimulation of visual pathways [14]. Beyond subjective responses elicited by electrostimulation such as phosphenes, blurred vision or hallucinations (e.g., metamorphopsia), a modified picture-naming task with two pictures placed diagonally on the screen can be used to optimize the reliability of this visual mapping. One picture is situated in the quadrant that the surgeon plans to save in order to avoid homonymous

hemianopia (while quadrantanopia can be tolerated) and another picture is situated in the opposite quadrant. Therefore, in the case of the wrong answer during stimulation, it is possible to know whether the error is due to a disturbance of the language network or a visual disorder. Improvement in the sensitivity of mapping is crucial to preserve optimal quality of life in glioma patients.

How would you recommend that post-operative brain function is measured? What are the key difficulties in this?

In traditional routine practice, only a standard clinical examination is generally performed before and after glioma surgery. This is not sufficient. Indeed, cognitive deficits are often observed when objective cognitive assessments are performed at the time of diagnosis, even in LGG patients who enjoy normal social and professional lives. Many glioma patients experience disorders of executive function, attention, concentration, working memory or emotion [15,16]. This neuropsychological evaluation is very important at the individual level in order to select the more appropriate tasks that will be applied during awake surgery and to serve as a baseline that will be compared with the postoperative assessment. Indeed, objective cognitive testing should also be systematically carried out following resection in order to plan personalized functional rehabilitation. Beyond neuropsychological scores, reaction time is also crucial, as demonstrated in a recent study that showed a significant relationship between reaction time during a postoperative naming task and the return to work [17]. Therefore, standardized batteries of tasks have recently been proposed, to facilitate the systematic pre- and post-operative cognitive evaluation in clinical practice [18].

What are the main challenges in neurosurgery at the moment with regard to optimizing both resection & postoperative outcome? How far do you see these being overcome in the next 5 years?

To maximize the benefit–risk ratio of glioma surgery, the first issue will be to optimize the quality of intraoperative mapping. It means that the goal is not only to wake patients

to test language, but also to test complex movements, visuospatial cognition, executive functions (working memory and judgement; and attention), and even emotion and behavior (social cognition). This includes patients with tumors involving the ‘non-dominant hemisphere’ [19]. The ultimate aim is not only to avoid aphasia and hemiplegia, but also to be able to certify to the patient before surgery that, except in exceptional cases of stroke (which occurs in less than 2% of cases), he/she will recover a good quality of life after surgery. Such an increase in the reliability of the surgical act will allow clinicians to propose early surgery, especially in LGG patients, that is, after a first seizures or even in asymptomatic patients with MRI performed for another reason (e.g., mild injury). Indeed, preliminary data have demonstrated a higher rate of total and supratotal resections in incidental LGG, because the tumor is smaller, with an increased impact on the natural course of the glioma [20]. On the other hand, when a complete resection is not possible for functional reasons, the neurosurgeon should more systematically consider a second (or even a third) surgery several years later, which may enable improvement of the extent of resection while preserving the quality of life thanks to the functional reorganization that has occurred in the meantime [21]. In other words, a multistage surgical approach will be routinely proposed as standard in the therapeutic management of (low-grade) glioma patients. Finally, if a (re-)operation cannot be performed because of a wide tumoral invasion (‘gliomatosis like’), neoadjuvant chemotherapy could be suggested in order to induce glioma shrinkage and, thus, a subsequent surgical resection [22]. In summary, it is time to move towards ‘individualized multimodal functional neuro-oncology’ [23,24].

Financial & competing interests disclosure

The author has 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

- 1 Duffau H. The challenge to remove diffuse low grade gliomas while preserving brain functions. *Acta Neurochir. (Wien)* 154, 569–574 (2012).
- 2 Yordanova Y, Moritz-Gasser S, Duffau H. Awake surgery for WHO grade II gliomas within “noneloquent” areas in the left dominant hemisphere: toward a “supratotal” resection. *J. Neurosurg.* 115, 232–239 (2011).
- 3 Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol.* 4, 476–486 (2005).
- 4 Leclercq D, Duffau H, Delmaire *et al.* Comparison of diffusion tensor imaging tractography of language tracts and intraoperative subcortical stimulations. *J. Neurosurg.* 112, 503–511 (2010).
- 5 Duffau H. New concepts in surgery of WHO grade II gliomas: functional brain mapping, connectionism and plasticity. *J. Neurooncol.* 13, 885–897 (2006).
- 6 Duffau H, Lopes M, Arthuis F *et al.* Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985–1996) and with (1996–2003) functional mapping in the same institution. *J. Neurol. Neurosurg. Psychiatry* 76, 845–851 (2005).
- 7 Desmurget M, Bonnetblanc F, Duffau H. Contrasting acute and slow growing lesions: a new door to brain plasticity. *Brain* 130, 898–914 (2007).
- 8 Duffau H, Gatignol P, Mandonnet E, Capelle L, Taillandier L. Contribution of intraoperative subcortical stimulation mapping of language pathways: a consecutive series of 115 patients operated on for a WHO grade II glioma in the left dominant hemisphere. *J. Neurosurg.* 109, 461–471 (2008).
- 9 Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N. Engl. J. Med.* 358, 18–27 (2008).
- 10 de Witt Hamer PC, Gil Robles S, Zwinderman A, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. *J. Clin. Oncol.* 30, 2559–2565 (2012).
- 11 Capelle L, Fontaine D, Mandonnet E *et al.* Spontaneous and therapeutic prognostic factors in adult hemispheric WHO grade II gliomas: a series of 1097 cases. *J. Neurosurg.* (2012) (In Press).
- 12 Soffietti R, Baumert B, Bello L *et al.* Guidelines on management of low grade gliomas: report of an EFNS–EANO task force. *Eur. J. Neurol.* 17, 1124–1133 (2010).
- 13 Deras P, Moulinié G, Maldonado IL, Moritz-Gasser S, Duffau H, Bertram L. Intermittent general anesthesia with controlled ventilation for asleep–awake–asleep brain surgery: a prospective series of 140 gliomas in eloquent areas. *Neurosurgery* 71, 764–772 (2012).
- 14 Gras-Combe G, Moritz-Gasser S, Herbert G, Duffau H. Intraoperative subcortical electrical mapping of optic radiations in awake surgery for glioma involving visual pathways. *J. Neurosurg.* 117, 466–473 (2012).
- 15 Teixidor P, Gatignol P, Leroy M, Masuet-Aumatell C, Capelle L, Duffau H. Assessment of verbal working memory before and after surgery for low-grade glioma. *J. Neurooncol.* 81, 305–313 (2007).
- 16 Aaronson NK, Taphoorn MJ, Heimans JJ *et al.* Compromised health-related quality of life in patients with low-grade glioma. *J. Clin. Oncol.* 29, 4430–4435 (2011).
- 17 Moritz-Gasser S, Herbert G, Maldonado IL, Duffau H. Lexical access speed is significantly correlated with the return to professional activities after awake surgery for low-grade gliomas. *J. Neurooncol.* 107, 633–641 (2012).
- 18 Klein M, Duffau H, De Witt Hamer PC. Cognition and resective surgery for diffuse infiltrative glioma: an overview. *J. Neurooncol.* 108, 309–318 (2012).
- 19 Duffau H. Awake surgery for nonlanguage mapping. *Neurosurgery* 66, 523–528 (2010).
- 20 Duffau H. Awake surgery for incidental WHO grade II gliomas involving eloquent areas. *Acta Neurochir. (Wien)* 154, 575–584 (2012).
- 21 Gil Robles S, Gatignol P, Lehericy S, Duffau H. Long-term brain plasticity allowing multiple-stages surgical approach for WHO grade II gliomas in eloquent areas: a combined study using longitudinal functional MRI and intraoperative electrical stimulation. *J. Neurosurg.* 109, 615–624 (2008).
- 22 Blonski M, Taillandier L, Herbert G *et al.* Combination of neoadjuvant chemotherapy followed by surgical resection as new strategy for WHO grade II gliomas: a study of cognitive status and quality of life. *J. Neurooncol.* 106, 353–366 (2012).
- 23 Duffau H. Surgery of low-grade gliomas: towards a “functional neurooncology”. *Curr. Opin. Oncol.* 21, 543–549 (2009).
- 24 Duffau H. *Diffuse Low-Grade Gliomas In Adults: Natural History, Interaction With The Brain, And New Individualized Therapeutic Strategies.* Duffau H (Ed.). Springer London, UK (In Press).

The editorial team is eager to receive any comments our readers might have on this topic for potential publication in future issues. Please direct any such communications to:
Tess O'Neill, Commissioning Editor, *CNS Oncology*
t.oneill@futuremedicine.com